Kyle K. Seo

Botulinum Toxin for Asians

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To my mother, In-Soon Kim, and my late father, Jae-Kwan Seo, who passed away 8 years ago and is dearly missed. Their love, encouragement, and inspiration challenged me to dream bigger and to reach higher.

Foreword

We first had the pleasure of meeting Dr. Kyle Seo in 2000 when we visited Seoul. We were immediately impressed with his high level of understanding of botulinum toxin therapy as well as other therapeutic modalities in the cosmetic arena. Since that time, our admiration of him and our appreciation of his knowledge and innovation have rapidly grown. Dr. Seo is truly one of the great international experts in this field. We always pay attention when he presents or writes.

The areas where he has extensive knowledge and experience include the botulinum toxins and other noninvasive cosmetic treatment modalities. He is especially expert in the differences between Korean and Asian patients' ideals of beauty and those of Caucasian patients. He has published extensively on these and has helped us all to better understand these differences. This book is titled *Botulinum Toxin for Asians* and in the preface Dr. Seo writes "In this regard the book is aimed at providing practical guidance not only for Asian doctors but also for Western doctors in treating patients of Asian ethnicity." This would lead one to believe that this describes the main virtue of this book, and in our estimation, this book has much wider appeal than that. Dr. Seo has extensive knowledge and experience of the underlying biochemistry and physiology and anatomy which is beautifully summarized in this book. The illustrations are world class. We believe that this volume is essential reading for all individuals concerned with the cosmetic treatment of men and women throughout the world be they Asians and non-Asians!!

This book is an elegant distillation of Dr. Seo's knowledge and experience in this area, and as such he has advanced the clinical use of botulinum toxin to improve both facial and nonfacial problems. It is essential reading for all of us who use botulinum toxin cosmetically and those who are interested in this indication.

We salute Dr. Seo for all that he has done for us over the past years!

Alastair Carruthers

Jean Carruthers

Preface

Botulinum toxin treatment serves as a doorway for patients who are entering the world of cosmetic procedures for the very first time. Any vague concern or fear they might have had of cosmetic treatments in general is quickly dispelled with this simple 5-min procedure, leaving them amazed and thrilled at how effortless it can be to restore their youth and beauty. Happy patients in turn become loyal patients who are more apt to take the next big step into trying other more invasive cosmetic procedures. From a financial point of view, therefore, botulinum toxin treatments can become a significant contributor to the clinic's overall bottom line. Conversely, however, patients who experience negative results from their initial botulinum toxin treatment may never visit the clinic again. This underlines the significance of botulinum toxin treatments as the essential starting point and stepping stone for doctors in laying the foundation for mutual trust and relationship with their patients.

One common misconception regarding botulinum toxin treatments, perhaps relating to the simplicity of the procedure which involves only a few injections, is that the outcomes obtained would be more or less consistent regardless of the skill or experience of the individual practitioner. However, in my practice, I have seen many of my former patients return only after suffering from adverse effects from botulinum toxin procedures they received from other clinics. In case of a botulinum toxin procedure gone awry, there exists unfortunately little room for medical intervention, and patients are left to bear with their unnatural facial expressions for at least 2 months with no recourse other than waiting for the effects of the toxin to fade away. This is because there are no effective antidotes for botulinum toxin. Indeed, the importance of taking proper precautions in performing botulinum toxin procedures cannot be emphasized enough. Shortly after I began practicing botulinum toxin procedures, I also encountered various adverse effects with my patients, which had caused me great anguish at the time and to this day I am still unable to completely shake off. It is against this backdrop that this book was written, with the hope of providing fellow practitioners who are either just starting out on their career in botulinum toxin treatments or who still lack confidence in performing this procedure with the equivalent of a *Driver's Manual* laying out the safe treatment practices based on the trials

and errors which I personally confess to have committed during the early days of my own practice.

Upon reflection, many of my earlier mistakes arose from the failure to fully appreciate the difference in facial shape and beauty standards between Asians and Caucasians. For example, the Asian face tends to be wider and flatter compared to the more dimensional and relatively narrower Caucasian face. Whereas having a prominent zygoma and square jaws is regarded within Western cultures as an appealing beauty trait, zygoma reduction surgery and square jaw reduction with botulinum toxin are popular among Asians who wish to reduce the size of their wide faces. The higher cases of negative results I had encountered with Asian patients were most probably due to applying the same injection methods suitable for Caucasians to Asians, producing outcomes which deviated from the Asian beauty standard. In these pages, I have attempted, therefore, to provide a comprehensive summary of the various botulinum toxin injection techniques suitable for Asians based on my clinical cases and field experiences. In this regard, the book is aimed at providing practical guidance not only for Asian doctors but also for Western doctors in treating patients of Asian ethnicity. Of course, Asians are not a homogeneous group, and the term “Asian” in this book is used in a narrow sense, referring primarily to people from East Asia such as the Chinese, Japanese, and Koreans, and does not extend to cover those from other parts of Asia such as Arabics or Indians. That said, however, Korean beauty, for what it is worth, is currently the dominant Asian beauty standard, driven by the strong influence of the Korean wave in many parts of the world through K-pop, K-dramas, etc. In fact, it is attracting many foreign patients from China, Japan, and Southeast Asia to visit Korea for cosmetic treatment. In some respects, therefore, this book can offer solutions generally applicable to Asian patients who aspire to attain features of the dominant Asian beauty standard regardless of their individual nationality.

The injection methods prescribed in this book do not reflect the Asian consensus data but instead illustrate the specific techniques I actually employ in my field practice. In fairness, different doctors may have different views and ideas on some of the points I cover. That notwithstanding, the injection methods presented in this book have been established based on thousands of cases performed over the past 18 years and will be of relevance for those seeking helpful practical pointers. To the extent that no single method can be upheld as absolutely perfect, however, I am more than happy to receive wise

contrary advice from learned colleagues reading this book.

It is my sincere hope that this English version of *Botulinum Toxin for Asians* will become a valuable and beloved source of new knowledge and advice for interested readers all over the world.

Kyle K. Seo
Seoul, Korea
May, 2016

Acknowledgments

Many people assisted in the publication of this book. I am grateful to my staff for compiling the numerous underlying materials and pictures for this book. I am greatly indebted to my friend, anatomist Professor Hee-Jin Kim who provided me with excellent photos and valuable input in the field of anatomy and Mr. Kwan-hyun Yoon, the Mediart representative who helped to greatly improve the quality of this book with his accurate and elaborate anatomic illustrations. Most importantly, I owe a special thanks to my mentor and essayist Professor Hee Chul Eun who prepared the initial draft for the English edition of this book drawing on his extensive medical knowledge and literary sense. Finally, my thanks goes to Mr. Sam Oh and Ms. San-Hyo Kim, English editors whose efforts helped to bridge the language barrier and put together what I hope will be a compelling medical textbook for readers across the world.

Contents

About the Author

Kyle Koo-Il Seo

is a dermatologist based in Seoul. He received his M.D. and Ph.D. from Seoul National University's College of Medicine, Seoul, South Korea. He became a Clinical Associate Professor in the Department of Dermatology of Seoul National University College of Medicine as the chief of the Botox Clinic. Presently he is also the Director of Modelo Clinic in Seoul, South Korea.

Dr. Seo has worldwide reputation as an authority in the field of botulinum toxin and fillers. He was the first doctor in Korea to have launched a hands-on training course on botulinum toxin and fillers, namely, the 'Modelo Academy', open since 2002. He has also published extensively on the areas of botulinum toxin and filler treatments including Botulinum Toxin for Asians (in Korean) (Seoul Medical Publishing Ltd, 2014) and *Clinical Anatomy of Face for Botulinum Toxin and Filler Injection* (Springer, 2016). In recognition of his exceptional dedication and prominent academic achievements, Dr. Seo was ultimately selected as the sole keynote speaker to represent the entire global cosmetic field at the plenary session of the 23rd World Congress of Dermatology (Vancouver 2015).

Dr. Seo also dedicated himself to promoting global academic activity in the dermatology society as the Vice President of the local organizing committee for the 22nd World Congress of Dermatology (WCD) (Seoul, 2011) and the Secretary General of the local organizing committee for the 36th annual meeting of the International Society for Dermatologic Surgery (ISDS).

Kyle K Seo, Botulinum Toxin for Asians, DOI 10.1007/978-981-10-0204-5_1

1. Botoxology

Kyle K. Seo[1]

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1.1 Introduction

Botulinum toxin type A (BoNT-A) is a neurotoxin produced by the gram-negative, rod-shaped bacterium *Clostridium botulinum*. It causes muscle paralysis through inhibition of acetylcholine release at the neuromuscular junction. Since the ingenious American ophthalmologist Dr. Alan Scott first used the BoNT-A to treat patients with strabismus, BoNT-A exploded in popularity and has since been used in treating a number of inappropriate excessive muscle contractions including blepharospasm and cervical dystonia. In the late 1980s, during a clinical study for treating blepharospasm with BoNT-A, a Canadian ophthalmologist, Jean Carruthers, observed that patients participating in the study wanted to continue to receive BoNT-A injection despite of improvement of blepharospasm because glabellar lines and periorbital lines disappeared along with blepharospasm. She mentioned this interesting observation to her husband, Alastair Carruthers, a dermatologist. This led to publish the world's first article using BoNT-A for wrinkle treatment [1]. Since then BoNT-A has become a byword for the treatment of wrinkles.

Since approved to treat blepharospasm and strabismus by the US FDA in 1989, BoNT-A has continued to expand its indication for the treatment of inappropriate excessive muscle contractions including cervical dystonia (approved by the US FDA in 2000), focal upper limb spasticity (approved by the US FDA in 2010), detrusor overactivity (neurogenic bladder) (approved by the US FDA in 2011), juvenile cerebral palsy, stroke (for rehabilitation

therapy), and anal fissure. The BoNT-A has also been proven highly effective in treating focal hyperhidrosis of the axillae (approved by the US FDA in 2004), palms, and soles, since it inhibits secretion of the eccrine sweat glands innervated by the sympathetic nervous system. In addition, though exact mechanism is not elucidated in humans yet, it was found in an animal experiment that the BoNT-A inhibited secretion of pain-inducing neurotransmitters such as substance P. Pain relief such as in chronic migraine (approved by the US FDA in 2010) is an another good example of the continually broadening applications of BoNT-A.

The use of BoNT-A for aesthetic purposes is also beyond traditional wrinkle treatment. For example, intradermal BoNT-A, considered as a full package of antiaging effects that BoNT-A can deliver, is not only for the reduction of dynamic facial wrinkles but also for the reduction of static wrinkles and pore sizes, as well as creating the so-called perceived “lifted look”. What’s more, nonsurgical cosmetic treatments such as facial contouring and body contouring based on the principle of disuse muscle atrophy have recently come in to the limelight.

Indeed, BoNT-A is a so fantastic drug continuously expanding its applications in various fields such that the term “botoxology” may be used for this new field of study. However, this new realm of study requires more organized and evidence-based knowledge. In this chapter, basic science and some important knowledge for BoNT-A will be covered in order to deal with particular indications.

1.2 Terminology Related to Wrinkles

Translating this text into English proved difficult from the beginning especially choosing terminology related to wrinkles. I found the terms used to describe wrinkles are not well defined. Several words, such as wrinkle, rhytid, line, crease, groove, and fold, share similar definitions and may be used interchangeably from source to source. Facial expression wrinkles can be classified into dynamic and static wrinkles; however, the word “dynamic” can be sometimes expressed as hyperfunctional or hyperkinetic depending on the authors. The literatures often refer to lines in describing regional wrinkles on specific areas of the face with a combination of other words such as bunny lines. In addition to this, different researchers utilizing different terminology present obvious challenges. I think precise definition and agreement of the

terms related to wrinkles are necessary.

Severity is another problem when selecting wrinkle terminology. Adjectives such as deep, severe, and fine can be used to describe wrinkles with a combination. Though image analysis seems to be more thorough than clinical assessments of severity, common terms are necessary for communication between doctors and patients. With consideration to the above, I will define the terms below with precise definitions and additional explanation. These terms will be used throughout the text.

Facial wrinkles and aging signs in Asians are shown in 70-year-old Korean man (Fig. 1.1).

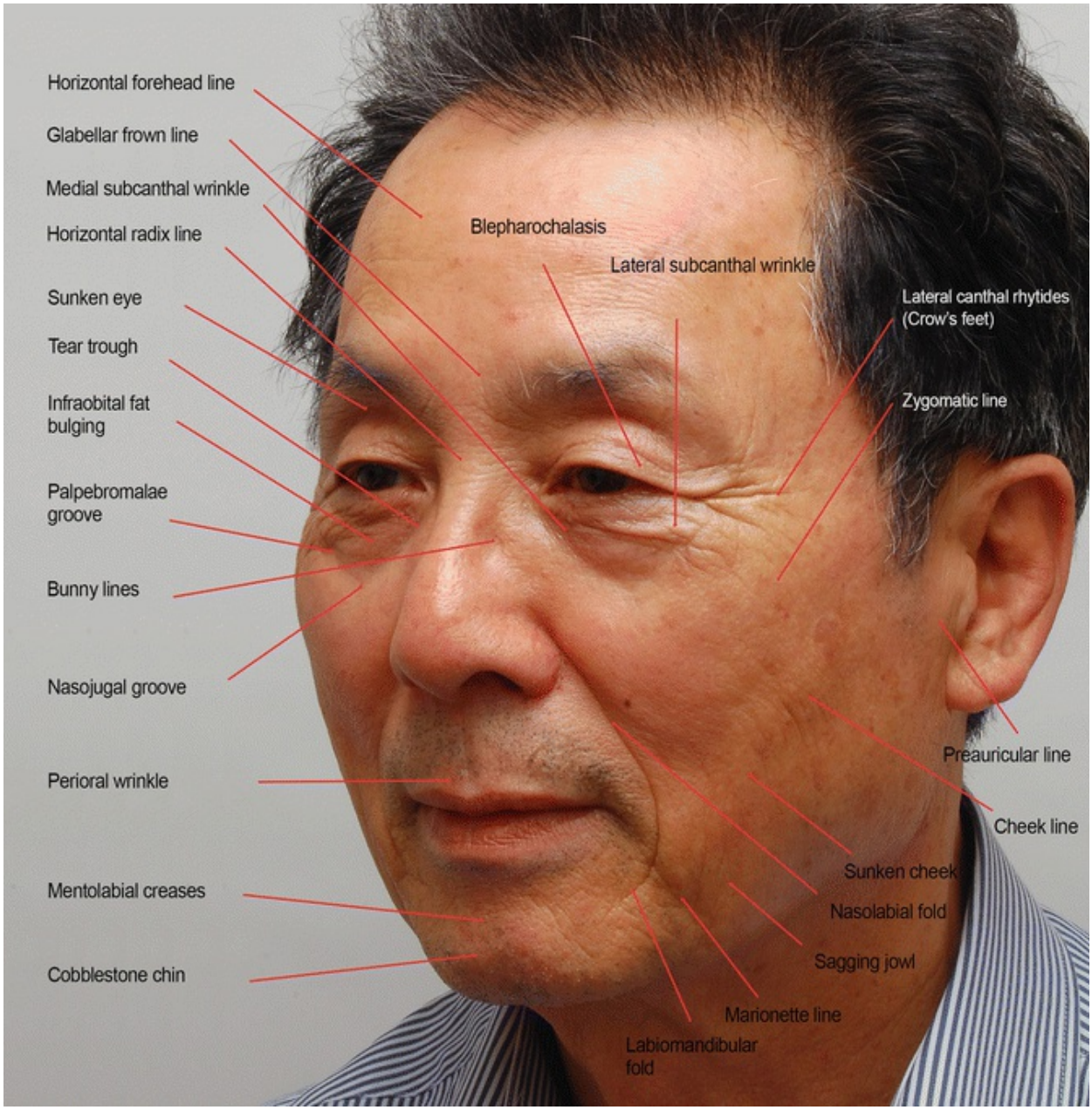

Fig. 1.1 Facial wrinkles in Asians

1.2.1 Basic Terminology Related to Wrinkles

Wrinkle

This term is the most common word for the general public and covers the most comprehensive concept. Dermatologists use this term when explaining general aspects such as wrinkle treatment, wrinkle severity, and wrinkle prevention.

Rhytid
Etymologically, this term is Greek in origin. The rhytid (pluralized as rhytides) has essentially the same meaning of wrinkle [2]. I used the term wrinkle instead of literary expression “rhytid” in this book except lateral canthal rhytides if possible. Except when referencing specific literature from the past, I think this term “rhytid” should be avoided in communication with patients and the general public.

Line
Lines are most commonly interchangeable with wrinkles. However, lines usually mean a mild form of wrinkles in severity or wrinkles which are not caused by aging process such as horizontal necklines and bunny lines. Lines sometimes describe the wrinkle in certain locations, such as bunny lines, marionette lines, infraorbital lines, horizontal forehead lines, glabellar frown lines, and preauricular lines.

Crease
Crease is also interchangeable with wrinkles and lines. However, a crease is conceptually similar to a mild form of wrinkles in severity. And crease sometimes describes the specific wrinkle in certain locations, such as labiomental crease and proximal wrist crease.

Fold
The term fold is quite limited in use but can be used when describing a nasolabial fold, a Mongolian fold (epicanthal fold), and a labiomandibular fold. A fold is conceptually similar to a wrinkle, but with nuances such as linear depression and a mild recurved margin on one side, like pleating. I did not use fold in other situations except to describe the words mentioned above.

Groove
The term groove is quite limited in use but can be used when describing a nasojugal groove and a palpebromalar groove. A groove is conceptually similar to a wrinkle, but with nuances such as shallow linear depression, which is slightly wider than a line.

1.2.2 Functional Aspect

Static Wrinkle

Defined as wrinkles unaffected by facial expressions. Commonly referred to as “wrinkles at rest,” I believe the term static wrinkle is clearer and more illustrative.

Dynamic Wrinkle
The opposite of a static wrinkle, dynamic wrinkles are reversible wrinkles caused by contractions of facial expression muscles. Commonly referred to as “wrinkles at animation,” I believe the term dynamic wrinkle is clearer and more illustrative.

Hyperfunctional/Hyperkinetic Wrinkles
I have omitted these two terms because the words are a little difficult for general public to understand that they mean wrinkles of facial expressions.

1.2.3 Severity Aspect

Wrinkles can be divided into grades based on severity. I used the terminologies fine line, line (fine wrinkle), moderate wrinkle, and deep wrinkle, defined as follows:

Grade 1 Fine line: wrinkle with barely visible linear depression

Grade 2 Fine wrinkle (line): wrinkle with mild linear depression
Line: used as a synonym of fine wrinkle.

Grade 3 Moderate wrinkle: wrinkle between fine and deep wrinkle

Grade 4 Deep wrinkle: static wrinkle associated with deep furrow

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1.3 Basic Science of Botulinum Toxin

1.3.1 Serotypes and Mechanism of Action of Botulinum Toxin

There are seven serotypes of botulinum toxin(BoNT): A, B, C1, D, E, F, and G based on their immunologic properties. Among them, serotypes A, B, and F are well-known neurotoxins. The duration of efficacy and potency differs between serotypes; type A is the most potent and has the longest duration of efficacy. As the muscle paralytic effect of type B is far weaker than type A in humans, a 100-times higher dose is necessary to achieve the same

effectiveness. The duration of efficacy of type B is also shorter, allowing muscle function to recover nearly by half after 4 weeks. Type F is potency.

BoNT blocks the release of acetylcholine, a neurotransmitter, by binding to the presynaptic cholinergic nerve terminals in neuromuscular junctions (Fig. 1.2). For synapses, “acetylcholine vesicles” containing acetylcholine should be fused with the plasma membrane of the nerve branch for the release of acetylcholine into neuromuscular synapses. BoNT cleaves the soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) complex, a plasma membrane receptor essential for this process. Specific serotypes of the BoNT cleave different plasma membrane receptors; types A and E cleave 25 kDa synaptosomal-associated protein (SNAP-25); types B, D, and F cleave vesicle-associated membrane proteins (VAMP, also known as synaptobrevin), and type C1 cleaves two plasma membrane receptors, syntaxin and SNAP-25 (Fig. 1.3). When injected, BoNT blocks acetylcholine release into the cholinergic synapse, resulting in “chemodenervation.”

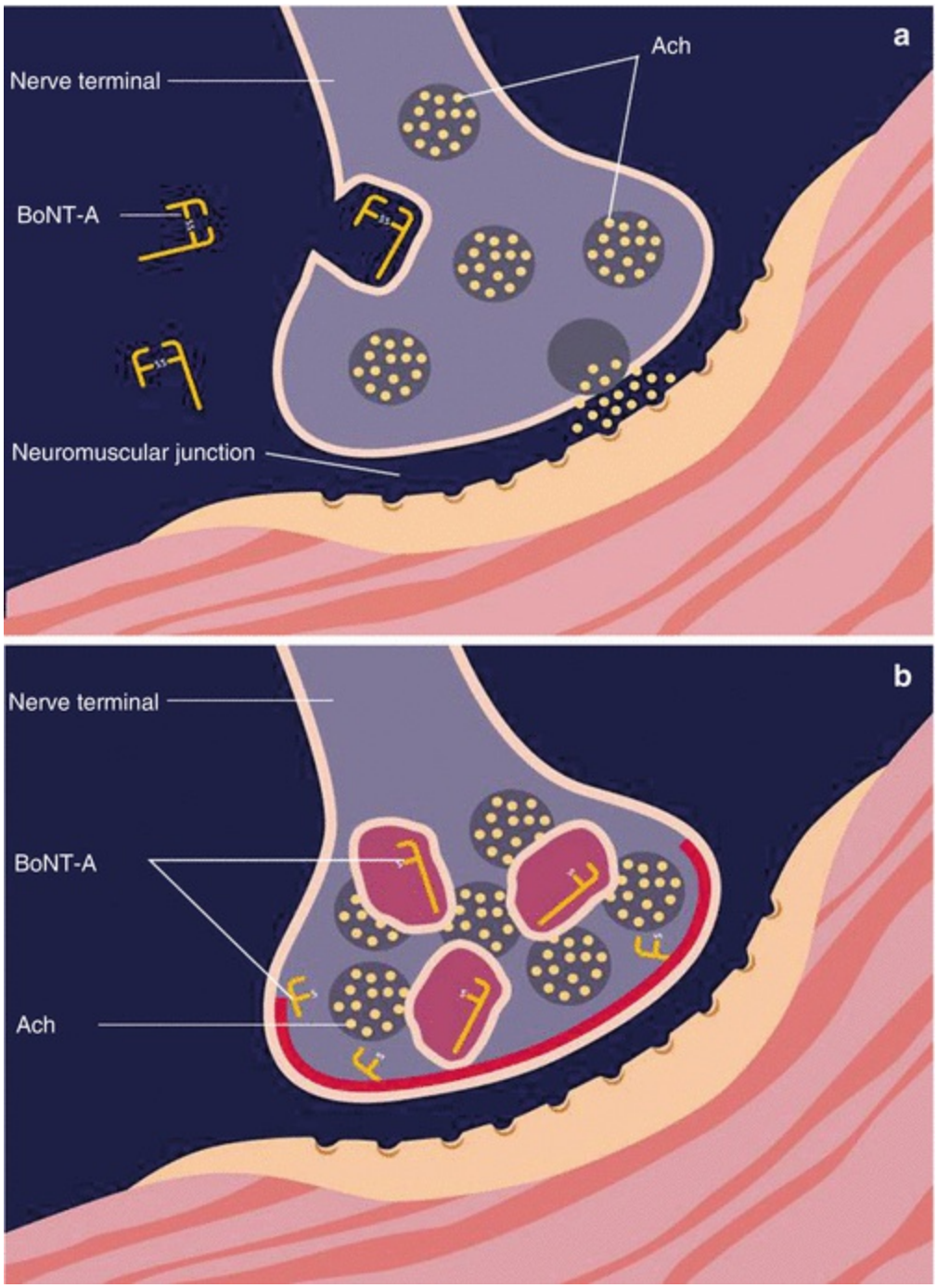

Fig. 1.2 Action mechanism of botulinum toxin (Photo, courtesy of Allergan Korea). (**a**) Normal neuromuscular junction. Acetylcholine (Ach) is released into the neuromuscular junction. (**b**) Neuromuscular junction blocked by botulinum toxin. Acetylcholine release into the neuromuscular junction is blocked

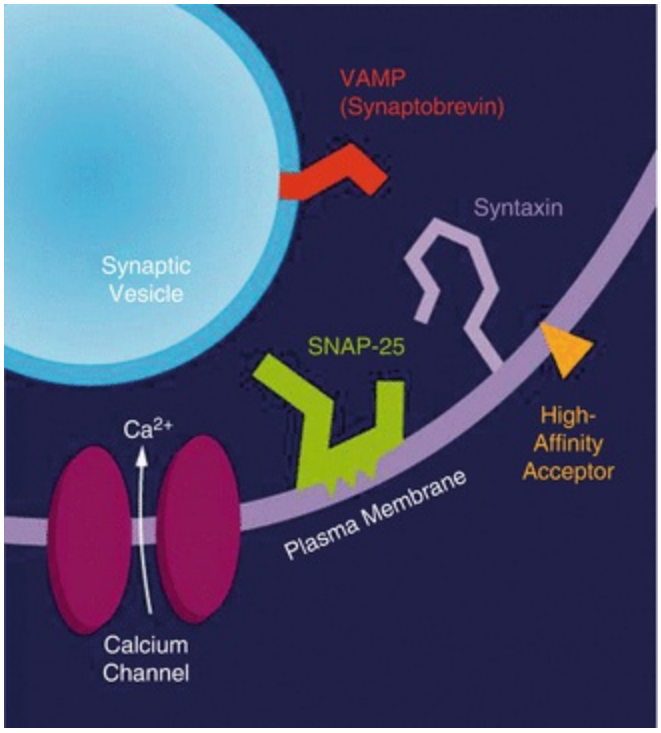

Fig. 1.3 Intracellular target receptors of botulinum toxin (Photo, courtesy of Allergan Korea)

1.3.2 Molecular Structure of Botulinum Toxin Type A

BoNT-A is a 150 kDa neurotoxin molecule composed of a 100 kDa heavy chain linked via a disulfide bond to a 50 kDa light chain (Fig. 1.4). The heavy chain plays a crucial role in binding the neurotoxin molecule to the axon terminal entering the nerve, while the light chain actually cleaves the plasma membrane receptors (e.g., SNARE complex, SNAP-25) to prevent intracellular fusion of acetylcholine vesicles with the plasma membrane [3]. The neurotoxin molecule of BoNT-A is surrounded and protected by large complexing protein molecules called neurotoxin-associated proteins (NAPs). NAPs are composed of hemagglutinins and a non-toxin non-hemagglutinin (NTNH). Hemagglutinins include four types of proteins, while a single type of NTNH always combines with the neurotoxin. Molecular weights of BoNT-A vary: 300 kDa, 500 kDa, and 900 kDa depending on the size of complexing proteins. Complexing proteins encircle the neurotoxin at acidic pH, while separated from it at a neutral or basic condition. They protect the neurotoxin molecules from the proteases of the gastrointestinal tract (e.g., pancreatic enzymes, pepsin) and gastric acid when ingested by animals. At neutral pH, they are dissociated and the neurotoxin is released. Thus,

complexing proteins are the product of evolution, making the bacterial neurotoxin effective to the target animals (how clever it is!) [4]. Their role in the skin and muscles, however, is not well known. On the contrary, they seem to induce immunologic responses and promote antibody formation.

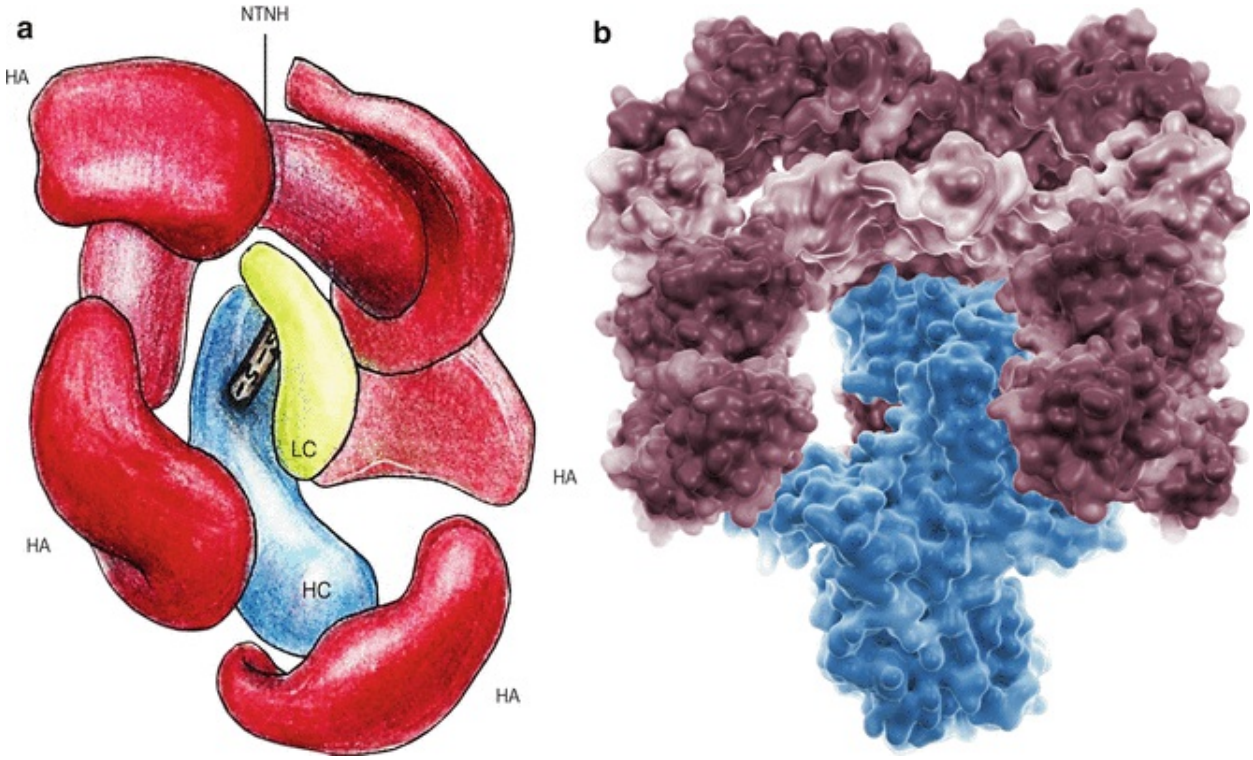

Fig. 1.4 Three-dimensional structure of the botulinum toxin type A protein. (**a**) Structure of botulinum toxin A with 900 kDa molecular weight. The core neurotoxin consisting of light chain and heavy chain is only 150 kDa; the rest is comprised of hemagglutinins (HA) and nontoxic non-hemagglutinin (NTNH) protein that protect the core neurotoxin (illustrated by Jina Seo) (*LC* light chain, *HC* heavy chain, *S–S* disulfide bond). (**b**) The 150 kDa core neurotoxin (blue colored) and surrounding complexing proteins (brown colored) (photo, courtesy of Merz Korea)

Allergan has claimed that BOTOX® of high molecular weight (900 kD) is safer than Dysport® of low molecular weight (500–900 kD) because the BoNT-A with larger molecular weight diffuses less to the adjacent muscles. According to Eisele's study, however, once BOTOX® is diluted with normal saline, 85 % of the neurotoxin is present in a free form, and the rest of it is also dissociated to a reduced form of 500 kD molecular weight [5]. Additionally, once injected into the skin of a neutral pH, the complexing protein is released from the core neurotoxin in less than a minute. In summary, the molecular weight of BoNT-A is not an issue of clinical significance.

1.3.3 Sites of Action

The neuromuscular junction is the representative of cholinergic synapses that release acetylcholine. Blockage of acetylcholine release in the neuromuscular junction by BoNT-A leads to muscle paralysis. BoNT-A also inhibits sweat and salivary secretion since the sweat gland and salivary gland are cholinergic synapses [6, 7]. The sympathetic ganglia may also be suppressed by BoNT-A injection because they are also cholinergic synapses [8].

1.3.4 Recovery

The “chemodenervation” phenomenon by BoNT-A is not permanent but recovers gradually over 1–3 months because of new neuromuscular junction generation (Fig. 1.5). Neuromuscular junctions are in dynamic homeostasis between constant generation and decay; blockage of nerve conduction by BoNT-A induces new axonal sprout, resulting in muscle strength recovery. In humans, the muscle paralytic effect of BoNT-A is known to recover by half after 8 weeks. Therefore, symptoms of blepharospasm may recur when muscle strength recovers only by half, requiring repeat treatment every 2–3 months. Wrinkles, on the other hand, do not need to be completely removed and may be treated every 3–6 months.

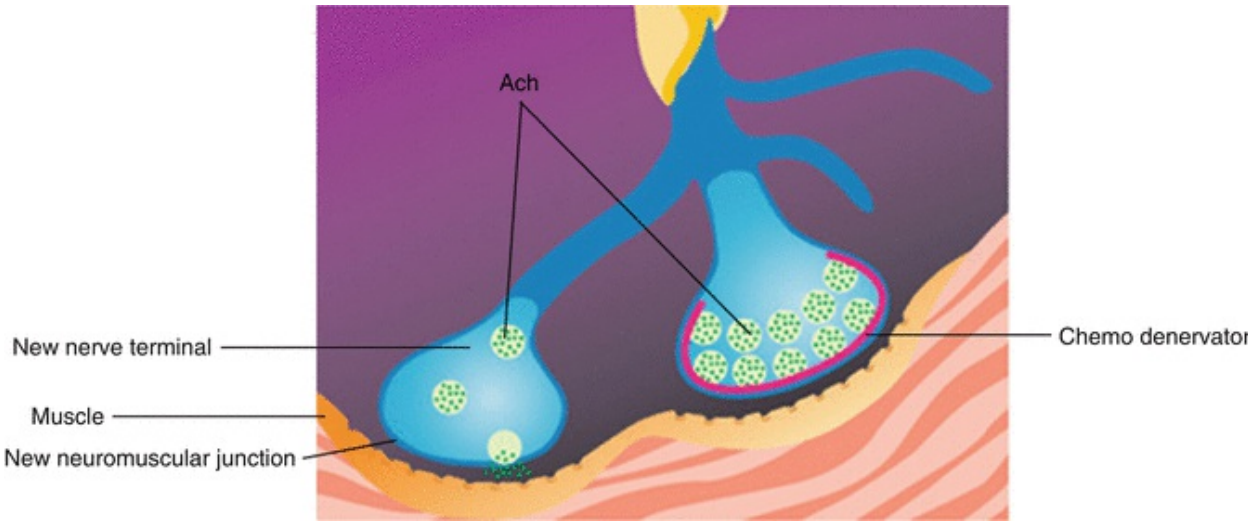

Fig. 1.5 Generation of new axonal sprout (Photo, courtesy of Allergan Korea)

Recovery time differs between the somatic and autonomic nervous

system. It takes 3–4 months in the neuromuscular junction of voluntary muscles for recovery, while 6 months or longer is necessary for the recovery of autonomic nerves such as the detrusor muscle of the urinary bladder or the sweat glands [9]. In axillary hyperhidrosis or gustatory hyperhidrosis, repeat injection may induce longer durations of clinical efficacy, decreased severity, and even a complete cure without recurrence [10]. This effect may be attributed to slow regeneration of sympathetic nerve fibers in sweat glands compared to the neuromuscular junction [11].

1.3.5 Dosage and Potency Assays

BoNT is a biologic agent and the dosage of BoNT is expressed in units of biological activity instead of weight (e.g., milligrams). The biological activity of 1 unit (U) is defined on the basis of the median lethal dose (LD50) bioassay: the dose of BoNT that is lethal in 50 % of 18–20 g Swiss Webster mice 72 h after an intraperitoneal injection. Though not completely precise, LD50 assay is the most widely used metric defining the activity of BoNT.

The results of LD50 assays, however, are hard to simply compare with each other because each manufacturer utilizes different methodology including different diluents and different reference standards. The same product yields different results when measured by different LD50 assays: the Allergan LD50 for BOTOX®, the Merz LD50 assay for Xeomin®, and Speywood LD50 assay for Dysport®. Hunt and Clarke have reported that when measuring Xeomin® with the Allergan LD50 assay, different values are obtained than with the Merz LD50 assay [12]. Furthermore, Speywood LD50 assay uses phosphate buffer saline (PBS) containing gelatin in order to stabilize neurotoxin, thus giving higher values than the Allergan LD50 assay that used normal saline as a diluent. When measured with Speywood LD50 assay, as low as 0.3 U of BOTOX® reached well up to LD50 and was three times higher than that measured with the Allergan LD50 assay, as reported by Hambleton et al. [13] For these reasons, the conversion ratio of BOTOX® to Dysport® varies from 1:1 to 1:8 (BOTOX®/Dysport®). A detailed comparison of BOTOX® and Dysport® can be found in Sect. 1.4.1 “Comparison of Potency.”

In 2009, recognizing the differences in potency and noninterchangeability among products, the US FDA and US Adopted Names (USAN) Council assigned a nonproprietary name for each product to emphasize the differences. The nonproprietary names are onabotulinumtoxinA for

BOTOX®, incobotulinumtoxinA for Xeomin®, abobotulinumtoxinA for Dysport®, and rimabotulinumtoxinB for Myobloc®; most clinical studies have adopted these nonproprietary names since then.

Recent developments of cell line-based assays have been applied to proper estimations of potency differences, reducing the need for animal experimentation worldwide. In 2011, Allergan's cell-based potency assay (CBPA) was approved by the US FDA [14]. Merz also developed its own assay and is awaiting approval. Currently, the US FDA approval for Allergan's CBPA applies only to onabotulinumtoxinA. However, it is anticipated that it will soon be applied to all BoNT-As because of its high sensitivity and cross validity.

Nonetheless, potency as measured in mice is not always indicative of human efficacy. Sloop et al. developed a human model to overcome the differences between species and accurately measure the potency of BoNT-A when applied to humans [15]. They injected 2.5 U of BoNT-A to the extensor digitorum brevis (EDB) muscle and measured compound muscle action potential (CMAP) using electroneurography (Fig. 1.6). According to this model, the effect of BoNT-A on muscle paralysis increases according to the log dose–response curve. Once the BoNT-A is saturated at the neuromuscular junction, the effect is nearly the same even if higher dose of BoNT-A is injected [15].

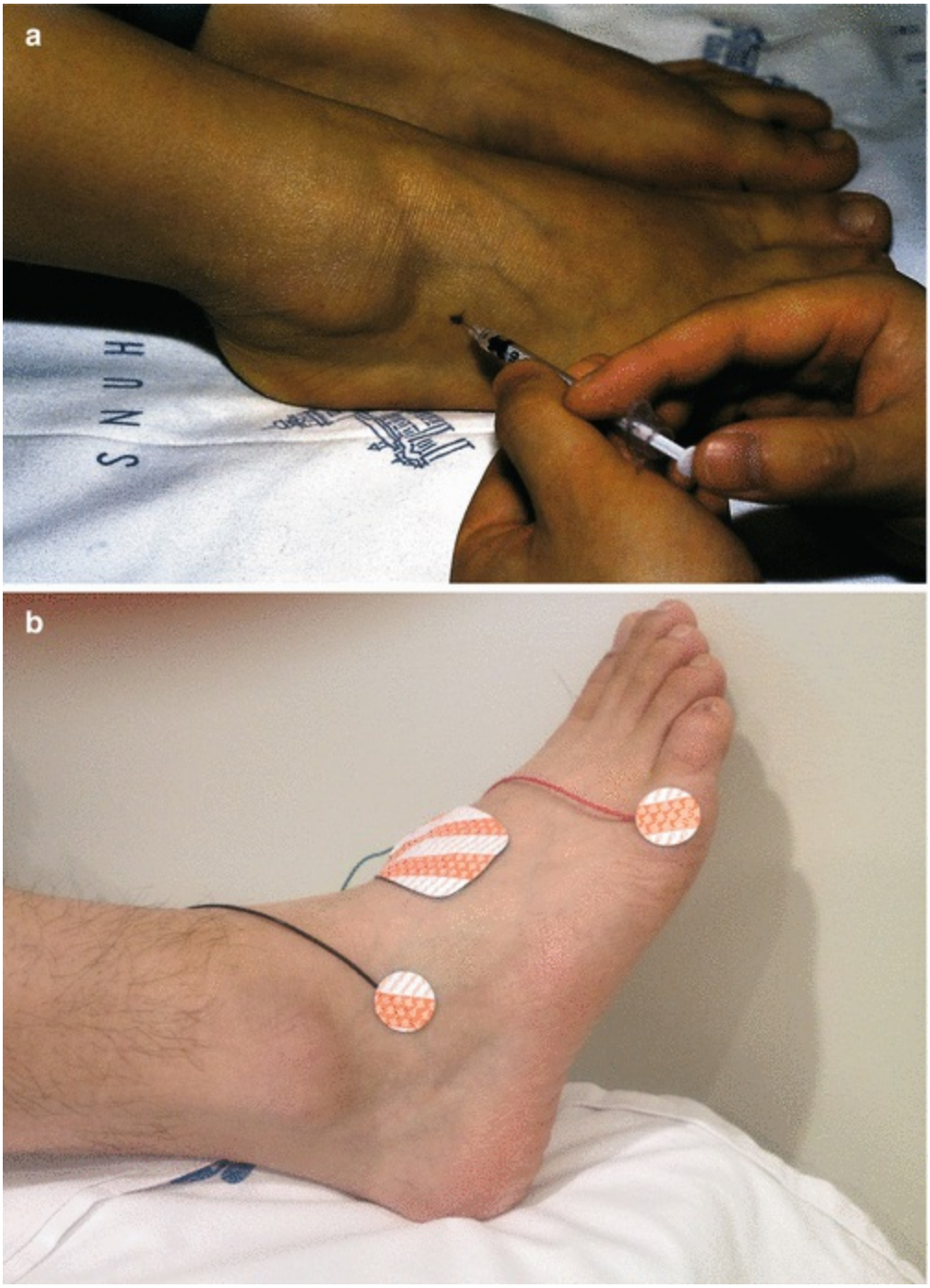

Fig. 1.6 Human model for measuring the potency of botulinum toxin. (**a**) 2.5 U of botulinum toxin A is injected into the extensor digitorum brevis muscle. (**b**) Measurement of compound muscle action potential. After applying the active surface electrode on the extensor digitorum brevis muscle and the reference surface electrode on the fifth metatarsal head, stimulate at the point 8 cm proximal to the recording electrode

1.3.6 Difference in Personal Sensitivity

Personal sensitivity to BoNT-A varies widely; however, no clear mention has been reported about this in literature. For example, at the consensus meetings of BOTOX® or Dysport®, the recommended dosages for wrinkle treatment had been always suggested with ranges, and the maximum dose can be more than twice that of the minimum [16]. I have also experienced that some of my patients could hardly move their frontalis muscle following just a small dose (2 U) of BoNT-A. In facial contouring with BoNT-A, the atrophy of the masseter muscle and temporalis muscle usually begins 2 weeks after injection peaking after 2–3 months, but some patients have shown prominent muscle mass decrease after just 2 weeks (Fig. 1.7). In addition to muscle volume differences between people, personal sensitivity to BoNT-A likely contributes to these different responses. Since there currently are no other methods to detect differences in sensitivity prior to the procedure, it is safer to start with the minimum dosage. Conversely, if the effect is less than the expectation following the BoNT-A injection, insufficient dosage for the individual should be suspected first rather than immunoresistance to BoNT-A, and thus, booster injections are necessary.

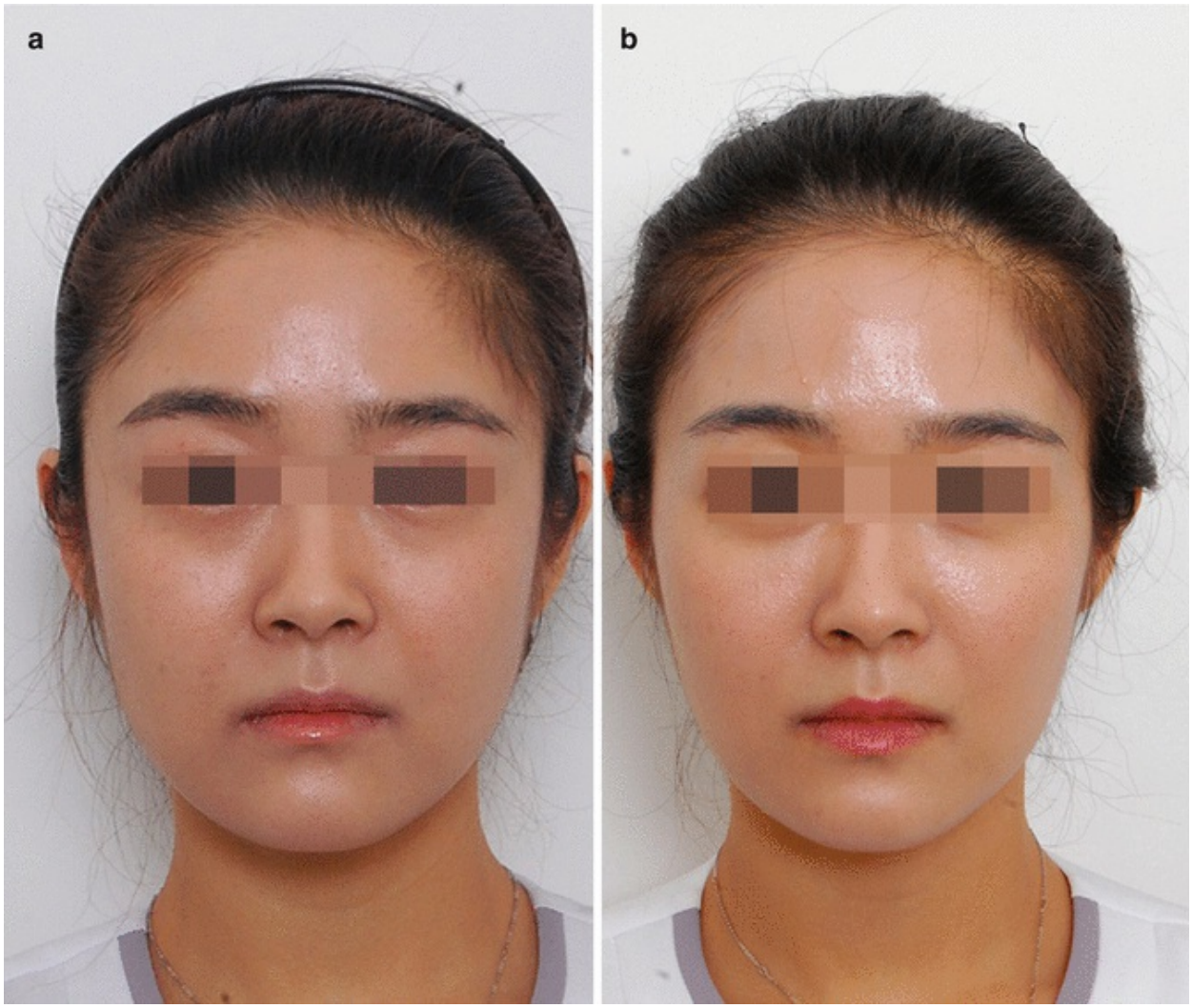

Fig. 1.7 Difference in personal sensitivity to botulinum toxin. Marked volume reduction of the temporalis muscle is noticeable only 2 weeks after injecting 30 U of botulinum toxin into the temporalis muscle ((a) before, (b) after)

Tip: The Origin of the Term “Botox”

“Forest Fire (山火)” is a classic short novel written by Dong-Lee Kim, one of Korea’s most esteemed authors of modern literature. It offers a vivid portrayal of the miserable life led by the Korean people during the Japanese colonial period in the early twentieth century. In the story, the protagonist and his family learn about a dead cow that suffered from an illness and was buried in the neighboring village. Hungry, the protagonist’s father ventures out in the middle of the night to dig up the dead cow and brings home the carcass for his family. Indeed, it had been long since the family had sat down together for a hearty meal where meat broth was put on the table. Later that

night, however, the family begins to experience terrible ailments during sleep such as vomiting, dizziness, muscle paralysis, and convulsion. The novel ends with the piercing cry of the desperate father, “meat poison!”

I was in high school when I read this short novel and was not familiar with the term meat poisoning. Later, in medical school I vaguely suspected that must be something akin to either botulinum or tetanus toxin. So tragic and heart wrenching was the story that I couldn’t get it out of my head for a long period of time afterward. It was by some coincidence many years later that I finally got the answer.

In May of 2002, I was invited as a lecturer to the Taiwan Dermatological Society. To my amazement, I realized that the term “BoNT” as was used by the local press was represented in Chinese characters as “meat poison (肉毒).” It turned out that within the East Asian countries sharing the use of Chinese characters, the term “meat poison (肉毒),” literally meaning poison produced from the putrefaction of meat, had been historically used to refer to botulinum toxin. Meanwhile, the English term “botulinum” is said to have originated from the Latin term *botulunus*, meaning sausage, implying that BoNT is produced from the putrefaction of sausage. This reveals that in both the Eastern and Western cultures, the relevant term was based on the etiology of the disease.

The term *botox* was first coined by the neurology research team of the Columbia University, as a shorthand for the compound term *botulinum toxin,* which they had been studying since the 1980s, which makes it a US nomenclature. This eventually caught on elsewhere when later BOTOX became a registered trademark of Allergan for its own commercial botulinum toxin. In much the same vein, in Korea the original term “wrinkle treatment procedure using botulinum toxin” is known more popularly today as referred to as “botox procedure.” Not only is the term “botox procedure” used widely by the general public and the media including the papers, TV, and magazines, it has even penetrated official abstract books published by various academic societies. In 2002, the term “botox” was even listed in the Oxford English Dictionary. One might imagine that Allergan would simply be happy that its brand has become so famous that it is almost a common household name, but a deeper look reveals the more complex challenges this presents. While having a popular brand is generally good for business, once the brand becomes too common that it becomes a generic term for the product rage itself, the brand owner loses its proprietary rights in the trademark. When

BOTOX® was the only product available on the market, the catchy brand name provided Allergan with a distinct advantage in marketing and communicating its product. However, the market entry of competing brands, such as France's Dysport®, China's BTXA®, and Korea's Neuronox®, collectively recognized as *Botox* by the consumers has caused Allergan's BOTOX® to lose its significance as a brand, eroding its point of differentiation. This can be a source of great frustration on Allergan's perspective considering the time and resources it initially expended on breaking the barriers and creating new markets, only to give its competitors a free ride on its valuable BOTOX® brand. Such examples are not uncommon in other industries. "Jeep" was originally a brand name owned by the Chrysler company before it became a generic term for "four-wheel-drive vehicles" in general. Once BOTOX® officially becomes a generic term, Allergan is at risk of losing its trademark. In order to prevent such loss of trademark, Allergan is keen to instruct customers to signify its trademark BOTOX® whenever referring to their product in order to distinguish it from the generic term botox.

1.3.7 Effects on Sensory Nervous System

In the 1990s, Binder et al. found that patients injected with BoNT-A in the glabellar area experienced alleviation of migraine pain. Since then, BoNT-A has proven an effective pain reliever for migraine. Since the US FDA approved the BoNT-A for chronic migraine treatment in 2010, the pain treatment using BoNT-A has expanded to tension headache, temporomandibular disorder, trigeminal pain, back pain, myofascial pain, and post-herpetic neuralgia.

The mechanism by which BoNT-A reduces pain is not yet fully understood. However, preliminary studies indicate the BoNT-A may inhibit the secretion of pain-mediating neurotransmitters from afferent fibers of sensory neurons, including substance P, calcitonin gene-related protein (CGRP), and glutamate from peripheral sensory nerves [4]. It has been also proposed that inhibition of TRPV1 by the BoNT-A may contribute to pain control using the BoNT-A [17]. TRPV1 is an ion channel found on sensory neurons that increases during chronic pain and inflammation. It is commonly activated by capsaicin or burn injuries. Fortunately, the actions of the BoNT-A on the pain-mediating system are selective since the pain-mediating

substances inhibited by BoNT-A are not secreted from A-delta or A-beta fibers, which conduct acute pain signals and mediate pressure and touch sensation, respectively. As a result, injection of BoNT-A does not affect the acute pain sense and general sensation that normally protects us.

Episode: Does Prolonged and Repeated Botox Injection Freeze Facial Expressions and Induce Sensory Nerve Disturbance?

In November 2002, there was intense week-long media coverage in Korea of the long-term side effects associated with the BoNT-A treatment for wrinkles. Citing a Reuters report, the allegations centered around the claim that BoNT-A could induce sensory nerve disturbance leading to an expressionless, masklike face. Reproduced below is the text of the actual report that aired on the 9 o'clock news at one of the major TV broadcasting stations in Korea:

Anchor: " According to a recently released report, Botox, widely claimed as an effective anti-wrinkle treatment may cause certain fatal side effects if used over the long term. Symptoms allegedly include complete loss of facial expression and even sensory disturbance in the nerve system."

Reporter "The research team of the National Hospital for Neurology and Neurosurgery in UK warned today that Botox may negatively affect sensory nerve transmission from the peripheral to the central nervous system. As Botox may also affect secretion of neurotransmitters, the team pointed out, long term care should be taken regarding possible adverse effects such as frozen facial expressions."

From the average viewer's perspective, the message was loud and clear; that *Botox* carries serious long-term adverse effects, including disruptions to the nervous system and frozen facial expressions.

Meanwhile, the relevant article published by the *British Medical Journal* cited as the source of the report reads as follows [18]:

-Although no conclusive evidence is available as yet to establish whether BoNT-A impacts the sensory nerve cells, to the extent that it interferes with the neurotransmission of the sensory nerve, it could be effective for the treatment of migraine or other pain ….(omitted)….In the (present day) setting where the concept of "botox parties" is not

altogether unusual, it is easy to neglect the fact that BoNT-A is indeed a neurotoxin the long term effects of which have yet to be established.

The contrast here is quite remarkable. Whereas the BMJ report describes "interference with sensory transmission" as the mechanism by which BoNT-A can be used as a migraine treatment, this was conveyed in the media as a "detrimental effect on the central nervous system." Further, whereas the relevant wording in the original report was that *the long-term effects of BoNT-A over extended periods had yet to be established, and therefore caution is required against its overuse,* this was altered in the Korean report as "…may block the secretion of neurotransmitters over the long term… should not rule out the possible harmful effects such as frozen facial expression…." This is by no means a simple translation error, but borders on media manipulation. Such creativity and imagination are to be greatly admired in creative writing but have no place in news reporting by a public media institution. The author of the original BMJ report had this to say on this point in his statement to the media "(What is reported in the media)…is overblown and clearly misses the point."

Understandably, after a week-long media frenzy highlighting the purported side effects of *BoNT-A*, my clinic was inundated by calls from disturbed patients, and appointments for *BoNT-A* treatment fell by more than half the normal level over the next few months. This goes to illustrate the enormous power wielded by the mass media as well as the public harm that could be inflicted when media disregards its public responsibility by resorting to sensationalism.

1.4 Comparison of Products

There is no manufacturing patent required to purify BoNT-A, the process having already been disclosed by articles in the 1970s. The US Department of Defense, however, strictly controls the bacterial strains since BoNT can be used as a biological weapon. As a result, having a proper strain is a critical manufacturing advantage. Most of the available commercial products are supposedly made from the so-called "Hall" strain extensively studied at the University of Wisconsin, an active place for the research for BoNT in the 1970s. Dr. Alan Scott's Oculinum® (the predecessor of BOTOX®), Neuronox®, BTXA®, Dysport®, and Xeomin® are all derived from this

strain.

In addition to Allergan's BOTOX®, commercially available BoNT-A includes Dysport® (Ipsen Biopharmaceuticals, France), Xeomin® (Merz, Germany), and BTXA® (Lanzhou Biological Products Institute, China). Three Korean companies produce four preparations: Neuronox® and a liquid preparation of BoNT-A, Innotox® manufactured by Medytox Inc., Botulax® by Hugel Pharma, and Nabota® by Daewoong Pharmaceutical. Myobloc® is a botulinum toxin type B (BoNT-B) product produced by the American company Solstice Neurosciences Inc. (Table 1.1).

Table 1.1 Comparison of botulinum toxin products

Trade name	**Botox®**	**Dysport®**	**BTXA®**	**Meditoxin®**	**Myobloc®**	**Xeomin®**
Alternative name	Vistabel® Vistabex®	Reloxin® Azzalure®	CBTX-A® Prosigne®	Neuronox® Siax®	Neurobloc®	Bocouture®
Nonproprietary name	Onabotulinum-toxinA	Abobotulinum-toxinA			Rimabotulinum-toxinB	Incobotulin toxinA
Manufacturer	Allergan	Ipsen	Lanzhou	Medytox Inc.	Solstice Neurosciences Inc.	Merz
Subtype	Type A	Type A	Type A	Type A	Type B	Type A
Strain	Hall	Hall NCTC2916	Hall	Hall	Bean B	Hall ATCC3502
Molecular weight	900 kD	500 ~ 900 kD	900 kD	904 kD	700 kD	150 kD
Target of action	SNAP-25	SNAP-25	SNAP-25	SNAP-25	VAMP	SNAP-25
Units/package	50, 100	300, 500	100	50, 100, 150, 200	2500, 5000, 10,000	100
Form Drying method	Powder Vacuum dried	Powder Lyophilization	Powder Lyophili-zation	Powder Lyophili-zation	Liquid form	Powder Lyophilizat
Conversion ratio (Botox®: product)		1:2.5 (1:2 ~ 1:2.5)	1:1	1:1	1:50 ~ 1:100 (muscle) 1:10 ~ 1:30 (sweat gland)	1:1
pH	6.8 ± 0.5	appx. 7.0	6.0 ± 0.4	6.8 ± 0.5	appx. 5.6	appx. 7.0
Excipients	HSA 0.5 mg, NaCl 0.9 mg	HSA 125 mg, lactose 2.5 mg	Gelatin, dextran, sucrose	HSA 0.5 mg, NaCl 0.9 mg	HSA 500 g/mL, Nacl 6 mg/mL, sodium succinate	HSA 1 mg, sucrose 4.7

Protein load	4.5 ng/100 U	12.7 ng/500 U		4.5 ng/100 U	50 ng/5000 U	0.44 ng/10(
Storage (unopened) Shelf life	2 ~ 8 °C 36 (24) months	2 ~ 8 °C 15 months	−20 ~ 5 °C 36 months	2 ~ 8 °C 24 months	2 ~ 8 °C (avoid freezing) 24 months	Up to 25 °C 48 months

HSA human serum albumin

1.4.1 Comparison of Potency

BOTOX® was first approved by the US FDA in 1989 and has shown excellent efficacy not just in treating disease but also as an anesthetic. Therefore, all subsequently produced commercial BoNT-A products put stress on the interchangeability of their product with BOTOX® in terms of the potency and efficacy. The results of LD50 assays, however, are hard to simply compare with each other because each manufacturer utilizes different methodology (see Sect. 1.3.6) such that the US FDA assigned a nonproprietary name for each product to emphasize the differences.

Nonetheless, innumerable studies have been conducted on comparison of potencies between other products and BOTOX®. For example, although the conversion ratio between BOTOX® and Dysport® was reported 1:3–1:4 in early studies, the ratio of 1:2.5 (BOTOX®:Dysport®) seems to be the most commonly used ratio in recent studies [19]. The US FDA-approved dosage for glabellar line treatment is 20 U for BOTOX® and 50 U for Dysport®, which also supports the conversation ratio of 1:2.5. Further studies, such as Kerscher et al., however, suggest that a ratio of 1:2 (BOTOX®:Dysport®) is more reasonable, considering the fact that Dysport® produces a greater anhidrotic area than BOTOX at the conversation ratio of 1:2.5 [20].

Although some practitioners believe Xeomin® to be less potent than BOTOX®, the conversion ratio between two products is generally thought to be 1:1 [20]. The US FDA-approved dosage for glabellar line treatment is 20 U for both BOTOX® and Xeomin®. Neuronox®, marketed as a direct substitute for BOTOX® with the same manufacturing process and components, is also used at a conversation ratio of 1:1 (BOTOX®:Neuronox®) [21].

1.4.2 Comparison of Excipients

Each product has a different manufacturing process in isolating and purifying BoNT-A. The molecular size and presence of complexing proteins as well as stabilizing agents used to prevent degradation also differ from product to product. One of the differences in the purification processes is the drying method. For the BOTOX®, vacuum-drying method is used, while for Xeomin®, Neuronox®, and Dysport®, the freeze-drying method is used to minimize the risk of protein denaturation caused by high temperatures during vacuum-drying method, resulting in the formation of thicker powder cakes than that of BOTOX®.

Molecular weights vary depending on the size of complexing proteins; BOTOX® and Neuronox® have larger molecules of 900 kDa, while Dysport® and Myobloc® have 500–900 kDa and 700 kDa, respectively. Xeomin® is a purified neurotoxin of 150 kDa free from complexing proteins. Complexing proteins protect the core neurotoxin molecules from gastric acid and digestive enzymes when ingested by animals. Since the complexing proteins are dissociated immediately at neutral pH and the neurotoxin is released, they have no significance when injected into the human body. Consequently, molecular weight differences and their effects on diffusion are not clinically significant. When BOTOX® and Xeomin® are injected into the forehead of patients using the same technique at a conversion ratio of 1:1, the anhidrotic areas are nearly identical [20]. Early reports that Dysport® diffuses more broadly than BOTOX® are now thought to be the result of overdose by misapplication of the conversion ratio (1:4 between BOTOX® and Dysport®). Hexsel also reported that injections of BOTOX® and Dysport® using a conversion ratio of 1:2.5 showed no major difference in the anhidrotic areas [22].

As stabilizers, human serum albumin is used in BOTOX®, Xeomin®, Dysport®, Neuronox®, Botulax®, and Nabota®, while a bovine gelatin protein is used in BTXA®. Human serum albumin is not used only in Innotox® (Medytox, Korea) which contains L-methionine and polysorbate. Additional excipients were also added: sodium chloride in BOTOX® and Neuronox®, lactose monohydrate in Dysport®, and sucrose in Xeomin®.

1.4.3 BOTOX®: “Golden Standard”

The first approved and commercialized BoNT-A was Dr. Alan Scott’s Oculinum®, which was later acquired by Allergan (Irvine CA, USA) and

renamed BOTOX® (Fig. 1.8). The Hall strain from the University of Wisconsin laboratory is used to manufacture BOTOX® (also known as onabotulinumtoxinA, or Vistabel®). It is formulated as a vacuum-dried powder with a molecular weight of 900 kDa. It is available in 50 U and 100 U vials which contain 0.9 mg of sodium chloride and 0.5 mg of human serum albumin as excipients. Since first approved in 1989 by the US FDA for the treatment of blepharospasm, BOTOX® has been adapted for the various applications and was validated as a safe product based on numerous clinical studies. Originally kept frozen, BOTOX® is now recommended for refrigerator storage since 2004.

Fig. 1.8 Vial of BOTOX®

1.4.4 Dysport®: "European Standard"

Dysport® (also known as abobotulinumtoxinA, or Azzalure®) is manufactured by the Ipsen using Hall strain NCTC 2916 (Fig. 1.9). Molecular weights vary from 500 to 900 kDa. It is available in 300 U and 500 U vials. The conversion ratio to BOTOX® is believed to be 1:2–1:2.5 (BOTOX®/Dysport®) with the latter ratio more commonly used. A 500 U vial of Dysport® corresponds to 200 U of BOTOX®. Since the vial is small,

it is conveniently reconstituted with 2.5 ml of normal saline. And after taking out the required amount with a syringe, it is further diluted by half before use.

Fig. 1.9 Vial of Dysport®

1.4.5 Neuronox®: "The First Korean Botulinum Toxin"

Neuronox® (other names: Medytoxin®, Botulift®, Cunox®, Siax®), manufactured by Medytox Inc. (Osong, Korea), was the first Korean BoNT-A product (Fig. 1.10). Neuronox® is produced using the Hall strain brought by a Korean researcher who studied *Clostridium botulinum* at the University of Wisconsin in the 1970s. It is the exact same strain as that used to make BOTOX®. Since it is produced from the same Hall strain through the same manufacturing process, the amino acid sequence and the molecular weight are the same as those of BOTOX® [23]. It is widely accepted that Neuronox® is equal to BOTOX® in terms of efficacy and safety through several clinical studies. The conversion ratio between BOTOX® and Neuronox® is also 1:1 [21, 24]. Neuronox® is available in four types of vials: 50 U, 100 U, and 200 U.

Fig. 1.10 Vial of Neuronox®

1.4.6 Myobloc®: "Unique Type B Botulinum Toxin"

Myobloc® (rimabotulinumtoxinB) is the only botulinum toxin type B (BoNT-B) product manufactured by Solstice Neurosciences Inc. (Fig. 1.11). Since the potency is lower than BoNT-A, it is available in vials of 2500, 5000, and 10,000 U. The conversion ratio between BoNT-A and BoNT-B is believed to be 1:50–1:100 at the neuromuscular junction [25, 26]. However, lower conversion ratios of 1:10–30 have been observed to be effective for sweat glands innervated by sympathetic nerves [27, 28]. When measured in LD50 assay used for BoNT-A, the potency differed up to 100 times between mice and human subjects due to sensitivity differences between the species. Unlike humans, mice have selective receptors for BoNT-B and are 100 times more sensitive to BoNT-B [29].

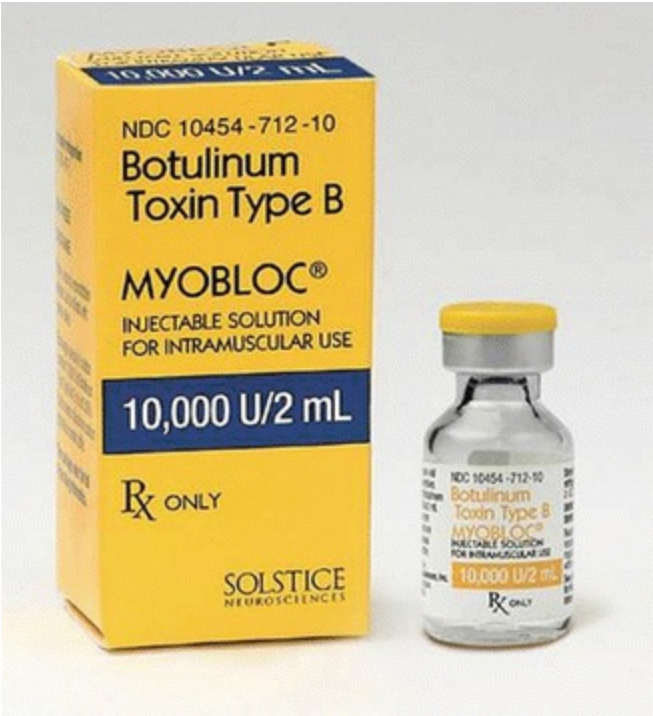

Fig. 1.11 Vial of Myobloc®

Myobloc® is a mildly acidic (pH 5.6) liquid formulation which may induce local pain when injected. Thus, it is recommended that the solution be neutralized with 0.01–0.05 ml of $NaHCO_3$ before injection. According to manufacturer data, efficacy was maintained for a month after neutralized. Myobloc® has a more rapid onset of effect compared to type A, but this is of little clinical significance. It has a lower potency and shorter duration than BoNT-A. The effect of wrinkle removal lasts just 2–3 months compared to 3–6 months with BoNT-A [30]. The duration of efficacy in sweat glands innervated by sympathetic nerves is, however, similar to, or slightly shorter than, BoNT-A. Since the amino acid sequence homology between types A and B is approximately 40 % [31], BoNT-B can be used for patients developing immunoresistance to type A. However, it should not be applied too liberally since the protein content is high (50 ng/5000 U), neither. Myobloc® is a liquid formulation and must be refrigerated, not be frozen.

1.4.7 Xeomin®: “Second-Generation Botulinum Toxin”

Xeomin® (other names: incobotulinumtoxinA, Xeomeen®, Bocouture®,

XEOMIN Cosmetic™) is manufactured by Merz Pharmaceuticals GmbH (Frankfurt, Germany) using Hall strain ATCC3502 (Fig. 1.12). Xeomin® contains only the purified neurotoxin of 150 kDa, eliminating complexing proteins from BoNT-A. The protein content of Xeomin® is only 0.44 ng/100 U, compared to 4.5 ng/100 U commonly found in other products [32]. Merz claims that Xeomin® is a purified neurotoxin and has a decreased risk of antibody formation based on the animal study on the induction capacity of neutralizing antibodies among different BoNT-A products. According to the result of the animal study, only incobotulinumtoxinA did not induce the production of neutralizing antibodies, while neutralizing antibodies were detected after abobotulinumtoxinA and onabotulinumtoxinA treatments [32]. However, the clinical basis of this claim has not been objectively verified in humans since the incidence of neutralizing antibody formation from BoNT-A treatment in aesthetic use is very low. As dosage of BoNT-A per session and incidence of neutralizing antibody formation are definitely correlated based on the meta-analysis study, however, the use of Xeomin® would be better considered when large dose of BoNT-A is required in one session such as hyperhidrosis treatment and body contouring. A vial of Xeomin® contains 100 U of BoNT-A, and the conversion ratio to BOTOX® is 1:1 [20]. Xeomin® can be stored at room temperature lower than 25 °C.

Fig. 1.12 Vial of Xeomin®

1.4.8 BTXA®: "China Toxin"

BTXA® (other names: Prosigne®, CBTX-A), manufactured by China's Lanzhou Biological Products Institute, is also produced from a Hall strain brought from the University of Wisconsin (Fig. 1.13). Since it uses gelatin, an animal origin protein as a stabilizer, it may cause an allergic reaction following repeated injections. Based on the animal experimental data about the allergenicity of gelatin, the Allergan has continually brought attention to this issue since BTXA® was first introduced in the market, but allergic reactions to BTXA® have been seldom reported. Even though the conversion ratio between BOTOX® and BTXA® is known to be also 1:1 [33], it is true that there are controversies about the 1:1 conversion ratio because some comparative studies on the efficacy between BOTOX® and BTXA® showed different results between two products [34, 35].

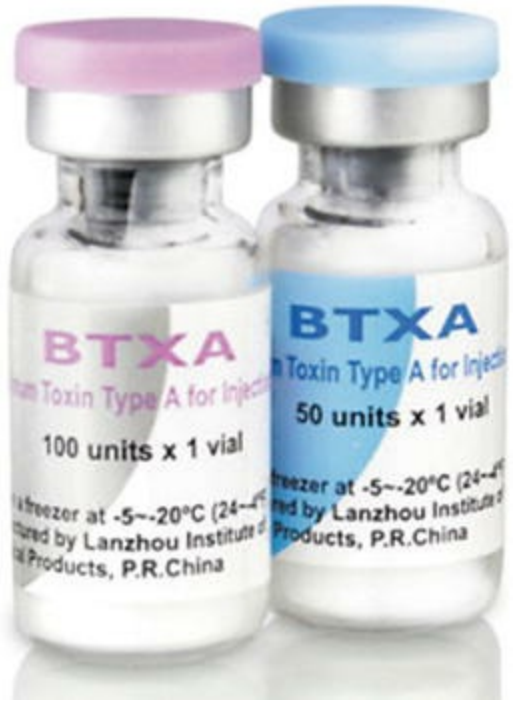

Fig. 1.13 Vial of BTXA®

1.4.9 Botulax®

Botulax® (other names: RegenOx®, Zentox®), manufactured by the Hugel Pharma, Korea, is the second Korean BoNT-A product (Fig. 1.14). It is produced using the bacterial strain CBFC26. Botulax® is in a freeze-drying formulation with molecular weight of 900 kDa. Excipients include 0.9 mg of sodium chloride as an additive and 0.5 mg of human serum albumin as a stabilizer. The conversion ratio to BOTOX® is known to be 1:1. Botulax® is available in vials of 50 U, 100 U, and 200 U. It remains stable for 24 months when stored at 2–8 °C.

Fig. 1.14 Vial of Botulax®

1.4.10 Nabota®

Nabota® (also known as Evosyal®), manufactured by Daewoong Pharmaceutical, is another Korean BoNT-A product using the GenBank KJ997761 strain (Fig. 1.15). It is a freeze-drying formulation with a molecular weight of 900 kDa. Excipients include 0.9 mg of sodium chloride as an additive and 0.5 mg of human serum albumin as a stabilizer. It was approved by the Korean FDA for the treatment of glabellar lines in late 2013. The conversion ratio to BOTOX® is known to be 1:1. Nabota® is available in vials of 100 U and remains stable for 24 months when stored at 2–8 °C.

Fig. 1.15 Vial of Nabota®

1.4.11 Innotox®: "Botulinum Toxin Endorsed by BOTOX®"

Innotox® (Medytox Inc., South Korea) is the world's first liquid injectable form of BoNT-A, approved by the Ministry of Food and Drug Safety in South Korea in 2013 (Fig. 1.16). Innotox® is provided as a ready-to-use sterile liquid with 4 U/0.1 mL concentration. Therefore, no risk of contamination or inaccurate dosing due to human errors during reconstitution exists, which ultimately enhances the treatment safety and efficacy. Furthermore, its storage and reuse are more convenient, and Innotox® has a long stability with an expiration of 36 months under 2–8 °C storage conditions.

Fig. 1.16 Vial of Innotox®

Innotox® is produced by the same Hall strain of *C. botulinum* as Neuronox® and BOTOX®. The molecular weight of Innotox® analyzed using size exclusion SE-HPLC is approximately 900 kDa, which is highly comparable to those of Neuronox® and BOTOX®.

Another key characteristic of Innotox® is that it excludes the use of substances of animal origin in the manufacturing process to eliminate the risks associated with animal-based proteins. Moreover, it excludes human serum albumin as an excipient of the final product to avoid any risk associated with diseases of human blood origin. Instead, it contains methionine and polysorbate as stabilizers.

With these advantages, Allergan, the BOTOX® manufacturer, made an exclusive license agreement to market Innotox® worldwide, excluding Korea and Japan. It is available in vials of 25 U and 50 U and remains stable for 24 months when stored at 2–8 °C.

1.5 Immunogenicity/Immunoresistance

BoNT is a foreign protein and is therefore antigenic. Therefore, repeated injections of BoNT can cause clinical nonresponse to it due to the production of neutralizing antibodies. Neutralizing antibody formation may lead to a lack of efficacy in treatments using BoNT. Since the incidence of antibody formation is extremely low, it used to be a concern only in the therapeutic field where 100 U or more of BoNT-A is used at one session, not in the cosmetic field where the dose used at one session is below this.

However, as worldwide usage for cosmetic purposes has increased since the mid-2000s, so too has reported incidence of resistance, even in patients injected with less than 100 U for cosmetic purposes. A case of antibody-induced failure following five sessions for square jaw contouring was reported in Korea; only 60 units of BoNT-A was injected during each session [36]. I personally have observed five patients from my clinic who developed immunoresistance to treatment following repeated injections of BoNT-A for cosmetic purposes. But if patients referred to me from other physicians are included, the total number of cases with clinical nonresponse to BoNT who I have ever seen would be more than 20. One of them also showed clinical nonresponse even to BoNT-B in addition to BoNT-A. Most cases exhibited nonresponse to the BoNT-A, with some showing diminished responsiveness to the BoNT-A. The immunoresistance cases, if any,usually occurred at least after 3–4 sessions of the BoNT-A for cosmetic purposes. Immunologic predisposition to botulinum neurotoxin of individuals seems to be thought to play an important role in formation of neutralizing antibodies.

Clinical diagnosis of immunoresistance is determined by immunoresistance test comparing the improvement of expression wrinkles observed 1 week after injection with 4 U of BoNT-A and 200 U of BoNT-B on each side of the forehead, respectively (Fig. 1.17). If immunoresistant to type A, wrinkles will remain on the side injected with BoNT-A but disappear on the type B side. For a serologic confirmation test, 5 ml of serum is separated and sent to a specialized laboratory where neutralizing antibodies in the serum are confirmed through tests such as the Western blot test or ELISA. As the DNA sequence homology between BoNT-A and BoNT-B is approximately 40 %, BoNT-B may be effective in patients exhibiting resistance to BoNT-A. It is not effective, however, in cases of cross immunoresistance to BoNT-B. Since people with type A antibodies are more likely to develop type B antibodies as well, BoNT-B should not be overused.

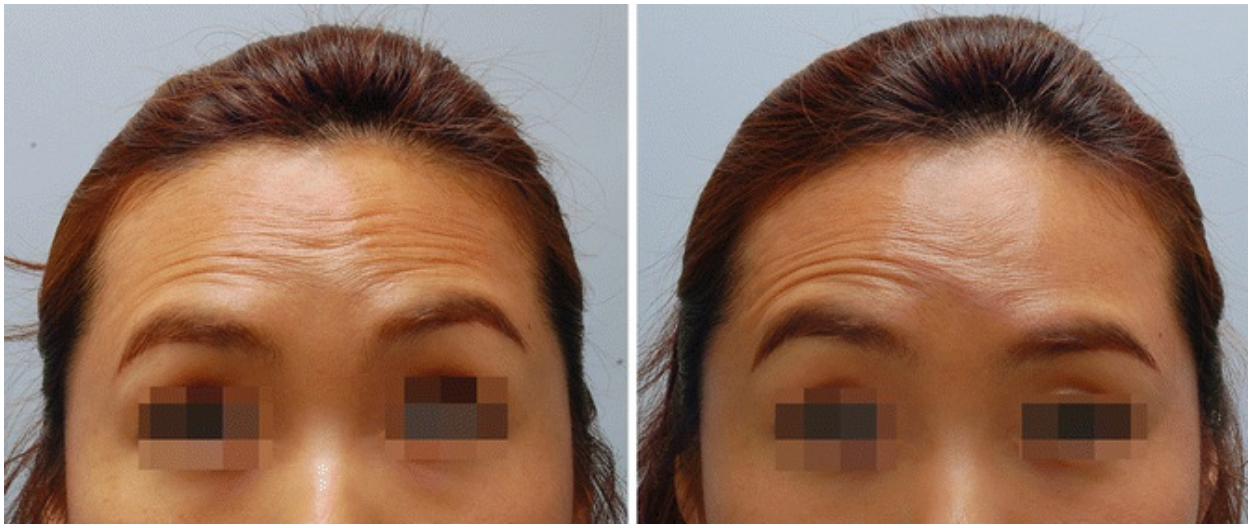

Fig. 1.17 Immunoresistance test. A patient who developed antibodies to toxin type A. Expression wrinkles remained on the right side where 4 U of botulinum toxin type A was injected, but disappeared on the left side after injecting with 200 U of botulinum toxin type B

According to a meta-analysis of risk factors for immunoresistance to neurotoxin, the high dose of toxin, increased frequencies of toxin injections, and high amount of protein load are linked to formation of neutralizing antibodies. The higher dose of toxin per session, the more cases are observed due to increased exposure to antigens. Therefore, precautions should be taken when high doses of BoNT-A are administered in one session such as hyperhidrosis treatment and body contouring. Pure neurotoxin products without complexing proteins would be better considered in such cases in terms of reducing protein load. Frequent antigen exposure with weekly or biweekly injections, which is performed in some clinics as a marketing, should also be avoided.

1.6 Safety

BoNT-A, like many drugs, may occasionally cause adverse effects such as headache, vertigo, allergic reaction, etc. However, the safety of BOTOX®, one of the representative BoNT-A products, is well established and the incidences of adverse effects have been extremely low since first approved in 1989. Not one fatality has been reported. It is regarded as one of the safest commercial drugs on the market. Dr. Carruthers, presenting at the Annual Meeting of the American Academy of Dermatology in 2004, reported an inconsequential number of adverse effects following 853 separate BOTOX®

injections in 50 patients, yet more evidence of the procedure's longterm safety.

1.6.1 Human Lethal Dose

BoNT is a representative neurotoxin that causes muscle paralysis and can be lethal: a single gram of the BoNT-A can kill more than one million people through respiratory muscle paralysis. BoNT as a biological weapon is a very real threat; thus the Pentagon in Washington, DC, strictly controls exports of the BoNT.

Commercialized BoNT products are purified to the nano level (one-billionth of a gram). They have a pharmacological effect for relaxing the injected muscles only locally without systemic adverse effects as long as the recommended dose is administered. Typical doses of BoNT-A for cosmetic purposes, therefore, pose no danger to humans. Extrapolating from animal experiments, the estimated lethal dose (LD50) in a 70 kg adult would be at least 3000 U. This corresponds to around 30 vials of 100 U BOTOX®. In short, injection of BoNT-A 100 U or less for cosmetic purposes such as wrinkle removal and square jaw contouring will not be harmful. Even in hyperhidrosis treatment or calf contouring that calls for higher dose of BoNT-A, symptoms of botulism will not appear unless more than 500 U is injected in one session.

1.6.2 Overdose

In the event of accidental overdose, signs and symptoms of systemic muscular weakness and paralysis of the oropharyngeal, esophageal, or respiratory muscles should be carefully monitored. If an overdose is immediately recognized, antitoxin should be used immediately. However, the antitoxin cannot enter the neurons and, therefore, will not reverse any BoNT-A-induced muscle paralysis already apparent. Mechanical ventilation and/or nasogastric tube feeding, in addition to other general supportive care, may be necessary until the patient makes a full recovery.

1.6.3 Botulinum Toxin and Children

How early can children and adolescents start the BoNT treatment for cosmetic purposes? In treating glabellar lines and hyperhidrosis with BoNT

in children and adolescents below the age of 18, the safety has not been confirmed. However, considering the fact that the BoNT treatment for children patients with cerebral palsy as young as 2 years of age has been already accepted worldwide, it is unlikely that cosmetic applications in adolescents will cause any extraordinary complications.

1.6.4 Botulinum Toxin and Pregnancy

BoNT-A is contraindicated during pregnancy or when breastfeeding because its safety is not well established. When BoNT-A was injected intramuscularly to pregnant mice or rats during organogenesis, reductions in fetal body weight and decreased fetal skeletal ossification were observed at high doses (4 U/kg). In rabbits, which are particularly sensitive to BoNT-A, severe reproductive toxicity, abortions, fatal anomalies, and even death were observed. In humans, so far, 24 pregnant women have been reported to receive injections of BoNT-A up to 250 U for treatment purpose or accidentally. All babies were born without complications aside from two miscarriages. Those two latter cases occurred in women with a history of prior spontaneous abortions, making it unclear if the BoNT-A was involved or not. Many experts believe that BoNT-A can be used during pregnancy in selective cases, such as severe pain from cervical dystonia [37]. Five cases of women with botulism during pregnancy have been reported to date. Fortunately, no evidence of BoNT-A diffusion to the fetus was noted in all cases [38]. Considering that FDA pregnancy category for BoNT-A is C, I do not think artificial abortion should be advised for a woman accidentally receiving BoNT-A injection during pregnancy.

If a woman is planning a pregnancy, until when BoNT is injected for cosmetic purposes? Most of BoNT injected irreversibly enters the neurons at the injection site within 72 h after injection. Thus, it will not affect the fetus after 72 h when it has been already cleared from circulation. That means it is safe to attempt pregnancy 3 days after BoNT-A injection. Moreover, it takes at least 1 week from the day of ovulation for the fertilized egg to become implanted in the endometrium. During this period, the fertilized egg does not receive blood from maternal circulation and will not be affected by drugs in that situation. In conclusion, BoNT-A treatment is safe within approximately 2 weeks from the first day of the last menstrual period.

1.6.5 Botulinum Toxin and Hypersensitivity

BoNT-A can cause an allergic reaction on the skin. Following repeated injections, delayed-type hypersensitivity reaction may occur due to a few components: neurotoxin itself, complexing proteins, and stabilizing agents such as albumin or gelatin. In particular, BTXA® containing gelatin as a stabilizer is more likely than other products to induce allergic reactions following repeat injections than other products, though this it is still quite rare. On the contrary, I have seen a case with itchy, erythematous rashes following two BOTOX® injections over a 6-month period. The rashes appeared at every injection site just hours after the injection (Fig. 1.18). As usual in acute eczema, the lesions were resolved without any sequelae after 1 week with dexamethasone injection combined with oral antihistamine and prednisolone treatment for 5 days. Although the effects of BoNT-A were visible after 1 week in spite of the rashes, no further injections were performed out of fear of further relapse. It was the only case of an allergic reaction I have experienced out of more than 20,000 sessions of BoNT-A injections.

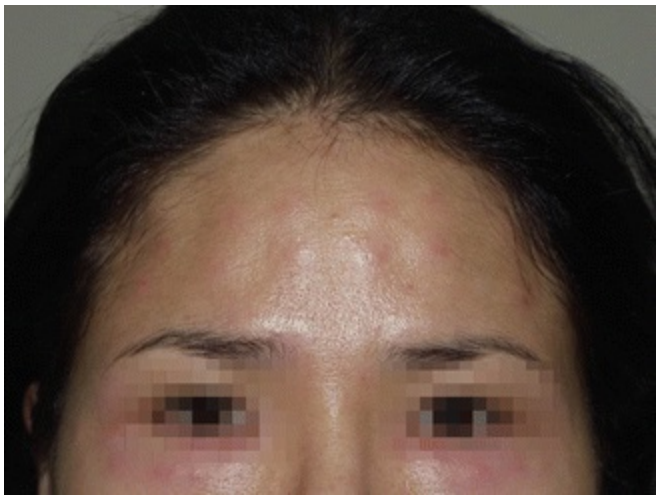

Fig. 1.18 Delayed-type hypersensitivity to botulinum toxin. Erythematous macules appeared at every injection site in a 32-year-old female patient after receiving Botox® injection for the treatment of horizontal forehead lines

Episode: Botox Blamed for the Death of 18 People?

In December 2008, CNN carried a report that at least 18 deaths, including the death of three teenagers, were associated with the use of botulinum toxin, citing findings by a consumer group.

Amid spread of public concern, the US FDA moved swiftly to issue its response within a 2-week period, cited in part as follows: “In each of the 18 cases, we note that the patient had a pre-existing neuromuscular condition, such as cervical dystonia or cerebral palsy. As such, while the injection of BoNT-A may not be the immediate cause of death, we find it reasonable to presume that the high doses of botulinum toxin injected in the muscles of the neck may be associated with the weakened respiratory muscle activity in these patients. While none of the deaths were associated with the injection of botulinum toxin for wrinkle treatment, precaution is nonetheless advised.”

This makes sense considering that when treating cervical dystonia approximately 10–30 times more BoNT-A is injected compared to wrinkle treatment, increasing the odds of the toxin to migrate from the site of injection to other parts of the body, resulting in the suppression of the respiratory muscles. Such overdose of botulinum toxin injection when coupled with the generally immunosuppressive states of the patients at the time of injection may likely have increased the odds of fatal complications, eventually leading to the death of these patients.

To the extent that it was the high dosage of the BoNT-A, rather than the BoNT-A injection itself, that was to blame, there is little cause for concern as regards BoNT-A injections for cosmetic purposes.

1.7 Reconstitution, Dilution, and Storage of Botulinum Toxin

1.7.1 Reconstitution and Dilution

Vacuum-dried powder of BOTOX® is reconstituted with normal saline, which does not contain preservatives (0.9 % benzyl alcohol). When the normal saline is injected into a vial, the white cake of BoNT-A at the bottom is instantly dissolves becoming a colorless, transparent solution. At this stage, it should be noted that the vacuum can pull the normal saline rapidly into the vial to make a foam. The foam made during reconstitution is believed to denature proteins of BoNT-A and inactivate BoNT-A. Thus, prior to injecting normal saline, the vacuum is released first by inserting a needle connected to the syringe filled with 6–8 ml of air. While there are a few articles claiming that the foam does not affect potency, it is better to release the vacuum since the foam can nevertheless cause inconveniences when injecting. Vials of

Dysport®, Xeomin®, and Neuronox® are all in a vacuum state (though less than that of BOTOX®) and should be reconstituted in the same way. Do not use the vial if the vacuum is disrupted since it may have been contaminated during distribution (Fig. 1.19).

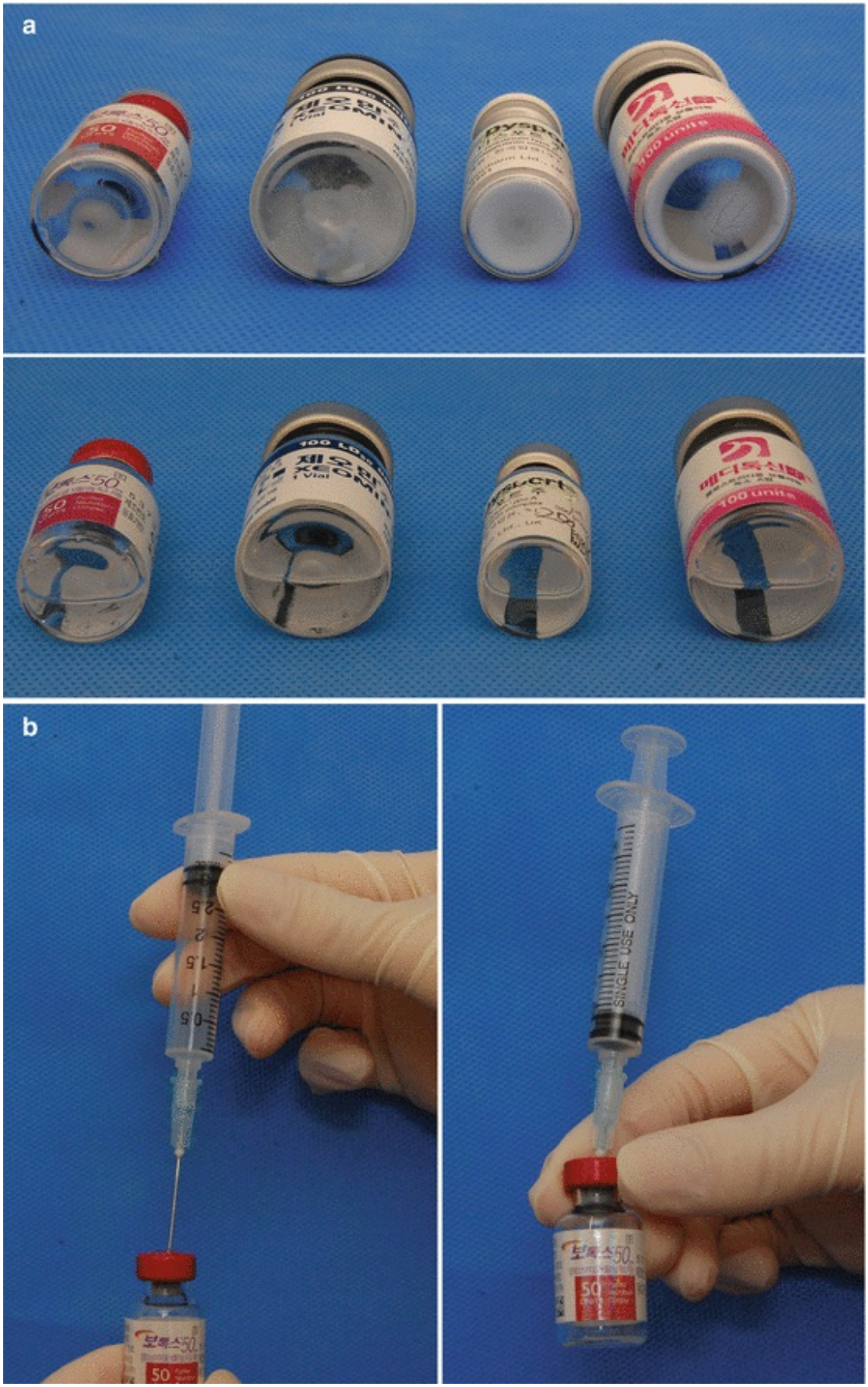
a
b
SINGLE USE ONLY

Fig. 1.19 Reconstitution of botulinum toxin. (**a**) Photographs before and after reconstitution of each product. White powder cake of botulinum toxin around the base of the vial is immediately dissolved after adding normal saline to the vial (from left: BOTOX®, Xeomin®, Dysport®, Neuronox®). (**b**) Vacuum-releasing method. Using air-filled vacant syringe removes negative pressure in a BOTOX ® vial. (**c**) Reconstitution. Inject normal saline into a Xeomin ® vial while directing the needle toward the side wall of the vial

The preferred volume of dilution varies from 1 to 10 ml, depending on the practitioner; the author dilutes with 2.5 ml of normal saline to use at a concentration of 4 U/0.1 ml. Large dilution volumes are associated with easier diffusion to the surrounding tissue. Therefore, higher dilutions may be beneficial for large muscles such as the calf, but when used in the face, they may paralyze unwanted sites causing abnormal facial expressions or ptosis. Dr. Carruthers still recommends 1 ml, which can minimize side effects from unwanted diffusion, but the loss from the remaining volume in the bottle and stopper is not negligible. 2.5 ml not only represents the most ideal volume for facial procedures, but also allows the ease of calculating the final potency following dilution to meet the 4U /0.1 ml. 5 ml of normal saline is used for body contouring or for hyperhidrosis treatment, while 10 ml is used for “intradermal botulinum injection” (see Chap. 4).

Distilled water can be used as a diluent, but this is generally painful and thus should be avoided. There was a suggestion that preserved saline containing benzyl alcohol should be avoided because it decreases BoNT-A potency [39]. However, benzyl alcohol content in the preserved saline is mere 0.9 %, and it may not affect the potency much [40]. Recently, in the West the preserved saline is used more because it produces less pain [41]. But there is no reference presenting the objective data that it does not affect the potency of BoNT-A. In the author's prospective clinical study on the potency of BoNT-A using Sloop's "human model" in volunteers, compound muscle action potential (CMAP) of extensor digitorum brevis was compared between the preserved saline group and the normal saline control group following BoNT-A injection. Although no difference was observed between the two groups 1 week after the procedure, there was a statistically significant decrease in efficacy observed at 4, 8, and 12 weeks in the preserved saline group than the controlled saline group ($p < 0.05$) (Fig. 1.20) [42]. This suggests preserved saline reduces BoNT-A potency and thus should not be used if at all possible even though mild pain is induced by normal saline.

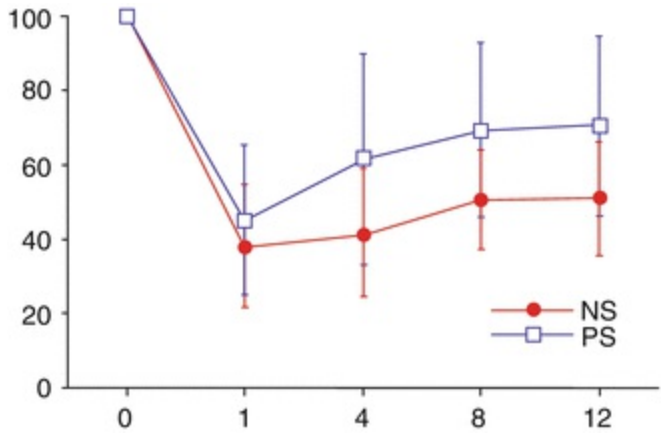

Fig. 1.20 Comparison of compound muscle action potential (CMAP) after botulinum toxin injections between the reconstituted groups: with preserved saline (PS) and normal saline (NS) [42]. Mean CMAP expressed as the relative percentage to the baseline action potential. The CMAP decreased more in the NS injection group than PS injection group at 4, 8, and 12 weeks after injection (*$P < 0.05$)

1.7.2 Storage

Following normal saline dilution, BoNT-A should be stored in the refrigerator. According to the guidelines of the manufacture and the Centers for Disease Control and Prevention (CDC), the BoNT-A should not be used

more than 4 h after reconstitution with normal saline due to a decrease of potency. As the BoNT-A is high cost, however, practically most of doctors reuse stored BoNT-A after refrigerator storage. Thus, there have been arguments in many reports for the past 20 years that storage in the refrigerator over 4 h after reconstitution with normal saline can affect the potency of the BoNT-A. Based on my own experiences and data from innumerous papers on this point, it is the author's conclusion that although potency may decrease to some extent by the refrigerator storage after reconstitution, it is not significant enough to noticeably reduce efficacy for the treatment of patients with BoNT-A.

How long can BoNT-A be stored in a refrigerator? In a 2003 multicenter prospective study of Brazilian researchers in 85 patients with glabellar wrinkles, potency was reported to be not significantly different after 6 weeks' storage in the refrigerator [43]. I also had an experience in using BoNT-A stored in the refrigerator for up to 4–8 weeks at unavoidable situations and found no significant difference in efficacy. However, due to worry about contamination, I seldom used over 2-week-stored BoNT-A. Fortunately, these days many patients seeking for BoNT-A procedures in my clinic made me free of worrying that point because there are no BoNT-A stored for more than 2 days. However, I think even 2-week-stored BoNT-A can be safely used if avoided contamination. Fortunately, a majority of physicians (68.6 %) routinely use the stored BoNT-A for longer than 1 week in a 2012 Internet survey conducted by the American Society for Dermatologic Surgery, and not a single case of infection has been observed [44].

But storage by freezing is not recommended for storage method because freezing may decrease its potency by as much as 70 % when dissolved since BoNT-A is a protein [45]. Of course there are some papers insisting that freezing doesn't affect the potency of BoNT-A. In one double-blind study, 40 patients with forehead wrinkles were treated with differently stored BoNT-A. There were no statistically significant differences between the fresh, 2-week-refrigerated BoNT-A and 2-week-frozen BoNT-A over the 4-month follow-up period [46]. But in addition to necessity for thawing of the frozen BoNT-A, freezing should be avoided considering the fact that repeated freezing and thawing caused by the refrozen procedure for the remnants would definitely result in denaturation of the BoNT-A protein.

Episode: Clinical Study for the Effect of Storage in Refrigerator on the

Potency of BoNT-A

The use of refrigerated BoNT-A was a hot topic of debate in 1999 and 2000. From a practical standpoint, it seemed a waste to discard remaining BoNT-A after 4 h of reconstitution due to its high cost. Therefore, many doctors, despite their guilty feelings, used leftover BoNT-A that had been stored in a refrigerator or freezer. At the time Sloop wrote the most credible article on this issue using a human model [47]. Electromyography was used to compare the percent decline in the extensor digitorum brevis between a group of four volunteers injected with freshly reconstituted BoNT-A and another group injected with BoNT-A that had been refrozen and refrigerated for 2 weeks after reconstitution. No statistical difference was found between the groups though the sample size was quite small with only eight total subjects.

At the time, our research group used the same method to determine if the storage in a refrigerator after reconstitution with normal saline decreases the potency of BoNT-A. We injected one side of the extensor digitorum brevis muscle with 2.5 units of BoNT-A that had been immediately reconstituted with saline, and the contralateral side with identical material that had been stored in a refrigerator for preselected periods (1, 2, and 4 weeks) in 33 healthy volunteers. Mean compound muscle action potential (CMAP) amplitudes expressed as a percentage of the baseline amplitude were more reduced in sides injected with immediately reconstituted BTA than in sides injected with BTA stored for 1 week or more ($P < 0.05$) (Fig. 1.21). Storage of reconstituted BTA for more than 1 week may affect the potency of the BoNT-A to some extent [48].

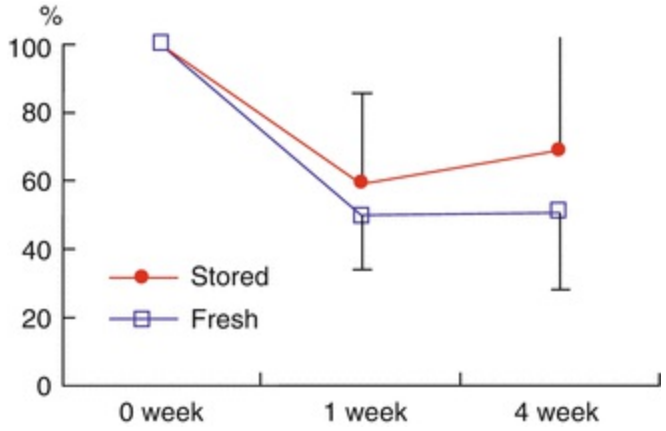

Fig. 1.21 Comparison of compound muscle action potential (CMAP) between immediately reconstituted botulinum toxin A (BoNT-A) and stored BoNT-A in a refrigerator after reconstitution [47]. Mean CMAP expressed as the relative percentage to the baseline action potential. The mean

CMAP reduced more in the side injected with immediately reconstituted BTA than in the side injected with BTA stored for 1 week or more, which was statistically different ($P < 0.05$)

1.8 Contraindications

1.8.1 Absolute Contraindications

- BoNT is absolutely contraindicated in patients who have systemic neuromuscular junction diseases (amyotrophic lateral sclerosis, myasthenia gravis, and Lambert–Eaton syndrome) as administration of BoNT with just minor amounts can produce dysphagia or systemic muscle paralysis.
- Commercial BoNT-A is stabilized in part by the addition of human serum albumin; therefore, it is absolutely contraindicated in patients who are allergic to human serum albumin.
- BoNT-A should not be injected into pregnant and breastfeeding women as its safety under these conditions has not yet been established.

1.8.2 Individuals Injected with Caution

- Patients who have taken aspirin or other anti-inflammatory agents within the 2 weeks prior to receiving an injection may easily become bruised.
- Patients taking spectinomycin or aminoglycoside derivative antibiotics should avoid receiving concomittant BoNT-A injections as these drugs may enhance the potency of the BoNT-A at neuromuscular junctions.
- BoNT-A should not be injected into patients taking muscle relaxants such as tubocurarine and dantrolene as it may cause enhanced muscle relaxation or dysphagia.

1.9 Characteristics of the Procedure (EAT Classification)

Based on my personal experiences, I have rated the characteristics of various procedures using BoNT-A in three different viewpoints: efficacy, adverse effects, and technique (EAT). Although this is an entirely subjective

classification system, I believe this can be helpful for beginner physicians as a guideline for the BoNT procedures like Michelin guide.

Efficacy (*E*)

A: Excellent efficacy

B: Good efficacy

C: Mild or minimal efficacy

Adverse Effects (*A*)

A: Negligible adverse effects

B: Mild adverse effects

C: Severe adverse effects which can result in social downtime

Technique (*T*)

A: Can be easily performed by beginners after a single observation.

B: Can be performed well after some experience.

C: Requires individualized treatment to avoid adverse effects. Experience and expert supervision are necessary to master.

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2. Wrinkle Treatment with Botulinum Toxin

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2.1 Introduction

Ever since the use of botulinum toxin type A (BoNT-A) for the treatment of glabellar rhytides was first reported by Dr. Carruthers in 1992, BoNT-A has become the byword for anti-wrinkle treatment owing to the convenience of the procedure as well as the remarkable outcome it produces.

The recent trend in BoNT-A treatment is the use of BoNT-A for preventative purposes among younger patients in their late 20s and early 30s to head off the formation of wrinkles which start to occur during this age range due to loss of skin elasticity.

Those in their 40s and 50s presenting static wrinkles that have already settled in the glabellar can just as well benefit from BoNT-A procedures, since the treatment if repeated over a period of several years can help diminish even these static wrinkles as well as correct dynamic wrinkles. Clearly, this is what makes BoNT-A procedures the most compelling solution among all available antiaging solutions.

For BoNT-A procedures to produce the best results, however, certain caution must be needed on the part of the practitioner.

As it is well known, there is no effective antidote for BoNT-A; although an antitoxin does exist, it is capable only of neutralizing the BoNT-A circulating in the bloodstream and is not effective once BoNT-A enters the neurons and begins acting on the affected neuromuscular junctions. This

implies that any unwanted adverse effect from the procedure cannot be reversed for at least 2~3 months until the effects finally wear off.

In addition, individual difference in facial muscle development is as diverse and varied as the many different varieties of the human face, which calls for an individually tailored approach in treating each patient.

Furthermore, considering that animation of the human face is based on a complex network of interconnected expression muscles, inadvertent disruption to the muscular balance by BoNT-A injection may lead to undesirable results such as the “samurai eyebrows” (the “Mephisto” or “Spock” effect) or trigger new wrinkle formation in the non-injected areas due to the rebalancing mechanism. Facial expression muscles allow us to express our feelings and emotions such as anger, sadness, and happiness. Too much BoNT-A injected in the wrong place, however, can deprive the face from expressing the full range of emotions, leading to a froze masklike face, fixing the forehead or making it impossible to smile with the eyes.

Back during 1999–2000 when BoNT-A treatment had just been introduced in Korea, I used to make a point, in my BoNT-A training sessions for doctors, of highlighting the 3S, standing for ‘Safety, Simplicity and Satisfaction’ to communicate the advantages of performing BoNT-A treatments. The doctors attending these sessions had previously been introduced to botulinum toxin at medical school as the most acutely lethal neurotoxin known and were not comfortable about the prospect of injecting the toxin into a patient’s face. Obviously, I had felt the need to give them some level of comfort.

But of course, BoNT-A treatment is neither as safe nor simple as I had made it out to be. As a beginner you would probably exercise utmost care with your first ten patients out of fear for a potential ptosis. Once you’ve been lucky enough to clear your first ten cases without encountering a serious problem, you are led to believe you’ve nailed the technique and tend to downplay the risks. By the time you’ve handled some 100 cases and having stumbled across various odd adverse effects and patient complaints, you get to know what you are dealing with. It is only when you have around 1000 cases under your belt that you are finally prepared to develop your own know-how and expertise. Such is the nature of BoNT-A procedures; with more experience comes tougher challenges.

The goal of this chapter therefore is to lay out the essentials of performing BoNT-A procedure for Asian patients in light of my own trials and errors,

which practitioners must understand in order to perform highly effective yet natural-looking wrinkle treatments with minimum adverse effects.

Tip: Who is the best candidate for Botulinum toxin Treatments?
As a new practitioner starting out on BoNT-A for the treatment of wrinkles, who would you consider as your ideal candidate? Apparently, the safest bet would be your own parents, since they are the people most unlikely to sue you for a procedure that has gone wrong. However, when dealing with patients outside your immediate inner circle, there are several factors to consider. It is typically the case in other treatments that the more severe the patient's condition, the greater the advantageous, since the outcome of the treatment is all the more dramatic. However, in BoNT-A injections for the treatment of wrinkles, where the target of treatment is the dynamic wrinkles, the case is different. It is a different case altogether. Although signs of aging are more apparent in patients in their late 40s or above, by this stage, the dynamic wrinkles on their face have progressed to static deep wrinkles, which cannot be effectively corrected with BoNT-A injections alone. As regards patients in their 50s and above, the accompanying presence of sagging eyebrows and drooping eyelids makes them more susceptible to adverse effects. In fact, for new practitioners, the best candidates are patients in their 20s and 30s, since this is the age at which dynamic wrinkles—the target of BoNT-A for the treatment of wrinkle treatment—are just beginning to appear.

2.1.1 Effective and Noneffective Wrinkles in Botulinum Toxin Treatment (Fig. 2.1)

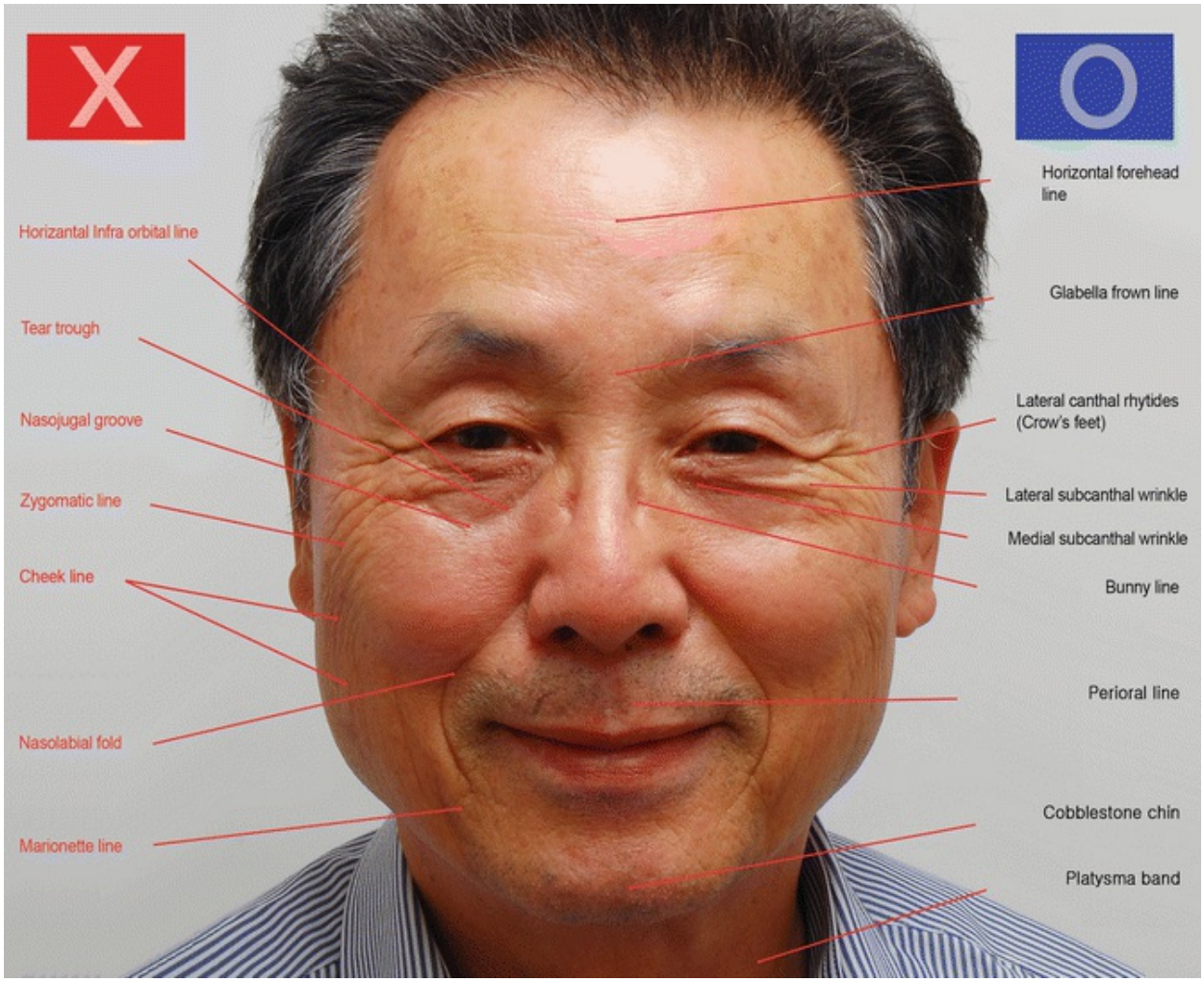


Fig. 2.1 Effective (*O*) and noneffective (*X*) wrinkles with botulinum toxin treatment

Wrinkles can be classified into dynamic and static wrinkles, and static wrinkles may be further subclassified as deep, moderate, and fine wrinkles (fine wrinkles may also be referred to as lines). Common examples of dynamic wrinkles are glabellar frowning lines and crow's feet around the eyes. Nasolabial folds and glabellar furrow are the prototype of deep wrinkles. Fine wrinkles (lines) around the lips, forehead, and infraorbital areas are the initial stage of static wrinkles. Examining the process of wrinkle formation reveals that dynamic wrinkles become fine wrinkles gradually progressing to deep wrinkles with a reduction of underlying soft tissue. As "BOTOX" has become synonymous with anti-wrinkle therapy, patients will often visit a clinic and ask for "BOTOX" without much knowledge. Many believe that "BOTOX" can solve all kinds of wrinkles, but this idea is

incorrect.

BoNT-A is primarily used for the effacement of dynamic wrinkles in the forehead, glabella, around the eyes, dorsum of the nose, around the lips, and vertical platysma bands of the neck. The procedure is not effective in treating static deep wrinkles at rest. Moreover, even some dynamic wrinkles cannot be treated effectively with BoNT-A. For example, the infraorbital horizontal lines while smiling are produced by the mouth corner elevator muscles and therefore are not treated by BoNT-A injections into the infraorbital area. I also experienced a major headache when I found that BoNT-A injection into the infraorbital area was not effective for effacing infraorbital horizontal lines after a total of three to four sessions at 1-week intervals. BoNT-A injections are not generally advised for the treatment of dynamic wrinkles of the nasolabial folds, marionette lines, and lines on the zygomatic and cheek areas which can be seen in the smile of George Clooney. This is due to the fact that injections around these areas cause paralysis of the zygomaticus major which cause weird smiles. Although we can inject BoNT-A for the treatment of the nasolabial folds with much caution in selective cases, this is likely to result in an awkward smile like that of Jack Nicholson's Joker character in the 1989 Batman film due to paralysis of the lip elevator muscles. Instead, the multiple intradermal injection of hyaluronic acid (hydrolifting) by elevating the skin elasticity is recommended for the treatment of dynamic wrinkles in these areas where BoNT-A cannot be used.

Filler injections are absolutely necessary for the correction of deep wrinkles such as glabellar deep furrow, nasolabial folds, and marionette lines (Fig. 2.2). Deep forehead wrinkles also cannot be addressed only with BoNT-A. Fillers are necessary to fill the deep furrows of the forehead in addition to BoNT-A treatment. Furthermore, the BoNT-A is not effective for neck horizontal lines and wrist lines which are innate lines for flexion area since birth. Clearly, BoNT-A is not a panacea for every type of wrinkle, and it is therefore necessary to choose the most appropriate treatment methods according to the different types and states of wrinkles.

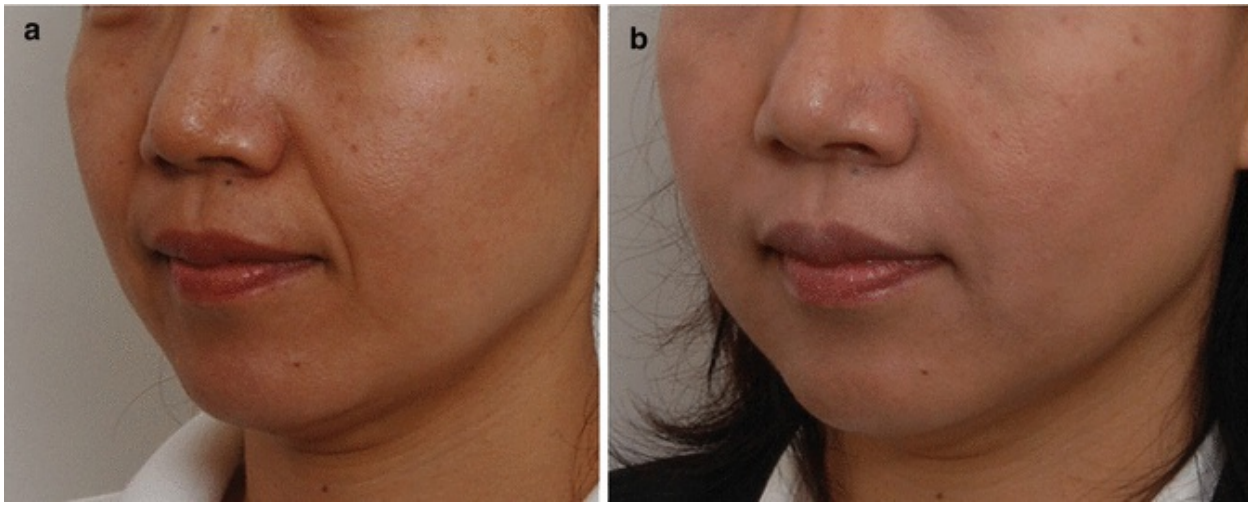


Fig. 2.2 Nasolabial folds treated with hyaluronic acid filler. (**a**) Before. (**b**) After

Tip: Does BoNT-A Injection Work for Fine Static Wrinkles Too (Fig. 2.3)?

As the skin begins to lose elasticity during one's late 20s, fine wrinkles at rest (repose state) also begin to appear in the areas most affected by facial animation, such as around the eyes, infraorbital skin, glabella, and forehead. While it is easy to assume BoNT-A does not work for fine wrinkles which constitute static wrinkles, in fact the effects can be quite remarkable. Typical cases involve the fine lines located in the forehead, glabellar, and around the eyes. Along with the improvement of fine wrinkles, BoNT-A can also induce reduction of pore size, which altogether leads to shining and tightening of the skin. In 2007, Dessy et al. assessed the changes in glabellar static wrinkles following the treatment of the glabellar wrinkles with BoNT-A using a replica [1]. The results showed significant improvement of the static wrinkles within 1 month, with relapse to the baseline occurring 6 months after the treatment.

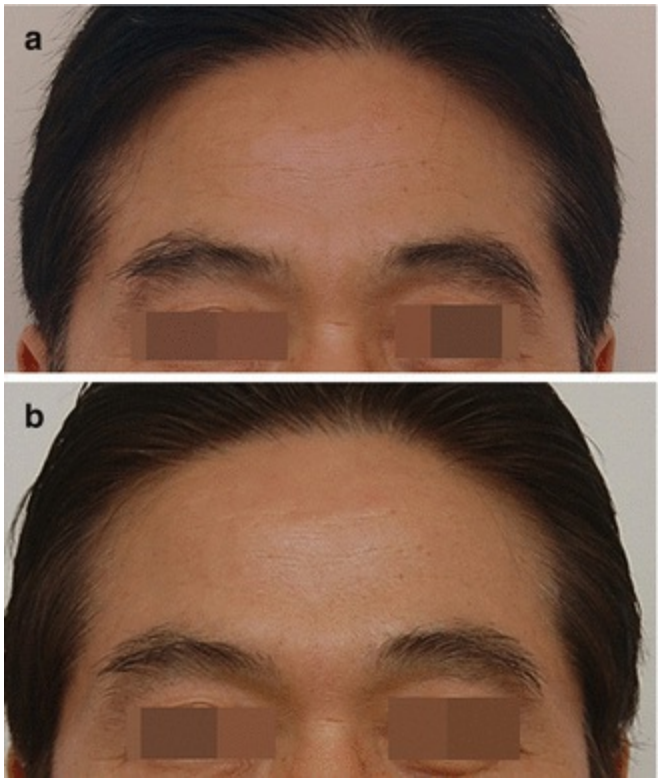


Fig. 2.3 Improved forehead fine wrinkles with botulinum toxin treatment. Glistening and tightening of skin are noticeable due to the improvement of fine wrinkles on the glabella and forehead. (**a**) Before. (**b**) After

The exact mechanism by which BoNT-A improves the static fine wrinkles is subject to different interpretations. One theory, as proposed by Dessy et al, hypothesizes that such improvement of fine lines due to the reduced contractile force of the facial expression muscles directly attached to the skin, where the said muscles have been paralyzed with botulinum toxin. I would suggest another contributing factor, that is, the edema caused by poor lymphatic circulation secondary to muscle paralysis. Similar to the frequent observations of lower leg edema after a long flight, I believe the mild skin edema following muscle paralysis may also contribute to diminishing fine wrinkles while also reducing the pore size.

It bears pointing out however that while BoNT-A treatment can be effective for Fine Static wrinkles, the kind which disappears easily when tangential forces are applied to the skin surface, such as by tightening the skin by the hand, *deep* static wrinkles, which have settled over a long period of time in much the same way as permanent scars, cannot be fixed by BoNT-A procedure. Deep static wrinkles on the skin are analogous to scratch marks

on a car and thus should be removed through such methods as chemical peeling, dermabrasion, laserbrasion, and fractional laser instruments.

2.1.2 Communication

Proper communication between doctors and patients is essential to fully satisfy a patient's needs, and this is true for nearly all cosmetic procedures. It is important for doctors to accurately convey expected results to the patient after grasping what they really want. Patients' satisfaction with the treatment is greatly increased when they are fully and accurately informed of the possible results. Therefore, before each procedure, I usually discuss these expectations with my patients directly, even though they have already gone through consultations with a coworker or consulting nurse. This is because I want to confirm and explain again what exactly I can do help to resolve the distressing problems set in their minds.

One of the best methods for uncovering the exact needs and desires of patients is to use either a mirror or photograph and ask them to directly point out the target wrinkles and other problems they would like to have addressed (Fig. 2.4). Some patients believe that BoNT-A can solve all types of wrinkle problems. For example, although "crow's feet" respond well to BoNT-A, while infraorbital horizontal lines do not, patients do not recognize the therapeutic differences and think of them as the same wrinkles around the eyes. Sometimes, patients' needs are so vague that using mirrors or photographs during pre-consultations is an absolute necessity to avoid potential conflicts following treatment.

Fig. 2.4 Diagnosis with mirror

Another important aspect of communication is education. You may think that most patients who come to your clinic will be well informed about the procedures and expected results, thanks to the well-developed Internet. However, you should be aware that patients are frequently exposed to websites and advertisements which encourage unrealistically positive expectations. Therefore, it is important from the start to provide relevant information to patients with the assumption that they know nothing about BoNT-A or fillers. It is necessary to simply and accurately inform patients about which wrinkles can be treated effectively, the duration of the treatment, repeat injection schedule, preventative effects, reasons for early treatment, adverse effects, etc. Having received all of this information, patients can form more accurate expectations of the actual outcome leading to greater overall satisfaction.

It is preferable to have patients view their own faces in a mirror while you explain the expected outcome. After seeing the general status of their static

wrinkles, patients should be asked to make facial expressions so they can see their own dynamic wrinkles in the periorbital and glabellar areas. It is worthwhile to stress that the major wrinkles which can benefit from BoNT-A treatment are dynamic wrinkles on the glabella, lateral side of the eyes, and forehead and not deep wrinkles on the glabella. Patients should also be informed that even among dynamic wrinkles, wrinkles in the infraorbital and zygomatic areas, the cheek, and the nasolabial folds do not benefit from BoNT-A treatment due to the risk of awkward facial expressions. It can be beneficial to let patients know alternative treatment methods for these cases such as hydrolifting (intradermal injection of hyaluronic acid, Fig. 2.5) for dynamic wrinkles where BoNT-A is not an indication, fillers for nasolabial folds, and chemical peeling or fractional lasers for static wrinkles in the infraorbital area. Showing patients before and after treatment photographs can help give them a good idea of the expected results.

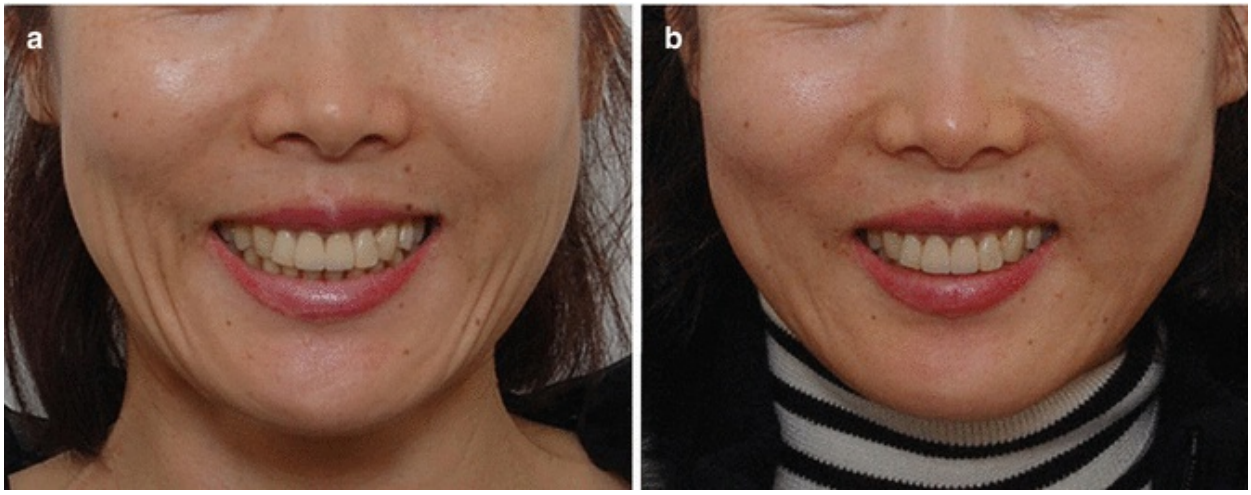


Fig. 2.5 Cheek lines treated with hyaluronic acid filler. (**a**) Before. (**b**) After

It is important to screen patients for psychological problems or unrealistic expectations during consultations. It may not be easy to differentiate between patients who have true psychological problems and those who simply have some picky characteristics. However, we can intuitively gain some sense of these problems through a few minutes of conversation.

One of the most frequent mistakes doctors make is to use too many professional medical terms during communications with patients. It is generally better to use common terms while communicating with patients, for example, “BOTOX” rather than “botulinum toxin” and “jaw muscle” instead

of “masseter muscle.”

Episode: Importance of Communication (“It’s My Mouth That Shoots Those Lasers!”)

Shortly after I began my practice, I was visited by a patient who wished to receive BoNT-A treatment prior to her daughter’s wedding ceremony. She asked me to remove the lines around her eyes, and this was confirmed in the record of her pre-consultation with my nurse. However, 1 week after the treatment, she visited my office again and complained that the procedure was not effective. Subsequently, I highlighted the disappearance of her crow’s feet while she squinted or smiled at her face in a mirror. In response, she pointed to her infraorbital horizontal lines stating that those were what she came to have treated. Alas, “infraorbital” lines are also commonly referred to as “lines around the eyes” by laypeople.

Laypeople commonly refer to infraorbital lines, which do not respond to BoNT-A treatment, as “lines around the eyes!” This event always reminds me of the importance of good communication whenever we perform a procedure. Following that painful experience, I have learned to always pass a mirror to patients so they can point out exactly which lines they would like to have removed. This practice allows me to more accurately grasp patients’ needs and explain how much I can help them before the procedure. I believe this is the result of proper communication which greatly enhances patients’ satisfaction with the procedure.

Feeling proud of myself one day, I commented privately to a senior doctor who is an expert with lasers, “I think my communication technique has improved tremendously over the past several years much more than injection techniques.” He jokingly replied, “ Dr. Seo, You mean you didn’t know that already after many years of practice? Well, get this! It’s my mouth that shoots those lasers!”

2.1.3 Pretreatment Assessment

During the patient consultation, items to be evaluated can be separated into the following categories: subjective, objective, sociocultural, financial, and previous history of cosmetic procedures. True “custom-tailored” treatment is only possible when the treatment plan fully takes into account the results of a comprehensive evaluation covering various aspects along with an understanding of individual characteristics.

Since beauty is a subjective concept, it is important to know which points a patient is primarily concerned about. In other words, do you grasp what a patient is truly aiming for? Some patients might point out specific wrinkles that they would like to have removed, but others may simply say that they want to look younger or tender. A thorough analysis is required especially in the latter cases. Patients are usually not satisfied unless they receive the improvements they want even if their needs are met in other areas. Once you feel that you have truly grasped a patient's needs, you should evaluate their expected results in the next step. If the expectation level is too high, it will be extremely difficult to satisfy a patient despite what you feel may be a successful outcome.

The objective evaluation is a summary of the patient's physiological characteristics such as age, gender, facial shapes, and facial aging features: wrinkle characteristics, follicular pores, depression, sagging, skin thickness, elasticity, etc. BoNT-A dose and injection sites vary by age and gender. Accurately grasping your patients' problems is the first step toward the effective treatment of any disease, and cosmetic treatment is no exception.

Once you have gathered information about patients' characteristics and general aging state, it is important to assess the appropriate indications and potential adverse effects of treating them with BoNT-A. For example, fillers are required as a supplement to BoNT-A for deep wrinkles in the glabellar area and fractional lasers for infraorbital lines. Patients with ptosis may experience difficulties to open their eyes after injection of BoNT-A into the forehead unless the dose of BoNT-A is lowered and patients with infraorbital fat bulging are likely to experience some aggravation of fat bulging. Developing an acute sense of "doctor's insight" to grasp patients' problems before treatment is essential for providing successful care.

It is helpful to develop meticulous observation skills for examining patients from the forehead to the neck when they are at rest and while giving forced facial expressions. As prolonged staring at patient's face may be a bit uncomfortable, "diagnosis with mirror," allowing patients to observe themselves through a mirror, is a good alternative for doctors to find their problems. "Mirror diagnosis" is not only helpful for catching problems in detail but also allows patients to find new problems that may have been unnoticed previously, which motivates patients to receive treatments for new problems. It is also important to observe patients' facial expressions during consultations, including their involuntary habits. It can be helpful to naturally

observe all of a patient's habitual movements such as lifting of the eyebrows, twitching of the nose, glabellar frowning, applying force to the anterior jaw, and peculiar expressions accompanied by tics and to also watch for periorbital lines and nasolabial folds that appear while smiling or speaking and the shape of lines around the lips.

Among sociocultural aspects, it is helpful to know the profession, marital status, nationality, and ethnicity of your patients. You should also determine to what extent bruising or edema may interfere with their daily lives in case they occur. If patients are celebrities or models who must frequently rely on the glabellar area for facial expressions, it may be preferable to either skip or only use low doses of BoNT-A for the glabellar area. For male CEOs in their 60s, the procedure should be minimal without social downtime. As people of different races and ethnicities have their own preferred facial shapes and treatment goals, treatments should be adjusted as necessary according to these factors. For example, BoNT-A treatment for masseter hypertrophy is not popular in western countries since most Caucasians do not care much about square jaw with mandibular angles and masseter hypertrophy. Volumization using filler for sunken lower cheek which is popular in Asians is not performed since Caucasians prefer sunken cheeks.

It is important to check your patients' previous history of cosmetic treatments such as the removal of infraorbital lines, nose surgery, fat transplantation, BoNT-A injections, and filler injections. With regard to fillers, it is helpful to know which products were used and how satisfied they were with the treatment. If the patient has received prior treatments with BoNT-A, it is important to find out if they had experienced any adverse effects after the injections, particularly eyebrow drooping or change of facial expressions. It may also be possible to glean something about a patient's character through their cosmetic treatment history. For example, patients who are completely new to cosmetic surgery or procedures are often sensitive to edema and bruising due to the burden of the initial treatment. However, patients who have already had mandibular angle reduction surgery for square jaw or face-lifts are not likely to be afraid of injection procedures, and patients who have had fat transplantations usually do not feel any burden at all from filler treatments. However, one key point you should always bear in mind is that, in the beginning, patients usually do not fully reveal their full prior treatment histories.

Finally, financial situation is one of the most important, yet often

overlooked, aspects of a patient evaluation. Budgetary constraint is an important factor in customer purchase decisions. For patients to whom money is not an issue, they could pay up for the full range of treatments at once, but realistically, most patients need to weigh up the cost and benefits of a given treatment. If you explain various treatment options to patients who feel great financial burden, it may only cause them deep distress. They may think to themselves, “who would refuse those treatments if we had enough money!” And there is no need for doctors to explain all of the various options in such a situation. However, it is difficult to question someone directly about their financial status; therefore, doctors should use intuition to estimate a patient’s financial situation considering their age, profession, and other tips such as their dresses and cars. If there is true financial burden, it is better to initially recommend the best cost–benefit options with the most noticeable results in order of priority. It is with this in mind that practitioners assist patients prioritize the necessary treatments they need to receive. For example, upon assessing a patients’ face, I would suggest they start with treatment of the glabellar wrinkle and anterior malar depression as their first priority. I would then suggest they could do with a nose filler and chin augmentation later to add more definition to the face, but for now their priority should be the glabellar wrinkle and malar depression treatments for the younger appearance. Or it can be a good idea to drop patients who come in with unrealistically low-cost estimations. Patients who are under cost pressure tend to have disproportionately higher expectations about the results and will most likely end up being an unhappy customer. In this sense, BoNT-A can be recommended early for these situations since it is less expensive compared with fillers and has minimal impact on patients’ daily lives. I believe treating wrinkles with BoNT-A can give highly satisfactory results with minimal psychological resistance from patients who are receiving a cosmetic procedure for the first time. Furthermore, it can act as an initial “gateway” to the world of cosmetic procedures.

2.1.4 Ethnic Differences Between Asians and Caucasians

Some people consider the phi mask or golden ratio to be the standard of an ideal face. However, concepts on aesthetic ideals change according to time and region, East and West [2]. When I first began treatments with BoNT-A

and fillers, I was in doubt about one theory from western speakers and western literature—the so-called triangle of beauty as an ideal face shape. This triangle made by the intersection of the lines connecting two zygions and one gnathion drawn on the face of Brigitte Bardot was considered to be the definitive aesthetic ideal in the Caucasians. However, Koreans prefer slimmer, oval, and slightly chubby, baby-like faces with less prominent zygoma as opposed to the western standard with prominent zygoma and sunken cheeks (Fig. 2.6). Therefore, the procedure to inject fillers on the lateral part of zygomatic arch and lateral side of the eyebrows to stress “the triangle of beauty” cannot be applied directly in Asian patients who hate prominent zygoma and wide face. These differences of beauty concept partly come from the different facial shapes between Asians and Caucasians. While the “triangle of beauty” is well suited to the western dolichocephalic (long and narrow) face type, the perception would be of a much larger face with prominent zygomatic outlines, which is not considered attractive if it is applied to Asian brachiocephalic (short and wide) faces (Fig. 2.35).

Fig. 2.6 Beautiful Asian and Caucasian woman

2.1.4.1 Attractive Composite Faces Between Asians and Caucasians

This ethnic difference in the concept of beauty is well described in an article by Rhee who conducted an analysis based on the composite faces of celebrities of different ethnicities [3]. Composite photographs of the faces of beautiful western women such as Angelina Jolie and Hilary Duff look somewhat masculine from Asian viewpoint. They reveal slightly larger and more prominent facial features (eyes, nose, and lips), a narrower space between the eyebrows and eyes, and a more masculine facial shape with angulated jawline and prominent zygoma compared to beautiful Asian women (Figs. 2.6 and 2.7a). Conceptual differences exist not only between the East and the West but also between Asian countries such as China, Japan, and Korea (Fig. 2.7b) [4]. Chinese attractive face shows slimmer face, fuller lips, and high nose compared with Korean and Japanese. Although a shared concept of beauty exists to a certain degree, there is no golden standard or ideal facial shape. Therefore, we should choose appropriate individualized treatment options taking into consideration the existence of biological and cultural differences depending on the ethnicity and region.

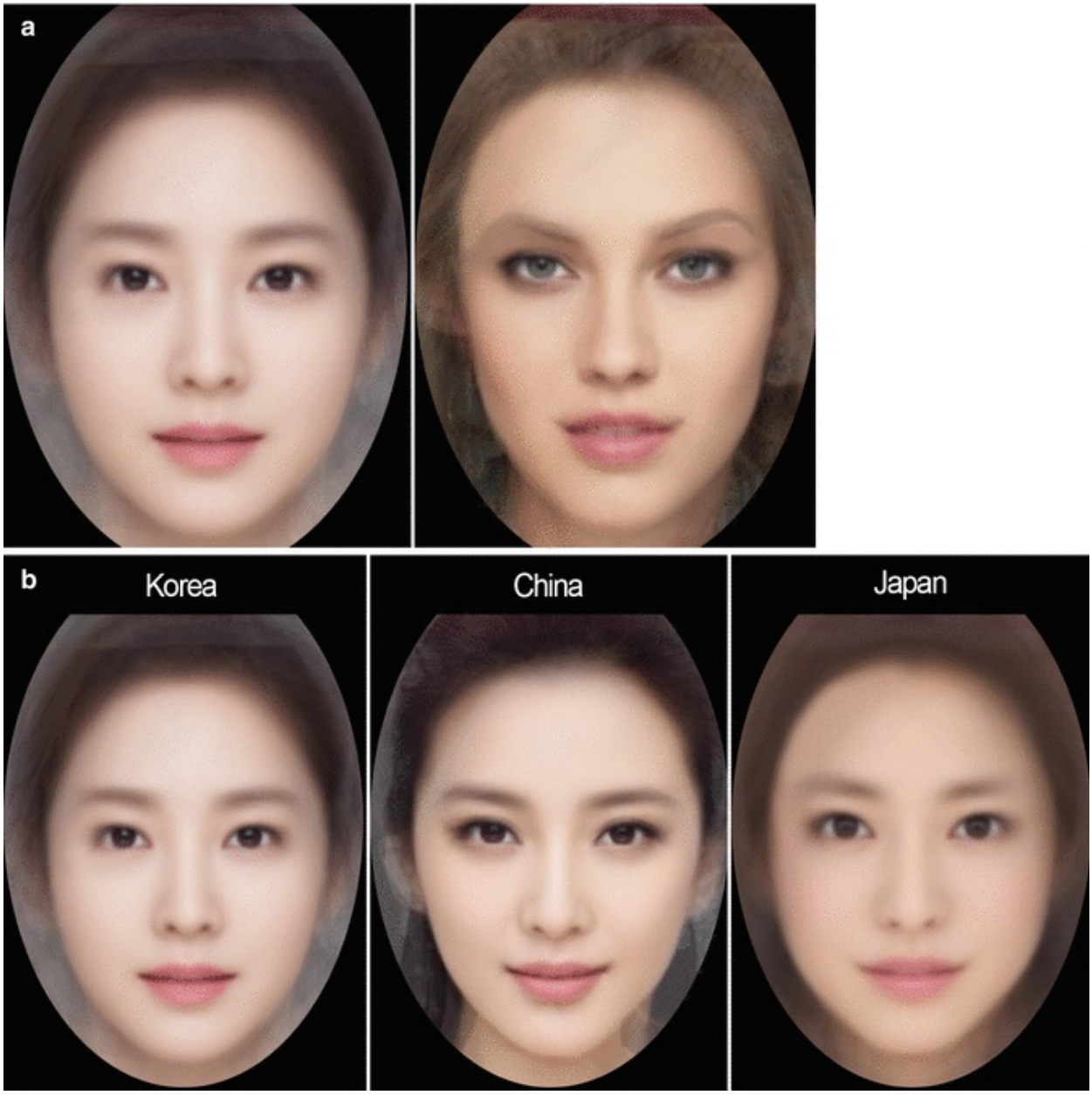


Fig. 2.7 Comparison of attractive composite faces. (**a**) Attractive composite face for Asian and Caucasian woman. (**b**) Attractive composite face for Korean, Chinese, and Japanese

2.1.4.2 Different Facial Shapes and Different Aesthetic Standards Between Asians and Caucasians

Asians have a relatively wide, round, and flat face compared to Caucasians [5]. For this reason, while angulated jaw, high cheekbone, and square face are regarded as individuality in Caucasians such as in cases of Miranda Kerr and

Angelina Jolie, however, bone surgeries for reducing facial width such as zygoma reduction and mandibular angle resection have been popular among Asians who consider a smaller, narrower, and more three-dimensional face to be more attractive. Likewise, Asians may wish to achieve this ideal using BoNT-A. One of the most typical examples of this is the treatment for masseter hypertrophy using BoNT-A, which is not popular in western countries even though it was first developed in western countries more than 20 years ago [6]. This novel treatment helps those Asians with a square-looking face to achieve a decreased facial width and a "V" shape to their face in their front view without surgery. In a similar context, BoNT-A treatment for temporalis hypertrophy and for the parotid gland enlargement is also gaining more and more popularity among Asians as a method of decreasing facial width.

BoNT-A injection for widening the palpebral aperture (the eye-opening) is another typical example of the ethnic difference in treatment approaches between Asians and Caucasians. BoNT-A injection can remove the pretarsal muscular roll and slightly lower the inferior ciliary margin to widen the palpebral aperture [7]. From the viewpoint of Caucasians, this treatment may help Asians's smaller eyes to become bigger. Actually, this treatment is appealing to some Southeast Asians who regard almond-shaped eyes as a beautiful hallmark because eliminating the pretarsal roll creates more of an almond-shaped eye. However, it is important not to apply this treatment to East Asians, who consider pretarsal roll as one of the important hallmarks of female beauty [8]. The pretarsal muscular roll is usually exaggerated when people smile by the action of orbicularis oculi muscle. Therefore, it is called as "charming roll" in East Asians because the people with pretarsal muscular roll in repose look soft and friendly. Another reason for explaining the popularity of "charming roll" in East Asians is that the "charming roll" brings the optical illusion of a "big eye" like double-eyelid surgery in Asians with inherently smaller eyes. The purpose of the double-eyelid surgery is to create an upper eyelid with a supratarsal crease (i.e., "double eyelid") from an eyelid that is naturally without a supratarsal crease. Therefore, physicians even enhance "charming roll" by the injection of filler in Asians (Fig. 2.8). In such a context, BoNT-A injection for widening the palpebral aperture by removing the pretarsal bulge at the lower eyelid should be avoided in Asians.

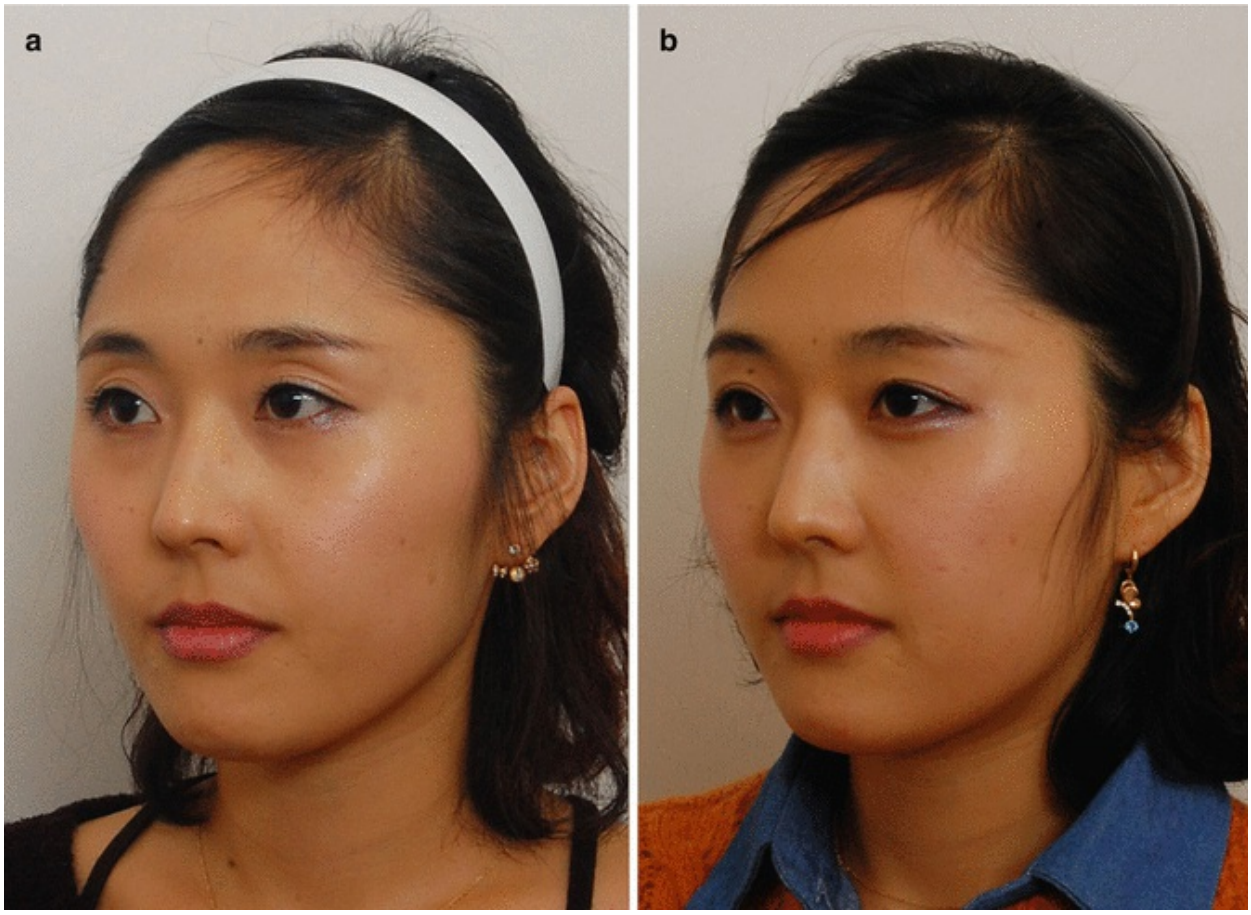


Fig. 2.8 Filler injection for pretarsal roll (charming roll). The pretarsal roll in a woman in her 20s was augmented with fillers adjunct with volumization for sunken eyes, resulting in a young and tender impression from Asian viewpoint. (**a**) Before. (**b**) After

Eyebrow "shaping" with BoNT-A, popular in Caucasians [9, 10], is also not recommended for East Asians, especially Koreans, who consider flat eyebrow beautiful shape for women (Fig. 2.6) [11]. High arched eyebrows are generally considered as tough looking in this region of Asia and are even called "samurai eyebrow." Aesthetically high arched eyebrows may look unnatural in an Asian with wide facial shape. Consequently, eyebrow "shaping" with BoNT-A resulting in high arched eyebrows is not recommended for Asians.

Episode: Infraorbital Eye-Opening, Contraindication in East Asia
BoNT-A injection for widening the palpebral aperture (the eye-opening) is a typical example of the ethnic difference in BoNT-A treatment approaches between Asians and Caucasians. Hypertrophic pretarsal muscle roll (muscle

bulge) appears and becomes prominent due to the contraction of the pretarsal portion of the orbicularis oculi during a smile. A person with pretarsal roll at rest gives the impression of a smile. The impression of tender and big eyes has earned it the nickname “charming roll” and “infraorbital double eyelids” (eyelid with a supratarsal crease) in Korea. Therefore, “filler for pretarsal roll” is one of the most popular aesthetic items in Korea (Fig. 2.8). However, Caucasians who do not have this pretarsal roll seem to believe that this may make Asians’s small eyes look smaller. This may be the reason why Dr. Carruthers developed a technique to remove the roll by injection of BoNT-A. Dr. Carruthers reported that by injecting 2 U of BoNT-A in the midpupillary line below the ciliary margin, they were not only able to efface hypertrophic pretarsal roll but also increase palpebral aperture by 0.5 mm at rest and 1.3 mm at full smile [7].

However, this indication is contraindicated in Koreans and other Asians who consider the “charming roll” a hallmark of female beauty. When Dr. Carruthers visited Seoul in 2001, he demonstrated this technique on a receptionist in my clinic. However, about 1 week after the procedure, the receptionist’s face looked unnaturally scared from the Korean viewpoint because her “charming roll” was removed and an exposed white sclera was noticeable (Fig. 2.9). Moreover, her smile looked unnatural because her smile was not accompanied with a narrowing of the eye aperture, which should be naturally seen in Koreans. Through this experience I came to definitely know the different perspectives between the East and West. Needless to say, I have never tried this technique to Koreans since then.

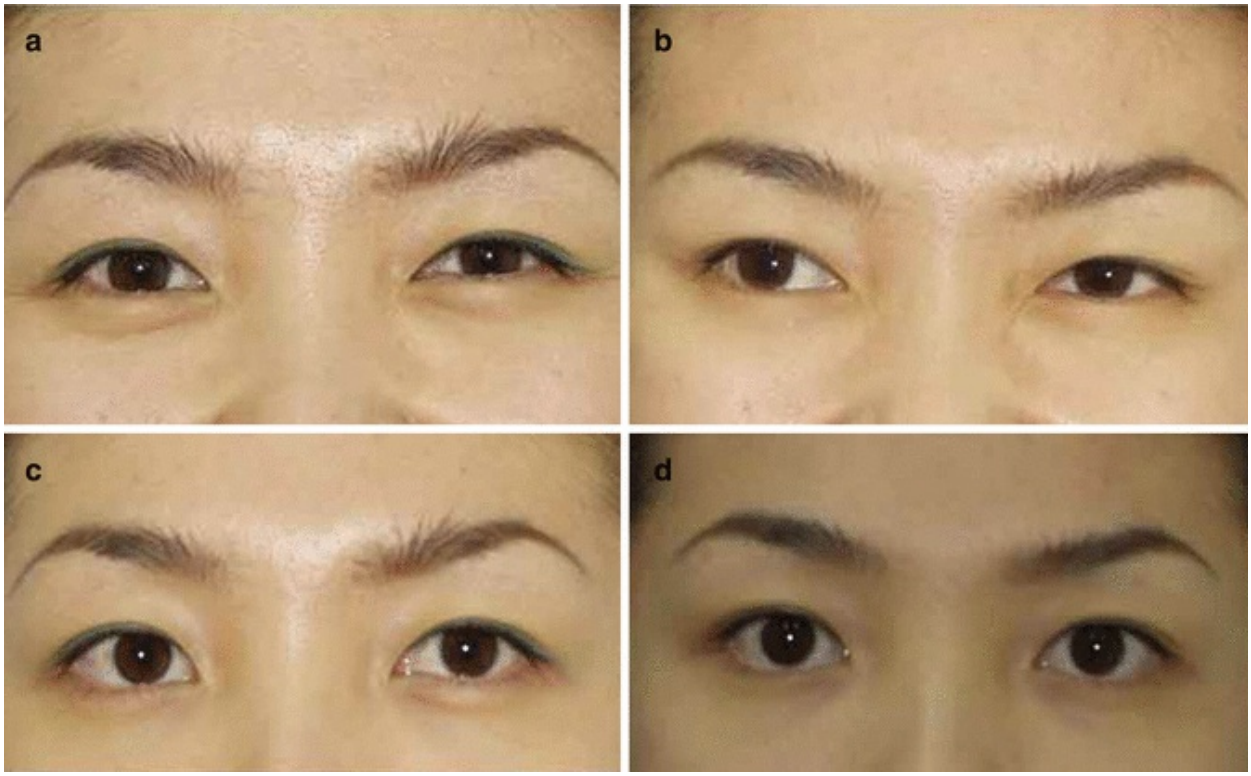


Fig. 2.9 Infraorbital eye-opening with botulinum toxin injection (**a**, **c**) before and (**b**, **d**) 2 weeks after 2 U injection of BOTOX®. (**a**) Although widening of the eye aperture when smiling was achieved by injecting botulinum toxin into the lower eyelids, disappearance of pretarsal roll was accompanied by unnatural facial expressions from the Korean standard. (**b**) Although widening of eye aperture at rest was also achieved by injecting botulinum toxin into the lower eyelids, disappearance of pretarsal roll was accompanied by exposed sclerae, resulting in somewhat scary facial expressions

2.1.4.3 Three Asian Facial Types

Asians are sometimes mistakenly presumed to be homogeneous. Since Asia is a huge continent, however, Asians are a notably heterogeneous group and therefore cannot be treated as a uniform population. To guide patient-tailored treatment with BoNT-A, classification of Asian facial morphotype is required. Ethnic groups in East Asia and South East Asia can be simply classified into three Asian facial morphotypes with Northern, Intermediate, and Southern type (Fig. 2.10) [11]. Indians and Arabs are excluded from this classification because they are not within this scope. Northern facial type has a narrow palpebral fissure with no supratarsal crease, high and long nose with narrow nasal ala, prominent zygoma, well-developed mandibular angle which gives a square face or square jaw, and relatively white skin. Ethnic groups in Northern type are many individuals from Mongolia, some from Korea, and

Northern China. Southern facial type has the wide palpebral fissure with a supratarsal crease, flat and short nose with wide nasal ala, less prominent zygoma, less developed bony mandibular angle which gives a narrow and oval facial shape, and relatively dark skin with a Fitzpatrick phototype of III to IV. Ethnic groups in Southern facial type are many individuals from the Southeast Asian countries such as the Philippines, Thailand, Indonesia, etc. Intermediate type shows the intermediate characteristics between Northern type and Southern type. Intermediate type has round face with small chin, round bulbous nose tip, wide nasal ala, supratarsal crease, and chubby cheeks. This type may be seen in Southern China, Hong Kong, and Taiwan.

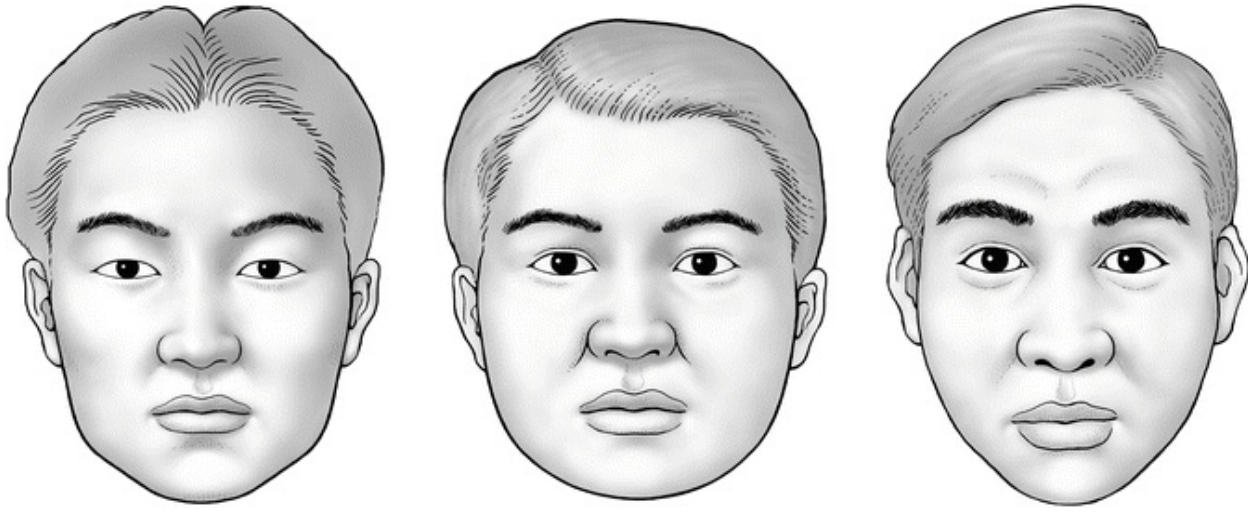


Fig. 2.10 Three Asian facial morphotypes with Northern, Intermediate, and Southern type (from the left to the right)

Of course, this classification does not cover all ethnicities in this region, and mixed characteristics and variation exist even within the same ethnic group. For example, some Koreans show typical characteristics of the Northern type, while others show the Southern type. And also, it is possible for an Asian subject in one area to possess mixed characteristics of different facial type. Therefore, BoNT-A injection strategy in Asians should be guided individually not by just facial type in their geographic region even though the Asian facial type is a good reference when planning BoNT-A injection.

2.1.4.4 Anatomic Differences Between Asians and Caucasians

Asians generally tend to have a smaller muscle mass and less hyperdynamic activity compared with Caucasians. Specifically, Asians are reported to have shorter corrugator muscles than Caucasians [12]. The smaller muscle mass of Asians seems to come not only from genetic differences but also from cultural differences related with facial expression. According to one paper analyzing the facial expressions by videotaping, Caucasians tend to use their upper facial expression muscles more than Asians up to 30 % [13]. Moreover, Asians have fewer wrinkles, compared with Caucasians, because Asians have a thicker dermis [14], increased fat, and denser fat in comparison with Caucasians [15]. All these mean that lower doses of BoNT-A should be administered in Asians than in Caucasians.

Tip: Safe, Natural-Looking Wrinkle Treatment with Botulinum Toxin (The Art of Subtlety)

One thing to keep in mind when performing BoNT-A treatments is that the goal of the treatment is to *reduce*, not *eliminate* wrinkles. Even Miranda Kerr has wrinkles around her eyes when she smiles. Attempts to completely eliminate wrinkles around the eyes can prevent the eyes from smiling, leading to a frozen masklike face. Since sensitivity to BoNT-A varies between individuals by up to three times and no effective antidote is available for BoNT-A, adverse effects from the overdosage of BoNT-A have to last for at least 2 months. Therefore, the safer approach is to start the initial treatment on a lower dose. If the desired results are not obtained, have the patient return after a couple of weeks for touch-up as needed. Thereafter, the adjusted dose can be used for each session. Given the dose–duration relationship, the effects may disappear sooner than expected on low-dose treatments. Nonetheless, applying small doses on an incremental basis clearly is a better alternative to adverse effects.

2.1.4.5 Differences in Techniques and Dose

In the late 1990s, when BoNT-A for wrinkle treatment was first introduced in Korea, doctors closely followed the recommended methods and doses published in western literature. However, this led to the frequent occurrence of adverse effects such as eyebrow ptosis, masklike face, disappearance of facial expressions, “samurai eyebrows,” etc. In 2000, not long after the start of my career with BoNT-A procedures, I made a similar mistake in an educational video, “Wrinkle Treatment with BoNT-A for Asians” (Hana

Movies). At that time, I used 14 U of BOTOX® for the treatment of forehead wrinkles, lower than the 20–30 U recommended in western publications. However, I often encountered eyebrow ptosis and resultant narrow eye aperture with a gloomy impression, particularly in patients in their 50s and over. When I realized this was due to an overdose, I was able to minimize adverse effects by reducing the dose for forehead wrinkles to 3–6 U. This same trend also occurred in the West. Initially, western doctors focused on removing wrinkles with BoNT-A. However, they gradually shifted to lower doses which provide for more natural facial expressions. We can find this trend in an article published by Dr. Carruthers in 2013 [16], and, in the American consensus recommendations, it was reduced to 6–15 U for horizontal forehead wrinkles in women in 2008 [17] from 10 to 20 U in 2004 [18].

Although the recommended dose for Caucasians was greatly reduced, it is still higher compared with Asian recommendation (Tables 2.1 and 2.2) [19]. The dose difference between Asians and Caucasians may be based not only on ethnic factors but also on cultural differences in the strength of facial expressions. An article comparing facial movements between Europeans and Asians found that Europeans make 30 % more facial expressions in some facial areas such as the glabella and forehead [13]. This increase in facial expressions induces greater development of facial muscles. Therefore, higher doses are necessary for Caucasians in the glabellar and forehead areas, whereas smaller doses are sufficient for Asians who make fewer facial expressions.

Table 2.1 Change in average doses of botulinum toxin A for cosmetic purposes (Western standard)

Location	**Dose of BOTOX® (U)**	
	2004[a]	**2008[b]**
Glabella		
Women	20–30	10–30
Men	30–40	20–40
Horizontal Forehead lines		
Women	10–20	6–15
Men	20–30	6–15
Crow’s feet		
Women	12–30	10–30
Men	12–30	20–30

[a]Consensus recommendations from the USA, 2004 [17]
[b]Recommendations update, 2008 [18]

Table 2.2 Average initial dose of BOTOX® for wrinkle treatment in Koreans (unit)

	Female (standard)	Male
Forehead	2–6	2–10
Crow's feet (per side)	4–7	4–8
Glabellar frown line	10–12	10–14
Bunny lines	6	8
Perioral (upper lip) wrinkles	2–4	4
Mentalis	8	10
DAO (per side)	3	4
Platysma band (per side)	20–30	30–40

Data from Modelo Clinic

2.1.5 Appropriate Interval for Touch-Up Injection and Repeat Injection

The effects of the BoNT-A may start 2–3 days after injection and reach full effect after 1–2 weeks. Therefore, it is wise to wait at least 1–2 weeks after the initial injection before determining if touch-up injections are needed. Two weeks is best for touch-up injection as full effect is more definitely observed at that time than after 1 week. Therefore, physicians should generally try to avoid administering touch-up injections if patients complain about a lack of effect after only 3–4 days. However, touch-up injections in the lateral side of the frontalis muscle with 0.5 U per site would be better performed even after only 3–4 days for the purpose of early correction of adverse effects in case the patient experiences samurai eyebrows.

The peak period of effective wrinkle treatment with BoNT-A is 2–4 weeks after the initial injection. After 2 months muscle power begins to return partially and partial movements are possible. After 3 months, muscles recover over 50 % of their power and full recovery takes place after 5–6 months. In case of neuromuscular diseases including blepharospasm and cervical dystonia, partial recovery of the muscle movements may hinder normal life of patients, and therefore, repeat injections at 2–4-month intervals are necessary. However, given that the purpose of wrinkle treatment with the

BoNT-A is not perfect removal of wrinkles but partial effacement of wrinkles, it is preferable to give repeat injections at 3–6-month intervals after the final treatment. If the goal of wrinkle treatment with the BoNT-A is to prevent wrinkle progress, I recommend repeat injections at 3–4-month intervals when muscles are half recovered, as opposed to conventional 5–6-month interval when the effects of BoNT-A are almost gone.

Regarding the duration of the effect depending on areas, wrinkles in the periorbital area seem to reappear first followed by the glabella and forehead. Since the effect lasts upto 5–6 months in the forehead, longer than in the glabella, a repeat injection after 3–4 months only in the glabella region could be administered in patients who still show good effects in the forehead at 3–4 months after the injection. Injection of BoNT-A should be individually tailored.

2.1.6 Preventative Effect of Botulinum Toxin for the Treatment of Wrinkles

During the consultation with patients who consider BoNT-A injections for wrinkle treatment for the first time in their life, patients in their 20s and 30s often express strong concern about starting this treatment too early because BoNT-A injections should be repeated every 3–6 months for their whole life. Whenever I encounter these concerns, I always stress the preventative effects of BoNT-A injections for wrinkle treatment. Through repeat injections we can not only remove wrinkles but can also prevent further progressive wrinkle formation. In theory, patients who have been repeatedly treated for 5 years with BoNT-A injections for wrinkle treatment should appear the same now, in terms of wrinkle development, as they did 5 years before they began BoNT-A treatments. But actually by repeat treatment, the wrinkle state at present is much better than the starting point of treatment. In my experience, I have even observed marked improvements in static wrinkles through repeated BoNT-A injections at 3–6-month intervals for several years. This preventative effect of BoNT-A injections on wrinkles has been disclosed in many publications [20]. One of the reasons for this improvement of glabellar wrinkles is that unconscious glabellar frowning can be corrected by BoNT-A injections (see Sect. 2.9). Thanks to this preventative effect, more and more people are choosing to begin BoNT-A treatments in their late 20s and early 30s.

2.1.7 Botulinum Rebalancing (Compensatory Hyperactivity)

Facial expression muscles are one of the primary causes of facial wrinkles. Unlike other muscles, facial expression muscle fibers are directly attached to the dermis, and facial expression wrinkles are formed through the contraction of these muscles when smiling, crying, or frowning. The skin of young people is elastic, and expression wrinkles go away completely after facial expressions, but nonelastic skin in old ages does not recover completely and leaves static wrinkles. The principle behind treating wrinkles with BoNT-A is the reduction of facial expressions by relaxing facial expression muscles.

Facial expression muscles are not separated with the fascia, but rather intermingled with each other to make the characteristic superficial musculoaponeurotic system (SMAS). Interconnected facial expression muscles create equilibrium by interacting with each other in all directions. When one side of the face is paralyzed due to a stroke, facial muscles only on the healthy side can move during speech and facial expressions, which results in the distortion of facial expression on the healthy side. Similarly, if the equilibrium between facial expression muscles is broken by injection of BoNT-A, it breaks equilibrium and causes the muscles on the other side to become more active. As a result, various delicate changes to facial expressions may appear by injection of BoNT-A. We can call this phenomenon “botulinum rebalancing” or “compensatory hyperactivity.”

If botulinum rebalancing works horizontally leading to asymmetry, the resulting appearance could be distressful similar to a stroke patient. However, vertical rebalancing can be used constructively for cosmetic purposes. Facial expression muscles can be divided into two categories: depressors and elevators. The former depresses the facial elements and the latter elevates them (Fig. 2.11, Table 2.3). Only the frontalis muscle elevates the eyebrows. The orbicularis oculi, corrugator supercilii, depressor supercilii, and procerus are depressors of the eyebrows. A total of five muscles act as lip elevators: zygomaticus major, zygomaticus minor, levator labii superioris alaeque nasi (LLSAN), and levator labii superioris (LLS). Lip depressors are the depressor labii inferioris (DLI), depressor anguli oris (DAO), and platysma. The aging process causes facial elements (eyebrows, mouth corner, jawlines, etc.) to droop. In these cases, facial elements can be lifted by injecting BoNT-A into the depressor muscles, restoring a youthful appearance.

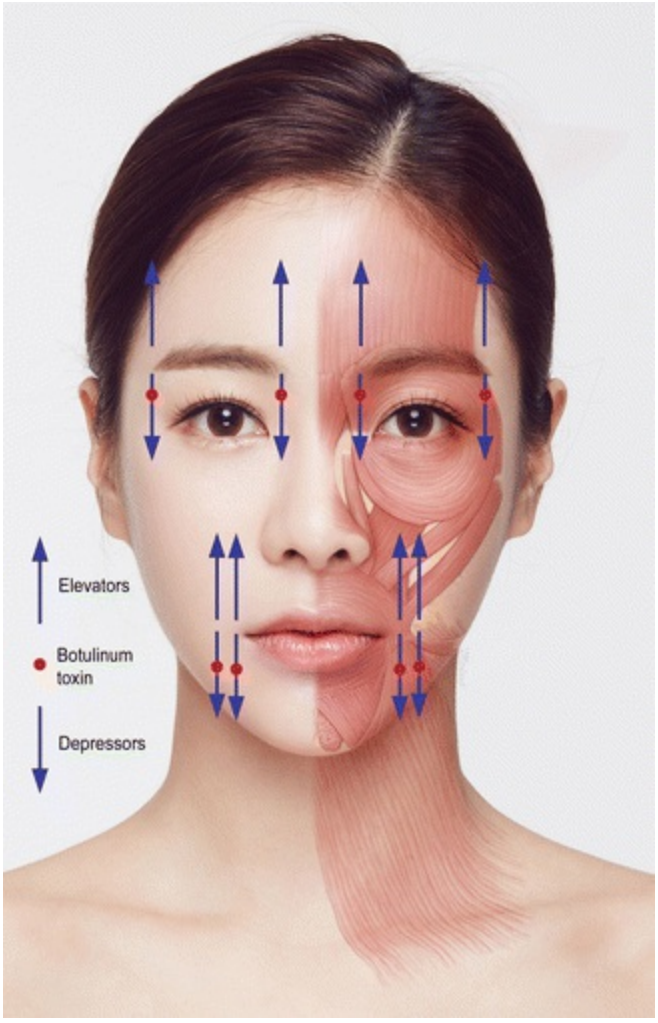


Fig. 2.11 Botulinum rebalancing. Elevators and depressors for the eyebrows and the mouth corners are in equilibrium in the normal state. However, botulinum toxin injection into the depressors shifts more activity in the elevators, resulting in elevation of the eyebrows and the mouth corners

Table 2.3 Botulinum-rebalancing target muscles in longitudinal direction

	Elevators	**Depressors**
Eyebrow	Frontalis	Orbicularis oculi, corrugator supercilii, depressor supercilii, procerus
Lip/jawline	Levator labii superioris alaeque nasi, levator labii superioris, levator anguli oris, zygomaticus minor, zygomaticus major	Depressor labii inferioris, depressor anguli oris, platysma
Upper eyelid	Levator palpebrae superioris, Muller muscle	Palpebral portion of the orbicularis oculi

For example, we can lift eyebrow drooping by paralyzing the depressor

muscles of the eyebrows (see Sect. 2.17). We can widen eye aperture in patients with ptosis by paralyzing the pretarsal part of the orbicularis oculi muscle responsible for the eye-closing (see Sect. 2.13). We can also elevate a drooped mouth corner and jawline by paralyzing the depressor muscles of the lips (see Sect. 2.27). The best examples of using botulinum rebalancing are the "mesobotox," intradermal BoNT-A injection technique, and Nefertiti lift (see Sect. 4.1).

The phenomenon of botulinum rebalancing is not always functionally good. New wrinkles may form in the non-paralyzed skin areas near the injection sites after BoNT-A injection. If we inject the lateral side of the eyes, wrinkles are pushed toward the medial side, and new wrinkles can form around the dorsum of the nose after injections to the glabellar area (Fig. 2.12). "Samurai eyebrows," which often appear when treating wrinkles with BoNT-A, result from the compensatory hyperactivity of non-paralyzed muscles due to either excessive injections in the center of the frontalis muscle or small doses in the lateral side of the eyes. Bulging of the masseter muscle on mastication, one of the embarrassing adverse effects for the treatment of masseteric hypertrophy with BoNT-A (Fig. 3.20), is also considered one type of rebalancing phenomenon caused by the muscle imbalance between injected and non-injected areas (see Sect. 3.1.11.5).

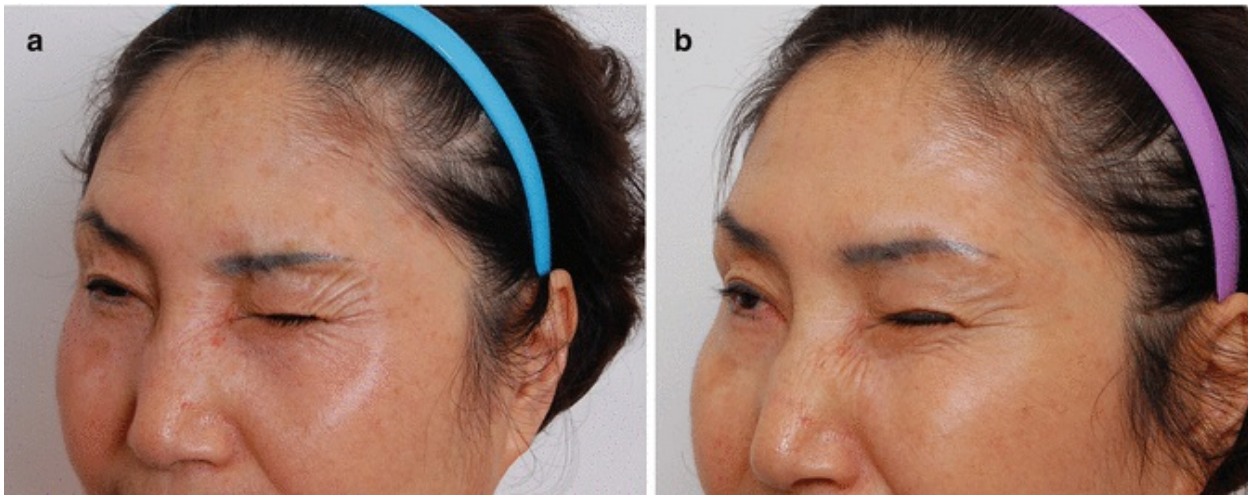


Fig. 2.12 If botulinum toxin is injected only into the lateral side of the eyes, new wrinkles can form through botulinum-rebalancing phenomenon on the medial side of the infraorbital area and around the nose bridge after 1.2 weeks. (**a**) Before. (**b**) After

Tip: "New Wrinkles Formed After BOTOX!"

In early 2003 a foreign news report claimed that new wrinkles could be formed after BoNT-A injections. The report was released just after another news report from London in late 2002 which incorrectly claimed that repeated BoNT-A injections could disturb sensory nerves (see Sect. 1.3.7). I received an urgent phone call from a manager at Allergan Korea whose situation reminded me of the Korean proverb, “someone frightened by a turtle will be startled by the lid of a caldron” which is similar in meaning to the western proverb “once bitten, twice shy.” He asked me for some advice on a press release after reviewing the news. After thoroughly reading the content of the foreign news, I concluded that this effect was nothing new and was already well known to doctors who were treating wrinkles with BoNT-A.

To the general people, it may seem quite ironic that new wrinkles can form after BoNT-A injections. If this is true, why receive an injection which is supposed to help remove wrinkles? At first I was also skeptical until I encountered a patient who complained about the formation of new wrinkles in the paranasal area after receiving BoNT-A injections to the forehead, glabella, and periorbital areas 1 week earlier. With many doubts in my mind, I compared the patient’s before and after photographs and found the wrinkles she had complained about. I was at a bit of a loss at the time because I was not aware of any coping strategies nor could I find any pertinent references on this problem. If new wrinkles arise from BoNT-A used to reduce wrinkles, is it really a major cause for concern?

Later, I came to know that this adverse effect (?) is caused by the botulinum rebalancing. Then, how should we handle these new wrinkles? The answer is simple. Inject BoNT-A into the hyperactive muscles! It was quite funny and embarrassing that I did not know this simple principle at that time, but I always show this first patient’s photo in my lectures on the botulinum rebalancing so that audience will not follow in my footsteps. There is no need to worry about new wrinkle formation from BoNT-A injections because we can clear them away by injecting into the site of the new wrinkles. The typical case is samurai eyebrows. In this case we can inject 0.5–1 U in the upper part of the forehead over the lifted eyebrows. If the new wrinkles are formed to the medial side of the eyes after BoNT-A injection for crow’s feet, we can remove these new wrinkles by injecting 0.5 U in the medial canthus of the infraorbital area. To remove new wrinkles in the dorsum of the nose after injections to the glabellar area, a 6–8 U injection is necessary. In fact, it is wiser to inject BoNT-A to these areas during the initial

treatment for advance prevention.

Tip: Where Does the Forehead End on a Bald Head?
Where does the forehead end on a bald head? There is a witty remark, “At the border reached by the soap foams when you wash your face in the morning.” In medical terms though, the forehead ends at the area reached by the forehead wrinkles. This is because there are no facial expression muscles on the scalp. In this sense, injecting BoNT-A into the scalp can be a futile exercise.

During my early lectures on wrinkle treatment with BoNT-A, I made a point of marking out the standard injection sites for the benefit of the audience. During one lecture I was asked if injections were necessary in the points marked near the eyes where no wrinkles were present. At that time I replied in the affirmative, but upon reflection I guess my answer was only half correct. The absence of expression wrinkles in a certain facial area suggests lack of facial muscle activity, and hence no injection should be necessary. In fact this is in line with the recommendations made by the recently published academic article on the treatment of lateral canthal rhytides with BoNT-A, which concludes that that injections are not necessary in non-wrinkled areas [21].

However, upon deeper consideration this may not always be the case. This is because new wrinkle formation can be induced in odd areas at times due to the mechanism of botulinum rebalancing. Therefore, low-dose BoNT-A injections for preventative purposes can also be necessary in non-wrinkled areas. In the case of lateral canthal rhytides, even where wrinkles are noticeable only in the upper portion of the eyelids, it helps to inject 0.5 U below the horizontal line in the lateral canthal area to prevent botulinum rebalancing. Likewise, in the non-wrinkled portion of the forehead, injecting one-third of the recommended dose of BoNT-A can be helpful for preventative purposes.

2.1.8 Botulinum Remodeling of Facial Expression

Facial expression muscles which exist only in humans reveal all kinds of emotions through facial expressions. However, we do not consciously manipulate facial expression muscles to express emotion when we smile, cry, frown, or are angry. Facial expressions are usually made unconsciously according to our emotional state. In this sense, they act similarly to

involuntary muscles. As repeat injections of BoNT-A cause facial expression muscles to disobey orders from the brain, the facial expression center in the brain can become dull by feedback. The brain seemingly forgets how to use certain muscles to make corresponding facial expressions, which resultantly causes a change to the facial expression itself. I cautiously refer to this phenomenon as “botulinum remodeling of facial expression.”

A good example of “botulinum remodeling of facial expression” is the disappearance of the unconscious frowning habit as a result of repeat injections of BoNT-A for the treatment of the glabellar frown lines. Injections of BoNT-A prevent us from frowning even if we want to. If this state lasts for months, the feedback seems to cause our brains to forget how to frown. Repeated BoNT-A injections in the periorbital areas will result in fewer wrinkles with a slight change of wrinkle pattern on smile. I believe this is caused by “botulinum remodeling of facial expression” rather than increased elasticity. From time to time, I encounter patients who have been experiencing some adverse effects of weird facial expression caused by facial plastic surgery. If they display odd facial expressions or unwanted movements caused by misconnected facial expression muscles, several repeated sessions with injections of BoNT-A may provide a lasting effect without the need for continuous treatment. I also encountered a patient who, following a medial epicanthoplasty, showed contractions of the pretarsal part of orbicularis oculi muscle medially whenever she closed her eyes. Astonishingly, injection of only 1 U of BoNT-A provided permanent improvement for this condition.

While BoNT-A for the treatment of glabellar wrinkles, which are generally ignored except by celebrities, is a beneficial example of “botulinum remodeling of facial expression,” there are some difficult cases with negative adverse effects to patients. For example, paralysis of the risorius muscle from treating the masseter hypertrophy with BoNT-A may produce an asymmetrical odd smile with non-elevation of the mouth corner on one side. Recovery from this distortion may not occur even after 1 year due to “botulinum remodeling of facial expression.” Although physicians usually tell patients that the adverse effects of BoNT-A are reversible as the effect of BoNT-A is temporary, in reality this is not always the case.

2.1.9 Injection Techniques

Draw the reconstituted solution of BoNT-A into a 1 ml syringe with 26-

gauge needle, and replace with a 30-gauge needle. An insulin syringe with 30-gauge needle or 30-gauge needle attached to 1 ml syringe is not directly used for drawing the reconstituted solution of BoNT-A as it becomes blunted after passing through the rubber cap of BoNT-A vial.

Before the injection, wipe off any makeup and clean the skin area with chlorhexidine. In case you are a beginner, you may mark the injection sites in advance with either a marking pen or sign pen. But marking is no more necessary when you become an expert. If the sites were marked, the marks should be lightly wiped off after the procedure. When treating periorbital or glabellar lines, you should be careful to wipe from an inward to outward direction while cleansing with an alcohol sponge to prevent accidental diffusion of BoNT-A to the orbits. You should also be careful to make injections two to three millimeters away from any pen marks to avoid inserting pigments into the skin and creating tattoos.

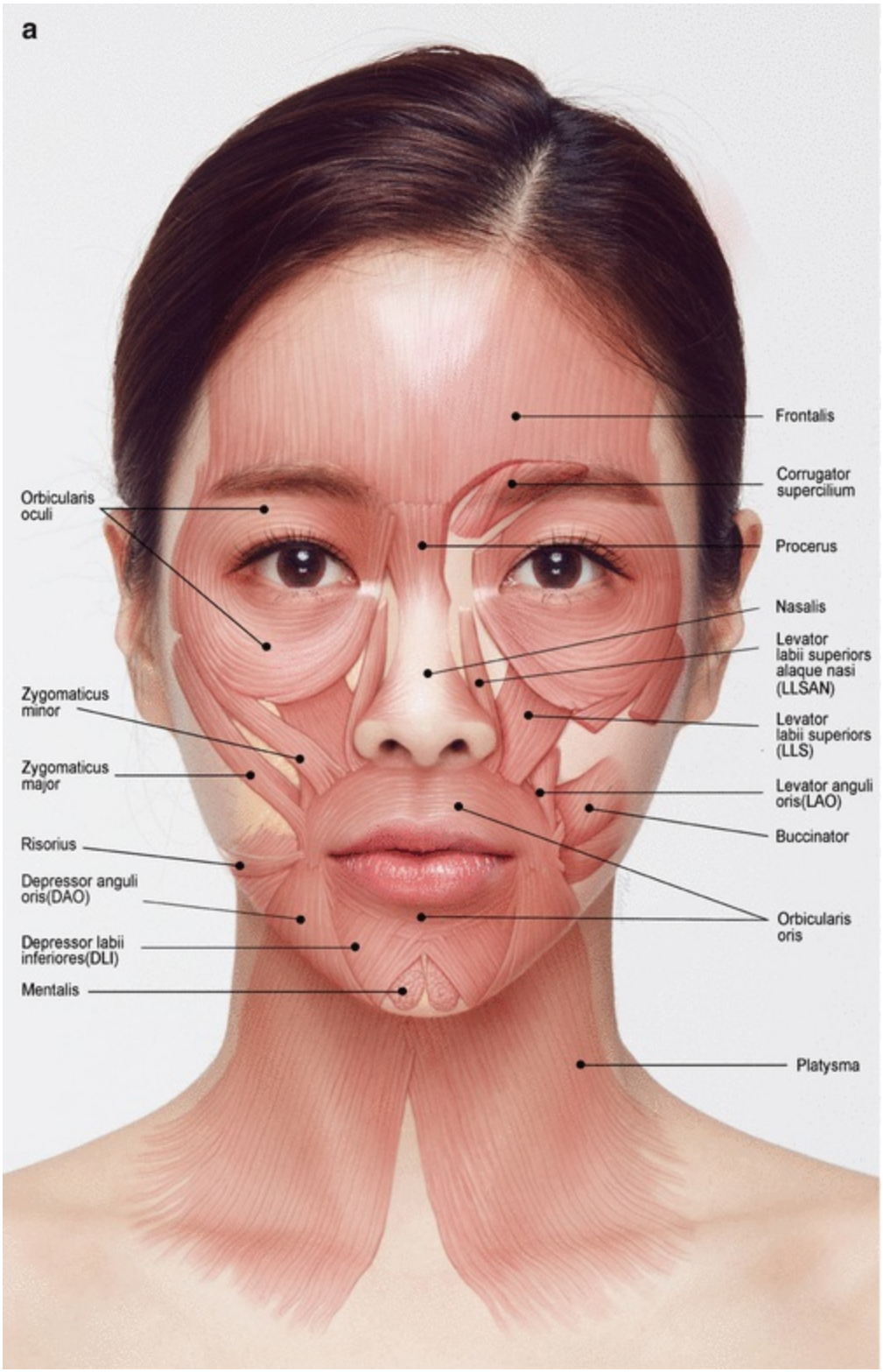
Regarding the needle depth, the subdermal injection would be sufficient for most of wrinkles except glabellar frown lines. For superficial injections such as intradermal or subdermal injection, a 30-gauge needle should be slanted at less than 15° from the skin surface and be inserted only at the bevel part. At first I recommended deep subcutaneous injections—reaching the periosteum first and withdraw the needle slightly in order to target directly the facial expression muscles. However, this method has some drawbacks. It may induce some pain by stimulating the periosteum and also bruising by damaging blood vessels underlying the skin before the needle reaches the periosteum. Additionally, BoNT-A diffuses in all directions after injection and the facial expression muscles are very thin. Therefore, the BoNT-A is highly likely to diffuse well into the facial expression muscles via a subdermal injection. Of course, deep injections are necessary at some sites because of the deep location of the muscles, for example, corrugator supercilii in glabellar wrinkles, masseter and temporalis muscles, zygomaticus muscles in asymmetric smiles, mentalis muscle in cobblestone chins, and platysma muscle in neck platysma bands.

The procedure can be performed while the patient is either seated or lying down on his or her back. Some doctors claim that a seated position is better for the prevention of ptosis. Since the patient’s position is not a crucial element of the procedure, I recommend choosing the option which is most comfortable for both doctors and their patients.

If the patient is seated during the procedure, it is preferable to stand on

either the left or the right side of the patient and look him or her in the face (Fig. 2.13). When injecting in the glabellar or periorbital areas, it is very important to make sure the BoNT-A does not diffuse into the patient's eyes. This can be prevented by switching physician's positions to the either the left or the right and ensuring that the needle is always pointed from inward to outward. If the patient is lying down, the physician should perform the procedure behind the patient's head.

Fig. 2.13 Posture of physicians for treating wrinkles with botulinum toxin injection


a
Frontalis
Corrugator supercilium
Orbicularis oculi
Procerus
Nasalis
Levator labii superiors alaque nasi (LLSAN)
Zygomaticus minor
Levator labii superiors (LLS)
Zygomaticus major
Levator anguli oris(LAO)
Buccinator
Risorius
Depressor anguli oris(DAO)
Orbicularis oris
Depressor labii inferiores(DLI)
Mentalis
Platysma

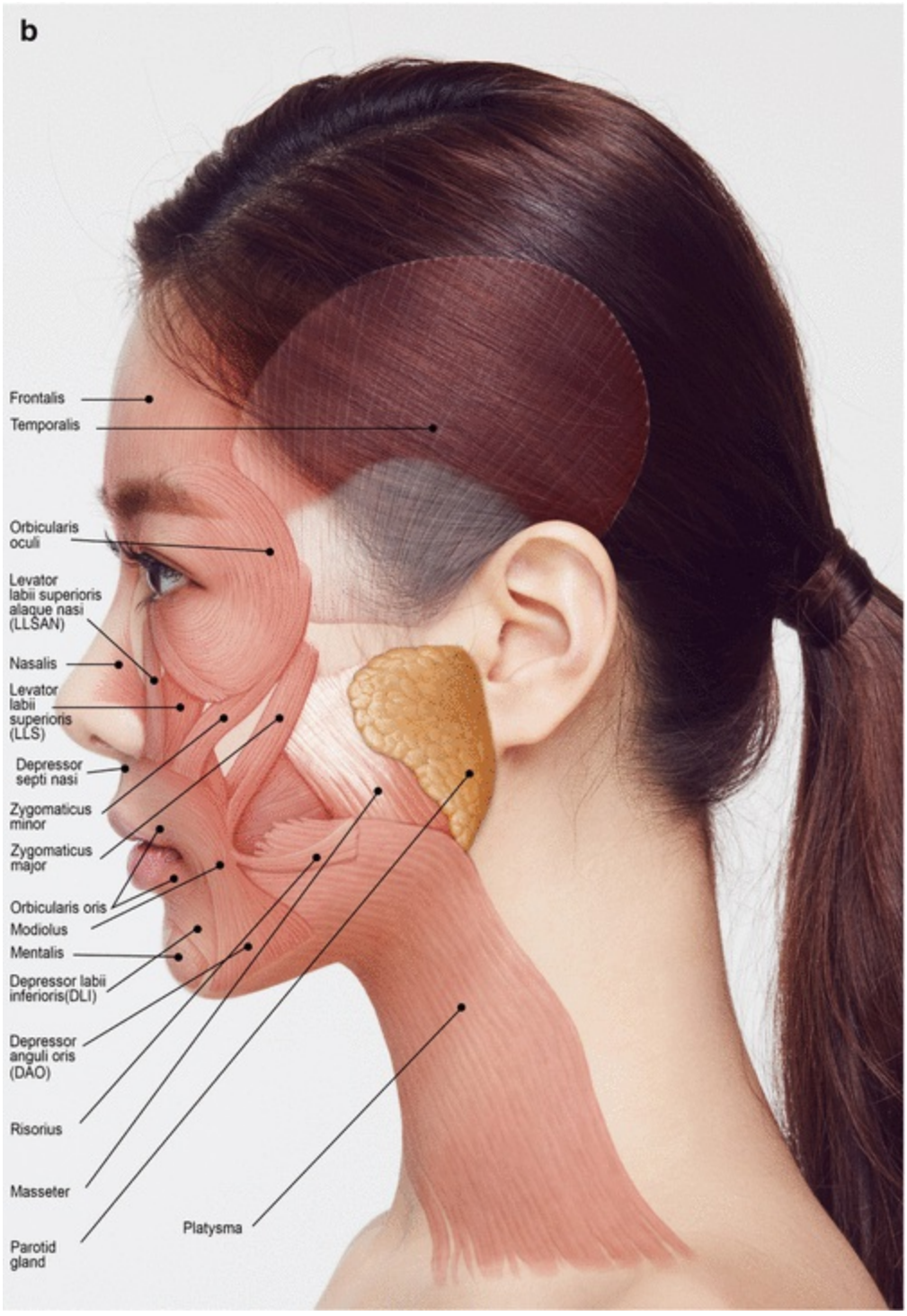


Fig. 2.14 Facial expression muscles. (**a**) Frontal view (*LLSAN* levator labii superioris alaeque nasi, *LLS* levator labii superioris, *DAO* depressor anguli oris, *DLI* depressor labii inferioris, *LAO* levator anguli oris). (**b**) Lateral view

2.1.10 Adverse Effects

When doctors first begin BoNT-A treatment, they are quite cautious and worry greatly about ptosis after treatment of glabellar wrinkles. I still remember having worried for 1 week about possible risk of ptosis after treating my first patient's glabella. In contrast with HA fillers, however, there are no effective antidotes for the BoNT-A. If the procedure is carelessly performed, patients are likely to experience abnormal facial expressions for at least 2 months with no recourse other than waiting for the effects of the BoNT-A to fade away. More importantly, patients may never visit your clinic again if adverse effects occur from their first treatment with you. This is because of lost trust and confidence for the doctor. Therefore, it is extremely important to minimize adverse effects when treating wrinkles with BoNT-A.

While general adverse effects in common with BoNT-A treatment are dealt here, some important and specific adverse effects such as eyelid ptosis (see Sect. 2.2.7.5), eyebrow drooping (see Sect. 2.2.5.5), and xerophthalmia (see Sect. 2.2.1.5) will be covered by regional particulars concerned.

2.1.10.1 Headaches

Although BoNT-A is sometimes used to treat migraine and tension headaches, ironically it may cause headaches which usually last 1–3 days. In a 2002 American FDA clinical study on the effect of the BoNT-A for the treatment of glabellar wrinkles, headaches were experienced by 13.3 % of the BoNT-A-injected group and 17.7 % of the control group using saline as a placebo [20]. This suggested that the headaches after the injection of BoNT-A may be related to nonspecific stimulation from needles. As the headaches usually subside within 1 week, specific treatment is not necessary aside from the use of acetaminophen derivatives. For persistent headaches which last longer than 1 week, patients are recommended to visit the neurologist to detect other potential causes. A patient of mine who experienced persistent headaches lasting nearly 1 month after the injection of BoNT-A was eventually diagnosed with severe trigeminal neuralgia and had an operation.

2.1.10.2 Allergic Reactions

In rare cases patients may experience allergic reactions such as skin eruption and urticaria. Once I witnessed a case of skin eruption on the BOTOX® injection sites. The patient was injected two times at 6-month intervals and had no trouble after the first injection. However, just after the second

injection, skin eruption appeared on all injected areas. After treatment with steroids and antihistamines, the patient completely recovered from the eruption 1 week later (see Sect. 1.6.5).

2.1.10.3 Bruise

Bruise is one of the frequently seen adverse effects during the injection of BoNT-A for wrinkles. Even though bruise caused by the injection of BoNT-A is generally temporary and mild in severity, we should reduce the bruising as much as possible in order to reduce the social downtime.

Tip: 100 % Bruise Prevention

1. Perform subdermal or intradermal injections. Deep subcutaneous injections may unknowingly damage underlying deep vessels. Although intradermal injections are more painful than subcutaneous injections, they have the advantage of not causing bruising.

2. After completely removing makeup around the eyes, perform the procedure while closely watching the veins in the infraorbital and lateral side of the eyes. Since the large veins are well developed in these areas, large bruising may result from accidentally ruptured veins.

3. When you inject BoNT-A into the vertical medial subcanthal wrinkles, you may damage the angular vein. As periorbital skin is extremely thin, even a slightly deep injection may damage the vein. Moreover, the tissue in this area is very loose, so bleeding cannot be stopped spontaneously and may result in a large bruising, similar in nature to a hematoma. Therefore, it is absolutely necessary to make superficial injections in the medial subcanthal area.

4. Change needles frequently. A 30-gauge needle is very thin and is therefore easily blunted by repeat injections. Blunted needles can cause pain when it penetrates the skin and tend to make an abrupt deep insertion—potentially resulting in damage to blood vessels.

5. Apply gentle pressure with gauze for 5 min in case a blood vessel is

ruptured. Applying pressure is the best way to cope with bleeding.

6. Needle marks are also a type of tiny bruising. After the procedure, apply gentle pressure to all marks with gauze for 3–5 minutes.

7. Stop taking aspirin for 2 weeks and anticoagulants, including warfarin, for 1 week if possible. It is necessary to stop taking these medications for bruise prevention. If a short suspension is not possible, apply a topical anesthetic cream for 30 min, inject slowly, and apply pressure to the site for 3–5 min after the injection is complete.

8. Since topical anesthetic cream also has a vasoconstrictive effect, it would be better to use the topical anesthetic cream before the BoNT-A injections for bruise prevention.

9. If you actually want to fade away a bruise quickly, use a pulsed dye laser. They are especially effective for superficial bruises. Irradiation with 7.5 J at 595 nm using a V-beam Perfecta will cause bruises to decrease quickly.

2.1.10.4 Edema

Edema most frequently occurs when treating forehead wrinkles but also occasionally occurs when treating glabellar and periorbital wrinkles. There are marked individual differences in the degree of edema: some patients may experience severe edema, while for others it is barely noticeable. Occasionally, focal edema may occur such as in the eyelids or the center of the forehead near injected areas after glabellar wrinkle treatment. Some patients also complain about eyelid edema or chubby eyelids after periorbital wrinkle treatment.

Edema which follows BoNT-A treatment is thought to be a kind of insufficient lymphatic circulation in the paralyzed muscles as in the case with foot and lower leg edema produced during long flight. Ironically, this edema due to muscle paralysis is helpful for effacing fine static wrinkles and pores,

which may be regarded as “a double-edged sword.” In other words, an appropriate degree of secondary lymphedema caused by BoNT-A can produce a positive effect as is the case with “mesobotox,” while an excessive state results in eyelid edema (see Sect. 4.1).

Eyelid edema usually subsides after 2–4 weeks though it may take up to 2 months in some severe cases. As lymphatic edema occurs secondary to muscle paralysis, there are no methods for obtaining relief aside from physically massaging swollen eyes and forehead daily in case it persists. I have found that steroid therapy is not effective for patients with eyelid edema by BoNT-A injection because this edema is not caused by inflammation.

2.1.10.5 Heavy Feeling

Heavy feeling in the injection site is a frequent complaint given by nearly half of all patients who receive BoNT-A treatment for the first time in their life. This unnatural sensation is caused by muscle paralysis as opposed to paralysis of the sensory nerves. It usually subsides within 2–4 weeks although it is uncertain whether the feeling actually disappears or patients just become accustomed to the feeling.

2.1.10.6 Masklike Face

This indicates a face which cannot make natural facial expressions or a face which appears unnatural due to the excessive paralysis of facial expression muscles by BoNT-A. Patients are usually told that they lack facial expressions due to smiling without eyelid smile, alteration or unnatural expressions, and having scary eyes. Although this may not greatly affect most people, it can pose serious problems for public figures and celebrities who rely on facial expressions whenever they are before an audience. To avoid this problem, I advise injecting only half of the commonly used dose. Keep in mind, however, that smaller doses must be injected more frequently as the therapeutic effect will fade more quickly according to the dose–duration relationship.

Tip: Frequently Asked Questions (FAQ)

1. The BoNT-A was accidentally diluted with distilled water. Can it still be used?

BoNT-A which has been diluted with distilled water should retain similar efficacy. However, since this mixture may cause severe pain during the injection, BoNT-A should always be diluted with normal saline.

2. What should I do if I find a product with a broken vacuum?

It is very rare to find a product with a broken vacuum seal. Although it is not likely to affect efficacy, there is a small risk that the product may be contaminated by germs. Therefore, it is wise to return the product to the company in this situation.

3. Should we advise patients not to lie down for 4 h following the BoNT-A procedure?

Some physicians claim that it is necessary to avoid lying down for 4 h following the procedure to prevent ptosis. However, I do not make this recommendation as it does not seem to be based on evidence.

4. I have heard that there is an antitoxin for BoNT-A.

Although an antitoxin for BoNT-A does in fact exist, it is not effective in actual situations. After the injection, almost all BoNT-A enters the nerve branches at neuromuscular junction within 72 h. Once it enters the nerve branches, antitoxin is no longer effective.

5. I have a patient who complained about minimum effects on wrinkles 1–2 weeks after the BoNT-A injection. Is the patient a nonresponder to BoNT-A?

It is very unlikely that the patient is a secondary nonresponder with neutralizing antibodies. Overly insufficient dose for that patient is much more likely to be the actual cause. Appropriate dose of BoNT-A can vary two- or threefold depending on individuals because of difference in the degree of muscle development and individual susceptibility to the BoNT-A. Do not be disappointed if you observe no effects 1–2 weeks after an injection of BoNT-A and give a touch-up injection at half to two-thirds of the initial dose. Or the original patient’s concern is actually not the wrinkles that can be treated with BoNT-A injection. Infraorbital horizontal lines and static deep wrinkles are

such examples.

6. I accidentally injected 50 U into the forehead due to a dilution mistake. Is this safe?

Do not worry too much about this. The effect of BoNT-A on muscle paralysis increases according to the log dose–response curve. Once the BoNT-A is saturated at the neuromuscular junction, the effect is nearly the same even if you inject a much higher dose of BoNT-A than standard dose (see Sect. 1.3.5). Of course you have to endure the patient's complain such as the masklike face.

7. While injecting BoNT-A for the treatment of glabellar wrinkles, I accidentally injected BoNT-A directly into a blood vessel.

From time to time, we may find that we have injected BoNT-A directly into a blood vessel. Particularly, if we make an intravascular injection into the superior orbital artery or supratrochlear artery when injecting BoNT-A for the treatment of glabellar wrinkles, we can see the immediate spreading of reconstituted BoNT-A solution through the vessels toward the forehead. However, there is little cause for concern about systemic adverse effects since each injection typically contains only a small dose of 2 to 4 U.

8. Please provide a summary of post-procedure instructions for patients.

Do not vigorously rub the glabella and periorbital area where the BoNT-A is injected. Try to move your muscles around injection area for 2–4 h after the injection as this active movement will help absorb the BoNT-A into the neuromuscular junctions. If you make a frown or smile every time you recall this instruction, it will assist in your wrinkle treatment.

2.2 Regional Particulars

2.2.1 Lateral Canthal Rhytides

Effect (A), Adverse Effect (B), and Technique (B)

2.2.1.1 Anatomy

The orbicular oculi muscle encircling the eye is responsible for eye closure, and it is classified into two areas: the orbital portion and the palpebral portion. The palpebral portion is subclassified into the preseptal part and the pretarsal part (Fig. 2.15). The fibers of the orbital portion originate from the superior and inferior orbital edges inserted into the medial and lateral canthal ligaments, frontalis muscle, procerus muscle, corrugator supercilii muscle, and skin. For Koreans, the average width of the lateral portion of the orbicularis oculi is 3.1 cm from the lateral canthus. The lateral muscular band of the orbicularis oculi muscle is found in 54 % of Koreans [22].

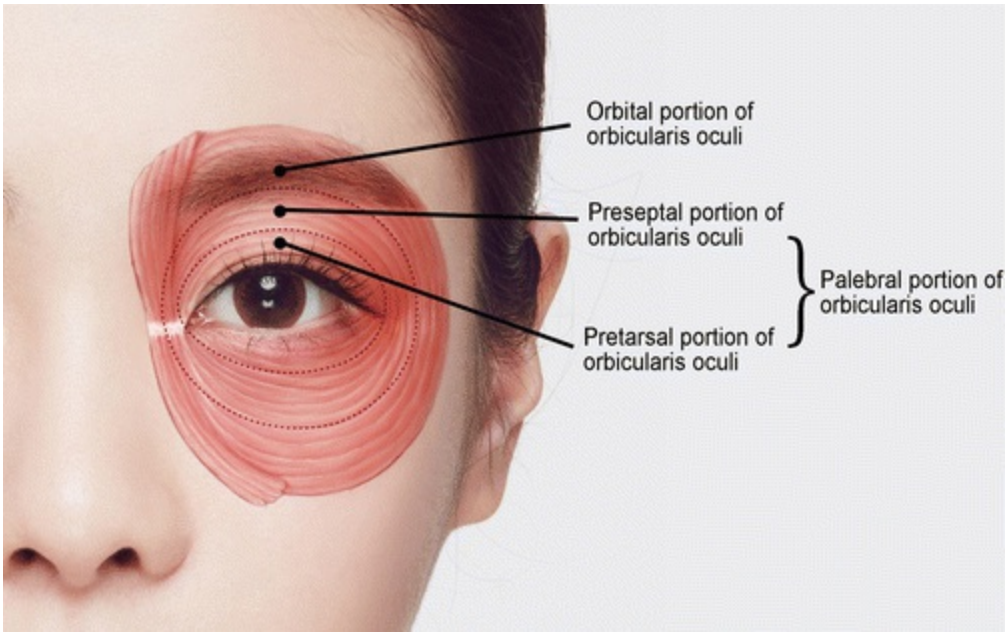


Fig. 2.15 Anatomy of orbicularis oculi muscle

The muscle fibers of the orbital portion close the eyelid and depress the eyebrows. They also contribute to facial expression wrinkles around the eyes (crow's feet, infraorbital wrinkles) especially while smiling. The muscle fibers of the palpebral portion consisting of preseptal and pretarsal parts lie in the outer portion of the orbital septum and tarsal plate, respectively. The muscle fibers of the palpebral part close the eyelids during unconscious blinking and make wrinkles around the medial canthus.

As orbicularis oculi encircles the eye, the direction of wrinkles caused by the orbicular oculi differs depending on areas. Facial expression wrinkles appear vertically to muscle fiber directions. Therefore, wrinkles are formed horizontally in the medial and lateral portion of the periorbital area where

muscle fibers run vertically, at a 30°–60° angle in the lateroinferior area and laterosuperior area, and vertically in the infraorbital area and the middle of the upper eyelid where muscle fibers run horizontally (Fig. 2.16).

Fig. 2.16 Direction of muscle fibers and wrinkles. Facial expression wrinkles appear vertically to the muscle fiber directions

To efface the lateral canthal rhytides, colloquially referred to as crow's feet, it is necessary to inject the BoNT-A into the muscle fibers of the orbital portion in the lateral part of the lateral canthus and inferiorly down to the upper cheek (zygoma). The pattern of lateral canthal rhytides, which differ from person to person, should be assessed before the treatment in order to deliver individualized treatment. Kane classified lateral canthal rhytides into four types: (1) full-fan type, full distribution of wrinkles from the upper eyelid to the upper cheek; (2) superior type, wrinkles of the upper eyelid skin

down to the lateral canthus; (3) inferior type, wrinkles of the lower eyelid/upper cheek; and (4) central type, central zone of wrinkles at the lateral canthus only [23]. However, in regard to Koreans specifically, I take just two classifications into account, (1) full-fan type and (2) superior type (Fig. 2.17), because 81 % of Koreans show full-fan type according to the clinical study on lateral canthal line pattern in Koreans [21]. Since malar fat pads in the zygoma are well developed in middle-aged Korean women, therefore wrinkles are not well formed in the upper cheek due to the support by malar fat pad. This most closely falls under the superior-type classification. Only small dose of BoNT-A is required in this case due to the scanty line characteristics in the infraorbital area.

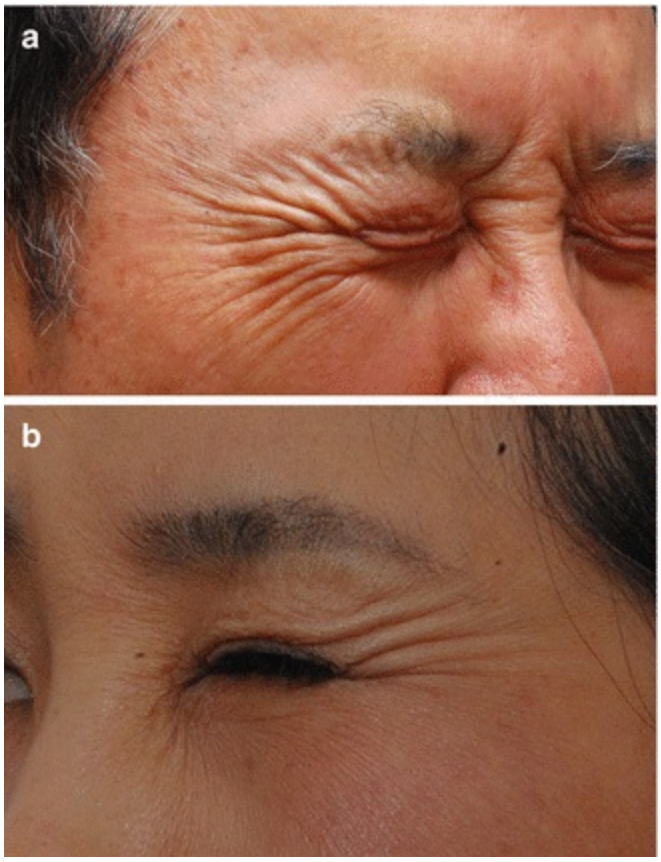


Fig. 2.17 Clinical types of lateral canthal rhytides. (**a**) full-fan type. (**b**) superior type

Among the lateral canthal rhytides, there are lines from the lateral canthus to infraorbital region at the upper cheek which run downward laterally at a 30–45° angle from the horizontal plane. Since these lines are formed not only by the orbicularis oculi but also through the shifting of the upper cheek skin

by the zygomaticus muscles when smiling, approximately half of them are responsive to BoNT-A treatment. A typical example of lines induced by the zygomaticus muscles is shown well in actor George Clooney. Here, I would like to suggest a new name, “zygomatic lines,” to describe this type of wrinkles which run diagonally from the lateral canthus and infraorbital area toward the mid and lateral cheeks. Great care should be taken not to give deep injections into the zygomaticus major muscle and not to give large dose of BoNT-A even though superficially injected. Because the mouth corner cannot be elevated by zygomaticus muscle paralysis when smiling.

2.2.1.2 Pretreatment Assessment

While there are standard injection techniques, treatment must be individualized according to various aspects of the patient: lateral canthal line patterns, skin elasticity and infraorbital fat bulging, malar fat pads, and wrinkle severity. In case of decreased skin elasticity, the “snap test” is useful to check for infraorbital skin elasticity. After holding the patient’s palpebral skin with your index and thumb fingers, gently pull it downward and laterally and release it quickly. If the patient has normal elasticity, the skin should return to its original position before blinking. If the pulled skin returns to its original position after blinking or after a few seconds, it suggests a decrease in skin elasticity. Even though decreased skin elasticity in infraorbital area is not a big problem in Asians, patients over 50s with fine wrinkles and obvious photoaged skin or those with a past history of surgical resection procedure for infraorbital wrinkles should be regarded as high-risk group and demand extra care. Ectropion or scleral show may occur in these high-risk patients with decreased skin elasticity if the injection sites are very close to the eyes. However, physicians should pay more attention to concomitant excessive infraorbital fat bulging in Asian patients with decreased skin elasticity because dark circles may be exacerbated by drooping of the infraorbital fat bulging after BoNT-A injections only in the lateral canthal area. Physicians should reduce the dose of the BoNT-A to avoid any exacerbation of infraorbital fat bulging in patients with decreased skin elasticity. It should be also mentioned to these patients before treatment that a filler injection should be necessary in the infraorbital sunken area to improve the dark circle if this adverse effect occurs.

Malar fat pads at the zygoma is also considered importantly when treating BoNT-A for lateral canthal rhytides in Asians. Patients with prominent malar

fat pads at the zygoma especially below the lateral canthal area tend to complain about the prominence of their zygoma while smiling after BoNT-A treatment. Since Asians dislike a prominent zygoma, therefore it is necessary to minimize BoNT-A doses in the zygomatic area.

At age fifty or above, the effectiveness of BoNT-A decreases due to an increase in static wrinkles. Filler is useful in static wrinkles with deep furrows, while dermabrasion or fractional laser is useful for static wrinkles without deep furrows. It is necessary to explain prior to treatment that adjunctive procedures may be required. Though it is generally less effective, at least partial effacement of static wrinkles such as fine wrinkles can be obtained through BoNT-A treatment (see Fig. 2.3 and Sect. 2.2). Moreover, static wrinkles generally respond well to the preventative effects of repeated injections.

It is also necessary to check in advance whether the patient has xerophthalmia when treating periorbital wrinkles with BoNT-A. Xerophthalmia may be exacerbated due to the reduction of an unconscious blinking produced by the BoNT-A treatment. The BoNT-A should not be injected into the areas close to the eyes in patients with xerophthalmia even though this may lessen the effect.

2.2.1.3 Injection Techniques (Fig. 2.18)

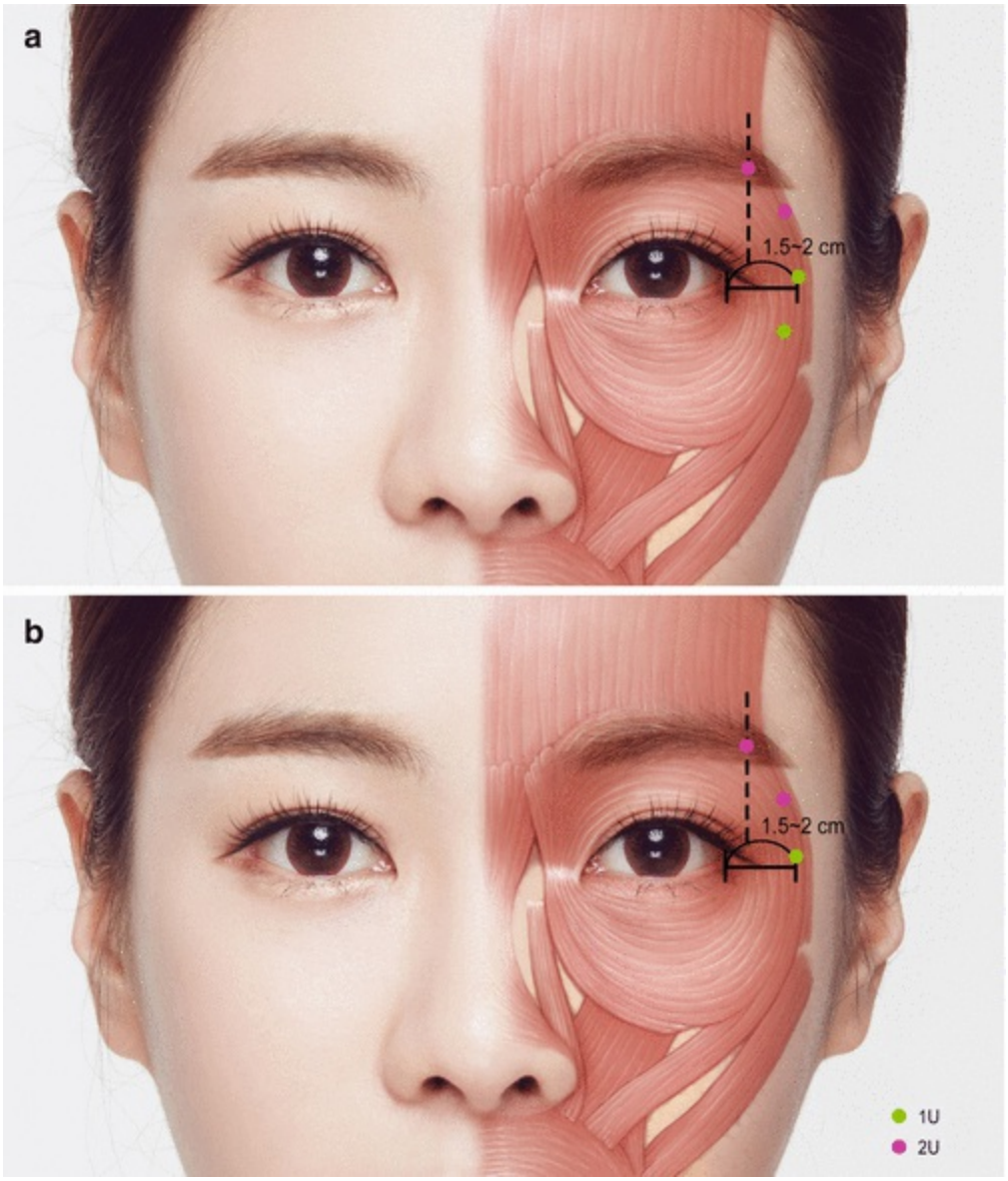


Fig. 2.18 Injection points for lateral canthal rhytides. (**a**) standard type. (**b**) superior type

For the treatment of the lateral canthal rhytides, it is necessary to determine the reference point at 1.5 to 2 cm lateral to the lateral canthus. After injecting 2 U at the reference point, further injections are performed along the orbital rim arc as follows: 2 U into the point 0.5 cm medial and 1 cm superior to the reference point, 2 U into the point 1 cm medial and 2 cm superior to the reference point, and 1 U into the point 0.5 cm medial and 1 cm inferior to the reference point (Fig. 2.18a). The total dosage is 7 U per side for the standard technique. As the average width of the orbicularis oculi in Korean is 3.1 cm from the lateral canthus, it is not necessary to inject outside

3 cm from the lateral canthus. Note, however, that these injection techniques are not fixed and can vary according to the wrinkle patterns, wrinkle severity, hypertrophied malar fat pad at the zygoma, and skin elasticity. If the wrinkle pattern is the superior type, you can inject a total of 5 U only in the upper part including reference point while skipping the lower injection point (Fig. 2.18b). If the patient also shows prominent malar fat pad at the zygoma with the superior wrinkle type, you should reduce the dose to 3–4 U in order to avoid the prominence of their zygoma. When injecting BoNT-A for the treatment of lateral canthal rhytides, additional injection of BoNT-A with 1–2 U at the infraorbital area can prevent the new wrinkle formation in the infraorbital area produced by the botulinum-rebalancing phenomenon (Fig. 2.18c).

To prevent BoNT-A diffusion toward the eyes, the direction of the needle should always be positioned outward. Press the lateral area of the patient's orbital margin with your nondominant thumb during injections to prevent diffusion toward the eye (Fig. 2.19).

Fig. 2.19 The needle should always be directed outward from the orbital rim. Press the lateral area of the patient's orbital rim with your nondominant thumb during injections

Regarding the depth of injection, superficial injections such as subdermal injection or intradermal injection are necessary considering the fact that the

orbicularis oculi, a component of the superficial musculoaponeurotic system (SMAS), is located just below the skin. When a deep injection is accidentally made at the lateral part, the BoNT-A would be injected into the temporalis muscle.

2.2.1.4 Injection Dosage

For full-fan type, a 4–8 U is required while 3–5 U is sufficient for superior type.

2.2.1.5 Adverse Effects

Bruise

One of the most common adverse effects is bruise. Large vessels around the periorbital area are susceptible to rupture. Specifically, two large veins, the medial zygomaticotemporal vein (MZTV) and the periorbital vein (Fig. 2.20), should be avoided with great care. The MZTV, the so-called sentinel vein, receives blood flow drained from the branches in the forehead, parietal, and temporal areas. The degree of sentinel vein development varies according to the individual. As one ages, sentinel vein running vertically in the lateral canthal area becomes more visible. The periorbital vein runs horizontally along the inside of the orbital rim between the upper and lower palpebral junctions, connecting the angular vein inward and the sentinel vein outward.

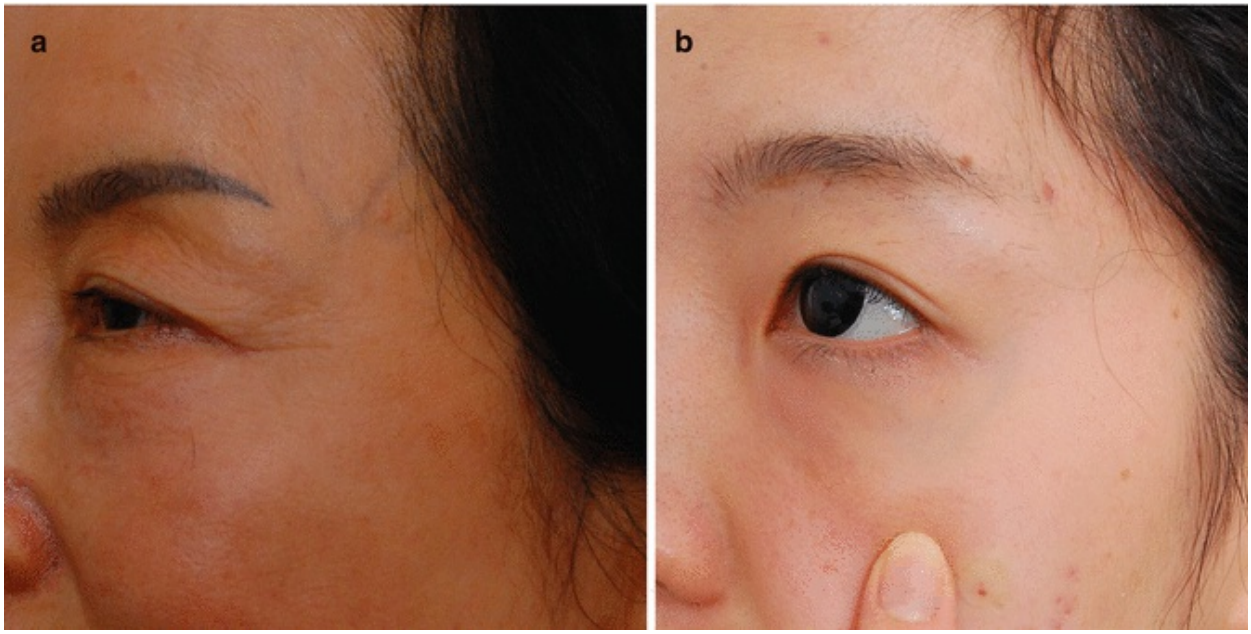


Fig. 2.20 Important veins to be mindful when injecting botulinum toxin into the periorbital area. (**a**) Sentinel vein. (**b**) Inferior palpebral vein

To prevent bruise, subdermal or intradermal injections may be necessary. Press gently for 5 min with gauze in case of vessel rupture during the procedure. As needle marks are a kind of tiny bruise, press all of them for about 3–5 min gently with gauze after the procedure (see Sect. 2.11.6).

Alteration of Facial Expressions

This is the most serious adverse effect. If the wrinkles in the lateral canthal area are not visible at all by BoNT-A injection when smiling, the masklike face or "smile without smiling" can occur. It even appears scary while smiling in some Asian patients with Northern facial type who have small eye aperture and upper eyelids without supratarsal crease. To prevent this, you should inject a small dose (1 U) of BoNT-A in the reference point at least 2 cm laterally to the lateral canthus.

Patients with prominent malar fat pads at the zygoma, especially below the lateral canthal area, are likely to experience a much more prominent zygoma when smiling after the treatment. Since Asians dislike a prominent zygoma, it is not a desirable feature. Therefore, it is absolutely necessary to prevent such a result. We can hypothesize the causes of this adverse effect in several ways. While smiling, muscle fibers in the lateral orbicular oculi pull the malar fat pads at the zygoma upward to smooth out the contour. However, this is disturbed by BoNT-A injection at the lateral canthal area, which contributes to prominence of the zygoma. In addition, the zygomaticus major and minor muscle, which pushes the zygomatic soft tissues upward, becomes more active due to the botulinum-rebalancing phenomenon. This dynamic gives the appearance of zygomatic soft tissues sticking together. The insufficient lymphatic circulation and lymphatic edema produced by less movement of the orbicularis oculi muscle would be another cause of this adverse effect. To prevent a change of facial expressions in patients with prominent malar fat pads at the zygoma, it is necessary to reduce the administered amount of BoNT-A to 0.5–1 U in the reference point lateral to the lateral canthus. Further, it is required either not to inject or inject with a minimal amount of BoNT-A under 0.5 U in inferior point.

Diplopia

Rarely, BoNT-A may diffuse and affect the extraocular muscles during the treatment for lateral canthal rhytides with BoNT-A. Theoretically speaking, extraocular muscles located far from the injection sites should not be affected by BoNT-A, but occasionally the BoNT-A diffuses toward the lateral rectus muscle. In such cases diplopia usually occurs in only one side. If one side of the lateral rectus is paralyzed, both eyes cannot focus symmetrically when focusing medially. In case of a paralyzed lateral rectus muscle, the medial rectus becomes hyperactive, causing the pupil to shift toward the medial canthus. A prism lens test can help confirm the diagnosis; however, if the paralysis is not severe enough, even ophthalmologists may struggle to diagnose the condition.

If diplopia occurs, patients may experience double vision and/or suffer from headaches and nausea. This presents obvious difficulties in one's daily life and makes driving or reading virtually impossible. If diplopia occurs after BoNT-A treatment, the patient must see an ophthalmologist for more advanced eye examination. The patient must inform the ophthalmologist of the BoNT-A treatment. Glasses with prism lenses may be recommended in severe cases. Ensure the patient is aware that these complications often go away within 1 month, and only in very rare cases exceed 2–3 months.

Ptosis
BoNT-A injection for lateral canthal rhytides can also induce eyelid ptosis under a few circumstances: too large a dose, injected too near to the bony orbital rim, may paralyze the levator palpebrae superioris muscle by diffusion (see Sect. 2.18.5).

Xerophthalmia
Weakening of muscle fibers in the palpebral portion of the orbicularis oculi by BoNT-A may reduce involuntary blinking and exacerbating xerophthalmia. Xerophthalmia may also be induced when the BoNT-A is injected in the superolateral portion of the lateral canthus or the lacrimal glands nearby. Since neurotransmitters of lacrimal glands are the same acetylcholine as in neuromuscular junction, therefore lacrimal secretion is decreased by BoNT-A. A Schirmer test, performed by an ophthalmologist, can easily diagnose xerophthalmia. Patients with the condition, particularly the elderly or those who use contact lenses, may complain about eye

congestion and tightness. The BoNT-A should not be injected into the areas close to the eyes in patients with xerophthalmia. Artificial tear drops or normal saline solution should be frequently administered in cases with severe xerophthalmia.

2.2.1.6 Photography

For best results, the patient should be smiling. If this is difficult, ask for winking to the best of their abilities. Take photographs in various positions: a full front view with a frown and with glabellar lines as well as a lateral view at a 45° angle while winking (Fig. 2.21).

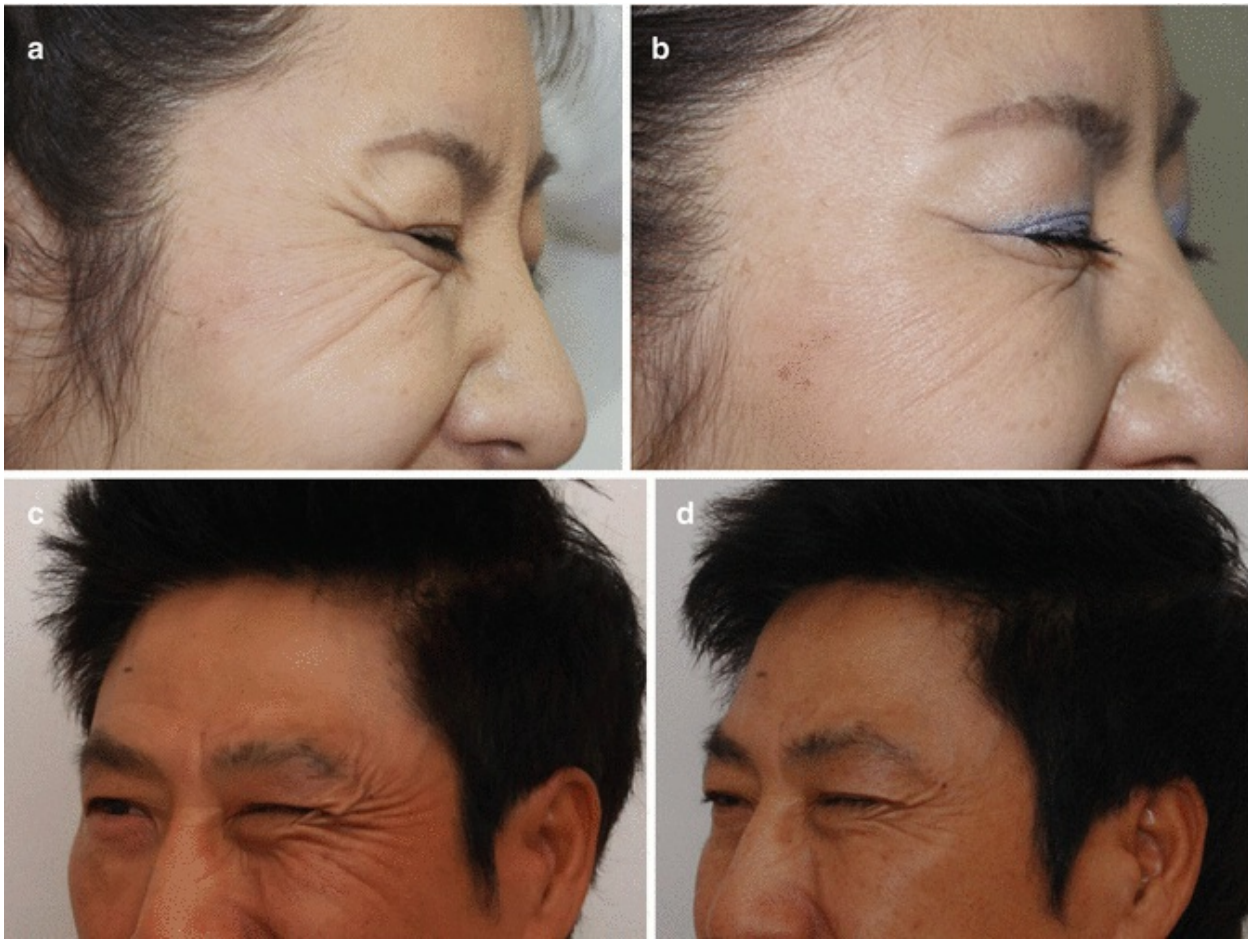


Fig. 2.21 Lateral canthal rhytides: (**a**, **c**) before and (**b**, **d**) 2 weeks after 7 U injection of BOTOX® per side

Tip: Who Is the Highest-Risk Patient for the Treatment of Crow's Feet with BoNT-A?

Patients in their late 40s with nonelastic skin and significant infraorbital fat bulging and malar fat pads at the zygoma have the highest risk from BoNT-A injection for the treatment of crow's feet. If you treat crow's feet in these patients with standard technique suing BoNT-A, they typically reveal a weird facial expression, nearly "crying face" while smiling. They may smile without periorbital lines, with more prominent infraorbital fat bulging and more prominent zygoma. It may be better not to treat wrinkles in such a patient. If you really want to treat these patients with BoNT-A, read carefully the relevant part in this book and then you can come to find the answer.

2.2.2 Eyelid Ptosis

Effect (A), Adverse Effect (C), and Technique (C)

Lid ptosis is a condition wherein the eyelid droops due to the weakness of levator palpebrae superioris muscle partially covering the iris and pupil and giving the impression of drowsiness and fatigue. Causes of a weakening of the levator palpebrae superioris muscle are either a congenital origin or a kind of aging process. Sufferers of ptosis rely on the frontalis muscle to open the eyes resulting in an aged look with prominent forehead wrinkles and sunken upper eyelids. Surgery is required to strengthen the weakened muscle; however, mild cases can be improved with BoNT-A injection to some extent (Fig. 2.22).

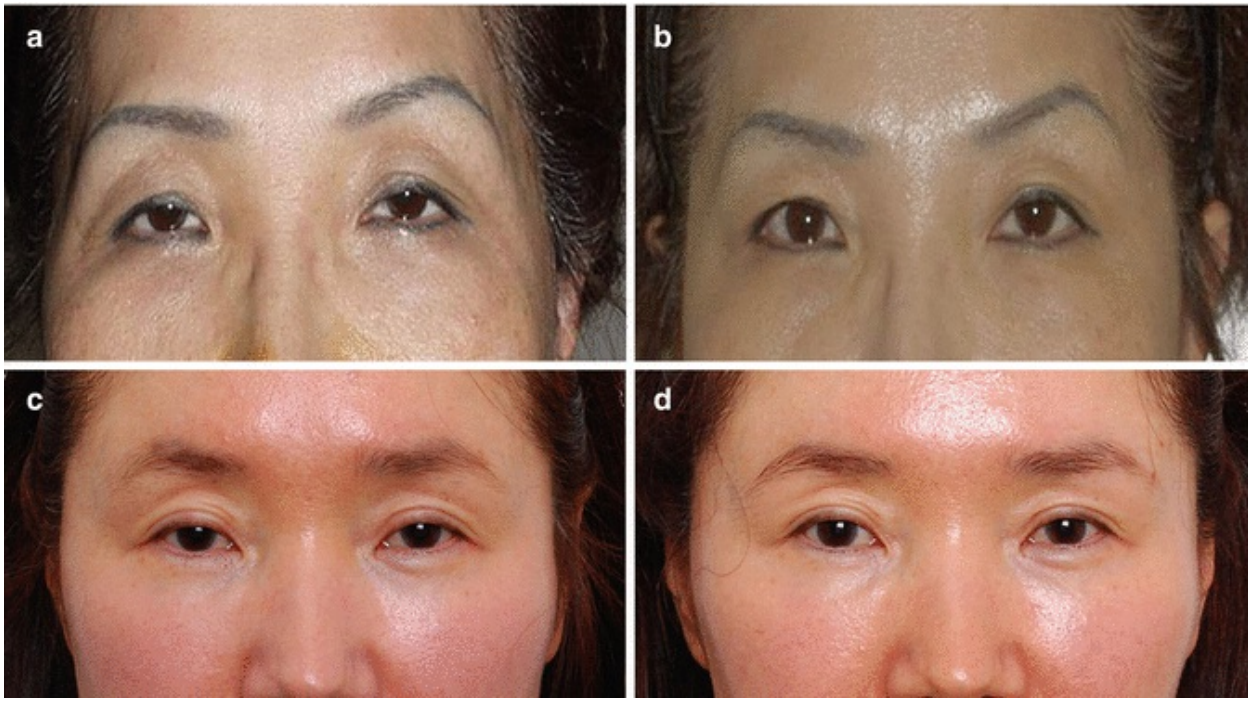


Fig. 2.22 Eyelid ptosis: (**a, c**) before and (**b**, **d**) 2 weeks after 0.5 U injection of BOTOX® per point

If we inject BoNT-A into the orbital portion and the pretarsal part of the orbicularis oculi and glabellar muscles for the treatment of blepharospasm, a widening of the eyes becomes apparent along with recovery of blepharospasm due to the hyperactivity of the levator palpebrae superioris and the Müller muscle by botulinum-rebalancing phenomenon (Fig. 2.23). Likewise, injection of BoNT-A into pretarsal part of the orbicularis oculi muscle also induces widening of eye-opening in patients with mild eyelid ptosis by leveraging the hyperactivity of the levator palpebrae superioris and the Müller muscle.

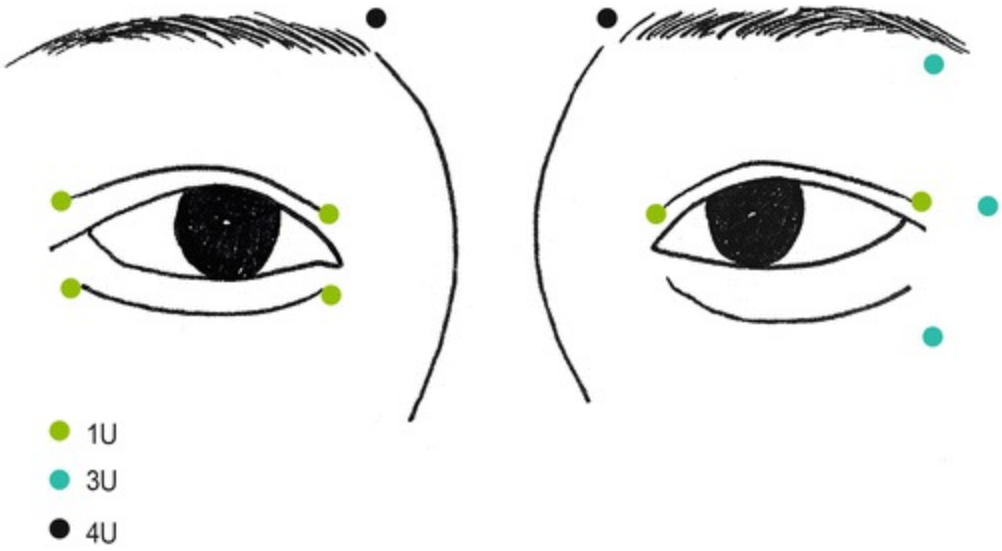


Fig. 2.23 Injection points for blepharospasm

We should verify whether the muscle function is well preserved in the pre-assessment. Ask the patients to forcibly open their eyes; only those able to reveal their entire cornea are suitable candidates. This indication is contraindicated to patients with xerophthalmia because this may reduce involuntary blinking, thereby exacerbating xerophthalmia. In addition to xerophthalmia, soap water may enter the eye during washing the face due to incompetence of eye-closing if the dose of BoNT-A is too much.

2.2.2.1 Injection Techniques

Inject subdermally 0.5–1 U into the extreme medial and lateral regions of pretarsal part of orbicularis oculi muscle just above the eyelash line (Fig. 2.24). To prevent eyelid ptosis, the needle must be directed downward and outward from the eyeball.

Fig. 2.24 Injection points for ptosis

2.2.3 Upper Palpebral Lines

Effect (B), Adverse Effect (C), and Technique (C)

After BoNT-A treatment for the periorbital and glabellar wrinkles, we can see a marked improvement of dynamic wrinkles around the eyes. However, there is only one area left without improvement of dynamic wrinkles: the upper eyelid below the eyebrow. This area occasionally has more dynamic wrinkles after BoNT-A treatment due to the botulinum rebalancing. The wrinkles at the upper eyelid below the eyebrow are used to be considered an absolute contraindication regarding BoNT-A treatment due to the high risk of eyelid ptosis. However, it is possible to treat upper eyelid wrinkles by carefully administering a highly diluted BoNT-A (Fig. 2.25). No more than 0.5 U per side is subdermally injected at 5–10 points with the concentration of 0.5 U/0.1 ml (Fig. 2.26). Extreme caution must be taken not to inject deeply as the chances for eyelid ptosis are high. Considering the risk of ptosis, high likelihood to bruise, and anesthesia problem, however, it would be better not to recommend this indication to patients if possible.

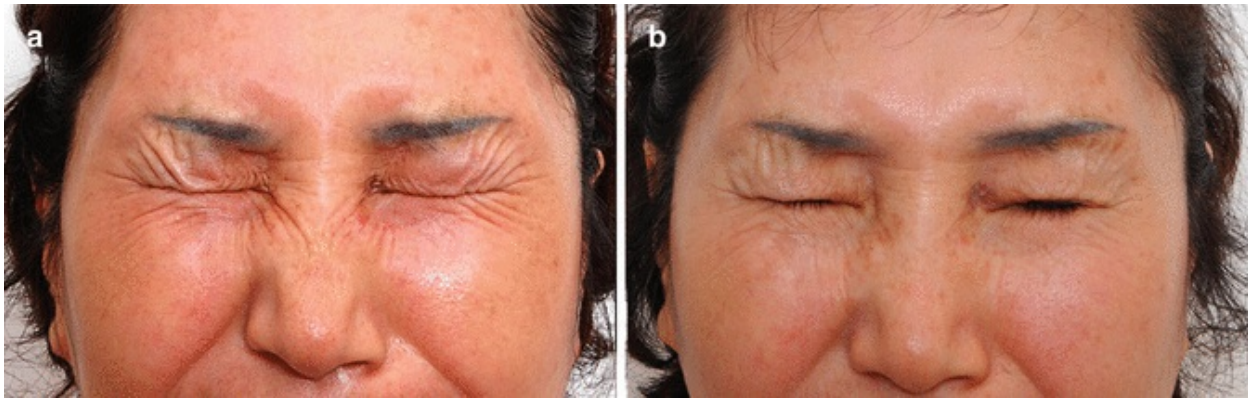


Fig. 2.25 Upper palpebral lines: (**a**) before and (**b**) 2 weeks after 1 U injection of BOTOX® per side

Fig. 2.26 Injection points for upper palpebral lines

2.2.4 Infraorbital Wrinkles

Effect (A), Adverse Effect (C), and Technique (B)

Infraorbital wrinkles can be subclassified into three types: horizontal infraorbital wrinkles, medial subcanthal wrinkles, and lateral subcanthal wrinkles. Horizontal infraorbital wrinkles are formed by a shifting of zygomatic soft tissue while smiling caused by a contraction of the zygomaticus major and minor muscles responsible for elevating the corners of the mouth. Therefore, as long as the zygomaticus muscles move, it cannot be improved with BoNT-A injection into the infraorbital area. In contrast, vertical wrinkles below the medial canthus, called “medial subcanthal wrinkles” formed by the orbicularis oculi, respond well to BoNT-A therapy (Fig. 2.27).

After injecting BoNT-A for treatment of lateral canthal rhytides, medial

subcanthal wrinkles are more exaggerated due to botulinum rebalancing. Wrinkles are pushed to the infraorbital area particularly toward the medial side. Likewise, if we inject BoNT-A only into the medial and lateral subcanthal area, vertical lines appear in the central part of the infraorbital area due to botulinum rebalancing. Thus, during the initial treatment for the lateral canthal rhytides, it is better to concomitantly inject 1–2 U at the junction between the preseptal part and orbital portion of the orbicularis oculi muscle along the orbital rim arc from the medial to lateral canthus in order to prevent the new wrinkle formation in the infraorbital area (Fig. 2.28c). As over administering the BoNT-A in the medial subcanthal area is likely to produce rather unnatural facial expressions without any wrinkles at all, it is better to inject only 0.5 U at initial treatment session.

Lateral subcanthal wrinkles which run short at a 45° angle inferolaterally from the lateral canthus can give a charming look when smiling (Fig. 2.27). Since this is often observed even in teenagers, we believe it results from the development of the orbicularis oculi rather than aging process. However, people may falsely contribute this to aging, especially when lateral subcanthal wrinkles mingle with increased lateral canthal rhytides. Subdermal injections of 1 U BoNT-A with concentration of 2 U/0.1 ml would efface these wrinkles (Fig. 2.28). After the injection of BoNT-A for lateral subcanthal wrinkles, however, some patients may complain about slightly odd or unnatural facial expressions or tightness in the eyes for some time.

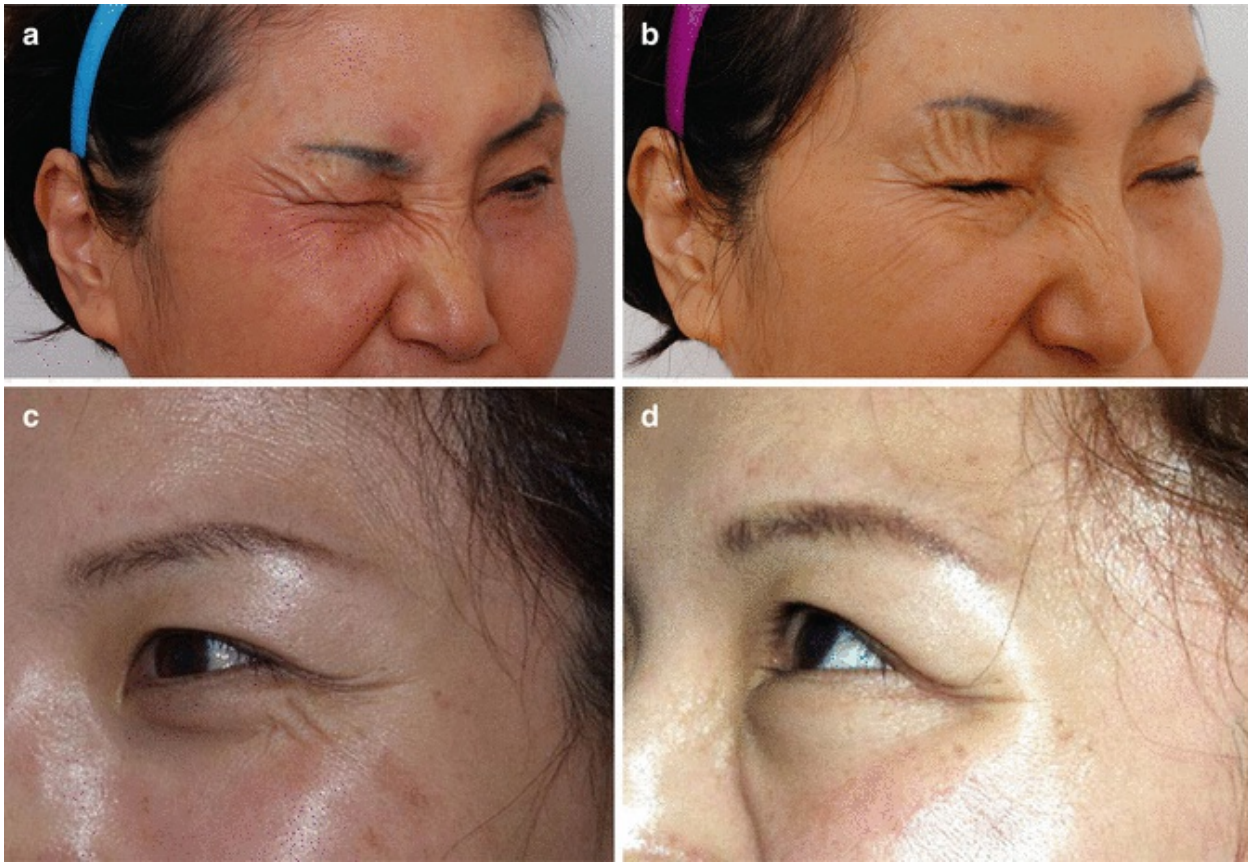


Fig. 2.27 Infraorbital wrinkles: (**a**, **c**) before and (**b**, **d**) 2 weeks after 1 U injection of BOTOX® per side. (**a**, **b**) Medial subcanthal wrinkles. (**c**, **d**) Lateral subcanthal wrinkles

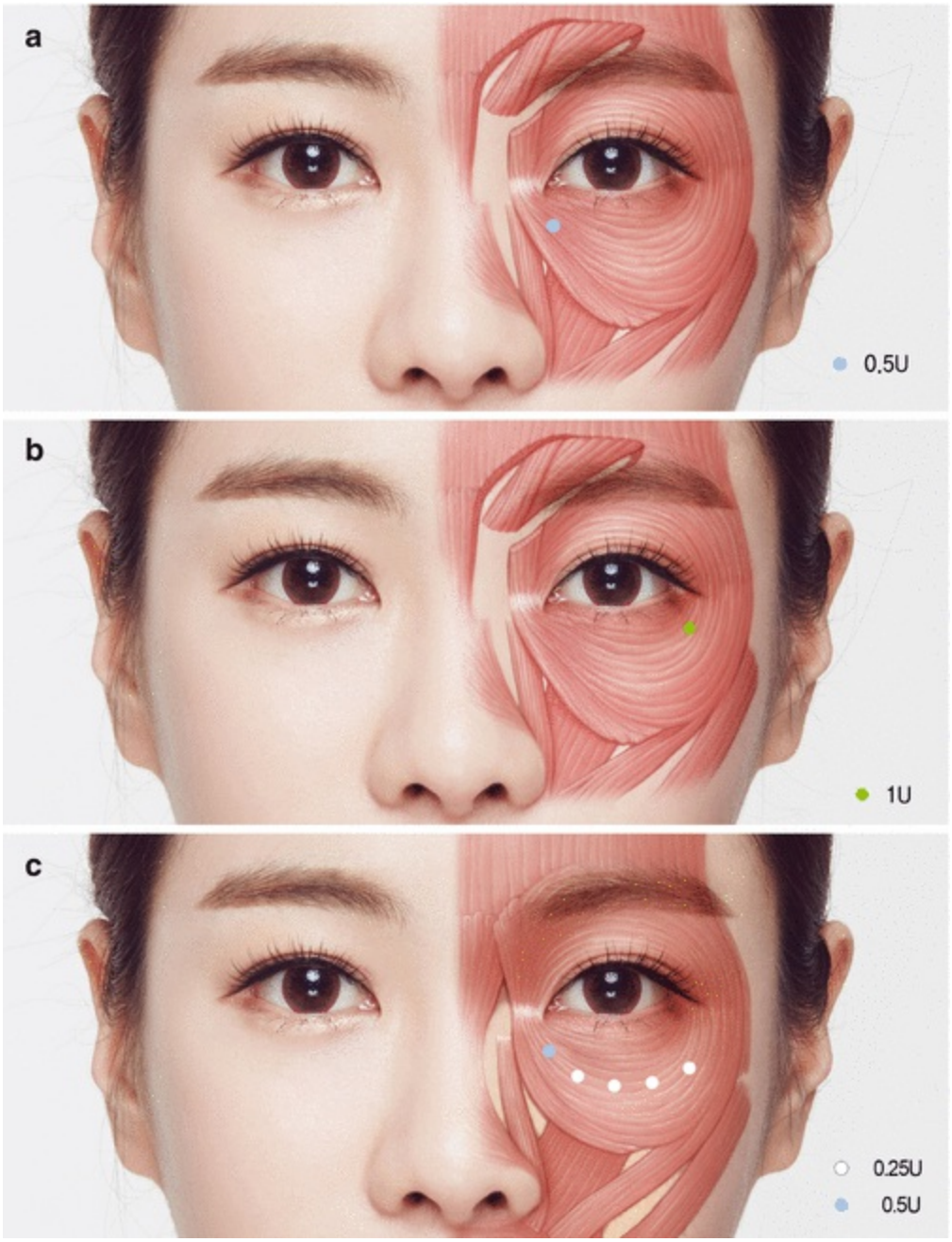


Fig. 2.28 Injection points. (**a**) Medial subcanthal wrinkles. (**b**) Lateral subcanthal wrinkles. (**c**) Infraorbital wrinkles

When treating infraorbital wrinkles, excessive BoNT-A administration or exceedingly deep injections may affect the levator labii superioris. This may cause drooping of the upper lip or an abnormal smile. Overdosage of the BoNT-A may also efface the hypertrophic pretarsal roll and expose the white sclera (scleral show), revealing scary look. Therefore, the total dose of

BoNT-A injected into the infraorbital area should not exceed 2 U. We should also be very cautious about ectropion or exaggeration of the infraorbital fat bulging which is much more likely to occur in patients with decreased skin elasticity.

You should carefully perform superficial injections into medial canthal wrinkles because deep injection may damage the angular vein. As the tissue in this area is relatively loose, bleeding does not stop well spontaneously, which results in hematoma. If you suddenly notice bulging near the medial canthus after injection, you should assume angular vein rupture and press firmly over the site for at least 5 minutes.

2.2.5 Horizontal Forehead Lines

Effect (A), Adverse Effect (C), and Technique (C)

While the recommended dose for forehead lines in American women was 10–20 U from consensus recommendations in 2004, this was reduced to 6–15 U in 2008, reflecting a desire to retain more natural facial expressions [16]. However, the appropriate dose for Asian women is only 2–6 U, a quite lower than Caucasians' recommendations (Table 2.2).

The difference in BoNT-A doses for forehead lines between the Asian and Caucasian is likely due to genetic differences in forehead length. Even though there are no articles comparing the forehead length between two races, Caucasians tend to have wider foreheads than that of Asians based on data from some papers related with the forehead. Ascher et al. in France recommend injecting the BoNT-A for the treatment of forehead lines 4 cm above the eyebrow which is regarded to be approximately the midpoint of the forehead in Caucasians [24]. Oszoy et al. insisted different technique of BoNT-A for the treatment of forehead lines according to the forehead length. Patients with a vertical forehead length exceeding 70 mm were regarded as having a wide forehead. On the other hand, individuals with a vertical forehead length of less than 60 mm were regarded as having a narrow forehead [25]. But vertical forehead length of 6 cm is not a narrow forehead from the Korean viewpoint. The fact that hair removal laser for widening the narrow forehead is unique laser procedure in Asia compared with Caucasian seems to support the narrower forehead in Asians. Wide foreheads tend to have larger muscles, which means that a larger dose of BoNT-A would be necessary for Caucasians.

In addition to genetic differences in forehead length, cultural differences

related with facial expression also differ between Asians and Caucasians. According to one paper analyzing the facial expressions by videotaping, Caucasians tend to use their upper facial expression muscles more than Asians up to 30 % [13] Thus, higher doses are generally necessary in Caucasians with more active facial expressions compared with Asians.

Tip: President's Forehead Wrinkles

Patients with congenital ptosis may exhibit forehead wrinkles from childhood because they use their frontalis muscles to elevate their upper eyelids. Additionally, while not technically full ptosis, there are people who open their eyes using their frontalis muscles. When a standard dose of BoNT-A is used for the treatment of forehead wrinkles in such patients, be aware of the possibility of exacerbation of ptosis as well as eyebrow drooping. A good example of such patients is the late Korean president Roh Moo-hyun.

In 2002, while campaigning for the presidency, someone suggested to him that he should get BoNT-A injection for his forehead wrinkles. Mr. Roh replied that he had actually undergone it already and that unfortunately he suffered from eyelid edema as an adverse effect of BoNT-A without any effects on forehead wrinkles. The exchange was picked up in the media, driving public concern about BoNT-A. In fact, Allergan Korea, the Korean distributor of BOTOX®, stated publicly that what Mr. Roh used was in fact Dysport®, different product from BOTOX®. This brought about positive effect to introduce BoNT-A treatment to general people in Korea even though the news focused on negative aspects of BoNT-A treatment.

In reality, it would not have mattered which product he used, neither would have worked. The forehead wrinkles of patients with eyelid ptosis are usually deep furrows like a scar. Therefore, the BoNT-A alone would likely not solve the problem. On the contrary patients would suffer from difficulties to open their eyes.

As a strategy for the treatment of forehead wrinkles in these patients with ptosis, lower dose of BoNT-A should be administered in order to maintain the function of frontalis muscle. In addition, it is necessary to use fillers in combination with BoNT-A. Especially multiple intradermal injection of hyaluronic acid filler, the so-called hydrolifting, would be helpful to improve both the dynamic and static wrinkles at the forehead in these patients to some extent. Even though static wrinkles will not disappear completely, the expression wrinkles to which BoNT-A cannot be administered with full dose

would be improved to some extent by this “hydrolifting” technique due to increased skin elasticity. Please remember that our goal of BoNT-A treatment is not 100 % effacement of wrinkles, but rather a happy life for our patients.

2.2.5.1 Anatomy (Fig. 2.14)

The frontalis muscle, which causes forehead horizontal lines, originates from the galea aponeurotica near the coronal suture and inserts into the superciliary ridge of the frontal bone and muscle fibers of the procerus, the corrugators supercilii, and the orbicularis oculi muscle. The muscle runs not vertically but rather inferomedially from the aponeurosis. From 3.5 cm over the eyebrow ridge, it bifurcates like a sunken V shape, and its superomedial portion is comprised of the aponeurosis rather than muscle fibers. Therefore, only a small dose of BoNT-A is required for the V-shaped sunken area of the frontalis muscle.

The frontalis muscle is the only facial expression muscles that elevate the eyebrows. In this sense, the muscle plays an important role in facial expressions. As one ages, the eyebrow droops and the eyelid skin becomes lax, which results in a narrower eyelid aperture (opening). To compensate this the frontalis muscle is activated, so that elevating the eyebrows and fully opening the eyes become possible. If the frontalis muscle is entirely paralyzed with BoNT-A, such compensation becomes impossible and drooping becomes apparent, giving an aged and gloomy look. This is one of the most important adverse effects we should be cautious about when treating wrinkles with BoNT-A.

2.2.5.2 Pretreatment Assessment

Firstly, consider the age and sex of the patient. Eyebrow drooping usually does not appear until a patient reaches their 30s and becomes especially apparent from age 40s and onward. As muscles tend to be more developed in males than females, we may use up to 20–30 % more BoNT-A in males, although this is not absolute.

Secondly, carefully observe the forehead width and muscle movements of the forehead. Muscle volume varies depending on the width and this may affect the doses and injection sites. If the distance from the patient’s eyebrow to the hairline is over 6 cm, 20–30 % more dose than standard dose may be required. This may also be the case in more expressive individuals that have

more developed forehead muscles.

Thirdly, gauge the severity of static and dynamic wrinkles. Among static wrinkles, fine wrinkles can be improved by the BoNT-A to a certain extent. However, the patient should be made aware that deeper wrinkles will likely require fillers in addition to BoNT-A injections. Since particularly fine wrinkles in patients in their 20s to early 40s are not yet scarified under the dermis, administering just the BoNT-A in such cases could result in marked improvement of fine wrinkles even to an extent the patients' forehead is glistening (see Fig. 2.3).

Lastly, to be fully prepared for any adverse effects, the following should be thoroughly examined: ptosis, eyebrow drooping, blepharochalasis, upper eyelid swelling, and frontalis muscle activation when opening the eyes either congenitally or by acquired form. It may be easier to determine blepharochalasis in a patient with supratarsal crease over those without supratarsal crease. In the latter case, directly pulling the lateral hooding upward can reveal whether the patient has originally small eye aperture or small eyes caused by blepharochalasis or lateral hooding.

Tip: High-Risk Group Screening for the Treatment of Forehead Wrinkles with BoNT-A

1. Individuals in their late 40s above
2. Individuals with ptosis
3. Individuals with blepharochalasis or lateral hooding
4. Individuals using their frontalis muscle to elevate eyebrows when opening eyes (Fig. 2.29)
5. Individuals who show exacerbation of forehead wrinkles when opening the eyes or those that exhibit difficulty in opening the eyes when pressing the forehead above the eyebrows
6. Individuals with thick and edematous eyelids

7. Males in their 40s above without supratarsal crease

2.2.5.3 Injection Techniques (Fig. 2.30)

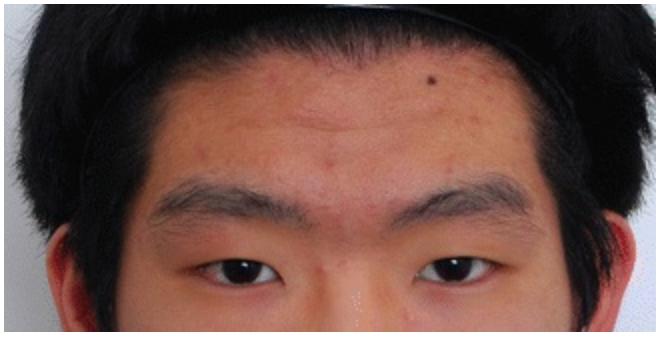


Fig. 2.29 16-year-old individuals who open their eyes with their frontalis muscles

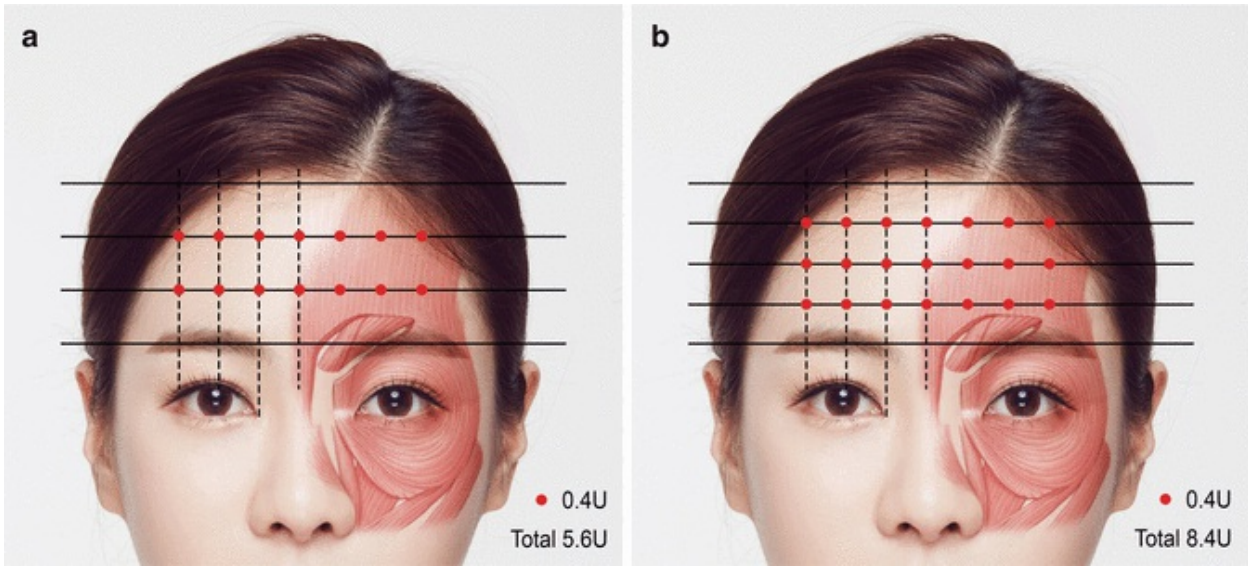


Fig. 2.30 Injection points for forehead wrinkles. (**a**) Standard type. (**b**) Wide forehead

As conditions and severity vary from patient to patient, treatment should be individualized when treating forehead wrinkles with BoNT-A. It is necessary to check first the width of the patient's forehead. When assessing a patient with standard forehead width (under 6 cm from the apex of the eyebrows to the hairline), two horizontal lines, dividing the forehead height into three parts, are drawn as reference lines. Next, two midpupillary lines are

adapted as the vertical reference lines, and we draw two more imaginary vertical lines (one is medial canthal line and another is lateral canthal line) 1.5–2 cm apart from the midpupillary lines. Seven vertical lines including median line are now drawn. By crossing two horizontal lines and seven vertical lines, we can make 14 different intersection points and inject into these points 0.4 U of BoNT-A each, totaling 5.6 U. In case of a narrow forehead (less than 4 cm from the apex of the eyebrows to the hairline), we inject 0.3 U into each of the fourteen points, totaling 4.2 U. In case of a wide forehead (more than 6 cm from the apex of the eyebrows to the hairline), we draw three horizontal lines dividing the forehead into four parts. By crossing these three horizontal lines with the seven vertical lines mentioned above, we can make 21 different intersection points and inject into each of these points 0.4 U of BoNT-A, totaling 8.4 U. Patients exhibiting one or more high-risk factors listed above should receive approximately one-third or half the standard dose of BoNT-A.

As the dose is quite low, a large dilution (1 U/0.1 ml) and intradermal injection would be helpful for the accurate injection of small dose of BoNT-A into the forehead.

2.2.5.4 Injection Dose

The initial injection dose is 1–8 U depending on the individuals. The standard dose is 5.6 U (narrow forehead under 4 cm, 4.2 U, and the forehead over 6 cm, 8.4 U). It is necessary to reduce the dose in half if there is ptosis or eyebrow ptosis.

2.2.5.5 Adverse Effects

Irregularity

When a small dose of BoNT-A is used in patients with ptosis and eyebrow ptosis, the area between injected and non-injected areas may transiently become slightly irregular 2–3 days after treatment due to the “botulinum-rebalancing phenomenon.” Severe cases may require additional injections into the highly mobile areas even at 2–3 days after injection. However, after 2 weeks when the BoNT-A will affect most areas, the irregularity will disappear spontaneously. Thus, further injections may not be usually required. For similar reasons, if we inject only into the forehead lines while excluding glabellar lines, the muscles in the glabellar area bulge or form lines

due to increased mobility [26] (kang 참고문헌). To solve this problem, it is better to inject the BoNT-A in both the glabella and forehead lines together at the start of treatment with BoNT-A.

Samurai Eyebrow (Mephisto Eyebrow)

In case we inject only in the center of the forehead or do not inject enough into the lateral side compared to the medial side, the forehead muscle fibers in the lateral side may pull the eyebrow superolaterally, resulting in a condition called “samurai eyebrow” (Fig. 2.31). In the West, it is called also “Mephisto eyebrow,” named after a popular demon in German folklore. Initially, many Korean doctors followed Western guidelines which advise not to administer injections into the lateral part of the midpupillary lines in order to avoid eyebrow ptosis [27]. I also followed these guidelines but experienced many “samurai eyebrows.” I was unsure how to manage this adverse effect which made patients look more aggressive than before. Fortunately, I came to find the solution through trials and errors that the elevated eyebrows return to their normal state after an additional injection of 0.5–1 U into the superolateral part of the frontalis muscle. Now, samurai eyebrow can be prevented by injecting the whole area of frontalis muscle including lateral portion during the initial treatment.

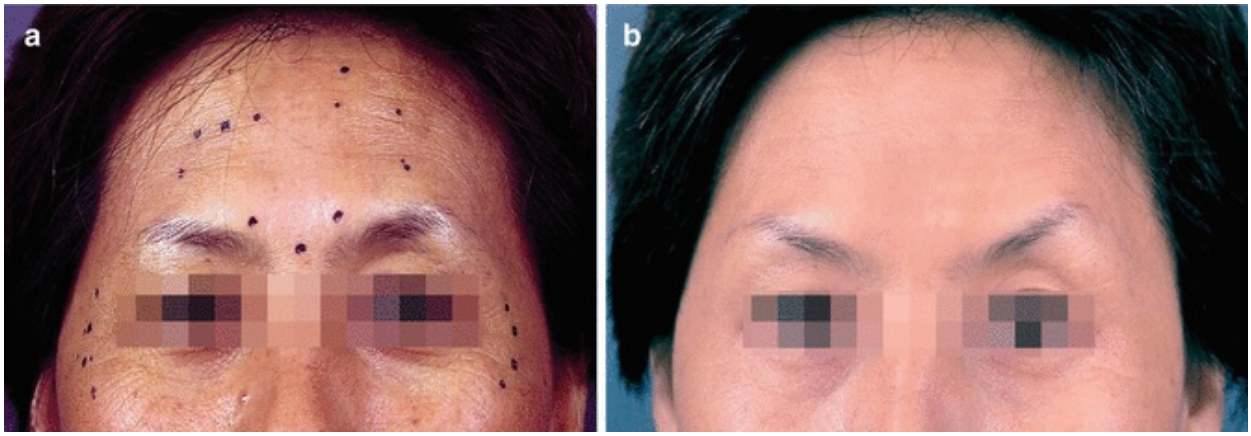


Fig. 2.31 Samurai eyebrow. (Mephisto Eyebrow) (**a**) Before. (**b**) After

Eyebrow Ptosis

Patients in their late 40s above with eyebrow drooping, blepharochalasis, or lateral hooding or eyelid ptosis are the highest-risk group for the treatment of forehead wrinkles with BoNT-A. As these patients try to elevate their

eyebrows using the frontalis muscle in compensation for their condition mentioned above, the overdosage of BoNT-A for them may cause exacerbation of eyebrow drooping or blepharochalasis, resulting in an aged and gloomy look. This is of course unacceptable, and unfortunately there is no effective way to resolve this complication because there is no effective antitoxin for BoNT-A (Fig. 2.32).

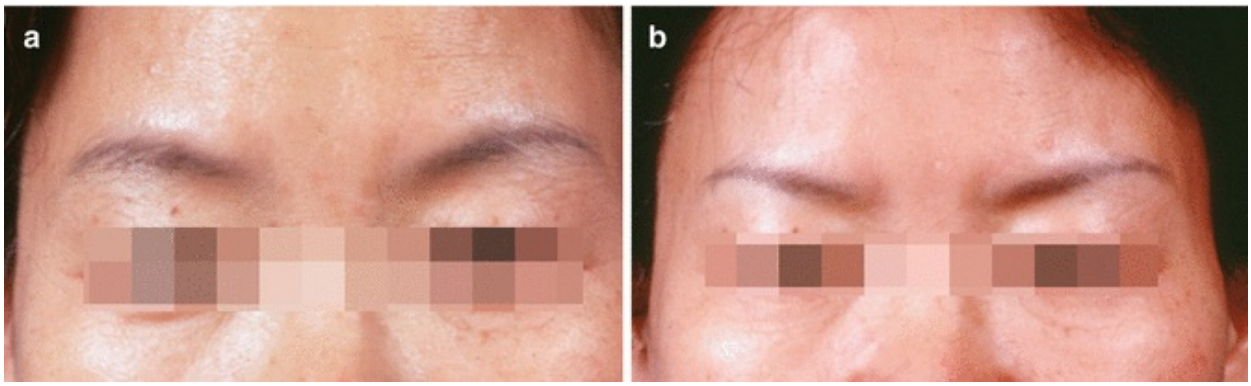


Fig. 2.32 Eyebrow ptosis. (**a**) Before. (**b**) After

However, if the BoNT-A was injected only into the forehead or the forehead and glabellar areas, we can mildly mitigate the problem by injecting the BoNT-A into the eyebrow depressors: the orbicularis oculi, the procerus, and the corrugator supercilii (see Sect. 2.17). In such circumstances it is important to inject 4 U into the most superior site of the orbicularis oculi lateral to the eyebrow, higher than the standard dose for treatment of crow's feet.

Eyelid Edema

Approximately 10–30 % of patients used to experience eyelid edema following BoNT-A treatment for forehead lines when I performed BoNT-A injection with 14 U. Severity varies from mild (barely visible) to severe (constant presence) according to the individual. One of the main causes for the eyelid edema seems to be the descent of soft tissue at the upper eyelid by eyebrow drooping. And also, it is suggested that local edema at the forehead caused by insufficient lymphatic circulation following muscle paralysis may play an important role in eyelid edema in addition to the eyebrow drooping. Edema may give the skin an elastic appearance, so that it does not always look bad. But of course, if it is severe enough, it may descend toward the eyelids and cause eyelid edema.

We do not have any effective treatments for the eyelid edema. We should also bear in mind that the chances and severity of eyelid edema increase along with age. In 2000, I performed the dose–effect relationship of BoNT-A for forehead wrinkle treatment. It was a prospective clinical study with a total of 37 volunteers, 13 in their 30s and 40s, respectively, along with 11 volunteers in their 50s. One side of the forehead in each patient was randomly injected with one of the three different units (6, 9, or 12 U per side), and the other side was injected with one of the other two different units. The effects were observed 1, 4, 8, and 12 weeks after injection (unpublished data; at that time the dose was high, 20 U for forehead wrinkles following instructions in Western literatures). The results showed that eyelid edema occurred in up to 29 % of volunteers, with two subjects in their 50s, experiencing particularly severe symptoms. In cases where different doses of BoNT-A were administered on different sides of the forehead, the eyelid edema was more frequent in those receiving 12 U than other doses. In conclusion, the older age group and higher-dose groups were more prone to develop the eyelid edema. As some volunteers in even 6 U per side group experienced the adverse effects, I changed the dose of BoNT-A for the treatment of forehead wrinkles thereafter: the standard dose is 6 U for the whole forehead and the initial dose must be adjusted to under 4 U for patients over 50s.

Mild eyelid edema usually subsides within 2–4 weeks, with severe cases taking up to 2 months. If the edema occurs, there is no way to remedy it except for direct massaging the eyelids and forehead daily.

2.2.5.6 Photography (Fig. 2.33)

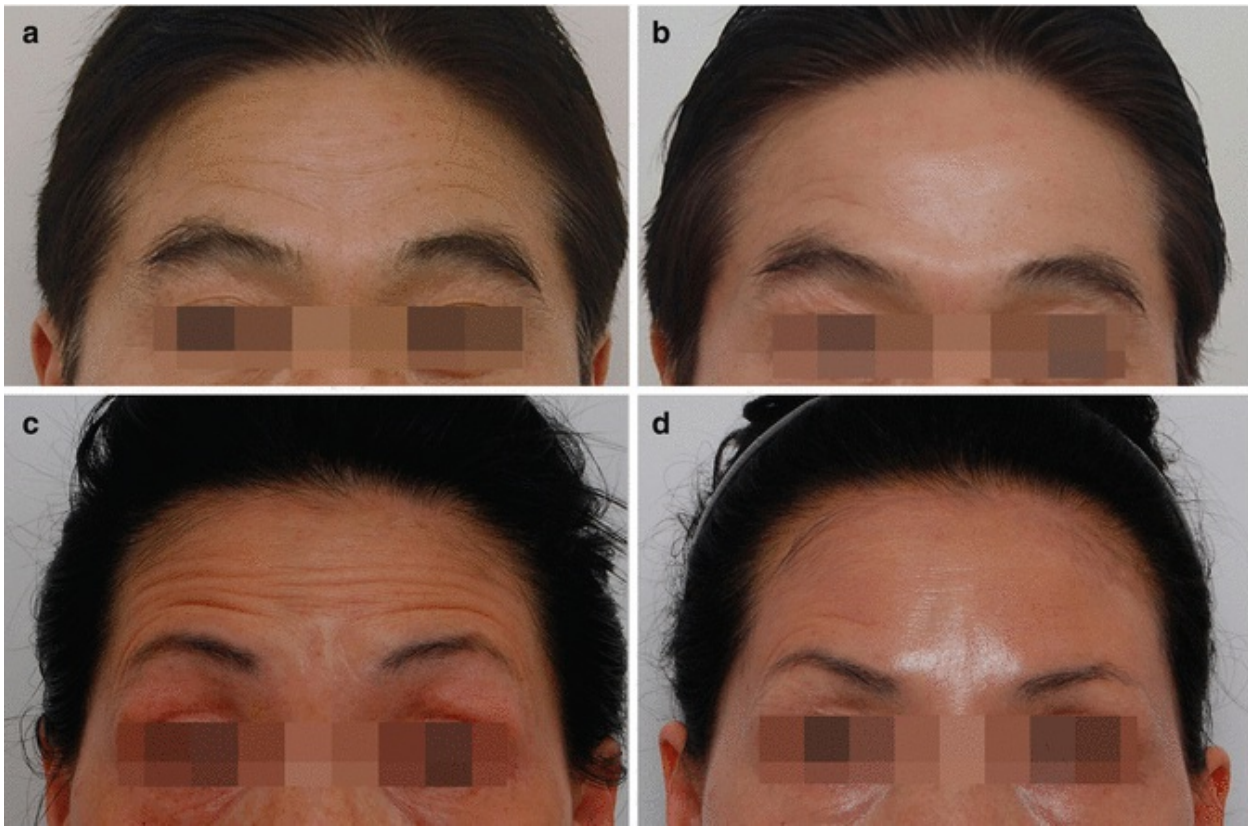


Fig. 2.33 Horizontal forehead lines: (**a**, **c**) before and (**b**, **d**) 2 weeks after 5.6 U injection of BOTOX®

Take two front views, at rest and while lifting eyebrows.

Episode: "I Injected Botulinum Toxin for the Treatment of the Forehead Lines and Now My Life Is in Danger"

Of all the facial areas, the forehead is the most vulnerable to alterations in facial expression following BoNT-A treatment. Unnatural facial expressions resulting from the treatment include droopy inner eyebrows and the arching of the outer eyebrow, both of which cause the face to look angry and hostile. When BoNT-A was first introduced, many Korean doctors, including myself, injected BoNT-A only in the center of the forehead, out of concern of possible eyebrow sagging. This resulted in many cases of so-called samurai eyebrows induced by the superolateral pulling of the eyebrows by the non-paralyzed lateral fibers of the forehead muscles. After various trials and errors, it later turned out that the problem could be resolved by injecting 0.5–1 U of the BoNT-A into the lateral sites of the lifted eyebrow. Unfortunately though, there were still many doctors who were unaware of this technique at that time, for which some had to face some unnerving consequences.

During my early years as a practitioner, I had treated a decent elderly female patient in her mid-60s for forehead wrinkles, but ended up giving her a severely altered facial expression. Her eyebrows became uneven and droopy with the outer corners soaring upward, a classic example of the so-called samurai eyebrows. Since I had missed the initial 1–2-week window available for corrective treatment, all she could do was to wait for her spiteful expression to wear off with time. In the meantime, she had to encounter various awkward situations in her daily social interactions. She related to me the time when she was queuing up the station to buy a ticket when a young woman jumped the queue in front of her. Politely as ever, she suggested to the young lady “Excuse me, I think we have a queue here” to which the young woman indignantly retorted, “I will step aside! You don’t have to scowl at me like that!”

A fellow doctor related to the anecdote of one of his patients who ended up in a confrontation while drinking at a bar because of the frown fixed to his face after receiving BoNT-A treatment on the forehead. The patient was merely glancing at the next table a few times, when the man sitting at the table accused him of “glaring for no reason” which ultimately lead to the angry exchange between the two.

Perhaps the most nightmarish incident, though, would be the time I was put through on a long district call sometime around 2003, from a caller, who had introduced himself as a doctor. Despite having been told numerous times that I was engaged in the treatment room, he had adamantly insisted on talking to me. When I finally pick up the phone, to my amazement, the doctor was pleading with me to spare him his life since he was facing a life-threatening situation. He related to me the following account. He had given a female patient in her late 40s BoNT-A injections in the forehead. One week later she appeared with samurai eyebrows. The woman’s husband, a heavyset gangster type of a character, was so upset he vowed to kill the doctor if he couldn’t restore his wife’s face. The dread and fear in the doctor’s voice were palpable from his trembling tone. After hearing him out, I advised him to inject 0.5 U of the BoNT-A into the lifted eyebrows to help relax the arched eyebrows. Extreme as it may be, I suppose the husband’s outrage is not completely without reason, considering that all his wife had wanted was to look younger and prettier and what she got instead was a nasty frown.

2.2.6 Eyebrow Shaping/Eyebrow Lifting

Effect (C), Adverse Effect (B), and Technique (B)

The shape and location of the eyebrows play a big role in facial expressions; thus, patients, particularly women, pay great attention to them, especially when applying makeup. Interestingly, you can lift the eyebrow and alter the shape of the eyebrow using the botulinum-rebalancing effect. The shape and position of the eyebrows depend on the equilibrium of the muscles responsible for lifting (frontalis) and depressing (orbicularis oculi, corrugator supercilii, depressor supercilii, procerus). If BoNT-A is injected only into the muscle responsible for depressing, a 1–3 mm lifting of the eyebrow is visible (Fig. 2.34) [28]. And if an injection of BoNT-A is made only into some part of the frontalis muscle, lifting of the non-injected area is noticed through botulinum rebalancing. Marked lifting on the lateral part of the eyebrow produces “samurai eyebrows,” but appropriate elevation is quite useful to lift the drooped eyebrow due to aging.

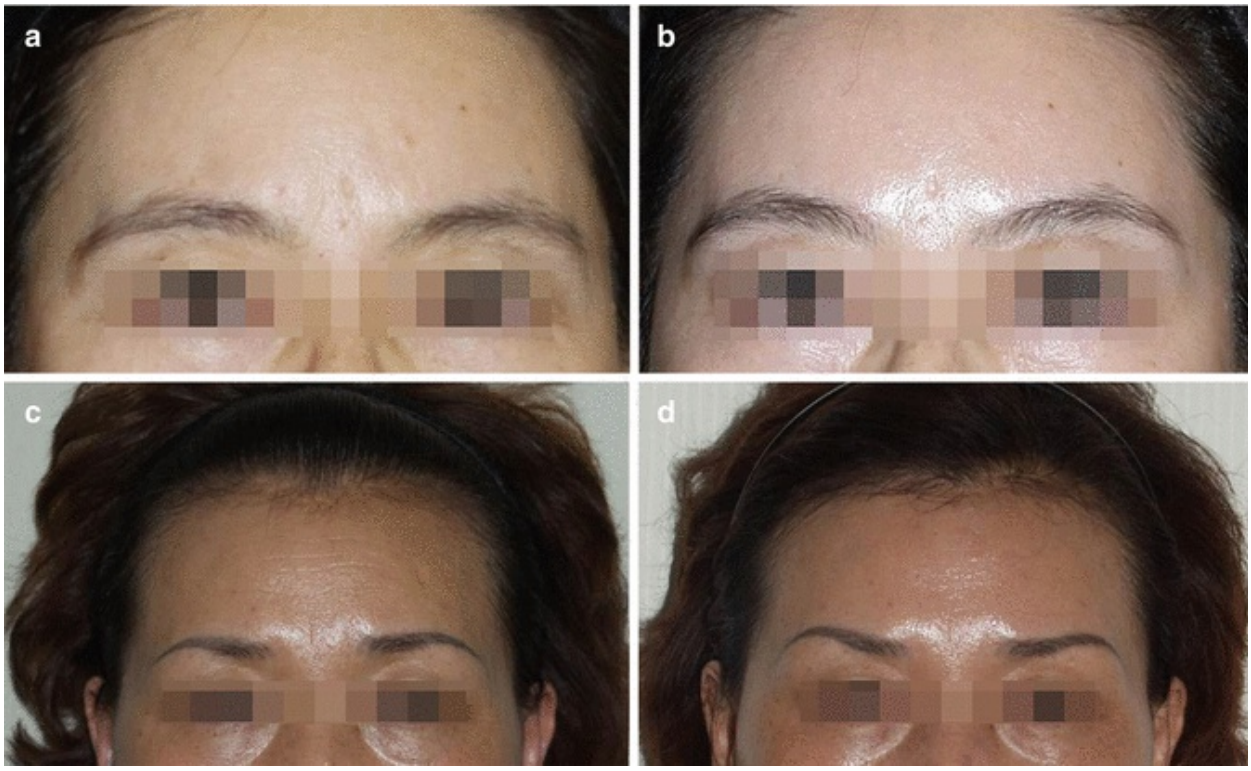


Fig. 2.34 Eyebrow lifting: (**a**, **c**) before and (**b**, **d**) 2 weeks after injection of BOTOX®

Female eyebrow shaping with BoNT-A to make high arched eyebrow is especially popular in the West. The topic of eyebrow shaping using BoNT-A is so extensively described in many western literatures and publications on

BoNT-A such that the separate chapter is often dedicated to covering this indication in great detail [9, 18, 28]. From the Caucasian perspective, high arched eyebrow goes well with round face, square face, and face with prominent zygoma [9]. However, the preferred brow shape for the Asian female is flat or lower in the lateral two-thirds than has been traditionally advocated for Caucasians (Fig. 2.6). The high arched eyebrows preferred by Caucasians give Asians the impression of a “samurai eyebrow” with a fierce look.

This different preference may be related to the different shape of the face between Asian and Caucasian. Although prominently arched brow matches well with narrow Caucasian face shapes, it gives too strong of an impression to Asians with wide face shapes. This is also similar in hair transplantation. M-type hairline matches well to narrow Caucasian face; however, M type is too prominent to Asian and slight flatter linear hairline rather matches well (Fig. 2.35) [29].

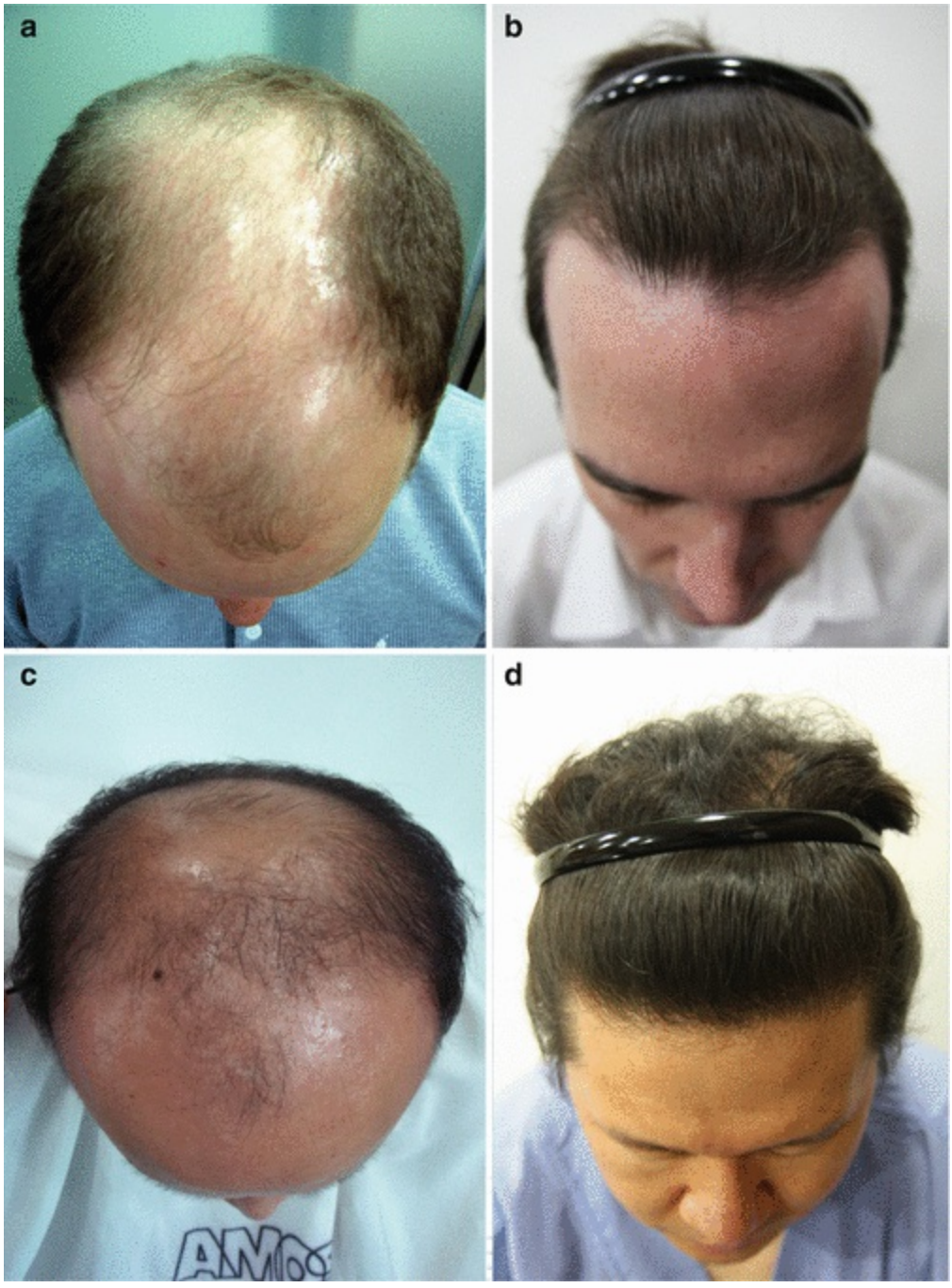


Fig. 2.35 Comparison of hairline and skull shape between Asians and Caucasians. (**a**, **b**) M-shaped hairline matches well with Caucasian faces, long anteroposterior and narrow right to left. (**c**, **d**) Slightly flat linear hairline matches well with Asian faces, wide right to left (Photo, courtesy of dermatologist Tommy S. Hwang)

Nevertheless, eyebrow lifting is worthwhile to mention here because eyebrow lifting with BoNT-A is also quite useful even for Asian patients with eyebrow drooping in case we use appropriately. The same technique for

the treatment of the glabellar lines and lateral canthal rhytides is applied to eyebrow lifting. However, there is a difference between the two procedures: the BoNT-A should be injected 4 U just below the lateral side of the eyebrow instead of 2 U for the treatment of lateral canthal rhytides. All the depressors of the eyebrows are weakened by this method (Fig. 2.36a). If you want to elevate slightly only the lateral tail portion of the eyebrow like high arched eyebrows preferred by Caucasians, you should inject 1–4 U of the BoNT-A into the medial portion of forehead to the midpupillary line. To avoid "samurai eyebrow" which is produced by too much lifting of the lateral part, the BoNT-A should be injected 0.5 U into the upper lateral forehead 1.5 cm apart from the midpupillary line (Fig. 2.36b).

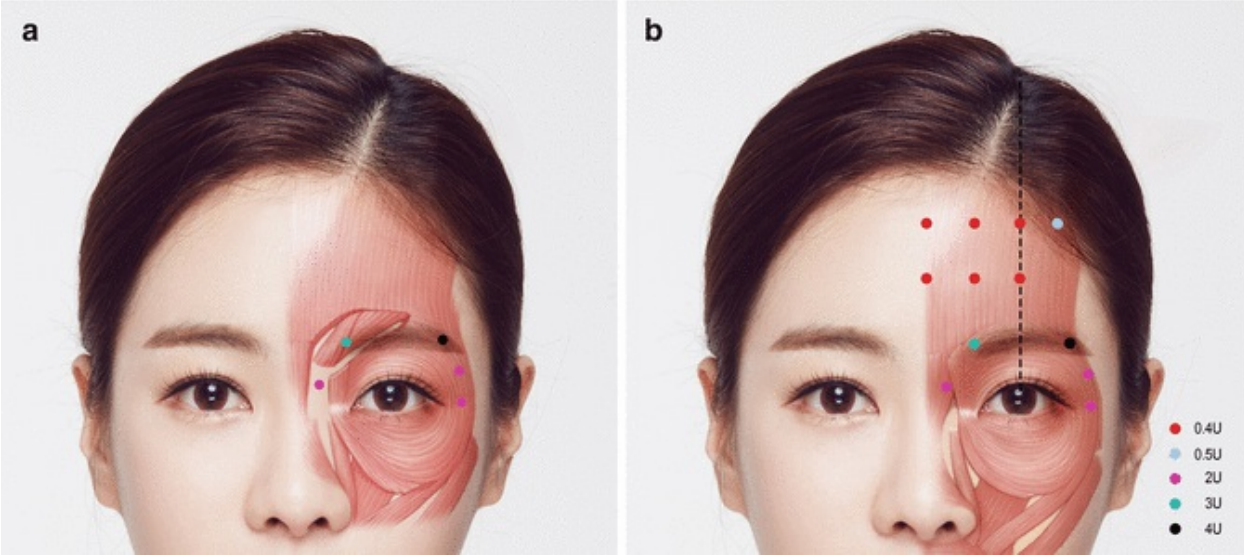


Fig. 2.36 Injection points for eyebrow lifting. (**a**) Standard type. (**b**) Tail elevation of the eyebrow

2.2.7 Glabellar Frown Lines

Effect (A), Adverse Effect (B), and Technique (B)

Treatment of glabellar lines with BoNT-A reported by Dr. Carruthers in 1992 first introduced the efficacy of BoNT-A as an innovative treatment modality for wrinkles to the world. And also treatment of glabellar lines with BoNT-A is in fact the only cosmetic indication of BoNT-A approved by the US FDA. Glabellar frowning lines can give bad impression to others from the Asian viewpoint because this wrinkle is believed to bring about bad fortune according to old Asian phrenology. Therefore, I usually recommend this indication as a top priority to patients (Fig. 2.37). We also anticipate some

preventative effects by repeated injections of BoNT-A, thanks to the diminished involuntary habit of glabellar frowning through botulinum-remodeling phenomenon.

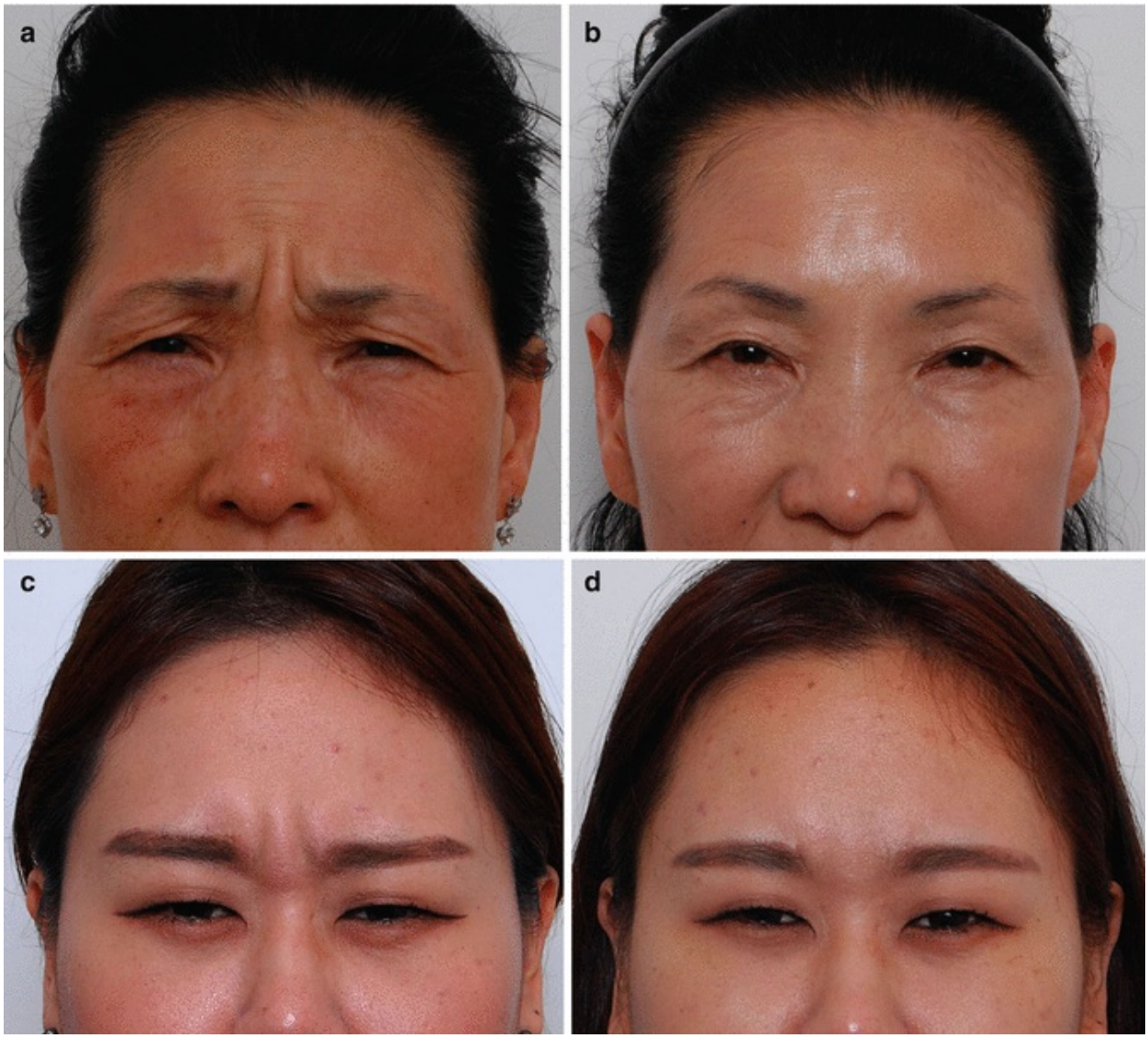


Fig. 2.37 Glabellar frown lines: (**a**, **c**) before and (**b**, **d**) 2 weeks after 10 U injection of BOTOX®

As pretreatment assessment, first identify deep static wrinkles and inform patients with deep static wrinkles of necessity of filler injection together with BoNT-A. Second, recommend concomitant BoNT-A injection for forehead lines because forehead lines may exaggerated through the botulinum-rebalancing phenomenon if treatment is confined to the glabellar area. Third, identify the existence of active movement of corrugator tail inserted into the

skin above the orbital rim at the midpupillary line during facial expressions along with prominent glabellar lines. In such case, it is better to inject additional 1 U just above the orbital rim at the midpupillary line.

Episode: Adverse Effects of Glabellar Treatment with BOTOX® Reported in the Clinical Trials for the US FDA Approval (No Laughing Matter)

The clinical study on glabellar lines with BOTOX® submitted for the US FDA approval in 2002 reported a 5.4 % incidence of ptosis even though most of them were mild. With a dash of sarcasm, I used questioned whether the study was not approved by a Korean FDA, since the picky Korean patients would not allow such embarrassing adverse effects.

In my personal experience, I sidestepped the risk of ptosis on my very first patient, but later had two cases of mild ptosis in ten of my initial cases. The angle, the position, the BoNT-A dosage, and the speed of injections are significant factors. Indeed, in one of the cases where ptosis occurred, the injected volume was as high as 30 U, which presumably played a significant role. Thereafter though, I have encountered significantly less incidence of ptosis, three cases in total to be exact, or one in every 3~4 years. High injection speed while injecting multiple different sites such as facial wrinkles, the jaw and temporal area during one session, and the bad posture of the practitioner may likely have factored into these rare cases.

Of late I came to see the value of pressing down the area just below the injection site while performing BoNT-A injections. Individual differences in soft tissue slack and connections can occasionally send BoNT-A flowing downward, which can be detected by the practitioner during the injection by applying pressure with the thumb and index fingers just below the injection site. Whenever my finger detects the BoNT-A flowing downward, I let out a silent sigh of relief, to imagine what might have happened had I not done so.

The junior doctors at my clinic have occasionally found themselves in a bind when an eyelid ptosis occurred in their patients. One junior doctor had three cases of eyelid ptosis in an 8-month period. One of his patients with eyelid ptosis, a staff nurse at the clinic, had to miss work for nearly 2 months and put up with her husband’s complaints. In another case where symptoms were relatively milder by comparison, we offered another aesthetic procedure as a complimentary service and amicably settled the case. Unfortunately, the third case could not be resolved, and we ended up issuing a full refund of all

other procedures performed together with BoNT-A injections. Three cases of eyelid ptosis from a junior doctor who was handling significantly less than 100 cases of glabella wrinkle treatment were significantly high in terms of incidence. Indeed, this represented a serious challenge to the clinic's reputation as the leader in antiaging and BoNT-A treatment. What made the situation worse was the fact that the young doctor himself had no idea as to the cause.

The junior doctor claimed he was faithfully following my instructions concerned and just as baffled I got him to perform the procedure in my attendance and was able to spot the problem right away; it had to do with in his posture. To avoid BoNT-A inflow toward the eyes, the needle should be positioned superolaterally at a 30° angle from the skin surface; therefore, the practitioner is advised to stand to the left of the patient when injecting the right side of the face and stand to the right when injecting the left side. Personally, I was more comfortable performing the injections on the right side of the patient only, rather than switching sides every now and then during the procedure. Little did I know the junior doctor was picking up on my modus operandi. Specifically, when he was injecting the left side of the patient's face, the needle was correctly inserted exactly at a 30° angle from the horizontal line but when injecting into the right side of the face, where the doctor was standing, the needle was inserted almost vertically in a slightly downward direction. Needless to say, in all cases where ptosis had occurred, the affected area was on the right side of the face. While I had been consciously aware of the required needle entry angle while injecting from only one side of the patient, this significance had been lost on the junior doctor. Indeed, a precious lesson was learned from this experience and that is the importance of "knowing the basics," although my junior colleague has yet to pay me for this one point lesson.

Another case involved a female patient in her 20s who received BoNT-A treatment for axillary hyperhidrosis with BoNT-A as well as glabellar line treatment offered as a complimentary service from our staff doctor, which unfortunately led to an eyebrow ptosis. In trying to identify the cause of the problem, before joining my clinic, the doctor had previously worked at another clinic for 2~3 years where she had apparently learned a slightly different technique for the treatment of glabellar lines. Specifically, BoNT-A was injected vertically into the insertion point of the corrugator supercilii over the medial canthus. The doctor was sufficiently experienced in treating

glabellar lines and claimed to have encountered no major adverse effects from his technique until then. Indeed, there may have been other factors at play apart from the injection technique. However, in order to avoid any serious complications such as ptosis, it is probably best to err on the side of caution and to exclude any technique with even the slightest likelihood of increase the odds of adverse effects. Patients invest their time and money in getting these cosmetic procedures so as to look and feel better about themselves. This considered, risks of any unwanted side effect, never mind how small, be it one in 1000, or one in 10,000, should be avoided at all costs. No doubt, several days later, we were made a visit by a tough-looking man claiming to be the patient's brother and bearing all the essentials of a gangster. His intense glare and angry threats are still vivid in my memory as he yelled "Listen doc, you'd better put my baby sister's eyes right where they belong!" I wonder if the doctor still uses his injection techniques.

2.2.7.1 Anatomy

The glabellar frown lines are produced by three key muscles: the frontalis, procerus, and corrugator supercilii muscle (CSM). Superomedial fibers of the orbicularis oculi interconnect with the frontalis or procerus, referred to separately as the depressor supercilii muscle. The most important muscle, the CSM that induces the glabellar lines, similar to the Chinese character (川 means stream), is located medial to the eyebrows. It originates from the superomedial part of the orbital rim of the frontal bone, runs superolaterally, and inserts into the frontalis and dermis located above the eyebrow at the midpupillary line.

The CSM pulls the eyebrows downward and medially and contributes vertical lines while frowning. If the CSM is paralyzed, effacement of glabellar lines and widening between the eyebrows are noticed. As the CSM is located deeply, you can see the origin site beneath the frontalis muscle. When administering the BoNT-A into the CSM, advance the needle until it contacts the bone, and then slightly withdraw and inject BoNT-A.

The procerus muscle, which contributes to horizontal lines in the radix, originates from the lower part of the nasal bone and upper part of the lateral nasal cartilage. Its fibers run vertically and insert into the frontalis muscle with some of them attaching the skin over the glabellar area and the radix. The depressor supercilii, the medial fibers of orbicularis oculi, depresses the eyebrows. If this muscle is paralyzed by the BoNT-A, the eyebrows can be

lifted upward. Glabellar muscles are not separated from each other, but instead closely interconnected. Therefore, the BoNT-A injected into the CSM, the main target, will rapidly diffuse to the surrounding muscles.

Tip: Characteristics of Asian Corrugator Supercilii Muscle

According to Yang and Kim, the CSM in Koreans generally originates 16 mm above the horizontal intercanthal plane, 4–14 mm laterally from the vertical median line, inserting into the frontalis and dermis 30 mm above the horizontal intercanthal plane and 16–35 mm laterally at the vertical median line [12]. The vertical length of the muscle is 15 mm in Koreans, slightly shorter than 21 mm of Caucasians. Morphologically, the CSM is comprised of two distinct bellies, the oblique belly (OB) and transverse belly (TB) (Fig. 2.38). OB arises and runs superficial to TB. TB originates more superolaterally and runs horizontally. OB has two types: narrow vertical type and broad triangular type. The narrow vertical type attaches to the frontalis muscle at one-third the medial portion of TB. In contrast the broad triangular type covers nearly half of TB (Fig. 2.38). Koreans generally exhibit more narrow vertical-type OB (63 %) than the broad triangular type (37 %). It has been suggested that persons with a prominent OB have much more contraction at the midpupillary line above the eyebrows.

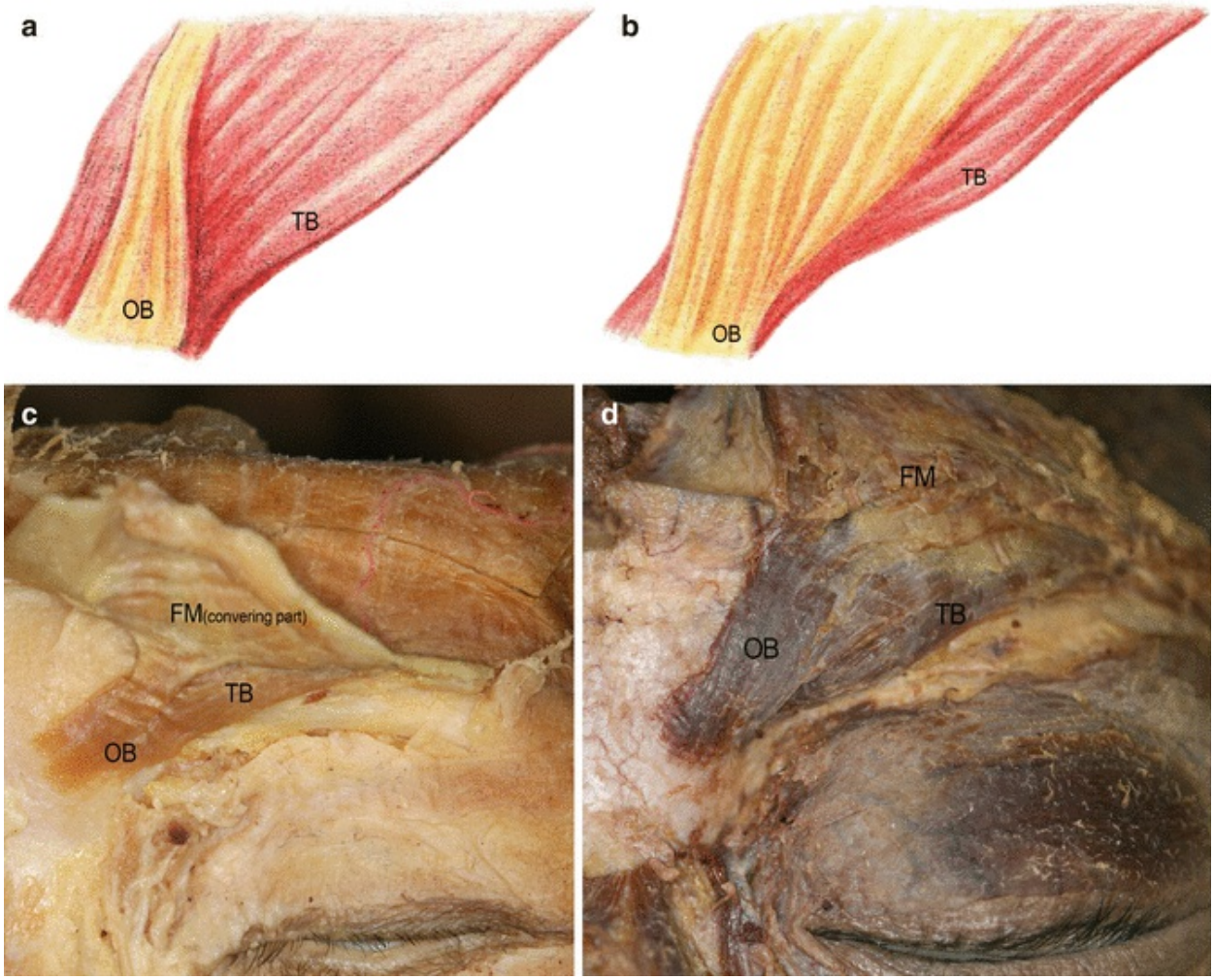


Fig. 2.38 Two types of oblique belly of corrugator supercilii muscle (*TB* transverse belly, *OB* oblique belly, *FM* frontalis muscle, *OOc* orbicularis oculi.) (**a, c**) Narrow vertical type (after removal of the frontalis covering the muscle). (**b, d**) Broad triangular type (courtesy of professor Hee-Jin Kim)

2.2.7.2 Injection Techniques

3 U (4 U for male) is injected 1 cm above the orbital rim in line with the medial canthus, the origin site of the CSM. 2 U is injected into the midpoint between the insertion area of the CSM and the intercanthal midpoint in order to treat the procerus and the depressor supercilii muscle on each side (standard type for Asians, Fig. 2.39a).

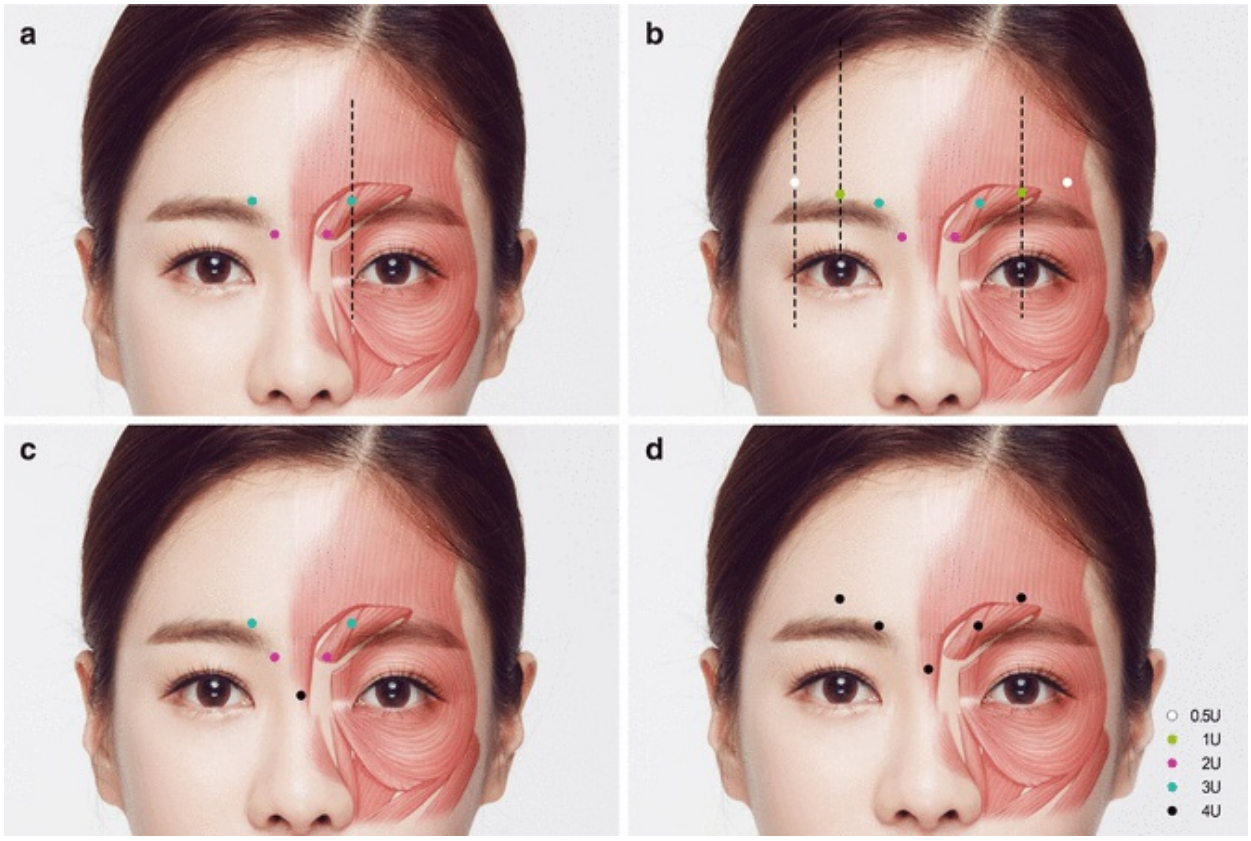


Fig. 2.39 Injection points for glabellar frown lines. (**a**) Standard type for Asian. (**b**) Severe type for Asian. (**c**) Horizontal Radix line type. (**d**) Standard type for Caucasian

In Asians, the narrow vertical type of the oblique belly (OB) of the CSM is found to be 63 % more frequently than 37 % of the broad triangular type. Moreover, the OB length is shorter than Caucasians. Therefore, injection of toxin only into the medial part of CSM as shown in a standard form for Asians would be sufficient in Asians compared to the standard form for Caucasians which includes additional injection points just above the orbital rim in the midpupillary line side (standard type for Caucasians, Fig. 2.39d). However, if Asian patients show active movement above the eyebrows in the midpupillary line when making glabellar expression lines, then additional 1 U per side should be injected intradermally into the same injection points above the orbital rim in the midpupillary line, as in Caucasians. It may be necessary to inject an additional 0.5–1 U of BoNT-A 2 cm above the eyebrow in line with the lateral canthus to prevent “samurai eyebrow” (severe type for Asian, Fig. 2.39b). If the horizontal lines between the eyes are well developed in the radix, root of the nose, it may be necessary to inject 4 U subdermally into the intercanthal midpoint to paralyze the procerus muscle (radix transverse line

type, Fig. 2.39c). In such a case, we may face more wrinkles at nasal sidewalls (bunny lines) through the botulinum-rebalancing phenomenon. Therefore, treating bunny lines with BoNT-A together is preferable. In addition, above and below the medial canthus, many vertical lines may appear due to the botulinum rebalancing; in that situation it may be necessary to inject 0.5 U into the area above and below the medial canthus during follow-up sessions.

When treating glabellar lines with BoNT-A, great care should be taken to avoid ptosis. It is caused by partial paralysis of the levator palpebrae superioris muscle due to the BoNT-A diffusion through the orbital septum. When we inject the BoNT-A into the site of origin of the CSM, the needle should always be directed superolaterally and at 30° from the skin surface to prevent BoNT-A diffusion into the orbital cavity. As the CSM muscle attaches to the orbital rim in line with the medial canthus, the needle should advance deeply until touching the periosteum, withdrawn 2–3 mm, followed by slowly injection of BoNT-A into the muscle. Subdermal injection is preferable for the procerus muscle as other areas, but intradermal injection is desirable at the midpupillary line just above the orbital rim. When injecting the BoNT-A near the origin site of the CSM, it is recommended to press below the infraorbital rim using your fingers of nondominant hand to prevent inflow of the BoNT-A into the orbital cavity (Fig. 2.40).

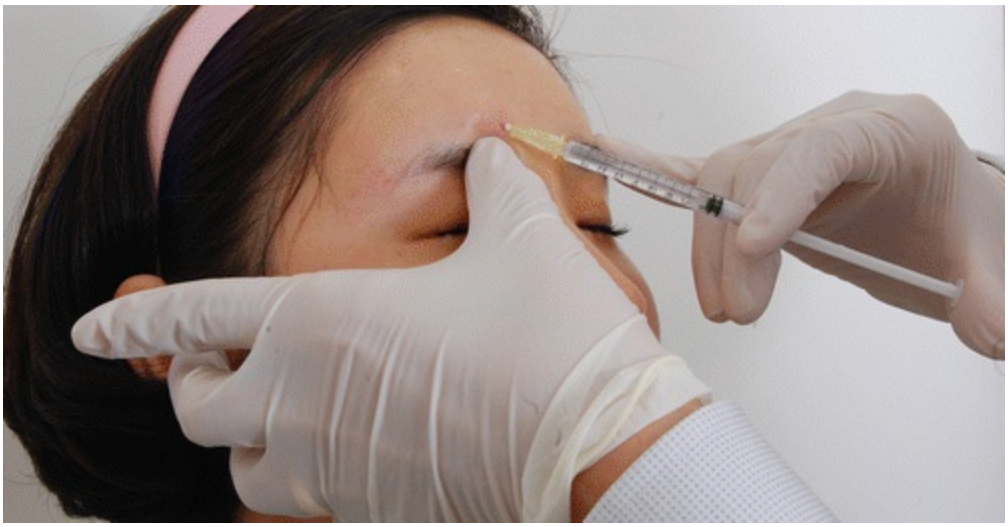


Fig. 2.40 Injection posture for glabellar frown lines. When injecting the toxin near the origin site of the corrugator supercilii, press below the orbital rim using the fingers of nondominant hand

Tip: How Do I Cope with a Patient Who Still Has Glabellar Lines

Even After Repeated BoNT-A Injections into the Corrugator Supercilii Muscle?

Occasionally, there are patients whose dynamic wrinkles do not disappear completely in spite of treatment to the CSM. I was once consulted about a patient that was unresponsive to repeated BoNT-A injections for the treatment of glabellar lines. The patient had already received three sessions of BoNT-A injection with 10 U into the designated sites (standard type for Asians). The last injection was performed just 2 weeks ago before the consultation, left the patient with a half-frown due to an incomplete removal of dynamic wrinkles. Upon closer examination, I found excessive muscle movement in the mid and lateral portion of the patient's orbicularis oculi just above the eyebrows along with shifting lines toward the glabellar area. Thus, this comes from the action of lateral fibers of the orbicularis oculi which do not disappear completely in spite of sufficient injections of BoNT-A into corrugator supercilii muscle. I resolved the problem with 1–2 U intradermal injections into the lateral portion of orbicularis oculi above the orbital rim.

2.2.7.3 Injection Dose

Recommended standard injection dosages: 10 U for women, 13–15 U in men (or women in severe cases), and 14 U for both sexes when treating radix transverse line type

2.2.7.4 Photography

Take two front views, the first at rest and the second during maximum glabellar frowning.

2.2.7.5 Adverse Effects

Common adverse effects from BoNT-A for the treatment of glabellar wrinkles are mild and include headache, bruise, and facial expressions alteration, but ptosis is the most serious. According to the data from the first multicenter double-blind study for the treatment of glabellar lines with BoNT-A in 264 subjects (BoNT-A 203, placebo 61) conducted by Carruthers et al. in 2002 for the purpose of FDA approval, adverse effects included transient headache (15 %) and mild unilateral blepharoptosis (5.4 %) that resolved mostly by Day 40 [20]. In the second multicenter double-blind study

by the same group in 2003 showed that in 273 subjects (BoNT-A 202, placebo 71), the most common adverse effect was headache (BoNT-A 11 %, placebo 20 %). In this second study, the incidence of blepharoptosis decreased to 1 % [30].

A meta-analysis on the adverse effects of onabotulinumtoxinA for the treatment of glabellar wrinkles and crow's feet has been reported by Brin et al. in 2009 [31]. The analysis was based on the nine manufacturer-sponsored clinical trials of onabotulinumtoxinA (two on crow's feet and seven on glabellar wrinkle) and included 1678 subjects with non-Hispanic white (43 %) and Asian (52 %). In this study, eyelid sensory disorder (2.5 %; verbatim phrases "tight," "pressured," "heavy," "drooping feeling," "feeling of droopiness"), eyelid ptosis (1.8 %), and eyelid edema were observed with significantly greater incidence in onabotulinumtoxinA group of glabellar studies. Interestingly, eyelid sensory disorder and eyelid edema were more common in Asian participants. Incidence of all three of these adverse effects significantly decreased as the number of treatment cycles increased.

Ptosis

BoNT-A injected into the glabellar area may diffuse downward affecting the levator palpebrae superioris muscle, which results in ptosis. Nearly 30–40 % of the cornea is covered with the upper eyelid in patients with ptosis (Fig. 2.41). Early literatures reported a 1–3 % incidence of ptosis, while the clinical study for the US FDA approval reported 5.4 % even though ptosis was mild and resolved mostly by Day 4 [20, 31]. As ptosis is a very severe adverse effect, I think a clinic should close if patients experience a 5.4 % incidence rate of ptosis. Other adverse effects, such as unfamiliar facial expressions, do not have the same negative impact on a patient's daily life as ptosis, which affects not only external appearances but also limits visibility and causes headache and nausea. Fortunately, a superiorly trained doctor can almost completely avoid ptosis.

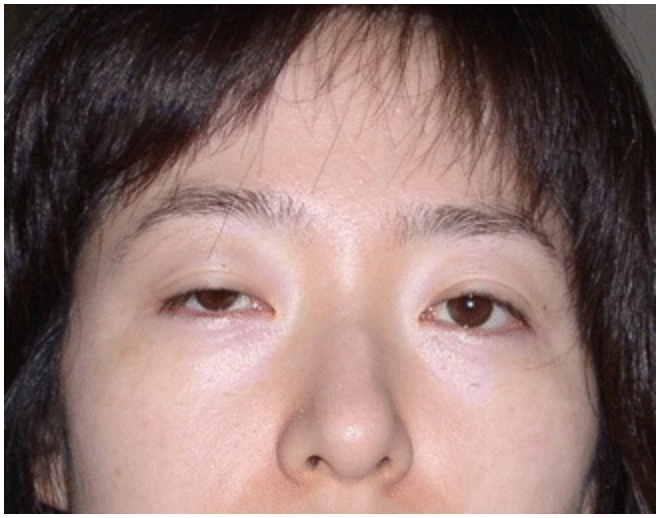


Fig. 2.41 Eyelid ptosis after the treatment of glabellar lines with botulinum toxin

Ptosis occurring after BoNT-A treatment is different from blepharochalasis due to eyebrow drooping after the treatment of forehead lines with BoNT-A in a few ways. Ptosis caused by the levator palpebrae superioris usually occurs unilaterally. However, blepharochalasis due to eyebrow drooping after the treatment of forehead lines with BoNT-A usually affects both sides. Blepharochalasis due to eyebrow drooping is recovered by manual lifting of eyebrows upward, but not in ptosis.

If ptosis occurs, make sure to remind patients they will recover 100 %, lest they become extremely emotional and distraught. For symptomatic treatment, eye drops containing an α-adrenergic agonist that activates the Müller muscle should be used 3–4 times a day. The Müller muscle located between the levator palpebrae superioris and mucosa enables the auxiliary function of lifting the upper eyelid (Fig. 2.43). Since Müller muscle receives sympathetic innervation, 0.5 % apraclonidine eye drop (Iopidine®, Alcon Labs), an α-adrenergic agonist can activate the Müller muscle absorbed through the mucosa and can elevate the eyelid 1–2 mm. To ensure the eye drops fully affect the mucosa, you should instruct the patient to tilt their head backward, gaze downward, and drop the solution above the cornea. After keeping the same position for 3–4 min with closed eyes, instruct them to open their eyes. The eyelid should elevate and ptosis should disappear entirely in mild cases, along with congestion, for about 2–3 h. α-Adrenergic agonist eye drops were originally developed for glaucoma treatment and include 0.5 % apraclonidine eye drop (Iopidine®, Alcon Labs), brimonidine

tartrate (Alphagan P® 0.15 %), phenylephrine (Mydfrin® 2.5 %, Alcon Labs), etc.

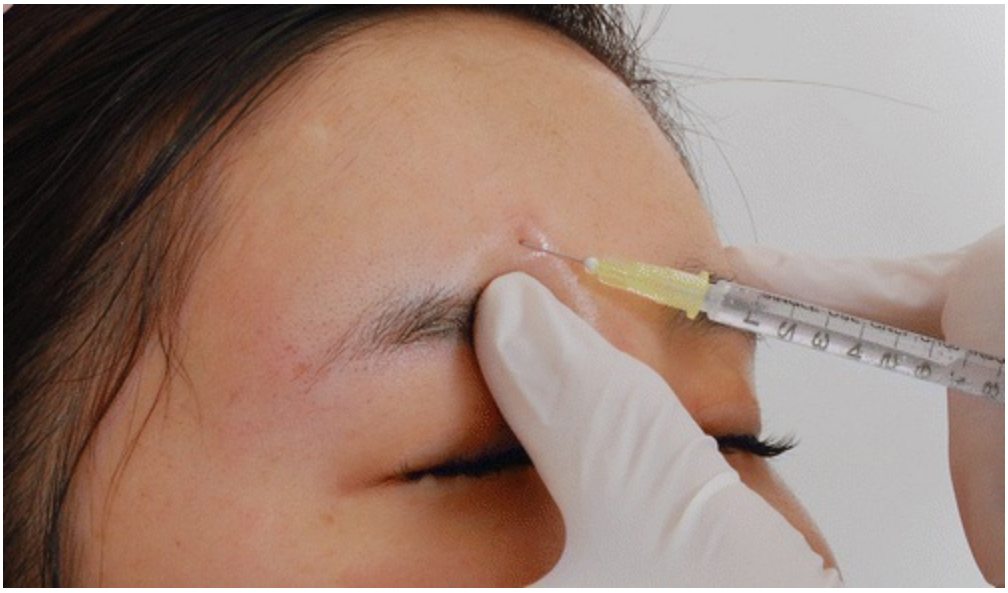


Fig. 2.42 Needle direction and angle for the treatment of glabellar lines

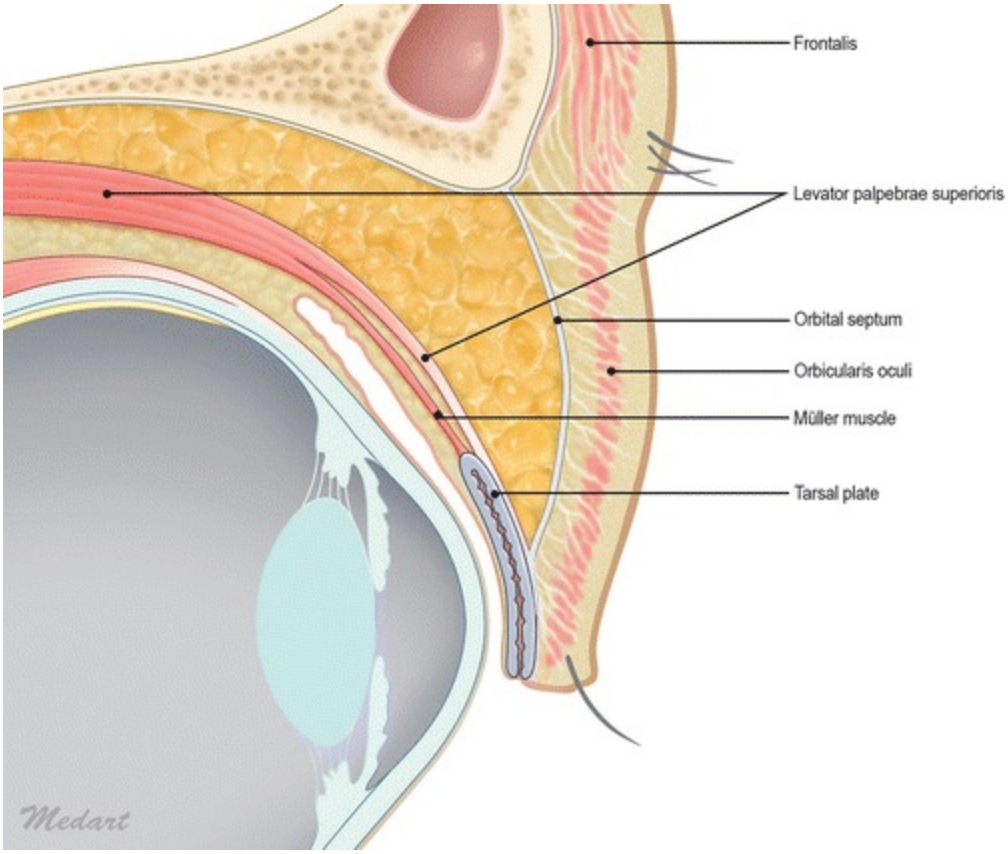


Fig. 2.43 Müller muscle. The Müller muscle located just beneath the conjunctiva receives sympathetic innervation and lifts the upper eyelid. Eye drops contain 0.5 %, and an α-adrenergic agonist can elevate the eyelid immediately to some extent

Interestingly, BoNT-A for the treatment of ptosis would be helpful to improve ptosis caused by BoNT-A injection (see Sect. 2.13). Ptosis may last up to 2–3 months; thus, you should be very careful during the initial treatment.

Tip: 100 % Prevention of Ptosis

Preventing ptosis requires careful attention to various factors such as injection site, dosage and concentration of BoNT-A, needle direction, hand positioning, and speed and posture of injections.

1. The injection site is the most important and should be located in the areas above the orbital rim. The origin site of the CSM is the orbital rim above the medial canthus, but to avoid downward diffusion, the needle tip should be positioned 1 cm superior to the orbital rim. Since the BoNT-A diffuses around 1 cm, a slightly higher injection site does not change its effectiveness. The eyebrows are not recommended as the reference site for injections, especially in patients with eyebrow drooping in their late 50s even though some doctors inject the BoNT-A just above the eyebrow in line with the medial canthus believing that the eyebrow is located on the orbital rim. However, in patients with eyebrow drooping, this approach substantially increases the chance of ptosis. Instead, orbital rim is recommended as the reference site for injections, by palpation with the fingers.

2. As a large volume of BoNT-A and a large dose may diffuse downward, it is recommended to keep the concentration at 4 U/0.1 ml and not to exceed 4 U per point.

3. The needle should be directed superolaterally not to diffuse the BoNT-A to the orbital cavity and kept at a 30° angle from the horizontal line of the eyebrow and at a 30° angle from the skin surface (Fig. 2.42).

4. It is necessary to inject slowly in order not to avoid inflow to the orbital

cavity. Press firmly below the orbital rim with your nondominant hand. The bevel should also be directed upward.

5. During the procedure the doctor usually stands in front of the seated patient. To avoid BoNT-A inflow toward the orbital cavity, the needle should be positioned superolaterally at a 30° angle from the skin surface; therefore, it is better to stand to the left of the patient when injecting into their right side, and vice versa.

6. Patients used to be told not lie down for 3–4 h after injection of BoNT-A for the treatment of glabellar wrinkles, as suggested by some doctors such as Dr. Klein. This is to prevent downward diffusion of the BoNT-A injected into the glabellar area. However, there is no evidence for this insist, and moreover, there had been a claim that lying down position might also prevent the BoNT-A inflow downward, so that it is not recommended no more.

Eyebrow Shape Shifting

After treating glabellar lines with BoNT-A, eyebrow drooping, “samurai eyebrow,” or a widened distance between eyebrows may occur. Even though meant to efface only the glabellar lines, the BoNT-A injected near the origin site of CSM may diffuse to the frontalis muscle, and the head of the eyebrow may droop. Even so, you cannot inject the BoNT-A near the orbital rim without high risk of ptosis. Therefore, patients with high risk for eyebrow drooping should also receive smaller doses of BoNT-A even for the treatment of glabellar lines.

High arched brow which is not preferred by Asian women can also appear after treatment of the glabellar lines with the BoNT-A [32]. This is due to relaxations of depressor actions of CSM and procerus muscle, as well as inactivation of medial part of the frontalis muscle, with resultant increased muscle tone of lateral part of the frontalis muscle through botulinum-rebalancing phenomenon. It is frequently caused by injection into the insertion site of the CSM just above the orbital rim in the midpupillary line. At the beginning of my practice with BoNT-A, I performed prospective

intraindividual comparison study on the effects of BoNT-A injections into the skin above the orbital rim at the midpupillary line for the treatment of glabellar lines (unpublished data). Additional 2 U of BoNT-A was injected in one side of the forehead above the orbital rim at the midpupillary line together with injection points in standard Asian type for the treatment of glabellar lines in twelve human volunteers, and the other side was not injected. While wrinkle effacement was nearly the same between both sides, "samurai eyebrow" appeared in nearly 30 % of cases, always on the side that was injected with additional 2 U of BoNT-A above the orbital rim at the midpupillary line. Therefore, when injections are made above the orbital rim at the midpupillary line for the treatment of glabellar lines, it is recommended to inject an additional 0.5–1 U into the lateral side of the frontalis muscle during the initial treatment in order to avoid "samurai eyebrow" (Fig. 2.39b).

Tip: My First Case with Botulinum Toxin Treatment

My very first BoNT-A patient was a female staff member of the Seoul National University Hospital, whom I treated the glabellar lines some 17 years ago. I recall the agitation I felt after the procedure and nights of lost sleep fearing of a possible ptosis. It was only after the patient revisited my office a week later with a bright smile and a brilliantly smooth glabella that my mind was finally put to rest. To this day, she has remained my regular client, and I recently had the pleasure of also treating her husband. Meanwhile, her glabella is in much better condition than when I first met her.

Sometimes, I wonder what might have happened had I encountered ptosis on my very first case. I doubt I would have taken up BoNT-A treatments at all. Given the significantly higher risks involved in treating the glabella area, I would suggest new practitioners to start with less challenging cases, for example, lateral canthal rhytides, on their first case, since the outcome is generally more dramatic in periorbital lines, while involving significantly lower risks compared to the glabellar and forehead lines. One might also consider trying out their first cases on family members or close relatives, since they are much less likely to bring claims in the event of any adverse events. As for the patient age group, patients in their 20s or 30s are preferably to elderly patients, since BoNT-A does not work on the deep static wrinkles on an aged face, while their sagging eyelids and bulging infraorbital fat are much more likely to cause severe adverse effects.

2.2.8 Bunny Lines/Nasal Side Wall Scrunch Wrinkles

Effect (A), Adverse Effect A), and Technique (A)

These are oblique lines on both sides of the dorsum of the nose that appear while smiling and frowning (Fig. 2.44). Though not solely a product of aging, aging does generally exacerbate bunny lines. Further, treating glabellar lines with BoNT-A may make bunny lines more prominent due to the botulinum-rebalancing phenomenon.

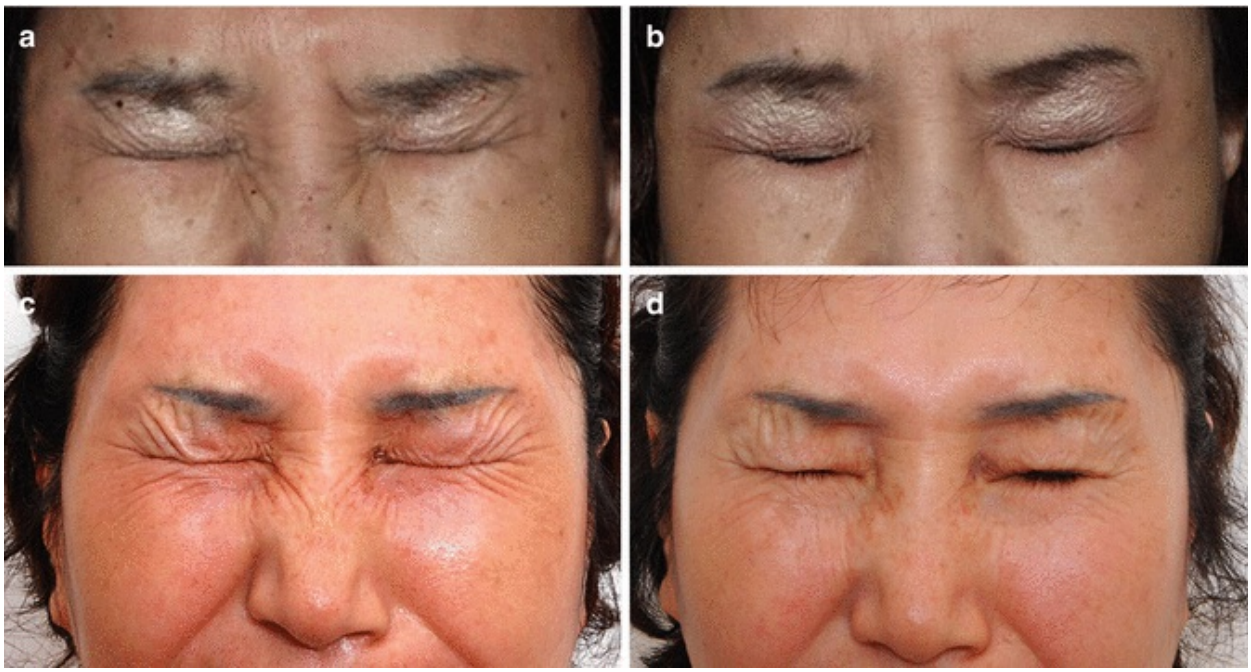


Fig. 2.44 Bunny lines: (**a**, **c**) before and (**b**, **d**) 2 weeks after 6 U injection of BOTOX®

2.2.8.1 Anatomy

It is widely believed that bunny lines are caused by the nasalis muscle. But actually only the vertical lines in the center are caused by the nasalis muscle. Oblique lines at a 45° angle on both sides of the dorsum of the nose are caused primarily by the levator labii superioris alaeque nasi (LLSAN) and the additional medial muscular band of the orbicularis oculi muscle (see Sect. 2.23).

The nasalis is comprised of the transverse and alar parts. The alar part is a C-shaped muscle that originates from the maxilla and canine fossa. The transverse part receives fibers from the superficial part of LLSAN. The alar part is a square-shaped muscle that originates from the maxilla above the

maxillary lateral incisor and inserts deep into the skin surface at the inferior part of the ala nasi, the alar facial crease, and the alar lobule. The transverse part presses the naris and makes it narrow, while the alar part widens it.

2.2.8.2 Injection Techniques

Inject 2 U of BoNT-A into both the center and sidewalls of the nasal dorsum (Fig. 2.45). As the LLSAN should not be paralyzed completely, the lines do not completely disappear and a few shallow lines remain around the nasofacial groove. You should be careful about unwanted facial expression changes such as lengthening of the philtrum caused by complete paralysis of LLSAN by the injections into the lateral side of the nasolabial groove. In fact, there is no muscle under the injection points on both sidewalls of the nasal dorsum as shown in Fig. 2.45, but the BoNT-A partially affects LLSAN through diffusion.

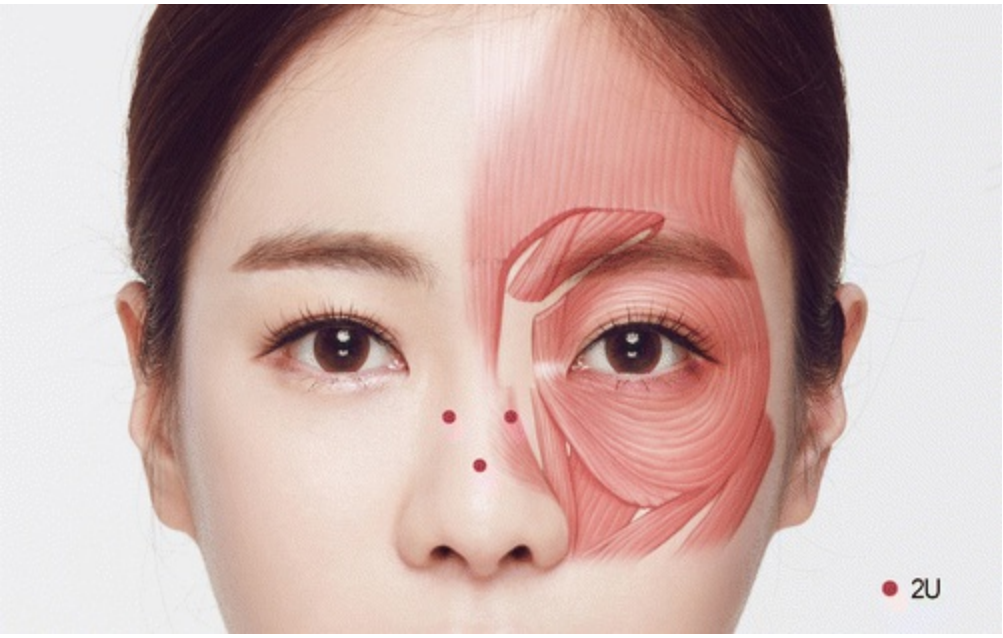


Fig. 2.45 Injection points for bunny lines

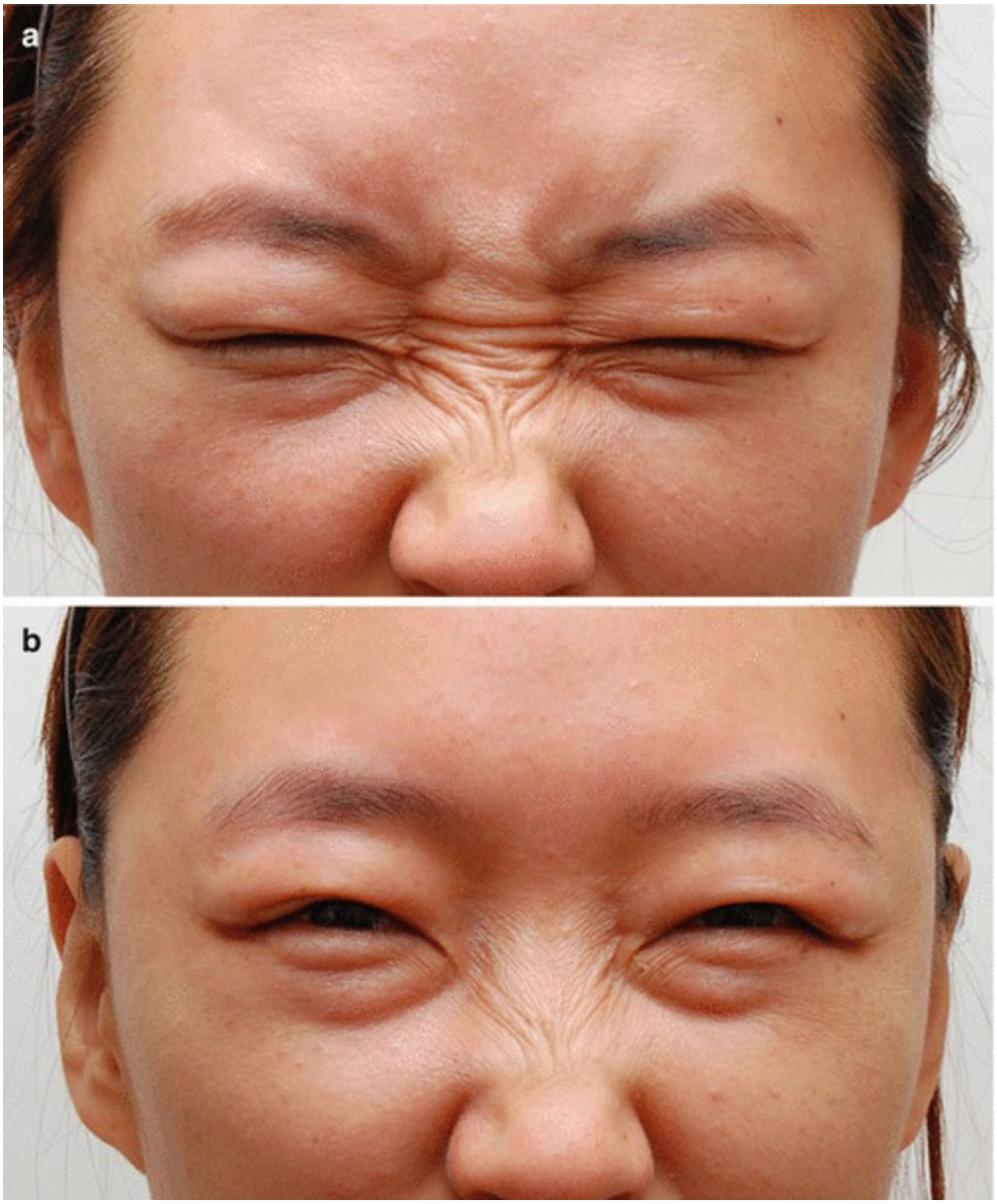


Fig. 2.46 Horizontal radix lines: (**a**) before and (**b**) 2 weeks after 18 U injection of BOTOX®

2.2.9 Horizontal Radix Lines

Effect (A), Adverse Effect (A), and Technique (A)

While the procerus is the main cause of horizontal lines on radix between the eyes (Fig. 2.46), however, the CSM, which presses the radix from above to downward, is also partially involved. Injections should be made in the same way as when treating glabellar lines, with an additional injection of 8 U into the procerus divided by four points (Fig. 2.47).

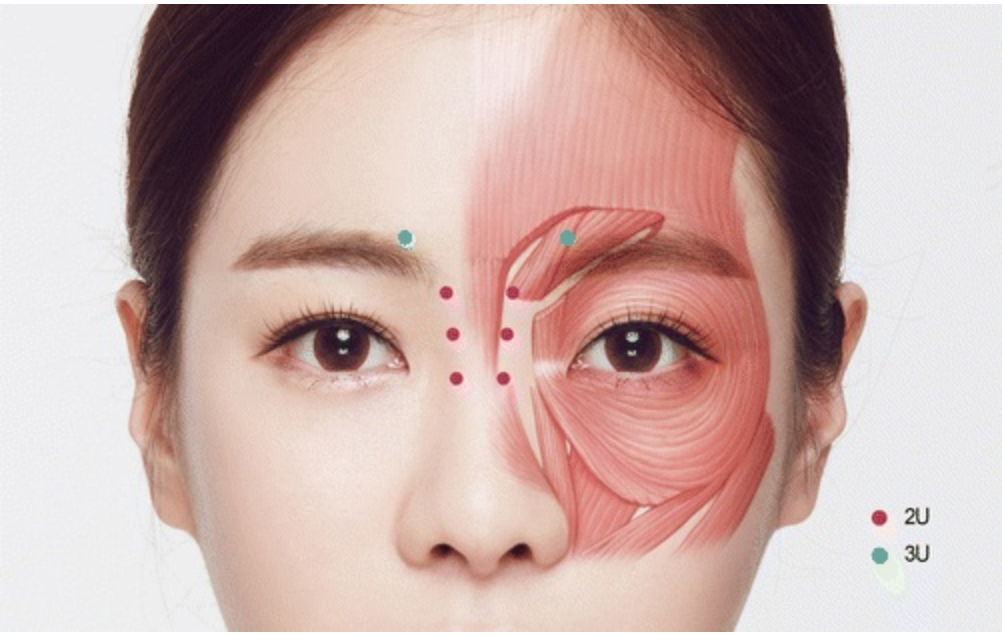


Fig. 2.47 Injection points for Horizontal radix lines

2.2.10 Nasal Tip Elevation

Effect (C), Adverse Effect (B), and Technique (B)

In persons with well-developed nasalis and depressor septi nasi muscles, you can achieve elevation of the nose tip by paralyzing these muscles with BoNT-A. Francisco Perez-Atamoros of Mexico reported at a 2002 Vancouver meeting organized by Dr. Carruthers that the nose tip can be lifted 3–5 mm for 3.8 months through BoNT-A injections. However, it seems that not all patients show good effect from this treatment. Instead only patients with developed muscles pushing down nose tips respond well to this treatment. I also tried the same technique in ten Korean patients but only one showed some effects. I believe this is partly due to evaluation target which focuses only on resting state, not the state of facial expressions.

When a patient's nose tip droops while smiling, it can be improved by BoNT-A injection into the depressor septi nasi, levator labii superioris (LLS), and LLSAN. In 2013, Cigna of Italy performed a double-blind prospective study on the effect of BoNT-A for the plunged tip and found that the nose tip is elevated and the philtrum lengthened by BoNT-A injected into the depressor septi nasi [33].

Even though filler should be considered primarily for the elevation of the nose tip, BoNT-A may be helpful for stabilizing and sustaining the shape of

the nose filler by minimizing absorption and migration during nasal muscle movement.

2.2.10.1 Anatomy

When a patient's nose tip droops while smiling, it can be improved through BoNT-A injections into the depressor septi nasi, LLS, and LLSAN. The depressor septi nasi originates from the nasal spine and inserts into the nasal tip, pulling and flattening the nose tip while smiling. LISAN and LLS insert into the ala nasi, pulling the ala nasi superolaterally resulting in a plunged nose (see Sect. 2.23). The nasalis is also involved in drooping nose tip because it is responsible for pressing and widening or narrowing the naris (see Sect. 2.19).

2.2.10.2 Injection Techniques

4 U is injected into the subnasale inferior to the columella and the ala of the nose at both sides with a total of 12 U doses. Additionally, 2 U is injected into the LLSAN at lateral side to the ala in line with the upper margin of the ala only if the patients present a droopy nasal tip when smiling (Fig. 2.48).

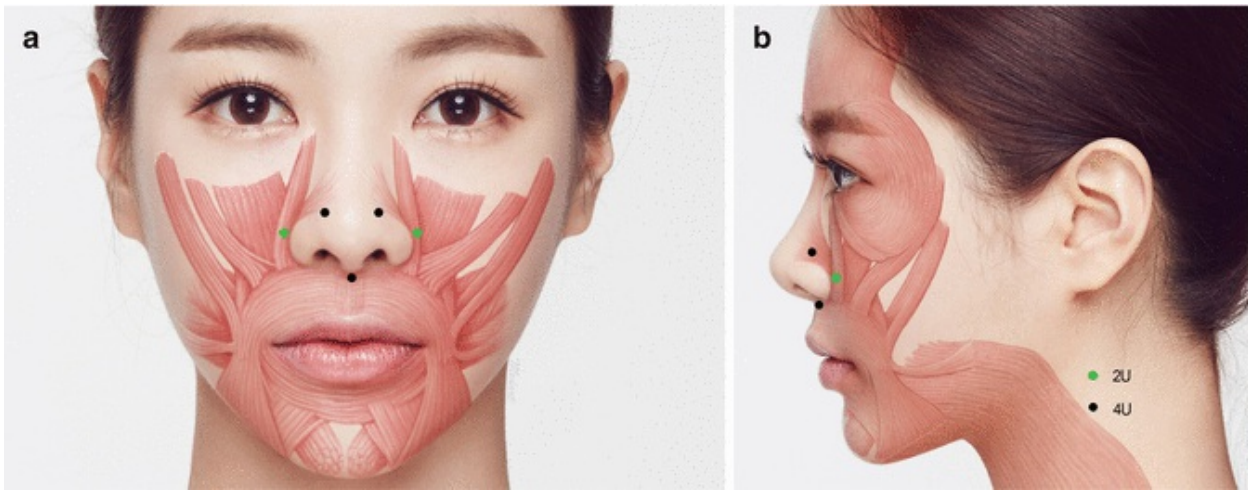


Fig. 2.48 Injection points for nasal tip elevation (**a**) front view, (**b**) profile view

2.2.11 Excessive Gingival Display/Gummy Smile

Effect (B), Adverse Effect (C), and Technique (B)

Excessive gingival display, known as a "gummy smile," occurs when the

gum is excessively exposed by the hyperactivity of lip elevators while smiling (Fig. 2.49). It is possible to correct excessive gingival display with BoNT-A by mitigating strong contraction of the lip elevators such as levator labii superioris alaeque nasi (LLSAN), levator labii superioris (LLS), zygomaticus minor, and the zygomaticus major. However, complete paralysis of the LLS and zygomaticus minor will result in a simian-like face due to the disappearance of the nasolabial folds. Moreover, it is impossible to smile if the zygomaticus major is paralyzed. Therefore, the LLSAN and LLS should be partially paralyzed.

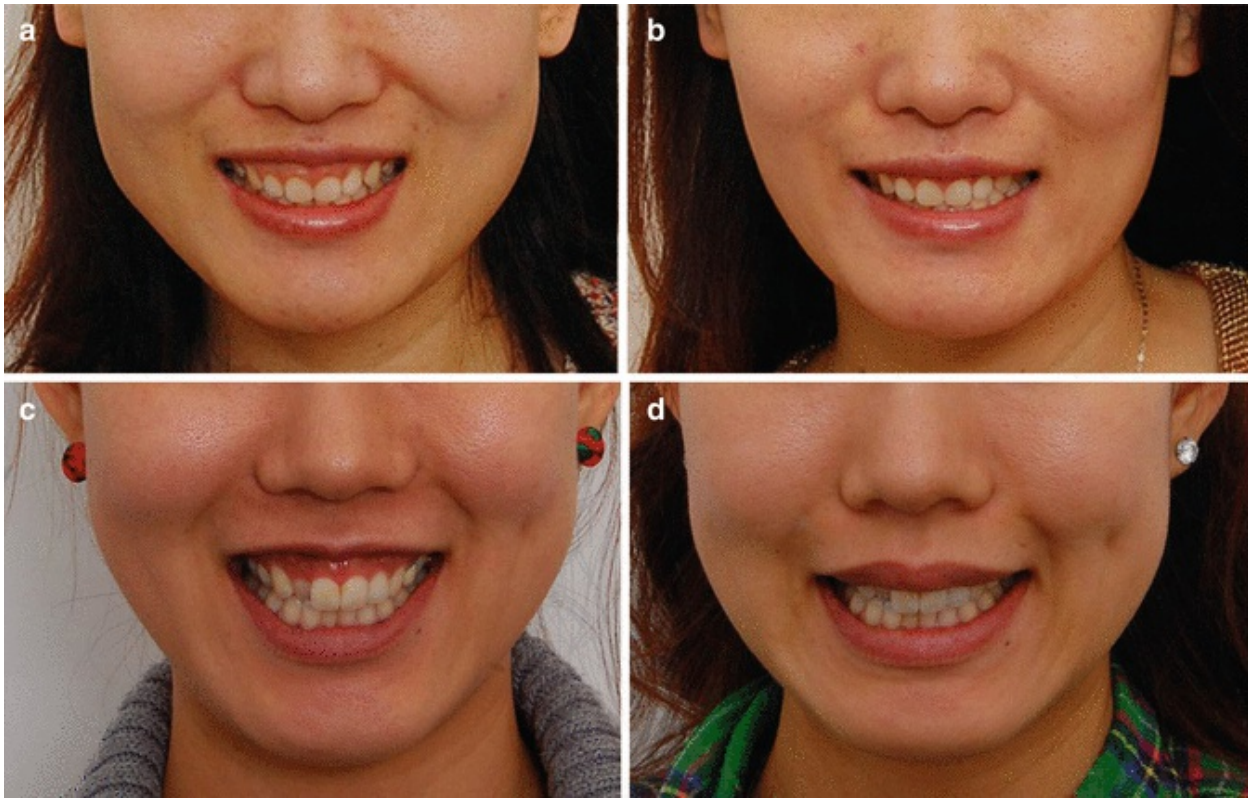


Fig. 2.49 Excessive gingival display: (**a, c**) before and (**b, d**) 2 weeks after 2 U injection of BOTOX® per side

2.2.11.1 Anatomy

The LLSAN originates from the frontal process of the maxilla and the maxillary process of the frontal bone. It then runs down vertically and inserts into the mid-central part of the orbicularis oris, the nasal ala, and the skin of the ala of the nose. It pulls the middle of the upper lip upward and pulls the nasal ala both upward and laterally. Therefore, it is involved in forming the

medial upper portion of the nasolabial fold. It also pulls the tip of the nose down, which is also known as the plunged nose.

The LLS originates from the orbital rim of the maxilla and inserts into the upper lip. Most muscle fibers of the medial half of LLS are also attached to the ala of the nose (90 %). Therefore, the LLSAN and the LLS not only pull the middle of the upper lip upward but also pull the nasal ala both upward and laterally. The zygomaticus minor originates from the zygomatic bone and inserts into the upper lip and partially into the ala nasi. Among these upper lip elevators, the LLS locates most deeply, the LLSAN lays medially, and the zygomaticus minor lies laterally superficial to LLS. The infraorbital nerve appears from the infraorbital foramen beneath the LLS. These three muscles converge to the lateral portion of ala nasi and are intertwined at the upper lip (Fig. 2.50).

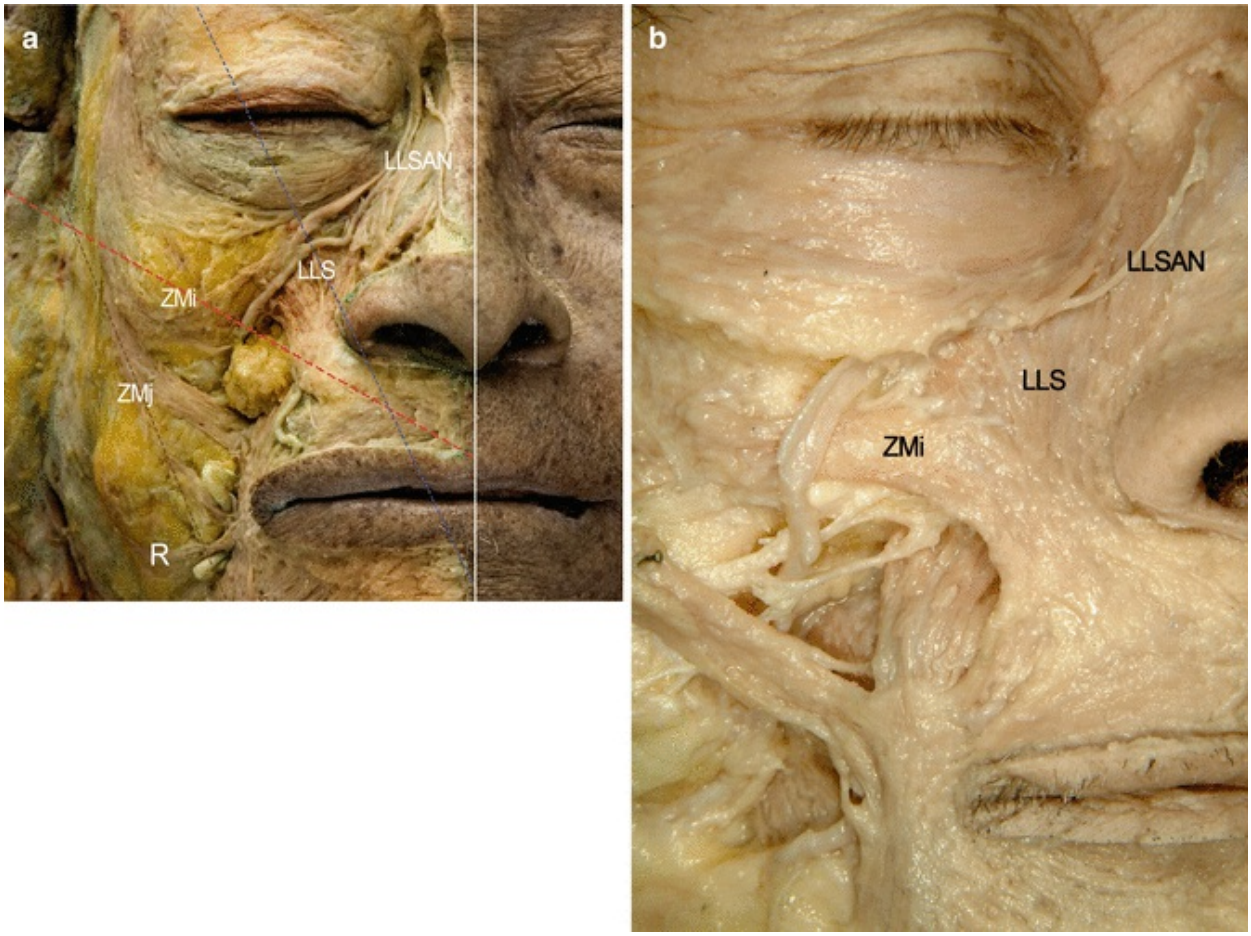


Fig. 2.50 Elevators for the upper lip. (*LLS* levator labii superioris, *LLSAN* levator labii superioris ala nasi, *Zmi* zygomaticus minor) (Photo: courtesy from Professor Hee-Jin Kim). (**a**) Vectors of lip elevators. (**b**) LLSAN, LLS, and ZMi muscles merge near the lateral portion of the ala nasi

2.2.11.2 Injection Techniques

1–2 U of BoNT-A should be injected into the LLSAN in line with the upper margin of the ala nasi (Fig. 2.51). If the LLSAN is excessively paralyzed, the upper lip will droop, which alters facial expressions. Furthermore, if the BoNT-A diffuses laterally to the LLS and zygomaticus minor, it is almost impossible to elevate the upper lip when smiling. Therefore, the minimum dose is recommended during the initial treatment with an additional injection after 2 weeks if necessary.

Fig. 2.51 Injection points for excessive gingival display

2.2.12 Nasolabial Folds, Asymmetric Smile

Effect (C), Adverse Effect (C), and Technique (B)

Nasolabial folds are static wrinkles with deep furrows which are generally considered to be untreatable with BoNT-A. Since some dynamic components are also involved in the formation of the nasolabial folds in addition to the static components, however, a selective approach can be attempted with the BoNT-A for the treatment of nasolabial fold when smiling exaggerated the severity of nasolabial fold or asymmetry. BoNT-A can also be useful for the treatment of the “zygomaticus major-type” nasolabial folds caused by excessive contraction of the zygomaticus major resulting in elongation of

nasolabial fold up to the lateral cheek (Fig. 2.52). Since an overdose can result in a simian-like appearance or masklike face, however, great care should be taken to avoid overdose, and this indication would not be recommended for beginners.

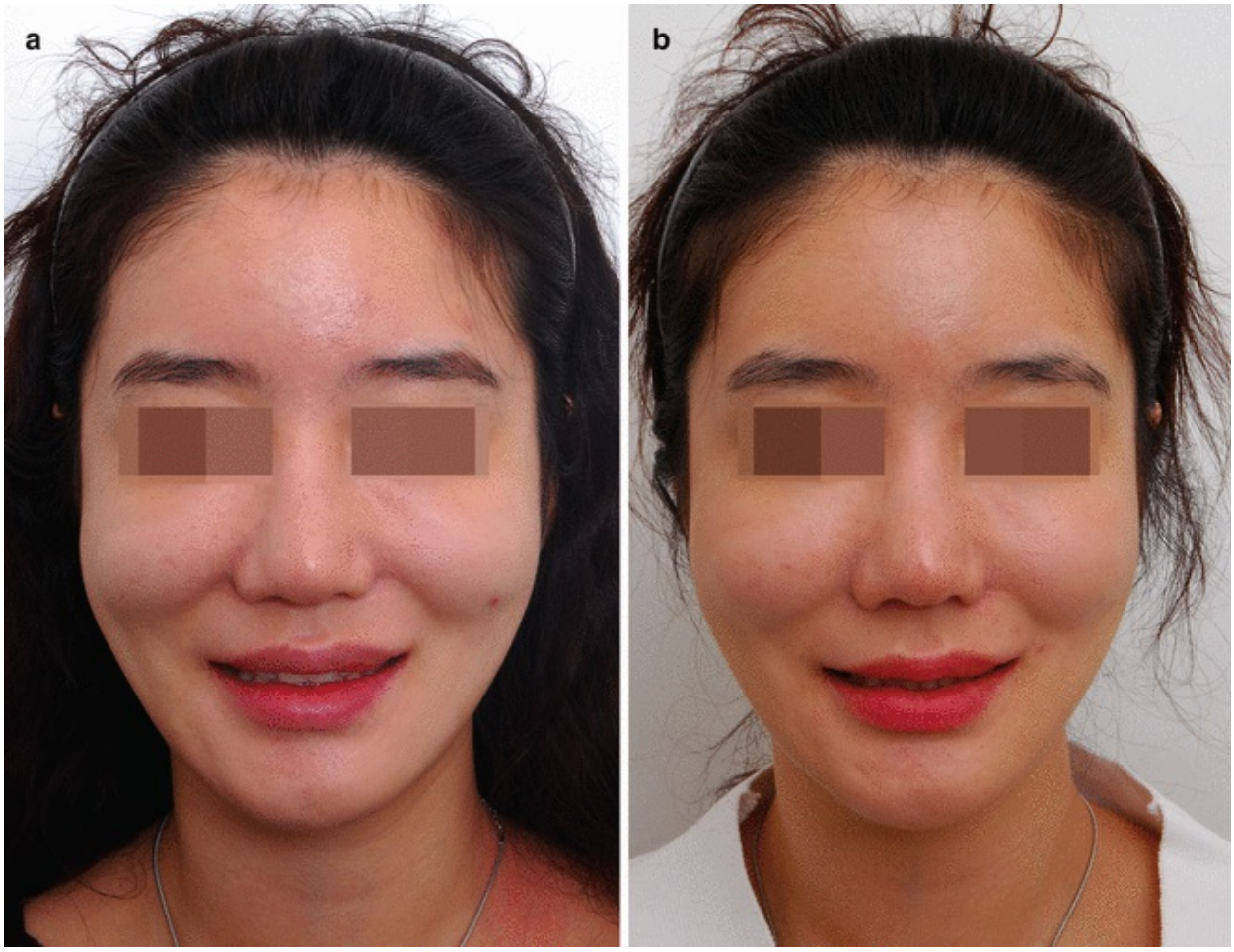


Fig. 2.52 Zygomaticus major-type nasolabial folds: (**a**) before and (**b**) 2 weeks after 2 U injection of BOTOX® per side

Episode: Doctors Who Dare to Use Botulinum Toxin for the Treatment of Nasolabial Folds

About 10 years ago, a Korean female celebrity who regularly appeared in a prime-time TV drama became the main target of celebrity gossip. Apparently, she had some work done on her face which had left her with a crooked lip, which she was self-consciously trying to hide by refusing to look directly into the camera. According to rumors, she had undergone a jawline surgery which narrowed her face line but fatally hit a nerve, hence the awkward lips. As

plausible as that may sound, I knew for a fact that the cause was a BoNT-A injection into the nasolabial folds which she received with BoNT-A for masseter reduction, because she was a regular client of the notorious Dr. “K.” At that time, Dr. “K” was gaining fame by making outrageous claims on the benefits of BoNT-A as a cure-all solution for countless indications including breast augmentation, hip lifts, and nasolabial fold correction. I know of another famous comedian who also received BoNT-A injection for nasolabial fold from his clinic and suffered from the same adverse effect for some period of time. The problem is that even today doctors who trained under Dr. K’s apprenticeship are still attempting to treat static component of nasolabial folds with BoNT-A. As concerns nasolabial folds, the odds of getting adverse events such as altered facial expression far outweigh the benefits. Unless performed on the right patient, it can result in the elongation of the philtrum, creating a simian face, similar to Joker played by Jack Nicholson in the movie Batman (1989). In a nutshell, don’t dare doing it unless you are 100 % confident of doing it just right.

2.2.12.1 Anatomy

The dynamic factors in the formation of nasolabial folds are associated with the LLSAN, LLS, zygomaticus minor, and zygomaticus major. Some of the muscle fibers are directly inserted into the skin and form the nasolabial folds. If we consider the origins, insertions, and vectors of each muscle, the medial one-third of nasolabial folds seems to be formed by the LLSAN and LLS, with the middle one-third by the zygomaticus minor and the lateral one-third by the zygomaticus major.

2.2.12.2 Injection Techniques

The principle for the treatment of the dynamic nasolabial fold with the BoNT-A is an individualized approach based on the pattern of hyperactive muscles. It is advised to weaken the LLSAN first in order to prevent severe facial expression changes. 1–2 U is injected shallowly into the point just lateral to the upper margin of the ala nasi (Fig. 2.53a).

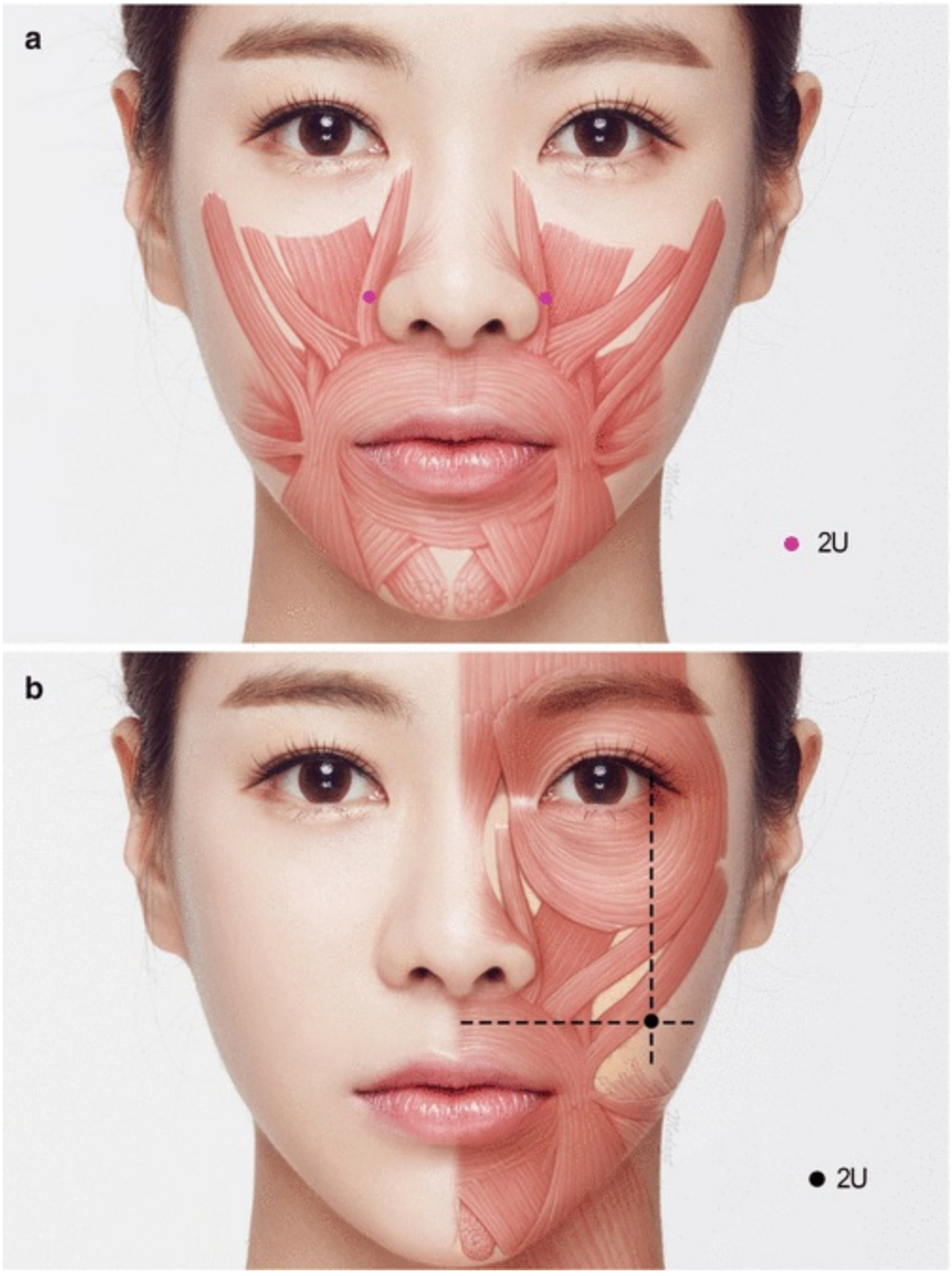


Fig. 2.53 Injection points for nasolabial folds. (**a**) Standard type. (**b**) Zygomaticus major type

For zygomaticus major-type nasolabial folds, direct injection of BoNT-A into the zygomaticus major muscle is recommended. According to western literature, a deep injection should be made at the intersection of the horizontal base line of the ala nasi and the vertical lateral canthal line when treating facial spasms with BoNT-A [34]. For Asians, however, it would be better to

make a deep injection into a point slightly lower than that of Caucasians at the intersection of the horizontal mid-philtrum line and the vertical lateral canthal line as the modiolus is located lower in Asians than the Caucasians (Fig. 2.53b).

Even though custom-tailored approach should be basically made for the treatment of the asymmetric smile, the zygomaticus major would be considered first as the target. In general, BoNT-A should be injected into hyperfunctional side which is abnormally active. However, in case with facial palsy or stroke, BoNT-A should be injected into the normal side to establish an equilibrium between the right and left sides. For the treatment of asymmetric smile caused by malformation of the maxillary bone, right–left equilibrium can be also attained by injecting BoNT-A into the side with excessive gum display (Fig. 2.54). The same method used to treat "zygomaticus major-type" nasolabial folds can be applied for the asymmetric smile caused by the zygomaticus major. When the zygomaticus minor is suspicious as a cause of asymmetric smile, BoNT-A should be injected deeply at the intersection of the horizontal base line of the ala nasi and the lines connecting the lateral canthus and mouth corner (Fig. 2.55).

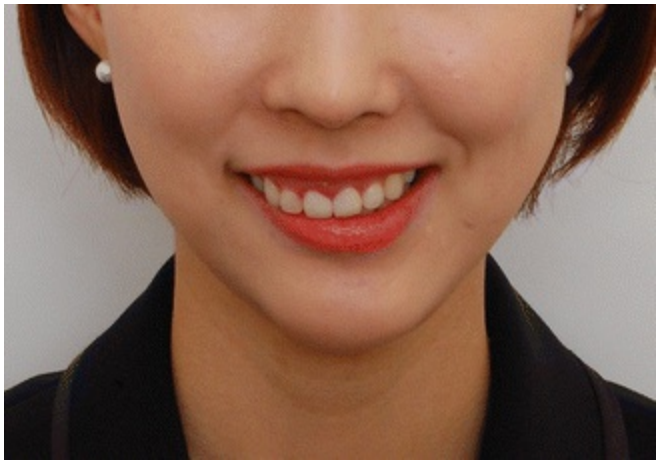


Fig. 2.54 Smile asymmetry caused by maldevelopment of the maxillary bone

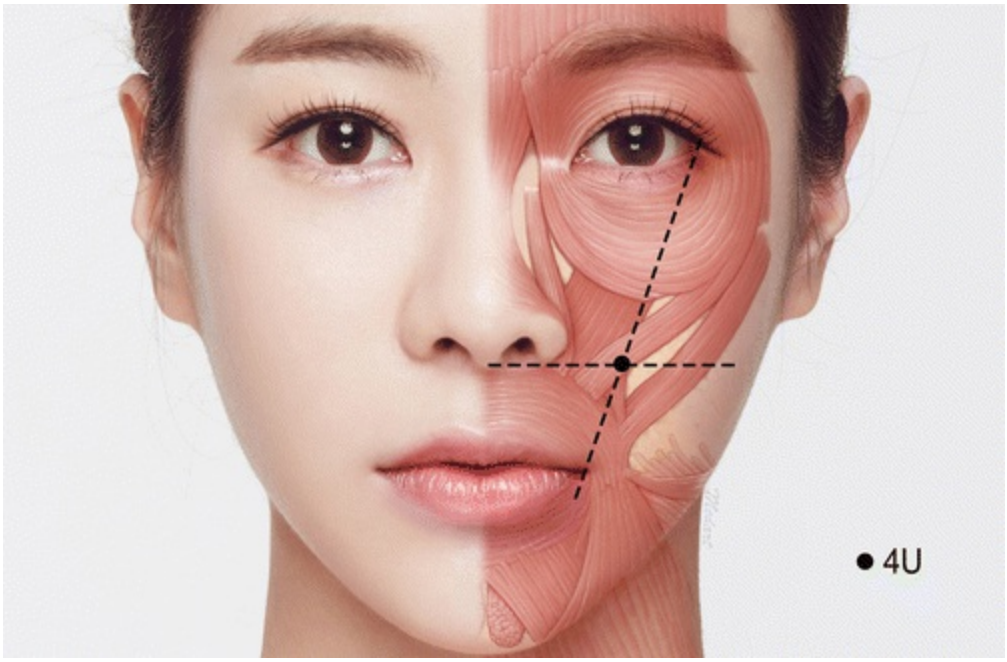


Fig. 2.55 Injection points for zygomatic minor muscle

Since an overdose can result in a simian-like appearance or masklike face, it is advised to give just 2 U during the initial treatment and to consider touch-up injection at follow-up if necessary.

2.2.13 Ala Band and Dimpling

Effect (B), Adverse Effect (C), and Technique (B)

There are some individuals who have noticeable bulging in the paranasal area when they smile. This occurs when the zygomaticus minor inserts into the ala nasi [35]. The zygomaticus minor basically originates from the zygomatic bone and inserts into the upper lip. However, in 28 % of Koreans some of the muscle fibers are attached to the ala nasi. A superficial injection of 1–2 U of BoNT-A should be made directly into the ala band (Fig. 2.56). Extreme caution should be exercised to avoid injecting either too deeply or with overdose as paralysis of the LLSAN can result in altered facial expressions.

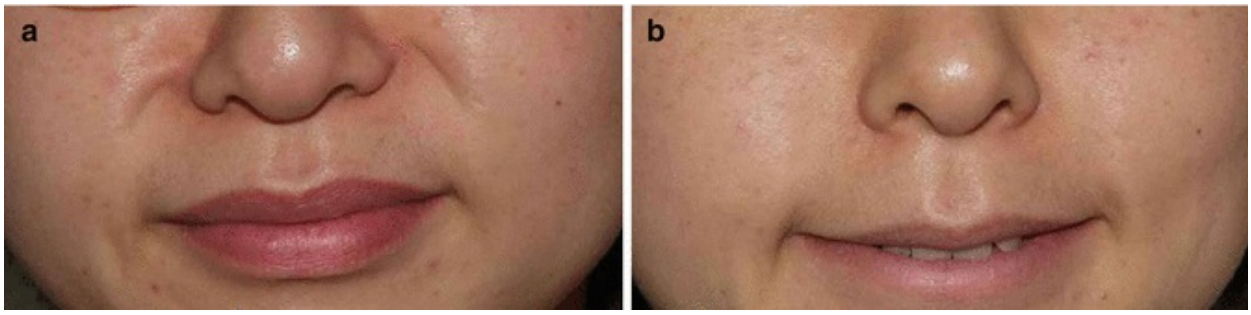


Fig. 2.56 Ala band: (**a**) before and (**b**) 2 weeks after 2 U injection of BOTOX® per side

Dimpling is caused by the attachment of facial expression muscles to the skin and occurs frequently around the nasolabial fold and lips. The most common type is buccal dimpling which occurs in 23.4 % of Koreans [36]. Buccal dimples appear when the lower muscle fibers of the zygomaticus major are attached to the skin around the buccal area lateral to the mouth angle. They also appear when the lateral band of the orbicularis oculi is attached to the skin [22]. The dimples around the nasolabial folds and lips are caused by the attachment of the risorius to the skin. A superficial injection of 0.5–1 U of BoNT-A should be made into the corresponding site (Fig. 2.57). Great care should be taken to avoid overdose or deep injection because the underlying muscles can be affected.

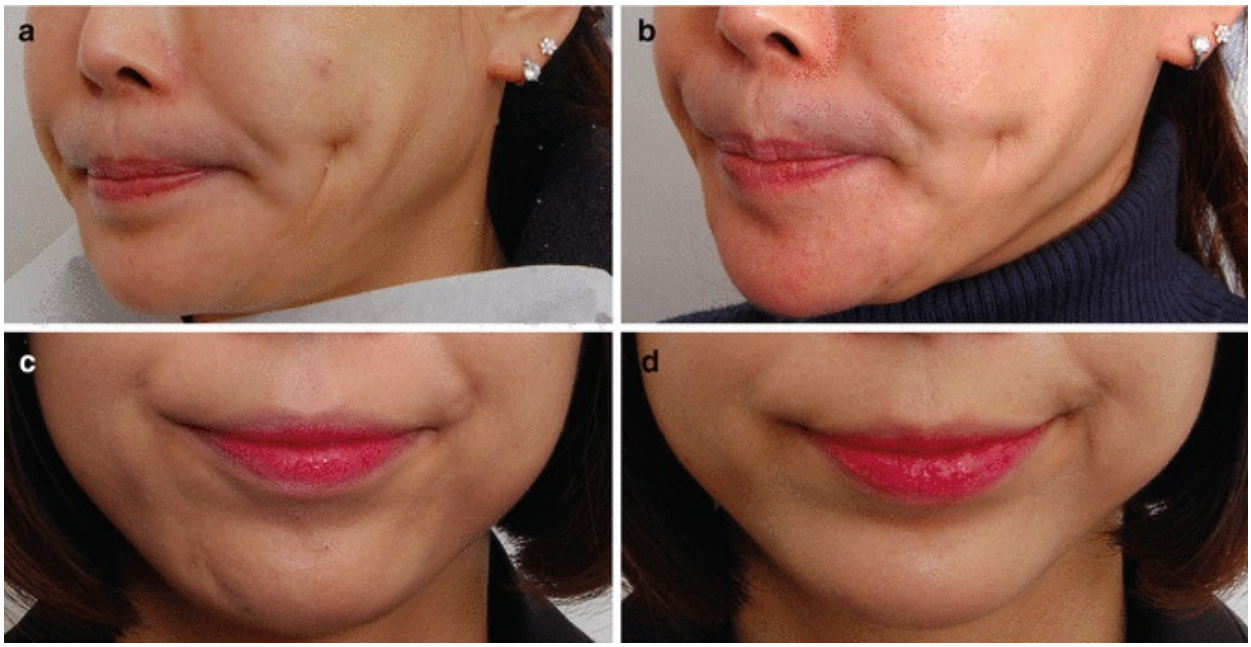


Fig. 2.57 Dimpling: (**a**, **c**) before and (**b**, **d**) 2 weeks after 0.5 U injection of BOTOX® per point

2.2.14 Perioral Lines (Purse-String Lips)

Effect (B), Adverse Effect (C), and Technique (B)

2.2.14.1 Anatomy

The orbicularis oris muscle, the mouth's sphincter muscle, encircles the mouth. It is responsible for puckering the lips and closing the mouth. While the inner fibers of the orbicularis oris originate from the alveolar bone of the maxilla above the incisors, most of muscle fibers consisting orbicularis oris are neighboring facial muscular fibers attached to the lips. The upper lip is connected to the LLSAN, LLS, levator anguli oris (LAO), zygomaticus minor, and zygomaticus major. The lower lip is connected to the depressor anguli oris (DAO), depressor labii inferioris (DLI), risorius, mentalis, platysma, and buccinators.

2.2.14.2 Injection Techniques

1 U is injected superficially into the two points per side 1–2 mm above the vermilion border of the upper lip: the points are imaginary marks dividing the whole length from the midpoint of the upper lip to the left and right mouth corner into three parts each (lip standard, Fig. 2.58a). If the wrinkles are severe, you may add one more injection into the point above the two points (severe form, Fig. 2.58b). For severe wrinkles below the lower lip, a total of 4 U can be injected into the lower lip using the same method. Reconstitution with 5 ml resulting in a concentration with 2 U/0.1 ml can be helpful to perform an accurate injection. In order to avoid altered facial expressions caused by close injection to the mouth corner while smiling or talking, the injection points should be within two-third of the entire length of the upper lip. The overdose makes patients drool when they brush their teeth, and moreover rice grains or other small food particles can become stuck between their gums and upper lip. Therefore, caution must be exercised to avoid injecting overdose during the initial treatment. For severe wrinkles around the lips, filler should be used in conjunction with BoNT-A.

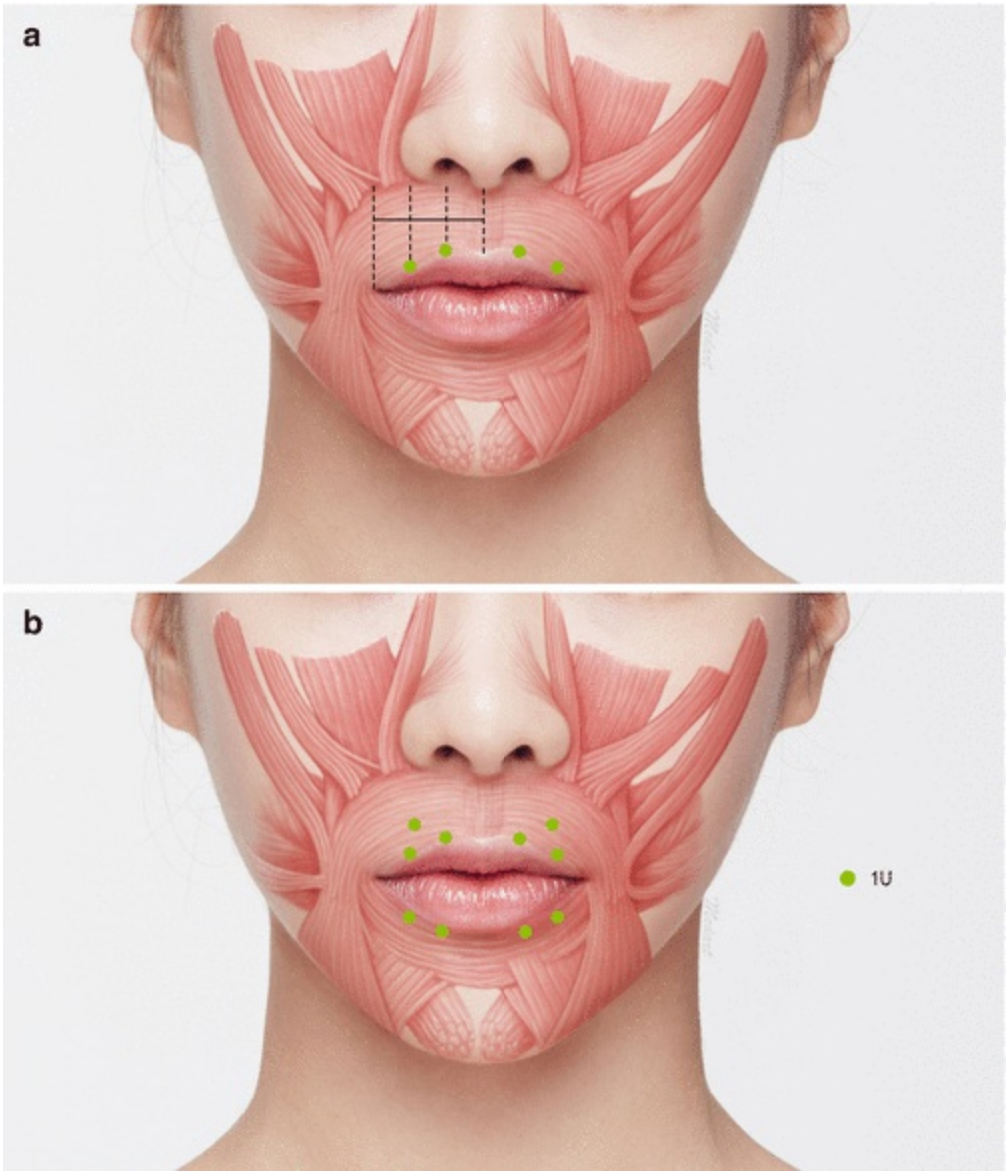


Fig. 2.58 Injection points for perioral lines (purse-string lips). (**a**) Standard type. (**b**) Severe type

2.2.14.3 Photographs

Take two front views, at rest and while the patient is whistling (Fig. 2.59).

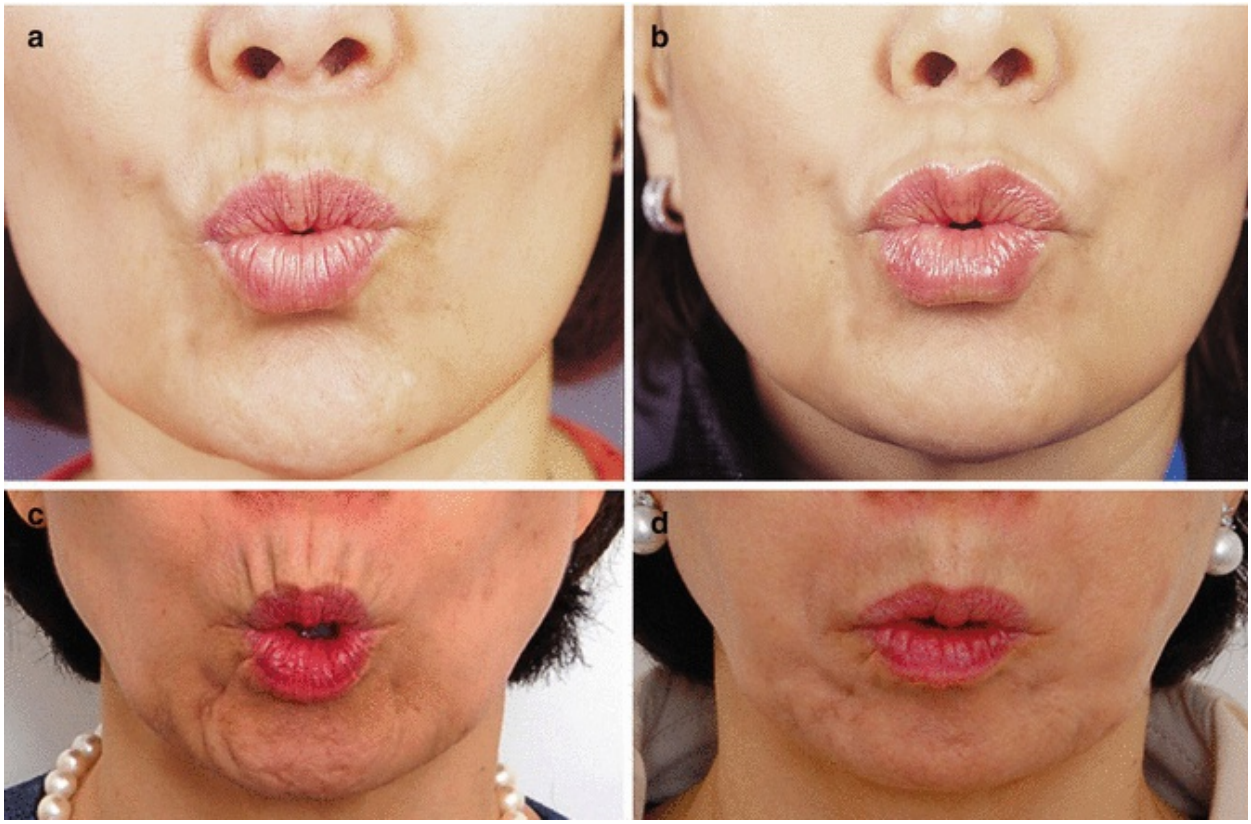


Fig. 2.59 Perioral lines: (**a**, **c**) before and (**b**, **d**) 2 weeks after 4 U injection of BOTOX®

2.2.15 Mouth Corner Elevation

Effect (B), Adverse Effect (C), and Technique (B)

The elevator and depressor muscles for the mouth corner form an equilibrium in the modiolus. Botulinum toxin has been used to elevate the corner of the mouth by weakening the DAO, the typical mouth corner depressor due to relative reinforcing of the elevators. After the procedure, the mouth corner is lifted upward to some extent similar to Meg Ryan's while gently smiling or even at rest (Fig. 2.60).

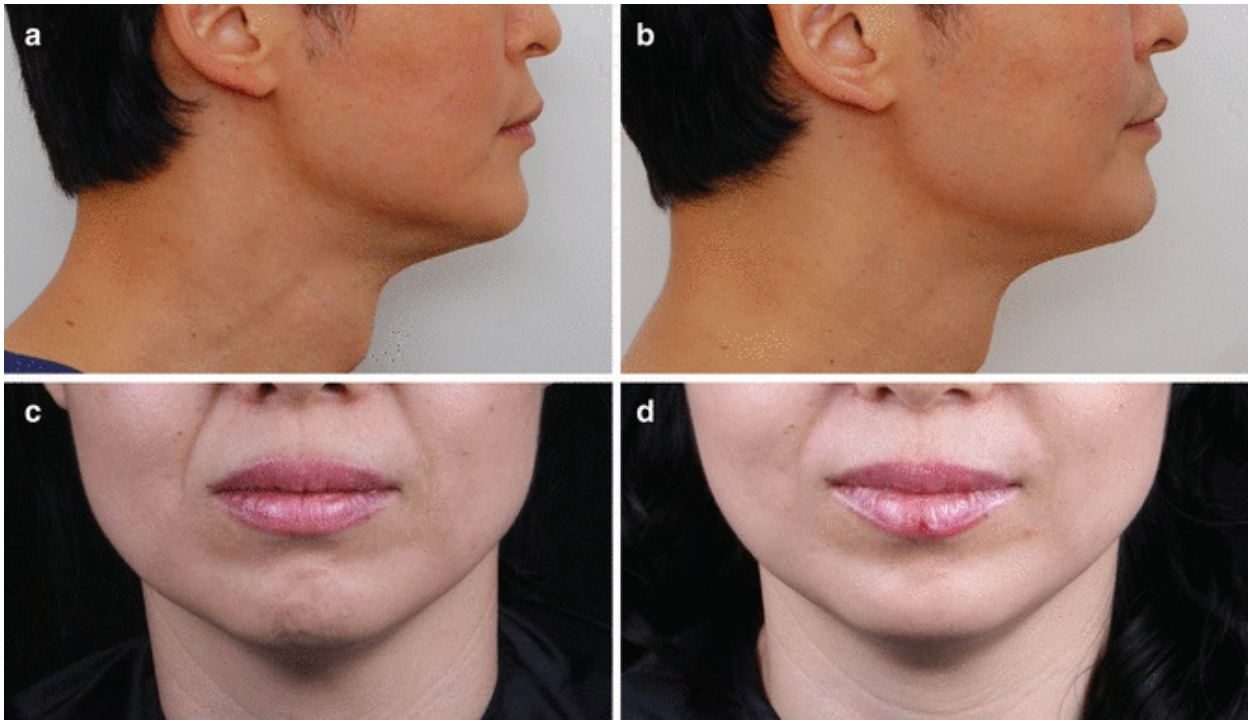


Fig. 2.60 Mouth corner elevation: (**a**, **c**) before and (**b**, **d**) 2 weeks after 3 U injection of BOTOX® per side. (**c**, **d**) (Photo: courtesy of Dr. Jee-young Bae)

Since platysma also plays an important role in pulling down the mouth corner, it would be better to inject BoNT-A into the platysma muscle together with injection into DAO for the purpose of elevating the mouth corner (see Sect. 2.29).

Tip: Anatomy of Muscles Around the Mouth

A total of 22 muscles in 11 pairs surrounding the orbicularis oris are responsible for moving the lips. They can be classified into the following categories according to the direction of lip movement: five elevators (levator labii superioris alaeque nasi, levator labii superioris, zygomaticus minor, zygomaticus major, and levator anguli oris), three depressors (depressor anguli oris, depressor labii inferioris, and platysma), two muscles which pull the mouth angle laterally (risorius and buccinator), and only one lower lip elevator (mentalis) (Fig. 2.61).

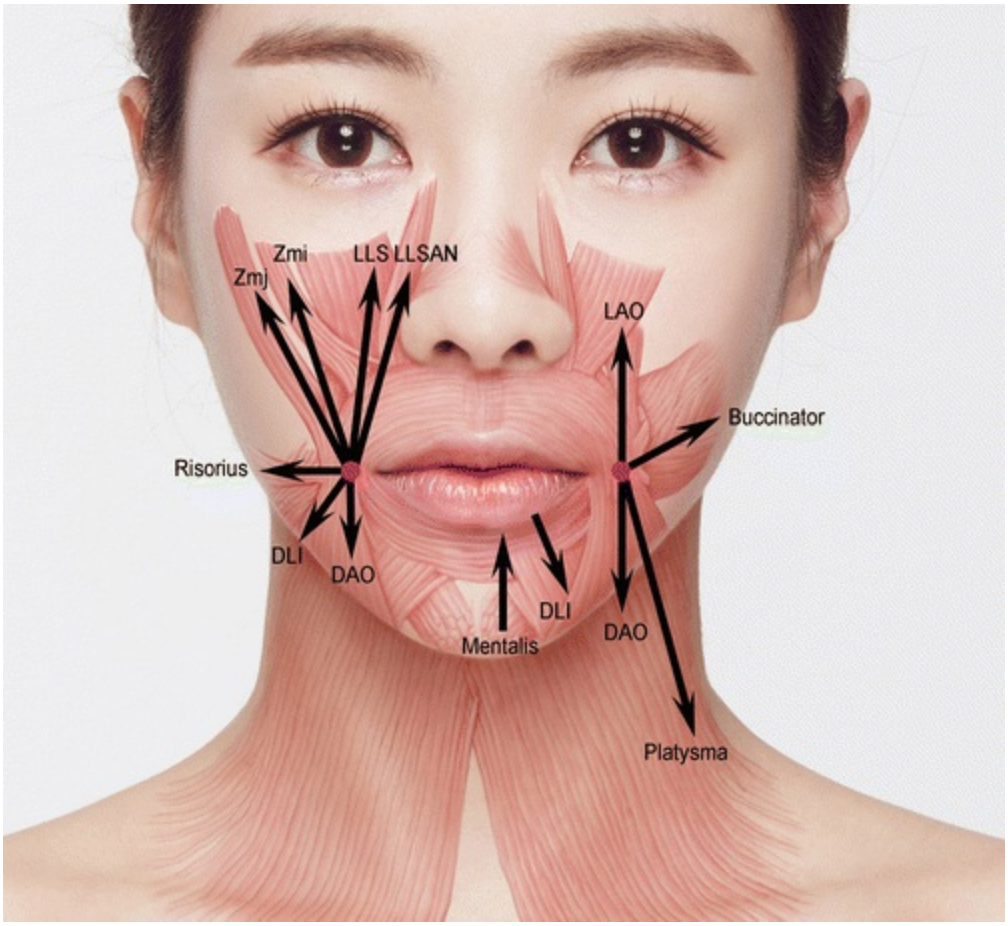


Fig. 2.61 Vectors of perioral muscles. A total of 22 muscles in 11 pairs surrounding the orbicularis oris: five elevators, three depressors, and two muscles which pull the mouth angle laterally and only one lower lip elevator, mentalis. *LLSAN* levator labii superioris alaeque nasi, *LLS* levator labii superioris, *Zmi* zygomaticus minor, *Zmj* zygomaticus major, *LAO* levator anguli oris, *DAO* depressor anguli oris, *DLI* depressor labii inferioris

Based on muscle depth, they can also be classified as superficial layer and deep layer, and the superficial layer can be further subclassified into three sublayers, totaling four layers. The first superficial layer includes the depressor anguli oris, the orbicularis oris, and the superficial part of the zygomaticus major. The second layer includes the depressor labii inferioris (DLI), platysma, risorius, zygomaticus minor, levator labii superioris alaeque nasi (LLSAN), and the deeper part of the zygomaticus major. The third layer includes the levator labii superioris (LLS) and orbicularis oris. Lastly, the fourth layer includes the levator anguli oris (LAO), mentalis, and buccinator.

2.2.15.1 Anatomy

The DAO, which is triangular shaped, arises from the oblique line of the mandible where its fibers converge with depressor labii inferioris muscle fibers. The DAO inserts into the modiolus and interlaces with the orbicularis oris and the risorius. The inferior and medial borderline in Asians is located 1.5 cm lateral to the mandibular symphysis. The inferior width of the DAO is known to be 3.6 cm on average (Fig. 2.62) [37].

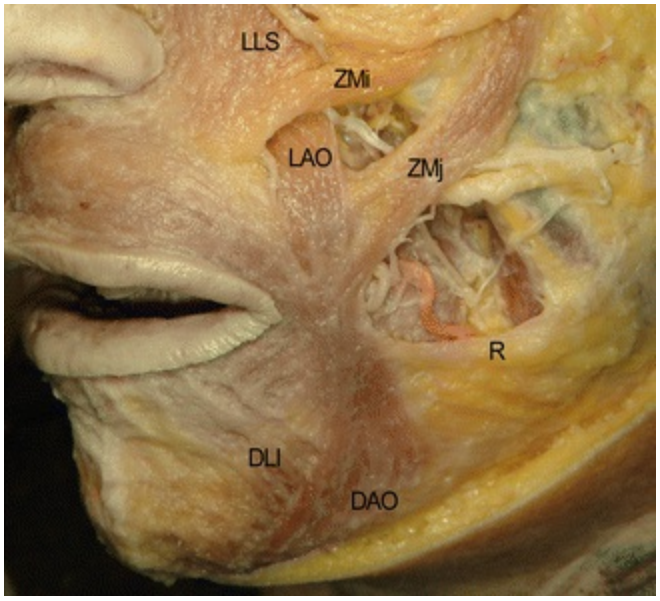


Fig. 2.62 Depressor anguli oris (DAO) (Photo: courtesy from Professor Hee-Jin Kim). *DAO* depressor anguli oris, *DLI* depressor labii inferioris, *MS* masseter, *MM* mandibular marginal branch, *Zmj* zygomaticus major

Tip: Modiolus in Koreans

The term “modiolus” is derived from Latin meaning the hub of a wheel. The modiolus is a dense, thick, muscular mass formed by interlacing the muscle fibers converging toward the mouth corner with the zygomaticus major, levator anguli oris, depressor anguli oris, risorius, buccinators, and orbicularis oris muscle (Fig. 2.63). Histologically, it is a dense tissue with plenty of collagen, which can be seen by the naked eye in 21.4 % of Koreans [39]. In short, the modiolus is a common insertion point of facial expression muscles around the lips. As a result, it is heavily involved in the formation of facial expressions around the lips in a variety of emotional states in addition to the formation of the nasolabial folds.

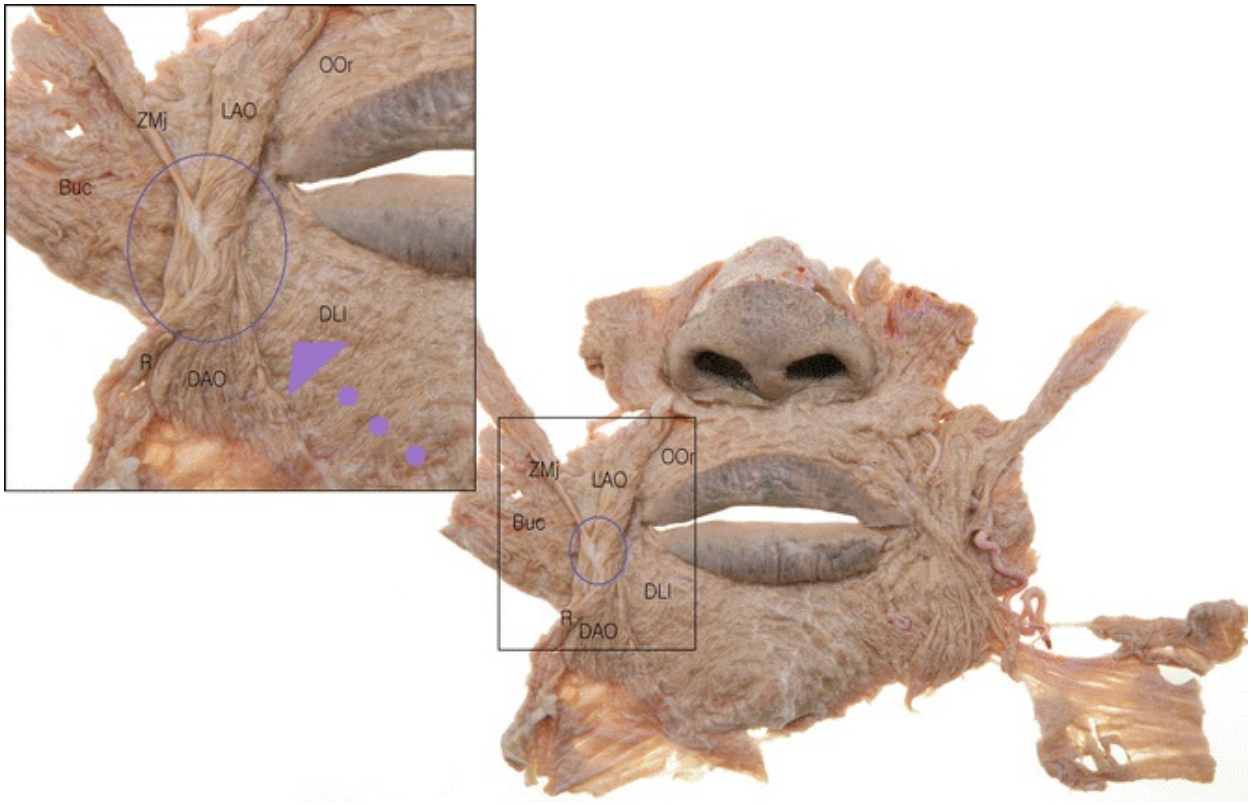


Fig. 2.63 The modiolus. The structure in the blue circle is the tendinous nodule located in the center of the modiolus. To clearly see the tendinous nodule, the LAO and the risorius were folded open to the medial side. *OOr* orbicularis oris, *Zmj* zygomaticus major, *Buc* buccinators, *R* risorius, *LAO* levator anguli oris, *DAO* depressor anguli oris, *DLI* depressor labii inferioris (Photo: courtesy from Professor Hee-Jin Kim)

In contrast with Caucasians whose modiolus is more commonly located above the intercheilion horizontal line (66 %), modiolus in Koreans is more commonly located below this line (58.4 %) (Fig. 2.64). It is primarily located 10–20 mm laterally and 10 mm below the mouth angle [38]. Based on this, it is recommended that botulinum toxin type A should be injected into the lower part of the depressor anguli oris to minimize the risk of unwanted spread to other muscles responsible for movement of the corners of the mouth.

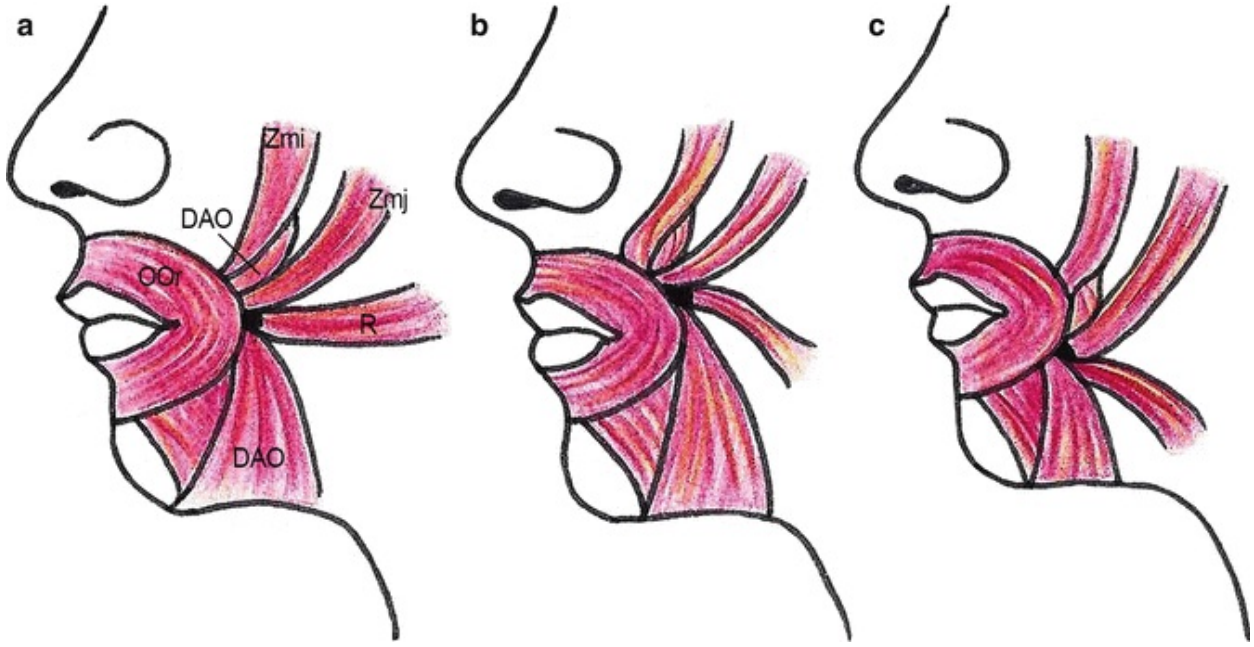


Fig. 2.64 Position of the modiolus based on the intercheilion horizontal line [38]. (**a**) Type—the modiolus is located lateral to the cheilion on the intercheilion horizontal line. (**b**) Type—the modiolus is more commonly located above the intercheilion horizontal line. (**c**) Type—the modiolus is more commonly located below the intercheilion horizontal line. *OOr* orbicularis oculi, *DAO* depressor anguli oris, *R* risorius, *Zmj* zygomaticus major, *Zmi* zygomaticus minor, *LAO* levator anguli oris (illustrated by Jina Seo)

2.2.15.2 Injection Techniques

Since the modiolus generally lies lower in Asians than in Caucasians, it is recommended that BoNT-A should be injected into the lower part of the depressor anguli oris to minimize the risk of unwanted spread to other muscles responsible for movement of the corners of the mouth. Injection of 3–4 U should be performed into the point at lower one-third of the DAO 1 cm lateral to the mouth corner (Fig. 2.65). And also care should be taken to avoid inadvertent diffusion of the depressor labii inferioris which leads to asymmetric smile. Therefore, the injection point should be located at 1 cm lateral to the mouth angle, and the needle should be directed laterally. Since the DAO is a thin muscle and located in the most superficial layer among facial expression muscles around the lips, injection should be made intradermally or subdermally. If the BoNT-A is injected too high, flaccid cheeks, asymmetric smile, and lower lip weakness may occur.

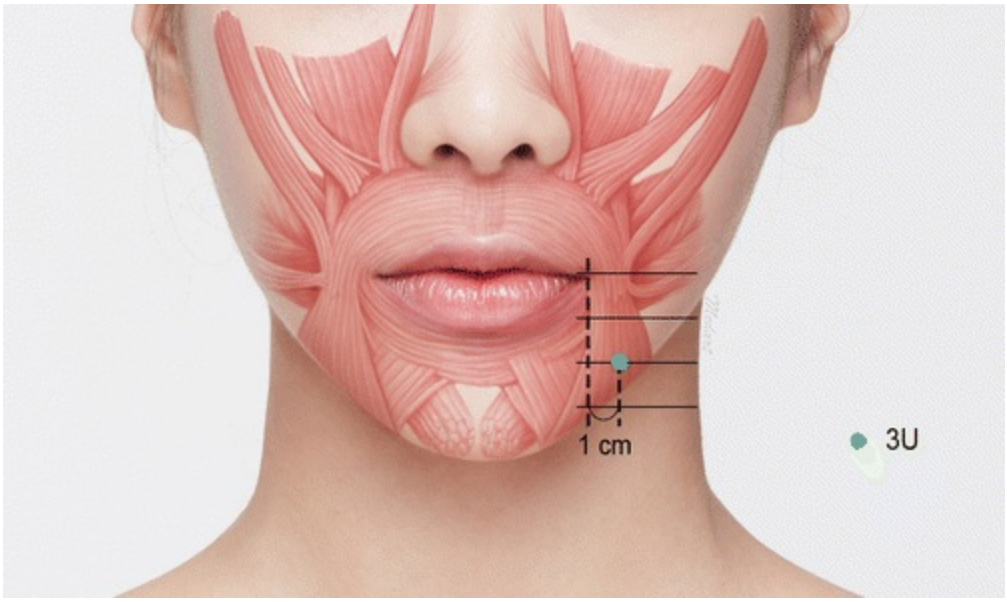


Fig. 2.65 Injection points for the mouth corner elevation

2.2.16 Mentalis Hyperactivity/Cobblestone Chin

Effect (A), Adverse Effect (C), and Technique (B)

Cobblestone chin caused by the hyperactive mentalis muscle is frequently seen in Asians. This can worsen with aging and as volume loss occurs. Since the mentalis is chin and lower lip elevator, the hyperactivity of the mentalis shortens the chin and exacerbates the recession of the chin. Moreover, the cobblestone appearance may settle into the static wrinkles and can also disturb the smooth V line from a front view. Especially the cobblestone appearance can make people look much older when sagging jowl is combined. BoNT-A injections can relax the mentalis, restoring a smooth V line from a front view and slightly protruding the chin which creates a more refined appearance from the lateral view (Fig. 2.66).

Fig. 2.66 Cobblestone chin treated with botulinum toxin: (**a**, **c**, **e**) before and (**b**, **d**, **f**) 2 weeks after 8 U injection of BOTOX®

2.2.16.1 Anatomy

The mentalis muscle is the only elevator for the lower lip and the chin, and it provides major vertical support for the lower lip. This muscle originates from the alveolar bone of the mandible inferior to the lateral incisor, descends anteromedially, and inserts into the skin of the chin and DLI and the orbicular oris forming a continuous structure with the orbicular oris (Fig. 2.67) [39]. These continuous structures can help the mentalis support and raise the lip.

The mentalis contraction forms mental creases at the tip of the chin.

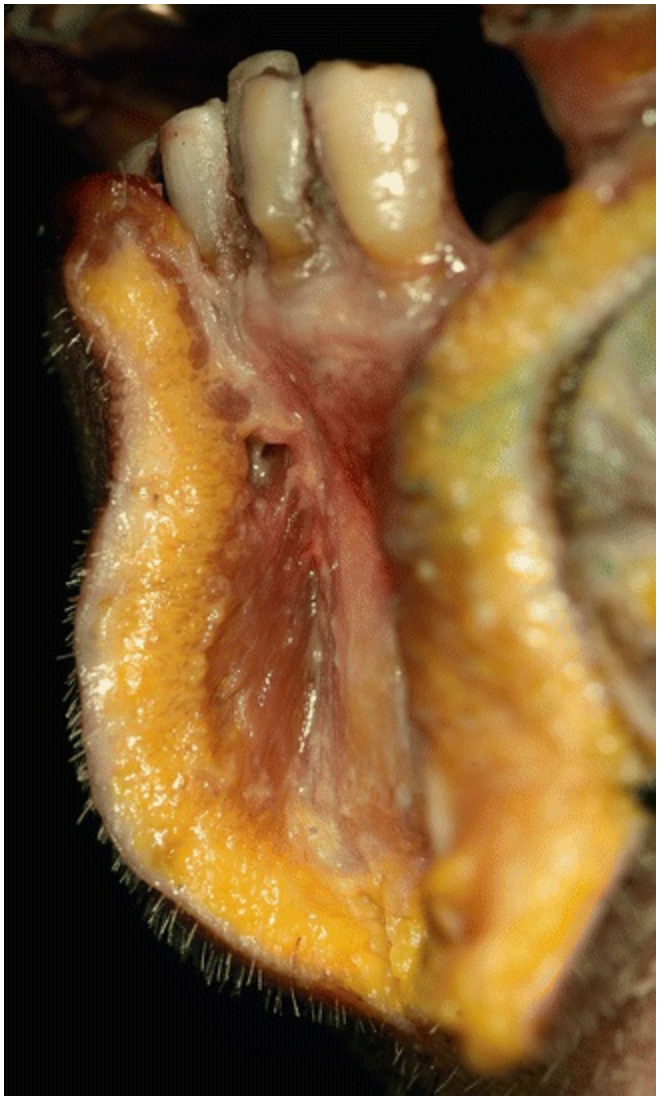


Fig. 2.67 The mentalis. The mentalis muscle originates from below the incisors descends anteromedially and insert into the skin of the chin (Photo: courtesy of Professor Hee-jin Kim)

In Asians, the average length and width of the mentalis are 2.0 and 1.2 cm per side [39].

2.2.16.2 Injection Techniques

3–4 U per side is injected into each point 1 cm lateral to the midline along the mandibular lower border. 1–2 U per side is additionally injected into each point superficially 1–2 cm superior to the mandibular lower border and 0.5 cm lateral to the midline for upper part of the mentalis (Fig. 2.68).

Considering the average width of the mentalis at the mandibular lower border is 2.3 cm (unpublished data from Professor Kim H.), injection of BoNT-A into two points 1 cm lateral to the midline of the mandible is sufficient to cover the lower part of the mentalis muscle. Injection of the BoNT-A at upper part of the mentalis too deeply or too laterally from the midline of the mandible may affect the depressor labii inferioris muscle, which would lead to asymmetric expression change of the lower lip when talking or smiling (Fig. 2.69a). If asymmetry occurs, superficial injection of 0.5–2 U into the non-paralyzed hyperactive part of DLI 1.5–2 cm apart from the lower lip would be helpful to improve the asymmetry (Fig. 2.69b).

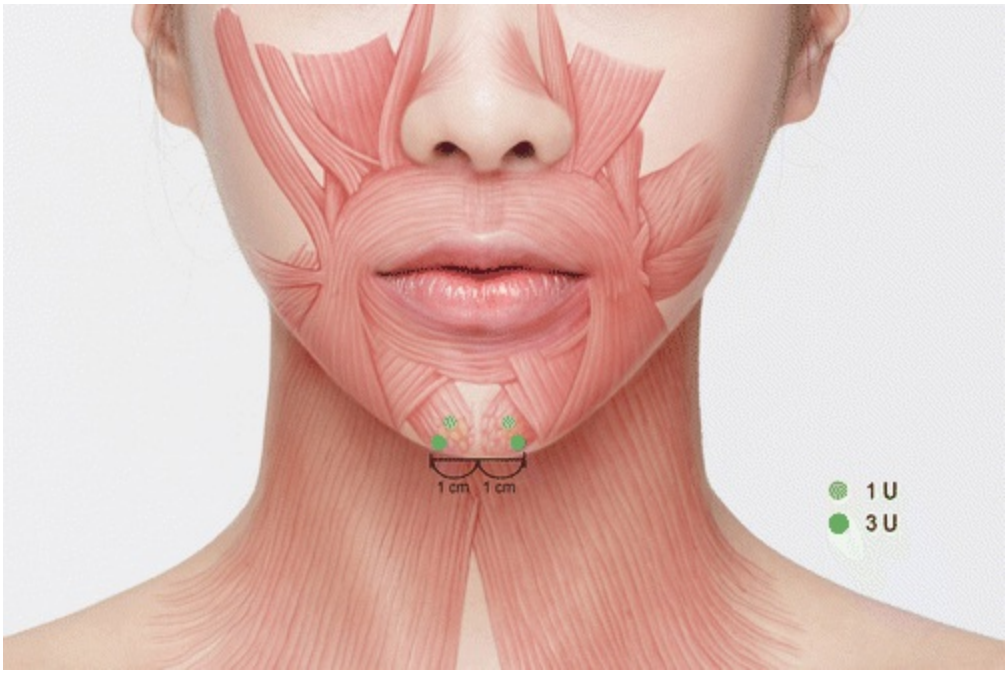


Fig. 2.68 Injection points for cobblestone chin

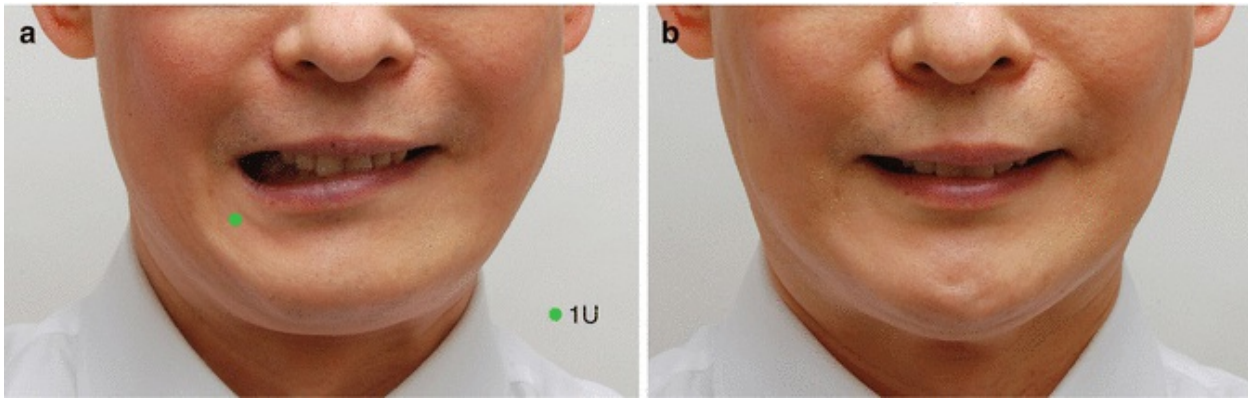


Fig. 2.69 Correction of lower lip asymmetry due to the treatment of cobblestone chin with botulinum toxin. (**a**) Superficial injection of 0.5–2 U botulinum toxin into the non-paralyzed hyperactive part of depressor labii inferioris 1.5–2 cm apart from the lower lip. (**b**) 2 weeks after 1 U of botulinum toxin injection

2.2.17 Platysma Band

Effect (A), Adverse Effect (B), and Technique (B)

Neck horizontal lines are a kind of innate lines in the flexural areas which we have from birth. Therefore, these cannot be removed with BoNT-A. Among necklines, BoNT-A can be used to treat the vertical platysma bands (Fig. 2.70). Platysma bands occur due to the contraction of the platysma muscle while speaking or even at rest and become more prominent with age. Since the platysma muscle pulls down the modiolus, mouth angle, and the lower face in general, repeated contraction of platysma muscle leads to a drooping mouth angle and sagging jowls. Additionally, anterior and posterior bands form at the medial and lateral borders of the muscle. If fat is also present, it can lead to the “gobbler neck” deformity which is frequently witnessed in older Caucasians. Injecting BoNT-A into the platysma muscle can improve not only the vertical bands (Fig. 2.70) but also the drooping mouth angle and jawline.

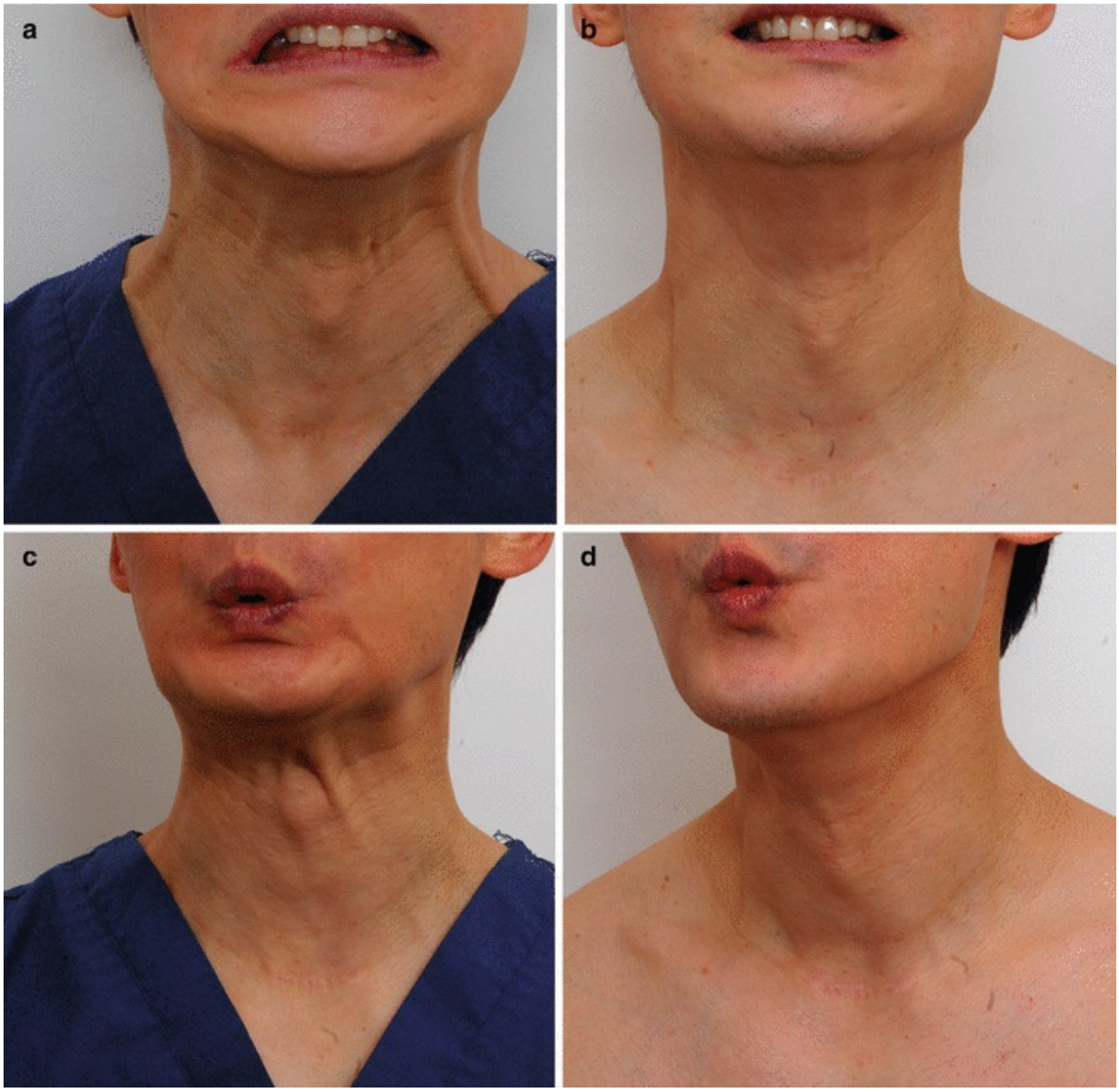


Fig. 2.70 Platysma bands: (**a**, **c**) before and (**b**, **d**) 2 weeks after 50 U injection of BOTOX® per side

The Nefertiti lift is an injection technique to create the sharp jawline by injecting BoNT-A into the platysma muscle at the mandibular border and posterior bands [40]. Employing the botulinum-rebalancing phenomenon which modulates the balance between depressors and elevators for the jawline, the sagging jawline and drooping mouth corner are lifted by weakening the platysma responsible for depressing the mouth angle and the lower face. Moreover, the volume reduction of the masseter muscle caused by the BoNT-A injected into the lower margin of the mandible may play a

role in the “lifted look” to some extent as is seen in “mesobotox/dermatoxin” (see Sect. 4.1).

2.2.17.1 Anatomy

The platysma is a thin, superficial muscle which originates from the fascia of deltoid and pectoralis major, passes the clavicle, and covers the entire neck and lower part of the face. Some of the muscle fibers are inserted to the mandible, but most of the fibers pass over the mandible; blend inward into the modiolus, the lower lip, the DAO, and the DLI; and form the SMAS toward the cheek covering the masseter muscle and the parotid gland. In the midline of the neck, the platysma is absent except some fibers partly decussated with the other side under the chin.

Decussation Patterns of the Platysma in Asians (Fig. 2.71)

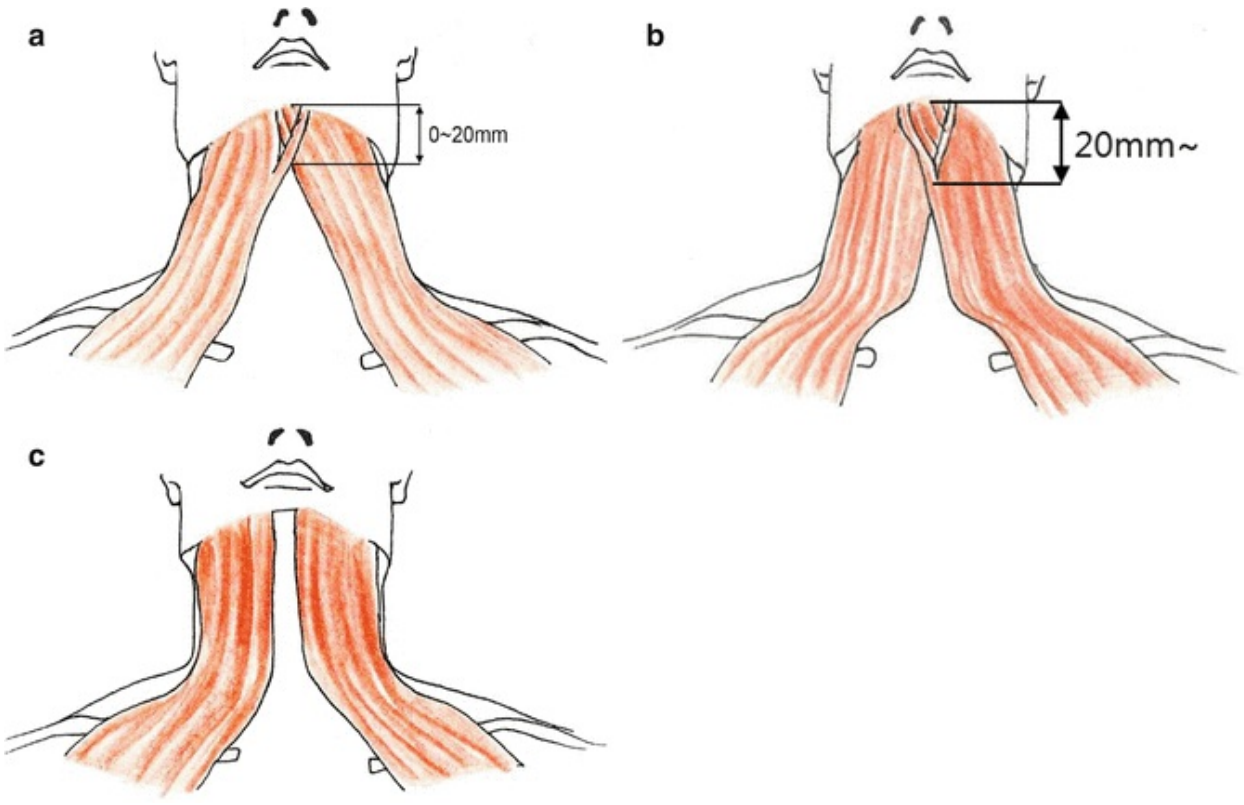


Fig. 2.71 Classification according to the pattern of platysma band decussation between both sides in the submental area. (**a**) Type I—decussation within 0–20 mm below the mandibular border. (**b**) Type II—decussation more than 20 mm below the mandibular border. (**c**) Type III—no decussation between both sides

There are no platysma muscle fibers in the middle of the neck. Some

fibers are decussated and interlaced under the chin, covering the submental region. In Asians, 85 % of bilateral medial platysmal fibers interlaced at the submental region [41]. And, in particular, 43 % showed decussation over 20 mm below the chin. On the other hand, non-decussation patterns were much more frequent in Caucasians (39 %) than in Asians (15 %). These findings may explain why Asians have a lower incidence of the “gobbler neck” deformity than Caucasians [41].

2.2.17.2 Injection Techniques

In order to identify the platysma band, ask the patients to pull down hard on the mouth angle and the platysma muscle. Grasping the muscle bands with your nondominant hand, inject the BoNT-A directly into the bands from the jawline to the clavicle, muscle origin. Inject 2 U each into several points (3–8 points) 1.5–2 cm apart along the anterior and posterior bands (Fig. 2.72). The standard dose is 20–25 U per side and a total of 40–50 U for the initial treatment. While it may be sometimes necessary to inject 100 U for patients with wide and well-developed platysma bands, adverse effects such as dysphonia, dysphagia, and the weakness of underlying neck muscles may be caused by overdose of BoNT-A. Therefore, the total dose should not exceed 100 U per treatment.

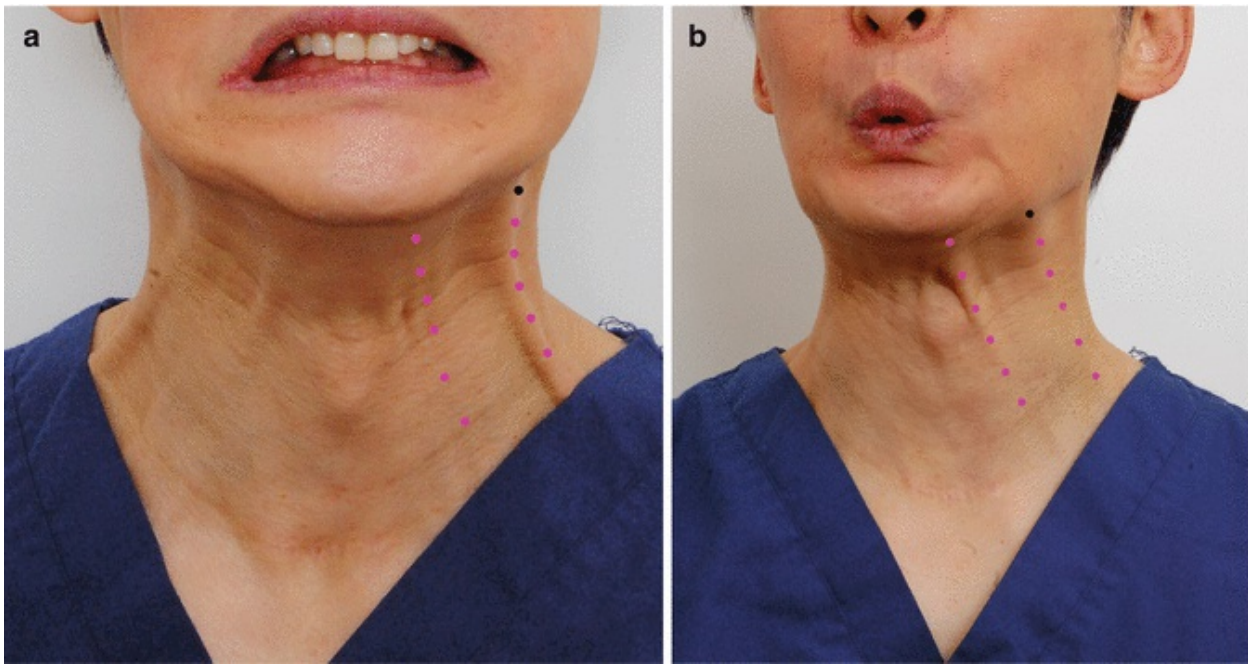


Fig. 2.72 Injection points for platysma bands: (a) front view, (b) 45˚ view

For the Nefertiti lift (Fig. 2.73), 15–20 U BoNT-A per side is injected into the mandibular lower border and posterior platysma band with 50 % split dose, respectively. In order to avoid diffusion into DLI, the injection into the mandibular lower border should be performed under the mandible and start 1 cm lateral to the nasolabial folds with needle directed toward the mandibular angle. In the posterior band, an intramuscular injection into the upper half of the posterior band would be sufficient. 2 U of BoNT-A should be injected into each point 1.5–2 cm apart along the mandibular lower border and the platysma bands. 4 U should be injected at the intersection point of the two lines.

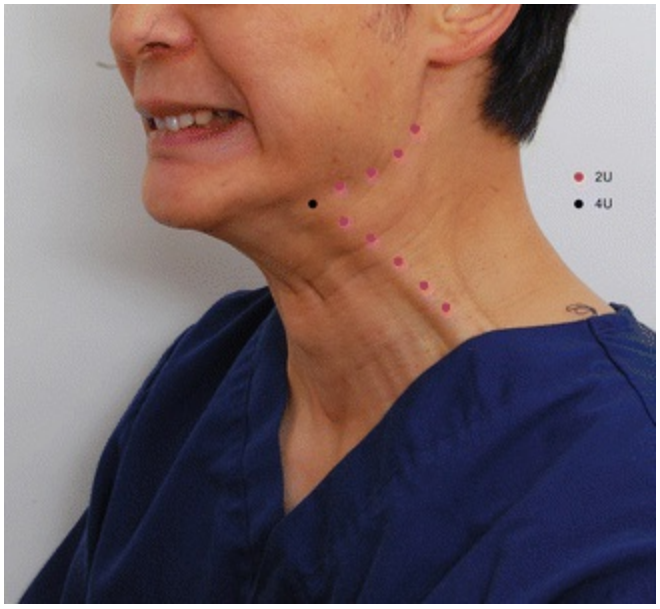


Fig. 2.73 Injection points for Nefertiti lift

2.2.17.3 Injection Dose

While the standard dose is 20–25 U per side, 100 U may be sometimes necessary for patients with well-developed platysma bands. For the Nefertiti lift, the standard dose is 15–20 U per side.

2.2.17.4 Adverse Effects

Bruising is the most common adverse effect. Press immediately for 5 minutes if the blood vessels are ruptured. Overdose may cause sometimes dysphonia, dysphagia, and the weakness of neck muscles by the diffusion of the BoNT-A

into the underlying muscles. Xerostomia may happen by the diffusion of the BoNT-A into the submandibular gland. And dysphonia is usually related with a “high-tone disturbance.” If the BoNT-A diffuses into the neck support muscles, it would be difficult to control the neck. Moreover, symptoms of patients with cervical necks disk may be exacerbated by the weakness of the neck support muscle. Therefore, less than 100 U at one session is strongly advised, and care should be taken not to inject deeper than the muscle bands.

Inadvertent diffusion of BoNT-A into DLI may result in asymmetric smile when the BoNT-A is injected into the mandibular lower border for the Nefertiti lift. 0.5–2 U injection into the non-paralyzed hyperactive part of DLI, 1.5–2 cm apart from the lower lip, would be helpful to improve the asymmetry (see Sect. 2.28).

2.2.17.5 Photographs

Take a front view and a 45° view while the patients forcibly pull down hard on their mouth angle and platysma to make platysma bands clearly visible.

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Kyle K Seo, Botulinum Toxin for Asians, DOI 10.1007/978-981-10-0204-5_3

3. Facial Contouring with Botulinum Toxin

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3.1 Square Jaw/Masseter Hypertrophy

Effect (A), Adverse Effect (C), and Technique (A)

In 1994, Smyth [1] and Moore [2] first reported a technique using botulinum toxin type A (BoNT-A) which reduces muscle volume in patients with masseter hypertrophy. Although subsequent cases were reported sporadically in western literatures, it did not gain popularity in western countries owing to lack of cosmetic needs among Caucasians. However, it has become a sensational method for the cosmetic treatment of square jaw since 2001 when this indication was first introduced in Asia. Since the face shape of Caucasians is narrow, square jaw is not considered a major cosmetic concern. The angled jawlines of Brooke Shields and Angelina Jolie are considered distinct and individualistic. However, Asians with relatively wide faces do not consider square jaws attractive and even regard people with square jaws as stubborn or even ill fated. Consequently, bone surgery such as mandibular angle resection had been developed in Asian long ago, and such patients receiving bone surgery had to endure the “severe pain of cutting off the bone” as mentioned in a Korean proverb. By contrast, BoNT-A for masseter hypertrophy, which transforms square jaws into slimmer face without undergoing bone surgery, was a revolutionary treatment from the public perspective (Fig. 3.1). In the beginning when this indication was first introduced into Korea, even plastic surgeons doing mandibular angle

resection were extremely skeptical about the effectiveness of this treatment before seeing the treatment results. One plastic surgeon near my clinic who specialized in mandibular bone resection even declared on his website that square jaw treatment with BoNT-A was a fraud. Now it is one of the most popular cosmetic indications among Asians, especially young women seeking for beautification using BoNT-A due the convenience of the procedure without social downtime compared with bone surgery (Table 3.1).


a
b
c
d

Fig. 3.1 Square jaw contouring: (**a**, **c**) before and (**b**, **d**) 2 months after 20 U injection of BOTOX® per side

Table 3.1 Comparison of advantages and disadvantages between square jaw contouring with botulinum toxin and mandibular angle resection

	Square jaw contouring with botulinum toxin	**Mandibular angle resection**
Procedure time	5 min	About 2 h
Anesthesia	Unnecessary	General anesthesia
Admission	Unnecessary	Necessary
Pain	Prickling during procedure	2–3 weeks after operation
Postoperative edema	None	2–3 weeks
Food ingestion	10–20 % may experience bite force decrease for 2 months when chewing hard foods	Fluid diet for 1 week and soft diet for 4 weeks
Daily life	No disturbance	2 weeks for recovery
Adverse effects	Focal bruising, decrease in chewing power, awkward smile	Hematoma, edema, bleeding, rarely death
Duration of effect	Temporary	Permanent
Effective candidates	Square shape from frontal view (muscle type)	Square shape from lateral view (bone type)

Since the slimming effect of jaw occurs not only in patients with masseter hypertrophy but also in anyone with a slightly prominent masseter muscle, I think that the name “BoNT-A treatment for masseteric hypertrophy” would be better revised to “BoNT-A treatment for square jaw.”

Episode: Was Square Jaw Treatment with BoNT-A First Developed in Korea?

I was surprised to face an article by von Lindern about “BoNT-A for the treatment of hypertrophy of masseter and temporal muscles” in the March 2001 issue of *Plastic and Reconstructive Surgery*. A simple injection that can transform a square jaw into a slimmer face without undergoing bone surgery is truly a fantastic treatment. I was more surprised to find that eight more papers on this novel indication had been already reported since 1994 in western literature. I was baffled as to why this novel indication did not receive more widespread recognition among doctors until much later. It was a stark contrast to wrinkle treatment with botulinum toxin, which had already

settle into second place among cosmetic treatments less than 10 years after it was first introduced.

I came to know that the main reason is ethnic differences about beauty concept. Compared with Asians, Caucasian face is relatively narrow. Therefore, square jaw is not a major concern to Caucasians. For this reasons, BoNT-A treatment for square jaw was not popular among Caucasians despite being introduced since 1994. By contrast, the treatment got an immediate highlight in 2001 when it was introduced in Korea where people consider slimmer oval face ideal facial shape. The CEO of Allergan Korea won the second place prize for the sales of BOTOX® at the Allergan global conference in 2001 thanks to a 100 % sales increase of BOTOX® in Korea compared with the previous year. Not surprisingly, I recall performing this indication in up to 15 patients a day in the end of 2001. This innovative indication also spread quickly from Korea to other Asian countries such as Japan, China, and Taiwan since 2001. It achieved great popularity among Asians, and the trend has continued to this day.

3.1.1 Mechanism of Action: Disuse Atrophy

Although the mandible is the primary cause of square jaw, the masseter muscle attached to outside the bone also plays a role in square jaw. If the masseter muscle is thick, the square jaw will look more exaggerated when viewed from the front [3]. In these cases, square jaw cannot be solved by resection of the bone alone, and volume reduction of the muscle is also necessary.

In his 2001 report on BoNT-A treatment for masseteric hypertrophy, von Lindern indicated that the BoNT-A induces muscular atrophy through paralysis [4]. If a patient's leg is kept in a cast for 3 months due to a fracture, the leg will be lean when the cast is removed 3 months later. This is because the muscle atrophied transiently from disuse. If BoNT-A is injected into a developed muscle, the same effect can be achieved through muscle paralysis. Therefore, BoNT-A can transform a square jaw into a slimmer oval shape without bone surgery.

3.1.2 Causes of Masseter Muscle Hypertrophy

The masseter, along with the temporalis and the medial pterygoid, is one of the mastication muscles and is responsible for closing the jaw. It is developed

according to the degree of mastication while chewing not only hard foods such as dried fish, squid, and nuts but also soft but chewy substances like chewing gums. Bruxism and habitual unconscious clenching of teeth are another causes of masseter muscle development. Masseters commonly develop asymmetrically depending on personal chewing habits to one side.

3.1.3 Pretreatment Assessment

BoNT-A treatment only applies to square jaw from the front view, not the lateral view. Square jaw from the lateral view is a problem of the mandible itself and therefore cannot be improved by reduction of the masseter muscle.

Even if facial shape is not really square jaw from the front view, facial width can be decreased by the BoNT-A injection through reducing the volume of the masseters, resulting in a smaller, slimmer, oval-shaped face to some extent. Since the average thickness of the masseter muscle in normal people is 0.8 cm, BoNT-A can reduce the facial width, more specifically lower facial width by nearly 1.6 cm [5]. Therefore, everyone can benefit to a certain degree from this procedure. However, the procedure is relatively not recommended for people with little masseter volume as little effect can be obtained. The volume of the masseter muscle can be roughly estimated by asking patients to clench their teeth. Similarly, a rough estimate of the posttreatment result can be predicted by observing the face shape change to slimmer, oval shape when pressing the muscles with hands.

Along with prediction of the effect, the next step in the pretreatment assessment is to screen for high-risk groups that make adverse effects much more likely to occur. Sunken cheeks, sagging jowls, the possibility of the masseter muscle bulging, and altered facial expressions when smiling should all be confirmed. Individuals have insufficient cheek fat which was not so apparent when they had well-developed masseter muscles providing rear support, but can hollow out quickly following BoNT-A injection due to sudden decrease in masseter volume, leaving them looking aged and haggard even though their face becomes slimmer. Since sunken cheeks are not adverse effects caused by the procedure but preexisting condition which individuals already have before treatment, individuals with insufficient cheek fat should be informed of this point clearly before the treatment. Otherwise patients may mistakenly assume that the sunken cheeks came from the procedure as an adverse effect. Sagging jowls act in the same way. If the sagging jowls exist together with the masseter hypertrophy, the sagging

portion from front view is relatively well connected to the posterior portion of the masseter muscle behind, resulting in smooth jawline and making the sagging appear less prominent. After the masseter muscle has atrophied by BoNT-A, however, only the sagging portion at anterior part remains making the sagging look more exaggerated. Masseter bulging on mastication and altered facial expressions when smiling are also very perplexing adverse effects. Therefore, screening the risk group before treatment is prerequisite (see Sect. 3.1.11).

Tip: Patients Not Suited for Botulinum Toxin for Masseter Reduction
Botulinum toxin for masseter treatment is not recommended for the following patients:

Individuals with well-developed mandible and little masseter muscle mass

Individuals with insufficient masseter muscle mass cannot expect dramatic results given the limitations in the volume of masseter muscle to be reduced. Where the patient is nonetheless willing to undergo treatment, it may be attempted, but only to the extent of softening the jawline.

Individuals over the age of 40 presenting sagging jowls

Individuals with insufficient facial cheek fat

Individuals with too much facial cheek fat

Facial contour is shaped by the masseter muscle in the rear part of the face and the facial cheek fat in the front. Therefore, individuals with prominently chubby cheeks may not benefit much from reducing the masseter muscle size alone. However, the procedure can help if the individual has both chubby cheeks *and* large masseter muscles, since the reduced muscle mass can help to reduce the size of the face, if not as dramatically as of those with slim cheeks. For best results, additional procedures for reducing cheek fat such as injection lipolysis, liposuction, and laser lipolysis are strongly recommended.

Patient Selection: Contraindication for Masseter Reduction with Botulinum Toxin
BoNT-A treatment for masseter reduction is not recommended for

individuals with excess facial cheek fat and lack of masseter muscle since it will have no apparent effect. It is neither recommended for patients over the age of 40 with sagging jowls and sunken cheek, unless they are willing to undergo other adjunctive treatments advised by the doctor. This is because the jowl sagging will become more pronounced once their faces become smaller, making them look even older. Of course, when combined with other appropriate treatment such as fillers or fat transplantation, they can also undergo BoNT-A for masseter reduction.

3.1.4 Self-Assessment

Patients who are considering BoNT-A for square jaw care most about whether or not the treatment will be effective for them. Patients can use the following methods to estimate the effectiveness of the procedure on their own faces. First, the patient should look in a mirror and clench his or her teeth. If the masseter muscle bulges behind the jaw or feels hard to the touch, it means that the masseter muscle is well developed and that they can be good candidates for this treatment. If the patients press the muscle without clenching, the extent their faces become slimmer can be used as an indicator for the efficacy prediction of BoNT-A for square jaw.

3.1.5 Anatomy

The masseter muscle originates from the zygomatic arch, runs downward–backward, and inserts into the mandibular angle and the ramus of the mandible. It consists of three layers according to depth. The superficial part originates from the zygomatic process of the maxilla and from the lower two-thirds of the zygomatic bone, runs downward–backward, and inserts into the mandibular angle (Fig. 3.2). From the deep surface of the anterior two-thirds of the zygomatic arch and from the lower border of the posterior one-third of the arch, it runs vertically and inserts on the upper and lateral surface of the ramus. The deepest part originates from the deep surface of the zygomatic arch and inserts into the ramus of the mandible. The middle and deepest part can be divided by the masseteric nerve which branches from the mandibular nerve. The superficial layer is the largest, and the inferior portion where the muscle fibers from three different parts merge is the thickest. Therefore, BoNT-A should be injected into the lower part of the muscle.

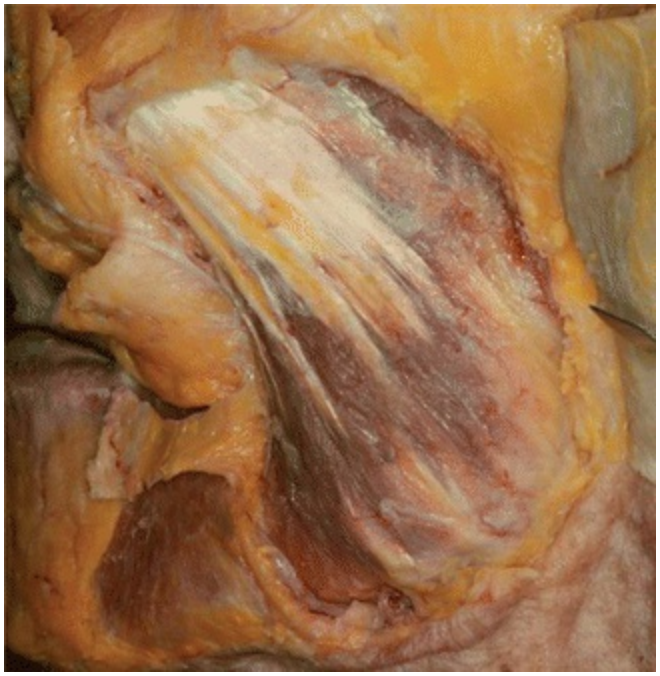

Fig. 3.2 The masseter. The superficial part of the masseter originating from the zygomatic arch runs downward–backward and inserts into the jaw angle of the mandible. It constitutes most of the volume of lower half of the muscle (Photo, courtesy of Professor Hee-Jin Kim)

Reports on the size of the masseter muscle in Asians are scarce. In a previous study, I conducted using computer tomography to analyze the dose–effect relationship of BoNT-A in 28 Korean female volunteers with square jaw, I found that the width of the lower portion of the masseter muscle was 34.7 ± 3.2 mm (25.0–40.0 mm), and the thickness was 14.9 ± 2.2 mm (10.6–20.1 mm) on average (unpublished data). According to a quantitative analysis of the masseter muscle using computer tomography in 65 Chinese patients, the average thickness was 1.3 cm in patients with masseter hypertrophy and 0.8 cm in normal persons [5].

Dr. Woo reported that the inferior portion of the masseter muscle is supplied with blood through four arteries: the masseteric branch of the facial artery (88 %), masseteric branch of the premasseteric artery (56 %), masseteric branch of the transverse facial artery (100 %), and masseteric branch of the external carotid artery (56 %) among seven different arteries supplying to the masseter muscle [6]. In rare instances, slight bulging of the masseter muscle may occur immediately after treating square jaw with BoNT-A. This seems to be due to hematoma from the rupturing of small blood vessels and usually subsides within a few days without any bruising.

Tip: Masseter Asymmetry
Since many people have a chewing habit of favoring one side to a certain degree, asymmetry of the masseter muscles is frequently observed. If the masseter muscles are asymmetrical, the BoNT-A dose for square jaw should be adjusted according to the corresponding muscle volume. On average, the dose difference between smaller side and larger sides is around 5–10 U depending on the muscle volume. If 20 U is injected into a normal sized muscle, 25–50 U would be injected into a larger muscle. Recurrence of asymmetry can be prevented by correcting chewing habits which favor one side. However, asymmetry frequently recurs because people's chewing habits of favoring one side are not easily corrected.

3.1.6 Injection Techniques

The BoNT-A should be injected deeply into 3–4 separate points in the lower one-third of the muscle. The line connecting the mouth angle and tragus roughly divides the masseter muscle into halves, and the injection should be made into the lower part of this area since this is where the muscle is most well developed. If it is injected into the upper part of the masseter muscle in Asians with prominent zygoma, it may result in an even more prominent zygoma along with the sunken muscle due to optical illusion. Additionally, if the BoNT-A diffuses into the zygomaticus major muscle around the zygomatic bone, the mouth angle may not elevate when smiling.

For the reference line of safe BoNT-A injection into the masseter, boundaries for injections should first be drawn: the anterior and posterior margin of the masseter muscle as the anterior and posterior border, respectively, the line connecting the mouth angle, and the tragus as the superior border and the lower mandibular border as the inferior border. The BoNT-A should be injected into points placed 1 cm away from each border in order to prevent unwanted diffusion of BoNT-A which may result in facial expression alteration. 10–40 U divided into four injection points per side is injected depending on the volume of the masseter. 20 U is a sufficient dose for individuals who have 3–5 cm width of masseter muscle (Fig. 3.3a). When I first developed this procedure for square jaw treatment, I injected 10 U into three points each, the three apexes of an imaginary triangle on the bulkiest area of the lower part of masseter muscle (Fig. 3.4), but later changed to four injection points for the purpose of more even distribution of the BoNT-A (see Sect. 3.1.7). An additional injection with 10 U per side should be made into

the upper portion of the masseter muscle if upper portion is also developed (Fig. 3.3b).

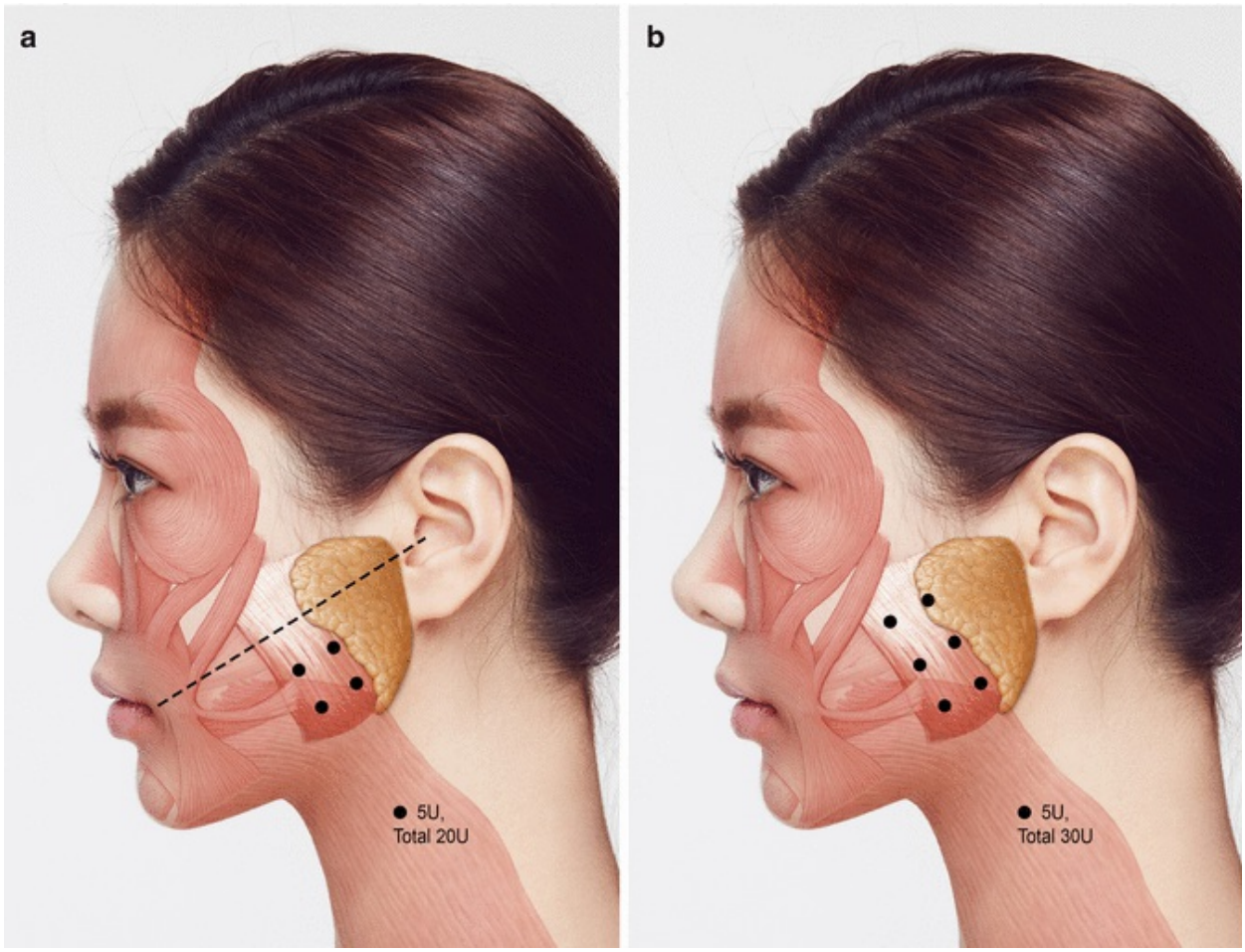

Fig. 3.3 Injection points for square jaw contouring. (**a**) Standard type. (**b**) Superior type: developed superior portion of masseter

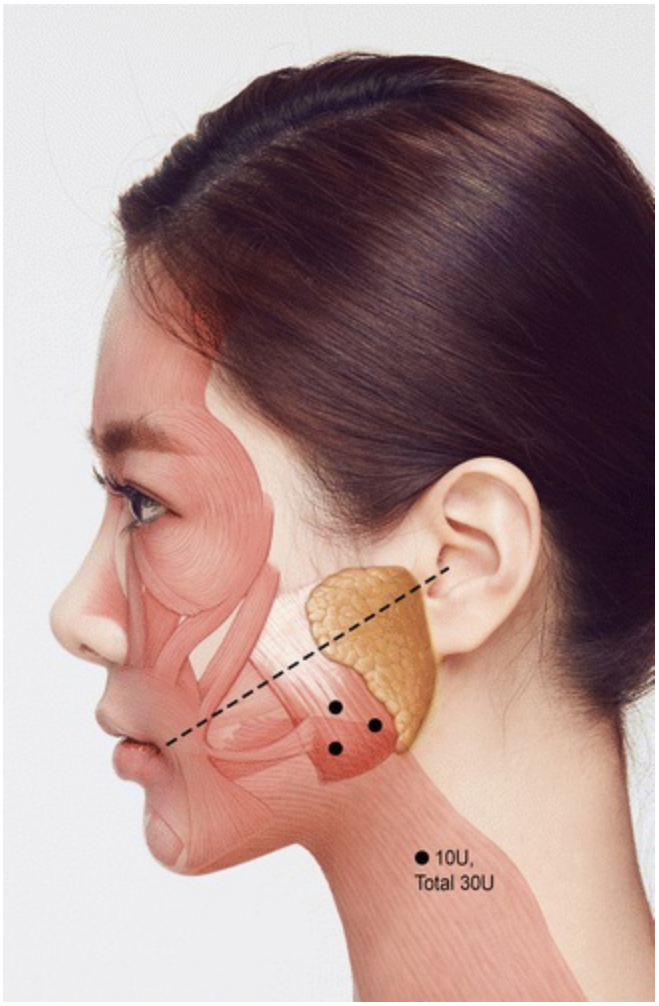

Fig. 3.4 Prototype injection points for square jaw contouring which was developed by the author in 2001

Regarding the depth of injection, deep intramuscular injection should be performed with needle positioned perpendicularly to the skin until the 1.25 cm needle tip nearly touches the periosteum. A superficial injection of BoNT-A into the masseter muscle may spread into the risorius muscle attached superficially to anterior part of the masseter muscle. Since the risorius is responsible for pulling the mouth corner superiorly and laterally when smiling, the affected side with BoNT-A cannot elevate the mouth corner when smiling, causing an awkward smile, one of the most embarrassing adverse effects from square jaw treatment with BoNT-A [7].

Episode: Is the Effect of Botulinum Toxin Permanent? Question of Duration and the 3-Year Guarantee Program

When BoNT-A treatment for masseter reduction was first introduced in Korea back in 2001, one of the most frequently asked questions was the duration of effect: While there were a handful of foreign publications reporting on a 1 ~ 2 year duration of action upon 2 ~ 3 repeat treatments, the findings were based on a sample size of only 5 ~ 7 patients and did not reflect the unique dietary habits of Korean, i.e., the regular consumption of hard and chewy food such as radish kimchi, nuts, dried fish and squid, etc. As such, my response on the question of duration was rather tentative. “It’s too early to tell, although the effects are reported to last around 2 years based on 2 ~ 3 repeat procedures. With the right care and maintenance, I guess we might expect fairly long-term duration.” Indeed, those were early days. There were some clinics blindly claiming permanent results, while others were contradicting themselves by maintaining that the effects should be permanent, but with that in the unlikely event where the effects were to wear off, the clinic would be prepared to offer a courtesy procedure within the first year after which such procedures would be unavailable.

As a practitioner I was just as eager to get the answer, yet it was the kind only time would tell. As such, I launched the “3-year guarantee program” for my patients comprising a total of seven procedures over a 3-year period at 6-month intervals. I felt that was the most reasonable way to give patients the assurance of prolonged results. How can patients have confidence if the doctor lacked it? In a way, the 3-year guarantee program was equivalent to an insurance policy, under which patients were covered for any relapse during the 3 years, while the program was in effect so they could maintain long-term duration.

3.1.7 Injection Dose

While the optimum dose of BoNT-A for the treatment of masseteric hypertrophy per side was reported to be 100–300 U of Dysport® and 20–60 U of BOTOX®, the dose varies among different authors. If it is for the treatment of square jaw for cosmetic purposes to make the face slimmer and oval shaped rather than masseteric hypertrophy, however, then 25–30 U of BOTOX® (all the following are units of BOTOX®) is the most common dose in Asian countries including Korea [8]. However, whether or not 25–30 U is really the optimum dose has not been well verified and research is still scarce. One of the challenges surrounding this topic is that it is difficult to generalize the dose–effect relationship as the size of the masseter and

chewing habits vary greatly among individuals. Moreover, 25–30 U of BoNT-A has been well accepted as an effective dose for the treatment of square jaw without many adverse effects. This may be another reason why little research has been performed on this topic.

There are two significant reports on the dose-effect relationship of BoNT-A for the treatment of square jaw. In the first report, the masseter muscle thickness was measured by ultrasound after being injected with different doses of BoNT-A (10, 20, and 30 U). The authors concluded that a minimum of 20 U is necessary as the effect of 10 U group was inferior to the 20 U and 30 U groups [9]. In the second report, the effect on the masseter muscles was evaluated by computed tomography and electromyography measurement after 12 weeks of treatment with BoNT-A using 25 U and 35 U doses. The authors concluded that 25 U is preferable because there was no statistical difference between the two groups [10].

After reviewing these two reports, I wondered if the standard dose of 30 U for square jaw treatment which I recommended from the beginning was a little too high. To address this question, I performed a prospective intraindividual comparison study on the effect of BoNT-A (Neuronox®) for the treatment of the square jaw in 28 female volunteers with a masseter width of 3–5 cm and evaluated the dose–effect relationship using 3D computed tomography at 12 weeks after injection of two different doses among three different doses (20, 30, and 40 U) was injected randomly into the right and left side in the same individual. According to the result of our clinical study, contrary to expectations, we found that there was no major difference in the volume reduction among the three different doses (unpublished data). Therefore we concluded that 20 U was enough to treat square jaw.

In general, the size of the motor end plate correlates well with the diameter of muscle fiber. Therefore, more BoNT-A should be injected for thick muscles [11]. However, if the BoNT-A level approaches a certain amount, the motor end plates become saturated, and additional paralysis effect from the BoNT-A is meager [12]. The dose–muscle paralysis effect has a log dose relationship within a certain range, but reaches a plateau if the dose increases beyond a certain point [13]. In my clinical study, the volume decrease of masseter muscle after BoNT-A injection compared with initial volume was 27.1 % in the 20 U group, 26.8 % in the 30 U group, and 29.4 % in the 40 U group (unpublished data). As there is no statistically significant difference between the three groups, I think 20 U of BoNT-A is sufficient to

saturate the motor end plates for masseter muscle and higher dose than 20 will not improve the effect.

The notion that 20 U is an appropriate dose for square jaw treatment can also be inferred from the dose used for calf contouring with BoNT-A. Around 100–200 U for 200–300 cm^3, the average volume for gastrocnemius muscle is used for calf contouring with BoNT-A [14]. Moreover, only 150 U is the standard dose for the gastrocnemius muscle in stroke patients in order to resolve the spasticity of the gastrocnemius muscle [15]. Based on my clinical study using 3D computer tomography, the volume of the masseter below the zygomatic arch was only 20.8 cm^3—less than 1/10 of the gastrocnemius muscle (unpublished data). Moreover, considering the fact that the injection area of the masseter is limited to the lower half of the muscle, we can estimate that an optimum dose for square jaw would be less than 10–20 U.

In conclusion, 20 U is a sufficient dose for the treatment of square jaw with BoNT-A in females with the muscle width of 3–5 cm, while 10–40 U per side is sometimes necessary depending on the muscle volume. For males or patients with masseter hypertrophy with a muscle width of over 5 cm, 25–40 U is recommended. 6–10 U can be recommended in patients with thin masseter muscle or as a dose for repeat injections at 3–6-month follow-up (Table 3.2).

Table 3.2 Average doses of BOTOX® for facial contouring (units, per side)

	Female (standard)	Male	Mild type	Severe type
Masseter	20	20–30	10–15	30–40
Temporalis	25	30–40	15–20	30–50
Parotid glands	30	30–40	20	40
Submandibular glands	20	20	15	30

Data from Modelo Clinic

Episode: How 30 U Was Chosen as the Initial Dose for Masseter Treatment with BoNT-A

While 20–30 U per side is considered as standard dosage for botulinum toxin for masseter treatments these days, when the procedure was first developed in 2001, getting the right dosage and injection points presented a huge challenge, since no specific mention was made on those details in the available literature. Furthermore, all the relevant literature at the time were

related to Dysport®, since none had been available for BOTOX®, which meant that the right dosage for BOTOX® had to be extrapolated from the data used in the Dysport® studies. The reason I selected 30 U as the initial dosage was quite simple. In studies on Dysport®, the dosage for patients with masseter hypertrophy ranged anywhere between 100–150 U to 300 U. Since the masseter muscle of an average person is comparably smaller than someone with masseter hypertrophy, I figured it would be the safest to start at the equivalent of the lowest dose prescribed for Dysport. Assume rough conversion ratio of 1:3 between BOTOX® and Dysport®, then the minimum dosage of 100 U for Dysport® translated to 33 U of BOTOX®, and hence the 30 U for BOTOX®. Regarding the injection points, prior publications only prescribed injecting into the most prominent area of the masseter, without mapping out in detail the exact injection points and number of injections to be performed. As such, in my first clinical study using BoNT-A at the Seoul National University Hospital, I took six points dividing masseter muscle equally by two columns and three rows, for making the injections. However, this method led to substantial distortions to the facial expression when smiling. Even though the awkward smile at the time was actually due to diffusion of BoNT-A into risorius muscle, it was mistakenly assumed that BoNT-A injected into the upper half of the masseter diffused into the adjacent zygomatic muscles. In treating actual patients therefore, I injected only the lower half of the masseter. Further, given the well-developed zygoma of a typical Korean face, injecting the superior part of the masseter ran the risk of making the zygoma appear more prominent due to optic illusion. As for dosage per site, when injection was initially performed into six points dividing masseter muscle equally by two columns and three rows, 30 U of BOTOX per side was injected based on 5 U per each point. However, after limiting the injection area to only the lower part of the masseter, I found that six points were too many, while four points were too impractical since 30 U had to be divided into four exact doses of 7.5 U each. Therefore, I settled on injecting 10 U in each of the three points, each representing the three vertices of a triangle (Fig. 3.4). Injecting a total of 30 U across the three vertices of a triangle subsequently became the standard procedure followed not only in Korea but in other Asian countries. This even became the standard injection technique for the treatment of bruxism (see Sect. 3.1.9).

A randomized double-blind dose-effect study on treatment of square jaw with botulinum toxin evaluated by three-dimensional computed

tomography.

Hye Chan Jeon, Seung Hwan Paik, Jae Woo Choi, Ji Hoon Kim, and Kyle K Seo

1. Subjects

A total of 28 women volunteers of ages ranging from 20 to 45 were included in this study. All had symmetric masseter muscles with widths ranging from 3 to 5 cm when clenching.

2. Injection Techniques

Two different doses among three different doses (20, 30, and 40 U of Neuronox®) were injected randomly into right and left masseter muscle in the same individuals.

3. Evaluation Method

The total volume of the masseter muscle was assessed before and 12 weeks after treatment using three-dimensional computed tomography with 1 mm-thick images from the zygomatic arch to the lower angle of the mandible. As the lower part of the masseter mostly affects the shape of the jawline and is esthetically more important, we also assessed the volumes of the lower parts of this muscle. Before and after the treatment, masseter muscle volume and percent reduction were compared between different doses. Clinical photographs were taken at front and lateral views at each visit (weeks 0, 1, 4, and 12), and those were evaluated by four blinded dermatologists using a four-point grading scale: 0 (0 ~ 25 % improvement), 1 (25 ~ 50 % improvement), 2 (50 ~ 75 % improvement), and 3 (75 ~ 100 % improvement). Patients' satisfaction was also evaluated using the same assessment method.

4. Results

Three-dimensional computer tomography evaluation before treatment showed the average volume of the masseter was 20.8 ± 4.4 cm^3 (12.0–30.7 cm^3), average width was 34.7 ± 3.2 mm (25.0–40.0 mm), and average thickness was 14.9 ± 2.2 mm (10.6–20.1 mm). Volume changes were

statistically significant in all groups: 27.1 % in the 20 U group, 26.8 % in the 30 U group, and 29.4 % in the 40 U group (p = 0.001). In the lower part of masseter, muscle volume decreased by 33.4 % in the 20 U group, 32.6 % in the 30 U group, and 35.1 % in the 40 U group (Fig. 3.5). However, according to a mixed model analysis, there were no statistically significant differences between the three groups in the lower muscle volume as well as in total volume. In a photographic assessment made by investigators (Fig. 3.6), the improvement grades at week 1, week 4, and week 12 were 0.3, 1.2, and 1.8, respectively, in the 20 U group; 0.2, 1.4, and 2.0, respectively, in the 30 U group; and 0.3, 1.2, and 1.8, respectively, in the 40 U group. Although there were no statistically significant differences between the three groups at each time point, the peak effect appeared at 12 weeks in all groups, which was a statistically significant difference.

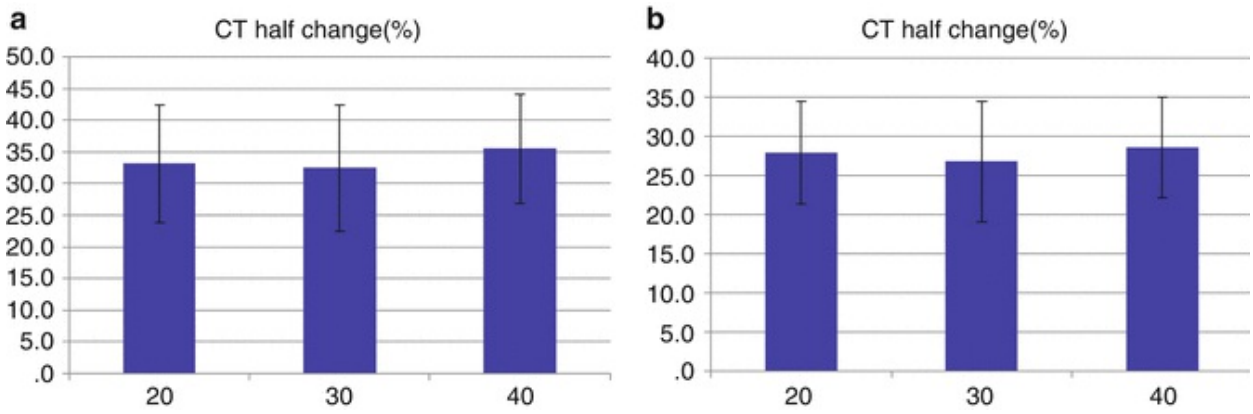

Fig. 3.5 Masseter volume change after botulinum toxin injection according to different doses. (**a**) Lower part of masseter muscle volume. (**b**) Total masseter muscle volume

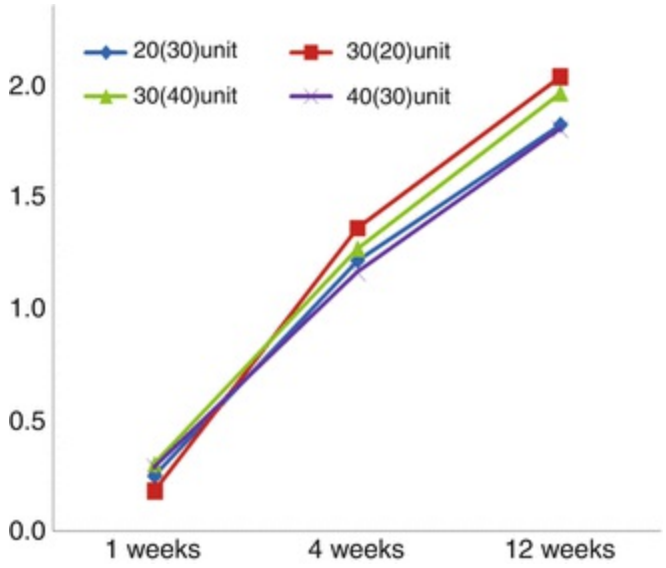

Fig. 3.6 Photographic evaluation of masseter volume change by the investigators according to different doses

5. Conclusion

In patients with a masseter width of 5 cm or less (average 34.7 ± 3.2 mm), 20 U of BoNT-A is sufficient for the cosmetic purpose to treat square jaw.

3.1.8 Change of Masseter Volume

There are several methods for objectively evaluating changes in masseter volume after the injection of BoNT-A for square jaw contouring: sonography, electromyography, and computer tomography have been reported in publications. Among these, computer tomography is the most effective method. I performed the first clinical study to evaluate the change of masseter volume in patients with masseteric hypertrophy after BoNT-A injection using computed tomography in 2003 [16]. Twelve weeks after injecting 30 U of BoNT-A into the masseter muscles of 11 patients, the mean volume reduction was 22 % with maximum 30 % in a few patients (Fig. 3.7).

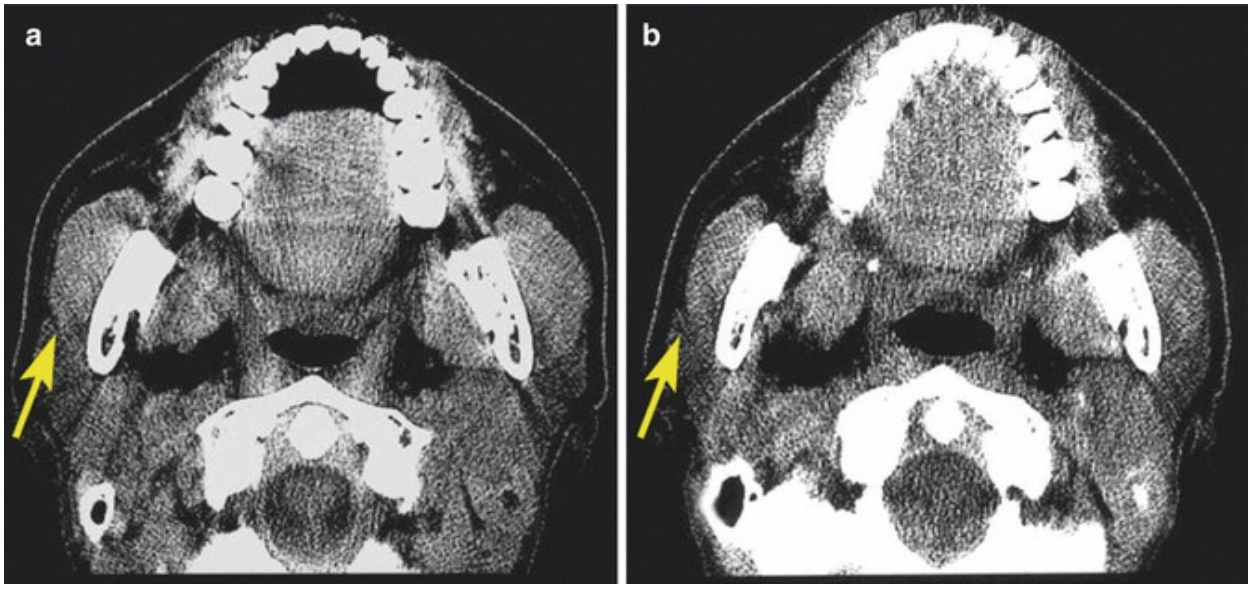

Fig. 3.7 Change of masseter volume evaluated by computed tomography in a patient with masseteric hypertrophy after 30 U botulinum toxin injection per side. After 3 months, the volume decreased 32 % compared to before the treatment [16]

In another clinical study on the dose-effect relationship of BoNT-A for the masseter muscle in 28 female volunteers using 3D computed tomography, 27.5 % reduction in masseter volume was observed (unpublished data, see Sect. 3.1.7). Another articles which used objective evaluation methods such as ultrasound and computer tomography showed similar volume reduction of masseter muscle between 20 and 30 % reduction [17, 18]. However, the clinical effect was much more dramatic after the procedure. In fact, 2–3 months after the treatment, the masseter muscle was barely palpable near the mandibular angle. The difference came from the fact that the total masseter volume was measured instead of the lower half of the masseter muscle which is more responsible for facial contouring. If they had measured the lower half of the masseter muscle after BoNT-A, the change must be more than 50 % reduction. From my clinical study described in the Sect. 3.1.7, the volume reduction at lower half was found to be 35.1 % when we measure the volume below the line connecting zygoma and tragus (since this line actually includes a some portion of the upper half, we had to measure the volume below the line connecting the mouth angle and tragus, which was impossible due to a technical issue with the CT angle) (Fig. 3.8).

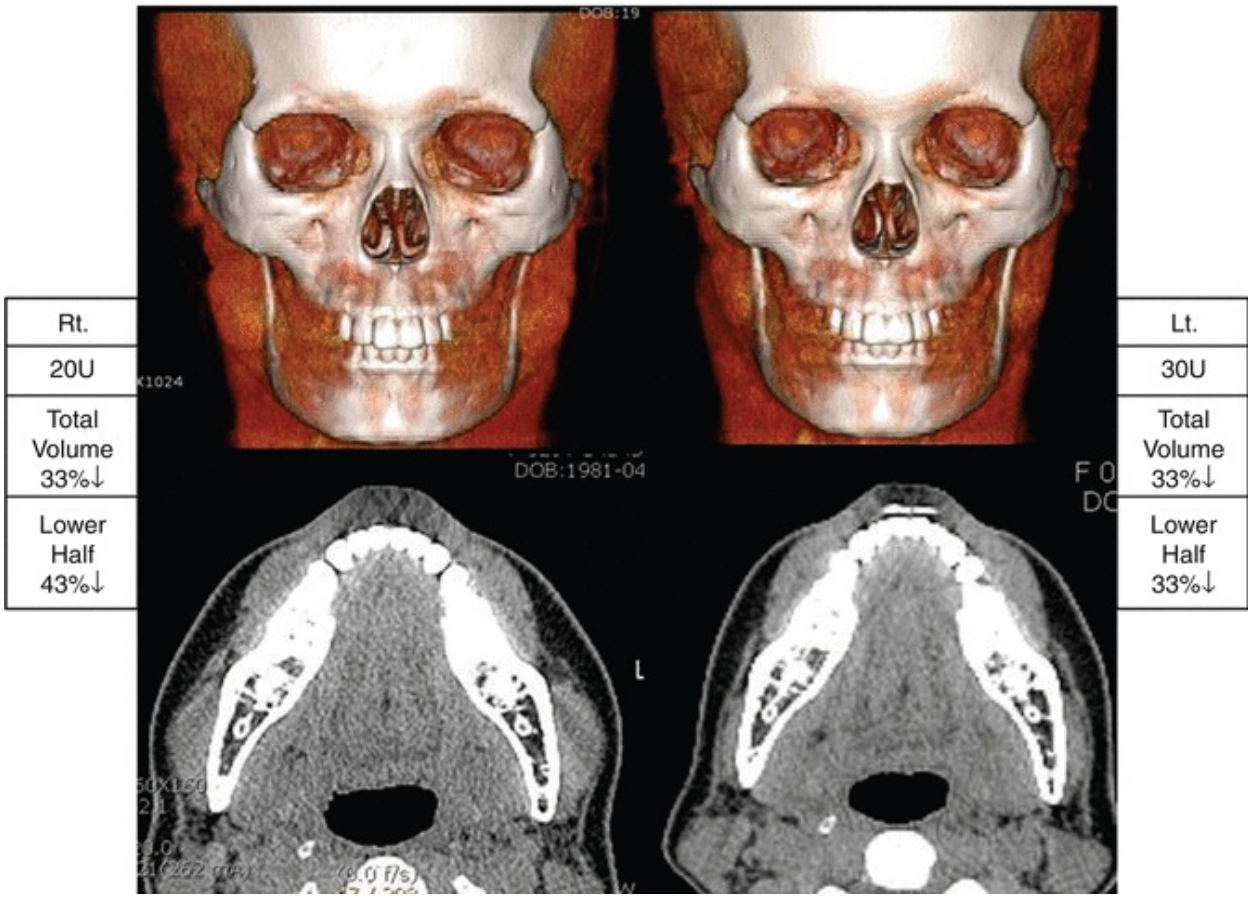

Fig. 3.8 Three-dimensional computed tomography before and 12 weeks after square jaw contouring with botulinum toxin 20 U in right side and 30 U in left side showed 33 % of volume reduction in both sides, while the lower half of masseter volume decreased by 43 % in the 20 U side and 37 % in the 30 U side

3.1.9 Onset and Duration of Effect

The onset and duration of effect for square jaw treatment with BoNT-A are different from wrinkle treatment with BoNT-A. The effect of BoNT-A for wrinkle treatment usually appears 1–3 days after the procedure and approaches the peak 1–2 weeks later which correlates well with onset and the peak time of muscle paralysis after BoNT-A injection. By contrast, the effect for square jaw treatment with BoNT-A does not come directly from muscle paralysis but rather by “disuse muscular atrophy”: muscle size decreases indirectly from lack of muscle use. If the onset of effect occurs early, muscle shrinkage may be noticed as soon as 2 weeks after injection. While muscle shrinkage effect is felt in everybody around 1 month, maximum reduction is 2–3 months after the injection (Fig. 3.6). This was already confirmed in

several prospective studies using CT and sonography [17, 18]. My prospective clinical study using three-dimensional CT in 28 female volunteers showed nearly similar results. The maximum effect appeared in 60 % of the subjects after 4 weeks and in 100 % of the subjects after 12 weeks (Fig. 3.6).

The duration of effect was reported to range from 4–6 months to 2 years according to several authors. Von Lindern reported that the effect from one treatment session lasted 15–17 months, while the effects from three treatment sessions lasted 25 months or more. Kim et al. [19] reported that 40 % of patients were satisfied with the results from two treatment sessions up to 2 years later. To et al. [20] reported that, according to muscle thickness evaluation using ultrasonography, 13.8 % volume reduction was observed from one treatment session after 1 year. The different durations of effect in these references seem to come from the different standards for comparison depending on investigators. If we take the maximum effect seen at 2–3 months after the procedure as the reference volume for comparison, most of patients at 6–10 months after the procedure are regarded as “recurrence” since more than half of the reduced volume recovered at the time. However, considering the true original state before the treatment as the reference volume for comparison, the effect is “still lasting” even after 1–2 years as long as muscle volume may not return to its pretreatment state. Based on my personal experience from thousands of cases over the past 15 years, I think the maximum effect is reached after 2–3 months, half of the reduced volume returns after 6–9 months, and complete recovery to the original state occurs after 10–18 months depending on individuals (unpublished data).

The duration of effect is affected by a few factors such as chewing habits, bruxism, and unconscious teeth clenching. Therefore, the duration depends greatly on patients’ effort to avoid bad chewing habit. Muscle volume may not recover 100 % even 1 year after only one session of the treatment as long as a patient should not only avoid hard foods such as nuts and dried fish or squid but also stop chewing gum (Fig. 3.9). Moreover, repeated injection could bring about long-term effect of volume reduction (Fig. 3.10).

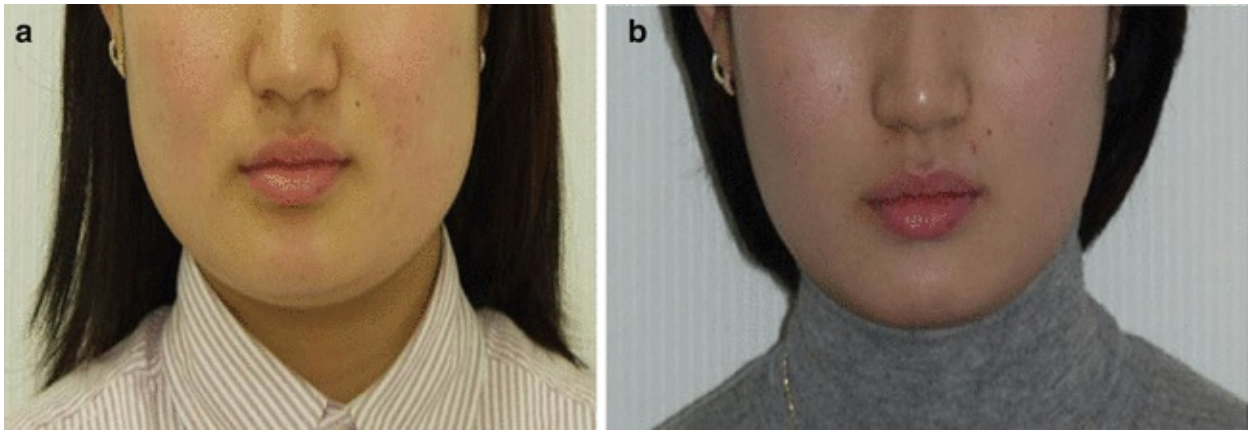

Fig. 3.9 One year after square jaw contouring with botulinum toxin. (**a**) Before, (**b**) even after 1 year, the masseter volume has not completely recovered to the original state

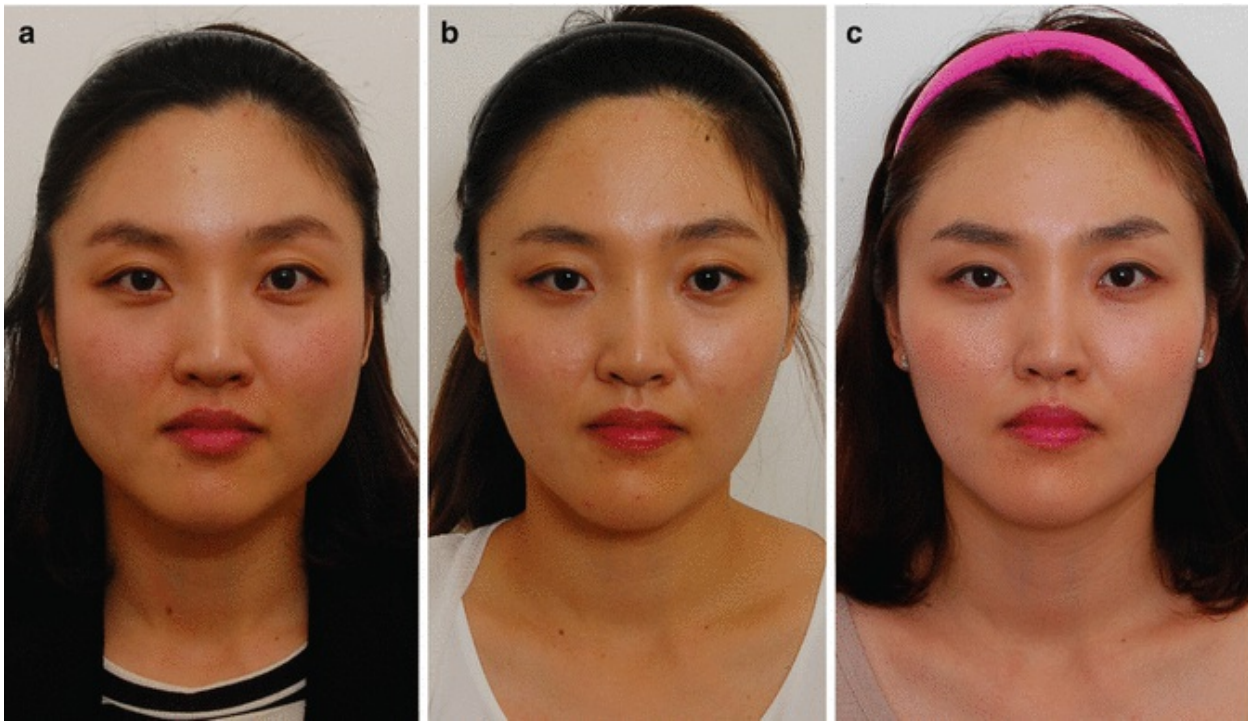

Fig. 3.10 Repeated case. (**a**) Before, (**b**) 3 months after first session, and (**c**) 2 years after three sessions of square jaw contouring with 20 U of botulinum toxin per side at the interval of 6 months. Two years after the last injection, a slimmer and oval-shaped jaw relative to the initial state was still retained

Masseter asymmetry commonly develops in people who give strong preference to one side when they chew and be improved semipermanently after BoNT-A injection as long as they correct this habit. However, in patients with bruxism, the muscle volume recovers quickly since they are

doing rehabilitation exercise every night. In short, the duration of effect is greatly influenced by chewing habits or other pertinent individual habits.

Tip: Bruxism and Botulinum Toxin

Some patients with bruxism or temporomandibular joint pain can be treated regularly with BoNT-A. The basis for the development of square jaw treatment with BoNT-A is indebted to temporomandibular disorder. The first report involving the use of BoNT-A for the masseter muscle was made in 1989 by Lagueney et al. who used the BoNT-A to treat a patient who could not open his/her mouth due to a temporomandibular disorder [21]. Temporomandibular disturbance is a general condition which involves pain in the oral cavity or face related to the surrounding structures without any specific causes. The condition can be treated effectively by injecting 20–30 U of BoNT-A into either the same points used in square jaw treatment or trigger points [22].

Since Van Zandijcke first reported the effect of BoNT-A for bruxism in 1990, injecting BoNT-A into the masseter muscle has become and remains a well-accepted form of treatment for bruxism [23]. In addition to injecting BoNT-A into the masseter muscle as performed in square jaw treatment, a combined injection into the temporalis muscle is also recommended. As proven by electromyography, the combined injection approach is more effective using 25 U doses at each muscle for a total of 100 U (Fig. 3.11). Bruxism and temporomandibular disturbance symptoms improve within 1 week but usually recur with the recovery of muscle power. Therefore, in contrast to square jaw treatment, the procedure must be repeated at 2–4-month intervals.

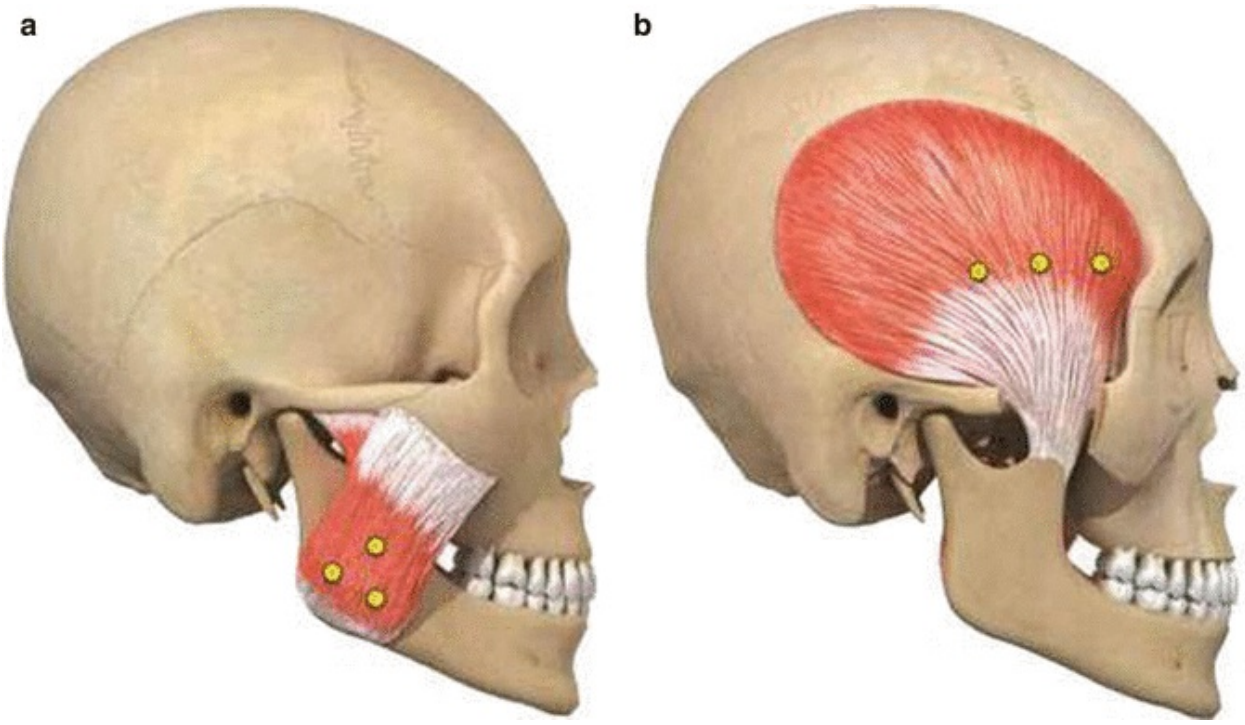

Fig. 3.11 Injection points for bruxism; (**a**) for masseter muscle, (**b**) for temporalis muscle (Photo, courtesy of Professor Sung-Taek Kim)

3.1.10 Appropriate Interval and Dose for Repeat Injections

The appropriate interval for repeat injection is absolutely dependent on the necessity of individuals who are receiving this treatment. To maintain the best condition, however, the procedure should be repeated every 6 months though it may also be repeated between 6 months and 1 year according to the muscle state if the goal is retaining a certain extent.

The appropriate dose for repeat injection depends on the muscle size at the time. It is preferable to inject 10–15 U after 6 months when muscle volume has partially recovered and 15–20 U 9–12 months after the initial treatment depending on the muscle size.

3.1.11 Adverse Effects

Adverse effects from square jaw treatment with BoNT-A are mostly transient and mild ones like bruising, stiffness, transient swelling, and weakening of biting force. Soreness and stiffness may last from 2 days to 1 week, and transient swelling caused by the minor rupturing of blood vessels may

disappear 2–3 days afterwards. Compensatory hypertrophy of temporalis muscle, a long-term complication, may also occur. However, there are also some adverse effects seriously affecting patient's social life such as altered facial expressions when smiling, masseter bulging when chewing, sunken cheeks, sagging jowls, etc.

3.1.11.1 Weakening of Biting Force

Ten to thirty percent of patients may experience a weakening of their biting force. However, the weakness is mild and usually disappears within 3 months. Kim et al. [24] reported on the change of maximal bite force over 18 months following a BoNT-A injection in 30 volunteers. Maximal bite force decreased by 20 % 2 weeks after the injection, recovered partially after 4 weeks, and returned to preinjection levels at 12 weeks (Fig. 3.12). The14 patients in booster injection group who received a booster injection at 18 weeks after the first injection also showed the same pattern—an initial decrease followed by complete recovery after 12 weeks. As the initial decrease in bite capacity was 20 %, which is also the change in maximal biting force capacity, the decrease may not have a significant impact on normal mastication in daily life. But some patients may feel some discomfort within 1 month after the injection when chewing hard foods such as radish kimchi, nuts, and dried fish including squid. While rare, there are some cases of patients who do not wish to receive repeat injection due to the bite force weakness. There was also a report that patients treated with Dysport® experience a greater weakening of bite force than those treated with BOTOX®. However, this is more likely caused by the application of a higher conversion ratio (1:3 or 1:4) resulting in a relatively larger amount of BoNT-A being injected into the Dysport® group [19].

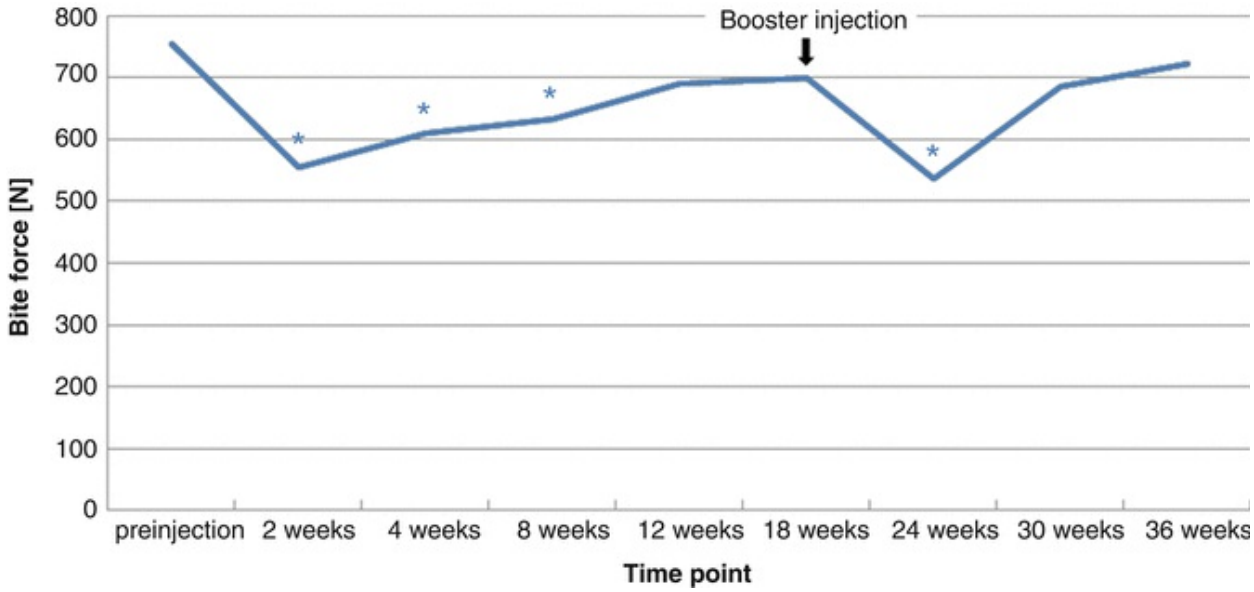

Fig. 3.12 After one or two injections of toxin into the masseter, maximal bite capacity decreased by 20 % but recovered completely after 12 weeks ($n = 14$, $*p < 0.05$) [24] (Data from Professor Sung-Taek Kim)

3.1.11.2 Sunken Cheek

Patients with sunken cheeks will appear haggard and older even if their faces become smaller and slimmer after square jaw treatment with BoNT-A. This type of face is most disliked by Korean women as they prefer slightly chubby, baby-like faces. Some doctors believe sunken cheeks are caused by skin laxity from a decrease in masseter volume. In my point of view, however, individuals with insufficient cheek fat which was not so apparent when they had well-developed masseter muscles providing rear support may reveal sunken cheek quickly following BoNT-A injection due to sudden decrease in masseter volume, leaving them looking aged and haggard. The worst combination is when the insufficient cheek fat is coupled with a prominent zygoma; the reduced masseter will accentuate the zygoma while hollowing out the cheek, making the face resemble the image in Edvard Munch's painting, "The Scream."

In short, it seems to be an inherent problem which is revealed through the treatment, rather than an adverse effect. However, patients may assume it is an adverse effect caused by the procedure, so this should be carefully explained beforehand. Sunken cheeks can be corrected by fillers. I advise injecting filler 1–2 ml into the posterior part of the cheek in each side of the face (Fig. 3.13). Alternatively, the entire face can be filled with either fat

graft or fillers. It is best to perform this procedure 2–4 weeks after the BoNT-A injection for square jaw when the masseter muscle volume has decreased to some extent. If a patient with sunken cheeks does not wish to receive additional treatment, then they should be instructed to chew gum daily. This is a type of rehabilitation program that helps sunken cheeks recover quickly.

Fig. 3.13 Sunken cheeks in the posterior cheek (**a**) after square jaw contouring can be improved by filler injection (**b**)

3.1.11.3 Jowl Sagging

Like sunken cheeks, this also seems to be an inherent problem which is revealed by the BoNT-A treatment rather than an adverse effect. While not immediately visible when firmly supported by the connection to the masseter muscles, the decrease in masseter volume following BoNT-A injection may make the sagging jowls appear more prominent. Unless this risk is clearly communicated in advance, patients might mistakenly assume such symptoms as an adverse effect. Meanwhile, injection of lipolysis, liposuction, high-

intensity focused ultrasonic surgical unit (HIFU), or thread lifting can be helpful in treating sagging jowls.

3.1.11.4 Asymmetric Smile/Awkward Smile

After square jaw treatment with BoNT-A, asymmetric smile or awkward smile may sometimes occur due to paralysis of risorius muscle by spread of BoNT-A injected into masseter muscle (Fig. 3.14a). This occurrence disturbs social life because this affects facial expressions whenever the patient smiles. Moreover, the brain may forget how to smile due to the "botulinum remodeling" phenomenon, so the asymmetry may not recover permanently (Fig. 3.14b). Therefore, this is one of the most serious adverse effects which must be addressed.

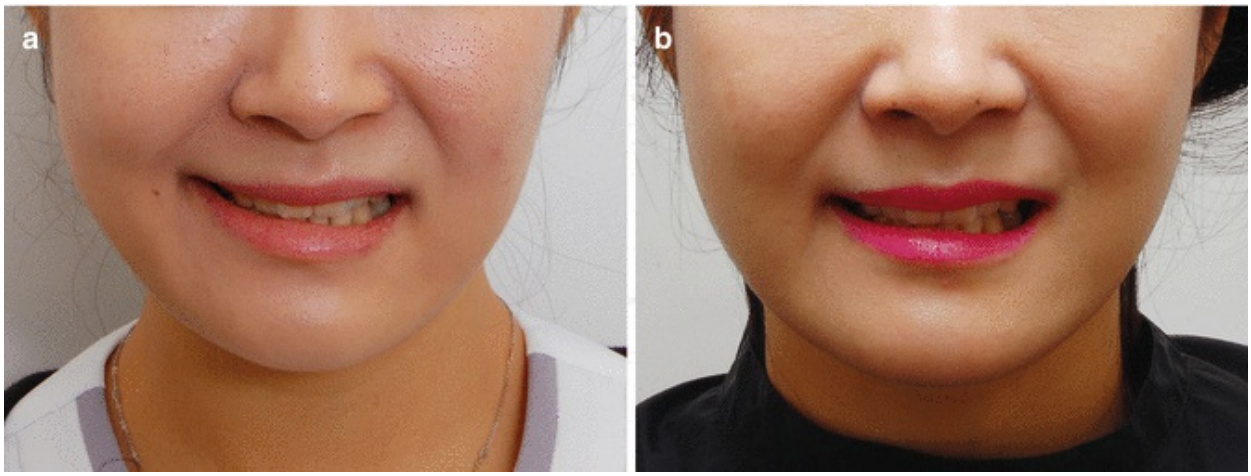

Fig. 3.14 *Awkward smile* after square jaw contouring with botulinum toxin; (**a**) 2 weeks and (**b**) 1 year after the injection of botulinum of toxin

Asymmetric smile can also occur by the paralysis of zygomaticus major if the BoNT-A is inadvertently injected too high into the superior part of the masseter muscle near the zygomatic bone. However, for square jaw treatment, BoNT-A is mainly injected into the lower half of the masseter muscle, which suggests that the main cause is paralysis of the risorius rather than the zygomaticus major. Therefore, it is worthwhile to learn more about the risorius muscle in detail.

Anatomy of the Risorius Muscle

In general, the risorius muscle originates from the muscular aponeurotic

system (SMAS), the parotid fascia, the masseteric fascia, the platysma, and, in rare cases, the tendon of masseter muscle. The muscle fibers insert into the modiolus. Since it is responsible for pulling the mouth angle superolaterally, it performs an important role in making large smiles along with the zygomaticus major. When the BoNT-A is inadvertently injected superficially into the masseter muscle, it may diffuse and paralyze the risorius muscle, causing an asymmetric smile.

In general, the origin site of the risorius muscle is located in the anterior one-third portion on the surface of the masseter if we divide the masseter into three parts longitudinally (Fig. 3.15). Rarely, it originates from the anterior two-third portion. If the risorius muscle is well developed, it passes beyond the fascia of the masseter muscle to the superior part of the parotid gland and covers the side of the face like a fan.

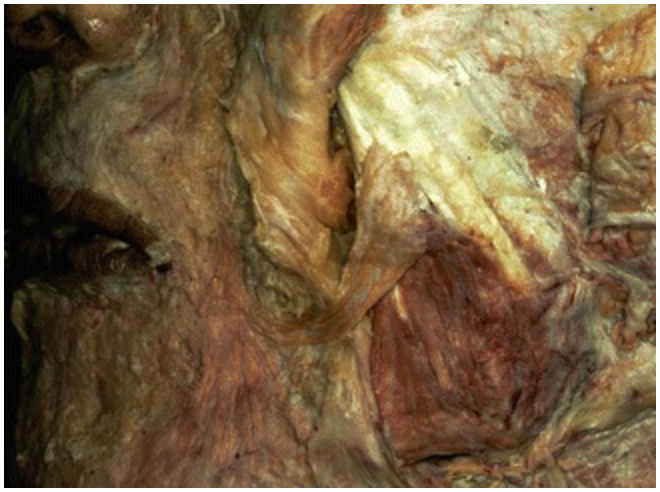

Fig. 3.15 Risorius muscle. The risorius muscle originates from anterior one-third portion on the fascia of the masseter (Photo, courtesy of Professor Hee-Jin Kim)

Well-developed risorius muscles may also cause the ears to move superiorly or laterally during a large smile. This is caused by the well-developed platysma muscle which constitutes the same layer as the risorius muscle passes to the zygomatic arch and connects to the fascia of the temporoparietalis and auricular muscles. When the risorius muscle and the SMAS move with the platysma, the ears move along with them. In these cases, BoNT-A injected superficially into the masseter muscle may diffuse into the SMAS and risorius muscle which run over the masseter, resulting in

an asymmetric smile.

Screening Risk Groups

Individuals whose mouth angles are strongly pulled superiorly during large smiles are high-risk group experiencing altered facial expressions. These patients can be screened by asking them to make a large smile or make an “ee—” sound while forcibly opening the mouth wide from left to right. During this exercise the SMAS will move the ear superiorly or laterally in patients with well-developed risorius muscles (Fig. 3.16).

Fig. 3.16 Screening *awkward smile* risk groups. These patients can be screened by asking them to make a large smile or an “ee—” sound. During this exercise the ear moves superiorly or laterally in patients with well-developed risorius muscles (**b**) compared with resting state (**a**)

Prevention

A small dose of BoNT-A should be injected deeply into the masseter muscle as if injecting over periosteum in order to prevent it from diffusing along the surface of the masseter in patients with well-developed risorius muscles. Dose of BoNT-A should not exceed 10 U per side at one session. 2 U per

point with a total of 8 U is usually recommended. Of course, the small dose may necessitate a second session with the same dose as initial treatment session after 2–3 months. BoNT-A must be injected deeply especially into the anterior portion of the masseter muscle, even for non-risk group patients, as the risorius originates in the anterior one-third of the masseter muscle. Therefore, intradermal injection of BoNT-A should be avoided near the masseter muscle.

Treatment
If asymmetric smile or awkward smile occurs, it may not be reversible back to the original state, and therefore, rehabilitation treatment involving excessive use of the risorius muscle is necessary. Patients should be asked to make an “ee—” sound while forcibly opening the mouth wide from left to right and should exercise to elevate their mouth corner forcibly in the side not easily elevated.

3.1.11.5 Masseter Bulging on Mastication

Individuals undergoing the BoNT-A injection for square jaw sometimes show the masseter bulging when a patient chews food (Fig. 3.17). This adverse effect gives the appearance of a chipmunk chewing on nuts. This is quite embarrassing as the patient may be unaware of this problem before others recognize and point it out. Therefore, it is preferable to mention this possibility before the procedure. Masseter bulging usually occurs 1–2 days after the injection and progresses within 3–7 days. Although it may improve to some extent after 2 weeks, it can last up to 2–3 months.

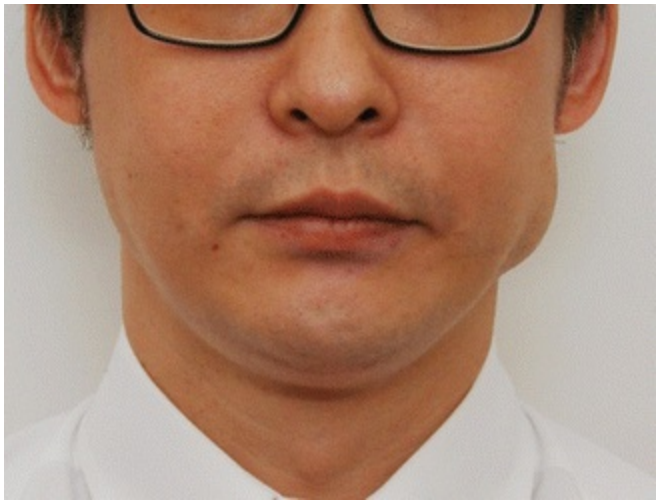

Fig. 3.17 Masseter muscle bulging after square jaw contouring with botulinum toxin

Masseter bulging is caused by imbalance of muscle activity between the lower part injected with BoNT-A and upper part of the masseter muscle which are not paralyzed by the BoNT-A. While the paralyzed muscle fibers in lower part do not contract, the contraction of hyperactive fibers in upper part not affected by the BoNT-A pushed the lower part laterally due to botulinum rebalancing. Therefore, the bulging part will feel soft to the touch on clenching, whereas the upper part of masseter muscle just above the bulge will feel hard to the touch.

This adverse effect frequently occurs when a small dose of BoNT-A is injected or the injection is focalized. Anatomically, it occurs frequently in people whose superficial part of the masseter muscle is well developed. Therefore, patients whose masseter bulges slightly before the treatment of BoNT-A when they clench may be considered part of the high-risk group.

This adverse effect spontaneously improves to some extent without any treatment within 2 weeks when muscle paralysis by BoNT-A reaches its peak effect, but can be resolved more quickly by injecting the 10–15 U of BoNT-A into the upper part of the masseter muscle which shows compensatory hyperactive muscle activity. Since an additive injection will of course reduce the masseter volume more, patients, especially those with insufficient cheek fat, should be informed of the possibility of sunken cheeks. Masseter bulging may disappear after 1–2 months along with a decrease in masseter volume in patients whose superficial part of the masseter muscle is well developed.

Tip: Does Xerostomia Occur if Botulinum Toxin Is Incorrectly Injected into the Parotid Gland?

The parotid gland covers the masseter muscle and lower mandible anterior to the ear and posterior to the mandibular angle. When I began treating square jaw with BoNT-A, I was worried about the possibility of xerostomia occurring due to BoNT-A diffusion into the parotid gland. Since the neurotransmitter of salivary glands is the same acetylcholine as in neuromuscular junctions, salivation can be affected by BoNT-A injection. Therefore, I selected injection points for masseter within 1 cm of the posterior border of the masseter muscle. However, we don’t have worry about xerostomia after BoNT-A injection for the masseter. I have experienced only one case with mild symptoms among thousands of cases undergoing this procedure from me. Moreover, xerostomia does not occur

even if the BoNT-A is injected directly into the parotid gland for the treatment of parotid gland enlargement. The reason is simple. The salivary glands consist of the parotid glands, submandibular glands, and submaxillary glands, and the submandibular glands are responsible for 71 % of the total saliva production [25]. Therefore, even if the parotid glands are totally paralyzed by the BoNT-A and produce no saliva as a result, xerostomia may not occur.

3.1.12 Effect of Botulinum Toxin Injection on the Mandibular Bone

There are many reports which suggest that bone develops secondary to increases in muscle activity and the mandibular angle develops according to increases in masseter muscle activity. Since the masseter muscle continuously stimulates the cortical bone of the mandibular angle, the mandibular angle develops well in patients with masseter hypertrophy.

In reverse, the theory that repeat BoNT-A injections into the masseter not only paralyze the muscle but also decrease the size, thickness, and density of the mandible may be plausible. Dr. Wu from Singapore once claimed that the mandible decreases in size through repeat BoNT-A injections [26]. Rafferty reported in an animal experiment using rabbits that mandible bone quantity and quality decreased 3 months after BoNT-A injections into the masseter muscle as evaluated by microcomputed tomography [27]. In a similar experiment using New Zealand white rabbits, a decrease in zygoma and mandibular volume was observed after paralysis of the masseter muscles with BoNT-A [28]. In contrast, Dr. Chang reported that there were no statistically significant mandibular changes in ten female patients evaluated by computed tomography, 3 months after BoNT-A injections [29]. However, the evaluation was made after just one session of injection, which seems to be insufficient to draw bony changes in humans. Therefore, I think more studies will be needed focusing on the effect of repeated injections with BoNT-A for bone change in humans.

3.2 Temporalis Hypertrophy

Effect (A), Adverse Effect (B), and Technique (A)

A well-developed temporalis muscle on the temple area contributes to wide

face and bulging of the temporalis muscle when chewing which is disfiguring condition to women. BoNT-A can be used to reduce the temporalis volume leveraging the disuse atrophy as in masseter hypertrophy (Fig. 3.18).


a
b
c
d

Fig. 3.18 Temporalis hypertrophy: (**a**, **c**) before and (**b**, **d**) 3 months after 30 U injection of BOTOX® per side

3.2.1 Anatomy

The temporalis is a flat fan-shaped muscle consisting of two layers. The superficial layer originates from the temporal muscle fascia, and the deep layer originates from the bone around the temporal fossa. Both layers insert into the choroid process of the mandible. The anterior muscle fibers run vertically, while most of the posterior muscle fibers run almost horizontally. The temporal fascia is a strong membrane which covers the muscle surface and attaches to the superior temporal line superiorly and the upper border of the zygomatic arch inferiorly. The muscle is supplied via the anterior and posterior deep temporal arteries. As the temporalis elevates the mandible and closes the mouth, it is one of mastication muscles along with the masseter. It also helps to keep the mouth closed against gravity by maintaining a specific tone.

3.2.2 Injection Techniques

Injection of BoNT-A should be focused into the muscle bulge at the superior temporal fusion line since the upper part of the temporalis is more important in upper facial contour.

A total of 30–40 U of BoNT-A should be deep intramuscularly injected into bulging area of temporalis muscle divided by 6–8 points similar to masseter muscle injections (Fig. 3.19). The onset and duration are also very similar to square jaw treatment. It is preferable to inject into the upper half of the temporalis as the upper portion of the muscle is more prominent and more responsible for the width of the forehead and the upper face. Since posterior part of the temporalis muscle is covered by the hairs which camouflage well the temporalis bulging, BoNT-A should be injected into the anterior part of the temporalis muscle in front of the imaginary vertical line parallel with the tragus. However, injection of BoNT-A into the anterior part of the temporalis muscle immediately behind the orbital rim should be avoided because this can bring about temple hollow which exaggerates the prominence of the zygoma and the lateral part of bony orbital rim conjoined with superciliary arch.

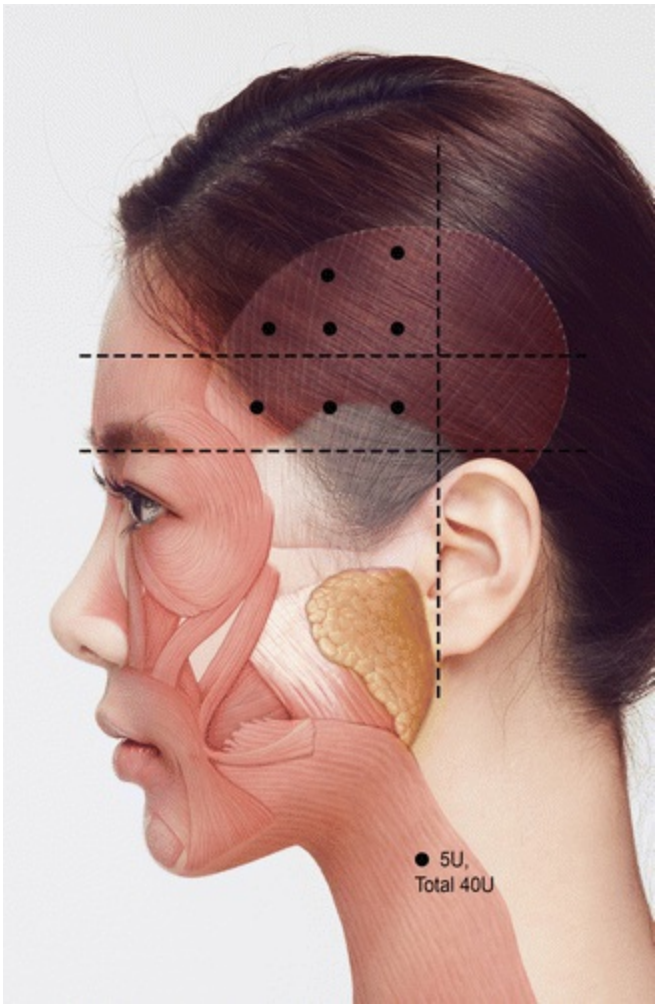

Fig. 3.19 Injection points for botulinum toxin temporal reduction. 6 U of toxin is injected into the anterior and superior half of the temporalis at five different sites, totaling 30 U

3.2.3 Adverse Effects

As the temporalis is a muscle of mastication, injecting BoNT-A into the temporalis will result in a mild temporary weakness of biting force in a small proportion of patients. Though not very severe, muscle weakness can be more exaggerated when the BoNT-A injection for temporalis is performed together with the masseter muscle.

A preexisting temporal hollow may become aggravated with the disappearance of the temporalis fullness. However, this would be treated by filler re-volumization or fat grafting.

3.3 Salivary Gland Enlargement

3.3.1 Parotid Gland Enlargement

Effect (A), Adverse Effect (A), and Technique (A)

Although BoNT-A is the choice of the treatment for the masseter hypertrophy, the treatment is not effective for reducing facial width in patients with parotid gland enlargement since the facial contour is shaped by the parotid gland in the rear part of the face behind masseter muscle (Fig. 3.20). Therefore, individuals with parotid gland enlargement may not benefit much from reducing the masseter muscle size alone. For best results in these patients, additional procedure for reducing parotid glands enlargement is prerequisite together with BoNT-A injection for the masseter hypertrophy.

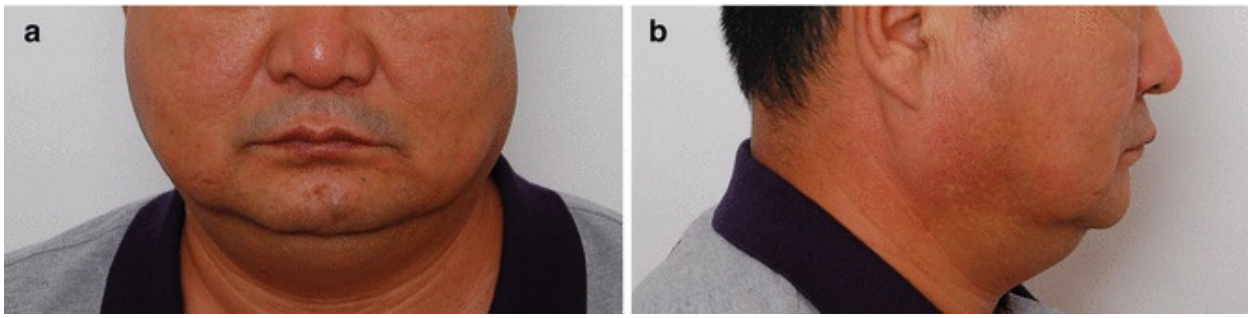

Fig. 3.20 Parotid gland enlargement. (**a**) Frontal view. (**b**) Lateral view

Since the neurotransmitter of salivary glands is the same acetylcholine as in neuromuscular junctions, BoNT-A injections into the parotid gland have long been used to reduce salivary secretion. In cases of cerebral palsy, Parkinson's disease, and amyotrophic lateral sclerosis, 10–100 U of BoNT-A injection per side is advised for the treatment of severe sialorrhea [30]. Based on the fact that the neurotransmitter of salivary glands is the acetylcholine, several doctors including me have already used the BoNT-A for reducing the size of the parotid gland enlargement [26] (Fig. 3.21) long before the volume reducing effect of BoNT-A in parotid gland was first reported by Teymoortash in 2007 [31]. Teymoortash demonstrated in an animal study that BoNT-A induces not only a functional reduction of saliva secretion but also a reduction in the size of the parotid glands [31]. Finally, our study group including Dr. Bae objectively elucidated the effect of BoNT-A injection on the volume change of the parotid gland in humans using

computed tomography volumetry (Fig. 3.22) [32]. One of our cases showed nearly 30 % size reduction after BoNT-A injection into the parotid gland [32].

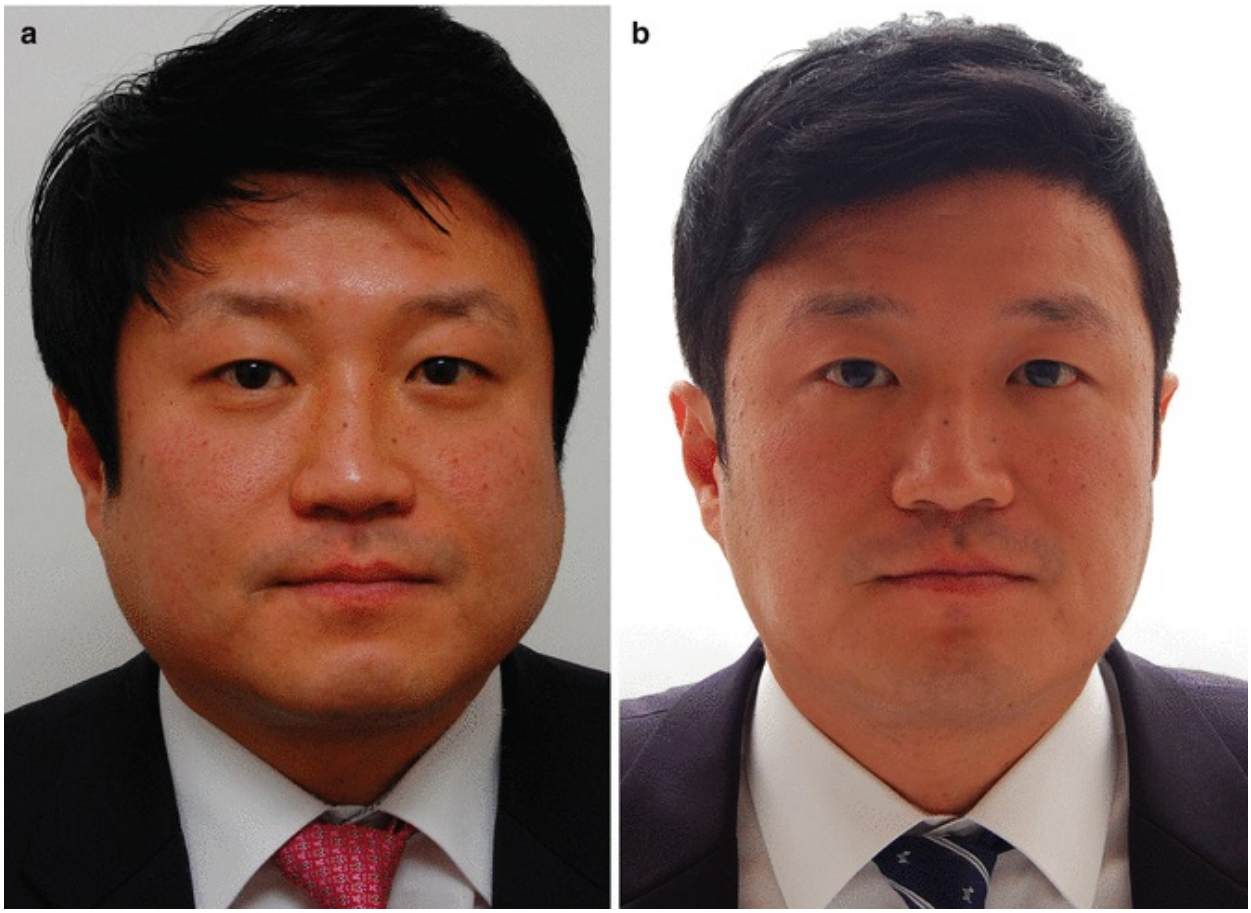

Fig. 3.21 Parotid gland enlargement: (**a**) before and (**b**) 3 months after 40 U injection of BOTOX® per side

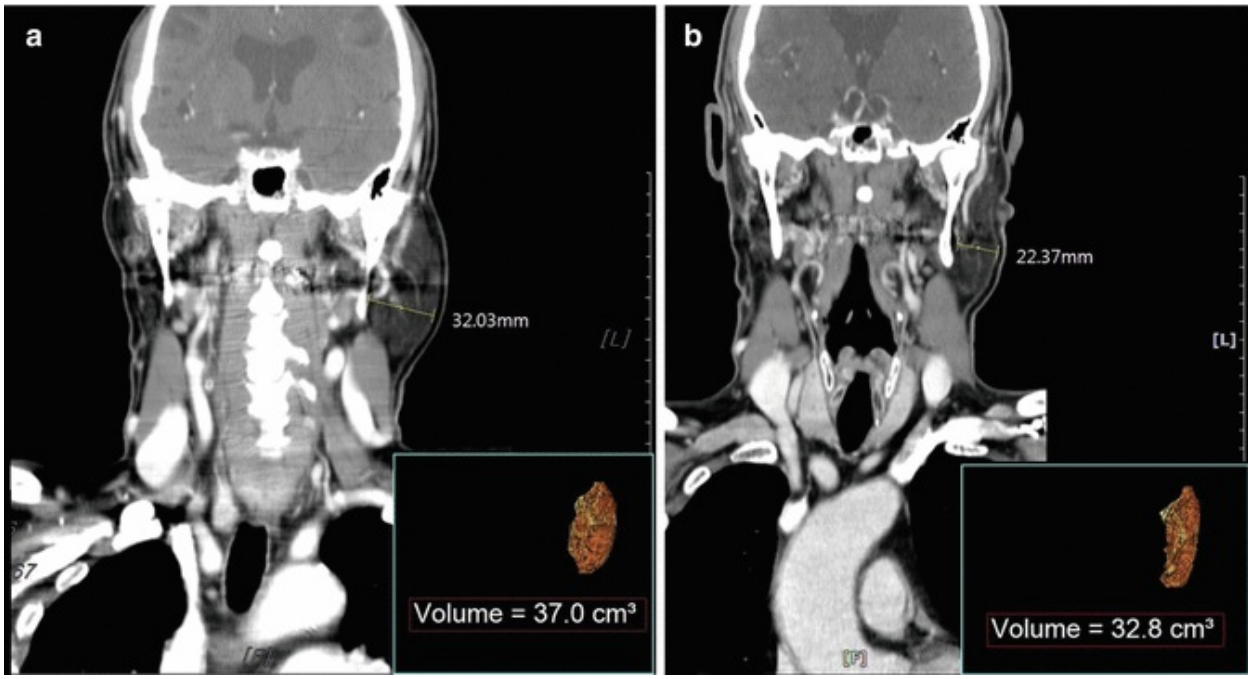

Fig. 3.22 MRI showed marked reduction of parotid gland enlargement 2 months after 40 U injection of botulinum toxin (**a**) before and (**b**) 2 month after (Photo, courtesy of dermatologist Jee-Young Bae)

While parotid gland hypertrophy can occur congenitally, it is also observed in various other abnormal conditions: alcoholism, HIV-associated salivary gland disorders (HIV-SGD), initial manifestation of HIV, eating disorders like bulimia, and anorexia nervosa.

The parotid glands are located anterior to the ears and the posterior border of the mandible, including the mandibular angle. The parotid gland is consisting of two layers enclosing the masseter and the mandible: the superficial layer, which lies over the fascia of the masseter muscle, and the deep layer, which stretches into the inner side of the mandibular ramus.

3.3.2 Submandibular Gland Enlargement

Efficacy (A), Adverse Effect (B), Technique (B)

Patients who underwent mandibular angle reduction sometimes showed the bulging in the submandibular neck area. This is a well-developed submandibular gland which is exposed by mandibular angle reduction surgery. The submandibular gland is situated inferior and superior to the submandibular triangle, producing the most amount of saliva. Patients, therefore, complain of xerostomia.

BoNT-A injection into the submandibular area can also reduce the

volume of the gland as well (Fig. 3.23). Extreme caution should be exercised to avoid affecting the neck support muscles. As the submandibular glands are responsible for 70 % of total salivary secretion, patients should be notified in advance that xerostomia may occur [25].

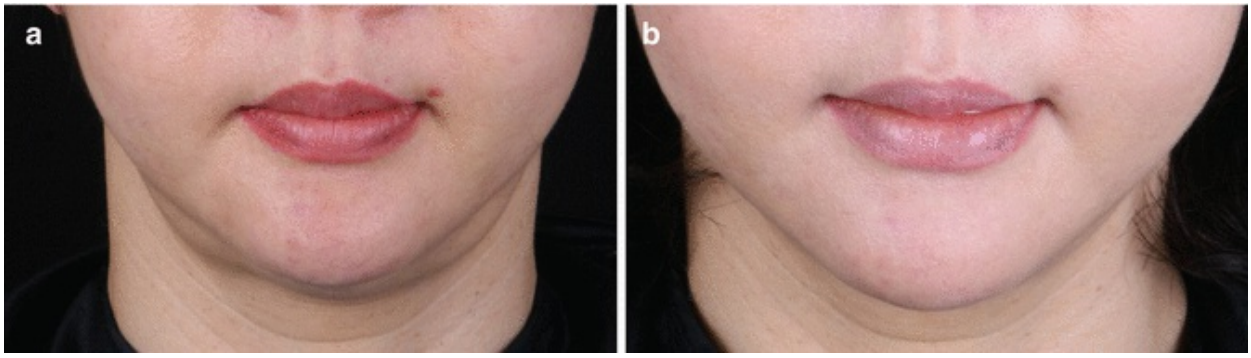

Fig. 3.23 Submandibular glands enlargement: (**a**) before and (**b**) 2 months after 30 U injection of BOTOX® per side (Photo, courtesy of dermatologist Jee-Young Bae)

3.3.3 Injection Techniques

A total of 30–40 U of BoNT-A per side depending on the volume of the gland should be deeply injected into the bulging area of parotid glands divided by 6–8 points. Injections should be made not only in the anterior part of the ear but also around the mandibular angle (Fig. 3.24).

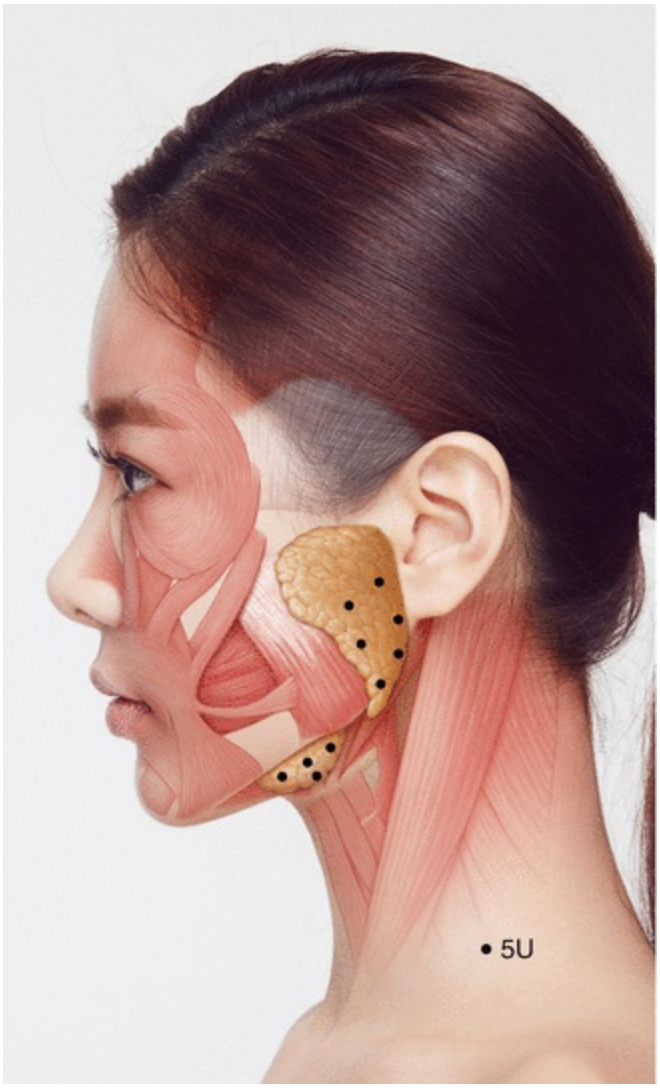

Fig. 3.24 Injection points for parotid gland enlargement and submandibular gland enlargement

An ultrasound guide helps identify the exact location of submandibular gland for the injection of the BoNT-A into the submandibular glands. If an ultrasound equipment is not available, however, palpation would be helpful to locate the boundary of the submandibular gland. A total of 20–30 U of BoNT-A per side depending on the volume of the gland should be deeply injected into the bulging area of the submandibular glands divided by 4–6 points.

Episode: “Honey, Have You Lost Weight?”

As a general rule, when patients revisit my clinic 3 months after their square jaw reduction, I show them the photos taken initially on their first visit. For

one thing, patients all too often forget what they used to look like before the procedure. Hence the old saying “To forget is human,” for another, patients often fail to appreciate changes affected after the procedure, since they see their faces every day. For this reason, at my clinic patient pictures are taken before the procedure, not for any marketing and advertising purposes but so as to give the patients a better idea of the outcome.

Before showing them their old pictures, I typically ask “So, what do you think? Do you think you’ve lost enough volume?” The response varies.

(Before picture is shown): “I’m not too sure really.”

(After picture is shown): “(incredulous) Don’t tell me that’s how I used to look!”

Me (thinking in my head): “That’s how you used to look.”

Before: “I am told I look thinner these days.”

- Me (in my head): “You need to be told.”

After: “I guess they were right. I can see its much slimmer now.”

Before: “Hmmm, I suppose I look slightly better.”

After:: “Oh my God, I look so weird in the old picture!”

Me (in my head): “Well that wasn’t any photoshop.”

Me: “Congratulations! Well done you! How about we print out your old picture so you can keep it as a small souvenir?”

Patient: No thanks. This is one secret I’m taking to the grave.

Before: I don’t know. Nobody seems to notice, you know what I mean?

After: I must say, it really has become slimmer!

Dr. Seo: Let me print that out for you. Let’s see what they’ll say now, shall we?

As you can see from the conversations quoted above, Koreans have a tendency to hold back on their compliments. Even where the improvements from the procedure are manifestly clear, patients’ feedback mostly consists of tentative and lukewarm comments such as “not bad” or “others seem to think I’ve lost bit of weight.” Rarely do you hear a patient openly express their satisfaction, saying “more than I expected” or “100 % happy” or “worked wonders.” This being the situation, one compliment I once got from a patient is worth a mention and that was “Getting BOTOX treatment was the best decision I made last year.” To this day that was the best compliment I had

ever received ever since I began performing BoNT-A treatment for facial contouring. Doctors are also human, and getting a compliment from patients can really make our day.

In fairness though the effects of BoNT-A for masseter treatment appear only gradually and not immediately noticeable after the procedure. Apart from the occasional bruising that usually goes unnoticed, there are no other tell-tale symptoms like edema or crust formation that suggest the person had some "work done" on them. Naturally, others would simply assume that the person had lost some weight rather than suspect any cosmetic procedure was involved the procedure. That is why patients who got BoNT-A for masseter treatment are often scheduled if they had lost weight lately. A newly married female patient once told me how pleased she was when her husband, looking genuinely concerned, said, "Hey honey, what's going on? You are losing so much weight these days. It must be the heavy workload. You've got to take it easy, babe. Leave the heavy lifting to me from now. I'll take care of the laundry."

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Kyle K Seo, Botulinum Toxin for Asians, DOI 10.1007/978-981-10-0204-5_4

4. Multiple Intradermal Botulinum Toxin Injections

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4.1 Concept

Effect (A), Adverse Effect (C), and Technique (B)

Intradermal botulinum toxin type A (BoNT-A) has been widely performed in Asia, under various names such as mesobotox, skinbotox, dermotoxin, microbotox, botox lift, or multiple intradermal small bolus injection of botulinum toxin (MISBIB). The purpose of this treatment is not only for the reduction of dynamic facial wrinkles but also for the reduction of static wrinkles and pore sizes, as well as creating the so-called perceived lifted look. Therefore, intradermal BoNT-A can be considered as a full package of antiaging effects that BoNT-A can deliver.

The same dynamic wrinkle reduction as in wrinkle treatment with BoNT-A can also be achieved by diffusion of intradermal BoNT-A into underlying muscles of facial expression, because BoNT-A spreads in a three-dimensional manner from the dermis and because several muscles of facial expression also have intracutaneous insertions.

The improvement of static wrinkles and tightening of pores, which imparts a shine and a tighter look to the skin, has been already reported in conventional BoNT-A injections for the treatment of glabellar and forehead wrinkles [1]. My hypothesis for this improvement of skin texture seems to be due to dermal edema resulting from a transient and mild lymphatic insufficiency induced by underlying muscular paralysis, in addition to

relaxation of the facial expression muscles. Thus, partial lymphatic edema in the skin leads to the improvement of fine wrinkles and tightening of pores, causing the skin to appear more elastic. The same effect may happen after intradermal BoNT-A [2] (Fig. 4.1). The effects of intradermal BoNT-A on the improvement of static wrinkles were first proven by Dr. Kim in his master's thesis of in 2010 using an objective method [3]. Some advocates for intradermal BoNT-A have suggested that this is due to the formation of new collagen by intradermal BoNT-A, but their hypothesis does not account for the disappearance of the effect after a few months of the BoNT-A injection.

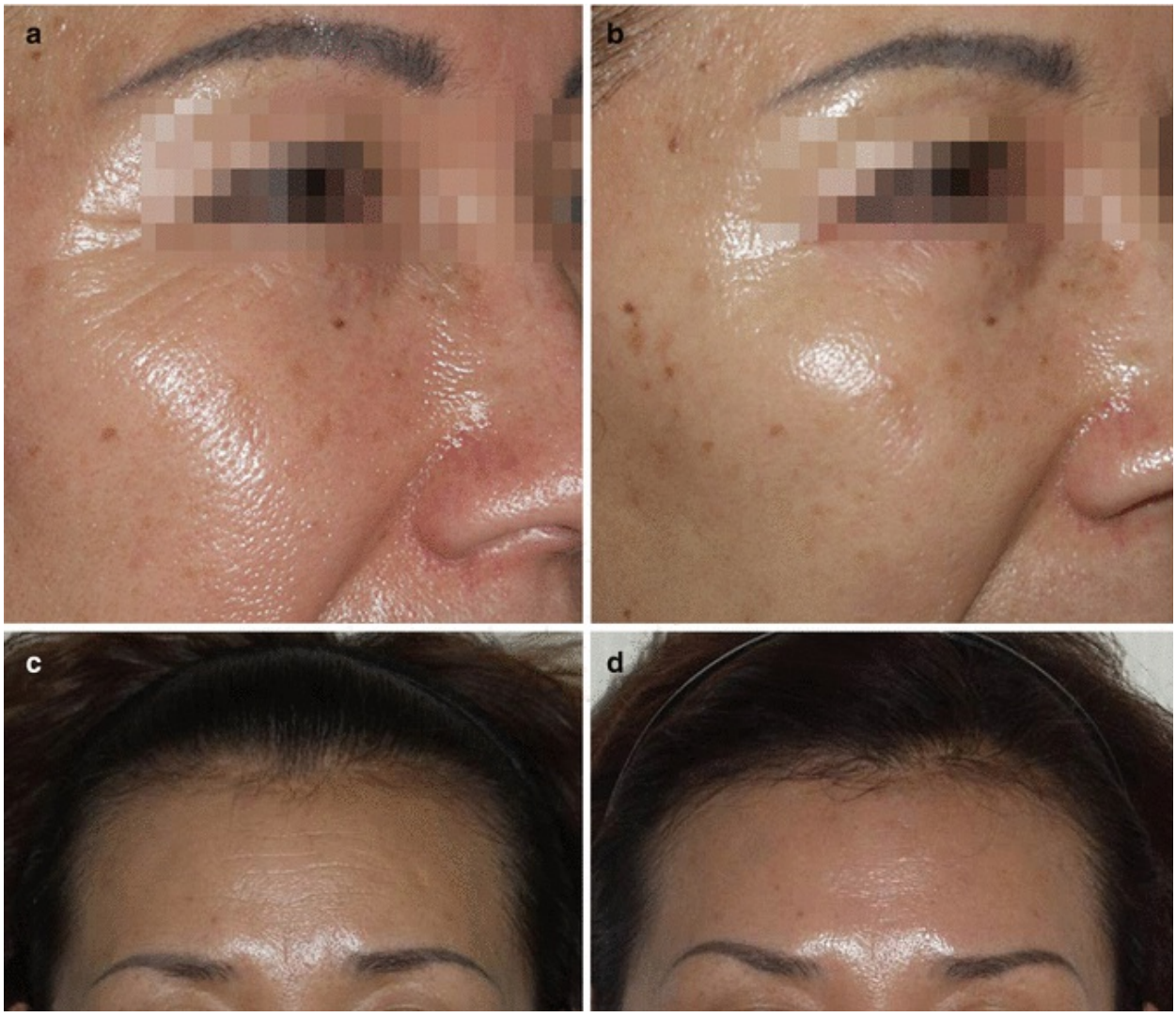

Fig. 4.1 Multiple intradermal botulinum toxin injection improves pores and static wrinkles before (**a**, **c**) and (**b**, **d**) 2 weeks after the injection

Another effect of intradermal BoNT-A is the reduction of sebum

production and pore size, thus improving the skin texture by giving it a smooth appearance [4, 5]. This might be due to a possible humoral effect of BoNT-A reducing the activity of the sebaceous gland and the pore size since acetylcholine receptors have been reported to be present in sebaceous glands [6]. The reduction of sebum production and pore size by intradermal BoNT-A in patients with oily skin was also objectively elucidated [7].

The lifted look of intradermal BoNT-A seems to come from both botulinum rebalancing phenomenon and pseudo-lift effect. Botulinum rebalancing phenomenon may result in an eyebrow lift, mouth corner lift, and Nefertiti lift by weakening the depressor muscles of eyebrows, mouth corner, and jawline, respectively. Pseudo-lift effect of intradermal BoNT-A is in fact not true lifting but a kind of visual illusion caused by reducing the lower part of the facial contour and thus elevating the center of gravity upward. This effect can be achieved by narrowing the width of the lower face with reducing the volume of the masseter. Anterior chin contouring with BoNT-A for the mentalis hyperactivity can also help produce a younger and slimmer V line from the front view in addition to lifted look of intradermal BoNT-A.

Intradermal BoNT-A employs multiple intradermal injection of BoNT-A combined with the conventional intramuscular injection of BoNT-A for wrinkle treatment and facial contouring. Injecting a small dose of diluted BoNT-A into the dermis of the face helps reserve the function of deeper part of facial expression muscles (Fig. 4.2), thereby resulting in a more natural appearance. Therefore, another advantage of this procedure is that it can be used on the entire face including cheeks where BoNT-A is not usually recommended.

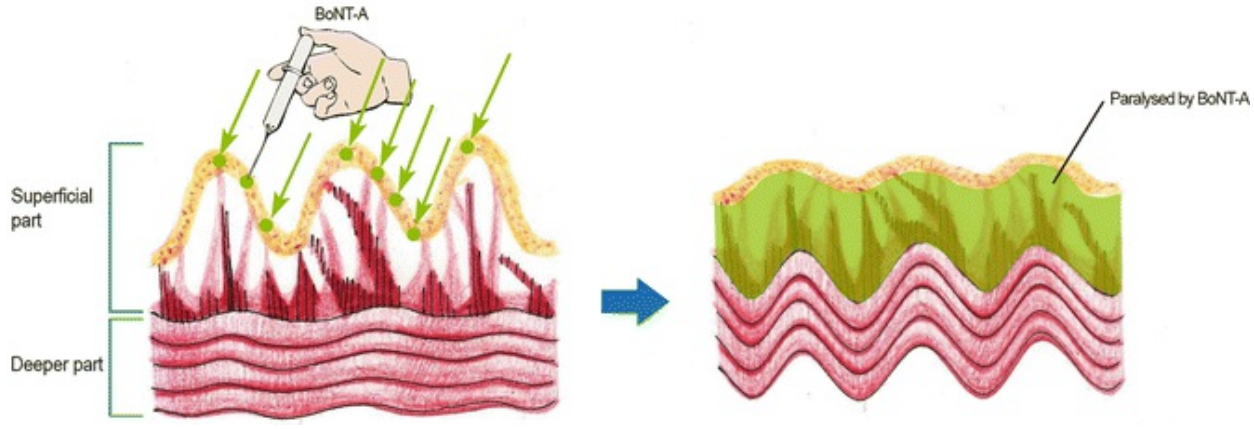

Fig. 4.2 The concept of intradermal BoNT-A. A small dose of diluted BoNT-A injected into the

dermis can diffuse only into the superficial part of the muscle, which helps reserve the function of deeper part of facial expression muscles, thereby resulting in a more natural appearance

Episode: Effects of Intradermal Botulinum Toxin Injections in the Skin by Objective Evaluation Methods (Master's Thesis of Dr. Dong-Hyun Kim 2010 Seoul National University College of Medicine)

1. Study Design

   Randomized, double blind, placebo-controlled, split face study

2. Methods

Twenty-four female volunteers with wrinkles under 3 on the grading scale were recruited. 15 U of BoNT-A (Neuronox®) was injected in one side of the cheek, and the other side was injected with normal saline as a placebo. Total 15 U was injected into points arranged along three columns and ten rows (Fig. 4.3). Patients were evaluated at different time points: before, 2 weeks, 4 weeks, and 12 weeks. Objective, noninvasive methods were used to measure and quantify the various skin conditions: wrinkles, elasticity, skin hydration, sebum secretion, hair follicle pore sizes, and skin thickness. Photographs were used to measure the fine wrinkle grade and evaluated by clinicians and also according to the degree of patient satisfaction.

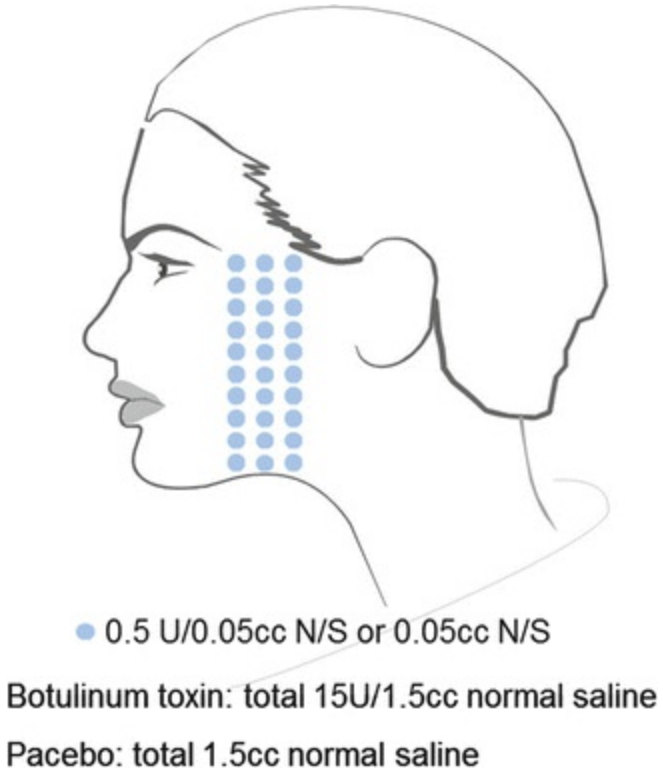

Fig. 4.3 Injection points in the clinical study for intradermal botulinum toxin injections. From the lateral canthus to the mandibular border, total 15 U (1 U/0.1 ml) was injected into points arranged along three columns and ten lines anterior to the ear

3. Results

Wrinkle depth showed statistically significant improvement at BoNT-A injected site compared with normal saline injected site evaluated by Skin Visiometer® (Fig. 4.4). However, there were no statistically significant differences in the other parameters. Although sebum secretion and pore size tended to decrease, it was statistically insignificant. BoNT-A led to marked improvements in wrinkle grade when measured by both clinicians' photographic evaluations and the degree of patient satisfaction (Fig. 4.5).

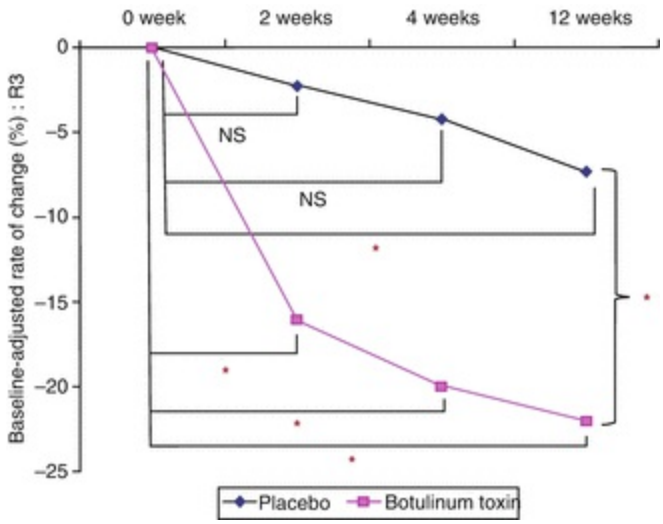

Fig. 4.4 Change of depth of static wrinkles in the lateral canthal area measured by Skin Visiometer® after intradermal botulinum toxin injections. Depth of wrinkles significantly decreased in toxin injected sites compared to saline injected sites

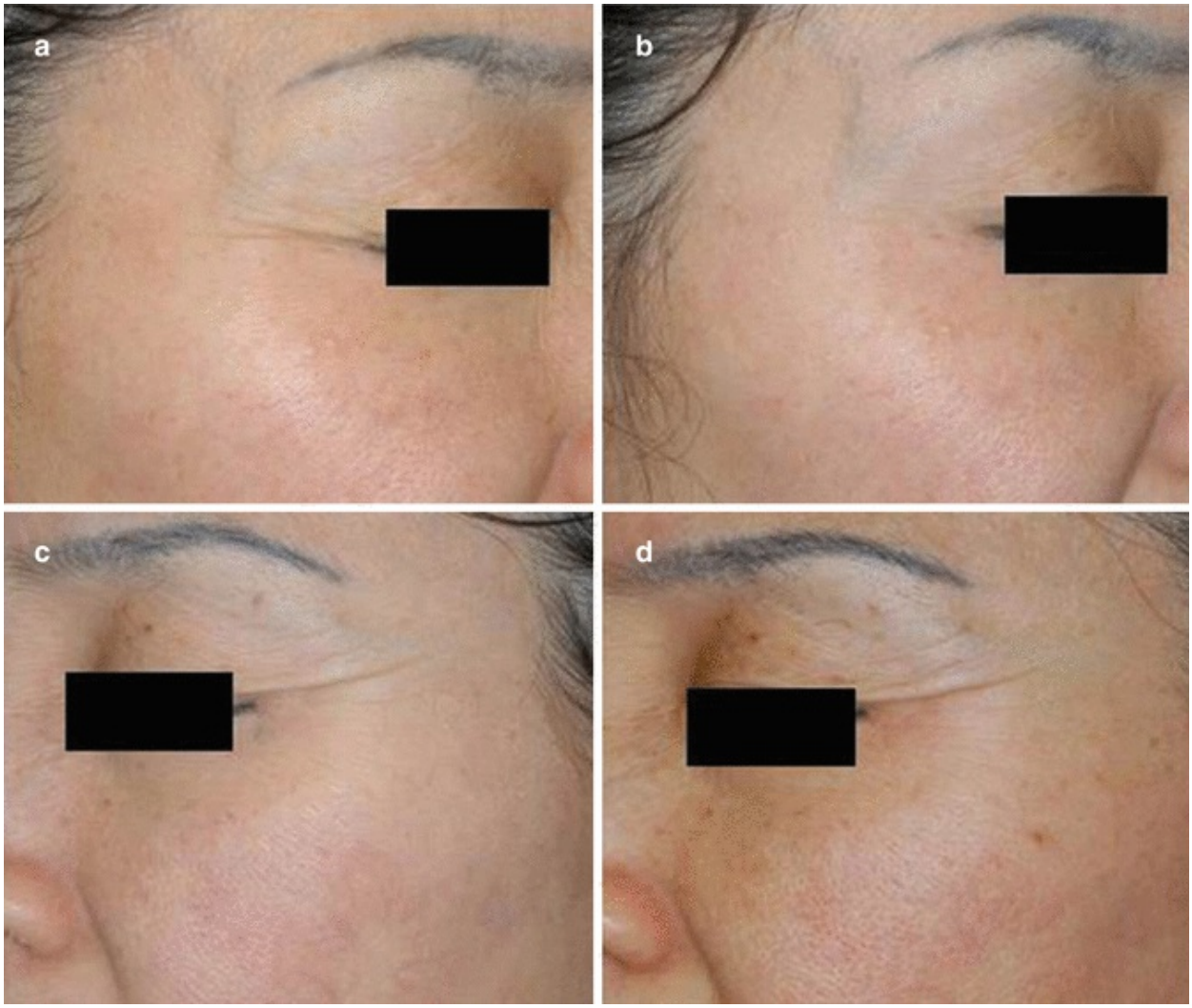

Fig. 4.5 Improvement of lateral canthal static wrinkles was evident in the right side 4 weeks after intradermal injection with botulinum toxin (**a**, **b**), while no change was observed in the left side injected with saline (**c**, **d**)

4. Conclusion

Intradermal BoNT-A injections were confirmed to be effective in reducing fine static wrinkles.

4.2 Injection Techniques

Since intradermal BoNT-A is a full package of antiaging effects that BoNT-A can deliver, combination injection of BoNT-A for dynamic wrinkle treatment, facial contouring, and facial muscle rebalancing is usually

employed together with multiple intradermal injections into some parts of the face such as lateral cheek and anterior malar area (Fig. 4.6). However, dose of BoNT-A for dynamic wrinkle treatment, facial contouring, and facial muscle rebalancing in the intradermal BoNT-A tends to be slightly lower than conventional techniques describe in previous chapters. Total of 60–100 U depending on individuals is administered for one session of the intradermal BoNT-A. Intradermal BoNT-A would be repeated every 3 months.

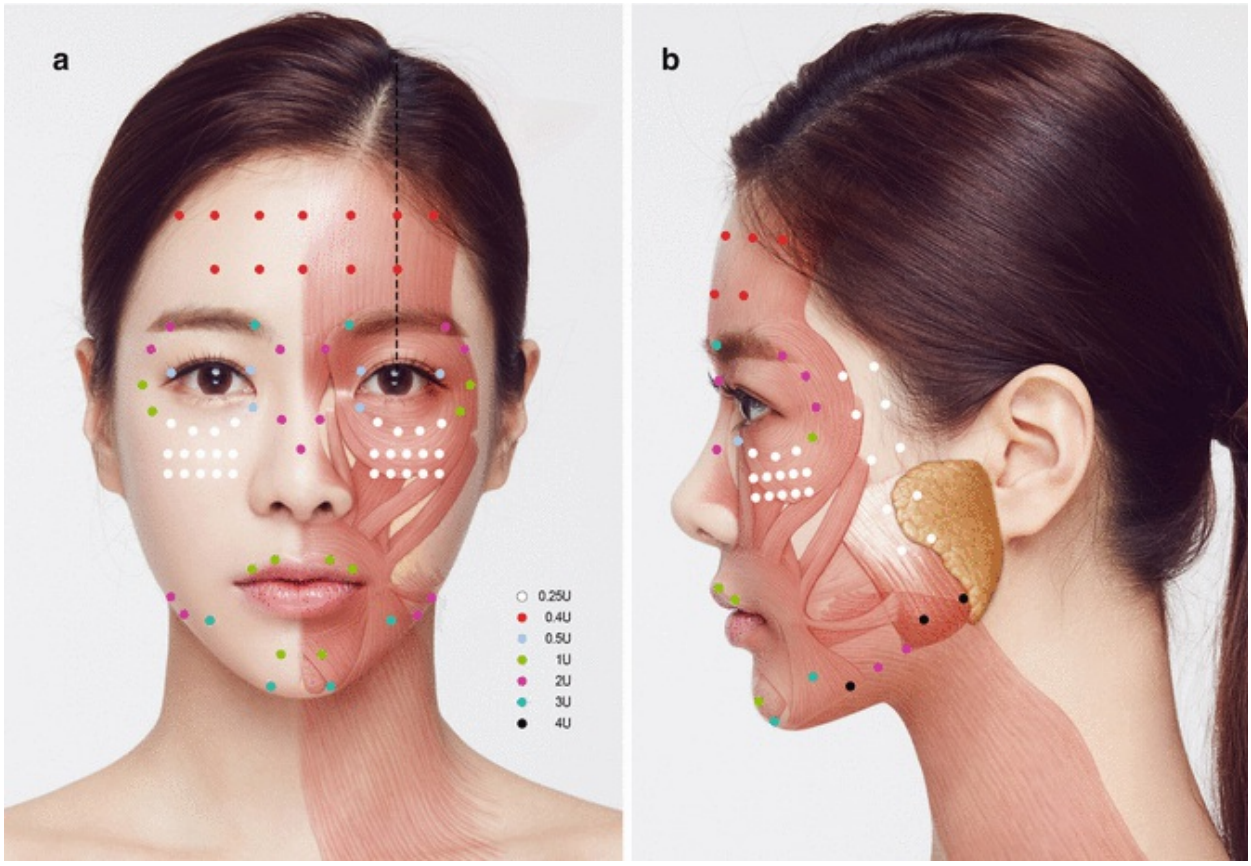

Fig. 4.6 Injection points for multiple intradermal botulinum toxin (**a**) front view and (**b**) lateral view

Conventional intramuscular injections can be used for supplementation in areas with deep muscles such as corrugator, mentalis, and masseter. Areas for intradermal injection are the forehead, periorbital, lateral cheek, perioral, and anterior malar area. However, intradermal injection of BoNT-A should be avoided at lower half of masseter muscle due to the risk of paralysis of risorius muscle.

Regarding the reconstitution method, the same reconstitution method mentioned in previous chapters is used for dynamic wrinkle treatment and

facial contouring. However, 100 U of BoNT-A should be reconstituted with 10 ml normal saline with 1 U/0.1 ml concentration for intradermal injections.

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Kyle K Seo, Botulinum Toxin for Asians, DOI 10.1007/978-981-10-0204-5_5

5. Body Contouring with Botulinum Toxin

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5.1 Introduction

Botulinum toxin type A (BoNT-A) produces the disuse atrophy by muscle paralysis. As with square jaw treatment, BoNT-A can be applied to making a thick and stocky contour smoother and slimmer by injection of BoNT-A into skeletal muscles of the extremities. If BoNT-A is injected into the medial head of gastrocnemius muscle, the thick muscle mass diminishes, resulting in a slim and smooth contour of the lower leg. Similarly, BoNT-A can produce a slender arm contour when applied to the deltoid muscle and more lengthened neckline when applied to the trapezius.

The effects of BoNT-A in body contouring begin to appear 2 weeks after the injection, become prominent after 1 month, and approach the maximum level after 2–3 months. After 6 months the muscle volume begins to redevelop partially and completely recover to the original state after 9–12 months. However, minimizing the use of the corresponding muscles can slow down the recovery process. Conversely, excessive use of the corresponding muscles can cause the muscle volume to recover more quickly as if undergoing rehabilitation physical therapy. If the muscle volume is large congenitally, the muscle volume recovers more easily due to homeostasis. However, acquired form of muscle hypertrophy through exercise does not easily recover to the original state as long as exercise for the corresponding muscles is avoided.

5.1.1 Reconstitution of Botulinum Toxin

For wrinkle treatment, 100 U of BoNT-A is reconstituted with 2.5 ml normal saline with final concentration of 4 U/0.1 ml. For body contouring, however, 100 U is reconstituted with 5 ml (4.8 ml of normal saline + 0.2 ml of epi-lidocaine) with final concentration of 2 U/0.1 ml. A large reconstitution volume is used so that the BoNT-A may diffuse well into the voluminous muscles, and 0.2 ml of epi-lidocaine (1:100,000 epinephrine) is added to prevent the BoNT-A from being easily washed off into the systemic circulation by the muscle's rich vascular supply.

5.1.2 Dose

70–100 U of BoNT-A per side is injected into the medial head of gastrocnemius, while 100–200 U per leg is injected into the entire calf. 50 U of BoNT-A per side is required for the trapezius and deltoid muscle, while 100 U per side is required for the quadriceps femoris (Table 5.1).

Table 5.1 Dose of botulinum toxin type A for body contouring (BOTOX®, per side)

	Minimum (U)	Average (U)	Maximum (U)
Calf (gastrocnemius, both heads)	100	150	200
Gastrocnemius medial head	50	70	100
Deltoid	30	50	70
Trapezius	30	50	70
Quadriceps femoris	100	150	200

Data from Modelo Clinic

5.1.3 Injection Techniques

A 0.5-inch (1.25 cm) 30-gauge needle is usually used, but a 3/4 or 1-inch needle is preferred when injecting into the area with abundant subcutaneous fat or deep muscle in the calf such as upper part of the soleus. The injection should be performed deep enough to allow the whole length of needle to be inserted into the muscle with the needle directed perpendicularly to the skin. If there is an abundant subcutaneous fat, stretching the skin tight with your nondominant hand helps perform deep injection of BoNT-A into the muscle. Inject 0.2 ml (4 U) of BoNT-A into each site 2 cm apart on average.

5.1.4 Appropriate Time and Dose for Repeated Injection

The appropriate time for repeat injection is absolutely dependent on the necessity of individuals who are receiving this treatment as is the case with BoNT-A injection for square jaw. To maintain the best condition, however, the procedure should be repeated every 6 months though it may also be repeated between 6 months and 1 year according to the muscle state if the initial volume of muscle is considered as a reference of recurrence. The appropriate dose for repeat injection depends on the muscle size at the time. It is preferable to inject half of the initial dose after 6 months when muscle volume has partially recovered and half or three quarters of the initial dose after 9–12 months depending on the muscle size.

5.1.5 Adverse Effects

Transient muscle weakness is the common adverse effect in some patients. If overdose is administered compared with patient's muscle volume, a gait disturbance or difficulty of raising the upper arms may occur for 1–4 weeks after the procedure. Even though the muscle weakness generally disappears by 2 months, the dose should be adjusted based on the muscle size in order to avoid weakness (see Sect. 5.2). Other mild adverse effects symptoms such as stiffness, a heavy feeling, bruising, and lymphangitis may also occur [1].

5.2 Regional Particulars

5.2.1 Shoulder Contouring (Trapezius Muscle)

Effect (B), Adverse Effect (B), and Technique (A)

Although a thick and large trapezius muscle may be desirable to bodybuilders, for the general public, especially women, a well-developed trapezius makes the neck appear shorter with an unattractive shoulder line, and the face appears relatively larger. This may be a great impediment to wearing dresses which expose the shoulder and necklines such as a wedding dress. The continuous crouching posture often witnessed in computer or smart phone users aggravates the contraction of the trapezius muscle, which not only brings about hypertrophy of the trapezius muscle but also may induce myalgia and migraines. This is the reason why BoNT-A injections

into the trapezius muscle is included for the treatment of migraines.

If BoNT-A is injected into the trapezius, the muscle volume decreases in size and produces a slimmer shoulder line. In addition, it helps improve the symptoms of myalgia or migraines by relaxing the lumped muscles.

5.2.1.1 Anatomy

The trapezius is a thin superficial muscle which covers the posterior part of the neck and nearly half of the upper back (Fig. 5.1). It originates from the central skeletal bones such as the occipital bone superiorly and 12th thoracic vertebra inferiorly and inserts into the scapula and clavicle. Scapula movement is one of the major functions of the muscle. The superior part of the muscle elevates the scapula, the intermediate part retracts it, and the inferior part depresses it. The trapezius also supports the arms by connecting the skull, neck, and vertebrae (Table 5.2).

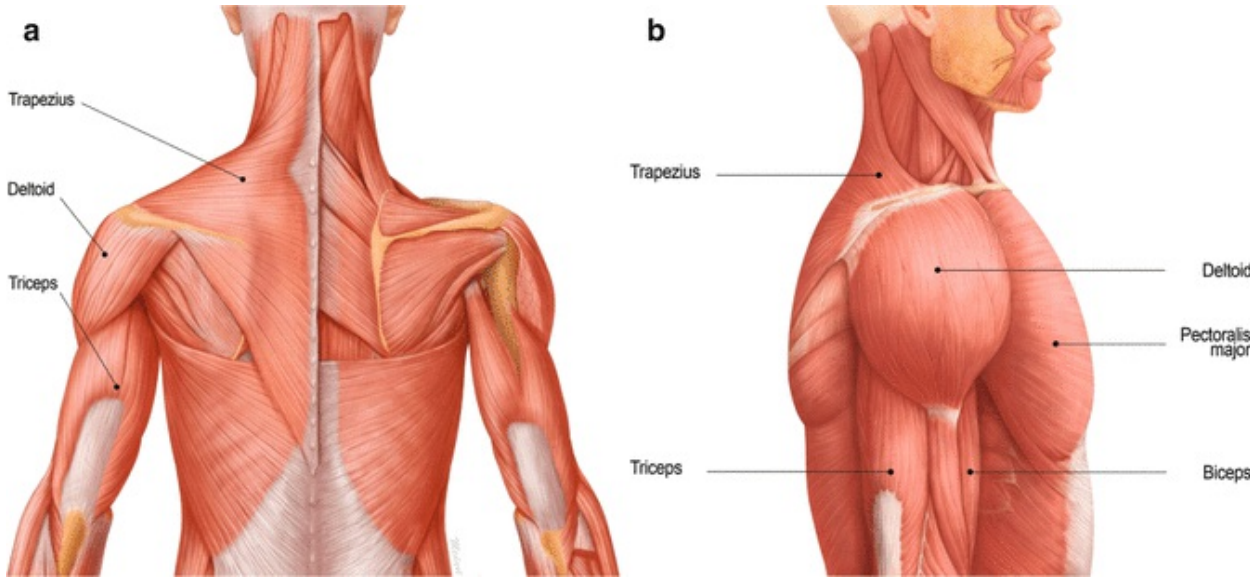

Fig. 5.1 Anatomy of the neck, shoulder, and back. (**a**) Back view and (**b**) Lateral view

Table 5.2 Related muscles in upper extremity for body contouring with botulinum toxin

Muscle	Origin	Insertion	Function
Trapezius	Trapezius superior region external occipital protuberance, superior nuchal line of occipital bone, C5 spinous process	Lateral third of the clavicle	Elevates the scapula upward Rotates the scapula Retracts the scapula

			Extends the head and neck Flexes the head and neck laterally Rotates the head and neck contralaterally
	Trapezius intermediate region C6–T3 spinous process, interspinal ligaments	Acromion process, superior margin of the spine of the scapula	Retract scapular backward Rotate scapula upward
	Trapezius inferior region T4–T12 spinous process, interspinal ligaments	Medial margin of the spine of the scapula	Depress the scapula downward Rotate the scapula upward
Deltoid	Lateral one-third of clavicle acromion inferior margin of scapula	Superior middle of lateral aspect of the humerus	Upper arm Anterior part → elevate forward Lateral part → elevates horizontally Posterior part → retracts posteriorly
Triceps brachii	Long head infraglenoid tubercle of the scapula	Posterosuperior surface of the olecranon process of the ulna	Extends the forearm at the elbow joint
	Lateral head dorsal upper half surface of the shaft of the humerus, lateral and proximal to the radial groove		
	Medial head dorsal lower half surface of the shaft of the humerus, medial and distal to the radial groove		

5.2.1.2 Injection Techniques

The BoNT-A is injected behind the patients while patients are seated. The major injection site is confined to the superior part of the trapezius muscle which connects the neck and shoulder: the slightly bulging triangular-shaped area borders the neckline, shoulder line, and the horizontal line at 2 cm medial to the acromion inferiorly. A total of 50 U (30–70 U) of BoNT-A per side depending on the muscle volume should be deeply injected into the

superior part of the trapezius muscle divided by 10–14 points spaced 2 cm apart (Fig. 5.2). Care should be taken not to inject medial to the neckline in order to avoid the weakness of the neck muscles.

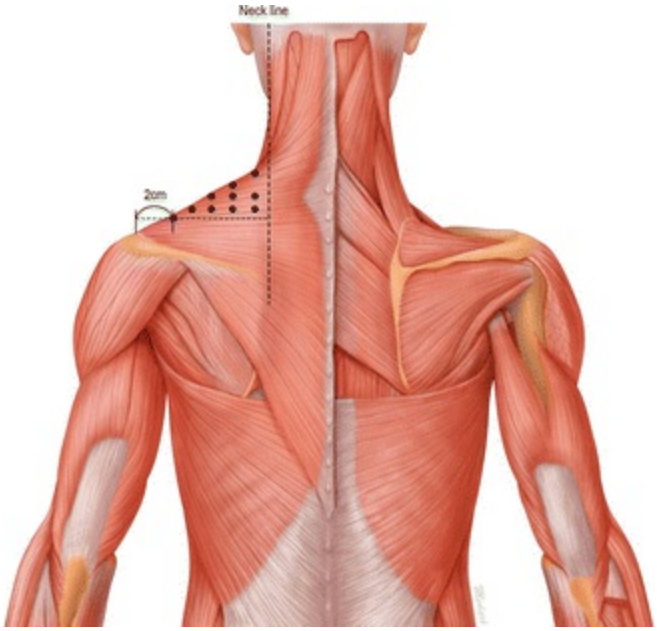

Fig. 5.2 Injection points for shoulder contouring

Repeat injections are necessary every 6 months when muscle volume recovers by nearly half. However, injections should be made every 3 months to maintain relief from shoulder pain or migraines.

5.2.1.3 Adverse Effects

50 U of BoNT-A does not usually cause major problems, but a few patients may encounter discomfort when attempting to lift objects due to weakened muscle power. Therefore, the dose should be adjusted based on individual's muscle size to avoid severe muscular weakness. Further, it should be avoided to perform arm contouring with BoNT-A at the same time which would also result in difficulty of lifting arms by deltoid paralysis.

5.2.1.4 Photography

Front view and back view are taken showing the face and entire upper half of the trunk (Fig. 5.3).

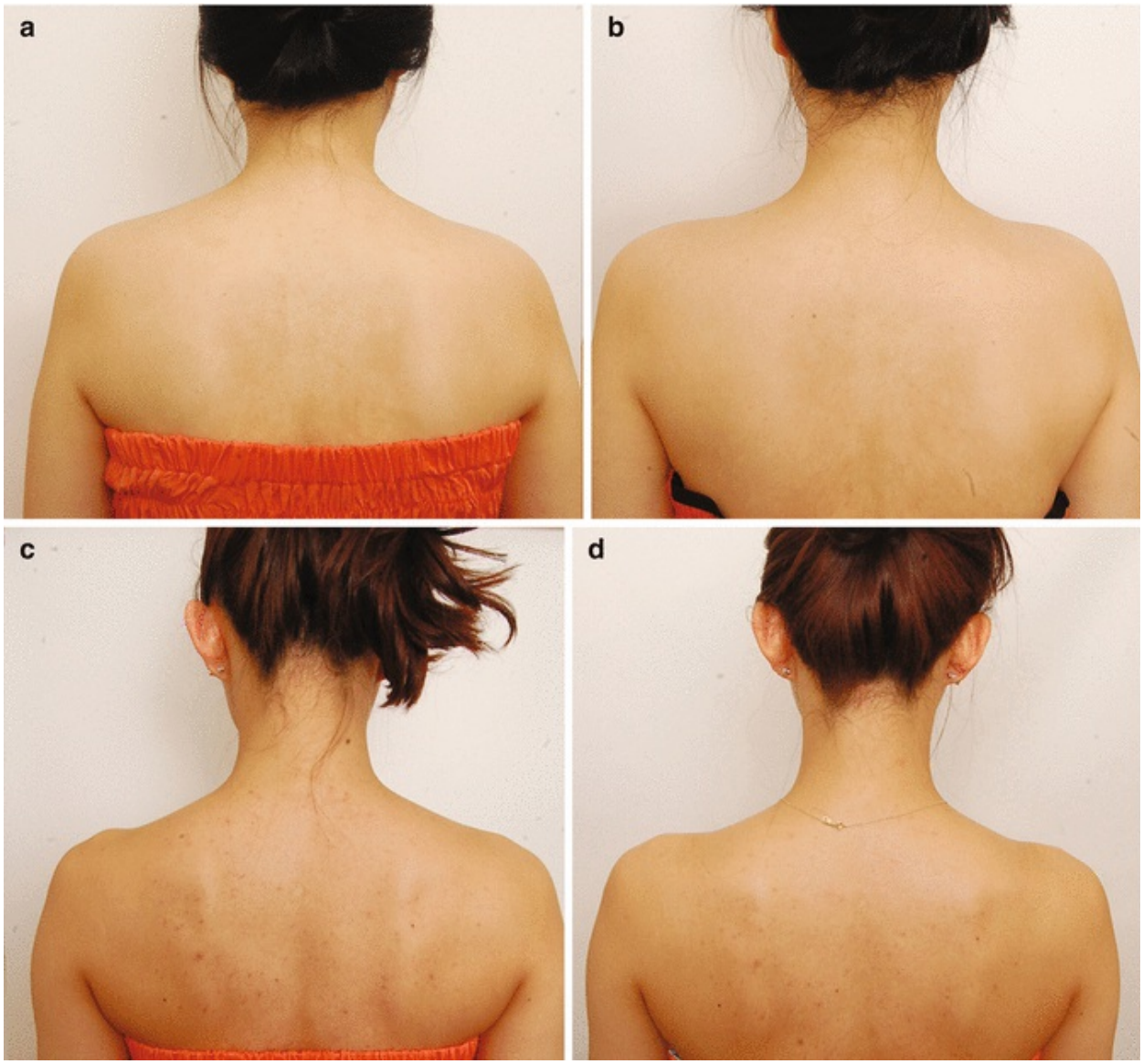

Fig. 5.3 Shoulder contouring: (**a**, **c**) before and (**b**, **d**) 2 months after 50 U injection of BOTOX® per side

5.2.2 Arm Contouring (Deltoid Muscle)

Effect (B), Adverse Effect (B), and Technique (A)

Men often desire defined shoulder and arm muscles, achieved by developing the deltoid, the biceps brachii, and the triceps brachii. Conversely, women generally look for an elegant and slender arm line. For many women, defined deltoids may give an undesirable masculine appearance. In case with the developed triceps, the arm line looks undulated. BoNT-A helps make slender and smooth arm line for those women. Previously undulated lines become

smooth and it is observed well when patient's arms are horizontally raised (Fig. 5.4). In the author's study on the effect of BoNT-A for the arm contouring in ten patients evaluated by MRI, muscle volume decreased by 17 % and 34 % with 50 U and 75 U BoNT-A injection, respectively, at 3 months after the injection of BoNT-A (unpublished data) (Fig. 5.5).

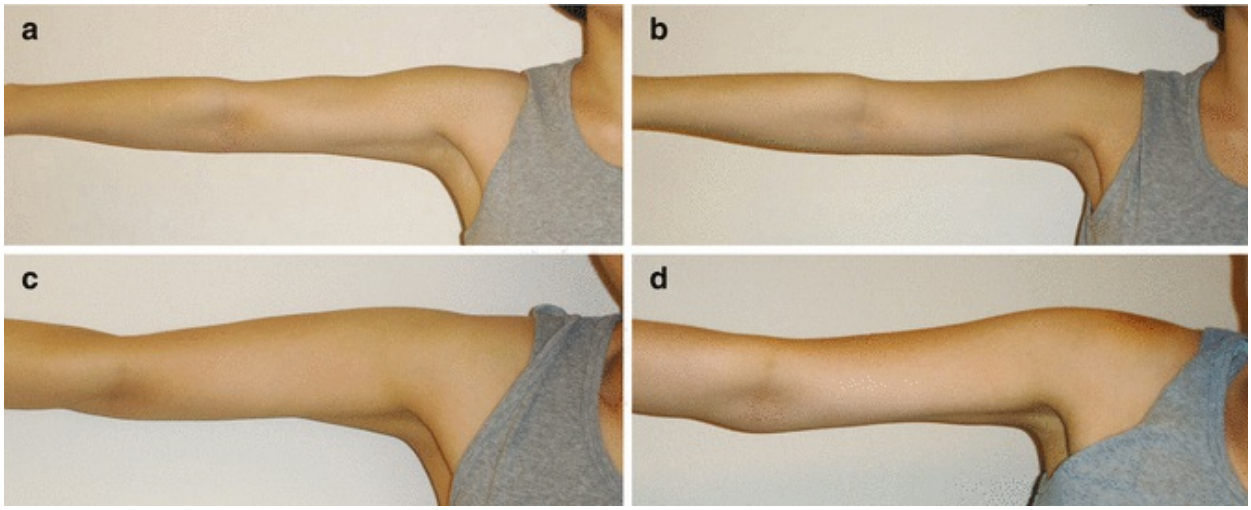

Fig. 5.4 Arm contouring. (**a**) 50 U and 20 U BOTOX® were injected, respectively, into the deltoid and lateral head of the triceps brachii. (**b**) After 2 months. (**c**) 50 U of botulinum toxin A was injected into the deltoid muscle. (**d**) After 2 months

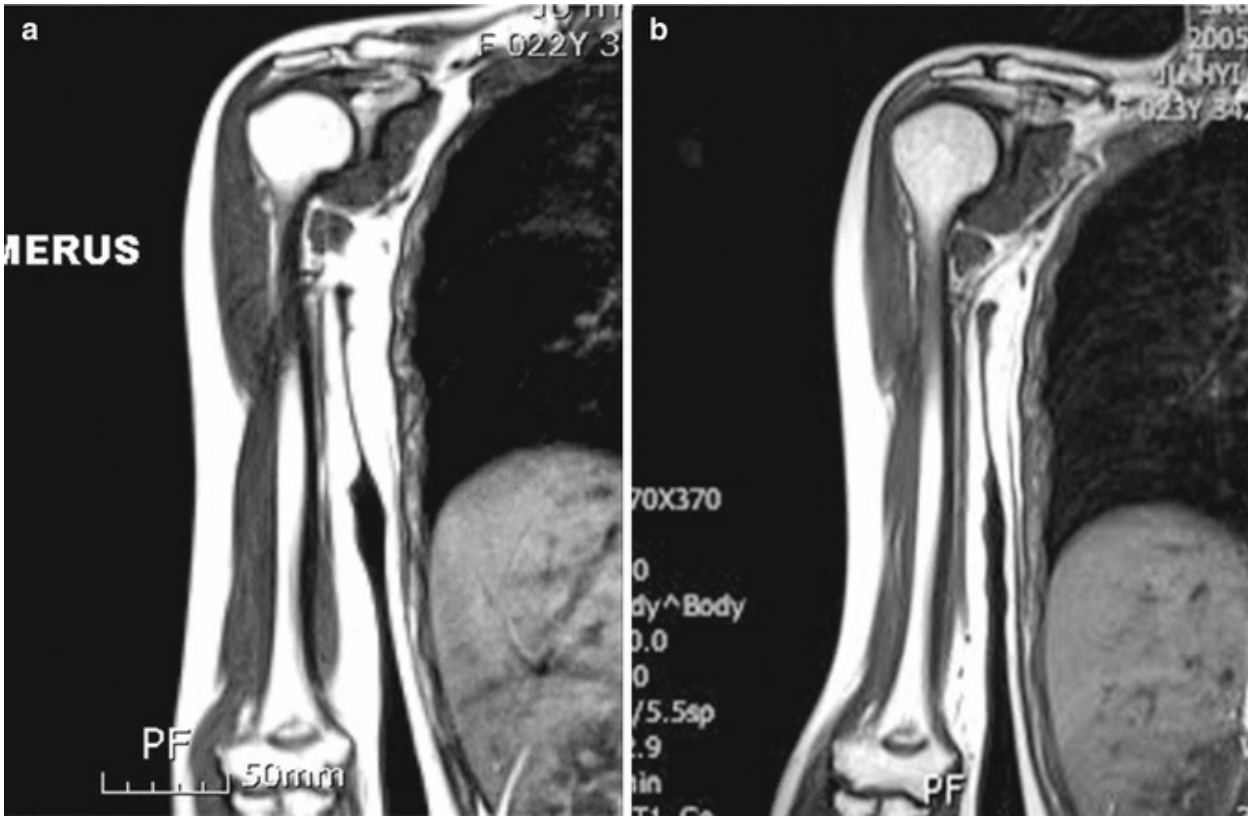

Fig. 5.5 MRI showed the reduction of deltoid muscle volume by 17 % at 2 months after injection of 50 U of BOTOX® per side. (**a**) Before. (**b**) After

5.2.2.1 Anatomy

In the upper arm, there are various muscles such as the deltoid, the biceps brachii, the triceps brachii, the brachialis, and the brachioradialis (Fig. 5.1). But the deltoid and the triceps brachii in charge of lateral contour of arms stand out as defining arm lines when standing at attention.

The deltoid originates from lateral one-third of the clavicle, the acromion, and spine of the scapula and inserts into the superior lateral part of the humerus (Table 5.2). Its primary functions are shoulder abduction, flexion, and extension. The triceps brachii muscle originates from the scapula and humerus and inserts into the ulna of the forearm and the olecranon. Its primary function is extending the elbow joint. The lateral head of the triceps brachii originates from the upper dorsal surface of the humerus and runs outward, thus defining the lateral contour of the upper arm below the deltoid when standing at attention or raising the arms.

5.2.2.2 Injection Techniques

To adequately expose the border of deltoid and the triceps brachialis, have the patient raise their arms horizontally and then outline the target area for injection. The central portion of the deltoid muscle is the target for the procedure. The most prominent central portion of the deltoid muscle from the lateral view is the reference point. Draw a central vertical line at the reference point and draw two more vertical lines parallel to the central vertical line at 2 cm apart, anterior and posterior to the reference point. The upper border is 2 cm below the acromion of the muscle origin site, and the lower border is 2 cm above the muscle insertion site to the humerus (Fig. 5.6a). The 4 U of BoNT-A with a total of 50 U per side should be injected into each point along the three lines 2 cm equidistant apart within the area between the upper and lower borders. Larger muscles may require additional injections which may be administered 4 cm apart from the central vertical line. While 50 U of the BoNT-A per side is the standard dose for the arm contouring with BoNT-A, the dose of BoNT-A would be variable from 30 to 75 U according to the size of the deltoid muscle. 30–40 U of BoNT-A would be sufficient for smaller muscles or for the second session of injection 3–6 months after the initial treatment.

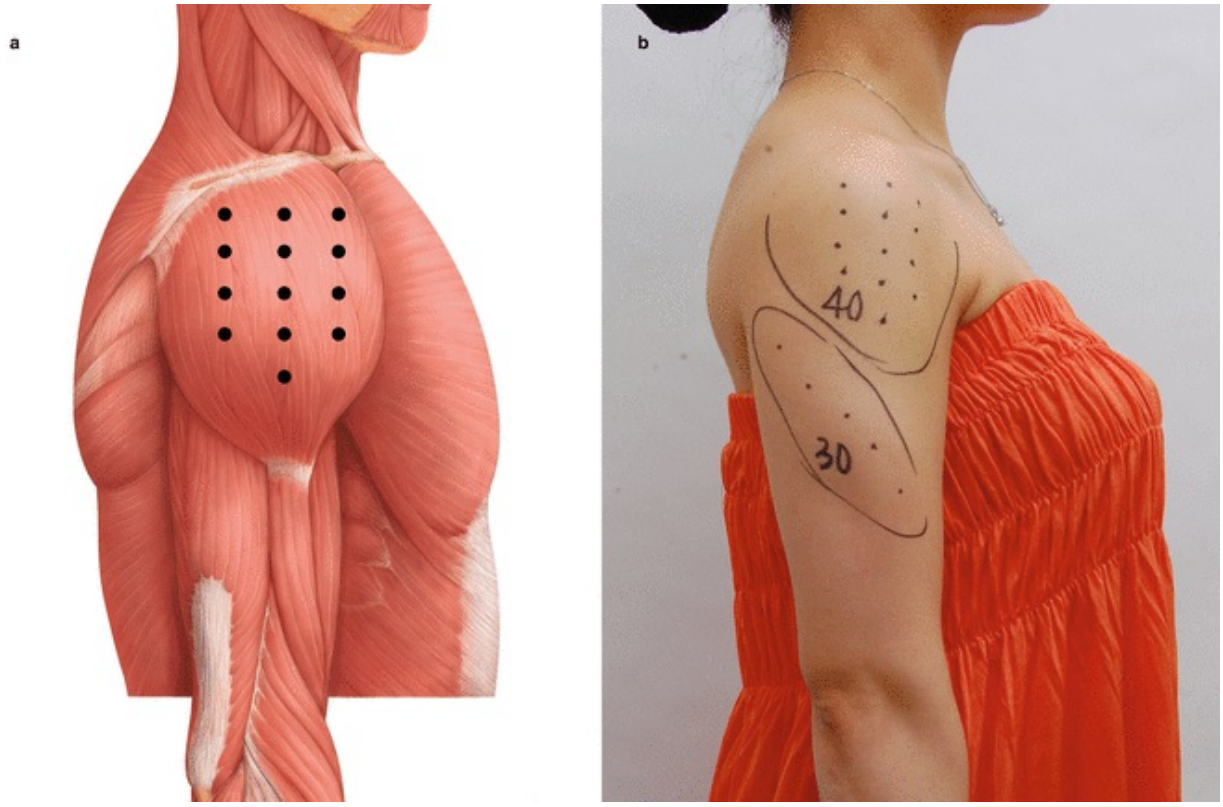

Fig. 5.6 Injection points for arm contouring. (**a**) Standard type. 50 U BOTOX® units are injected into the deltoid muscle. (**b**) Combined type with triceps. 40 and 30 U of BOTOX® are injected, respectively, into the deltoid and lateral head of the triceps brachii

For the lateral head of the triceps brachii, the BoNT-A should be injected linearly into the lateral bulging area when standing at attention or into the upper bulging area when raising their arms horizontally. 20–30 U of BoNT-A per side is required for the lateral head of the triceps brachialis (Fig. 5.6b).

5.2.2.3 Adverse Effects

The patient may experience slight discomfort raising their arms due to weakening of the deltoid muscle. In the author's study on the dose–efficacy relationship of BoNT-A for the arm contouring in ten patients evaluated by MRI, muscle weakness was more severe at 75 U side than 50 U side although the 75 U side showed much greater efficacy than the 50 U group in deltoid muscle volume reduction (31.4 % vs 17.0 %) (unpublished data). In particular, in cases where the BoNT-A is injected into the trapezius muscle together with the deltoid, it may cause greater discomfort to the patient when they raise their arms. Other symptoms such as stiffness and heavy feeling

may occur for several days in addition to bruising and myalgia.

5.2.2.4 Photography

Prior to treatment, the patient's arm is raised horizontally with the palm supinated to maximize deltoid muscle contraction. As the elbow is also extended, the triceps brachialis is as well by association, in such a way that the contraction of the lateral head of the triceps brachialis is fully observable. In this position photos from front view are taken from the fingertip to the neckline.

5.2.3 Thigh Contouring (Quadriceps Femoris Muscle)

Effect (A), Adverse Effect (A), and Technique (A)

Thigh muscles occupy nearly a third of the total muscle volume of our body; thus, athletes and nonathletes alike are quite keen on their development. Well-developed thighs in women in particular emanate strong health and fertility. For some, however, such definition may be unwelcome and regarded as rough and masculine. This is particularly the case for former athletes who relied on strong legs for performance, such as short-distance runners, skaters, and skiers. Well-developed quadriceps and vastus lateralis above the knee create a muscle bulge and undulated thigh lines, all of which can be greatly effaced by BoNT-A treatment.

5.2.3.1 Anatomy

The vastus lateralis muscle originates from the linea aspera of femur and runs over the knee joint and the patellar ligament and inserts into the tibial tuberosity (Fig. 5.7) (Table 5.3).

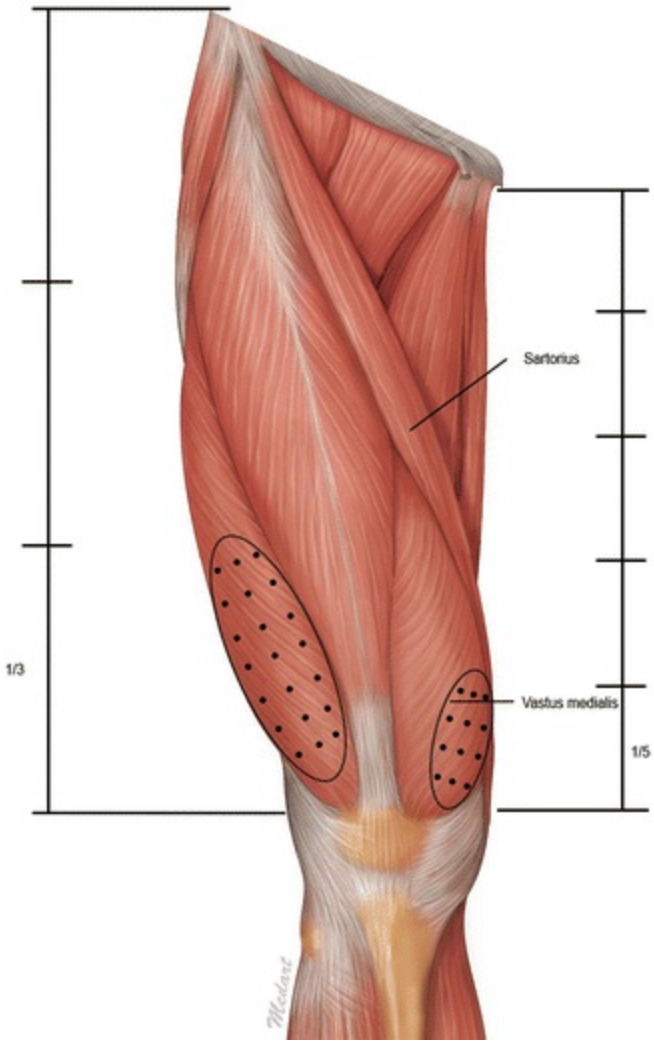

Fig. 5.7 Anatomy and injection points for thigh contouring. 50–100 U of botulinum toxin is injected into the lower one-third of the vastus lateralis, and 50–70 U of toxin can be injected into lower one-fifth of the vastus medialis

Table 5.5 Dose of botulinum toxin type A at second session for calf contouring (BOTOX®, unit)

	Mild hypertrophy (U)	**Moderate hypertrophy (U)**	**Severe hypertrophy (U)**
Total dose per side	100	150	200
Medial gastrocnemius	30	40	50
Lateral gastrocnemius	50	40	50
Peroneus longus	20	30	40
Lower part of soleus	–	40	60

Data from Modelo Clinic

5.2.3.2 Injection Techniques

Outline the target area while the patient is standing. The vastus lateralis is the main target for BoNT-A treatment for reducing lateral muscle bulge of the thigh. However, patients who have developed vastus medialis should be treated on both sides. The vastus lateralis injection site is in the lower one-third of the muscle, while the injection site of the vastus medialis is in the lower one-fifth of the muscle. This is because bulging typically occurs in these respective areas. The center of the most prominent portion of the vastus lateralis is the reference point. Draw a central vertical line at the reference point and two more vertical lines parallel to the central vertical line at 2 cm apart, anterior and posterior to the reference point. The upper border is the lower one-third of the whole length of the vastus lateralis, and the lower border is 2 cm above the patella. The 4 U of BoNT-A should be injected into each point equidistant apart along the three lines within the area between the upper and lower borders (Fig. 5.7). In case of a large muscle, additional injections may be necessary at the aforementioned points 4 cm apart from the anterior and posterior to the central vertical line. 50–100 U of the BoNT-A is injected into vastus lateralis and 50–70 U into the vastus medialis, according to muscle size.

5.2.3.3 Adverse Effects

Thigh muscles are quite large, therefore even doses as high as 100–150 U per side does not cause any noticeable discomfort due to muscle weakness. Other symptoms such as stiffness and heavy feeling may occur for several days in addition to bruising and myalgia.

5.2.3.4 Photography

Photographs are taken at a standing position from the feet to the thigh. Front view and lateral view are taken together, the latter of particular importance (Fig. 5.8).

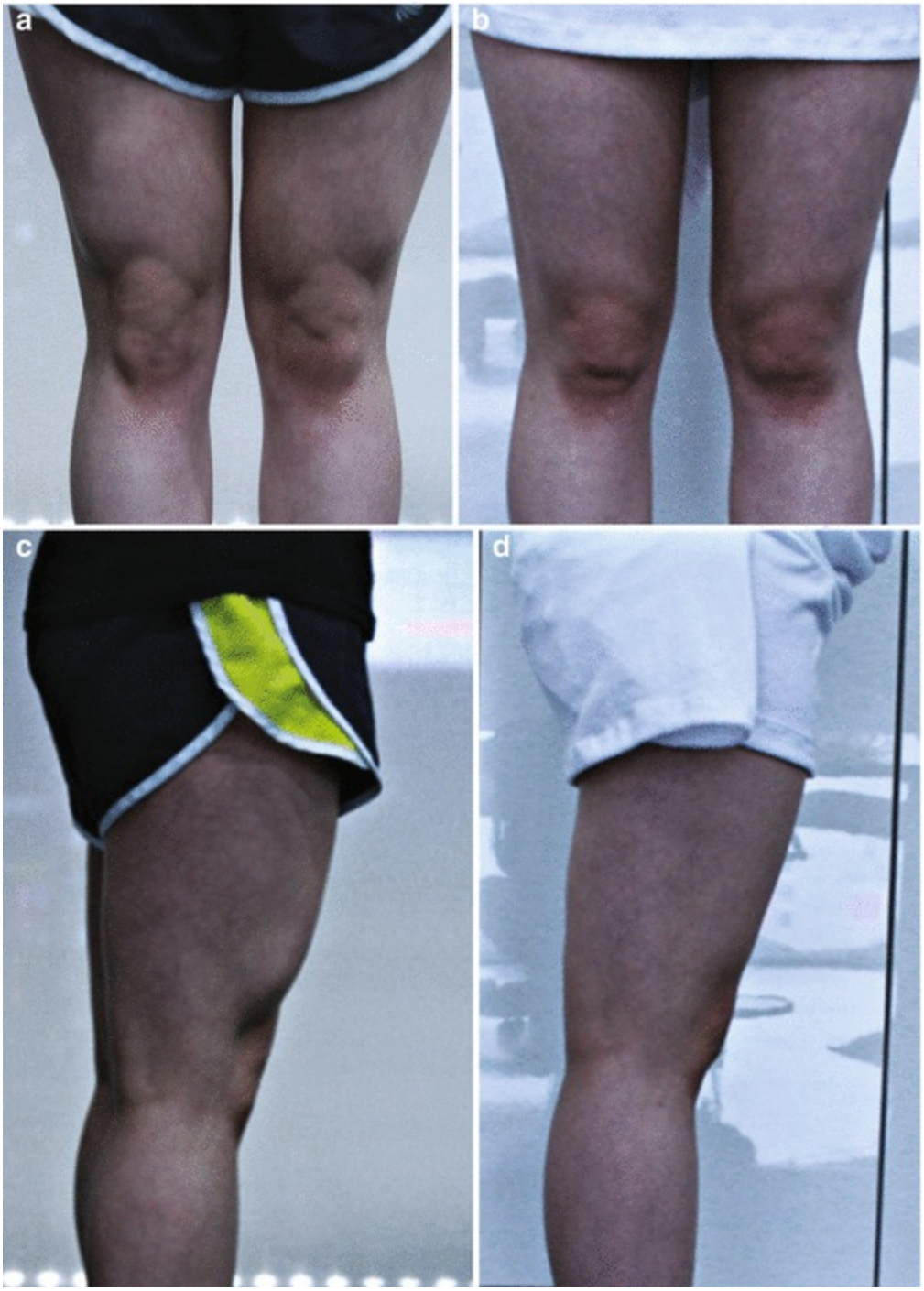

Fig. 5.8 Thigh contouring: (**a**, **c**) before and (**b**, **d**) 2 months after 100 U of Xeomin® injected into the vastus lateralis per side

5.2.4 Calf Contouring (Gastrocnemius Muscle)

Degree of Difficulty: Effect (B), Adverse Effect (B), and Technique (A)

A well-defined calf muscle, giving impression of chicken leg, is regarded as unattractive for many Asian women. Since the 1990s the resection of the tibial nerve branch behind the knee that innervates the gastrocnemius muscle has been a popular solution for this condition. However, this surgical procedure has some drawbacks such as a 2–3 cm scar, ineffectiveness due to individual variations of nerve branch and an irreversible sensation decrease or paresthesia caused by sensory nerve injury. Since the early 2000s, a new electroneurography guided destruction of the tibial nerve with anhydrous alcohol was introduced, but irreversible nerve damage also remains an issue.

In contrast, BoNT-A treatment for the calf muscle contouring of which I first reported the effectiveness in 2002 is a safe and effective treatment that leaves no scar and has substantially lower adverse effects without affecting daily life [1]. Moreover, BoNT-A always guarantees the effective and reproducible result regardless of individual variations of nerve branch. Only one drawback was cost-benefit issue because compared with temporary effect of BoNT-A, the cost was high due to the necessity for large dose of BoNT-A. As the BoNT-A price has decreased substantially over the past 10 years, however, patients' economic burden for this indication of BoNT-A has been lessened to some extent. If the feminine, smooth leg line without calf muscle bulge is the purpose of the treatment, the BoNT-A could be injected only into the medial gastrocnemius. However, BoNT-A should be injected into the whole lower leg muscles including the medial and lateral head of gastrocnemius, the lower part of soleus, and the peroneus longus in order to reduce overall calf size.

5.2.4.1 Anatomy

The medial and lateral head of gastrocnemius, which originates from the medial and lateral condyles of femur and inserts to Achilles tendon and calcaneus, forms the muscle bulge in the lower leg from the back view (Fig. 5.9). The soleus muscle, which originates from the posterior aspect of tibia and fibula and inserts to Achilles tendon and calcaneus, lies deeply inside of the gastrocnemius muscle. Both muscles are responsible for plantar flexion at the ankle joint and calf flexion at the knee joint, which is important function for walking and standing. The deeply located soleus muscle plays a more important role in standing, supporting the legs, and preventing forward bowing. The peroneus longus and the peroneus brevis are located laterally, and the tibialis anterior is located frontally (Table 5.4). While the medial head

of gastrocnemius muscle mainly contributes to the prominent medial muscle bulge from the back view, the peroneus longus runs outside to the lateral head of gastrocnemius muscle, forming a long arch at lateral side from the knee to the ankle together with the lateral head of gastrocnemius. Therefore, the well-developed peroneus longus and the lateral head of gastrocnemius not only create “O-shaped” bowing of the legs rather than muscle bulge but also contribute to the most prominent part of lateral side at the upper two-thirds of lower leg, while the most prominent bulging at medial side is the lower two-thirds of medial head of gastrocnemius. This is due to the way the peroneus longus originating from the fibular head is located superiorly.

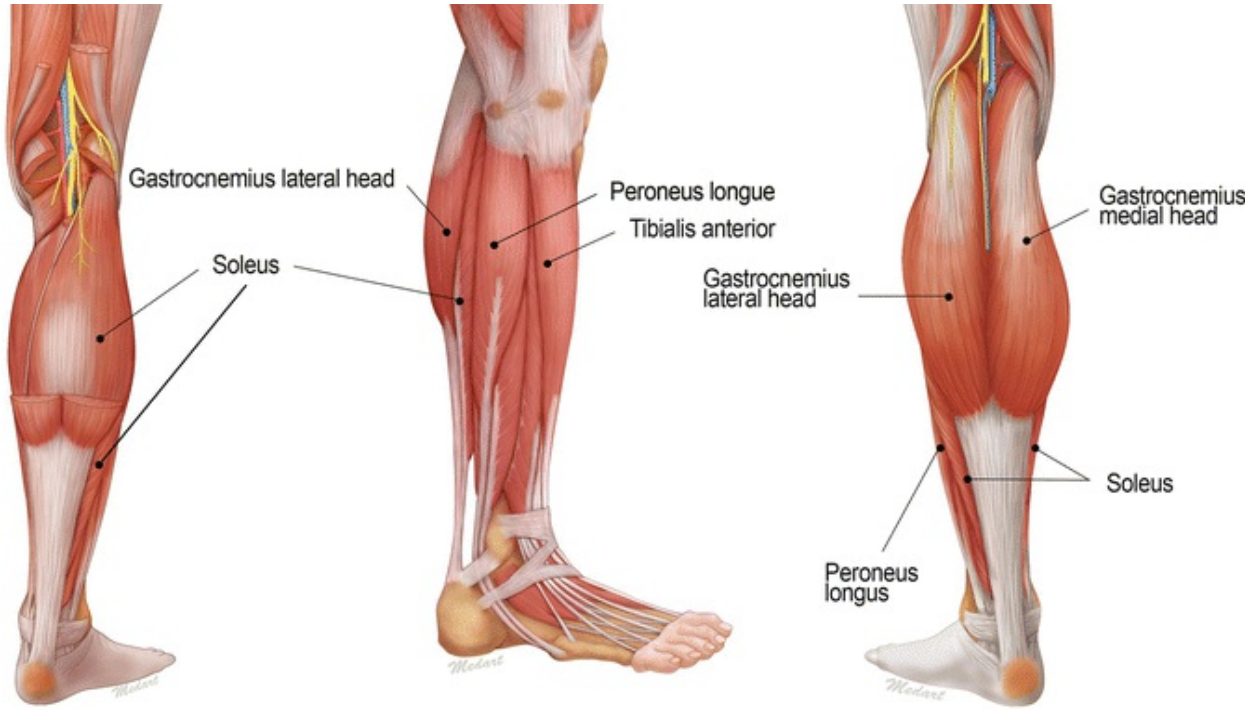

Fig. 5.9 Calf anatomy

Table 5.3 Related muscles in lower extremity for body contouring with botulinum toxin

Muscle		Origin	Insertion	Function
Quadriceps femoris	Rectus femoris	Anterior inferior iliac spine (AIIS)	Runs over the patella and the patellar ligament and inserts into the tibial tuberosity	Common function of quadriceps femoris: powerfully extend thigh and calf muscles at the knee joint Stabilize the knee joint Flex thigh at the hip joint and swing the
	Vastus lateralis, vastus medialis	Linea aspera		
	Vastus intermedius	Anterior femur shaft and linea		

		aspera		pelvis forward Stabilize pelvis and thigh at the hip joints
Gastrocnemius		Medial and lateral condyles of the femur	Achilles tendon, calcaneus	Plantar flexion at the ankle joint and calf flexion at the knee joint
Soleus		Posterior tibia and fibula	Achilles tendon, calcaneus	Plantar flexion at the ankle joint and calf flexion at the knee joint
Peroneus longus		Posterior tibia and posterolateral surface of the fibula	Cuneiform bone, first metatarsal bone	Abduction and eversion of foot
Tibialis anterior		Upper half lateral interosseous membrane of the tibia	Base of cuneiform, first metatarsal bone	Dorsiflexion and inversion of the foot

5.2.4.2 Injection Sites

The medial head of gastrocnemius on the medial side and the lateral gastrocnemius and the peroneus longus on the lateral side are major target muscles (Fig. 5.10). To remove the medial calf muscle bulge, the BoNT-A is injected into the medial head of gastrocnemius, resulting in a smooth calf line. “O-shaped” legs are likely exacerbated if only the medial muscle bulge is removed. Thus, injections of BoNT-A into only the lateral side are desirable. The same principle can be applied to case with the small medial muscle bulge and the large lateral side (Fig. 5.11). However, BoNT-A should be injected into the whole lower leg muscles including the medial and lateral head of gastrocnemius, the lower part of soleus, and the peroneus longus divided 2–3 times at the interval of 2–3 months in order to reduce overall calf size.

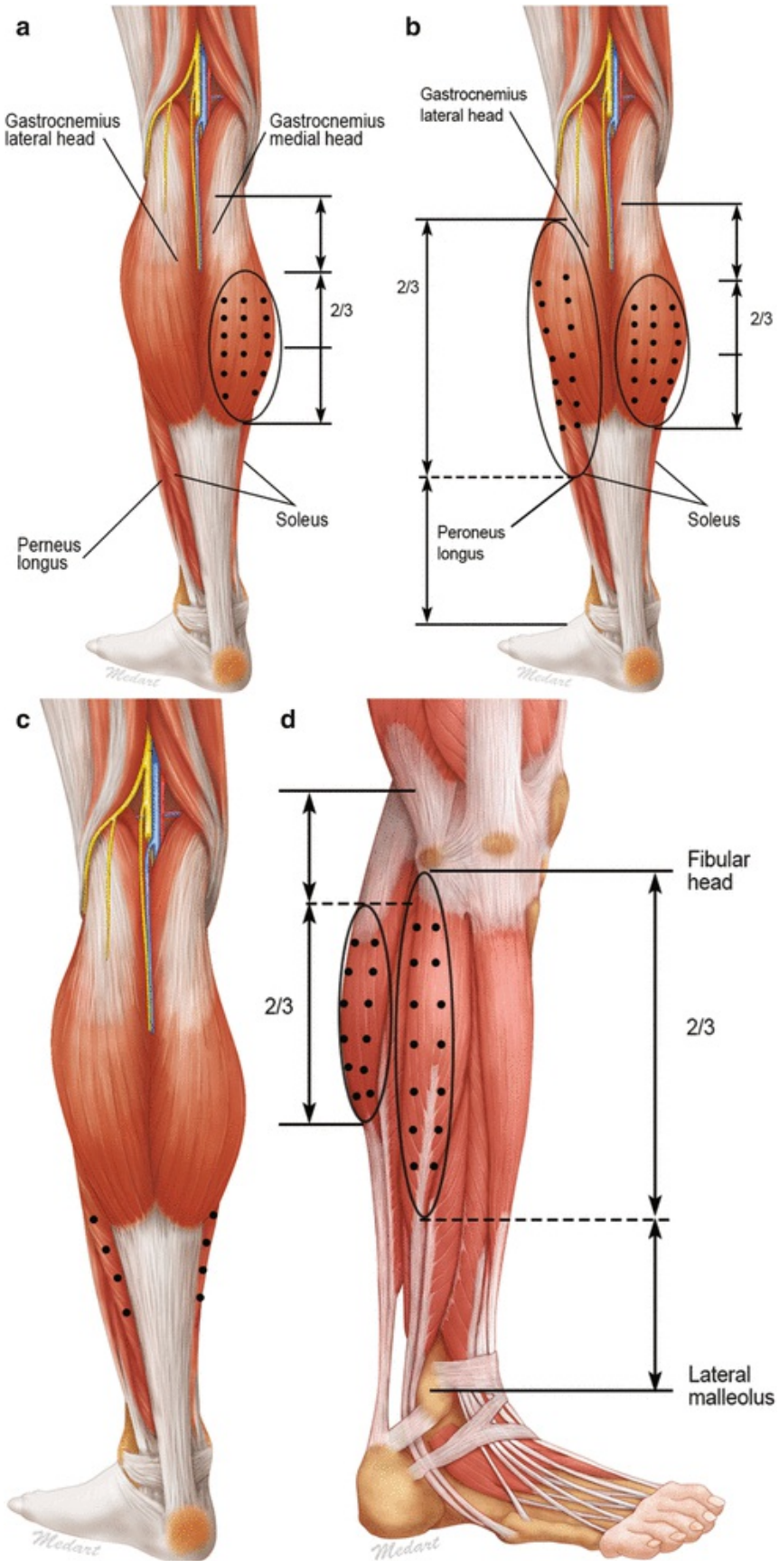
a
Gastrocnemius lateral head
Gastrocnemius medial head
2/3
Soleus
Perneus longus
b
Gastrocnemius lateral head
2/3
2/3
Peroneus longus
Soleus
c
d
Fibular head
2/3
2/3
Lateral malleolus

Fig. 5.10 Injection points for calf contouring. (**a**) Gastrocnemius medial head, lower two-thirds. (**b**) Gastrocnemius both heads. (**c**) Lower part of soleus. (**d**) Gastrocnemius lateral head 50–100 U and peroneus longus

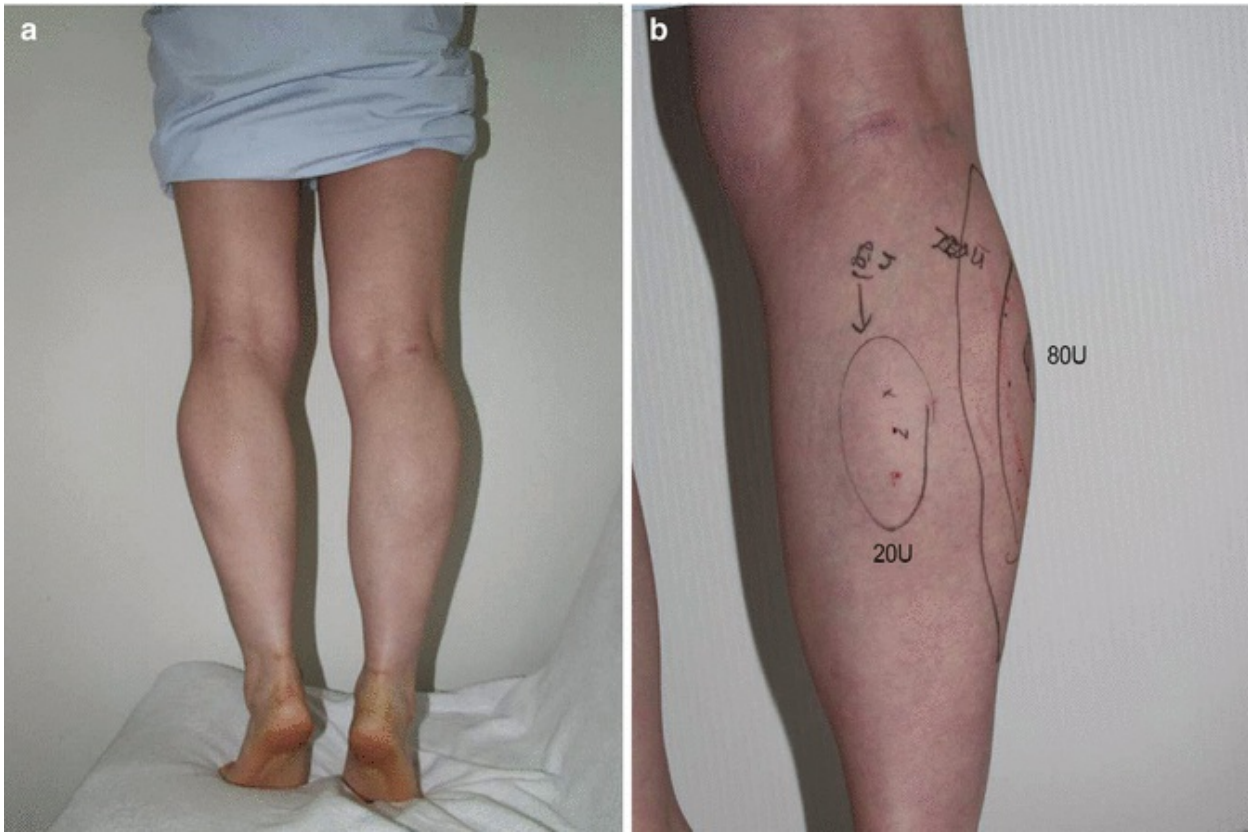

Fig. 5.11 (**a**) Lower leg with developed lateral part of calf muscles. (**b**) Injection points for lateral head of gastrocnemius

The injection site at the medial calf is the lower two-thirds of the medial head of gastrocnemius muscle, while the lateral calf is the upper two-thirds of the lower leg between the fibular head and the malleolus (Fig. 5.10). This difference comes from the peroneus longus running outside to the lateral head of gastrocnemius. Even though in principle, BoNT-A is not injected into the soleus muscle which plays a crucial part in maintaining posture while standing, the BoNT-A should be injected into the lower part of the soleus muscle at the second session of injection, 3 months after the first treatment, in case the lower part of the soleus muscle remains prominent near the Achilles tendon. It is better to avoid injections into the lower part of the soleus muscle during the first session because not only is high dose of BoNT-A necessary, but the muscle weakness due to high dose may occur. As an exception case,

the BoNT-A could be injected into even the upper part of the soleus muscle at 3 month's follow-up in order to decrease overall volume of exceptionally large calf muscles.

5.2.4.3 Dose

Dosing should be adjusted according to the muscles size: 50–100 U for the medial and lateral head of gastrocnemius, 50–100 U for the peroneus longus, and 20–30 U each for the lateral and medial part of lower soleus (totaling 40–60 U per side). If the total dose of BoNT-A injected at one session exceeds 400 U (200 U per side), excessive muscle weakness may occur. To avoid this, the BoNT-A should be administered over a period, often divided into two sessions at the interval of 2–3 month, so-called two-step approach (Table 5.4 and 5.5).

Table 5.4 Appropriate dose of botulinum toxin type A at first session for calf contouring (BOTOX® per side)

	Mild hypertrophy		**Moderate hypertrophy**	**Severe hypertrophy**
Total dose per side	100 U		150 U	200 U
Medial gastrocnemius	50 U		70 U	80 U
Lateral gastrocnemius	30 U		30 U	60 U
Peroneus longus	20 U		50 U	60 U

Data from Modelo Clinic

Injections into the medial head of gastrocnemius muscle to reduce the muscle bulge call for 50–100 U per side, according to muscle size. When BoNT-A is administered into the both heads of the gastrocnemius muscle for overall volume reduction, two-step approach at the interval of 2–3 months would be better recommended for the safety issue. The first session of injection with BoNT-A is better to focus on correcting the general contour lines rather than volume reduction. If the calf shows mild hypertrophy with the medial muscle bulge (Fig. 5.12a), the first injection mainly targets the medial head of gastrocnemius with 70 U. Or if the patient with mild hypertrophy is concerned about the total volume reduction of lower calf, the total dose of first injections is 100 U:50 U into the medial gastrocnemius, 20 U into the lateral gastrocnemius, and 30 U into the peroneus longus. If the calf shows moderate hypertrophy (Fig. 5.12b), the total dose of first

injections is 150 U:70 U into the medial gastrocnemius, 30 U into the lateral gastrocnemius, and 50 U into the peroneus longus. If the calf shows severe hypertrophy (Fig. 5.12c), the total dose of first injections is 200 U:80 U into the medial gastrocnemius, 60 U into the lateral gastrocnemius, and 60 U into the peroneus longus.

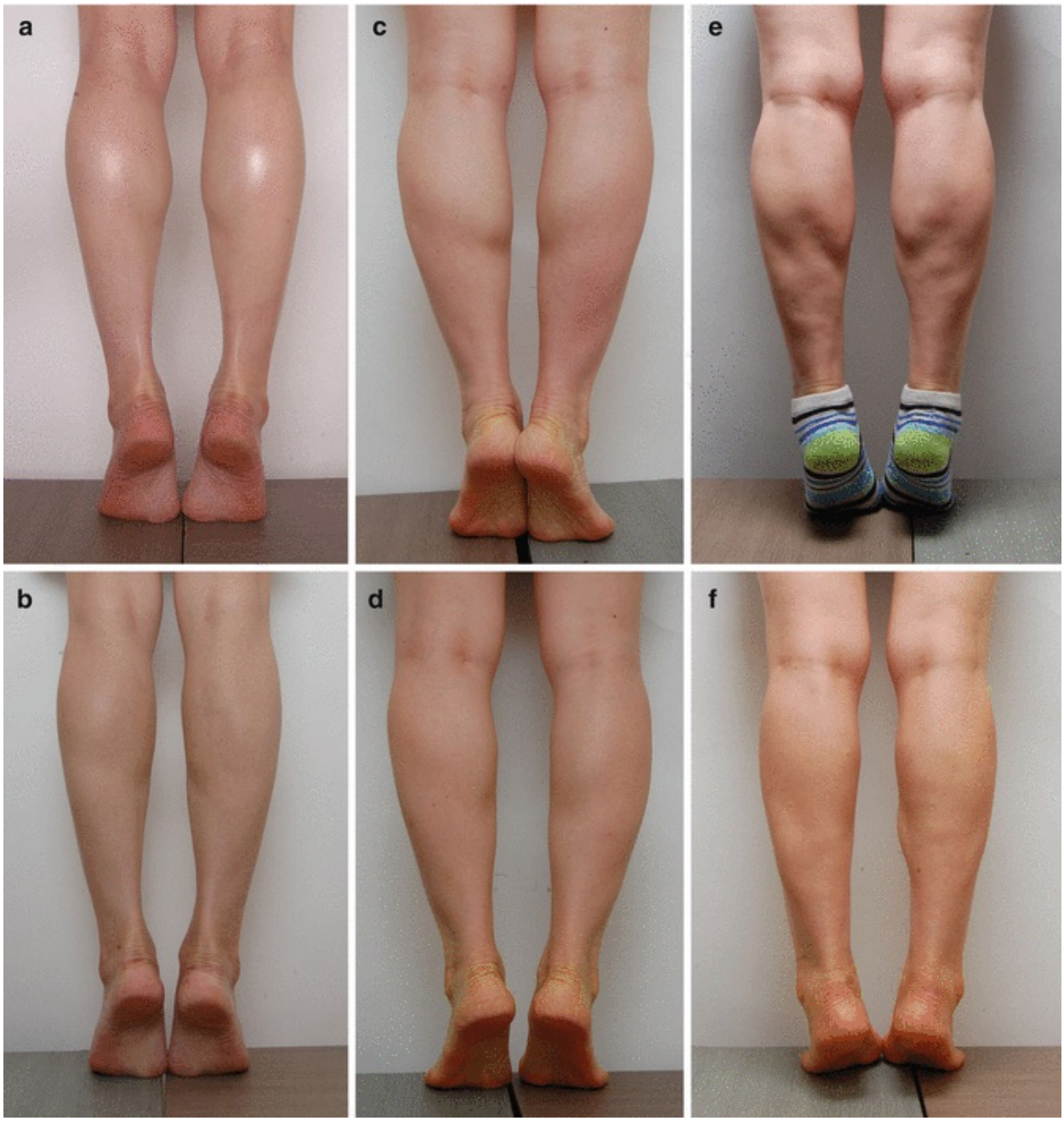

Fig. 5.12 Grading system for calf hypertrophy. Mild hypertrophy: (**a**) before and (**b**) 2 months after 100 U of Neuronox® injected into the medial head of gastrocnemius per side. Moderate hypertrophy: (**c**) before and (**d**) 2 months after 150 U of Neuronox® injected into both heads of gastrocnemius per

side. Severe hypertrophy: (**e**) before and (**f**) 2 months after 200 U of Neuronox® injected into both heads of gastrocnemius per side

The primary aim of the second session is further volume reduction of calf and improvement of the contour of the lower part of soleus muscle near the Achilles tendon. For the calf with mild hypertrophy, the total dose of second session is 100 U:30 U into the medial gastrocnemius, 50 U into the lateral gastrocnemius, and 20 U into the peroneus longus. For the calf with moderate hypertrophy, the second session should cover the lower part of the soleus with a total of 150 U:40 U into the medial gastrocnemius, 40 U into the lateral gastrocnemius, 30 U into the peroneus longus, and 20 U each into the medial and lateral part of the lower soleus. For the calf with severe hypertrophy, the second session should cover the lower part of the soleus with a total of 200 U:50 U into the medial gastrocnemius, 50 U into the lateral gastrocnemius, 40 U into the peroneus longus, and 30 U each for the lateral and medial part of lower soleus. For the calf with severe hypertrophy, the third injection may be tried at 2–3 months after the second session with 100 U per side.

5.2.4.4 Injection Techniques

To make the muscle bulges more prominent, inject while the patient stands in a tiptoe position after planning the target area. However, this may cause undue anxiety, and patients occasionally fall down due to pain shock, vasovagal shock [2]. Alternatively, the border of the calf is clearly observable in a prone position by keeping the patient's feet in a plantar flexion posture and pressing with their toes the abdomen of the operator or nurse's palms. However, since the gastrocnemius is quite large muscle, the BoNT-A can be injected in a prone position without plantar flexion posture in case the subcutaneous tissue in calf is not too excessive.

5.2.4.5 Onset and Duration of Effects

Calf muscle atrophy after BoNT-A injection also appears 1–2 weeks after injection up to a maximum of 2–3 months as is seen in other biotoxin indications. After 2–3 months, the muscle bulges in the medial gastrocnemius muscle disappear resulting in a smooth calf line (Fig. 5.12). According to my clinical study on the effect of BoNT-A for the volume of gastrocnemius muscle evaluated by the MRI, the medial head of gastrocnemius muscle

showed 35 % volume reduction (Fig. 5.13) [1].

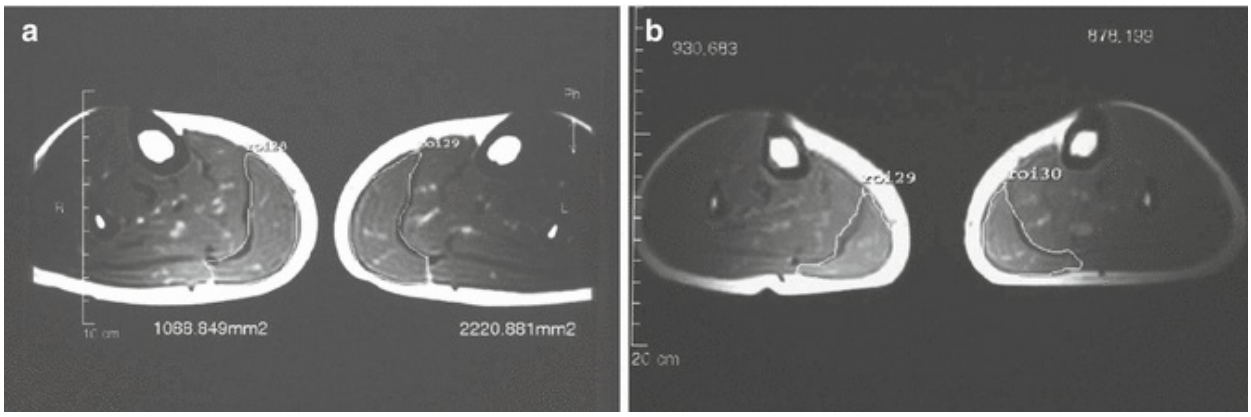

Fig. 5.13 Botulinum toxin calf contouring, MRI photographs, (**a**) before and (**b**) after. 100 U of botulinum toxin A was injected into the medial gastrocnemius, and the muscle volume decreased markedly after 2 months

After 2–3 months after BoNT-A injection, the muscle paralysis effects of the BoNT-A start to fade, and the muscle strength and hardness recovers. After 6 months the muscle gains approximately half of its volume back, and muscle volume returns mostly to the original state after 9–12 months, though not quite a complete recovery. Full recovery may be prevented by avoiding physical exercise such as ascending stairs or hiking which strengthens the calf muscles, as is seen well in my nurse's calf which still showed good effect of volume reduction, 13 months after two sessions at the interval of 6 months (Fig. 5.14). Dr. Han also demonstrated in his article that calf circumference in some patients did not fully recover 8 months postinjection [3].

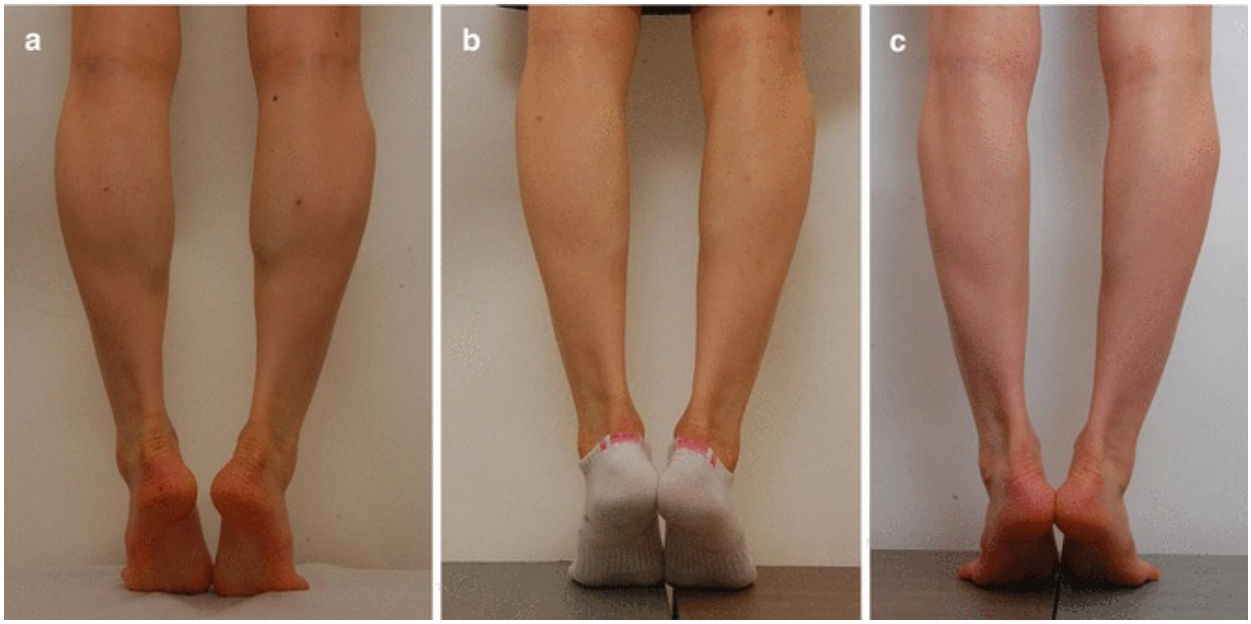

Fig. 5.14 Repeated case. (**a**) Before, (**b**) 2 months after first session of calf contouring with 150 U of xeomin® per side, and (**c**) 18 months after two sessions of calf contouring with the first 150U and the 2nd 100 U of xeomin® per side

5.2.4.6 Adverse Effects

Some patients may encounter temporary difficulty when walking due to a weakening of the calf muscles [1]. This may not cause significant issues in patients injected with 100 U or less of BoNT-A per leg, but higher dose over 150 U per leg may cause the aforementioned weakening in patients with mild hypertrophy (Fig. 5.15). Extreme caution must be taken when descending stairs wearing high heels lest the patient lose their balance. Muscle weakness generally begins 1 week after treatment, lasts a severe state for nearly 1 month, and recovers after 2 months.

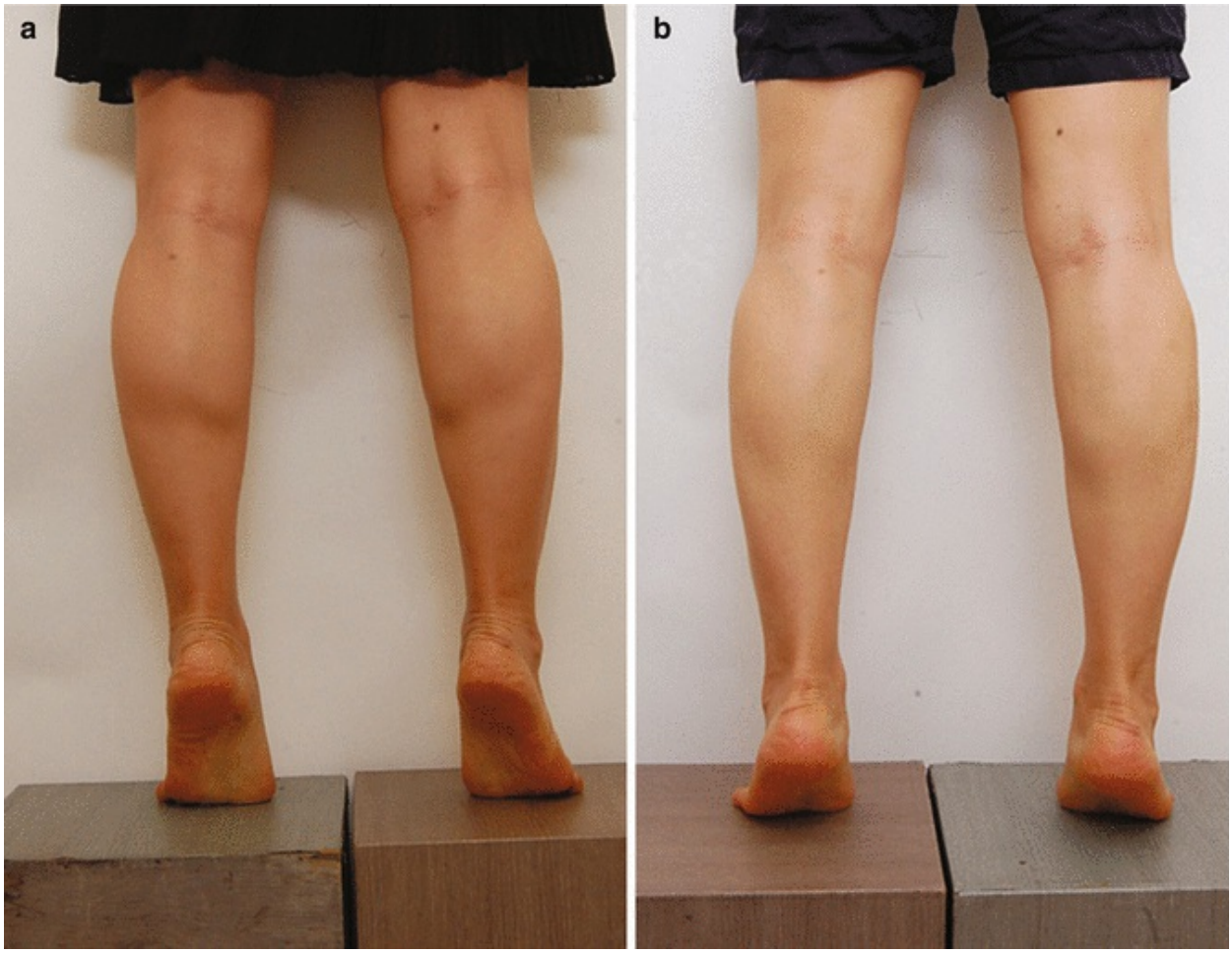

Fig. 5.15 One month after calf contouring with 200 U of botulinum toxin type A per leg. The patient cannot fully elevate the heels due to muscle weakness: (**a**) Before and (**b**) After

The gastrocnemius muscle is responsible for plantar flexion at the ankle joint and calf flexion at the knee joint. However, even in cases of complete resection of the gastrocnemius muscle or the tibial nerve innervating this muscle, leg mechanics can remain unimpeded thanks to same function of soleus muscle [4]. Other symptoms such as stiffness and heavy feeling may occur for several days in addition to bruising, myalgia, and lymphangitis [1].

5.2.4.7 Photography

Keep the patient standing with two feet adducted in front of the wall standing in a tiptoe position to accentuate the muscle bulges. Photographs for back view are taken at this posture from the feet to mid-thigh. To show the muscle bulges prominently, additional photos are taken of the patient in a standing

position with their feet slightly abducted at a 45 angle from right and left.

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6. Hyperhidrosis Treatment with Botulinum Toxin

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6.1 Introduction

6.1.1 Etiology and Classification of Hyperhidrosis

Sweating, an essential physiological phenomenon for thermoregulatory control, is regulated by a control center in the preoptic area and anterior hypothalamus via a signal by the sympathetic nervous system which is stimulated when body core temperature is increased by the weather outside or physical activity [1]. While sweating generally occurs at the whole body in case with thermoregulatory control, however, sweating may occur focally in the palms, soles, and the axillae stimulated by stress, excitement, and pain regardless of body temperature. Hyperhidrosis can be defined as sweating that affects their daily lives without a discernible cause in excess of the normal physiological needs of the body [1].

Hyperhidrosis may be categorized as generalized or focal disease. General hyperhidrosis involves sweating over the entire body and may be secondary to a variety of conditions [2]. Major causes of secondary hyperhidrosis include endocrine origin: hyperthyroidism, menopause, diabetes, hypoglycemia, pheochromocytoma, and carcinoid tumors. Other contributing factors include drug side effects (antiemetics, fluoxetine, etc.), drug abuse, cardiovascular disease, respiratory insufficiency, chronic hepatitis, cancer, Parkinson's disease, and other neurological diseases [2–4].

Focal, or localized, hyperhidrosis occurs primarily in otherwise healthy

individuals. Focal hyperhidrosis may be idiopathic [1, 4], which is the most common type, or it may be secondary to spinal disease, stroke, gustatory hyperhidrosis (Frey syndrome), eccrine nevus, or injury or associated with various peripheral neuropathies [1, 2]. In the presence of unilateral or asymmetric presentation, particular care must be taken to rule out a neurological lesion or malignancy [1]. Idiopathic hyperhidrosis occurs bilaterally and symmetrically on the palms, soles, axillae, face, and scalp without specific causes [4]. In idiopathic hyperhidrosis, no morphological or functional defect in the eccrine glands is observed. However, functional defects in the sympathetic nervous system related to sweating have been suggested [3]. Focal sweating of the palms and soles does not occur while sleeping, suggesting that this is not related by the thermoregulatory center but under cortical control. In contrast, both centers of the brain are involved in axillary hyperhidrosis [1].

6.1.2 Epidemiology of Focal Hyperhidrosis

Thirty to sixty five percent of focal hyperhidrosis patients have a familial history [5]. In the USA, a 2008 consumer survey of 15,000 families, approximately 2.8 % of the population suffer from the condition [6].

Regarding the onset of hyperhidrosis, two studies revealed similar conclusions. Herbst reported that among 323 patients, 61 % first experienced focal hyperhidrosis in childhood, 30 % in puberty, and 8.9 % after age over 18 [7]. In a similar study by Drott with 850 subjects, the onset was 62 % in childhood, 33 % in puberty, and 5 % after age over 18 [8]. Palmar hyperhidrosis, plantar hyperhidrosis, and axillary hyperhidrosis may occur independently or concurrently in the same individual.

6.1.3 Diagnosis of Focal Hyperhidrosis

There are still no objective criteria of sweating amount for the diagnosis of hyperhidrosis. Since focal hyperhidrosis is very much influenced by psychological variables such as excitement or stress, some of those affected by focal hyperhidrosis sometimes may not visibly sweat at all. This is one of the reasons why definitive objective diagnostic criteria for hyperhidrosis remain elusive. The severity of palmar hyperhidrosis can be categorized as mild (palms frequently moist), moderate (palms wet enough to soak handkerchief), and severe (palms drip sweat when patient makes fist).

6.1.4 Effects of Focal Hyperhidrosis on the Patients' Daily Lives

While focal hyperhidrosis does not directly affect the patient's life, focal hyperhidrosis presents obvious social, psychological, and emotional challenges to their daily lives. Many patients find palmar hyperhidrosis socially disabling, occupationally disruptive, and emotionally disabling [9]. Palmar hyperhidrosis significantly affects patients' ability to perform everyday tasks and causes considerable social embarrassment. Patients suffering from palmar hyperhidrosis frequently experience wet and cold hands, creating a reptilian sensation to others when touching hand. This often causes great psychological and emotional stress when in social or romantic situations. The patients' wet and cold hands are vulnerable to frostbite during winter, handicapping outdoor activities. Dexterous activities, such as playing musical instrument, are equally challenging. When writing or drawing, many patients developed a technique using two sheets of paper in which the top sheet was used to absorb sweat and the other to write on. Mechanics and electricians reported experiencing frequent electrical shocks to their moist hands, and others reported dropping glass objects or having difficulty knitting or playing musical instruments. Amir et al. reported that more than 50 % of patients experienced difficulty driving a car [9]. In cases of axillary hyperhidrosis, the axillae are frequently wet, and they look very unhygienic when wearing bright and/or thin blouses or T-shirts especially in spring and summer seasons [10].

6.1.5 Treatment of Focal Hyperhidrosis

Various treatments have been tried to remedy focal hyperhidrosis: topical agents, iontophoresis, BoNT-A, microwave treatment, endoscopic sympathectomy, etc. However, it is unfortunate that as of yet no perfect treatment for focal hyperhidrosis has been discovered.

There are more than 90 topical compounds available to treat focal hyperhidrosis. These topical agents achieve their effect either by blocking the excretory ducts of the eccrine glands or are astringent. Acting on the sweat glands and epithelium, they generally offer short-term action and are effective in mild cases [2]. A commonly used effective antiperspirant, aluminum chloride hexahydrate (20–25 % solution in water or ethanol), is thought to cause distal duct occlusion [1, 2]. Drawbacks to this treatment

include its short-lived effect, with continued success depending on daily application, and itching or burning sensation, particularly around the axilla [1]. Moreover, the patients should wear white shirts while the treatment is administered since the chloride component may cause decolorization of the clothes, therefore. Additionally, studies have demonstrated histologic damage (degeneration of eccrine acini with atrophy of secretory cells) after long-term use [11]. Other agents that can be used are formaldehyde, propantheline, and potassium permanganate [11]. Application of topical solutions can be messy and time-consuming, and over prolonged periods of time, these difficulties may lead to reduced patient compliance [2]. Despite these disadvantages, however, aluminum chloride is among the safest and cheapest treatments of focal hyperhidrosis and is often one of the first recommended treatments.

Focal hyperhidrosis can be treated with iontophoresis using an ionized substance (usually tap water), which is introduced through an intact skin by the application of a direct, 15–30 mA DC current or 220 V AC current for up to 20–30 min [2, 3, 13]. There are a few iontophoresis devices available in the market: Drionic® in the USA, Idromed® in Germany, and Hydro-X in Korea®. Drionic using 15–30 mA DC current requires continuous swapping out of the battery. Idromed® and Hydro-X®, use 220 V AC current. While the precise mechanism of action is not fully understood, it may be a temporary blockage of the sweat duct at the level of the stratum corneum [2]. For the treatment of palmar and plantar hyperhidrosis, good results can be achieved with iontophoresis, although this may require numerous applications, and maintenance therapy is required [2]. The effect is sustained from 2 months to 14 months after cessation of treatment [2]. The process is easy and convenient to perform, cost-effective, and generally well tolerated [2, 4]. Complications of treatment are generally mild and transient, consisting of erythema, vesicular rash, and paresthesia [2]. Iontophoresis may be more appropriate for treatment of the palms and soles and less appropriate for treatment of the axillae due to their concave shape. The process needs to be repeated at least two times a week to obtain desired results, and maintenance therapy can be scheduled as needed or once a week. Adding anticholinergic substances to the tap water produces a more rapid therapeutic success that also lasts longer. However, due to adverse effects, such as dryness of the mucous membranes of the mouth, nose, and throat and urinary retention, pure tap water iontophoresis is to be given preference as an initial treatment measure before adding anticholinergic agents [12]. Synergistic effects can be

anticipated together with topical treatment, but continuous treatment is still necessary. It is contraindicated in patients with an artificial pacemaker, in pregnant women, and in patients with orthopedic metal implants [2]. Iontophoresis may be recommended in cases where aluminum chloride is ineffective or BoNT-A treatment is not affordable.

In some patients, benzodiazepines may be useful in decreasing anxiety and reducing the emotional stimulus to excessive perspiration. As long-term use can lead to dependency, these agents are not recommended for long-term use. Additionally, many patients find the common side effects of lethargy and drowsiness unacceptable [2]. Glycopyrrolate, an anticholinergic agent, is another option for focal hyperhidrosis. But in addition to inhibiting sweat, it can produce undesired autonomic nervous symptoms such as blurred vision, xerophthalmia, xerostomia, dysuria, and constipation. The author prescribes oral glycopyrrolate in cases of severe hyperhidrosis where BoNT-A treatment is difficult or impossible.

Endoscopic transthoracic sympathectomy (ETS) is a simple, inexpensive, and efficient surgical treatment and may be the method of choice for the treatment of disabling focal hyperhidrosis of the palms, axillae, and face. Plantar hyperhidrosis is not an indication for ETS since the sympathetic nerves that innervate the foot are located in the abdomen. It should, however, be reserved for patients indicating that their symptoms are disabling [1]. Reported surgical techniques have varied widely, with the sympathetic trunk or ganglion being sometimes divided with scissors, excised, ablated, clipped, or cauterized. The level of the procedure also varied among the surgeons choosing to interrupt the sympathetic chain at T2 only, T2–T3, T2–T4, or lower T1–T4. One study investigating whether ETS is efficient and safe in the treatment of hyperhidrosis ($N = 850$) showed no increase in recurrences over time indicated lasting effects from treatment [8]. The most frequent observed side effects following ETS are compensatory sweating on the chest or back caused by shifting of signals from the brain, which has been reported in 50–75 % of patients, and gustatory sweating, or Ross syndrome, which has been reported in 30–40 % of patients [8]. Compensatory sweating is the major reason for patient dissatisfaction with the procedure since it may lead to severe disruptions in daily life. Patients experiencing compensatory sweating as a side effect of ETS may benefit from the use of anticholinergic agents [8]. Other less common complications include pneumothorax/hemothorax, intercostal neuralgia, Horner syndrome, cardiac

sympathetic denervation leading to 10 % reduction in heart rate both at rest and during exercise, and sequelae of general anesthesia.

Microwave treatment (miraDry®) has been developed recently in the USA. When microwaves are applied to the skin, the moist sweat gland is more rapidly heated and selectively destroyed. This treatment is expensive and takes for 40 min or more for the one session, and one session of treatment would not be enough. However, I think it can be a competitive option for the treatments of focal hyperhidrosis in the future, if the cost has lowered down.

6.1.6 Treatment of Focal Hyperhidrosis with Botulinum Toxin

6.1.6.1 Introduction

Since the eccrine gland is innervated by cholinergic sympathetic fibers and its neurotransmitter is acetylcholine, the botulinum toxin type A (BoNT-A) injection would be applied for the treatment of the hyperhidrotic [14]. Accordingly, BoNT-A treatment has been widely used for the treatment of focal hyperhidrosis in the axilla, palms, and soles since the first report by Dr. Bushara in 1994 [15]. Both BOTOX® and Dysport® were approved by the US FDA for the treatment of axillary hyperhidrosis.

BoNT-A for the treatment of axillary hyperhidrosis is a fantastic treatment in terms of simplicity of the procedure, convenience for patients, and efficacy as well. The whole procedure takes just 5 min following topical anesthesia application for 30 min, and the efficacy lasts as long as 6 months with only 50 U of BoNT-A per side. However, BoNT-A for the treatment of palmoplantar hyperhidrosis is less satisfactory than axillary hyperhidrosis because it requires high dose of BoNT-A for treatment (150 U per side) and the treatment efficacy lasts only 3 months. Moreover, the pain control is not easy since the nerve block anesthesia is not always effective. In addition, multiple intradermal injection into thick dermis at the palm and sole makes the procedure take over 30 min per session.

The duration of efficacy varies among individuals, but usually lasts 6–9 months in the axillae and 3–6 months in other areas including palms and soles [16]. With the exception of the mouth and cheeks, all areas of the body can be treated with BoNT-A. Repeat injections exhibit longer periods of efficacy due in part to a feedback mechanism in the brain that controls sweat.

Dr. Heckmann reported that patients undergoing two sessions of BoNT-A injection for the treatment of axillary hyperhidrosis experienced significantly reduced sweating even at 48 weeks after the second session, while patients undergoing only one session of BoNT-A injection showed complete return of sweat production [17]. In addition to the axilla, repeated injections of BoNT-A for the treatment of focal hyperhidrosis at other areas can result in the similar effects of sweat reduction for prolonged period after 6 months and even permanent reduction in some cases. Regarding the gustatory hyperhidrosis, it was reported that repeat BoNT-A injections decreased the size of the affected area and increased duration of efficacy, ending up with the permanent cure [18]. This is partly because the regeneration capacity of autonomic nerve terminals is less active than neuromuscular junction as well as atrophy of the sweat glands.

I also experienced a patient with scalp hyperhidrosis who showed remission for more than 4 years after the last injection after seven sessions of BoNT-A injections. Moreover, some patients with axillary hyperhidrosis undergoing repeated injection of BoNT-A still showed sweat reduction 1 year after the last injection compared with before treatment. Therefore, BoNT-A for the treatment of focal hyperhidrosis should not be regarded just as temporary symptomatic treatment but should be considered an effective remedy that may even fully cure a patient.

Compensatory hyperhidrosis which is the main adverse effect of endoscopic transthoracic sympathectomy may also occur after BoNT-A treatment for focal hyperhidrosis, but it occurs in a very mild form. In 2001, Naumann and Lowe reported in their prospective study of 320 patients with axillary hyperhidrosis that compensatory hyperhidrosis in other parts of the body appeared in 5 % after treatment of BOTOX® for axillary hyperhidrosis [19]. They also noted that treatment of BoNT-A for focal hyperhidrosis on the nose may induce compensatory hyperhidrosis on the philtrum.

Considering the cost of the BoNT-A treatment for palmoplantar hyperhidrosis requiring 200–300 U per session, treatment of BoNT-A may be recommended only to the patients that didn’t get satisfactory effects with topical agents or iontophoresis treatment. However, BoNT-A treatment for axillary hyperhidrosis requiring 100 U per session could be first considered for patients in terms of convenience, safety, and efficacy of the treatment.

6.1.6.2 Injection Techniques

First, identify the target area to be treated using a starch–iodine test (Figs. 6.3 and 6.4). The BoNT-A should be reconstituted with 5 ml normal saline to use as concentration of 2 U/0.1 ml. Since the eccrine glands are located in the lower dermis and upper subcutaneous layers, intradermal injections with making a small wheal at the injection sites are the prototypes (wheal, Fig. 6.1). 0.5–1 U of BoNT-A is injected at each point 1–1.5 cm apart. After marking the injection points, the needle is inserted 3–4 mm apart from the injection points and advanced slightly beyond the injection point in order to make a tunnel for inflow. Then, withdraw 1–2 mm back and inject 0.025 ml (0.5 U) to 0.05 ml (1 U) of BoNT-A. Just prior to pulling out the needle, pause one second to let the BoNT-A diffuse into the tissue, and then gently pull the plunger backward to induce negative pressure, which is helpful in reducing the backflow of BoNT-A solution from the needle mark. It may be convenient to use 30 gauze of a 0.5 in. (1.25 cm) needle bended at a 30° angle (Fig. 6.2).

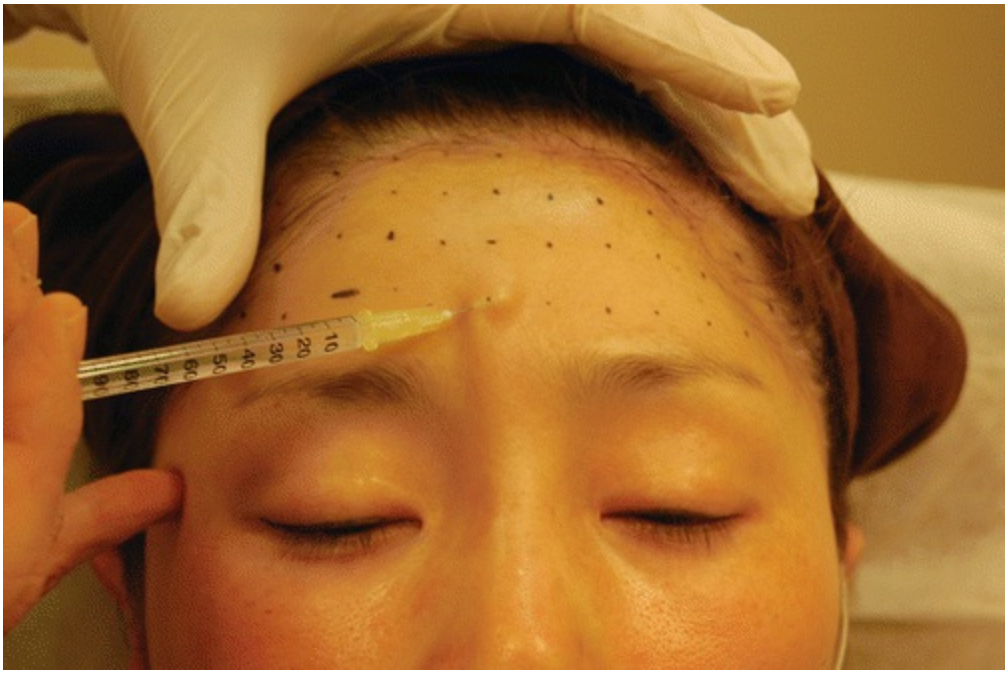


Fig. 6.1 Injection depth for the treatment of focal hyperhidrosis. Intradermal injection with making a small wheal at the injection site is more appropriate than subcutaneous injection

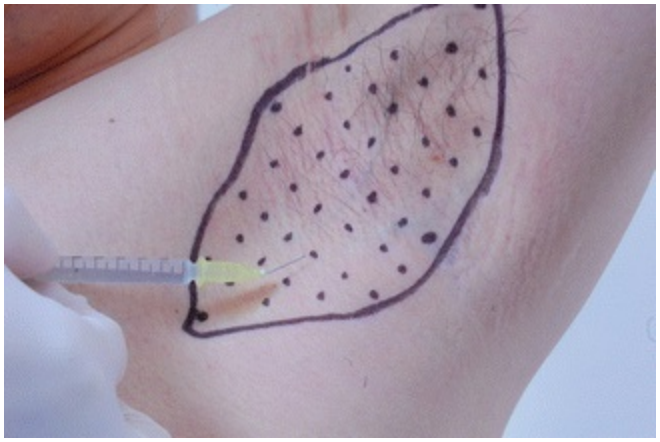


Fig. 6.2 Needle bending for the treatment of hyperhidrosis with botulinum toxin. Bending the needle at a 30° angle is convenient for the intradermal injection

The BoNT-A doses for hyperhidrosis are 100–200 U per side for the palm and sole each, 50 U (40–100 U) per side for the axilla, 20 U for the forehead, 16 U (10–20 U) for the nose, 200–300 U for the entire scalp, and 200–500 U depending on the area for compensatory hyperhidrosis (Table 6.1).

Table 6.1 Classification of hyperhidrosis

Focal	Primary (idiopathic)
	Neuropathy related
	Spinal disease/secondary to injuries
Systemic	Primary (idiopathic)
	Secondary to various diseases

6.1.6.3 Anesthesia

In order to reduce the pain during the procedure, topical anesthetic cream should be applied for 30 min prior to injection on the axilla, the forehead, and other areas affected by compensatory hyperhidrosis. Nerve block at the wrist and at the ankle is prerequisite for the palms and soles, respectively. The nerve block is also helpful for the entire scalp.

Tip: Starch–Iodine Test

1. Dry out the testing area with a fan or a blow-dryer.

2. Paint Betadine solution evenly on the testing area, and either let the area dry up spontaneously or use the cold setting on a blow-dryer.

3. After wrapping the starch with several sheets of 4 × 4 gauze, tap the gauze lightly on the testing area to spread the starch powder evenly on the skin surface (Fig. 6.3).

4. In case with axillary hyperhidrosis, raise the room temperature, and/or ask the patients to exercise squatting in order to increase the body core temperature. At this point, patients are instructed to keep their arms up. For palmoplantar hyperhidrosis which is not affected by ambient or core temperature, patients are sometimes pinched or pricked by a needle to stimulate the sympathetic nerves for inducing sweat (Fig. 6.4).

5. In cases of palmar hyperhidrosis, there is no need to perform starch–iodine test before the procedure because the entire palms are hyperhidrotic. However, it is helpful in follow-up sessions to ascertain the hidrotic area which requires touch-up injection. In some rare cases, the test may be required when the dorsum of the hand is also hyperhidrotic.

6. In case the test fails because sweating does not occur in the axilla, the BoNT-A could be injected primarily into hair-bearing areas which is a natural indicator of excessive sweating sites.

7. In cases of plantar hyperhidrosis, the test is necessary before the procedure because sweating would be variable depending on the area of the sole.

8. Take photos and print them out to review them together with the patient during follow-up sessions.

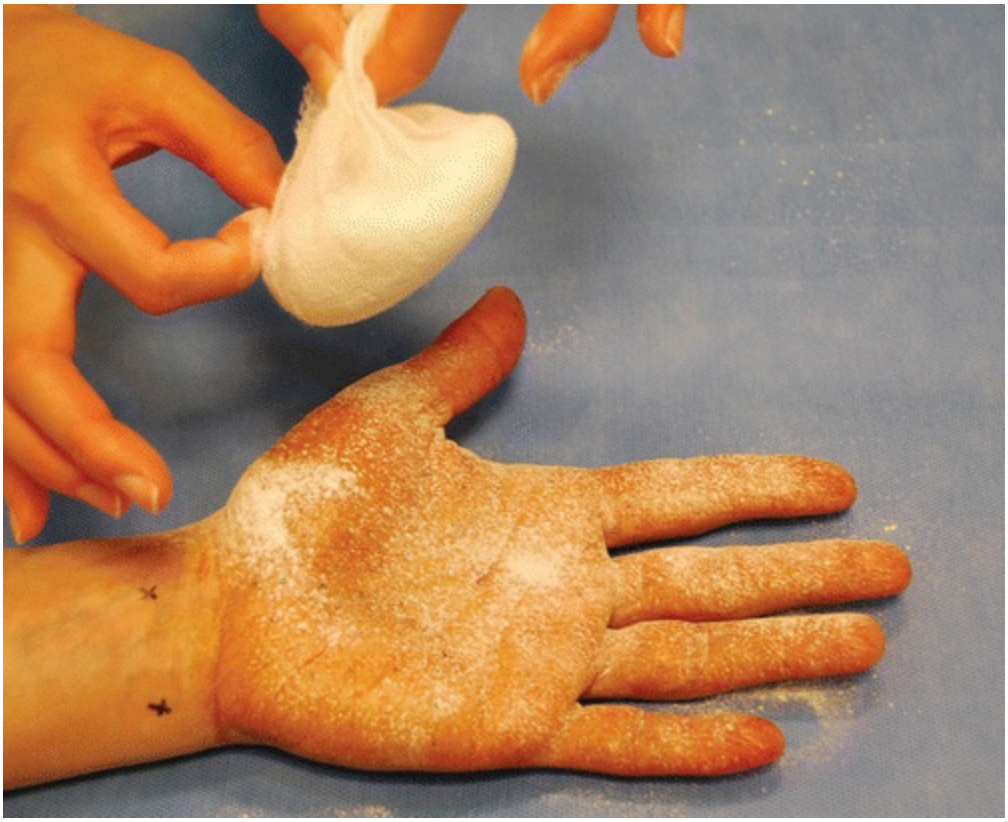


Fig. 6.3 Starch–iodine test. Sprinkling starch powder wrapped in several sheets of gauze evenly into the test area

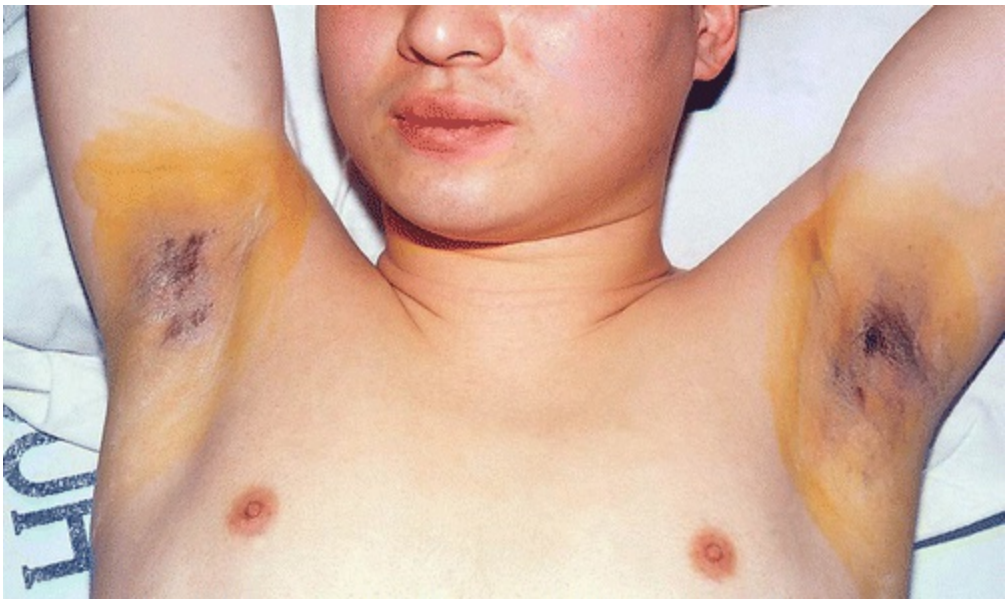


Fig. 6.4 Starch–iodine test for axillary hyperhidrosis. Patients are asked to hold their arms up for testing

Episode: My First Clinical Study with Botulinum Toxin

In the summer of 1998 after serving 3 years as a medical officer in the Korean military, I started my academic career as a fellow at the Seoul National University Hospital (SNUH), department of dermatoloy. Eager to choose a research topic for my dissertation, I pored over copious volumes of foreign academic journals. In one of these articles, I came across a fascinating study involving the injection of botulinum toxin on 11 hyperhidrosis patients. Significantly, the fact that the effects were found to last 5 months was a truly an eye-opener for me. Although several remedies for palmar hyperhidrosis were available at the dermatology department at that time, including topical agents, iontophoresis, and oral medicine, effects were at best transient and minimal, and in fact most patients were transferred to the department of cardiovascular surgery for a more invasive procedure, sympathectomy. However, the problem with sympathectomy was the potential risk of developing a compensatory hyperhidrosis, which once occurred, would remain permanent. Further, it was impossible to predict which of the patients were most susceptible to the risk. For this reason in 1998, the department of cardiovascular surgery at the Seoul National University Hospital eventually decided to discontinue the procedure. While clearly not a matter of life and death, such complications were nonetheless distressing to the patient, and yet there was nothing the doctors could do to treat the resulting symptom. As a result, there was little that the dermatology department could offer to patients who came in for palmar hyperhidrosis treatment, apart from prescribing topical agents if not referring them to other hospitals where sympathectomy procedures were still available. Put bluntly, palmar hyperhidrosis was the equivalent of a no man's land among the ailments treated at the SNUH.

I had some rather sore personal memories relating to palmar hyperhidrosis as well. During my first year of residency training at the SNUH in 1991, I was assigned as a research assistant to a fellowship professor who at that time was ambitiously conducting a study on palmar hyperhidrosis. My role was to measure the amount of sweat by individual palmar hyperhidrosis patients. The patients were to wear surgical gloves for 5 minutes, after which I had to weigh the amount of perspiration in the gloves with a precision scale with 0.1 mg graduation for comparison with tare weight of dry gloves. The exercise literally involved a lot of legwork, since the said scale was kept at the Central Research Office (which no longer exists now) on the 12th floor of the building, and each trip to the office took around 30 min. For all those trips

made and tests performed however, I was dismayed to find nothing much happened from the study. Patients were still being transferred off to cardiovascular surgery departments without receiving any helpful treatment. To me it seemed like a lost cause. So imagine the joy and elation I felt upon learning that a single injection could provide up to 5 months of relief for the patient.

Upon literature review, I found a few more case studies, but the research was still in its infancy, involving only a small sample size and providing limited findings. This inspired me to set out on my own research on BoNT-A. At that time, BOTOX® was available in Korea but was prohibitively expensive. After putting together a research proposal entitled "dose–effect relationship of BoNT-A in patients with palmar hyperhidrosis," I managed to secure initial sponsorship from Allergan Korea to conduct the research. The focus of my later research topics evolved to the effects of refrigerated storage period on the potency of BoNT-A, a hot research topic at the time, and BoNT-A for Koreans.

The late 1990s was the period when botulinum toxin treatment had just been introduced to Korea and was performed only by a handful of plastic surgeons. Indeed it was unchartered territory, and the fear of the unknown prevented many doctors from undertaking the procedure, particularly since they had to rely entirely on the few foreign literatures available for any guidance regarding dosage and injection points for Asians. Against this backdrop, the above studies received huge interest and kudos from other Korean practitioners and eventually won me the humble reputation I today enjoy in the field of botulinum toxin treatment. No doubt, palmar hyperhidrosis treatment with BoNT-A is arduous and time-consuming work, but which I am happy to perform with devotion, given the invaluable role it played in getting me where I am in the field of botulinum toxin treatment.

6.2 Regional Particulars

6.2.1 Axillary Hyperhidrosis

Effect (A), Adverse Effect (A), and Technique (A)

Axillary hyperhidrosis is highly affected by outside temperature and thus is more severe in summer than in winter. Sufferers of this condition have axillae that are frequently wet and look very unhygienic when wearing bright and/or

thin blouses or T-shirts. Light-colored clothes often become yellowish or brown due to frequent sweating.

BoNT-A treatment for axillary hyperhidrosis is a very attractive option in terms of simplicity of the procedure, convenience for patients, and efficacy as well. The procedure takes just 5 min following topical anesthesia application for 30 min, and the efficacy lasts as long as 6 months. If it is performed once a year in May, patients can tolerate well the hot summer without suffering from the severe perspiration. Repeated injections of BoNT-A can also result in prolonged effect of sweat reduction and even permanent cure in some cases.

6.2.1.1 Injection Techniques

Administer a starch–iodine test and check the hyperhidrotic area. In case the test fails when perspiration doesn't occur, the BoNT-A should be injected primarily into areas where hairs grow. In order to reduce the pain during the procedure, topical anesthetic cream should be applied for 30 min prior to injection.

Mark injection points 1 cm apart with a marking pen and inject 1 U into each point (Fig. 6.5). As intradermal injection is desirable, a small wheal should be noticeable at the injection site. The standard dose for the treatment of axillary hyperhidrosis is 50 U. This is based on the prospective clinical study result by Naumann and Lowe in 2001. In that study, 94 % of the 320 patients were satisfied with the results [19]. In 2004, the US FDA approved 50 U of BOTOX® for the treatment of axillary hyperhidrosis. In a prospective multicenter clinical study surveying 322 axillary hyperhidrosis patients, both 75 U of BOTOX® and 50 U of BOTOX® were administered. The result of this study showed no significant difference in the median duration of efficacy between 205 days in the 75 U of BOTOX® group and 197 days in the 50 U of BOTOX® group [20]. In another prospective intraindividual comparison study using Dysport® in 43 patients with axillary hyperhidrosis, there was no significant difference in the effect of sweat reduction between the 100 U and 200 U. Accordingly, 100 U has been used as a standard dose for Dysport® in the treatment of axillary hyperhidrosis [17]. If the target area is large in men, up to 100 U of BoNT-A per side can be used.

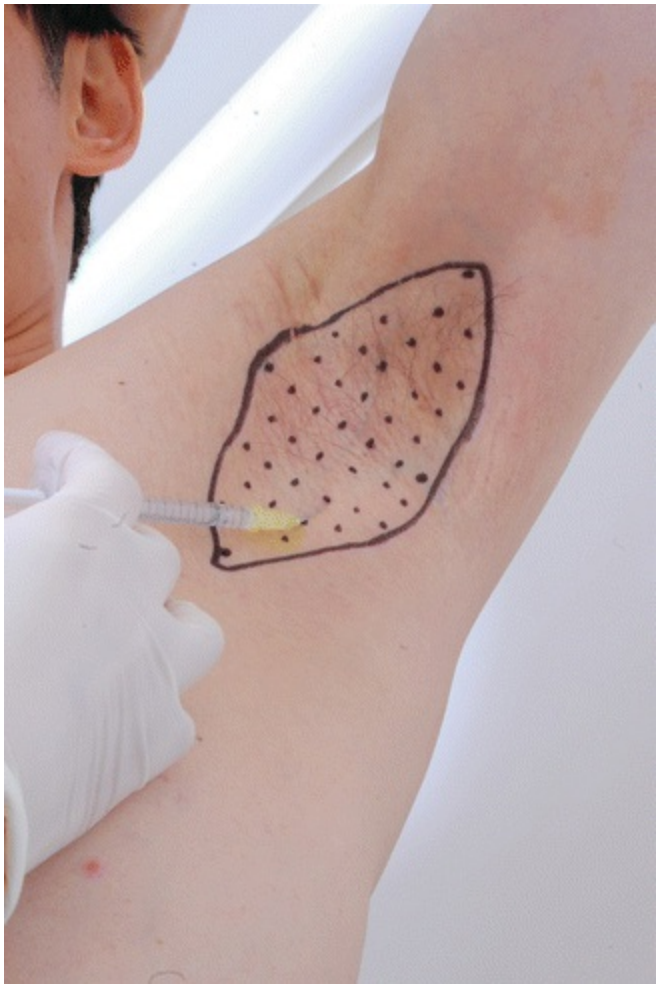


Fig. 6.5 Injection points for axillary hyperhidrosis. Marking of injection points is performed 1–1.5 cm apart in the hyperhidrotic area confirmed by starch–iodine test or in the hairy area in case when the test is not performed or shows negative results

6.2.1.2 Adverse Effects

Some bruising is the only adverse effect.

6.2.1.3 Evaluation Method

Objective Method

1. Gravimetric measurement: After applying pieces of gauze on the axilla, cover with a wrap and leave for 5 min. Then, estimate the sweat amount by comparing the gauze weight before and after. This method can be used for quantitative evaluation for the treatment of axillary

hyperhidrosis.

2. Starch–iodine test: This test is usually used to identify the hyperhidrotic areas, but can be used for quantitative evaluation after measuring the sweating area.

Subjective Method
The Hyperhidrosis Disease Severity Scale

Score 1: My (underarm) sweating is never noticeable and never interferes with my daily activity.

Score 2: My (underarm) sweating is tolerable but sometimes interferes with my daily activity.

Score 3: My (underarm) sweating is barely tolerable and frequently interferes with my daily activity.

Score 4: My (underarm) sweating is intolerable and always interferes with my daily activity.

(Lowe NJ, et al. *J Am Acad Dermatol*) [20]

6.2.2 Palmar Hyperhidrosis

Degree of Difficulty: Effect (B), Adverse Effect (B), and Technique (C)
Palmar hyperhidrosis appears symmetrically in most patients; however, some proportion of patients show unilateral hyperhidrosis appear in only one hand. While not physically painful and fatal to life, palmar hyperhidrosis presents obvious social, psychological, and emotional challenges [9]. Since patients with palmar hyperhidrosis tend to be daunted socially by the sweating on the hand, there was a report that the stress of patients with palmar hyperhidrosis are more severe than that of patients with chronic renal failure or patients with multiple myeloma [21, 22].

Treating palmar hyperhidrosis with BoNT-A is not a simple and easy procedure. For doctors, the procedure is arduous and time consuming. Nerve block at the wrist which requires experienced skill is prerequisite for the procedure since the tactile sense is highly developed in the hands. I think that nerve block at the wrist is the “alpha and omega” of the BoNT-A injection for the treatment of palmar hyperhidrosis. Further, it takes at least 30 min for

both palms, and the efficacy does not last long compared to the treatment of axillary hyperhidrosis. The duration of efficacy of the BoNT-A treatment in palmar hyperhidrosis seems to be 3–4 months, shorter than axillary hyperhidrosis. Moreover, the treatment cost remains high due to the high dose of BoNT-A used.

Therefore, BoNT-A injection for the treatment of palmar hyperhidrosis is not easily recommended procedure for patients. Nevertheless, I usually recommend this procedure to the patients who do not want an operation for fear of compensatory hyperhidrosis, students who should take an important examination such as *baccalaureate*, those requiring shaking hands many times such as politicians, and those who want "cure" since repeated injections through several sessions over a 1–2 year period may lead to fundamental remission of palmar hyperhidrosis.

6.2.2.1 Injection Techniques

Injection points are marked 1 cm apart with a marking pen, and patients are seated with their arm supinated. IU (0.05 ml) of BoNT-A per point (Fig. 6.6) is injected intradermally with making a small wheal at the injection sites. Since the dermis of the palm is thick, it would be important to make a "tunnel," space for BoNT-A injected in order to reduce the backflow of BoNT-A (see Sect. 6.1.6.2).

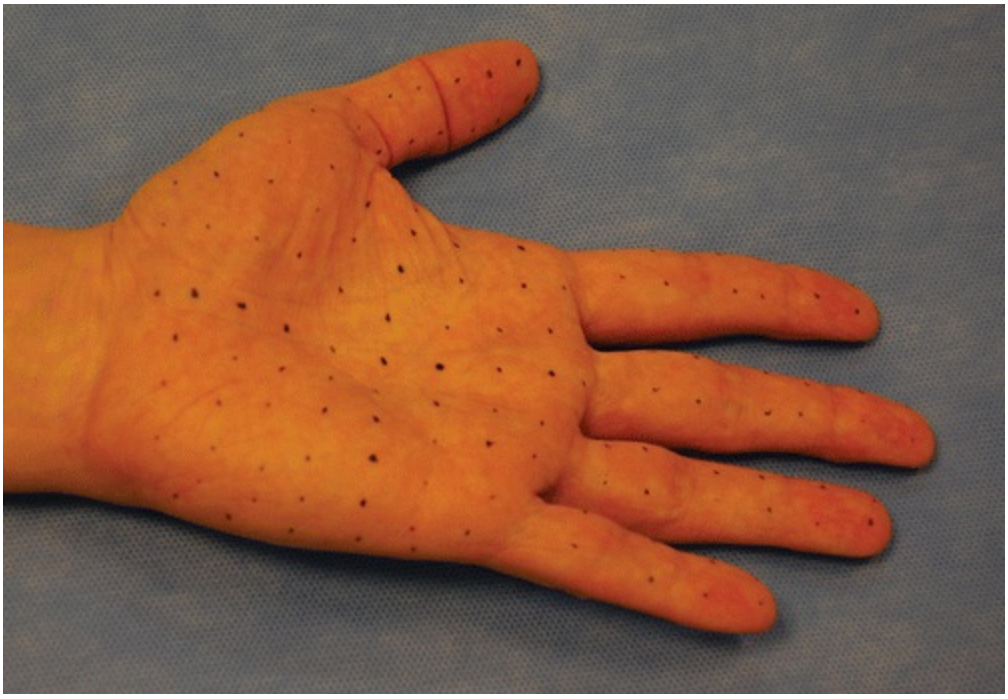


Fig. 6.6 Injection points for palmar hyperhidrosis

The dose of BoNT-A for the treatment of palmar hyperhidrosis varies depending on the severity and hand size. Dose ranges from 50 to 200 for BOTOX® per hand and 100–300 U for Dysport® per hand. 100 U, 150 U, and 200 U per hand are generally used for small, medium, and large hands, respectively (Table 6.1). Since patients with palmar hyperhidrosis are more concerned about the perspiration at the fingers than the palm, the fingers and the palms are injected equally with half the dose each. There is no need to worry about muscle weakness in the fingers where muscles are absent. More attention should be taken to cover the ulnar border of the palm with BoNT-A because sweating in this area affects the writing by wetting the paper.

6.2.2.2 Nerve Block at the Wrist

The pain control in this procedure is so important such that the report, "intravenous regional anesthesia with prilocaine for BoNT-A treatment of palmar hyperhidrosis," was published [23]. Therefore, nerve block at the wrist is prerequisite for the treatment of palmar hyperhidrosis. Even though nerve block is not always completely performed, there is a great difference of the severity of pain during procedure between patients partially nerve blocked and patients not undergoing nerve block. Patients may experience

excruciating pain if the procedure is performed without nerve block. If the patient complains of severe pain, physicians are likely to inject BoNT-A quickly and imprecisely, resulting in decreased efficacy of the BoNT-A injection for the treatment of palmar hyperhidrosis. Further, doctors may perform subcutaneous injection producing less pain rather than the intradermal injection, which increases the risk of intrinsic muscle paralysis. If you are unfamiliar or unsure about nerve block at the wrist, you would better give up the treatment of palmar hyperhidrosis with BoNT-A.

After the tendon of the palmaris longus is identified by wrist flexion (Fig. 6.7), the local anesthetic agent such as 2 % lidocaine or 2 % Xylocaine is injected subcutaneously into the point lateral to the tendon of the palmaris longus at the proximal crease in order to block the median nerve (Fig. 6.8a). The easy way to identify the tendon of the palmaris longus is asking patients to touch the thumb to the fifth finger with the wrist flexed. Since the median nerve is superficially located, a tingling sensation in the fingers can be perceived by patients when lidocaine is appropriately injected around the median nerve with the needle inserted perpendicularly 2–3 mm deep from the skin. For the ulnar nerve, lidocaine is injected deep subcutaneously into the point lateral to the flexor carpi ulnaris at the proximal crease (Fig. 6.8b). The needle is deeply inserted perpendicularly from the skin until the whole length of needle is nearly submerged. Before injection of lidocaine, aspiration test for blood is necessary to identify whether the needle is inadvertently inserted into the ulnar artery. For a radial nerve block, 2 ml of lidocaine is injected superficially subcutaneously both into the site over the radial artery at the proximal crease and into the site proximal to the snuffbox in the dorsal hand.

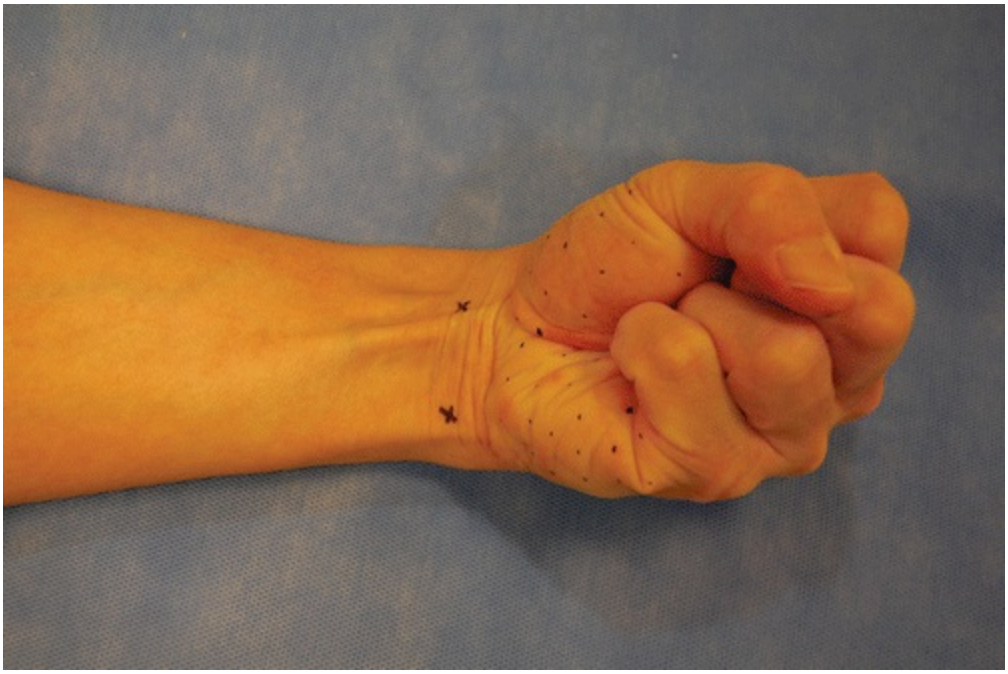


Fig. 6.7 Injection points for wrist block. With the wrist flexion, the injection point for the median nerve block and the ulnar nerve block is marked lateral to the palmaris longus and lateral to the flexor carpi ulnaris, respectively, at the proximal crease

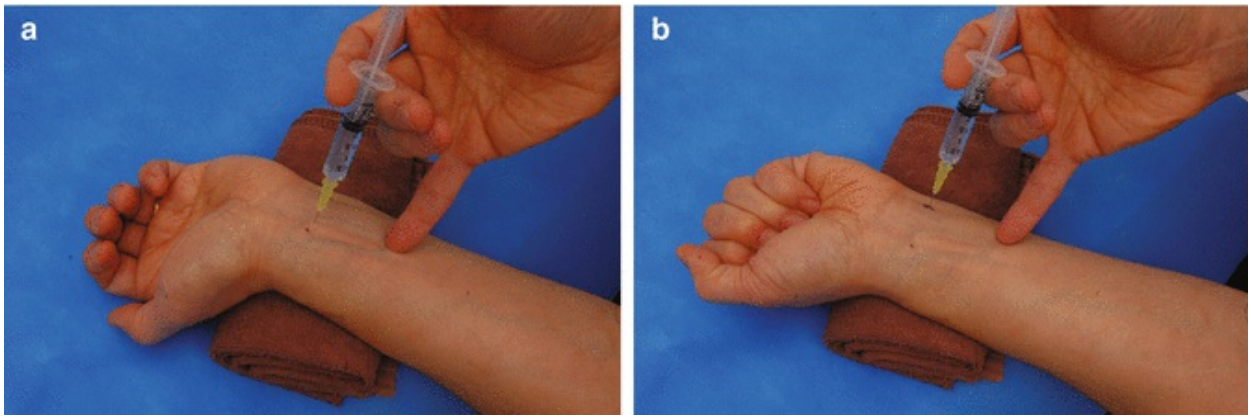


Fig. 6.8 Injection technique for the nerve block at the wrist. (**a**) Median nerve block. (**b**) Ulnar nerve block

For the nerve block, a 30-gauge needle with length of 1.25 cm is used. The 2 ml of lidocaine is required for each nerve. Since nerve block is not always completely performed due to the individual variation of nerves, however, additional 2 ml per nerve injection of lidocaine can be administered as needed up to a maximum of 20 ml in one session.

If the nerve block is successfully performed, sympathetic nerves will be

also paralyzed resulting in dry and warm skin in the palm and fingers. This can be used as an indirect end point of the nerve block's effectiveness.

Tip: Anatomy for Wrist Block (Fig. 6.9)

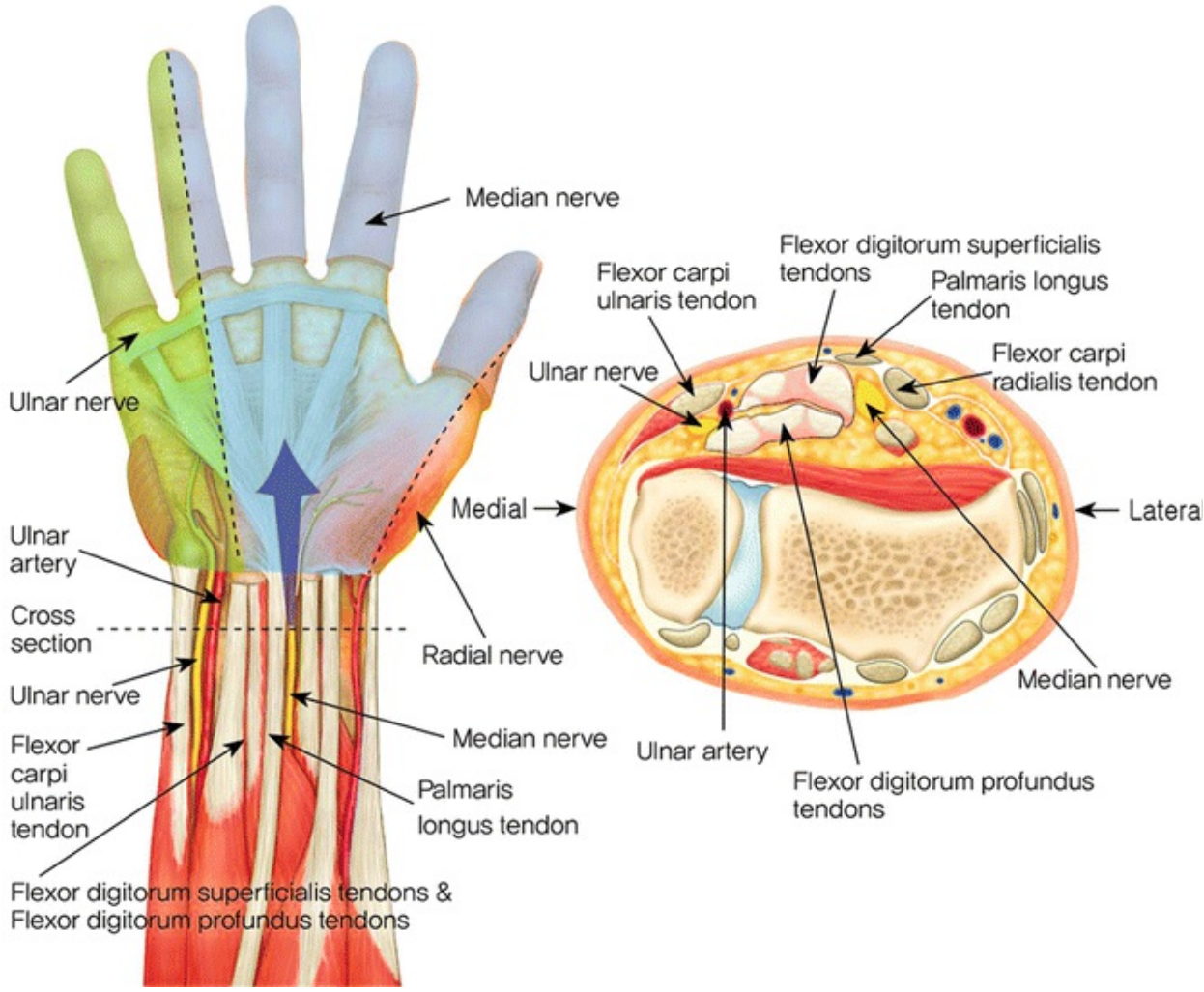


Fig. 6.9 Anatomy of the palm and wrist. (**a**) Sensory innervation of the palm. (**b**) Wrist cross section

The hand is innervated by three sensory nerves. The ulnar nerve and the median innervate the ventral side of the palm and fingers, while the radial nerve innervated the dorsal side of the fingers and hand. The ulnar nerve innervates the fifth finger and the medial half of the fourth finger as well as the corresponding part of the palm. The median nerve innervates the lateral half of the forth finger, third finger, index finger, thumb, and further lateral part of the palm, while the radial nerve innervates the dorsum of the hand and

finger and partially the lateral part of the thumb. Therefore, the ulnar and the median nerves must be blocked, with the radial nerve blocked depending on the situation for the treatment of palmar hyperhidrosis with BoNT-A injection. Since the median nerve is superficially located inferiorly and laterally to the palmaris longus tendon at the proximal crease, local anesthetic agent should be injected superficially into the site lateral to the palmaris longus. For the ulnar nerve, local anesthetic agent is deeply injected laterally to the flexor carpi ulnaris tendon. Before injection, aspiration for blood is necessary to avoid the inadvertent injection into the ulnar artery.

6.2.2.3 Starch–Iodine Test

When treating palmar hyperhidrosis, there is no need for a starch–iodine test because the entire palms are usually hyperhidrotic, but it would be helpful in follow-up sessions in order to localize the ineffective area where touch-up injection is required.

6.2.2.4 Adverse Effects

The most common adverse effect is a weakening of the intrinsic hand muscles. As the flexor muscles for fingers are located in the forearm, grasping power remains unaffected. However, some weakening of the intrinsic muscles may be felt during the thumb–index pinch motion or when attempting to touch two fingers together. Therefore, BoNT-A should not be administered to musicians or other professionals that rely on dexterity due to potential paralysis of the intrinsic hand muscles. Muscle weakness is proportional to the dosage administered. In the author's dose–response relationship study on the effect of BoNT-A for the treatment of palmar hyperhidrosis in 18 patients, muscular weakness did not occur at all with less than 50 U per hand (unpublished data). In contrast, 100–150 U per hand tends to bring about muscle weakness to some extent for 1–2 months in most patients. However, muscle weakness is mild and temporary.

There is interesting report on the difference of the efficacy and safety in patients with palmar hyperhidrosis between Dysport® and BOTOX® performed by Simonetta [24]. A randomized double-blind clinical study compared Dysport® and BOTOX® effectiveness in eight patients with palmar hyperhidrosis. 69 U of BOTOX® was randomly injected on one hand with 284 U of Dysport® on the other in eight patients with palmar

hyperhidrosis based on a conversion factor of 1:4 for BOTOX® to Dysport®. According to the result of the study, Dysport® was superior to BOTOX® at 3 months after injection, while efficacy was the same at 1 month. Notably, muscle weakness was more severe on the Dysport® side (50 %) than the BOTOX® side (25 %). Considering fact that the appropriate conversion ratio between BOTOX® and Dysport® is believed to be 1:2.5, a 1:4 ratio used in this study seems to be much higher, which explains the high incidence of muscle weakness and higher efficacy in the Dysport® side.

In rare cases, the nerve block also produces adverse effect, paresthesia caused either by mechanical damage from the needle or chemical damage from the lidocaine. There may be a local pain at the median nerve or radiating discomfort when pressed on the median nerve. It is mostly transient, but if severe, gabapentin (Neurontin®) would help relieve this adverse effect.

6.2.2.5 Evaluation Method

Gravimetric Measurement

Have the patient press one hand on an A4-size sheet for 1 min, and weigh the amount of perspiration by comparison of tare weight of A4-size sheet before and after the test. Another method involves the measuring weight of the gauze inserted inside a surgical glove which patients pulled on for 5 min.

Dose–Effect Relationship of Botulinum Toxin in Patients with Palmar Hyperhidrosis (Unpublished Data, (1999))

1. Background

BoNT-A has emerged as a new treatment method for palmar hyperhidrosis. Since Naumman's 1998 study on dose–effect relationship for the treatment of palmar hyperhidrosis where 50 U is reported to be appropriate dose, however, further study has not been performed.

2. Aim

To find the optimal dose of BoNT-A for the treatment of palmar hyperhidrosis

3. Subject

Total 18 subjects who sweat over 50 mg per minute

4. Study Design

Prospective, double-bind, intraindividual comparison study

5. Injection Techniques

Intradermal injection: 50 U into one hand and either 17 or 34 U into the other

6. Evaluation

Sweat production was measured at 2, 4, and 12 weeks, respectively, using gravimetric measuring: sweat absorbed in A4 paper and weighed. Muscle weakness was measured using a hand dynamometer and pinch dynamometer.

7. Results

Sweat production decreased as follows: 66 % (50 U), 62 % (33 U), and 45 % (17 U) at 2 weeks; 45 % (50 U), 36 % (33 U), and 26 % (17 U) at 4 weeks; and 22 % (50 U), 18 % (33 U), and -8 % (17 U) at 12 weeks (Fig. 6.10). However, 3 of the 18 patients did not show reduction of perspiration amount after the BoNT-A injection. No adverse effects were observed in all cases.

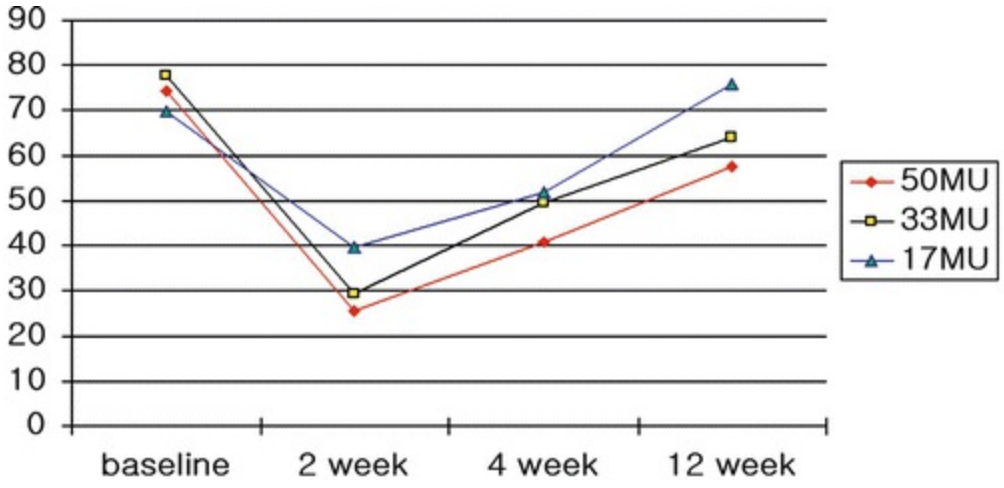


Fig. 6.10 Effect of botulinum toxin injection on sweat amount according to doses of botulinum toxin A

8. Conclusion

Though 50 U is known to be an effective dose, 3 out of 18 were not actually effective. Half of the patients returned to abnormal sweat levels after the first month, and nearly all patients returned to preinjection sweat levels after 12 weeks (Fig. 6.11). This data suggests that 50 U is not an appropriate dose, and further study is needed to evaluate proper BoNT-A dose for the treatment of palmar hyperhidrosis.

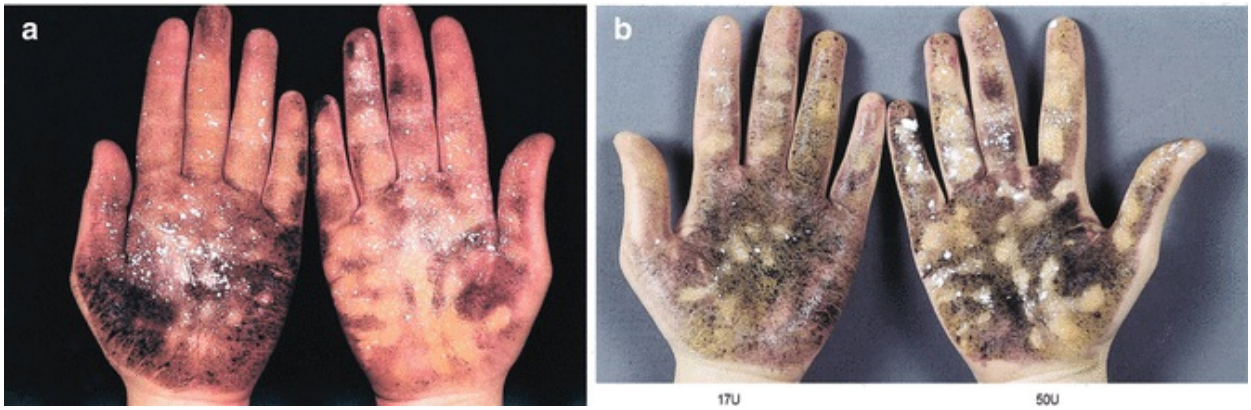


Fig. 6.11 Starch–iodine test before and after botulinum toxin injection for the treatment of palmar hyperhidrosis. (**a**) 2 weeks after injecting 17 U of BOTOX® in the left and 50 U in the right hands. (**b**) 12 weeks after injecting 17 U of BOTOX® in the left and 50 U in the right hands

9. Epilogue

In 1999, BoNT-A for the treatment of palmar hyperhidrosis made national headlines in Korea when I first introduced this novel treatment in Seoul National University Hospital. Thus, I could easily gathered patients with palmar hyperhidrosis to participate in my first clinical study. Although the results were not satisfactory, the objective evaluation method and experiment design allowed me to present these findings at the 1999 ISDS and 2000 AAD fellow sessions.

6.2.3 Plantar Hyperhidrosis

Effect (B), Adverse Effect (B), and Technique (C)

Palmar hyperhidrosis is usually accompanied by plantar hyperhidrosis. Perspiration occurs even in winter season regardless of ambient temperature;

a bad smell, tinea pedis, and/or frostbite is frequently associated. As socks easily become wet, they have to be changed frequently. Thus, indoor slippers or socks with separate toe compartments can be helpful for patients with plantar hyperhidrosis.

In contrast to palmar hyperhidrosis showing even perspiration on the whole palm, sweating does not occur evenly on the whole area of the sole in some cases. Sweating is sometimes less observed on the central portion of the sole. Therefore, it is necessary to identify the sweating area through a starch–iodine test before the BoNT-A injection. A nerve block should be also performed for pain control; the whole plantar surface could be anesthetized via a nerve block at the ankle targeting the posterior tibial nerve (Fig. 6.12).

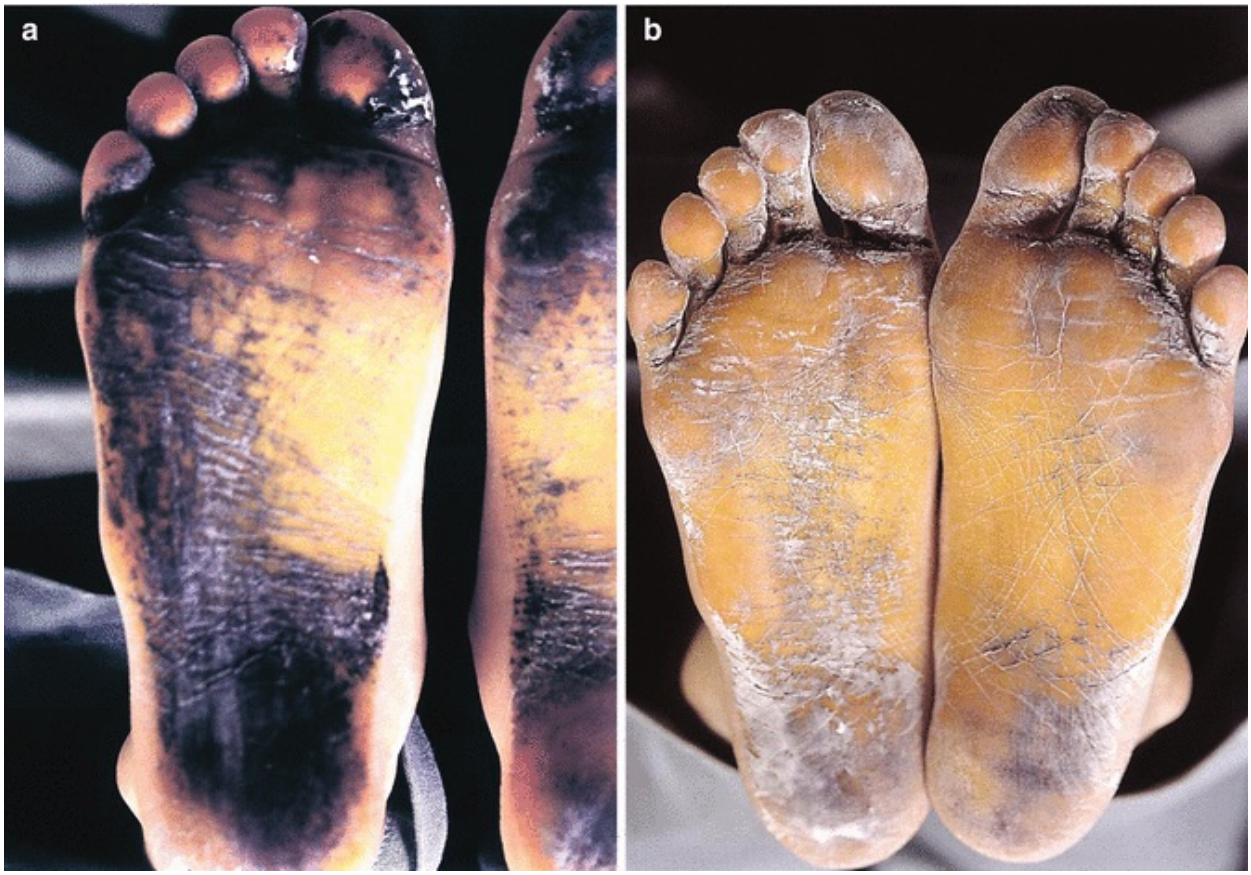


Fig. 6.12 Starch–iodine test (**a**) before and (**b**) 2 weeks after 100 U of BOTOX® injection per side for the treatment of plantar hyperhidrosis

The injection technique is similar to that of palmar hyperhidrosis. The total dosage of BoNT-A per side is 150 U with the range of 100–200 U.

Tip: Nerve Block at the Ankle

The posterior tibial nerve is responsible for the sensation in the sole. It curves around the posterior surface of the medial malleolus and runs into the sole. For the nerve block at the ankle, the anesthetic agent is injected into the point medial to the Achilles tendon at the upper border of the medial malleolus with the needle toward the medial malleolus. 2 ml of lidocaine is injected deeply until the 1 in. (2.5 cm) needle is fully inserted (Fig. 6.13). Blood aspiration test should be taken not to puncture the posterior tibial artery or posterior tibial vein near the nerve.

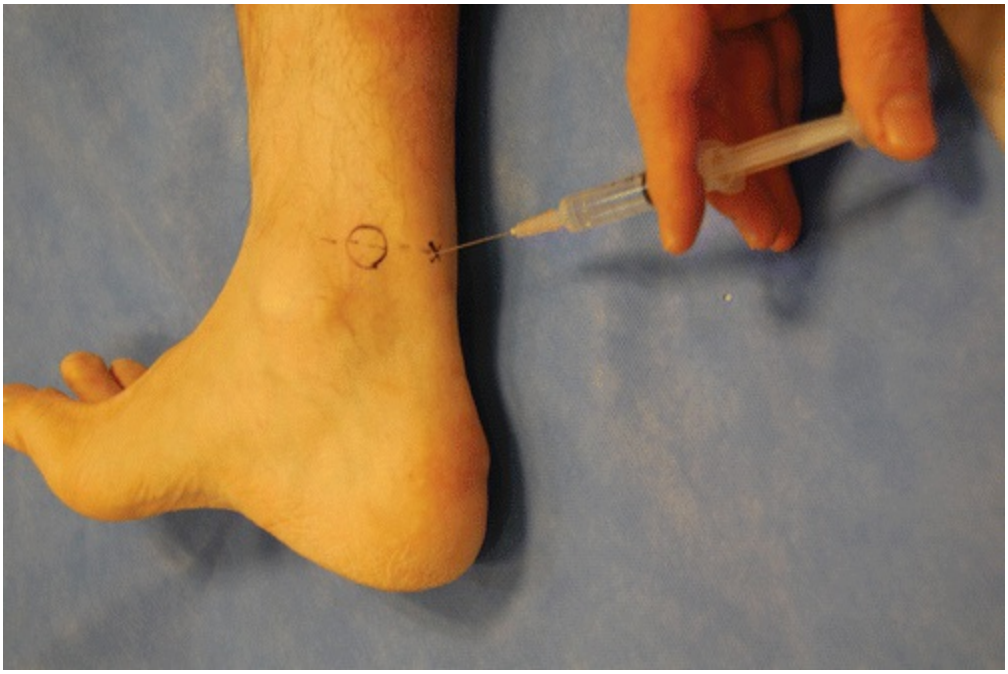


Fig. 6.13 Nerve block at the ankle

6.2.4 Facial Hyperhidrosis and Scalp Hyperhidrosis

Effect (A), Adverse Effect (B), and Technique (B)

Excessive sweat on the forehead, nose, cheeks, or scalp can disturb the social life of patients with facial or scalp hyperhidrosis. If patients with facial or scalp hyperhidrosis excessively sweat and wipe it off with a handkerchief frequently while dining, the partners may have even compassion for it. And it may be more severe when the person eats spicy foods.

BoNT-A for the treatment of facial and scalp hyperhidrosis can be performed at the whole face and scalp except lower cheeks, especially the

lateral side of the mouth and anteromedial cheek due to the possibility of alteration of facial expressions. In addition, BoNT-A injection over the philtrum should be also avoided because the philtrum will be elongated, and moreover, perplexing adverse effects such as disrupting speech and drooling may happen. It is necessary to perform the starch–iodine test prior to injection except the scalp. Since the scalp is a difficult area to do a starch–iodine test on, history taking is the only method to find the hyperhidrotic area.

Regarding the dose, 1 U/cm^2 of BoNT-A is injected intradermally, as per standard procedures. Since the overdose of BoNT-A at the forehead may cause the eyebrows to droop, the initial dosage should not exceed 20 U for the forehead. Further, injection for the forehead should be performed 1 cm above the eyebrows in order to avoid eyebrow drooping (Fig. 6.14). Patients over 40 should be informed of possible eyebrow drooping before the procedure. 10–15 U of BoNT-A is required for the nose (Fig. 6.15). Lateral cheeks over the parotid glands and the masseter are possible sites for injection of BoNT-A with 10–15 U per side similar to the gustatory hyperhidrosis. In case of scalp hyperhidrosis, 100 U is required for the anterior frontal area in front of the bregma, increasing to 200 U when the lateral temporal parts are included and up to 300 U for the entire scalp including the occipital area.

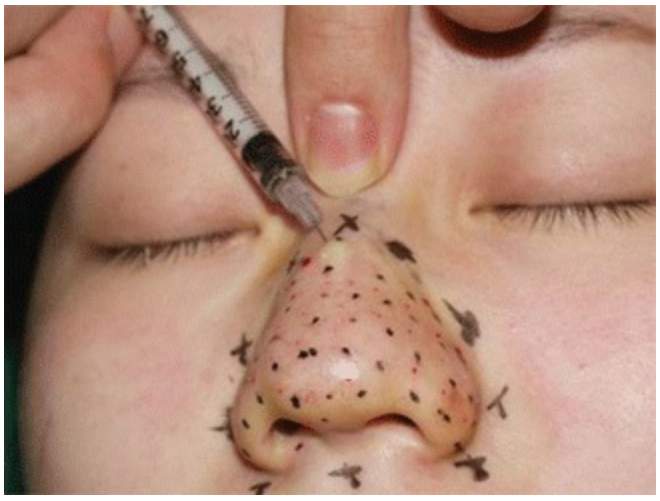


Fig. 6.14 Starch–iodine test (**a**) before and (**b**) 2 weeks after the treatment of forehead hyperhidrosis with 20 U of BOTOX® injection

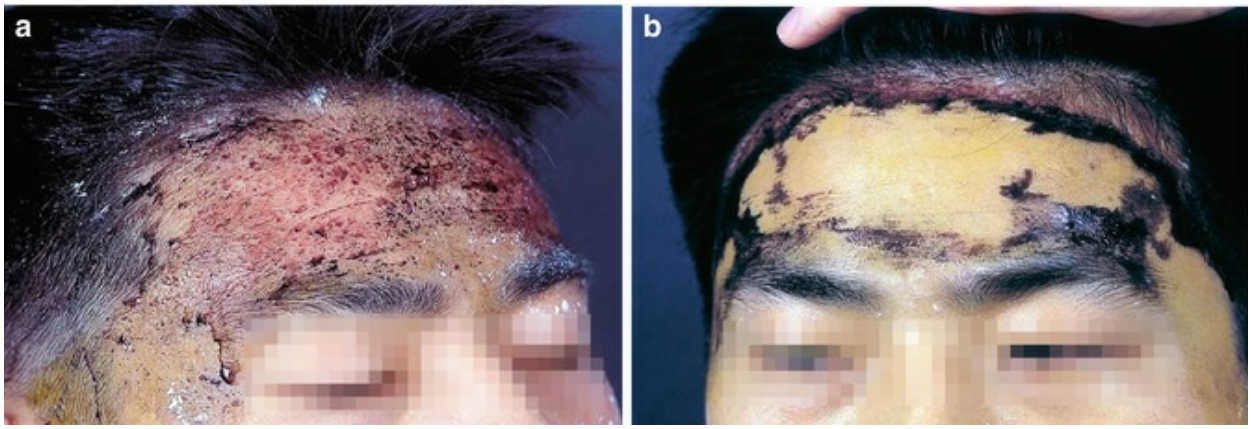
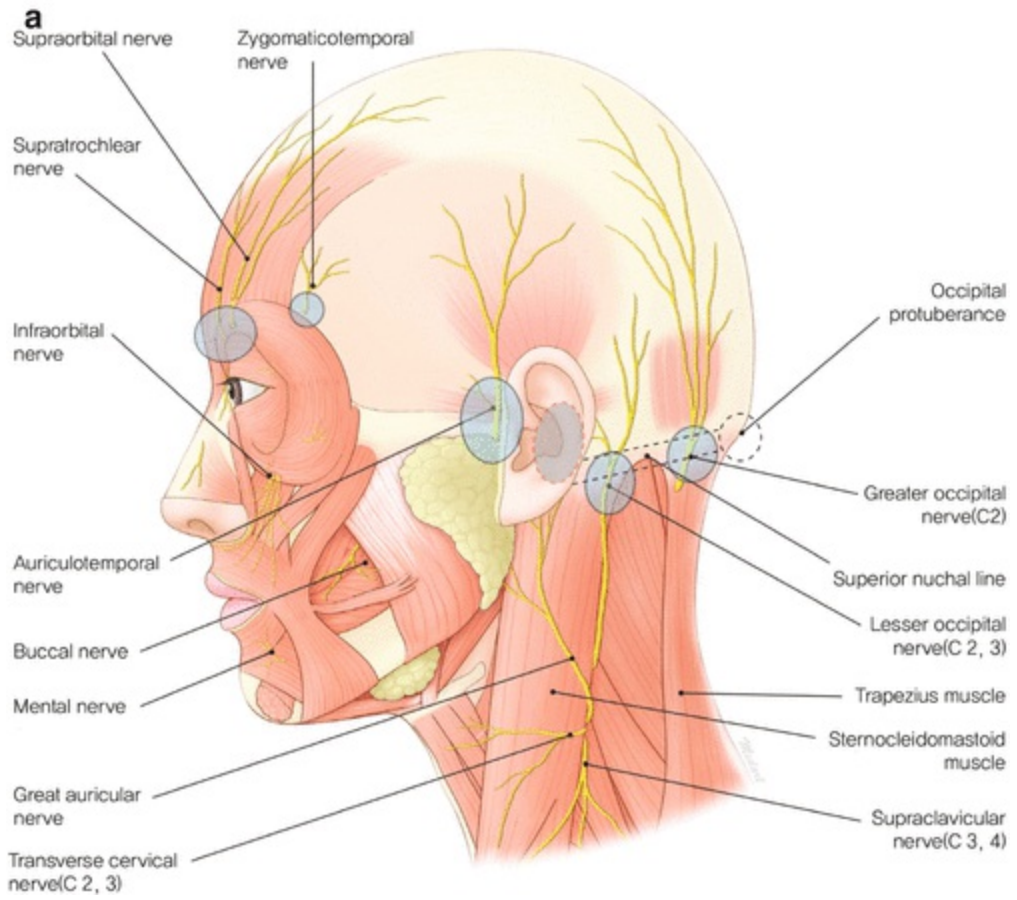


Fig. 6.15 Treatment of nose hyperhidrosis with 12 U of BOTOX®

While application of topical anesthetic ointment for 30–40 min would be sufficient to control the pain for the face, the forehead nerve block targeting supraorbital nerve and supratrochlear nerve should be performed for the forehead (Fig. 6.16a–c). For the entire scalp, either scalp block or a ring block encircling the hairline is recommended (Fig. 6.16d).



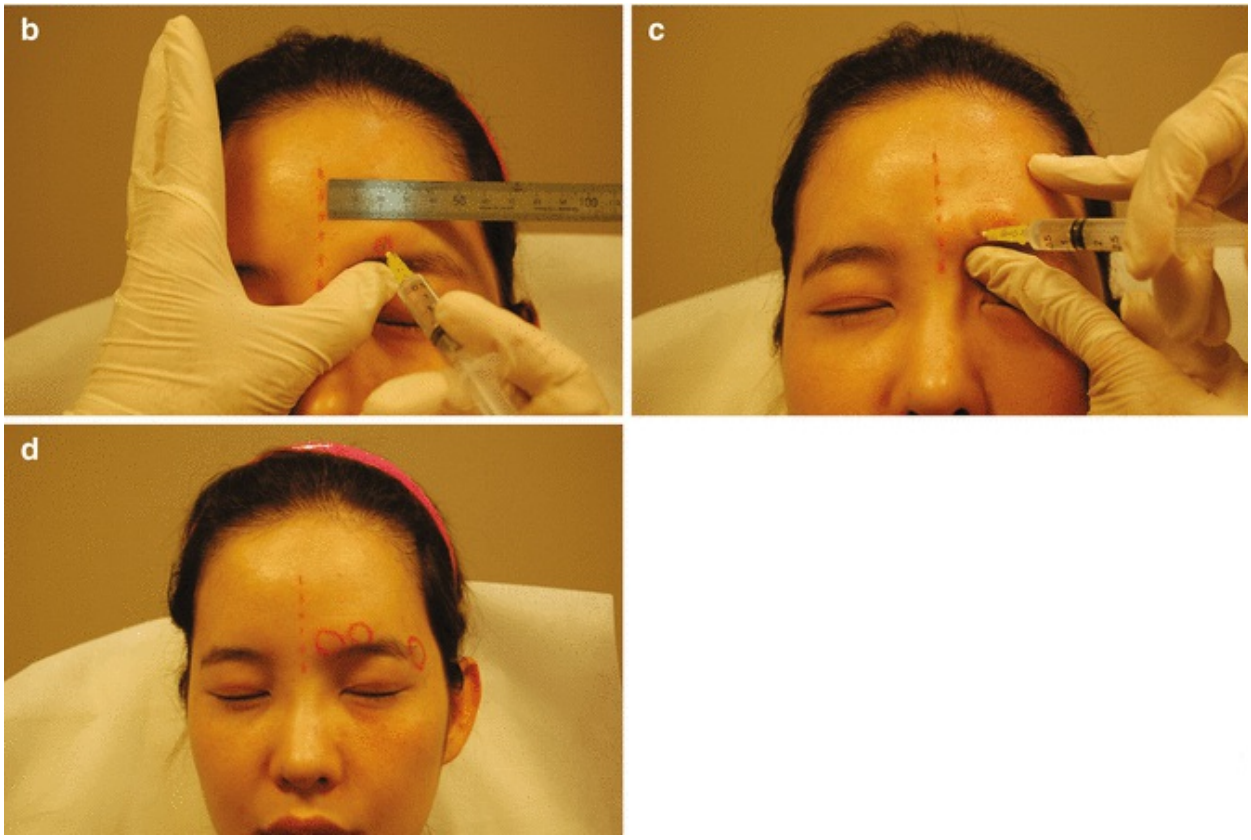


Fig. 6.16 (**a**) Sensory nerves of the face and the scalp, and injection points for the scalp block. (**b**) Supraorbital nerve block. (**c**) Supratrochlear nerve block. (**d**) Scalp block

Regarding adverse effects, patients may occasionally complain of compensatory hyperhidrosis on the philtrum when treating the nose, but this is usually mild. As the face is rich in vascular circulation, precautions should be taken to prevent bruising during the procedure even though bleeding is less likely to happen in case of intradermal injection. Meticulous pressing on the needle marks is necessary to minimize the needle mark. Application of topical anesthetic ointment is helpful for reducing bruising by the action of vasoconstriction.

Tip: Scalp Block

The sensory nerves that innervate the scalp are as follows: the forehead and frontal areas are innervated by the supraorbital nerve and the supratrochlear nerve arising from the ophthalmic branch of the trigeminal nerve, the occipital area is innervated by the greater occipital nerve and the lesser occipital nerve, and the temporal area is innervated by the zygomaticotemporal nerve, the auriculotemporal nerve, and the great

auricular nerve (Fig. 6.16a). It is called a scalp block when anesthesia is applied to six nerves: the supraorbital nerve, supratrochlear nerve, greater occipital nerve, lesser occipital nerve, zygomaticotemporal nerve, and auriculotemporal nerve.

In a forehead nerve block, the supraorbital and supratrochlear nerves are targeted. 1 ml of lidocaine is injected over the frontal bone after palpating the supraorbital notch and the supraorbital foramen medial to the orbital rim; the supraorbital nerve comes out through the supraorbital foramen. If the foramen is not palpated, lidocaine is injected into the point 20–25 mm lateral to the medial sagittal plane (Fig. 6.16b). The supratrochlear nerve often comes out from the same supraorbital foramen, but in case it does not by occasion, it can be found approximately 5–10 mm medial to the foramen. Therefore, an additional 1 ml of lidocaine is injected into the 10 mm medial point to the supraorbital foramen (Fig. 6.16c).

The greater occipital nerve arises from the C2 cervical nerve and perforates the muscle in the lower occipital area before spreading upward to provide sensation to the occipital area. The perforating point is located 2.5 cm lateral to the external occipital protuberance along the superior nuchal line, approximately medial one-third point between the external occipital protuberance and the mastoid process. As the greater occipital nerve is located just medial to the occipital artery, injections should be made medial to the artery following palpation.

The lesser occipital nerve arising from the C2 and C3 cervical nerves comes out from the posterior border of the sternocleidomastoid muscle at the point lower 6/10 between mastoid process and the origin site of the clavicle. Then, it runs toward the mastoid process until it perforates the muscle 2.5 cm lateral to the greater occipital nerve along the superior nuchal line, approximately lateral one-third point between the external occipital protuberance and the mastoid process. It also provides sensation to the lower occipital area.

The zygomaticotemporal nerve arises from the maxillary branch of the trigeminal nerve and provides sensation to the temporal area. The injection point is the superolateral margin of the orbital rim lateral to the eyebrow (Fig. 6.16d). The auriculotemporal nerve arises from the mandibular branch of the trigeminal nerve covering the scalp area in front and above the ear. Subcutaneous injection should be performed to block the auriculotemporal nerve at the point 1–1.5 cm anterior to the tragus. As the superficial temporal

artery runs just in front of the nerve, care should be taken not to inject into the artery [25].

The greater auricular nerve arises from the C2 and C3 cervical nerves that perforate from the border of the sternocleidomastoid muscle at the midpoint between the mastoid process and clavicle, entwines the muscle, and runs to the tragus. The posterior branch of the great auricular nerve provides sensation to the scalp behind the auricle and mastoid process. Lidocaine is injected at the point 1 cm behind the ear at the level of the tragus.

As the nerve block is not always successful, lidocaine can be injected along the line encircling from the whisker to the posterolateral hairline (ring block) for the lateral part of the scalp. 2 ml of 2 % lidocaine is an appropriate volume in each site (the supraorbital and supratrochlear nerves are regarded together as one site). When 2% lidocaine is injected along the line of a ring block, the total volume should not exceed 20 ml for safety.

6.2.5 Gustatory Hyperhidrosis

Gustatory hyperhidrosis is observed in 10–30 % after the parotid gland extirpation. Post-op abnormal regeneration of the parasympathetic fibers toward the eccrine gland and subcutaneous blood vessels between the otic ganglion and the parotid glands is the probable explanation. Flushing and sweat appear via gustatory stimulation over the preauricular and neck area where previously the parotids glands were located. As these symptoms are particularly noticeable while dining, it may be disruptive in one's social or professional life.

Gustatory hyperhidrosis can be significantly improved by BoNT-A. In 2009, de Bree et al. reported dramatic improvement from 3 to 7 injections of BoNT-A with the dose of 7.5 U/4 cm^2 in 22 patients with gustatory hyperhidrosis. The affected areas decreased according to the repeated injections: 54.2 cm^2 at the initial injection, 25.6 cm^2 at the second, and 16.0 cm^2 at the third. Efficacy lasted for 5.6, 9.6, and 15.1 months at the first, second, and third injections, respectively. Most of the patients showed nearly cure after repeated injection of BoNT-A [18]. This report may also suggest that the parasympathetic nerves do not regenerate well. Therefore, BoNT-A seems to be the treatment of choice for the gustatory hyperhidrosis when considering efficacy and safety. The BoNT-A is injected intradermally 1 cm apart with BOTOX® 1 U/cm^2 and Dysport®2 U/cm^2.

6.2.6 Compensatory Hyperhidrosis

Effect (A), Adverse Effect (A), and Technique (B)

Compensatory hyperhidrosis which may occur after the endoscopic transthoracic sympathectomy (ETS) is the most frequent observed side effects following ETS in 50–75 % of patients [8]. While sweating is generally not severe, it seriously disrupts daily life in some patients.

To treat compensatory hyperhidrosis with BoNT-A, a starch–iodine test should be performed before the procedure to identify the hyperhidrotic area (Fig. 6.17). Application of topical anesthetic ointment for 30–40 min would be sufficient to control the pain for compensatory hyperhidrosis. A total of 200–500 U is injected, 0.5–1 U/cm^2 as per standard. It is strongly advised not to exceed 500 U at one time in order to avoid possible adverse systemic effects.

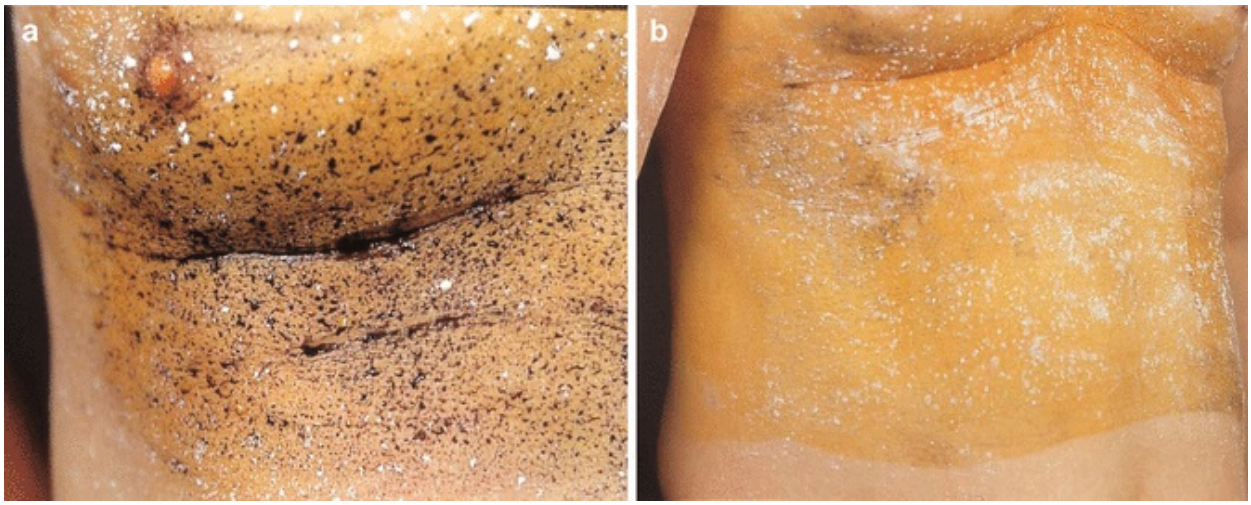


Fig. 6.17 Starch–iodine test (**a**) before and (**b**) 2 weeks after the treatment of compensatory hyperhidrosis at the abdomen with 300 U of BOTOX®

6.2.7 Bromhidrosis/Osmidrosis

The foul odor associated with sweat can be classified into three types: a slightly acidic smell in an excessively sweaty person, a peculiar odor which mainly originates from apocrine gland secretions, and a foot odor that occurs when sweat-soaked keratin degrades by various bacteria. Eccrine glands are found all over the body, while apocrine glands are mainly confined to the axilla, around the papilla, and perianal areas. The major component of eccrine gland secretion is water; in contrast the secretion of the apocrine glands is

rich in protein. The protein itself does not produce odor, but protein degraded by normal flora in the skin produces peculiar odor. Bromhidrosis causes discoloration of the clothes due to large amounts of protein, but more importantly it disrupts the social activities with a psychological distress.

Apocrine secretion is mainly controlled by catecholamine while cholinergic stimulations may play a role. But its receptor and secretory process are not well known. Lindsay et al. demonstrated the presence of beta-2 and beta-3 receptors of adrenaline, but no cholinergic receptors, in the apocrine glands [26]. In contrast to eccrine glands, no nerve fibers were found near the apocrine glands. This suggests that apocrine glands are influenced by catecholamine through humoral effects different from eccrine glands influenced by sympathetic nerve fibers [26].

To treat bromhidrosis, liposuction or the Inaba method, which curettes apocrine sweat glands in the subcutaneous tissue, is commonly performed. BoNT-A, proven effectively treating axillary hyperhidrosis, has been also tried for bromhidrosis. According to Heckmann's study in 16 healthy volunteers suffering from severe body odor, the odor decreased significantly after a 100 U injection of Dysport® in the axilla, as measured by a T-shirt sniff test [27]. In a randomized double-blind intra-comparison study in 51 healthy volunteers conducted by the same research team, 50 U of BOTOX® significantly reduced the severity of the smell in treated side compared to the control group, as measured by a sniff test [28].

Importantly, the odor of patients with bromhidrosis cannot completely disappear since apocrine glands are almost entirely controlled by adrenaline. He et al. reported a close positive relationship between the malodor and sweating in patients with bromhidrosis showing good results for BoNT-A treatment, remarking that the sweating could be used as a good marker for the suitability for BoNT-A treatment in patients with bromhidrosis [29]. His findings suggested that the decrease in eccrine sweat caused by the BoNT-A may affect apocrine secretions rather than directly affecting the apocrine glands themselves. One report claimed that genital odor in males was reduced following BoNT-A injection, with the effect lasting for approximately 9 months [30].

BoNT-A could be used for the treatment of bromhidrosis. However, BoNT-A seems to be helpful in patients showing simultaneous axillary hyperhidrosis and bromhidrosis. Importantly, it is necessary to inform the patients that the odor may decrease but not completely disappear prior to

treatment. In bromhidrosis, 50 U is injected in one side of the axilla as in axillary hyperhidrosis.

6.2.8 Other Diseases Responsive to Botulinum Toxin

Chromhidrosis is a rare disease that causes colored sweat on the face and axilla. As the lipofuscin granule is found in the apocrine epithelial cells, it has been suggested that the color originates from apocrine sweat glands [31]. Drugs as well as food have also been suggested as the causative agents; however, a definitive remains elusive. There have been several recent studies on the efficacy of BoNT-A for the treatment of chromhidrosis. There was one case report that noticeable improvement of chromhidrosis in the zygomatic area was observed 19 weeks after treatment with the BoNT-A [32]. Another report, in speculating on the efficacy of BoNT-Ain treating chromhidrosis, suggests that the coloring is caused by eccrine glands rather than apocrine glands, thus explaining why the BoNT-A is effective [33].

Eccrine hidrocystoma is a small, multiple, clear nodular translucent benign tumor of eccrine origin that primarily occurs around the eyes and zygomatic areas. Single nodule is usually removed by surgery, but in case with multiple lesions, BoNT-A has proven to be effective. 1 U of the BoNT-A is injected, with special care taken not to administer overdose into the zygomatic area lest the BoNT-A adversely affects the zygomaticus major muscle. Injections should be repeated every 5–6 months as needed (Fig. 6.18) [34, 35].

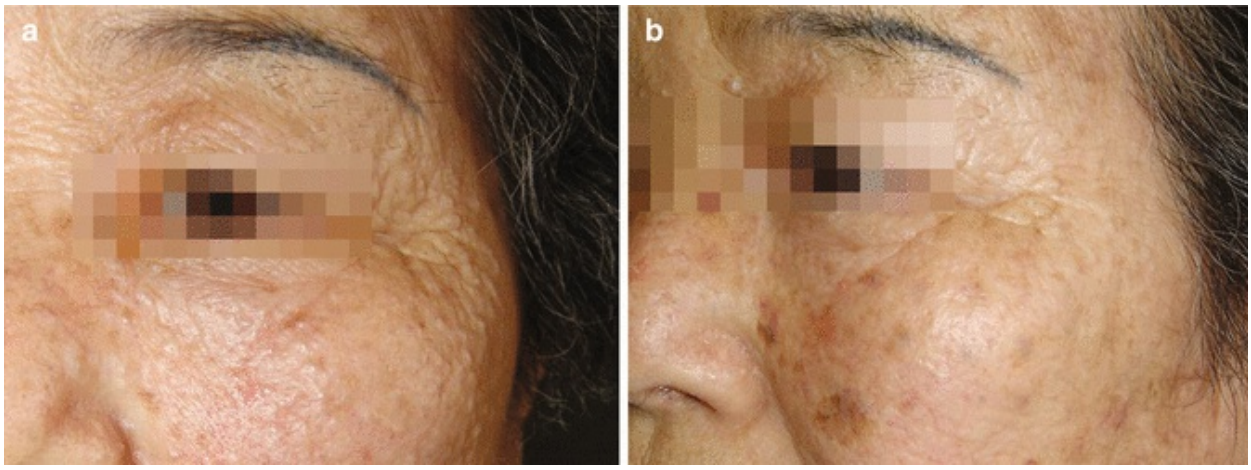


Fig. 6.18 Eccrine hidrocystoma, (**a**) before and (**b**) 2 weeks after injection of 10 U botulinum toxin per side (Photo, courtesy of dermatologist Sook-kyung Lee)

6.2.9 Effects of Botulinum Toxin Type B on Focal Hyperhidrosis

Botulinum toxin type B (BoNT-B) shows a more rapid effect for the treatment of focal hyperhidrosis with no major difference in duration of efficacy compared with BoNT-A. However, overdose of BoNT-B may more frequently result in systemic adverse effects such as xerostomia. BoNT-B is generally known to have a lower potency than type A; thus, higher doses of the BoNT-B are necessary. However, when treating hyperhidrosis, BoNT-B's conversion ratio is reported to be much lower than in the muscle. Comparing the potency between BoNT-A and BoNT-B, the conversion ratio was known to be 1:50–100 (BOTOX® to Myobloc®) in neuromuscular junction [36], but in the sweat gland, it is low as 1:20 [37]. When the efficacy of 2000 U of BoNT-B per side of the axilla was compared with 100 U of BOTOX® for the treatment of axillary hyperhidrosis, 2000 U of BoNT-B per side showed comparable results with 100 U of BOTOX® in which efficacy lasts 16 weeks compared with 100 U of BOTOX® [38]. Since the affinity of BoNT-B is believed to be higher in sympathetic nerve ending than in neuromuscular junctions [39], 1000–2000 U of BoNT-B per side is widely used for the treatment of axillary hyperhidrosis based on the conversion factor, BOTOX® to Myobloc® = 1:10–30. Similar results were obtained from my comparative study on the potency between BoNT-A and BoNT-B for the treatment of the axillary hyperhidrosis in 24 patients in which 1500 U of Myobloc® per side showed comparable efficacy and duration up to 20 weeks with 50 U of BOTOX® per side when the conversion ratio is estimated at 1:30 [40].

A clear disadvantage of BoNT-B is the increased preponderance of systemic adverse effects such as xerostomia and dysphagia. In a double-blind comparative study comparing BoNT serotypes A and B for the treatment of cervical dystonia in 139 patients, both showed similar efficacy at 4 weeks after injection. However, the duration of efficacy of serotype B was a little shorter than serotype A, but adverse effects were more common in the serotype B group: xerostomia (A:B = 41 %:80 %) and dysphagia (A:B = 19 %:48 %) [41].

Similar trend was also observed in palmar hyperhidrosis as well. According to the study on the effect of BoNT-A type B for the treatment of palmar hyperhidrosis in 20 patients performed by Baumann et al., the hyperhidrosis rapidly improved after 1 week, and efficacy lasted on average

3.8 months after injecting 5000 U of the BoNT-A per hand [42]. However, 90 % of patients experienced xerostomia and dry throat. In addition, excessive dryness of the hand (60 %), muscle weakness (60 %), and decrease in grip power (50 %) were also observed [39]. However, another study on the treatment of axillary hyperhidrosis with 2500 U of BoNT-A type B per side in 20 patients conducted by the same researchers showed no cases of xerostomia, while the duration of efficacy lasted for approximately 5 months, a longer efficacy period than the palmar hyperhidrosis (3.8 months) [43]. Significantly, in my own clinical study using 1,500 U of BoNT-A type B per side in patients with axillary hyperhidrosis, no patients reported xerostomia [40]. Based on the aforementioned studies, xerostomia will likely be avoided if the dose of BoNT-A type B is injected less than 5000 U for one session of injection. But over 10,000 U of BoNT-A type B is much more likely to cause severe systemic adverse effects.

In summary, 1000–1500 U of BoNT-A type B is recommended for the treatment of axillary hyperhidrosis and 3000–5000 U for the treatment of palmar hyperhidrosis. If axillary hyperhidrosis and palmoplantar hyperhidrosis are to be treated concurrently, it is recommended to perform the treatment at the interval of at least 2 months apart in order to avoid systemic adverse effects such as xerostomia. BoNT-A type B is not recommended for the treatment of compensatory hyperhidrosis since high dose of BoNT-A type B is required to cover the wide application area.

Tip: Coping with the Systemic Adverse Effects of Botulinum Toxin Type B

If severe xerostomia and dysphagia occur following BoNT-A type B treatment, pilocarpine has been shown to be effective [44]. It is a muscarinic receptor agonist that is often used to treat xerostomia in patients with head and neck cancer following radiation therapy. Dosage is usually 5 mg, taken three times a day. Pilocarpine may cause chills, headache, and fatigue as adverse effects.

The author also experienced severe xerostomia and dry throat in a 20-year-old female patient with palmoplantar hyperhidrosis after BoNT-A type B treatment when I first used the BoNT-A type B for the treatment of focal hyperhidrosis. She was injected 5000 U in each side of the palms and soles, totaling 20,000 U at one time. Without much trouble, the xerostomia and dry throat were controlled by pilocarpine.

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