Botulinum Toxin type A injection Versus Lidocaine Injection for Myofascial Pain Involving upper Trapezius

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The purpose of this double-blind study was to evaluate clinical effects of botulinum toxin type A (BTX-A) injection on myofascial pain syndrome (MPS) involving upper trapezius and compare with those of lidocaine injection. 21 patients presenting with active TrP1 and/or TrP2 in the upper trapezius over 6 months were selected for this study. The subjects were randomly divided into two groups; one group injected with BTX-A (15 unit of Botox® / 0.3 ml per trigger point (TrP)) and the other group injected with 0.5% lidocaine (0.3 ml /TrP). The clinical effects were evaluated by VAS and PPT at baseline, 2, 4, 6 and 8 weeks after treatment.

BTX-A group showed persistent decrease of VAS values and increase of PPT values following treatment. While there was no significant difference in VAS values between BTX-A and lidocaine groups (p=0.347), there was significant difference in PPT values after treatment between two groups (p=0.000). The subjects received BTX-A showed noticeable improvement in PPT values after treatment, suggesting more reliable effect of BTX-A injection compared with lidocaine injection. The results of this study support that the direct injection of BTX-A to a TrP is an effective and safe treatment for MPS involving upper trapezius.

Key words : Botulinum Toxin, Myofascial pain syndrome, Trapezius

Ⅰ. INTODUCTION

Myofascial pain syndrome (MPS) is a common pain condition with a high prevalence, characterized by acute or chronic regional muscle pain associated with single or multiple trigger points (TrPs). Myofascial TrPs are the hyper-irritable spots located in a palpable taut band of skeletal muscle. The clinical characteristics of MPS includes local and/or referred pain, local twitch response (LTR) induced by snapping palpation or needling, associated localized autonomic phenomena, muscular weakness, existence of an acute and latent TrPs and painful limit to full stretch range of motion[1,2].

A multidisciplinary approach is necessary for effective treatment of MPS and (F) its mainstream aims to break down the vicious pain cycle through the elimination of TrPs. Traditional treatment methods for TrPs include spray and stretch, TrPs pressure release, TrPs injection, physical modalities and home exercise program with muscle stretch etc.[1,3,4] Recently, injection of botulinum toxin has been tried for MPS.

Botulinum toxin type A (BTX-A), a 150 kDa protein produced by *Clostridium botulinum*, binds irreversibly to presynaptic cholinergic nerve terminals, and blocks the exocytosis of the

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neurotransmitter, acetylcholine, thereby inhibiting muscle contraction. Based on its muscle-relaxant properties, BTX-A has been used for treatment of several muscular conditions including spasticity, cervical dystonia and blepharospasm.[5-7] The researches concerning its use for MPS indicate that (E) BTX-A is better than physical therapy and most other drugs that are recommended for treatment of MPS[8]. However, controversial results are also being reported[9,10] and available evidence from double-blinded controlled studies is still lacking.

The purpose of this study was to investigate clinical effects of BTX-A on MPS involving upper trapezius and to compare with those of lidocaine injection in a double-blind trial.

Ⅱ. MATERIALS AND METHOD

1. Subjects

21 subjects presenting with MPS involving upper trapezius over 6 months were selected from dental students (Dankook University, Cheonan, Korea) and workers at Dankook University Dental Hospital. The diagnosis of MPS in this study was based on the criteria described by Travell and Simons1), including spot tenderness in one or more palpable taut bands in upper trapezius (active TrP_1 and/or TrP_2), referred pain, and local twitch responses (LTRs) on palpation at the tender spot.

They consisted of 6 men and 15 women with a mean age of 27.14 ± 4.49 years and were randomly assigned to two groups; BTX-A injection (N=12) and lidocaine injection (N=9). Patients with any serious medical or psychological conditions were excluded. Prior to study, protocol was approved by our hospital's committee on clinical experimentation and informed consent was obtained from all subjects.

2. Procedures

Single dose of BTX-A treatment was compared with lidocaine injection. BTX-A used was Botox® (Allergan. Inc.), which contained 100 unit botulinum toxin type A powder per one vial. BTX-A was diluted with saline without conservative to 100 unit / 2 ml and 15 unit / 0.3 ml was injected to each TrP with "near-by" technique[8] and further needle movements within TrP were not performed. In the lidocaine injection group, the same volume (0.3 ml) of 0.5% lidocaine HCl without epinephrine was injected in the same manner with BTX-A injection procedure. 29-gauge needles were used and LTR was identified whenever the needle inserted to each TrP during lidocaine or BTX-A injection. During the whole experimental period of 8 weeks, there was no additional injection of BTX-A or lidocaine.

3. Measurement

Clinical effects of treatment were evaluated by measurement of visual analog scale (VAS) and pressure pain threshold (PPT). All subjects were examined before injection and during the period of 8 weeks after injection with an interval of 2 weeks.

The range of VAS meter is 0 (no pain) to 100 mm (imaginable worst pain) and subjects were asked to mark the corresponding position to the line that most closely describes their pain at that moment. PPT was measured with a pressure algometer by placing the plastic tip perpendicularly to the skin over the TrP. Its measurement range is from 0 to 5.972 kg, with 0.001 kg division. Application of pressure was instantly ceased when the patients reported pain and the pressure values at that moment were recorded. After repeating twice, the mean value was determined as the PPT for each subject.

Injection procedures and measurement of VAS and PPT were performed by one dental practitioner and the study was done in a double-blind trial.

4. Statistical analysis

To compare the effects of botulinum toxin and lidocaine, repeated measures two-way ANOVA and multiple comparison t-test were used in this study.

Ⅲ. RESULTS

Table 1. shows the change of VAS during 8 weeks after injection of BTX-A and lidocaine. There was significant difference among the time groups (p=0.000) but there was no significant difference between injection agents (p=0.347). No interaction existed between time and injection agent (p=0.690). Concerning subjective pain score, VAS values at baseline and during 8 weeks following treatment, BTX-A group showed persistent decrease of VAS values after injection, exhibiting lower values compared to lidocaine group. Nevertheless, no significant difference between two groups existed at each time point

It is given in Table 2. how PPT changed during 8 weeks after injection of BTX-A and lidocaine. Significant differences were found between injection agents as well as among the time groups (p=0.008 and 0.000, respectively). There was interaction between time and injection agent (p=0.001). Contrary to the result of VAS, PPT values, as considered to be relatively objective parameter for pain, showed significant differences between two groups following treatment. The subjects with BTX-A injection exhibited significant increase in PPT values compared with those received lidocaine injection.

According to the results from multiple comparisons between time groups, BTX-A group shows significant reduction of subjective pain since 2 weeks following injection and significant improvement of objective pain since 4 weeks after treatment (Table 3). In lidocaine group, there were significant differences in VAS values between some follow-ups. However, significant difference of PPT values was present only between baseline and 2 weeks after injection due to decrease of PPT at that follow-up (p<0.05), suggesting little objective improvement(Table 4) .

Table 1. Change of Visual Analog Scale (VAS) during 8 weeks following botulinum toxin type A (BTX-A) and lidocaine injections. (unit : mm)

	Baseline	2 wks	4 wks	6 wks	8 wks	*ANOVA*
BTX-A (N=12)	51.2±18.1	39.1±20.9	29.3±17.7	25.0±14.3	24.5±16.3	p=0.374[b]
Lidocaine (N=9)	46.2±11.1	50.4±21.8	31.1±12.8	29.3±18.7	28.7±21.6	
Unpaired t-test	p=0.164	p=194	p=0.564	p=0.290	p=0.332	
ANOVA			p=0.000[a]			p=0.690[c]

a stands for statistical significance among the time groups, b for statistical insignificance between injection media, and c represents no interaction between time and injection media

Table 2. Change of Pressure Pain Threshold (PPT) following botulinum toxin type A (BTX-A) and lidocaine injections. (unit : kg force)

	Baseline	2 wks	4 wks	6 wks	8 wks	*ANOVA*
BTX-A (N=12)	1.513 ± 0.409	1.671 ± 0.516	1.793 ± 0.499	2.050 ± 0.359	2.123 ± 0.437	p=0.000[b]
Lidocaine (N=9)	1.598 ± 0.443	1.234 ± 0.407	1.367 ± 0.385	1.374 ± 0.449	1.463 ± 0.315	
Unpaired t-test	p=0.547	p=0.002	p=0.030	p=0.000	p=0.000	
ANOVA			p=0.008[a]			p=0.001[c]

a stands for statistical significance among the time groups, b for between botulinum toxin type A and lidocaine, and c represents interaction between time and injection media.

Table 3. Multiple comparisons of visual analog scale (VAS) and pressure pain threshold (PPT) values between time points in botulinum toxin type A (BTX-A) injected groups.

VAS / *PPT*	Baseline	2 wks	4 wks	6 wks	8 wks
Baseline		*	**	**	**
2 wks			*	**	**
4 wks	*				
6 wks	**	*			
8 wks	**	**	*		

** : p<0.05, ** : p<0.005*

Table 4. Multiple comparisons of visual analog scale (VAS) and pressure pain threshold (PPT) values between time points in lidocaine injected group.

VAS / *PPT*	Baseline	2 wks	4 wks	6 wks	8 wks
Baseline				*	*
2 wks	*		*	*	**
4 wks					
6 wks					
8 wks					

** : p<0.05, ** : p<0.005*

Ⅳ. DISCUSSION

The active myofascial TrP is the clinical hallmark of MPS and the evoked pain by stimulation of TrPs leads to a limited range of motion and is responsible for the symptoms the patient is suffering from.[8] TrPs injection has been proven effective and widely used in treatment of TrPs and it has two major treatment mechanisms; the one is the physical break of TrPs and the other is the medication effects by injection media including a local anesthetic, corticosteroid, saline and botulinum toxin that has been more recently tried. While effective treatment using either the injection of a local anesthetic or dry needling depends on mechanical disruption and inactivation of the active loci in TrP, inactivation of TrPs by BTX-A injection depends on its specific pharmacological destructive effect on motor endplates[1,2].

Based on the integrated hypothesis on the mechanism of the formation of TrPs by Simons *et al*,[1] an initial muscular overload causes a dysfunction of the neuromuscular endplate, leading to an excessive release of ACh and a prolonged depolarization of the postjunctional membrane with a consecutive release and inadequate reuptake of calcium ions from local sarcoplasmic reticulum. The result is a sustained contraction of sarcomeres and a compression of neighboring capillaries. Due to subsequent local hypoxemia and energy crisis, neurovasoactive substances and neurotransmitters from free nerve endings are released. Therefore,

primary peripheral as well as secondary central mechanisms of sensitization culmination in an altered cerebral modulation are promoted.

If this hypothesis is correct, injection of botulinum toxin into TrP is a causal therapy, because it abolishes the release of ACh in the neuromuscular junction that starts and maintains a TrP.[1,11-13] Besides to the basic mechanism of muscle relaxation, it has been recently discussed that botulinum toxin also has additional direct antinociceptive mechanism by inhibiting not only exocytosis of ACh but also of other neurotransmitters[8,11].

According to the results from this study, BTX-A injection showed significant improvement in MPS concerning the change of VAS and PPT values, which are consistent with other studies showing the efficacy of botulinum toxin for treating pain in MPS.[7,13] Kuan *et al*[14] demonstrated the suppressive effect of BTX-A on endplate noise prevalence in myofascial spot region of rabbit skeletal muscle. Some double-blind controlled clinical trials exhibited available evidence that BTX-A was an effective therapy for MPS comparing with conventional steroid therapy[7] and normal saline[13] and an open-label study[15] showed usefulness of BTX-A in patients with MPS resistant to both conventional management and to physical therapy. On the while, Kamanli *et al*[3] insisted that lidocaine injection was more cost effective than BTX-A and Wheeler *et al*[10] showed single dose treatment of BTX-A without physical therapy was not effective for chronic neck pain.

Since it is said that the effect of botulinum toxin is difficult to separate from the effects of dry needling or injection of other substance,[11] BTX-A injection procedure did not comprise the needle movements within a TrP in this study. Neither did lidocaine injection procedure, which was employed as a control of BTX-A. Therefore, lidocaine injection employed here is thought to be placebo rather than effective TrP injection, possibly explaining its little benefit in PPT values in spite of some improvement of VAS values. On the while, it is thought to be that positive therapeutic effect of BTX-A group shown here came from blocking of ACh release in the nerve ending around TrP injected with BTX-A and that direct antinociception effect was also associated with alleviation of pain. It can, therefore, be believed that BTX-A injection have long term effect until ACh release is recovered completely.

The result from the study of Kuan *et al*[14] demonstrated that the decrease of endplate noise prevalence was dose dependent. As overdosing should also be avoided to eliminate the side effects of BTX-A injection, it is of importance to establish the optimal therapeutic dose for each individual muscle. According to Reilich *et al*.[8] it should be at least 10 Mouse Unit (MU) Botox /TrP. 15 MU of BTX-A was injected for each TrP in this study, which exhibited effective results without noticeable side effects including muscle weakness.

In addition, exercise program following injection wasn't employed in this study because it was thought to be that its effect would depend on patient compliance and that was difficult to obtain the same degree of compliance from each patient. However, strict exercise regimen after injection is highly recommended in clinical setting to maximize benefit from BTX-A injection for TrPs, possibly leading to avoid repeated injections and subsequently to lessen extra visit and cost.

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국문요약

승모근 근막동통에 대한 보툴리눔 독소와 리도카인 주사의 치료효과 비교

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근막동통(myofascial pain syndrome, MPS)은 근막발통점에 의해 야기되는 지각, 운동 및 자율신경계의 증상으로 발통점이 자극되면 이환부에 동통을 발생할 뿐 아니라 연관통, 연관압통, 운동신경장애, 자율신경반응을 야기할 수 있다. 본 연구는 근막동통의 다양한 치료법 중에서 botulinum toxin type A(BTX-A)의 주사의 효과를 국소마취제인 lidocaine의 주사효과와 비교하였다. 상부 승모근에 6개월 이상 활동성 발통점을 가진 21명의 환자를 선정한 다음, 무작위로 두 군으로 나누어 한 군(BTX-A 주사군, n=12)에는 발통점에 BTX-A(15 unit of Botox® / 0.3 ml per trigger point (TrP))를 주사하고 다른 군(lidocaine 주사군, n=9)에는 0.5% lidocaine (0.3 ml /TrP)를 주사하였다. 두 군 모두 주사는 1 회만 시행하였으며 운동요법이나 물리치료 및 약물치료는 시행하지 않았다. 주사 후 동통의 변화를 관찰하기 위하여 주사 전 및 주사 후 2 주, 4 주, 6 주, 8 주에 주관적 동통척도인 VAS와 압력통각역치(PPT)를 측정하였으며 실험은 이중맹검으로 시행되었다.

실험결과, BTX-A 주사군은 주사 후 8 주의 시간이 경과되는 동안 VAS가 지속적으로 감소하였으며 PPT는 지속적으로 증가하였으나 lidocaine 주사군에서는 VAS의 감소만이 관찰되었다. 즉, 주관적인 동통척도에 있어서는 BTX-A 주사군과 lidocaine 주사군 사이에 유의한 통계학적 차이가 나타나지 않고(p=0.347), 두 군 모두 시간경과에 따라 동통이 감소하는 양상을 보여주었다. 그러나 PPT의 경우에는 BTX-A 주사군에서만 감소하여 두

군 사이에 유의한 통계학적 차이가 관찰되었다(p=0.000). 본 연구의 결과에 따르면 상부승모근 발통점에 대한 BTX-A 주사는 효과적이고 신뢰할 만한 치료법이라고 생각된다.

주제어 : 보툴리눔 독소, 근막동통, 승모근