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RimabotulinumtoxinB versus OnabotulinumtoxinA in the Treatment of Masseter Hypertrophy: A 24-Week Double-Blind Randomized Split-Face Study

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Key Words
Botulinum toxin · Masseter hypertrophy · OnabotulinumtoxinA · RimabotulinumtoxinB

Abstract
Background: Masseter hypertrophy can be ameliorated by botulinum toxin. ***Objective:*** To compare the efficacy and safety of RimabotulinumtoxinB (BTX-B) and OnabotulinumtoxinA (BTX-A) in the treatment of masseter hypertrophy. ***Methods:*** Sixteen women with bilateral masseter hypertrophy received single injections of BTX-A or BTX-B at a dose ratio of 1:50 or 1:70 in a 24-week double-blind randomized split-face study. ***Results:*** Both BTX-A and BTX-B produced significant improvements in masseter hypertrophy. The maximum volume reduction, as determined by computed tomography scanning, at week 12 was comparable between BTX-A and BTX-B at a dose ratio of 1:70 (15.6 and 14.2%, respectively). At week 24, only masseters treated with BTX-A maintained a significant volume reduction. Investigator ratings and patient satisfaction scores paralleled objective computed tomography measurements. ***Conclusion:*** Both BTX-A and BTX-B are effective in the treatment of masseter hypertrophy. BTX-B, at a dose ratio of 1:70, has a comparable efficacy but a shorter duration of action than BTX-A.

Introduction

The lower facial contour is determined by the size and width of the mandibular bone and surrounding masseter muscles as well as the amount of subcutaneous fat [1]. Masseter hypertrophy, resulting in a so-called square face, is characterized by a unilateral or bilateral benign enlargement of the masseter muscles and is frequent in Asians, occurring in association with ethnic differences and mastication habits [2]. As Asian women do not consider this condition aesthetically pleasing, there is a steady demand to create a slimmer profile of the lower face, achieved through mandibular contouring carried out ei-

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ther surgically or non-surgically. Surgical treatments, such as ostectomy, neurectomy or masseter muscle resection, pose a risk of bleeding, hematoma, persistent swelling and facial nerve injury. Non-surgical options include pharmacotherapy in the form of muscle relaxants, dental restoration and occlusal adjustments, albeit with limited degrees of success [2]. In the mid-1990s, a novel, off-label non-surgical approach using botulinum toxin was introduced [3]. The technique quickly became widespread due to its efficacy and safety [2]. According to the literature, 30 U of OnabotulinumtoxinA (BTX-A; Botox®, Allergan Inc., Irvine, Calif., USA) is effective in the treatment of masseter hypertrophy [4–6]. Another serotype of botulinum toxin, RimabotulinumtoxinB (BTX-B; Myobloc®, Solstice Neurosciences, Inc., South San Francisco, Calif., USA), has also shown good efficacy and safety profiles in various cosmetic indications [7–9]. As the two forms differ antigenically, BTX-B may be effective in patients with failure of or resistance to BTX-A [10, 11]. However, there are as yet no studies comparing the clinical efficacy of BTX-B with that of BTX-A for masseter hypertrophy. Thus, the objective of this study was to compare the efficacy and safety of BTX-B and BTX-A in the treatment of masseter hypertrophy and to determine the optimal dose ranges for BTX-B.

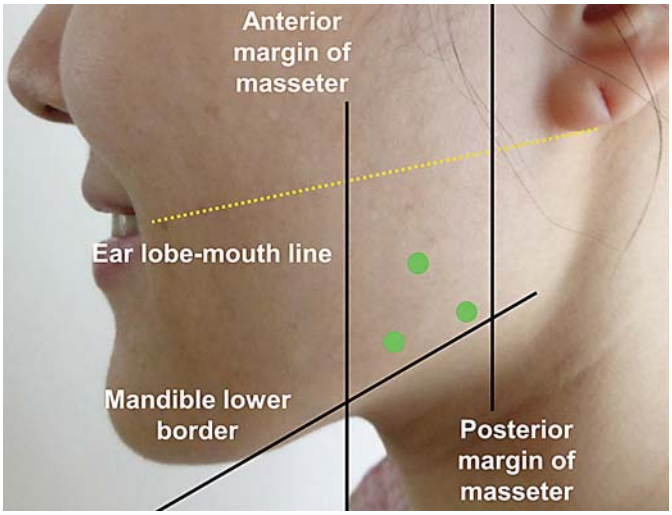

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Fig. 1. Injection site diagram for treating masseter hypertrophy. An arbitrary connecting line from the ear lobe to the corner of the mouth was used as the reference line. Below this line, we injected three points, forming the apex of an imaginary triangle toward the prominent point of the muscle formed when the jaw was clenched.

Patients and Methods

Patients

Sixteen Korean women, aged 20–40 years and with a clinical diagnosis of widened lower facial contour with hypertrophic masseter muscles, were enrolled in this study. Exclusion criteria were botulinum toxin injections into the masseter muscle within the last 12 months, substantial asymmetry, a history of allergic reaction to botulinum toxin or human serum albumin, pregnant or nursing women, and those with neuromuscular disorders such as myasthenia gravis or evidence of peripheral neuropathy. The procedures, benefits, risks and potential complications associated with the study were explained, and written informed consent was obtained from each participant before study entry. The study conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the local Institutional Review Board.

Study Procedures

This study was designed as a 24-week prospective double-blind randomized split-face study. Participants were randomized to receive BTX-A and BTX-B at dose ratios of 1:50 or 1:70. In addition, each participant was further randomized to receive BTX-A and BTX-B in either the right or left masseter. We used a fixed dose (30 U) of BTX-A, injected into the masseter muscle on one side, and either 1,500 U or 2,100 U of BTX-B, injected symmetrically into the muscle on the other side. The percutaneous intramuscular injection of botulinum toxin into the masseter muscles, identified by palpation, was performed using a 30-gauge needle. An arbitrary connecting line from the ear lobe to the corner of the mouth was used as the reference line. Below this line, we injected three points, forming the apex of an imaginary triangle toward the prominent point of the muscle formed when the jaw was clenched (fig. 1).

Outcome Measurements Reported by an Investigator and the Participants

All study participants were assessed at baseline and at each follow-up visit (weeks 4, 12 and 24). Standardized photographs were taken using identical camera settings (Nikon D80, Tokyo, Japan), lighting and patient positioning. Using these photographs, four board-certified dermatologists (S.E. Chang, J. An, C.S. Youn, G.-H. Park) unaware of the treatment allocations scored the degree of change using a 4-point scale ranging from 0 (no change) to 3 (markedly improved facial contour). The averaged values were used in the statistical analyses. The volume changes of the masseter muscle were objectively investigated by obtaining a computed tomography (CT) scan of the head at baseline (prior to toxin injection) and at each follow-up visit. Thyroid collars were used to protect the thyroid glands during scan acquisition. Non-contrast CT images were obtained as 1-mm-thick contiguous sections. The outlines of the masseter muscle of each side were manually traced and the entire masseter volume was determined. Specifically, cross-sectional areas were measured using the Rapidia image processing software (INFINITT Co., Ltd., Seoul, Korea) in soft tissue mode (window width 100, window level 20) and masseter muscle volume was calculated by summing all of the cross-sectional areas multiplied by the slice thickness. Both the tracing and the volume determination of the masseter muscle were repeated five times by one investigator. The highest and lowest values were discarded to

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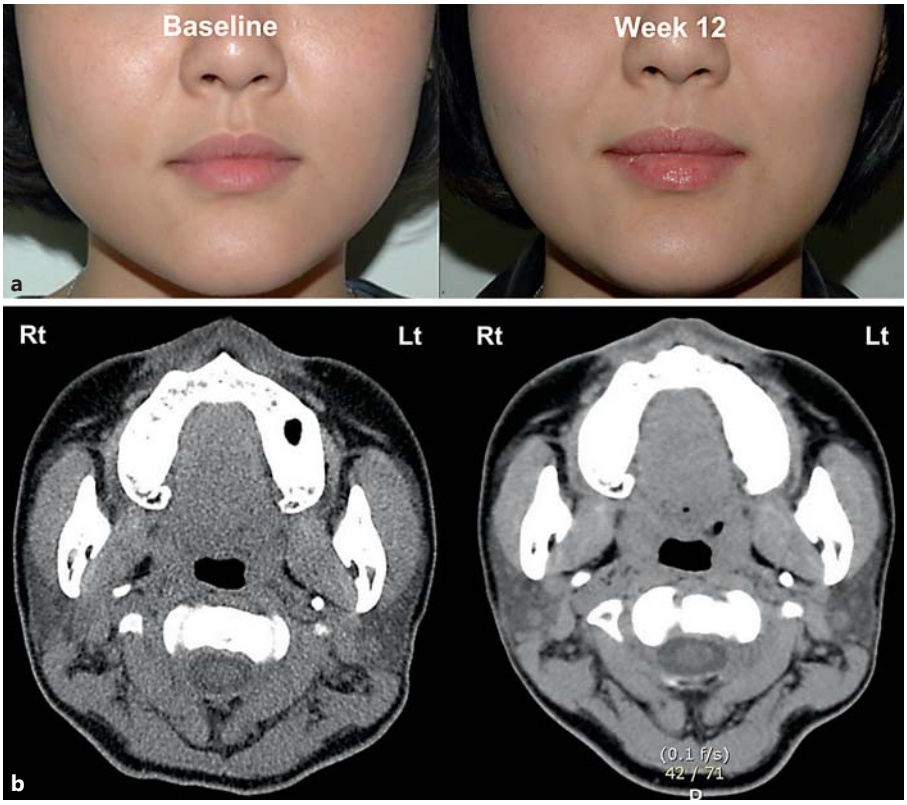

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Fig. 2. Representative digital photographs and CT images showing differential improvements during the study. The left masseter of this woman's face was treated with BTX-A and the right with BTX-B. Both botulinum toxins produced remarkable improvements in masseter hypertrophy. The muscle volumes of the right and left masseters were determined; the former exhibited an 87% reduction and the latter an 83% reduction of the original (baseline) volume. **a** Clinical photographs. **b** CT images.

eliminate outliers, and the mean of the remaining three values was set as the masseter muscle volume. The participants were also asked to rate their own satisfaction using a 5-grade scale, from 0 (completely dissatisfied) to 4 (completely satisfied). In addition, any subjective complaints by the participant were recorded at each visit.

Statistical Analysis

Statistical analysis was carried out using the Mann-Whitney test or the Wilcoxon signed-rank test using SPSS software (version 12.0, SPSS, Inc., Chicago, Ill., USA); $p < 0.05$ was considered statistically significant.

Results

All enrolled patients were naïve to botulinum toxin. Of the 16 women enrolled, 15 completed the study (mean age 32 ± 8 years). One participant dropped out after 4 weeks due to pregnancy. Seven patients received injections of 30 U BTX-A and 1,500 U BTX-B (1:50 dose ratio), and eight patients received injections of 30 U BTX-A and 2,100 U BTX-B (1:70 dose ratio). Neither the ages of the participants nor the baseline CT volume of the masseter muscle statistically differed between the two groups.

Table 1. Changes in the investigators' assessment of improvements during the 24-week study period (95% confidence interval in parentheses)

	BTX-A (30 U)	BTX-B (1,500 U)	BTX-B (2,100 U)
Week 4	1.6 (1.4–1.9)	1.3 (0.9–1.7)	2.0 (1.4–2.5)
Week 12	2.2 (1.9–2.5)	1.8 (1.2–2.3)	2.1 (1.7–2.5)
Week 24	1.7 (1.3–2.1)	1.0 (0.4–1.7)	1.5 (0.9–2.0)

Both BTX-A and BTX-B produced remarkable improvements in the lower face contours, as documented by CT scan and in clinical photographs (fig. 2). The investigators' ratings of the improvements in the BTX-A group increased from 1.6 at week 4 to 2.2 at week 12, with a final value of 1.7 at week 24. For the BTX-B group, the corresponding scores (1,500 U and 2,100 U, respectively) were 1.3 and 2.0 at week 4, with a peak at week 12 (1.8 and 2.1), and final values of 1.0 and 1.5 at week 24 (table 1, fig. 3). However, there was no significant difference between the BTX-A and BTX-B scores in these photographic assessments. The satisfaction scores of the participants con-

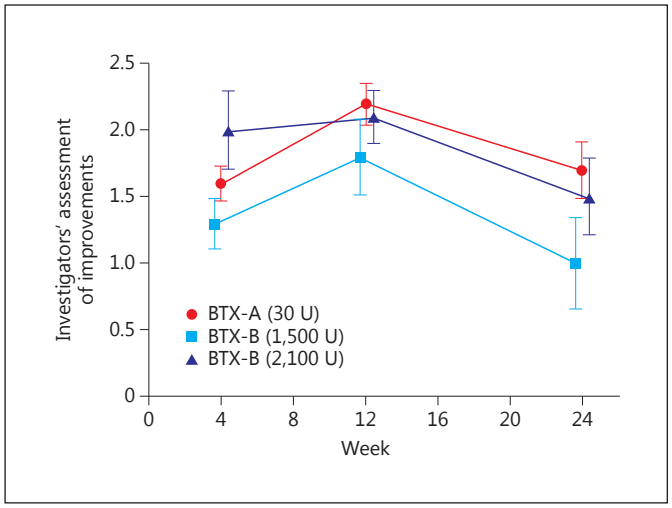

Fig. 3. Changes in the investigators' assessment of improvements during the 24-week study period. Statistical significances were tested by Mann-Whitney and Wilcoxon signed-rank test. Error bars denote standard errors of the mean.

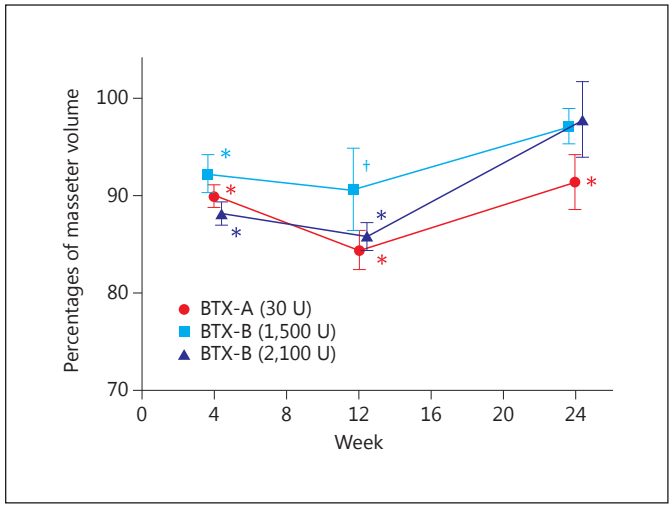

Fig. 4. Changes in the percentages of masseter volume during the 24-week study period. Statistical significances were tested by Mann-Whitney and Wilcoxon signed-rank test. * $p < 0.05$ vs. baseline (week 0); † $p < 0.05$ vs. BTX-A. Error bars denote standard errors of the mean.

Table 2. Changes in the percentages of masseter volume during the 24-week study period (95% confidence interval in parentheses); baseline volume was defined as 100%

	BTX-A (30 U)	BTX-B (1,500 U)	BTX-B (2,100 U)
Week 4	89.9 (87.7–92.2)	92.2 (88.8–96.1)	88.2 (85.9–90.5)
Week 12	84.4 (80.6–88.3)	90.6 (82.4–98.9)	85.8 (83.0–88.5)
Week 24	91.4 (85.9–96.9)	97.1 (93.5–100.7)	97.8 (90.2–105.4)

curred with these improvements. The mean participant satisfaction score at 12 weeks post-injection was 2.9 ± 0.9 for BTX-A, 2.2 ± 0.8 for 1,500 U BTX-B, and 2.7 ± 0.8 for 2,100 U BTX-B. Further quantification of CT images revealed that the two serotypes induced a significant amelioration of masseter hypertrophy. Masseter volume, expressed as percentage compared to baseline, of the BTX-A-treated sides was 89.9% at week 4 ($p < 0.05$ vs. baseline), 84.4% at week 12 ($p < 0.05$ vs. baseline) and 91.4% at week 24 ($p < 0.05$ vs. baseline). On the BTX-B-treated sides, the percentages were 92.2 and 88.2% at week 4 (1,500 U and 2,100 U, respectively, $p < 0.05$ vs. baseline), 90.6 and 85.8% at week 12 (1,500 U and 2,100 U, respectively, $p < 0.05$ vs. baseline for 2,100 U) and 97.1 and 97.8% at week 24 (1,500 U and 2,100 U, respectively) (table 2, fig. 4). At a dose ratio of 1:70, both toxins showed a comparable efficacy in maximum volume reduction (15.6 and 14.2% for BTX-A and BTX-B, respectively), which occurred at week 12. However, while the BTX-A-treated masseters continued to show significant efficacy at week 24, those treated with BTX-B returned to their original volume as measured by quantification of CT images.

The adverse events included one participant who complained of a slightly awkward facial expression when smiling, two who had xerostomia symptoms lasting 3–4 weeks, one who reported a headache immediately after injection, and two who had transient injection site pain associated with BTX-B injection. There were no serious adverse events associated with treatment, nor were there any cases of sunken cheek, dysphagia or systemic complications during the study.

Discussion

Cosmetic sculpturing of the lower face using botulinum toxin has been accepted as an effective and safe alternative to invasive surgical managements [2]. However, no single conversion ratio exists between different serotypes of the toxin [12] nor have there been any comparative split-face trials using BTX-A and BTX-B for the treatment of masseter hypertrophy. We therefore investigated dose ratios for BTX-B that may approximate 30 U BTX-A

in terms of efficacy in the treatment of masseter hypertrophy in a split-face study.

Using dose ratios of BTX-B to BTX-A of 50:1 and 70:1, we found that both toxins at the latter dose exhibited comparable efficacy with respect to maximum volume reduction 12 weeks after treatment. However, sustainability of muscle volume reduction was greater with BTX-A. These differences in duration of action were consistent with previous reports in which BTX-A and BTX-B were used for other indications [12]. Previous studies with BTX-A showed a maximum effect at 10–12 weeks [1, 5].

Morphometric analysis, electromyographic measurements and imaging modalities such as ultrasonography and CT have been used to objectively evaluate aesthetic improvements in the lower facial profile following treatment. CT scanning, considered to be the gold standard in confirming a clinical suspicion of masseter hypertrophy [2], showed a 21–30% volume reduction with BTX-A (Botox and Dysport) at 12 weeks post-treatment [6, 13]. In this study, masseter volume was calculated by the reconstruction of 1-mm-thick cross-sectioned CT images in order to improve the precision and reliability of the post-treatment evaluations. Compared to previous reports in the literature, in which CT scans with thicker sections were obtained, the 1-mm-thick cross-sectioned images acquired in this study provided a more precise and thorough representation of the treated masseter muscles. Among our follow-up time points, we found that the peak volume reduction of 15.6 and 14.2%, achieved with BTX-A and BTX-B, respectively, occurred 12 weeks post-injection. The volume reduction by BTX-A in this study was slightly less than that in previous reports in which the same BTX-A preparation (Botox) was used [5, 6], but comparable to that in a recent publication that measured volume changes by using thinner (5-mm-thick) CT sections [14]. Moreover, unlike previous studies in which follow-up by CT scanning was performed until 12 weeks after treatment [5, 6, 13, 15], our study participants were followed for 6 months, using CT scans to investigate the long-term efficacy of the two botulinum toxins. Whereas the BTX-A-treated sides continued to show a significant reduction compared to the baseline volume, on the BTX-B-treated sides the volume nearly returned to the baseline level 6 months post-treatment. This long-lasting effect of BTX-A has been attributed to an incomplete recovery of muscle function and to disuse atrophy [6, 16, 17].

Adverse event profiles associated with botulinum toxin treatment for masseter hypertrophy reportedly include swelling, bruising, injection site pain, headache, change in bite force, speech disturbance, muscle pain, facial asymmetry, xerostomia and prominent zygoma [18]. In our study, one patient complained of transient injection site pain after BTX-B injection. There are several reports that BTX-B injections cause more pain than BTX-A injections [7, 19]. Although the relative contribution of each toxin in the appearance of xerostomia could not be identified here, BTX-B is known to have a greater risk of inducing xerostomia than BTX-A [10].

In this study, we demonstrated that both BTX-A and BTX-B were effective in the treatment of masseter hypertrophy. This study has several limitations: (1) small sample size; (2) employment of a relative rating scale which assesses the degree of change and requires patient and physician to remember the degree of severity at baseline; (3) possibility of inaccurate split-face assessments which may regress towards an average; (4) follow-ups made only at weeks 4, 12 and 24 after the treatment, thus further study with more visits may determine the onset of action and the peak time point of each toxin more precisely. On the other hand, the strengths of our study lie in: (1) double-blind randomization design; (2) post-hoc photograph assessments by four dermatologists unaware of treatment allocations; (3) quantitative assessments of the masseter muscle with CT scanning; (4) long-term follow-up to week 24; (5) detailed publication of the injection paradigm. Conversion ratios between BTX-A and BTX-B were investigated first for this indication. BTX-B, at a dose ratio of 1:70, has a comparable efficacy but a shorter duration of action than BTX-A. Given the shorter duration of action of BTX-B, it probably will not provide additional benefit in the treatment of masseter hypertrophy, except for a few occasions such as existence of neutralizing antibody against BTX-A. BTX-A treatment maintained significant reduction of masseter volume at 24 weeks follow-up. Further studies using higher dose ratios for BTX-B are warranted to elucidate its dose-response relationship and optimal dose ranges. Further dose-finding studies of BTX-B are needed to optimize its use in the treatment of this condition.

Disclosure Statement

Botulinum toxins (Botox Cosmetics and Myobloc) and the cost of CT scanning were provided by DreamPharma (Seoul, Korea), but there was no conflict of interest. There were no funding sources.

References

1 Kim NH, Chung JH, Park RH, Park JB: The use of botulinum toxin type a in aesthetic mandibular contouring. Plast Reconstr Surg 2005;115:919–930.

2 Al-Muharraqi MA, Fedorowicz Z, Al Bareeq J, Al Bareeq R, Nasser M: Botulinum toxin for masseter hypertrophy. Cochrane Database Syst Rev 2009;1:CD007510.

3 Moore AP, Wood GD: The medical management of masseteric hypertrophy with botulinum toxin type A. Br J Oral Maxillofac Surg 1994;32:26–28.

4 Choe SW, Cho WI, Lee CK, Seo SJ: Effects of botulinum toxin type A on contouring of the lower face. Dermatol Surg 2005;31:502–507; discussion 507–508.

5 Park MY, Ahn KY, Jung DS: Botulinum toxin type A treatment for contouring of the lower face. Dermatol Surg 2003;29:477–483; discussion 483.

6 Kim HJ, Yum KW, Lee SS, Heo MS, Seo K: Effects of botulinum toxin type A on bilateral masseteric hypertrophy evaluated with computed tomographic measurement. Dermatol Surg 2003;29:484–489.

7 Carruthers A, Carruthers J, Flynn TC, Leong MS: Dose-finding, safety, and tolerability study of botulinum toxin type B for the treatment of hyperfunctional glabellar lines. Dermatol Surg 2007;33:S60–S68.

8 Sadick N, Sorhaindo L: The cosmetic use of botulinum toxin type B. Int Ophthalmol Clin 2005;45:153–161.

9 Lee DH, Kang SM, Feneran A, Youn CS, Kim JK, Cho S, Won CH, Chang SE, Lee MW, Choi JH, Moon KC: RimabotulinumtoxinB vs. onabotulinumtoxinA for the treatment of forehead lines: an evaluator-blind, randomized, pilot study. J Eur Acad Dermatol Venereol 2013;27:e1–e7.

10 Arezzo JC: NeuroBloc/Myobloc: unique features and findings. Toxicon 2009;54:690–696.

11 Lee SK: Antibody-induced failure of botulinum toxin type A therapy in a patient with masseteric hypertrophy. Dermatol Surg 2007;33:S105–S110.

12 Flynn TC: Botulinum toxin: examining duration of effect in facial aesthetic applications. Am J Clin Dermatol 2010;11:183–199.

13 Yu CC, Chen PK, Chen YR: Botulinum toxin A for lower facial contouring: a prospective study. Aesthetic Plast Surg 2007;31:445–451; discussion 452–453.

14 Kim JH, Shin JH, Kim ST, Kim CY: Effects of two different units of botulinum toxin type A evaluated by computed tomography and electromyographic measurements of human masseter muscle. Plast Reconstr Surg 2007;119:711–717.

15 Chang CS, Bergeron L, Yu CC, Chen PK, Chen YR: Mandible changes evaluated by computed tomography following botulinum toxin A injections in square-faced patients. Aesthetic Plast Surg 2011;35:452–455.

16 Lee CJ, Kim SG, Kim YJ, Han JY, Choi SH, Lee SI: Electrophysiologic change and facial contour following botulinum toxin A injection in square faces. Plast Reconstr Surg 2007;120:769–778.

17 To EW, Ahuja AT, Ho WS, King WW, Wong WK, Pang PC, Hui AC: A prospective study of the effect of botulinum toxin A on masseteric muscle hypertrophy with ultrasonographic and electromyographic measurement. Br J Plast Surg 2001;54:197–200.

18 Kim KS, Byun YS, Kim YJ, Kim ST: Muscle weakness after repeated injection of botulinum toxin type A evaluated according to bite force measurement of human masseter muscle. Dermatol Surg 2009;35:1902–1906.

19 Kranz G, Sycha T, Voller B, Gleiss A, Schnider P, Auff E: Pain sensation during intradermal injections of three different botulinum toxin preparations in different doses and dilutions. Dermatol Surg 2006;32:886–890.