Effect of Botulinum Toxin injection into human masseter muscle on the mandibular angle area

Hwa Jin Lee

The Graduate School

Yonsei University

Department of Dental Science

Effects of Botulinum Toxin injection into human masseter muscle on the mandibular angle area

Directed by Professor HYOUNG-SEON BAIK

The Doctor'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

Doctor of Dental Science

Hwa Jin Lee

June 2015

This certifies that the dissertation thesis
of Hwa Jin Lee is approved.

Thesis Supervisor: Hyoung-Seon, Baik

Hyung-Seog, Yu

Kee-Joon, Lee

Kee-Deog, Kim

Seong-Taek, Kim

The Graduate School
Yonsei University
JUNE 2015

감사의 글

논문이 완성되기까지 항상 아낌없는 지도와 격려로 이끌어주신 백형선 지도 교수님께 진심으로 감사 드립니다. 실험을 위해 소중한 도움을 주신 김성택 교수님께도 감사 드립니다. 또한 많은 관심과 조언으로 심사를 맡아주신 유형석 교수님, 김기덕 교수님, 이기준 교수님께 진심으로 감사 드립니다.

특히 바쁜 와중에도 실험을 위해 귀중한 시간을 내어 많은 도움을 준 이홍희 선생에게 깊이 감사합니다.

늘 걱정하시는 부모님과 가족들께 사랑하는 마음 전합니다. 멀리 있어서 자주 보지 못하지만 항상 응원을 아끼지 않는 동생과 논문을 위해 소중한 도움을 준 제부에게도 감사의 마음을 보냅니다.

옆에서 항상 용기를 북돋아주는 우리 가족들에게도 고마운 마음과 사랑을 전합니다.

2015 년 5 월

이 화 진

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABSTRACT

Effects of Botulinum Toxin injection into human masseter muscle on the mandibular angle area

Hwa Jin Lee

Department of Dental Science
The Graduate School, Yonsei University
(Directed by Prof. HYOUNG-SEON BAIK, D.D.S., M.S.D., Ph.D.)

Injection of botulinum toxin type (BoNT) into masseter muscle is a noninvasive treatment for the masseteric hypertrophy, which is safer than the surgical treatment. Most studies regarding the injection of BoNT reported its effect on reducing the masseter muscle using ultrasonography and computed tomography. Also, it was reported that localized masticatory muscle atrophy after injection of BoNT alters craniofacial growth and development in animal studies, such as decreased ramus height, increased gonial angle. However, most of those studies were performed on animals, thus, the effects of BoNT injection into masseter muscle on the craniofacial bony structure has not been fully elucidated in humans.

The aim of this study was to evaluate soft and hard tissue changes on the mandibular angle area after injection of BoNT in patients with massetric hypertrophy using three-dimensional cone-beam computed tomography (3D CBCT).

Twenty volunteers were randomly divided into two groups. Group I (n=10) received a single BoNT injection into the bilateral masseter muscle, while group II (n=10) received

double BoNT injections, the second being administered 4 months after the first. Each injection was comprised of 25 U of BoNT.

3D CBCT were taken before injection and after the first injection 6 months later in two groups.

Thicknesses and cross-sectional areas of the masseter muscle were measured on the 6 cutting images of masseter muscle parallel to the mandibular plane with interval of 5 mm distance, which were referred to as C5, C10, C15, C20, C25, and C30. For bony changes of mandibular angle area, three reference points were used (Go inf, Go post, distal surface of mandibular second molar). Inter-gonial width (inter Go inf Rt-Lt, inter Go post Rt-Lt) were measured. The bone volume of mandibular angle formulated by 3 reference points were measured.

The results of the present study were as follows,

1. The thicknesses and cross-sectional areas were significantly reduced in both groups (P<0.001), but the amount of reduction was significantly greater in group II.
2. The intergonial width of mandibular angle area was not significantly changed in groups I and II (P>0.05).
3. The bone volume of mandibular gonial angle area was significantly reduced only in group II (P<0.001).

BoNT injection reduced thicknesses and cross sectional areas of masseter muscle in both groups, but the amount of reduction were significantly greater in group II than group I. (P<0.05). The bone volume of mandibular angle area reduced only in group II. These finding demonstrate that the administration of double BoNT injections might induce change in bone volume at the mandibular angle area.

Key words**:** botulnium toxin (BoNT), human masseter muscle, cone beam computed tomography (CBCT), mandibular angle

Effects of Botulinum Toxin injection into human masseter muscle on the mandibular angle area

Hwa Jin Lee

Department of Dental Science
The Graduate School, Yonsei University
(Directed by Prof. HYOUNG-SEON BAIK, D.D.S., M.S.D., Ph.D.)

I. Introduction

Both genetic and environmental factors play an important role in the craniofacial morphology, and Moss noted that muscle function is one of the most important epigenetic factors involved in guiding facial bone growth, as well as bone shape and size.[1] According to Collins, the distinctive shape of the Inuit skull is related to vigorous chewing. Clinically, individuals with vigorous chewing habits have the lager muscle attachments and the lager mandibles.[2]

Both surgical and non-surgical methods have been applied to treat the masseteric hypertrophy. But surgical intervention for the masseteric reduction for patients with masseteric

hypertrophy such as external/ internal angle approach has been known to carry many risks that include – asymmetry, condyle fracture and inferior alveolar nerve injury. As more reversible and conservative methods, non surgical methods such as muscle relaxant and occlusal splints have been used to treat slight masseteric hypertrophy.

Botulnium toxin (BoNT) injection is an effective approach as a non-surgical method for masseteric hypertrophy. Botulium toxin produced Clostridium botulinum induces muscle paralysis and atrophy through the blockage of acetylcholine secretion in the neuromuscular junctions[3,4] which is effective for striated muscles.[5] BoNT is a noninvasive treatment that is safer than the surgical treatment for the masseteric hypertrophy. Kim et al reported that inducing atrophy with a BoNT injection reduces the masseter muscle in the case of masseteric hypertrophy[6] and other study reported the effect of BoNT in reducing the masseter muscle, documented by ultrasonography and computed tomography.[7]

Morphological changes in skeletal dimensions were demonstrated in previous studies using various methods to reduced muscle activity after BoNT injection.[8] In those studies, it has been shown that induction of localized masticatory muscle atrophy with BoNT alters craniofacial growth and development. BoNT injection showed a typical facial morphology of a dolichofacial profile : a short upper face accompanied by a long lower face with extended mandibular length, ramus height, constricted bicoronoidal and bigonal widths.[9] In adult animal studied, BoNT showed similar effect on mandibular bony structure, lower dentition, the weight of masseter, a decreased ramus height, increased gonial angle.[10] However, the effects of a BoNT injection on the structure of the craniofacial bone to reduce muscle activity have not been fully investigated in human adult bone structure.

In this study, we evaluated the effects of BoNT injection into masseter muscle on muscular and bony changes in the human adult mandibular angle area using three dimensional cone beam computed tomography (3D CBCT) images. For changes of masseter muscle, we

measured the masseter muscle thicknesses, cross sectional areas and for bony changes of mandibular angle area. We measured inter gonial widths and the bone volumes of mandibular angle area at before and after BoNT injections.

II. Subjects and Methods

1. Subjects

This 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 injection (group I), while the remaining ten volunteers (two males and eight females) aged 22~48 years (mean age, 28.5 years) received double BoNT injections, the second being administered 4 months after the first (group II). The exclusion criteria were the presence of facial asymmetry and/or severe malocclusion, pregnancy and a history of any serious medical illnesses including drug allergy.

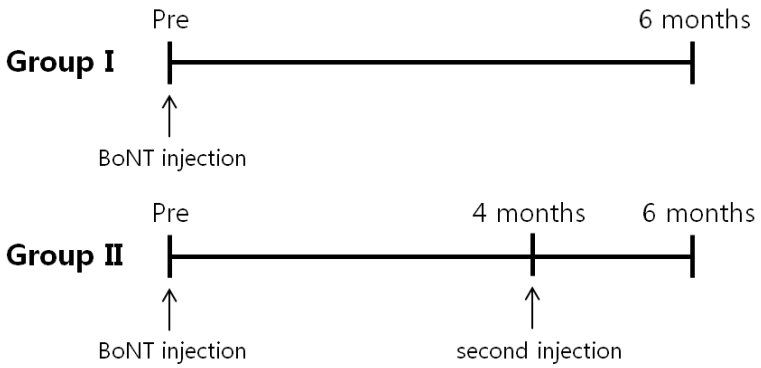

Figure 1. Injection time schedule for group I (i.e., a single BoNT injection) and group II (i.e., double BoNTi njections, administered 4 months apart). Pre = preinjection.

2. Methods

1) BoNT injection

BoNT (Botulax, Hugel, Chuncheon, Korea) was supplied as a freeze-dried powder, reconstituted at a concentration of 50 U/mL (100 U in 2 mL of sterile saline), and used immediately. A 25U volume of BoNT was injected into the masseter muscle bilaterally using a 1mL syringe with a 29G, 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) Three-dimensional CBCT taking

CBCT scans (Alphard3030; Asahi Roentgen Inc., Kyoto, Japan) were performed at 6 months before BoNT injection and after the first injection in both groups. The CBCT scans were obtained on the maxillofacial region for 17 seconds at a field of view of 20 cm × 17.9 cm, 80 kVp, and 5 mA. Patients were instructed to seat in upright position with maximum intercuspation. The CBCT datas were converted into digital imaging and communication in medicine (DICOM) files at a 0.39cm slice thickness and reconstructed into 3D images using the InVivo Dental software program (version 5.2; Anatomage, San Jose, CA, USA). For the hard tissue measurements, the reconstructed image was visualized using threshold value of 176 hounsfield unit. The mandible was separated from the whole images and the teeth above the alveolar bone were removed.

3) 3D measurements

A. Masseter muscle thickness and cross sectional area

The CBCT images of mandible were cut by 5 mm thickness parallel to mandibular plane, total 6 cuts. Each cutting images were named C5, C10, C15 ,C20 ,C25, C30. (Figure 2) Maximum thicknesses and cross sectional areas of masseter muscle were calculated at each CBCT images. (Figure 3)

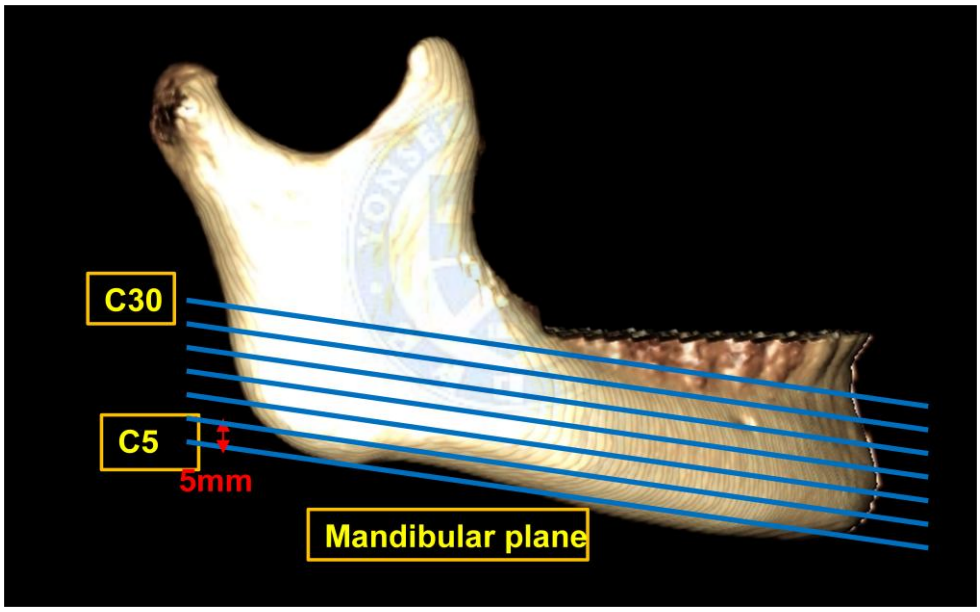

Figure 2. CBCT image cut level- C5, C10, C15, C20, C25, C30; mandiblular CBCT image were cut by 5 mm thickness parallel to mandibular plane.

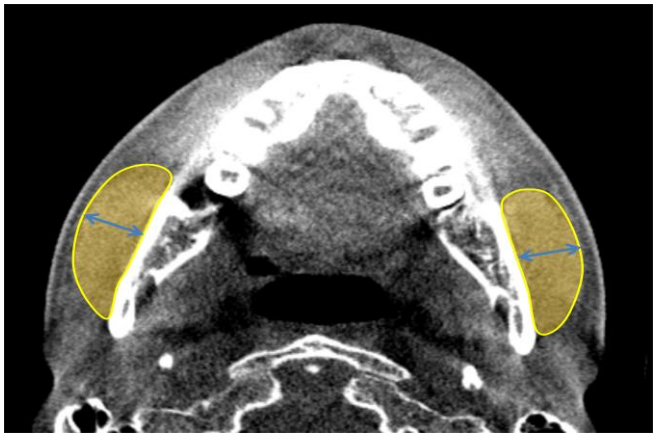

Figure 3. The thickness and cross sectional area of masseter muscle at each cutting level :

Blue arrow : the maximum thickness of masseter muscle

Yellow surface : the cross sectional area of masseter muscle

B. Width of mandibular angle area

The following reference points were used to measure widths of mandiblular angle area: Go post (Gonion posterius: most posterior point of posterior border of ramus) and Go inf (Gonion inferius; most inferior point of inferior border of ramus).[11] Widths of inter Go post Rt-Lt and inter Go inf Rt-Lt were measured bilaterally.

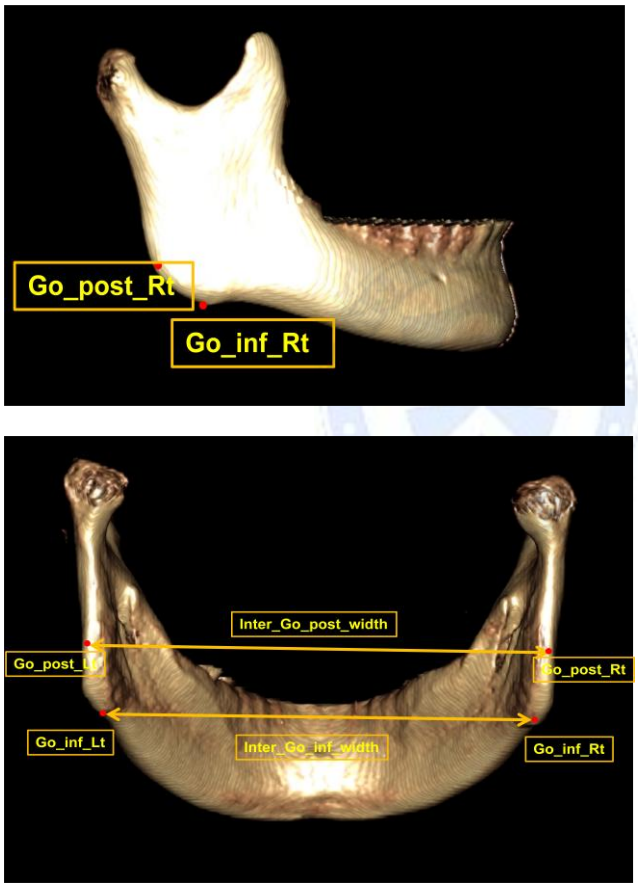

Figure 4. Upper) Reference points for width of mandibular angle area :

Go post (Goinon posterius) and Go inf (Gonion inferius)

Lower) Widths inter Go post Rt-Lt and inter Go inf Rt-Lt .

C. Volume of mandibular angle area

The volume of mandibular angle area formulated by three points (Go inf-Go post-distal surface of mandibular second molar as constant reference point) was calculated. The volumes within the border were measured bilaterally.

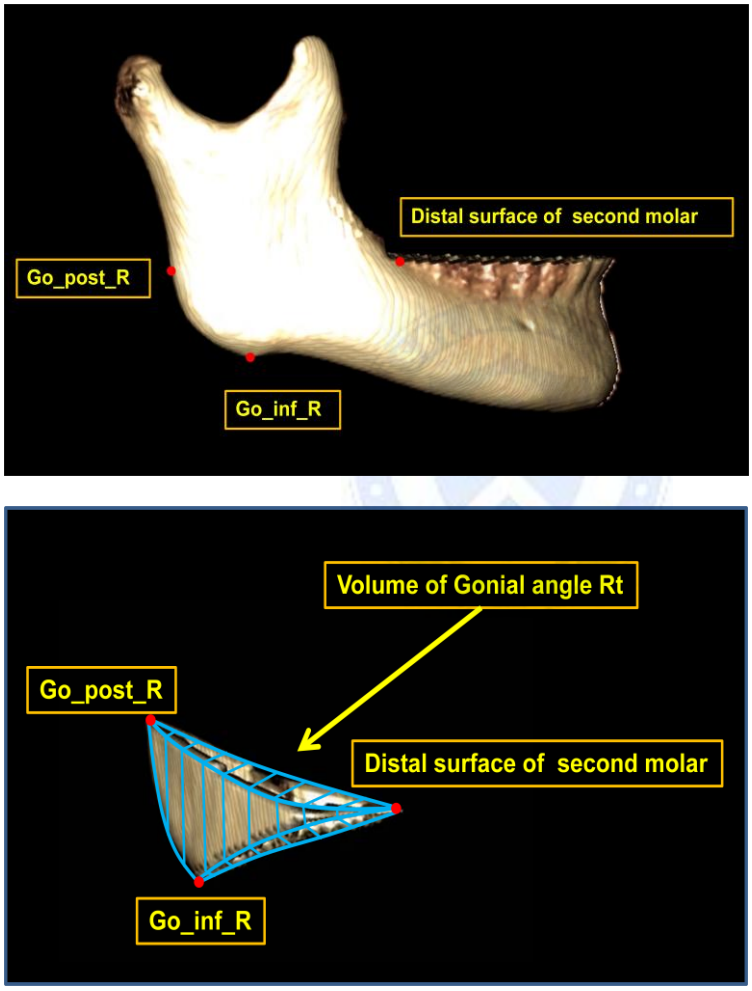

Figure 5. The volume of mandibular angle area formulated by three points (Go inf-Go post-distal surface of mandibular second molar)

4) Statistical analysis

The data was analyzed using SAS (version 9.3, SAS Institute, Cary, NC, USA) and the cut off for statistical significance was set at $P<0.05$. To evaluate reproducibility of measurements, all landmarks were measured twice with two weeks interval by the same person. We calculated intraclass correlation coefficients.

In this study, we measured both left and right parts of 20 patients and included them in our sample. We applied the linear mixed models because there may be correlation in measurements between the left and right parts.

Wilcoxon signed rank sum test was used to compare the measurements between before and 6 months after the first injection in two groups. Wilcoxon rank sum test was used to compare the measurements between two groups.

III. Results

Table 1. Mean changes of masseter muscle thickness (mm)

Measurements	Group I					Group II					I & II
			Δ					Δ			
	Pre	6M	Mean	S.D.	p	pre	6M	Mean	S.D.	p	P †
C5	8.00	6.59	1.41	0.88	<0.001	7.34	4.96	2.38	1.27	<0.001	<0.05
C10	11.11	9.39	1.72	0.84	<0.001	10.76	7.57	3.19	1.24	<0.001	<0.001
C15	13.37	11.38	1.99	0.79	<0.001	13.01	9.60	3.41	1.29	<0.001	<0.001
C20	14.59	12.55	2.04	0.81	<0.001	14.81	11.19	3.62	1.08	<0.001	<0.001
C25	14.99	13.11	1.88	0.71	<0.001	15.69	11.88	3.81	0.95	<0.001	<0.001
C30	15.18	13.58	1.60	0.99	<0.001	15.81	11.92	3.90	1.14	<0.001	<0.001

Δ, Change between preinjection (Pre) and 6 months after injection (6M);

P, comparison of the change between before and 6 months after injection(s) in each group (Wilcoxon signed rank sum test);

P†, intergroup comparison for the change between before and 6 months after injection (Wilcoxon rank sum test).

C5-30; The CBCT images of mandible were cut by 5 mm thickness parallel to mandibular plane

Table 2. Mean changes of masseter muscle cross sectional area (mm^2)

Measurements	Group I					Group II					I & II
	pre	6M	Δ			pre	6M	Δ			P †
			Mean	SD	p			Mean	SD	p	
C5	226.79	171.39	55.40	34.22	<0.001	211.50	130.24	81.26	50.68	<0.001	>0.05
C10	35143	281.66	69.77	30.17	<0.001	342.11	224.26	117.84	52.84	<0.001	<0.05
C15	439.57	367.70	71.88	30.17	<0.001	442.40	300.06	142.34	51.53	<0.001	<0.001
C20	485.86	400.22	85.64	37.17	<0.001	517.11	346.99	170.12	63.97	<0.001	<0.001
C25	495.12	413.17	81.94	33.42	<0.001	537.85	366.88	170.97	59.70	<0.001	<0.001
C30	497.86	434.48	63.37	31.77	<0.001	538.21	372.33	165.88	56.87	<0.001	<0.001

Δ, Change between preinjection (Pre) and 6 months after injection (6M);

P, comparison of the change between before and 6 months after injection(s) in each group (Wilcoxon signed rank sum test);

P†, intergroup comparison for the change between before and 6 months after injection (Wilcoxon rank sum test).

C5-30; The CBCT images of mandible were cut by 5 mm thickness parallel to mandibular plane

Table 3. Mean changes of width of mandibular angle area (mm)

Measurements	Group I					Group II					I & II
	pre	6M	Δ			pre	6M	Δ			P †
			Mean	SD	p			Mean	SD	p	
Inter Go post	93.76	93.81	-0.05	0.87	>0.05	99.44	99.44	0.00	1.02	>0.05	>0.05
Inter Go inf	91.34	91.32	0.02	0.78	>0.05	94.96	94.94	0.02	0.77	>0.05	>0.05

Δ, Change between preinjection (Pre) and 6 months after injection (6M);

P, comparison of the change between before and 6 months after injection(s) in each group (Wilcoxon signed rank sum test);

P†, intergroup comparison for the change between before and 6 months after injection (Wilcoxon rank sum test).

Table 4. Mean changes of volume of mandibular angle area (mm^3)

Measurements	Group I					Group II					I & II
	pre	6M	Δ			pre	6M	Δ			P †
			Mean	SD	p			Mean	SD	p	
mandibular angle volume	5289.65	5245.20	44.45	120.72	>0.05	6121.95	5935.05	186.90	151.97	<0.001	<0.001

Δ, Change between preinjection (Pre) and 6 months after injection (6M);

P, comparison of the change between before and 6 months after injection(s) in each group (Wilcoxon signed rank sum test);

P†, intergroup comparison for the change between before and 6 months after injection (Wilcoxon rank sum test).

A. Masseter muscle thickness and cross sectional area

The mean changes of the masseter muscle thickness and cross sectional area at each cutting level after BoNT injection are shown in table 1, 2. Masseter muscle thickness and cross sectional areas showed statistically significant differences between before BoNT injection and 6 months later. The group II who received the additional injection showed more decrease than the group I at all cutting levels.

B. Width of mandibular angle area

We measured the width of mandibular angle area before BoNT injection and 6 months later. We observed slight changes in the width, but it was not statistically significant in both groups and between two groups (Table 3).

C. Volume of mandibular angle area

We measured the volume of mandibular angle area before BoNT injection and 6 months later. In both groups, the average volume of mandibular angle area decreased after BoNT injection. But the differences were statistically significant in group II while it were not in group I. (Table 4)

IV. Discussion

BoNT has been known to acts specifically on muscles without undesirable side effects. It blocks the potential transmission action in neuromuscular junctions by inhibiting acetylcholine release. The toxin dose not damage the nerves and muscle structures, so muscle function is restored after neutralization of the toxin.[12] BoNT is rapidly (within hours), irreversibly bound to presynaptic neuron at the neuromuscular junction. After being internalized, it acts on a zinc-dependent endoprotease to disrupt some of the peptides necessary for acetylcholine release. [13] This action, which may take 2 weeks to complete, effectively destroys the affected neuromuscular junction, causing muscular paralysis.[5]

We demonstrated that the average of masseter muscle thicknesses and cross sectional areas decreased after BoNT injection, and these results were consistent with previous studies. Reduced muscle function decreased the muscle thickness and size. Park and et al reported that the average decrease of the muscle thickness was typically 18–20% of the pre-injection thickness as documented by ultrasonography and CT.[7, 14] Kim et al reported that the volume of the masseter muscle was lower after injecting of BoNT-A on each side, as documented by CT.[15]

We observed that the decrease in the muscle thickness was greater in the C20 and C30 area than C5. This might be because C20 and C30 areas are close to maximum height of contour of masseter muscle but C5 area is close to muscle attached site.

Most of the changes in the thickness and cross sectional areas of the masseter muscle appeared after 12 weeks, which is when the effect of BoNT on lower facial contouring is considered to peak. Shim et al reported that the average reductions in volume and thickness in the lower facial contour peaked at 12 weeks after injection.[16] After muscle paralysis, there is ongoing turnover at the neuromuscular junction, although toxin exposure enhances this

activity such that muscular function begins to return in approximately 3 months and is usually completed by 6 months.[5] Thus, muscle atrophy is a temporary event and new neuromuscular synapses can be resynthesized over a period of a few months.[7] Therefore, we injected an additional BoNT to group II after 4 months before completely muscular function recovery for more consistent muscle atrophy. We observed greater decrease in thickness and cross sectional areas of masseter muscle in group II than in group I. Injecting the double BoNT to individuals with masseteric hypertrophy may be considered more effective than only one injecting.

We observed that there were no changes in the width of mandibular angle area after BoNT injection in both groups. However, we observed the change in the volume of angle area in group II, not group I. This result implied that there was no change in the shape of the mandible after single BoNT injection but repetitive BoNT injection could affect bone volume of mandibular angle area.

According to the Moss' functional matrix theory, reduced muscle function can be an epigenetic factor in the craniofacial region that affects bone structure.[1] Direct and indirect loading such as tension or bending forces from the functioning of several muscles might contribute to alterations in the skeletal structure.[17] Tissue degradations in bone, which underlie the ability of loading to maintain bone homeostasis, are induced by a combination of ground reaction forces and muscle contractions.[18] The integral role that muscle serve to maintain bone health is revealed by pathologies in which muscle function is chronically altered .[19,20] In acute conditions that result in diminished or impaired muscle function, such as bed rest or spinal cord injury, the annualized percentage of bone loss can range between 5% and 25%, depending upon skeletal site and severity of impairment.[21,22] As a comparison, annual bone loss associated with menopause is typically reported at 2-3%.[23] Chappard et al reported that removal of normal mechanical loading decreased the mineral content in the unit cross sectional area, thus altering the internal skeletal structure.[24]

Chappard D. et al reported that bone loss assessed after BoNT injection in wistar rats.[24] Warner et al reported rapid degradations of muscle and bone in response to acute muscle paralysis induced by BoNT injection into hind limb muscle of murine. After BoNT injection, bone mineral contents and volume were diminished in hindlimb bone. In texture analysis of radiographs in the femur, the trabecular and cortical bone loss observed primarily via substantial bone resorption.[19]

The intimate physical proximity of muscle and bone suggests that biochemical factors released from contracting muscle (e.g., IL-6, TGF-β, TNF-α, glutamate, calcitonin gene related peptide(CGRP), or substance P) may also serve to enable bone homeostasis. BoNT reduces the full spectrum of normal muscle contractions and diminishes the release of biochemical factors into the local muscle-bone interactions. The diminished muscle forces cause the remodeling process of bone growth, which circumferentially reduces the bone thickness.

The changes of external shape and internal structure of maxilla and mandible were affected by various factors and oral and maxillofacial function is one of the most widely known factors. Van Limborgh reported that weakness of masticatory function is closely related to the structure of maxilla and mandible.[25] Kiliaridis et al controlled masticatory force on animals with varying density and intensity of feed and reported differences in external shape and internal structure of maxilla and mandible due to changes in masticatory force.[7] Matic et al. reported that masseter muscle function may be involved in maintaining mandibular and zygomatic bone through changes in bone metabolism.[26] Although weakened masseter muscle after BoNT injection can influence maxilla and mandible, exact mechanisms and effects on maxilla and mandible have not been explained. Park reported using adult rats that the weakened masseter muscle after BoNT injection influenced the growth of mandible and caused changes in length and shape of mandibular angle and in trabecular pattern of bone. [27]

Few study has reported how BoNT injected into masseter muscle affects the shape and structure of mandible in human adults. Nevertheless, it could be predicted that we would observe the similar changes to ones in the previous study like effects of BoNT on hindlimb bone that observed decrease in bone mineral density, trabecular bone and cortical bone thickness. We observed the less change of bone than one observed by the study that used hindlimb bone. This might be because the amount of BoNT injection used in this study could not reduce masseter muscle force enough to cause a bone change in mandible.

This was supported by the fact that we did not observe a change in group I with single BoNT injection, but observed a change in the volume of angle area and further decrease in muscle thickness and cross sectional area in group II with additional BoNT injection.

According to Grimston et al, bone mineral density of hindlimb bone decreased sharply during the first two or three weeks after BoNT injection.[28] However, remobility and refunction of muscle caused the bone mineral density to increase gradually afterwards. Bone mineral density increased up to 12 weeks after BoNT injection, and although it did not recover fully of the bone mineral density as in the before BoNT injection, they could be assumed that it increased further afterwards. The same recovery could be expected in the mandibular angle area. We would expect the bone change to last up to 12 weeks after BoNT injection when we observed the maximum decrease in the volume of masseter muscle. However, after the 12 weeks, we would expect that the bony structure of maxilla and mandible would be restored to the original structure through normal function recovery of the masseter muscle. But this study analyzed CT images captured only six months after BoNT injection so it did not confirm changes of mandibular angle area after six months. Further study about the bone change after six months in both groups will be needed.

Moreover, a study that analyzes whether the increasing number of BoNT injections may lead to a greater bone loss will be needed.

V. Conclusion

1. There were significant changes in the thickness and cross sectional area of the masseter muscle in the group I and II. The thickness reduced by 1.41 -2.04 mm (P<0.001) in group I and 2.38 -3.90 mm (P<0.001) in group II. The cross sectional area reduced by 55.40 -85.64 mm^2 (P<0.001) in group I and 81.26 -170.97 mm^2 (P<0.001) in group II , respectively.
2. There were no significant changes in the width of mandibular angle area in the group I and II.
3. There was significant change in the volume of mandibular angle area in the group II. The volume of mandibular angle area reduced by 186.90mm^3 (P<0.001) in group II.

BoNT injection could reduce masseter muscle thickness and cross sectional area. But the reductions in the thickness and cross sectional area of the masseter muscle were significantly greater in the group II than in the group I. (P<0.05). The volume of mandibular gonial angle area reduced only in group II. . These findings demonstrate that the administration of double BoNT injection might induce bony volume changes in the mandibular angle area.

VI. References

1. Moss ML. The primary of functional matrices in orofacial growth. Dent Pract Dent Rec 1968;19:65-73

2. Proffit WR, Fields HW, Nixon WL. Occlusal forces in normal and long face adults. J Dent Res 1983;62;566-70

3. Burgen AS, Dickens F, Zatman LJ. The action of botulium toxin on the neuro-muscular junction. J. Physiol 1949;109:10-24

4. Dressler D, Saberi FA. Botulium toxin: mechanisms of action. Eur Neurol 2005;53:3-9

5. Klein AW. Complications, adverse reaction, and insights with the use of botulium toxin. Dermatol Surg 2003;31:220-9

6. Kim NH, Chung JH, Park RH, et al. The use of botulium toxin type A in aesthetic mandibular contouring. Plast Reconstr Surg 2005;115:919-30

7. To EW, Ahuja AT, Ho WS, et al. A prospective study of the effect of botulium toxin A on massetereric hypertrophy with ultrasonographic and electromyographic measurement. Br J Plast Surg 2001;54:197-200

8. Kiliaridis S, Engstrom C, Thilander B. The relationship between masticatory function and craniofacial morphology. I. A cephalometric longitudinal analysis in the growing rat fed a soft diet. Eur J Ortho 1985;7:273-83.

9. CY Tsai, LY Yang, KT Che, et al. The influence of masticatory hypofunction on developing rat craniofacial structure. Int J Oral Maxillo Fac Sur 2010;39:6:593-8

10. CY Tsai, RY Huang, CM Lee, et al. Morphologic and bony structural changes in the mandible after a unilateral injection of botulinum neurotoxin in adult rats. J Oral Maxillo Sur 2010; 68:5:1081-7

11. SH park, Sh Yu, KD Kim, et al. A proposal for a new analysis of craio facial morphology by 3-dimensional computed tomography. Am J Orthod Dentofac Orthop 2006;129: 600:23-34

12. De paiva A, Meunier F A, Molgo J, et al. Functional repair of motor endplates after botulium neurotoxin type A poisoning; biphasic switch of synaptic activity between nerve sprouts and their parent terminals. Proc Natl Acad Sci USA 1999;96:3200-5

13. Hambleton P. Clostridium botulinum toxins; a general review of involvement in disease, structure,mode of action and preparation for clinical use. J Neurol 1992;239:16-20

14. Ahn J, Horn C, Blitzer A. Botulium toxin for masseter reduction in Asian patients. Arch Facial Plast Surg 2004;6:188-91

15. Kim HJ, Yum K, Lee S, et al. Effect of botulinum toxin type A on bilateral massetric hypertrophy evaluated with computed tomographic measurement. Dermatol Surg 2003;23:484-9

16. Shim WH, Yoon SH, et al. Effect of botulinum toxin type A injection on lower contouring evaluated using a three-dimensional laser scan. Dermatol Surg 2010;36:2161-6

17. Bresin A, Kiliaridis S, Strid KG. Effect of amsticatory function on the internal bone structure in the mandible of the growing rat. Eur J Oral Sci 1999;107:35-44

18. Sarah E. Warner, David A. Sanford, Blair A. Becker, et al. Botox induced muscle paralysis rapidly degraded bone. Bone.2006;38(2):257-64

19. Bianchi ML, Mazzanti A, Galbiati E, et al. Bone mineral density and bone metabolism in Duchenne muscular dystrophy. Osteoporos Int 2003;14:761–7

20. Lingam S, Joester J. Spontaneous fractures in children and adolescents with cerebral palsy. BMJ 1994;309:265

21. Kiratli BJ, Smith AE, Nauenberg T, et al. Bone mineral and geometric changes through the femur with immobilization due to spinal cord injury. J Rehabil Res Dev 2000;37:225–33

22. Leblanc AD, Schneider VS, Evans HJ, et al. Bone mineral loss and recovery after 17 weeks of bed rest. J Bone Miner Res 1990;5:843–50

23. Riggs BL, Melton LJ. Involutional osteoporosis. N Engl J Med 1986;314:1676–86

24. Chappard D, Chennebault A, Moreau M, et al. Texture analysis of X ray radiographs is a more reliable descriptor of bone loss than mineral content in a rat model of localized disuse induced by the Clostridium botolinum toxin. Bone 2001;28:72-9

25. Van Limborgh J. A new view of the control of the morphogenesis of the skull. Acta Morphol Neerl Scand 1970;2: 143-60

26. Matic DB, Yazdani A, Wells RG, et al. The effects of masseter muscle paralysis on facial bone growth, J Surg Res 2007;139:243

27. Park WS. Change of jaw growth and structure after injection of Botulinum Toxin Botulinum Toxin A on masticatory muscle in growing Rat, 2013 PhD Thesis, Dental Science in Graduate School of Yonsei University

28. Grimston SK., Silva MJ, et al. Bone loss after temporarily induced muscle paralysis by botox is not fully recovered after 12weeks. Ann NY Acad Sci 2007;1116:444-60

국 문 요 약

보툴리눔 독소 주사의
하악 우각부에 대한 효과

(지도교수: **백 형 선**)

연세대학교 대학원 치의학과

이 화 진

보툴리눔 독소 (BoNT) 주사는 저작근 비대 환자의 치료에 있어 비교적 안전하고 효과적인 방법이다. BoNT 주사의 저작근에 대한 효과 및 기전은 이미 알려진 바 있고 BoNT 주사를 통해 약화된 저작근이 악안면부, 특히 하안면부에 미치는 영향 - 하악 우각부 각도의 감소, 하악지의 높이 감소 등-에 대해서도 여러 연구를 통해 보고된 바 있다. 하지만 이들 대부분은 성장기의 동물을 대상으로 하여 BoNT 주사가 하안면부의 성장에 미치는 영향에 관련된 연구들이었다.

또한 저작근에 사용되는 미용 목적의 BoNT 주사는 성인이 대상인 경우가 대부분이지만, BoNT 주사 후 약화된 저작근이 하악골의 우각 부위에 미치는 영향에 대한 연구는 거의 보고된 바 없다.

이에 본 연구는 BoNT 주사가 성인의 교근과 하악 우각부의 골에 미치는 영향을 3차원 컴퓨터 단층 촬영 영상을 통해 관찰하였다. 연구를 위하여 20명의 지원자를 무작위로 두 군으로 나누었다. I군 (n=10)은 1회, II군 (n=10)은 2회 주사를 시행하였는데 2차 주사는 1차 주사 4개월 후 시행하였다. 매 주사 시 사용된 BoNT의 용량은 25U 이며 양쪽 교근에 동시에 주사하였다. I 군과 II 군 모두 BoNT 주사 전과 6개월 후에 3차원 컴퓨터 콘빔 전산화 단층사진 (CBCT) 을 촬영하여 3차원 영상 상에서 주사 효과를 평가하였다.

교근에 대한 효과를 평가하기 위해 하악 평면을 기준면으로 하여 이에 평행하게 상방 5 mm 간격으로 6개의 교근 단면 영상을 획득하였다. 각각의 단면에서 양측 교근의 두께 및 단면적 변화를 측정하였다. 또한 우각부의 골변화를 평가하기 위하여 양쪽 하악 우각부의 가장 후방점과 하방점을 기준점으로 사용하여 우각부간 골의 폭경의 변화와 하악 우각부의 골 부피의 변화를 측정하여 아래와 같은 결과를 얻었다.

1. 교근의 두께 및 단면적의 유의성 있는 변화가 I 군과 II 군 모두에서 관찰되었다.
2. 하악 우각부간 폭경은 I군과 II군 모두에서 유의성 있는 변화가 관찰되지 않았다.
3. 하악 우각부의 골 부피는 II 군에서만 유의성 있게 감소하였다. ($P<0.001$).

BoNT 주사는 교근의 두께 및 단면적의 감소를 보였고, BoNT의 반복 주사 시에는 그 효과는 더욱 컸으며, 반복 주사의 경우에서만 하악골 우각 부위의 골부피의

감소를 나타냈으며, 하악 우각부간 골의 폭경에는 변화가 없었다. 즉, 성인에서 BoNT의 반복 주사는 교근뿐 아니라 하악골 우각 부위의 골의 부피 감소에도 영향을 줄 수 있다.

핵심 되는 말: 보툴리늄 독소, 교근, 3차원 콘빔 전산화 단층 촬영 (CBCT), 하악 우각부 부피