Effects of Botulinum Toxin Type A on Bilateral Masseteric Hypertrophy Evaluated With Computed Tomographic Measurement

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BACKGROUND. A paucity of reports exist on the use of botulinum toxin type A injections as an alternative noninvasive treatment for masseteric hypertrophy.

OBJECTIVE. To evaluate the effects of botulinum toxin type A on masseteric hypertrophy using computed tomography.

METHODS. Percutaneous intramuscular injections of botulinum toxin type A of 30 U per side was carried out in 11 subjects with masseteric hypertrophy. The changes in the masseteric muscle volume before and 12 weeks after injection were evaluated using computed tomography. The changes in the lower facial contours on the photographs were evaluated as excellent, good, fair, and no changes.

RESULTS. Nine of the 11 subjects showed a mean reduction of approximately 22% in the masseteric muscle volume. The maximum reduction was 35.4% (range, 8.1% to 35.4%). Nine subjects showed aesthetically good results with a grade of good or excellent at 12 weeks after treatment.

CONCLUSION. Botulinum toxin injections are a noninvasive alternative method for treating masseteric hypertrophy.

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BOTOX TOXIN type A (BTX-A), a lethal toxin produced by Clostridium botulinum, binds to the presynaptic cholinergic nerve terminals and blocks the release of acetylcholine. It is commonly used for treating a variety of neuromuscular disorders such as strabismus, blepharospasm, hemifacial spasm, and torticollis.1,2

Masseteric hypertrophy (MH) is recognized as an asymptomatic enlargement of one or both masseter muscles. It is commonly associated with abnormal habits such as bruxism and habitual clenching. Recently, there have been a few reports showing that a BTX-A injection into the masseter muscle can be used as an alternative noninvasive treatment for MH.3–7 However, there is a paucity of controlled clinical studies concerning an objective and quantitative evaluation of this.

The purpose of this study was to evaluate objectively the outcome of BTX-A injections for treating bilateral MH in 11 subjects using computed tomography (CT). The quantitative analysis of the masseteric muscle using CT is known as the most reliable and accurate method.8

To the best of the authors’ knowledge, this study is the first to report a prospective clinical trial aimed at evaluating the effect of BTX-A on bilateral MH using CT.

Methods

This study was performed in accordance with the 1975 Declaration of Helsinki. Before admission to the study, a written consent form was obtained from each volunteer after the nature of the study had been fully explained.

After screening by a simple palpation, panoramic view, and cephalography (PA/lateral), a total of 11 volunteers (9 females and 2 males) who had no systemic diseases or dental problems were enrolled in this study. All volunteers were healthy (ASA 1). Their ages ranged from 25 to 45 years, with a mean age of 32.7 ± 6.7 years. All subjects had a bilateral subjective MH.

BTX-A (Botox; Allergan, Urbine) was supplied as a freeze-dried powder of 100 U and was reconstituted with 1 mL of sterile saline to a concentration...
of 10 U/0.1 mL. The reconstituted drug was used immediately, and any surplus was discarded, as the drug must be used within 4 hours of reconstitution. A total of 30 U of the toxin per side were injected percutaneously using a 1-mL syringe with a 30-gauge needle. An arbitrary connecting line was taken from the tragus of the ear to the corner of the mouth and was used as the reference. Five units of the toxin were injected into two points (distance; 1 cm) of the prominent hypertrophic masseter muscle at this line. Another two pairs of injection points (each distance; 1 cm) were decided as 1 cm above and below the reference line, respectively. All subjects were instructed to chew chewing gum for 1 hour after the injection.

The CT measurements of the masseteric muscle volume were performed before and 12 weeks after the injection according to the methods described by Xu et al. The CT examination was performed using an IQ scanner (Picker International), and images were obtained in soft tissue mode (window width 250, window level 60). Four-millimeter contiguous axial scans were performed parallel to the occlusal plane with patients in the rest position.

Initially, the whole masseter volume was measured. The outlines of the masseter muscle of both sides were traced on acetate paper. The tracings were scanned by a flat-bed scanner (Scantouch, Nikon, Japan) with a resolution of 200 dots per inch. The cross-sectional areas were measured using the Scion 3b (Scion Co.) program. The masseteric muscle volume was calculated by summing up all of the cross-sectional areas multiplied by the slice thickness (4 mm).

Both the tracing and measurements of the masseteric muscle volume were carried out five times by one investigator. The maximum and minimum of the five values were discarded, and the average of the other three measurements was regarded as the final masseteric muscle volume.

The clinical photographs and several open questions related to the side effects were taken before and 2, 4, 8, and 12 weeks after the injection. The body weights were also measured at each follow-up time. Five doctors evaluated the changes in the lower facial contour on the photographs as excellent, good, fair, and no changes. The final grade was determined by a majority decision.

Statistical analysis of the difference between pretreatment and posttreatment in the right and left masseter muscle was performed using the Sign test. The Spearman rank correlation analysis was also performed to evaluate the relationship between the pretreatment masseter muscle volume and the posttreatment masseter volume changes. A P value of less than 0.05 was considered to be statistically significant.

Results

The grades of the lower facial changes at 2, 4, 8, and 12 weeks after injection are shown in Table 1. None of the subjects showed marked body weight changes (over 5% of initial body weight) during this study. The earliest change was noticed only 2 weeks after the injection in 2 of 11 subjects. At 12 weeks, the subjects showed marked effects except for two subjects. Two subjects, who underwent apparent changes of the lower facial contour 12 weeks after the injection, are shown in Figure 1.

Two of the 11 subjects dropped out in the CT measurement. The CT images of the subject who underwent apparent changes after the injection are shown in Figure 2. The changes of the masseteric muscle volume were shown in Table 2. The pretreatment and posttreatment volumes of the left masseteric muscle were 27.0 ± 4.9 and 21.7 ± 5.6 cm³, respectively. Those of the right masseteric muscle were 26.6 ± 4.8 and 20.9 ± 4.4 cm³, respectively. There was significant reduction in the masseteric muscle volume in both sides (P = 0.004). The maximum reduction was 35.4%, ranging from 8.1 to 35.4%.

The mean percentage changes in the muscle volume were –22.6 ± 9.2% in the left side and –21.7 ± 6.8% in the right side. Figure 3 shows the correlation between the pretreatment muscle volume and the percentage change in both sides. There was a significant correlation between the pretreatment muscle volume and percentage change in the left side (R = 0.85, R² = 0.72, P = 0.004).

In three subjects (patients 2, 6, and 8) having an initial masseter muscle volume of more than 30 cm³, percentage changes were less than 17%. In contrast to this results, three subjects (patients 1, 4, and 5) with

Table 1. The Grades of the Lower Facial Contour Changes After the Botulinum Type A Toxin Injection Over Time*

<table>
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<tr>
<th>Weeks</th>
<th>Patient Number</th>
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<td>N</td>
<td>F</td>
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<td>N</td>
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<td>N</td>
<td>F</td>
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<td>F</td>
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<td>G</td>
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E = excellent; F = fair; G = good; N = no change.

*Clinical effects are counted if the subject showed over the grade of no change.
Figure 1. Photographs of the two subjects with masseteric muscle hypertrophy (A-1, B-1) before and (A-2, B-2) 12 weeks after the BTX-A injection.
smaller initial volume less than 23 cm³ showed percentage changes of more than 28%. However, a significant correlation was not shown in the right side ($R = 0.31, R^2 = 0.10, P = 0.41$).

The common side effects were a decrease in the mastication forces ($N = 7$), changes in the facial expression ($N = 3$), sunken cheek ($N = 2$), and taste sense changes ($N = 3$). Four subjects complained of a mild discomfort at the injection site within 48 hours of the injection. Changes in the facial expressions were observed when the subject was smiling. They could not elevate their mouth corner when they tried to smile. However, all side effects disappeared in 8 weeks.

More than 50% of the volunteers (6 of 11 volunteers) regained the muscle volume to some extent at 6 months after the injection.

Discussion

The treatment of MH by a surgical reduction of the muscle volume has been reported by several authors. The disadvantages of a surgical reduction include the risks associated with a general anesthesia, postoperative hemorrhage, edema, hematoma, infection, scarring, and facial nerve damage.

Since Smyth first reported good clinical results with the use of BTX-A to treat MH, there is a scarcity of reports showing that a BTX-A injection can be used as an alternative noninvasive treatment for MH. In reviewing the articles concerning BTX-A treatment for MH, most are just case reports with a small number of patients. Moreover, there is only one prospective study that focused on the quantitative effect of BTX-A for treating MH. To et al. reported...
a median reduction of 30.9% in MH patients at 3 months after a BTX-A injection. However, in this study, a BTX-A injection into the masseter muscles induced muscular atrophy to the extent of almost 22%. The discrepancy between the results reported by To et al.\(^7\) and this study can be attributed to the measurement methods and the number of cases. To et al.\(^7\) measured the mean masseteric muscle thickness by ultrasonography, which is limited by possible intermeasurement variations depending on the pressure applied to the probe. Moreover, they did not describe the exact extrapolation method from the muscle thickness to the muscle volume. Furthermore, they evaluated only five patients with MH, too small of a number to draw an adequate conclusion. Therefore, the results in this study, which were based on the nine subjects evaluated by CT, appear to be more objective.

This study also studied the dose–response relationship of a BTX-A treatment for MH. Therefore, the relationship between the pretreatment muscle volume and the percentage change in the masseter muscle volume was analyzed. As speculated, the data from the left side showed a statistically significant correlation between two parameters. The smaller the masseter muscle volume was, the smaller the amount of BTX-A was required. Based on the data from left side, more than 30 U per side seems to be required in order to induce adequate output in subject with initial muscle volume more than 30 cm\(^3\). However, data from the right side did not show any significant dose–response correlation. The authors were unable to find any reasonable answer to this discrepancy except for the small number of subjects.

Further studies aimed at elucidating the dose–response relationship of a BTX-A treatment for MH are recommended. Additional studies on individualized botulinum toxin doses according to the initial masseteric muscle volume and a more convenient and easier method for measuring the masseteric muscle volume are also needed.

Concerning the clinical effects, a clinical change in the lower facial contour was noticed in 2 of 11 subjects at 2 weeks after the injection. These changes became almost apparent in the subjects 8 weeks after injection. Because more changes in the grade were noticed after

### Table 2. Changes in the Masseter Muscle Volume 12 Weeks After the BTX-A Injection

<table>
<thead>
<tr>
<th>I.D.</th>
<th>Pre-T</th>
<th>Post-T</th>
<th>%Change</th>
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<th>Post-T</th>
<th>%Change</th>
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Median 27.21 21.70 -22.55 27.79 20.81 -23.38
Maximum 34.46 28.75 -35.41 36.16 28.22 -33.31
Minimum 20.56 13.28 -8.11 18.78 13.95 -12.42

Mean ± SD 27.04 ± 4.86 21.65 ± 5.57* 22.59 ± 9.17 26.64 ± 4.84 20.90 ± 4.39* 21.71 ± 6.78

*Statistically significant difference (p < 0.004) when compared with pretreatment value.

Pre-T, Pre-treatment (cm\(^3\)); Post-T, Post-treatment (cm\(^3\))

*Figure 3.* Correlation graph between the pretreatment muscle volume and percentage change in both sides of masseter muscles. There was a significant correlation between the pretreatment muscle volume and the percentage change in the left side (R = 0.85, R\(^2\) = 0.72, P = 0.004). However, a significant correlation was not shown in the right side (R = 0.31, R\(^2\) = 0.10, P = 0.41).
12 weeks in 6 of 10 subjects who had shown clinical effects at 8 weeks, it is believed that the peak effect of BTX-A for treating MH can be obtained at 12 weeks after an injection. The data regarding the clinical effect were similar to those reported by To et al.,7 with the highest satisfaction score obtained 3 months after the injection. In general, the maximum clinical effects of BTX-A occur 1 to 2 weeks after an injection, such as in muscular spasms or wrinkles. This is because the action of muscular paralysis by BTX-A reaches a peak 1 to 2 weeks after the injection.12 However, the maximum clinical effect of BTX-A for MH appears to require 3 months, as this effect, muscular atrophy, is secondary to muscular paralysis by BTX-A.

Regarding the longevity of this treatment, we are not sure whether the effect is permanent even though some reported that the effect went longer than 2.5 years with two session of BTX-A injection.6 In our data, more than 50% of volunteers (6 of 11 volunteers) regained the muscle volume to some extent at 6 months after the injection. This discrepancy may be due to various factors such as total number of injections, doses of BTX-A, and initial individual variation. We are now following them with CT until 2 years after one injection. We hope to report later the longevity of this new treatment after one injection of BTX-A for MH.

Opposed to previous studies reporting no side effects,3–7 various temporary, inconvenient side effects after the BTX-A injection were observed. In particular, the change in the facial smiling expression had some impact on some of the subjects (N=2) on social activity and satisfaction. The possible cause of this side effect is due to partial paralysis of zygomaticus major muscle, which is in charge of elevating mouth corner, by diffusion of the toxin injected into the upper part of masseter muscle. Another aesthetically disappointing side effect was sunken cheek (N=2). This may be also due to injection of the toxin into the upper part of masseter muscle just beneath the zygomatic arch, which brought about atrophy of masseter muscle at this area. As well known, Asians have more prominent zygoma than Whites. Therefore, the chance of aesthetically disappointing sunken cheek may be higher in Asians than in Whites when the botulinum toxin is injected into the upper part of masseter muscle. Considering all of these side effects, we should be more cautious about the injection of BTX-A into the upper part of masseter muscle, especially in Asians, when we treat MH with botulinum toxin.

This study is the first prospective study using CT to assess the response of the hypertrophic masseteric muscle to a BTX-A injection. It is believed that BTX-A can be safely used as a noninvasive treatment for patients with MH.

References