Muscle Weakness After Repeated Injection of Botulinum Toxin Type A Evaluated According to Bite Force Measurement of Human Masseter Muscle

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Muscle Weakness After Repeated Injection of Botulinum Toxin Type A Evaluated According to Bite Force Measurement of Human Masseter Muscle

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감사의 글

많은 분들의 도움으로 좋은 연구의 기회를 얻어 마침내 논문으로 그 결실을 맺게 되었습니다. 기나긴 학위 과정 동안 수많은 분들의 도움이 없었다면 홀로 이루어낼 수 없었을 것이기에 지면을 빌어 감사의 인사를 전하려 합니다.

박사과정을 무사히 마치고 논문을 발표하기까지 학문적인 가르침뿐만 아니라 인생의 멘토로서 저를 사랑으로 이끌어주신 최종훈 지도교수님께 먼저 깊은 감사를 드립니다. 또한 철없던 인턴시절 orofacial pain 이라는 분야에 눈을 띄워 주시고 항상 앞장서 이끌어주신 김성택 교수님께도 존경과 감사를 바칩니다. 때로는 스승으로서 때로는 형님처럼 관심과 애정을 가지고 지켜봐 주신 안형준 교수님, 권정승 교수님께도 감사의 인사를 드립니다.

연구 결과를 정리하여 논문으로 만드는데 많은 도움을 준 후배 변영섭 선생과 여러 가지로 바쁜 와중에도 싫은 내색 없이 실무적으로 많은 도움을 준 김영건 전공의와 의국원 여러분 에게도 감사드립니다.

멀리에서도 항상 격려와 사랑을 주시는 부모님과 가까이에서 물심양면으로 지원을 아끼지 않으신 장인어른, 장모님께도 감사의 마음을 말로 다 표현할 수 없으며, 마지막으로 언제나 저를 믿고 지지해주는 아내 정우와 사랑스러운 맏딸 유민이에게 감사와 사랑을 전합니다.

2011 년 6 월

저자 씀

TABLE OF CONTENTS

LIST OF FIGURES

ABSTRACT

Muscle Weakness After Repeated Injection of Botulinum Toxin Type A Evaluated According to Bite Force Measurement of Human Masseter Muscle

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Botulinum toxin type A (BTX-A) has been applied successfully to treat masseteric hypertrophy, but it can cause muscle weakness. To measure the change in maximum bite force (MBF) after BTX-A injection into the human masseter muscle and to evaluate the influence of a booster (repeated) injection, thirty volunteers completed 18-week follow-up, and MBF was measured. At 18 weeks after the first injection, a booster injection was given to 14 patients, and they were followed up until 18 weeks from the booster injection.

Mean MBF was approximately 20% lower at 2 weeks than before the injection, and it recovered gradually after 4 weeks to return to the preinjection level at 12 weeks. MBF differed significantly between before the injection and at 2, 4, and 8 weeks after the injection ($p<0.05$).

In the booster injection group (n = 14), MBF was markedly lower at 6 weeks (p<0.05), and it recovered gradually in 12 weeks.

In conclusion, MBF was significantly lower after booster injection of BTX-A into the human masseter muscle, but it gradually recovered in a predictable pattern, and the degree of discomfort experienced by the subjects had little effect on normal mastication.

Key Words : botulinum toxin, bite force, masseter hypertrophy

Muscle Weakness After Repeated Injection of Botulinum Toxin Type A Evaluated According to Bite Force Measurement of Human Masseter Muscle

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I. INTRODUCTION

Botulinum toxin type A (BTX-A), a potent neurotoxin that reversibly blocks presynaptic acetylcholine release, has been applied successfully to treat facial spastic conditions such as blepharospasm, strabismus, focal dystonia, spasmodic dysphonia, and achalasia(Jankovic J &

Brin MF 1991, Simpson LL 1996). Since the first reported application in cosmetics in 1992(Carruthers JD & Carruthers JA 1992), BTX-A has been used with great success to treat various types of hyperkinetic facial lines such as crow's feet, horizontal forehead lines, melomental folds, and glabellar rhytides (Blitzer A *et al.* 1993, Carruthers JA *et al.* 2002, Blitzer A *et al.* 1997). BTX-A is also used in the orofacial region to help treat masticatory and facial muscle spasm, severe bruxism, facial tics, and hypertrophy of the masticatory muscles(Clark GT 2003). BTX-A injection was first used for treating masseteric hypertrophy in 1994 (Moore AP & Wood GD), since then the underlying effects have been investigated using ultrasound, electromyography (EMG), computed tomography (CT), and three-dimensional (3D) reconstruction of CT (To EW *et al.* 2001, Choe SW *et al.* 2005, Kim NH *et al.* 2005, Kim HJ *et al.* 2003 , Park MY 2003, Kim JH *et al.* 2007, Yu CC *et al.* 2007). Most side effects associated with the application of BTX-A in the orofacial region are mild and transient. They include bruising, swelling, pain around the injection site, headache, and masticatory muscle weakness (Kim JH *et al.* 2007, Alam M *et al.* 2002). In terms of muscle weakness, we have previously investigated changes in maximum bite force (MBF) after BTX-A injection (Ahn KY & Kim ST 2007), but the small number of patients (n = 7), the short investigation period (12 weeks), and the fact that only the bite force of the molar area was measured limited that study.

The present study supplemented our previous study with a larger subject group, longer follow-up period, and the use of a more reliable and reproducible method to measure the bite force, and it also evaluated the influence of a booster (repeated) injection of BTX-A for treating masseteric hypertrophy.

II. MATERIAL AND METHOD

1. Patients and Methods

This study was performed in accordance with the 2004 revision in Tokyo of the 1975 Declaration of Helsinki. Before admission to the study, a signed written consent form was obtained from each volunteer after the nature and the established use of BTX-A and its potential side effects had been fully explained. All of the volunteers were dental students and staff at the College of Dentistry, Yonsei University, Seoul, Korea, in 2004 who complained of bulky masseter muscles. They were free to withdraw from the treatment at any time. Thirty of 35 volunteers (86%) who completed the 18-week follow-up were enrolled in this study (Figure 1).

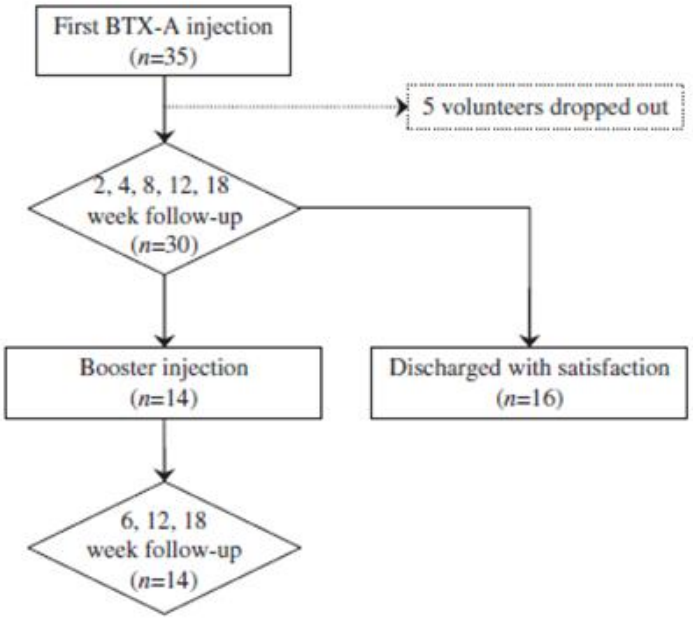

Fig 1. Number of study subjects

Their mean age was 28.1, and 29 were female. The exclusion criteria for this study included pregnancy, a history of drug allergy, and any other serious medical illness. One hundred units of BTX-A (Lanzhou Institute of Biological Products, Lanzhou, China) obtained as a freeze-dried powder was reconstituted to a concentration of 5U/0.1mL using 2mL of normal saline. The masseter muscles were identified using palpation and injected with 25U of BTX-A on each side (50mLU in total) at two points of the most prominent portions of the mandibular angle. Bite forces of each subject were measured before injection and at 2, 4, 8, 12, and 18 weeks after injection. At 18 weeks after the first injection, 16 patients were discharged, and a booster (repeated) injection of BTX-A was given to the remaining 14 patients who requested it, at the same dosage and method as for the first injection, and these subjects were followed up at 6, 12, and 18 weeks from the booster injection. MBF was measured using a system consisting of pressure-sensitive sheets (Dental Prescale, Fuji Film, Tokyo, Japan) (Figure 2) and an analyzing computer (Occluzer, GC, Tokyo, Japan). Each subject was seated in an upright position with the Frankfort horizontal plane and instructed to bite with maximal clenching.

All measurements were made with the subject seated with the head upright, looking forward, and in an unsupported natural position (Figure 3). The occlusal pressure was determined as the mean value of pressures measured on the contact area between the upper and lower teeth in occlusion for each subject. The paired *t*-test was used to evaluate change in MBF with SAS version 8.1 software (SAS Institute, Inc., Cary, NC).

Fig 2. Dental Prescale film (30H type-R, medium size, Fuji Film, Japan)

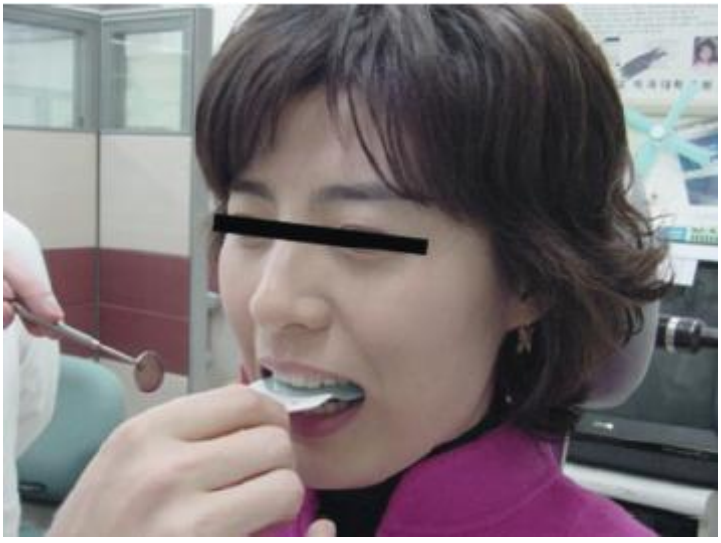

Fig 3. Measuring bite force with Dental Prescale film

III. RESULTS

Bite forces were measured in all 30 subjects for the first 18 weeks. Mean values of bite forces during maximal voluntary clenching are shown in Figure 4. Mean MBF was approximately 20% lower at 2 weeks than before the injection but recovered gradually after 4 weeks to return to the preinjection level at 12 weeks. MBF differed significantly between before the injection and at 2, 4, and 8 weeks after the injection (p<0.05) but not at 12 and 18 weeks postinjection (Figure 4).

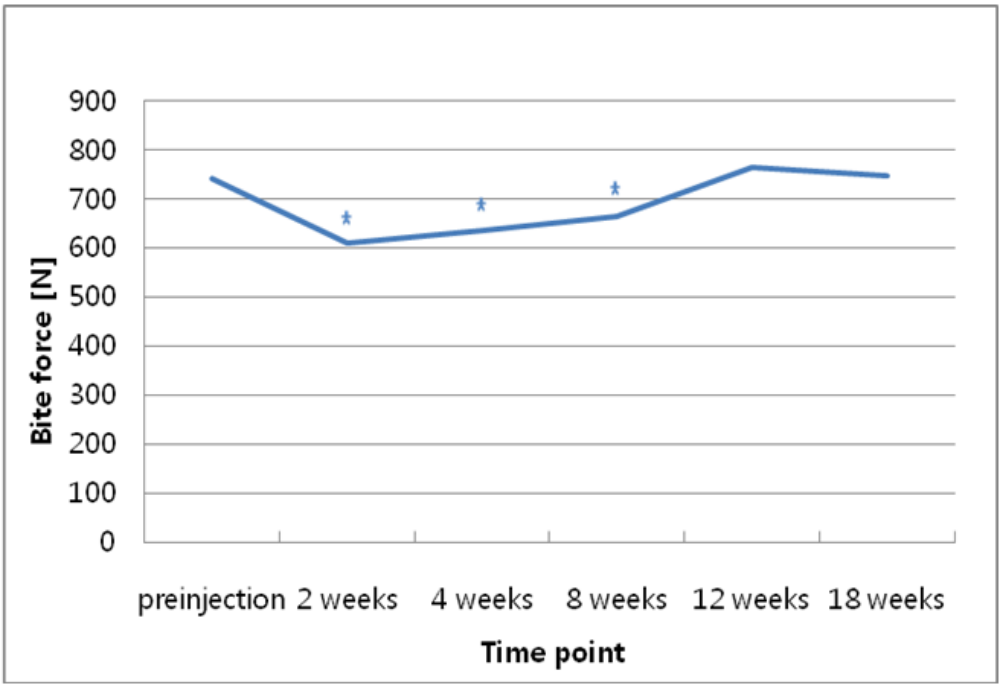

Fig 4. Mean bite forces during maximal voluntary clenching in the first-injection group (n=30 ; p<0.05)

Figure 5 shows that mean values of bite force during maximal voluntary clenching in the group that received a booster injection of BTX-A (n = 14) over 36 weeks. MBF was markedly lower at 6 weeks after the booster injection (p<0.05) but recovered gradually so that the value at 12 and 18 weeks did not differ significantly from the preinjection value.

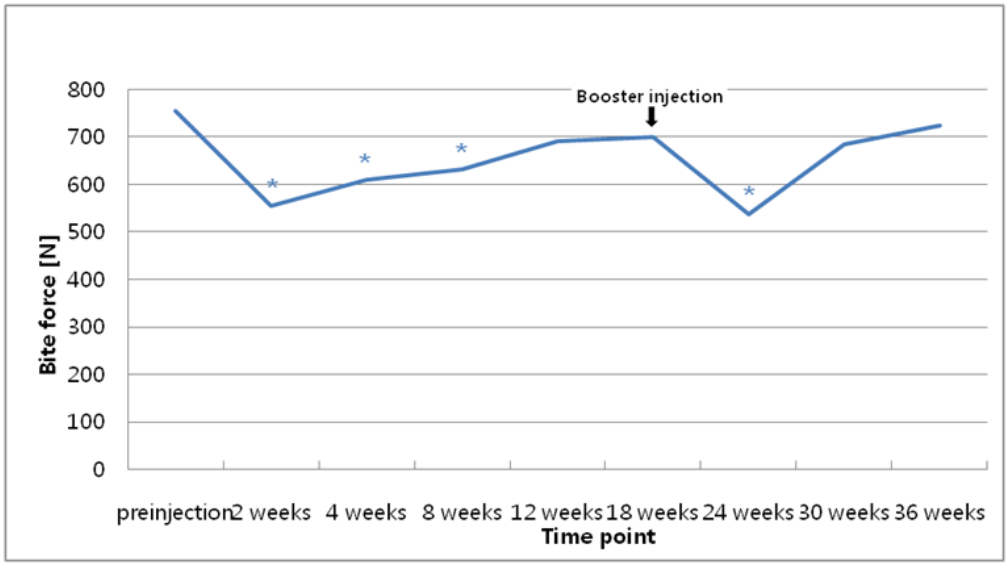

Fig 5. Mean bite forces duringmaximal voluntary clenching in the first and booster (repeated) injection group (n=14 ; p<0.05)

IV. DISCUSSION

Asian people generally do not like a square, widelooking face, which has made contouring of the lower face one of most popular esthetic procedures in Asia. The use of BTX-A has expanded as a treatment for masseteric hypertrophy in the presence of a square face because it is noninvasive and is safer than surgical procedures. Previous studies have used various imaging methods to assess muscle volume reduction. Using ultrasonography, the reported reduction in volume was approximately 31% (To EW *et al.* 2001, Kim NH *et al.* 2005). Using CT, Kim and colleagues (Kim HJ *et al.* 2003) reported a muscle reduction of 22%. Park and colleagues (Park MY *et al.* 2003) reported a series followed by ultrasonography and CT and found that CT tended to overestimate the volume whereas ultrasonography underestimated the muscle volume. Yu and colleagues (Yu CC *et al.* 2007) used 3D CT to estimate that the reduction of bulkiness was approximately 30% for the masseters. The main effect of BTX-A is temporary muscle atrophy that follows chemodenervation induced by acetylcholine blockade at the neuromuscular junction. The muscle fiber atrophy is a reversible phenomenon that usually recovers within 4 to 6 months (Borodic GE *et al.* 1994, Borodic GE & Ferrante R 1992). When the muscle atrophy effect does not last long, booster injection can be considered. The effects of repeated BTX-A injection in esthetic medicine was reported in 945 facial wrinkle patients, with high satisfaction rate, and there was no evidence of cumulative adverse effects (Rzany B & Dill-Müller D 2007). Various side effects of a BTX-A injection for masseteric hypertrophy have been reported, including change in bite force, speech disturbance, muscle pain, facial asymmetry, and prominent zygoma (Kim HJ *et al.* 2003, Kim JH *et al.* 2007, Oshima M *et al.* 1998). The change in bite force is an inevitable side effect of muscle atrophy, although it is normally only temporary.

We have previously investigated changes in MBF after BTX-A injection,17 but the small number of patients (n = 7), the short investigation period (12 weeks), and the fact that only the bite force of the molar area was measured limited that study. The present study supplemented our previous study with a larger subject group (n = 30), longer follow-up period (36 weeks), and the use of a more reliable and reproducible method to measure bite force (measuring the bite force on all teeth); it also evaluated the influence of a booster injection of BTX-A into the human masseter muscle.

In the present study, MBF fell to its lowest value 2 weeks after BTX-A injection and gradually recovered by 12 weeks. The recovery pattern of MBF was equivalent to that investigated in the previous study. The previous study found that bite force is approximately 40% lower 2 weeks after BTX-A injection, but the results of this study indicate that bite force is approximately 20% lower at the same time point. This difference may be attributed to the different methods of measuring bite force used in the two studies (Figure 6).

After booster injection, the recovery pattern of MBF was also similar to the pattern after first BTX-A injection. Lower muscle strength due to atrophic changes resulted in some subjects complaining of masticatory difficulties when chewing hard but not soft food.

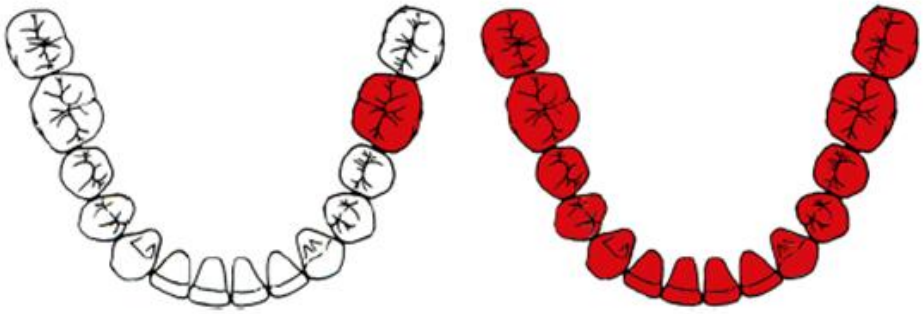

Fig 6. Different bite force measuring method. (Left) Measuring bite force on the first molar in the previous study. (Right)Measuring bite force on all teeth in the present study.

V. CONCLUSION

MBF was significantly lower after a BTX-A injection and a booster (repeated) injection into the human masseter muscle, but it gradually recovered in a predictable pattern, and the degree of discomfort that the subjects experienced had little effect on normal mastication.

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ABSTRACT (in Korean)

보툴리눔 A형 독소의 반복주사 이후 저작력 측정을 통해 평가한 사람 교근의 약화양상

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김 기 서

보툴리눔 A형 독소(BTX-A)는 운동신경의 말단에서 아세틸콜린(acetylcholine)의 분비를 가역적으로 억제함으로써 근 수축을 차단하는 역할을 하여 사시, 안검 경련 등의 치료에 사용되어왔으며, 1992년 이후에는 주름제거 등의 미용목적으로도 널리 사용되고 있다. 악안면 영역에서는 안면 근육경련, 이갈이, 교근 비대 등의 치료에 응용되고 있으며, 1994년 이후로 교근 비대에 대한 효과를 평가하기 위해 초음파, 근전도, 전산화 단층촬영(CT) 등에 의한 연구가 이루어지고 있다.

악안면 영역에서 BTX-A의 대표적인 부작용은 저작력의 약화를 들 수 있는데, 저작력의 측정은 과거에도 이루어져왔으나 실험군의 수나 측정기간 및 방법 면에서 한계가 있었다. 이번 연구에서는 기존 연구를 보완하여 BTX-A 주사 후 저작력의 약화에 대한 보다 신빙성있는 결과를 얻고자

하였으며 또한 반복주사 후 저작력의 변화에 대해서도 알아보고자 하였다.

35명 피험자의 주사 전 저작력을 측정하고 양쪽 하악각 주변 교근의 최대 풍융부에 각각 25U의 BTX-A(BTXA, Lanzhou Institute of Biological Products, Lanzhou, China)를 2지점으로 나누어 자입한 후 2, 4, 8, 12, 18주 후에 저작력을 측정하였다. 최초 주사 18주 후에 14명의 피험자에게 동일한 방식으로 2차 주사를 시행하였고 6, 12, 18주 후의 저작력을 측정하였다.

최초 주사 후 18주간 측정한 결과 평균 교합력은 주사 2주 후에 주사 전과 비교하여 약 20% 감소하는 양상을 보였으나 주사 후 4주 이후부터 점차 회복되어 주사 12주 후에는 주사 전과 유사한 수준으로 회복되었다. 주사 전과 2,4,8주 후의 평균 교합력은 서로간에 유의성 있는 차이를 보였으나 12, 18주 후의 평균 교합력은 주사 전에 비해 유의성 있는 차이를 나타내지 않았다.

2차 주사 후 18주간 측정한 결과 평균 교합력은 2차 주사 6주 후에 확연히 감소하였고 서서히 회복되어 12, 18주 후의 평균 교합력은 주사 전과 유의성 있는 차이를 보이지 않았다.

결론적으로, 사람의 교근에 대한 BTX-A의 최초 및 2차 주사 후 저작력은 현저하게 감소하였으나, 예측 가능한 양상으로 회복되었으며 피험자가 주사 후 느끼는 불편감은 일상적인 저작에 거의 영향을 미치지 않는 수준이었다.

핵심되는 말 : 보툴리눔 독소, 교합력, 교근비대