Efficacy and Safety of Single Botulinum Toxin Type A (Botox®) Injection for Relief of Upper Trapezius Myofascial Trigger Point: A Randomized, Double-Blind, Placebo-Controlled Study

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Objective: *Botulinum toxin injection has been applied for pain relief in various chronic pain syndromes. Recently, systematic review studies reported inconclusive effects of Botulinum toxin in myofascial pain management. The present study aimed to demonstrate the efficacy and safety of Botulinum toxin type A (BTxA) (Botox®) injection for pain reduction in myofascial trigger point (MTrP) of the upper trapezius muscle.*

Material and Method: *Thirty-three patients with 48 MTrP on the upper trapezius muscles over three months with moderate to severe pain intensity diagnosed at physical medicine and rehabilitation outpatient department were recruited between December 2011 and March 2012. Eligible patients were blinded and randomly injected with single 0.2 ml (20 IU) of BTxA for 24 MTrP and 0.2 ml of 0.9% NaCl solution for 24 MTrP at the most tender trigger point on the upper trapezius muscle. All patients were advised for stretching exercise and ergonomic adaptation throughout the study. At 3- and 6-week after injections, visual analogue scale (VAS), the pressure pain threshold (PPT), and reported adverse effects were measured.*

Results: *Both BTxA and control groups demonstrated statistically significant differences in VAS reduction and increased PPT after 3 weeks and 6 weeks compared with before treatment. There were no statistically significant differences in VAS reduction from baseline between the two groups at 3- and 6-week after treatment. A statistically significant difference in improvement of PPT from baseline and 6-week after BTxA injection compared with 0.9% NaCl group was shown (1.0±0.9 and 0.5±0.7, p = 0.036). There was mild degree side-effects that spontaneous resolved within one week in both groups without significant difference in percentage. No severe adverse effects were reported during the study.*

Conclusion: *The efficacy in VAS reduction of a single 20 IU of Botulinum toxin type A (Botox®) injection was not different from 0.9% NaCl for myofascial trigger point at the upper trapezius muscle. However, Botulinum toxin type A (Botox®) showed statistically significant more increased in pressure pain threshold at 6-week after injection without severe adverse effects.*

Keywords: *Myofascial trigger point, Botulinum toxin, Upper trapezius muscle*

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Myofascial pain syndrome (MPS) is a muscular pain symptom commonly found in clinical practices. The prevalence of MPS in patients is about 30 to 85% in pain specialist clinics[1]. Myofascial trigger point (MTrP) is an important characteristic of MPS defined as a very small, band of hardness, or taut band located within a muscle that can produce specific referred pain pattern from deep palpation[2]. The theory of integrated trigger point hypothesis is widely accepted to explain MTrP mechanism, which is composed of motor endplate dysfunction and intramuscular energy crisis[3].

Botulinum toxin has been studied in MTrP eradication of chronic MPS because an activation of toxin might be able to block a release of acetylcholine at the presynaptic terminal resulting in a muscle relaxation. Therefore, the pain is relieved by preventing the release of pain neurotransmitters at the sensory neuron[4-6]. However, the previous studies were not able to provide a clear conclusion with the efficacy of MTrP treatment by Botulinum toxin[7]. The present study aimed to demonstrate the efficacy and safety of

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a small quantity single injection of Botulinum toxin type A (BTxA) (Botox®) for pain relief in chronic MPS of upper trapezius muscle comparing with 0.9% sodium chloride injection.

Material and Method

Sample size

The present study calculated sample size based on using 1.38 cm differences in visual analogue scale (VAS) score with standard deviation of 1.36 from previous study[8]. The 21 MTrP in each group were required to provide 90% power for detecting the difference with 2-sided test ($\alpha = 0.05$). Allowing for 20% drop out, therefore, 48 MTrP were enrolled before randomization.

Study population

The patients with MTrP of the upper trapezius muscle diagnosed at physical medicine and rehabilitation outpatient department, Phramongkutklao Hospital were recruited between December 2011 and March 2012. The eligible criteria included patients aged 18 to 70 years, experienced MPS more than three months with previous standard treatment and a moderate to severe intensity (at least 3 points) of VAS score. The patients with pregnancy, rheumatologic disorder, neuromuscular diseases such as radiculopathy and myelopathy, conditions associated with coagulopathy or taking anticoagulant medicine, and previous Botulinum toxin therapy within three months were excluded. Patients were divided into two groups by a computer-generated randomization schedule. The allocation sequence was concealed in opaque envelop. The experimental group was injected with Botox®, Botulinum toxin type A (BTxA) (a mixture of 100 IU to 0.9% NaCl 1 ml) at the most painful MTrP of upper trapezius muscle for 0.2 ml (20 IU) single injection and single point with one inch in depth by using 1 ml insulin syringes and a 27 gauge needle. The control group was injected with 0.2 ml of 0.9% NaCl solution at the most painful MTrP with the same technique. The appearance of BTxA and 0.9% NaCl solution are clear and unable to differentiate by sight. A well-experienced physiatrist who performed the injection to the subjects was blinded from the type of injection and subject group identification.

All patients were advised to perform stretching exercise at upper trapezius muscle, suggested for ergonomic adaptation, stop the physiotherapy program, and allowed to take only paracetamol for pain relief. The other physician who did not perform the injection was the assessor and blinded from the subject group. The assessor measured the patients' pain intensity including VAS score and pressure pain threshold (PPT) by using Fisher algometer (FDK20, Wagner instruments, Greenwich CT, USA) at before treatment, 3-, and 6-week after injection. The adverse effects and recorded number of paracetamol taking were asked at the end of study (Fig. 1).

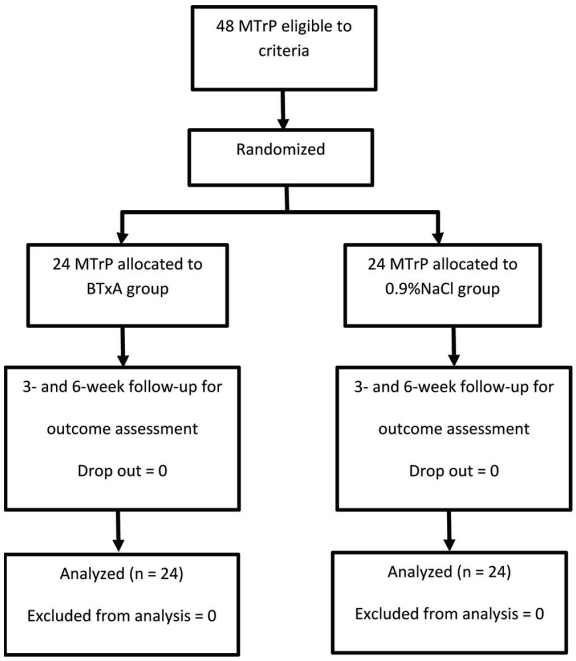

Fig. 1 Trial profile (CONSORT diagram).

Statistical analysis

Clinical data are presented using descriptive statistics including frequency, percentage, average, and standard deviation. The mean values of VAS score and PPT within each group at before injection, 3-, and 6-week after injection were compared by using one-way repeated measures ANOVA. Unpaired t-test was used to compare the mean differences from baseline of VAS score and PPT between two groups at two points of time including 3-week and 6-week after injection. Statistical analyses were performed using STATA/MP12 package version.

Results

Baseline demographic and clinical characteristics of the patients in comparison groups were shown in Table 1. All 33 patients with 48 MTrP were classified by pain type as 18 patients of unilateral

pain and 15 patients of bilateral pain. Eight patients of unilateral pain patients were injected with BTxA and the rest were injected with 0.9% NaCl. For those bilateral pain patients, four of them were injected with BTxA, three patients injected with 0.9% NaCl, and eight patients had different injection on each side.

At before treatment, 3-, and 6-week after injection, the mean of VAS score were 6.7±1.2, 3.5±2.5, and 2.4±2.0, respectively in BTxA group and 6.3±1.2, 3.3±2.8, and 3.4±3.6, respectively in control group (Fig. 2). The mean of PPT at before treatment, 3-, and 6-week after injection were 1.6±0.4, 2.1±0.6, and 2.6±0.8, respectively in BTxA group and 1.7±0.4, 2.0±0.5, and 2.2±0.7, respectively in saline injection group (Fig. 3). Within BTxA group, the data demonstrated statistically significant VAS reduction and increased PPT at 3- and 6-week compared with before treatment ($p<0.05$). The control group by using 0.9% NaCl injection also showed statistically significant VAS reduction and increased PPT at 3- and 6-week compared with before treatment ($p<0.05$). There were no statistically significant differences in VAS reduction (mean differences) from baseline between the two groups at 3- and 6-week after treatment. However, a statistically significant differences in higher PPT (mean differences) from baseline and 6-week after BTxA injection compared with 0.9% NaCl group was shown [-0.5 (95% CI -0.9, -0.1), $p = 0.036$] (Table 2).

Table 1. Baseline demographic and clinical characteristics of the patients in each group

	BTxA (n = 24)	0.9% NaCl (n = 24)
Sex		
Male	4 (16.7)	2 (8.3)
Female	20 (83.3)	22 (91.7)
Age (years)	39.8±10.1	38.8±10.8
BMI (kg/m^2)	24.7±4.0	25.6±4.6
Number of side of the body with upper trapezius MTrP (sides)		
Right	11 (45.8)	13 (54.2)
Left	13 (54.2)	11 (45.8)
Pain duration (months)	24.5±20.2	28.1±22.9
VAS (0-10)	6.7±1.2	6.3±1.4
PPT (kg/cm^2)	1.6±0.4	1.7±0.4

BTxA = Botulinum toxin type A; NaCl = sodium chloride; BMI = body mass index; VAS = visual analogue scale; PPT = pressure pain threshold; MTrP = myofascial trigger point
Data are expressed as n (%) or mean ± standard deviation

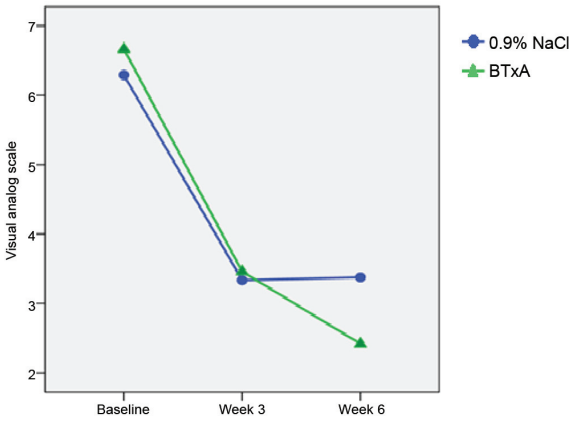

Fig. 2 VAS scores at before injection, 3-, and 6-week after injection (BTxA = Botulinum toxin type A; NaCl = sodium chloride; VAS = visual analogue scale).

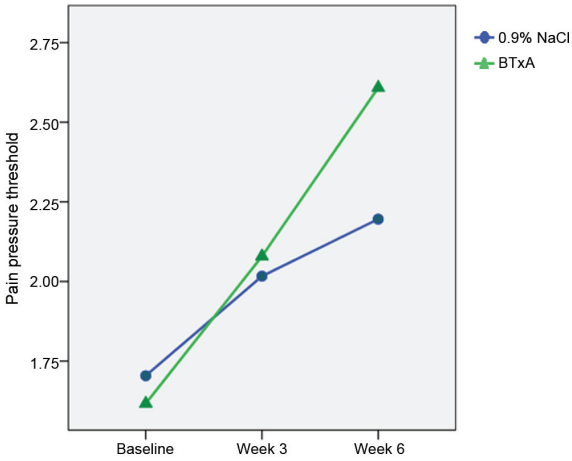

Fig. 3 PPT at before injection, 3-, and 6-week after injection (BTxA = Botulinum toxin type A; NaCl = sodium chloride; PPT = pressure pain threshold).

Paracetamol tablets were used to relieve pain in the first three weeks. Three patients (12.5%) in BTxA group took two tablets, while only two patients (8.3%) in 0.9% NaCl control group took the same amount of paracetamol. Hence, there were no statistically significant differences between the comparison groups ($p = 1.000$).

In terms of adverse events of injections, 11 patients in BTxA injection group (45.8%) had non-severe effects after a few days of the injection. One patient had 2 cm skin redness round the injection site, two patients felt feverish for one day, four patients felt tight on the injection site for one day, three patients felt stiff on injected shoulders for two days, and one patient had skin redness and felt stiff. Similarly,

Table 2. Comparison of mean differences from baseline of VAS score and PPT between 2 groups (BTxA and 0.9% NaCl)

	3-weeks after injection		6-week after injection	
	Mean differences between groups (95% CI)	*p*-value	Mean differences between groups (95% CI)	*p*-value
VAS	0.25 (-1.2, 1.7)	0.725	1.3 (-0.3, 3.0)	0.112
PPT	-0.2 (-0.5, 0.2)	0.344	-0.5 (-0.9,-0.1)	0.036

Data are analyzed by using the unpaired t-test for mean differences from baseline between 2 groups at 3-week and 6-week after injection

10 patients in saline injection group (41.7%) had non-severe effects after a few days of the injection. One patient had 2 cm skin redness around the injection site, two patients felt feverish for one day, three patients felt tight on the injection site for one day, two patients felt stiff on injected shoulders for two days, and two patients felt drowsier on injection days. These were mild degree side effects with spontaneous resolved within one week in both groups without significant difference in percentage between the two groups ($p = 0.771$).

Discussion

The presented study showed the efficacy of upper trapezius muscle myofascial pain relieved by a single BTxA (Botox®) injection. Patients injected by 20 IU of BTxA at the most painful tender point on the upper trapezius muscle had a statistically significant higher PPT by algometer than patients with 0.9% NaCl solution injection after six weeks of the injection. There were no statistically significant differences in VAS reduction from baseline between the two groups at 3- and 6-week after treatment. Adverse events found in treatment groups had no statistically significant differences. All 11 patients affected had non-severe adverse events and a complete recovery within three days.

When comparing with previous studies, there were some results consistent with the present study[8-10]. Regarding to previous studies that supported the efficacy of Botulinum toxin in MTrP pain relief, a significant pain reduction showed after four weeks of the injection and the pain relief remained for 12 weeks after the injection. These earlier studies were consistent with the present study that pain relief showed significantly on six weeks after the injection compared with the baseline.

A significant increase in PPT values in BTxA injection group certainly proved that Botulinum toxin could reduce MTrP pain. However, VAS scores of treatment groups showed no significant differences at 3- and 6-week in the present study. It might be an improper use of VAS for evaluation in local pain points. VAS scores could diverge if there was other pain muscle nearby and showed inaccurate scores that was not truly MTrP pain. VAS is a subjective assessment reference, which is uncertain and inaccurate whereas PPT is used at local pain points to evaluate pain intensity and get high accuracy by using algometer pressing directly on pain muscle points. As the present study evaluated only one MTrP, PPT should be a proper evaluation to measure pain intensity in myofascial pain treatment study. Furthermore, the algometer is able to evaluate inter- and intra-examiner reliability in high values so that it can be used for quantitative, objective measurement[11]. The algometer may specifically response to latent trigger point improvement so the results from the present study may indicate the specific effectiveness in MTrP eradication compared with normal saline control treatment.

A proper amount of Botulinum toxin injection on each point currently had no standard amount. A low amount (5 IU per point) of toxin might not have a significant pain relief and a high amount of toxin might cause more or severe adverse events[12-14]. Therefore, the present study chose moderate dosage of BTxA leading to the efficacy in pain relief and less adverse effects.

Conclusion

The present study concluded that the efficacy of a single 20 IU of Botulinum toxin type A (Botox®) in VAS reduction was not statistically different from 0.9% NaCl for myofascial trigger point at the upper trapezius muscle. However, Botulinum toxin type A (Botox®) was able to demonstrate statistically significant increased in pressure pain threshold at 6-week after injection without severe adverse effects.

Study limitation

There were some limitations of the presented study. The follow-up period was too short to identify the duration effect of Botulinum toxin. Further studies should extend the duration of follow-up until

medicine is ineffective. Only upper trapezius muscle was particularly selected in the treatment so the applied use of other muscles is needed in further studies to get a proper injected dosage. Additionally, the evaluation of pain reduction was specifically considered while other outcome evaluation such as functional aspect, quality of life, and cost-effectiveness were not included. Last but not least, the recording of co-interventions such as physical therapy, massage, and exercise were not covered in the present study. However, all participants were informed to avoid any co-interventions during the study.

What is already known on this topic?

Botulinum toxin has been studied to apply in MTrP treatment in chronic MPS by blockage the release of acetylcholine at presynaptic terminal resulting in muscle relaxation and preventing release of pain neurotransmitters at sensory neuron. In 2012, the systematic review of four high quality studies revealed no statistically significant improvement pain score and PPT of relatively high dosage BTxA compared to saline injection, indicating the inconclusive evidence to support the effectiveness in MPS treatment.

What this study adds?

The present randomized, double-blind, placebo-controlled study support the evidence that PPT on upper trapezius MTrP was improved statistically significantly as compared to saline injection at 6-week after the intermediate doses (20 IU) of single BTxA injection. This evidence tended to demonstrate the superiority of BTxA in MTrP eradication compared with 0.9% NaCl.

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Potential conflicts of interest

None.

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ประสิทธิภาพและความปลอดภัยของการฉีดโบทูลินั่มท็อกซิน ชนิดเอ (Botox®) ครั้งเดียวเพื่อการลดปวด myofascial trigger point กล้ามเนื้อ upper trapezius: การศึกษาแบบสุ่ม ปกปิดสองทาง และมีกลุ่มควบคุม

พศวีร์ ขวัญช่วย, ธวัชชัย เพ็ชรน้ำสิน,พิเชษฐ์ เยี่ยมศิริ, นัคมน ผาสุก, วรรณรัตน์ ศรีกนก, ชนศักดิ์ หทัยอารีย์รักษ์

วัตถุประสงค์: การฉีดโบทูลินั่มท็อกซินได้ถูกใช้เพื่อการลดความปวดในกลุ่มอาการปวดเรื้อรังหลากหลายสาเหตุ เมื่อไม่นานมานี้ การศึกษาแบบทบทวนอย่างเป็นระบบได้รายงานผลที่ยังสรุปไม่ได้ชัดเจนถึงผลของ โบทูลินั่มท็อกซิน ในการรักษา myofascial pain การศึกษาที่นำเสนอนี้ มีจุดมุ่งหมายเพื่อศึกษาประสิทธิภาพและความปลอดภัยของการฉีดโบทูลินั่มท็อกซิน ชนิดเอ (โบท็อกซ์) เพื่อรักษาจุดปวด myofascial trigger point ที่กล้ามเนื้อ upper trapezius

วัสดุและวิธีการ: ผู้ป่วย 33 ราย ที่มีจุดปวด myofascial trigger point ที่กล้ามเนื้อ upper trapezius มานานกว่า 3 เดือน ซึ่งมีความรุนแรงระดับปานกลางถึงมาก ที่เข้ารับการตรวจที่ห้องตรวจผู้ป่วยนอกแผนกเวชศาสตร์ฟื้นฟูระหว่างเดือนธันวาคม พ.ศ. 2554 ถึง มีนาคม พ.ศ. 2555 ผู้ป่วยที่เข้าเกณฑ์ทั้งหมดจะถูกปกปิดจากวิธีการรักษาและถูกสุ่มเป็น 2 กลุ่ม โดย 24 จุดปวดที่อยู่ในกลุ่มทดลองจะได้รับการฉีดโบทูลินั่มท็อกซิน ชนิดเอ (โบท็อกซ์) ที่จุดที่เจ็บที่สุดในกล้ามเนื้อ upper trapezius 1 จุด ในปริมาณ 0.2 มล. (20 ยูนิต) และอีก 24 จุดปวด จะอยู่ในกลุ่มควบคุมซึ่งได้รับการฉีดน้ำเกลือในปริมาณ 0.2 มล. ที่ตำแหน่งเดียวกันกับกลุ่มทดลอง ผู้ป่วยทุกรายจะได้รับคำแนะนำเกี่ยวกับการการยืดกล้ามเนื้อและการปรับเปลี่ยนท่าทางให้ถูกต้องตามหลักการยศาสตร์ โดยตลอดการศึกษา การประเมินผลการรักษาจะใช้การติดตามผลจากระดับความปวด visual analog scale (VAS) และ ค่าpressure pain threshold (PPT) และการรายงานผลข้างเคียง ที่ระยะเวลา 3 และ 6 สัปดาห์ หลังการฉีดยา

ผลการศึกษา: กลุ่มฉีดโบทูลินั่มท็อกซิน ชนิดเอ และกลุ่มควบคุมด้วยการฉีดน้ำเกลือสามารถลดระดับความปวด VAS และเพิ่มค่า PPT ได้อย่างมีนัยสำคัญทางสถิติเมื่อเปรียบเทียบก่อนและหลังฉีดที่ 3 และ 6 สัปดาห์ สำหรับค่าความแตกต่างของระดับความปวด VAS ที่ลดลง ระหว่างก่อนฉีด และที่ 3 และ 6 สัปดาห์ พบว่าไม่แตกต่างกันอย่างมีนัยสำคัญทางสถิติเปรียบเทียบระหว่าง 2 กลุ่ม ($p = 0.786$ และ 0.325 ตามลำดับ) แต่พบความแตกต่างกันอย่างมีนัยสำคัญทางสถิติของการเพิ่มขึ้นของค่า PPT จากช่วงเวลาก่อนฉีด และที่ 6 สัปดาห์ หลังการฉีดโบทูลินั่มท็อกซิน ชนิดเอ เปรียบเทียบกับกลุ่มควบคุม (1.0 ± 0.9 และ 0.5 ± 0.7, $p = 0.036$) ผลข้างเคียงจากการฉีดนั้นพบเพียงผลข้างเคียงที่มีความรุนแรงน้อยหายได้เองภายใน 1 สัปดาห์ และเปอร์เซ็นต์ของผลข้างเคียงดังกล่าวทั้ง 2 กลุ่ม ไม่แตกต่างกันอย่างมีนัยสำคัญทางสถิติโดยไม่พบผลข้างเคียงที่รุนแรงในกลุ่มโบทูลินั่มท็อกซิน ชนิดเอ เลย

สรุป: ประสิทธิภาพของการฉีดโบทูลินั่มท็อกซิน ชนิดเอ (โบท็อกซ์) ขนาด 20 ยูนิต ครั้งเดียวที่จุดที่เจ็บที่สุดของ myofascial trigger point ที่กล้ามเนื้อ upper trapezius ในการลดอาการปวดโดยวัดจากค่า VAS ไม่แตกต่างจากการฉีดด้วยน้ำเกลือ แต่มีประสิทธิภาพในการเพิ่มค่า PPT ได้มากกว่าที่ 6 สัปดาห์ หลังฉีดอย่างมีนัยสำคัญทางสถิติโดยไม่พบผลข้างเคียงที่รุนแรงแต่อย่างใด