Effect of a second injection of botulinum toxin on lower facial contouring, as evaluated using three-dimensional laser scanning

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The Master's Thesis

Submitted to the Department of Dental Science

and the Graduate School of Yonsei University

in partial fulfillment of the requirements for the degree of

Master of Dental Science

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June 2014

This certifies that the dissertation of

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감사의 글

부족한 저를 이끌어 주시고 논문의 시작부터 완성되기까지 세심한 배려와 가르침으로 이끌어 주신 백형선 지도 교수님께 진심으로 감사 드립니다. 바쁘신 와중에도 논문에 귀중한 시간을 내주시어 관심과 조언을 아끼지 않으신 김성택 교수님, 이기준 교수님께도 깊이 감사 드립니다.

교정과에 들어와서 3년간의 수련기간 동안 많은 가르침을 주신 박영철 교수님, 황충주 교수님, 김경호 교수님, 유형석 교수님, 차정열 교수님, 정주령 교수님, 최윤정 교수님께도 감사 드립니다.

실험부터 논문 집필까지 많은 조언과 도움을 주신 이화진 선생님께 깊은 감사를 드리며, 논문을 작성하는 동안 아낌없는 격려로 큰 힘이 되어 주신 김성진 선생님께 감사 드립니다. 수련 생활 동안 서로 힘이 되어주고 함께 고생한 의국 동기 구윤진, 윤지연, 이미림, 이영우, 최승완 선생과 항상 밝고 든든한 후배들 금병탁, 류제성, 문지훈, 안혜림, 임선영, 임현묵, 서승원 선생에게 이 자리를 빌려 감사의 마음을 전합니다.

마지막으로 현재의 제가 있기까지 항상 변함없는 사랑과 믿음으로 지원해주시는 부모님께 깊이 감사 드리며, 부족한 형을 잘 따라주고 늘 응원해주는 하나뿐인 동생에게 고마움을 전합니다.

2014 년 6 월

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ABSTRACT

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Botulinum toxin type A (BoNT-A) injection therapy—which is less invasive and safer than surgical treatment—has been widely used to treat masseteric hypertrophy to improve the lower facial contour. There have been many studies on BoNT-A therapy, but in most cases only a single BoNT-A injection was administered and the effects of that injection on the volume and thickness of the masseter muscle and the duration of those effects were evaluated

using ultrasonography and computed tomography. Few studies have compared changes in the facial contour resulting from single and double BoNT-A injections using three-dimensional (3D) laser scanning. This imaging method is a useful and accurate method of assessing changes in the external lower facial contour

The aim of this study was to characterize differences in the changes in the lower facial contour achieved with a single injection of BoNT-A and with two injections, using 3D laser scanning, with the aim of establishing the effect of a second injection.

In this study, twenty volunteers were randomly divided into two groups. The group I (n=10) received a single BoNT-A injection, while the group II (n=10) received two BoNT-A injections, the second being administered 4 months after the first. Each injection comprised 25 U of BoNT-A, and was administered to the masseter muscle, bilaterally. Evaluation of the effect of BoNT-A injection was performed using 3D laser scan images obtained before the injection and 6 months thereafter in the group I, and before the first injection and 6 months thereafter in the group II (i.e., 2 months after the second injection). The volume and thickness of the most prominent area of the lower face were measured bilaterally.

1. There were significant changes in the volume and thickness of the most prominent area of the lower face in the group I. The volume and thickness reduced by 1186 mm^3 (P<0.05) and 1.52 mm (P<0.001), respectively.
2. There were significant changes in the volume and thickness of the most prominent area of the lower face in the group II. The volume and thickness reduced by 4072 mm^3 (P<0.001) and 3.84 mm (P<0.001), respectively.
3. The reductions in volume and thickness were significantly greater in the group II than in the group I. (P<0.001).

The volume and thickness of the lower facial contour decreased significantly at 6 months after BoNT-A injection in groups I and II. However, the second injection administered 4 months after the first in the group II further reduced the volume and thickness compared to the group I. These findings demonstrate that the administration of a second BoNT-A injection is appropriate and effective for maximum esthetic results for the lower facial contour.

Key words: Botulinum toxin, Lower facial contour, Second injection, 3D laser scan

Effect of a second injection of botulinum toxin on lower facial contouring, as evaluated using three-dimensional laser scanning

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Ⅰ. Introduction

Botulinum toxin, which is a neurotoxin that is produced by a Gram-negative anaerobic bacterium, *Clostridium botulinum*, induces muscle paralysis and atrophy by inhibiting the secretion of acetylcholine at the cholinergic presynaptic nerve endings at various neuromuscular junctions, and has been widely used to treat neuromuscular disorders such as

blepharospasm, hemifacial spasm, tremor, and strabismus.[1-3] Various therapies using botulinum toxin type A (BoNT-A) have been introduced in many fields in recent years, including cosmesis (e.g., to resolve or reduce the appearance of facial wrinkles or crow's feet), conditions associated with pain (e.g., migraine and myofascial pain), glandular hypersecretion (e.g., hyperhidrosis and crocodile tear syndrome), and excessive muscle contraction (e.g., bruxism and myokymia).[3]

The use of BoNT-A to treat bilateral masseteric hypertrophy was first proposed in 1994,[4] and since then BoNT-A injection therapy—which is less invasive and safer than surgical treatment—has been widely used to treat masseteric hypertrophy to improve the lower facial contour. There have been many studies on BoNT-A therapy, but in most cases only a single BoNT-A injection was administered and the effects of that injection on the volume and thickness of the masseter muscle and the duration of those effects were evaluated using ultrasonography[5] and computed tomography.[6,7] Few studies have compared changes in the facial contour resulting from single and double BoNT-A injections using three-dimensional (3D) laser scanning. This imaging method is a useful and accurate method of assessing changes in the external lower facial contour,[8] which may be clinically more important for

patient satisfaction than changes in the masseter muscle itself.[9] The aim of this study was to characterize differences in the changes in the lower facial contour achieved with a single injection of BoNT-A and with two injections, using 3D laser scanning, with the aim of establishing the effect of a second injection.

Ⅱ. Subjects and Methods

1. Subjects

This study was performed in accordance with the Tokyo (2004) revision of the 1975 Declaration of Helsinki. The study population consisted of 20 volunteers who requested lower facial contouring in Seoul, Korea. The volunteers were randomly assigned to one of two groups: group I and group II. Ten volunteers (four males and six females) aged 23–40 years (mean age, 28.5 years) received a single BoNT-A injection (group I), while the remaining ten volunteers (two males and eight females) aged 22–48 years (mean age, 28.5 years) received two BoNT-A injections, the second being administered 4 months after the first (group II; Figure 1). The exclusion criteria were pregnancy and a history of any serious medical illnesses including drug allergy.

ANOVA was used to evaluate the influence of the side on each of the masseter muscles. Paired *t*-test revealed that the volume and the thickness of the most prominent area of the lower face did not differ significantly between the left and right sides ($P>0.20$), and so the number of samples was doubled by pooling the data from the two sides.

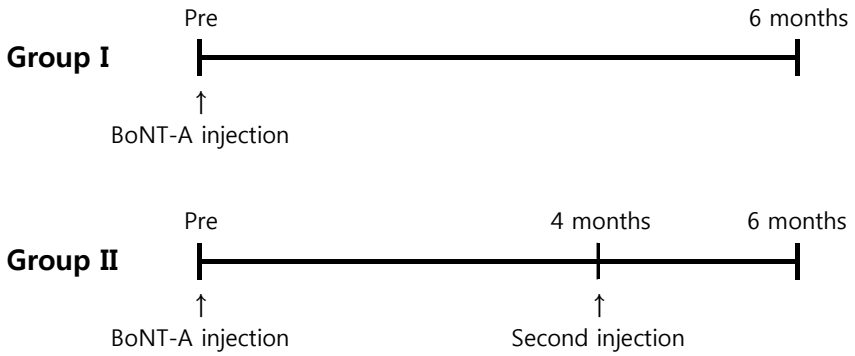

Figure 1. Injection time schedule for group I (i.e., a single BoNT-A injection) and group II (i.e., two BoNT-A injections, administered 4 months apart). Pre = preinjection.

2. Methods

1) BoNT-A injection

BoNT-A (Botulax, Hugel, Chuncheon, Korea) was supplied as a freeze-dried powder and reconstituted at a concentration of 50 U/mL (100 U in 2 mL of sterile saline), and used immediately. A 25-U volume of BoNT-A was injected into the masseter muscle bilaterally using a 1-mL syringe with a 29-G, 1/2-inch-long needle. Injections were performed at two points, 1 cm apart at the center of the lower one-third of the masseter muscle.

2) 3D Laser scanning and superimposition of 3D images

The effects of BoNT-A injection were evaluated using a 3D laser scanner (Vivid 9i, Minolta, Tokyo, Japan) before the injection and 6 months thereafter in group I, and before the first injection and 6 months thereafter in group II (i.e., 2 months after the second injection). The scanner emits a harmless class-I laser beam that is rated safe for the eyes by the US Food and Drug Administration.

Late-night dining and drinking, which could cause swelling of the face, were prohibited before 3D laser scanning. Patients were seated in an upright position, and asked not to breathe, swallow, or move their heads during laser scanning.

All of the scanned images were merged to create single 3D facial images using image processing software (Rapidform 2004, Inus Technology, Seoul, Korea).

The 3D facial images acquired preinjection and 6 months postinjection were superimposed using the wide surface of the forehead, an area of the face that was not influenced by the injection(s), as a reference, together with five soft-tissue landmarks: the right and left exocanthions, the right and left endocanthions, and the soft-tissue nasion.[10,11]

3) 3D measurement

A. Volume

The following reference points were used to delineate the border of the lower face: cheilion, soft-tissue pogonion, soft-tissue gonion, and tragion. The volume within the border was measured bilaterally (Figure 2).

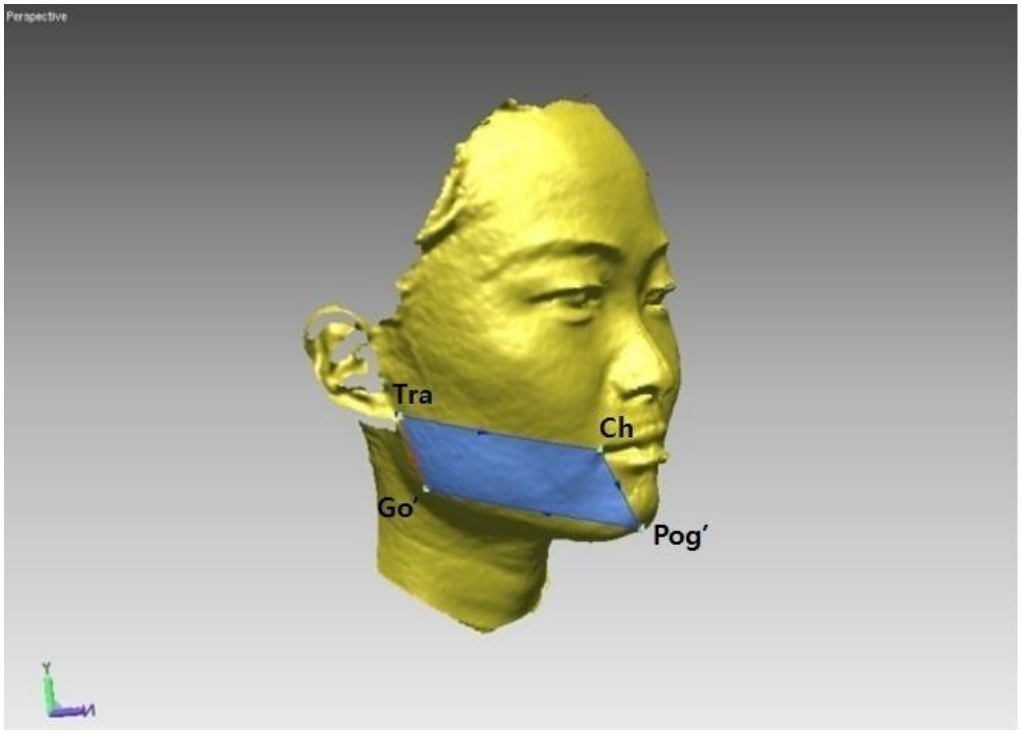

Figure 2. The volume of the lower face within the border delineated by the following reference points: cheilion (Ch), soft-tissue pogonion (Pog'), soft-tissue gonion (Go'), and tragion (Tra).

B. Thickness

The thickness of the most prominent area of the lower face was measured bilaterally (Figure 3). The software detected the largest change in the superimposition image.

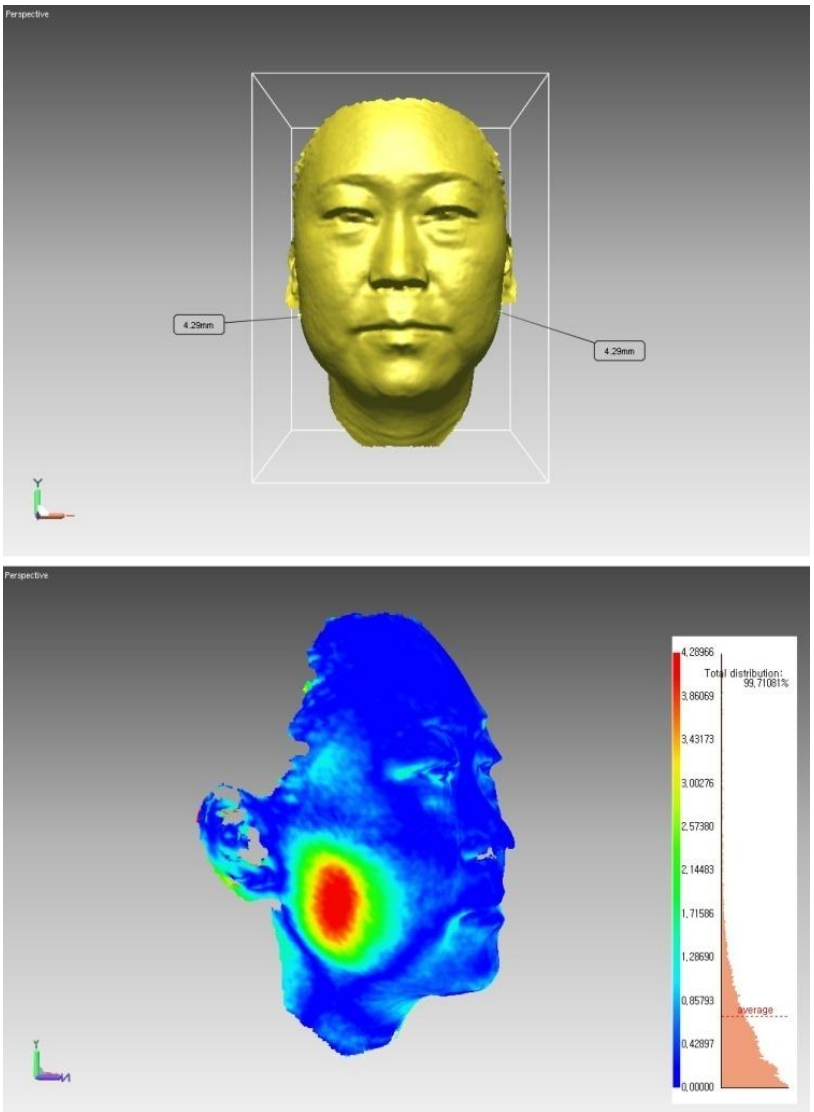

Figure 3. The thickness of the most prominent area (red color) of the lower face measured by superimposing 3D images.

4) Statistical analysis

The data were analyzed using SAS (version 9.3, SAS Institute, Cary, NC, USA), and the cutoff for statistical significance was set at $P<0.05$. Paired *t*-test was used to compare the mean values of the measurements between before and 6 months after the first injection in a group. Independent *t*-test was used to compare the mean values of the measurements between groups.

Ⅲ. Results

The mean changes in the volume and thickness of the lower face are listed in Table 1 and depicted in Figures 4 and 5, respectively. The volume and thickness of the lower face was significantly reduced in groups I and II between before and 6 months after the first injection. In group I the volume decreased from 43,861 mm^3 to 42,675 mm^3 (i.e., a change of –1186 mm^3), and the thickness decreased by 1.52 mm. In group II the volume decreased from 41,618 mm^3 to 37,546 mm^3 (i.e., a change of –4072 mm^3), and the thickness decreased by 3.84 mm. The reductions in both of these parameters were significantly greater in group II (after two injections) than in group I (P<0.001 for both).

Table 1. Mean changes in the volume and thickness of the lower face.

Measurements	Group I					Group II					Group I&II
	Pre	6M	*Δ*			Pre	6M	*Δ*			$P^{\dagger}$
			Mean	S.D.	*P*			Mean	S.D.	*P*	
Volume (mm^3)	43,861	42,675	1186	1916	**<0.05**	41,618	37,546	4072	2644	**<0.001**	**<0.001**
Thickness (mm)	0	-1.52	1.52	0.98	**<0.001**	0	-3.84	3.84	1.12	**<0.001**	**<0.001**

Δ, Change between preinjection (Pre) and 6 months postinjection (6M); *P*, comparison of the change between before and 6 months postinjection(s) in each group (paired *t*-test); $P^{\dagger}$, intergroup comparison for the change between before and 6 months postinjection (independent *t*-test).

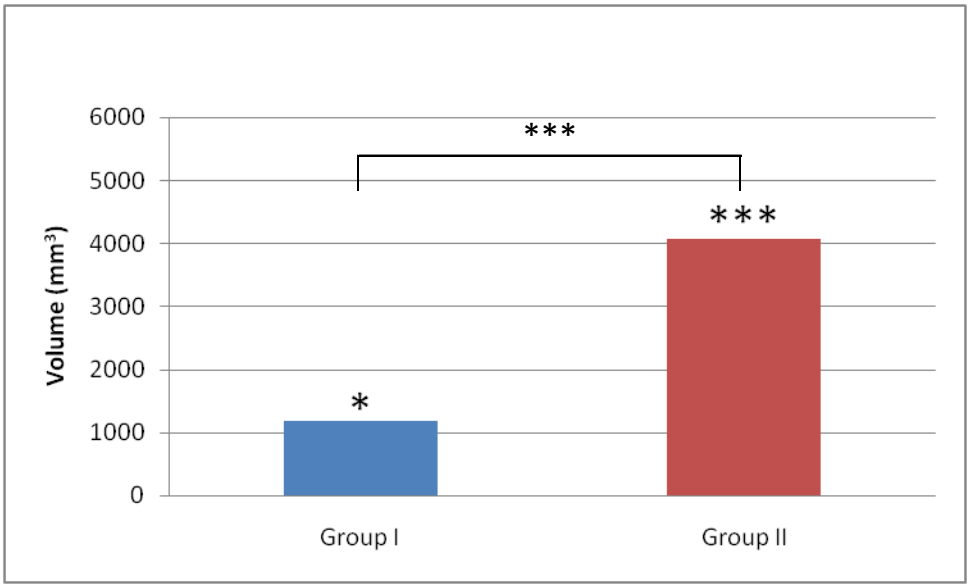

Figure 4. Mean change in the volume of the lower face. *P <0.05; ***P<0.001.

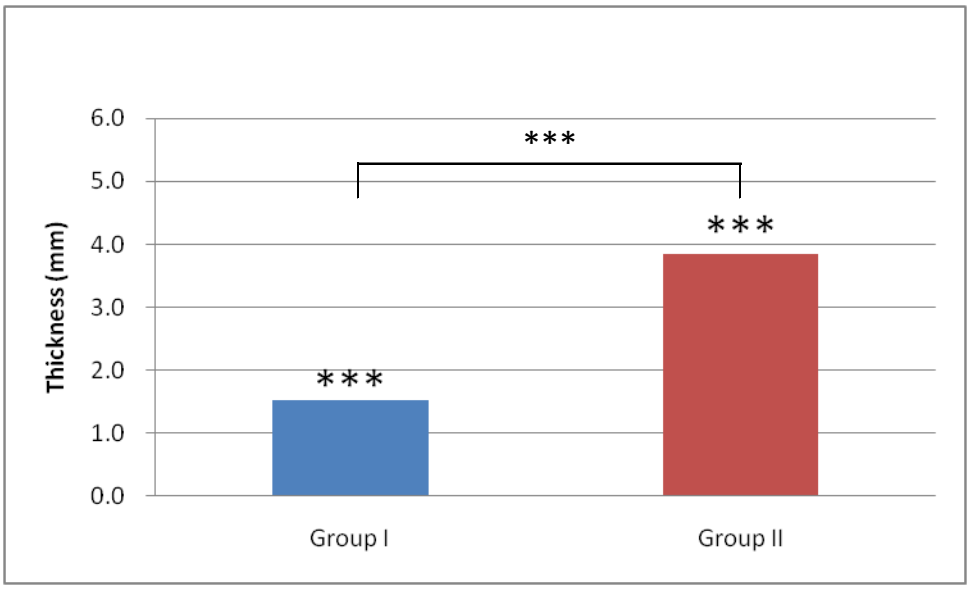

Figure 5. Mean change in the thickness of the lower face. ***P<0.001.

Ⅳ. Discussion

The origin of bilateral masseteric hypertrophy, a common cause of a square jaw and a broad-looking face, which people, especially in Asia, do not find esthetically pleasing,[12] is unclear.[13] In most cases this condition is thought to be a result of jaw clenching, bruxism, and overactivity of the masseter muscle.[14] It can be treated by a surgical procedure; however, surgery carries with it the risks and complications of general anesthesia, postoperative hemorrhage, infection, scarring, and facial nerve damage.[5] Intramuscular BoNT-A injection, which is less invasive and safer than surgical interventions, was recently proposed as an alternative treatment option for masseteric hypertrophy, and is now widely used for that purpose.

Several studies have shown that BoNT-A injection can effectively reduce the size of the masseter muscle. Choe and colleagues reported that BoNT-A injection produced satisfactory clinical results in masseteric muscle hypertrophy, and demonstrated this using clinical photographs.[15] Park and colleagues reported that the average reduction in thickness achieved was typically 18–20% of the muscle thickness at preinjection, as documented by

ultrasonography and CT.[7] Shim and colleagues reported that the average reductions in volume and thickness in the lower facial contour peaked at 12 weeks postinjection, at 2,833.86 mm^3 and 2.99 mm, respectively.[16] Their findings were obtained using 3D laser scanning, which can provide 3D information regarding changes in the facial contour,[8] which is clinically more important than the change in the masseter muscle itself, and is directly correlated with patient satisfaction.[9]

The present study evaluated changes in the lower facial contour using the Vivid 9i scanner, which emits a harmless class-I laser beam and allows safe and quick scanning of the face within 2.5 seconds, thus producing an image that is less susceptible to facial movements.[16] The 3D laser scanner can provide more reliable and useful images of the facial contour than can photography, ultrasonography, or CT, and makes it easy to create accurate 3D images. Furthermore, unlike CT it does not emit harmful radiation, and so multiple images can be safely obtained from each person.[8]

Most previous studies have focused on the results of a single injection of BoNT-A; few have investigated the effect of a second BoNT-A injection. Kim and colleagues found that maximum masseter muscle atrophy occurred at 3 months after the first injection, and the

beginning of the masseter muscle recovery was found at 4 months after the first injection.[12] A second injection performed 4–7 months after the first conferred a longer-term effect. Some authors have reported that multiple injections of BoNT-A could lead to antibody-induced failure of the therapy. Dressler reported that there are two categories of botulinum toxin therapy failure: primary and secondary.[17] Primary failure, in which the therapy fails from its first application, is due to either a lack of (or a reduced) sensitivity to botulinum toxin, such as in myasthenia gravis or antecollis. Secondary failure, in which the therapy is initially successful but fails in subsequent applications, is caused mainly by the formation of antibodies to botulinum toxin, which can be accelerated by short interinjection intervals and high injection doses. Repeated injections for maintenance of a maximally reduced masseter muscle volume are usually performed with an interval of 4–8 months, which is a reasonable time interval between treatments. Most cosmetic therapies involve administering less than 100 U of BoNT-A per injection,[18] which should minimize the risk of antibody-induced failure. In the present study a total of 50 U was used for each injection, and in group II the second injection was performed 4 months after the first.

The 3D laser scanning performed in this study revealed that the mean volume and thickness changes in the most prominent lower facial area between preinjection and 6 months postinjection were –1186 mm^3 and –1.52 mm, respectively, in group I, and –4072 mm^3 and –3.84 mm in group II. Shim and colleagues reported that the mean volume and bulkiest thickness reduced by 2176.93 mm^3 and 2.39 mm, respectively, between preinjection and 24 weeks postinjection,[16] changes that are consistent with but larger than the present findings for the group I. The volume area in the present study was determined using four reference points—the cheilion, soft-tissue pogonion, soft-tissue gonion, and tragion—which outlined a narrower area than that used in the study of Shim and colleagues, in was defined by seven points: ala, cheilion, labrale inferior, soft-tissue pogonion, soft-tissue menton, soft-tissue gonion, and tragion. We used fewer reference points in order to eliminate areas that would be irrelevant to the BoNT-A injection and might thus increase the measurement error.

In groups I and II, BoNT-A injection resulted in statistically significant reductions in the volume and thickness of the most prominent area of the lower face, which could be considered to reflect an effective improvement in the lower facial contour. The results for group II, in which a second injection was also performed, were far more dramatic than those for group I.

One explanation for this finding is that the second injection was able to maintain the maximum change achieved 3 months after the first injection up to 6 months, or else it helped to obtain the maximum change by boosting the effect of the first injection, which may somehow have failed to exert the maximum effect by 3 months. We therefore believe that administering a second injection 4 months after the first will at least help to maintain or may even achieve the maximum esthetic effect of BoNT-A on the lower facial contour.

The limitations of this study are the small sample and the lack of the long-term follow-up results (i.e., longer than 6 months). Thus, further investigations are needed to evaluate the long-term effect of multiple BoNT-A injections.

Ⅴ. Conclusion

The volume and thickness of the lower facial contour was significantly decreased at 6 months after bilateral BoNT-A injection into the masseter muscle in both the group I and group II. The administration of a second injection in the group II at 4 months after the first injection resulted in greater reductions in the volume and thickness measurements than in the group I. These findings suggest that administering a second BoNT-A injection is both appropriate and effective for producing the maximum esthetic outcomes on the lower facial contour.

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국 문 요 약

3차원 레이저 스캐닝을 이용한 보툴리눔 독소 2차 주사의 하안면부 윤곽에 대한 영향 평가

(지도교수: **백 형 선**)
연세대학교 대학원 치의학과

이 홍 희

보툴리눔 독소 A형 (BoNT-A) 주사는 수술적 방법에 비해 덜 침습적이고 안전하다는 이유로 하안면 윤곽 개선을 위한 치료에 널리 이용되고 있다. BoNT-A 치료에 대한 많은 연구들이 있으나 대부분 1회 주사 후 효과에 대한 것이며, 또한 초음파나 CT등을 통한 연구가 대부분이다. 하안면 외부 윤곽의 변화를 정확하고 쉽게 평가할 수 있는 3차원 레이저 스캔을 이용한, 1회 주사와 2회 주사의 안면 윤곽의 변화 차이를 비교한 연구는 거의 없는 실정이다.

본 연구의 목적은 1회 주사와 2회 주사에 의한 하안면 윤곽의 변화 차이를 3차원 레이저 스캔을 통해 비교하고 2차 주사의 효과를 알아보는 것이다.

본 연구에서는 20명의 지원자를 무작위로 두 군에 배정하였다. I 군 (n=10) 은 1회 주사를 시행하였으며, II 군 (n=10)은 2회 주사를 시행하였는데 2차 주사는 1차 주사 4개월 후 시행하였다. 각 주사는 BoNT-A 25 U 용량으로 양쪽의 교근에 시행하였다. I 군에서는 주사 전 및 주사 후 6개월에 3차원 레이저 스캔 영상을 획득하였고, II 군에서는 첫 주사 전 및 첫 주사 후 6개월 (즉, 2차 주사 후 2개월)에 영상을 획득하여 주사 효과를 평가하였다. 하안면 양측의 부피 및 두께 변화를 측정하였다.

1. I 군의 하안면 부피 및 두께에서 유의성 있는 변화가 나타났다. 부피와 두께 각각 1186 mm^3 ($P<0.05$), 1.52 mm ($P<0.001$) 감소하였다.
2. II 군의 하안면 부피 및 두께에서 유의성 있는 변화가 나타났다. 부피와 두께 각각 4072 mm^3 ($P<0.001$), 3.84 mm ($P<0.001$) 감소하였다.
3. II 군에서 I 군보다 유의성 있는 더 큰 부피 및 두께의 감소가 나타났다. ($P<0.001$)

I 군과 II 군 모두에서 BoNT-A 주사 6개월 후 하안면 윤곽의 부피 및 두께의 유의성 있는 감소가 나타났다. 하지만 첫 주사 4개월 후 2차 주사를 시행한 II 군에서 I 군에 비해 더 큰 부피 및 두께의 감소를 보였다. 이 결과를 바탕으로 BoNT-A 2차 주사가 하안면 윤곽에서 최대의 심미적 효과를 내는데 적절하고 효과적임을 알 수 있다.

핵심 되는 말: 보툴리눔 독소, 하안면 윤곽, 2차 주사, 3차원 레이저 스캔