Original Article

Incobotulinum Toxin A with a One-year Long-lasting Effect for Trapezius Contouring and Superior Efficacy for the Treatment of Trapezius Myalgia

Napamon Supornpun[1], Paisal Rummaneethorn[1], Thamthiwat Nararatwanchai[1], Tawee Saiwichai[2], Sirinthip Chaichalotornkul[1]

[1]School of Anti-Aging and Regenerative Medicine, Mae Fah Luang University, [2]Faculty of Public Health, Mahidol University, Bangkok, Thailand

Abstract

Context: Based on various Botulinum toxin A products, reports of the lower efficacy of Incobotulinum toxin A compared with Onabotulinum toxin A for muscle contouring were observed. In addition, complications of trapezius myalgia and shoulder contouring treatment from malpractice have been reported. **Aims:** The study aimed at comparing the efficacy between Incobotulinum toxin A and Onabotulinum toxin A; research was conducted on a safe treatment technique for trapezius hypertrophy and trapezius myalgia. **Materials and Methods:** A split-shoulder, double-blind, randomized controlled trial was performed. Twenty volunteers with trapezius hypertrophy and trapezius myalgia were randomly injected with 30 units of Incobotulinum toxin A and Onabotulinum toxin A in each trapezius muscle guided by ultrasound. **Results:** The trapezius thickness among those receiving treatment with Onabotulinum toxin A and Incobotulinum toxin A on day 60 was 7.35 ± 1.11 and 7.33 ± 1.21 mm, respectively, which did not portray a significant difference ($P = 0.991$). Compared with the muscle size from day 60 to one year, the size of the trapezius muscle that had been treated by Onabotulinum toxin type A regained a significantly larger size compared with that treated by Incobotulinum toxin A ($P = 0.027$). On comparing the size of the trapezius muscle treated by Incobotulinum toxin A between one year and day 0, it was observed that the trapezius thickness at one year had significantly decreased ($P < 0.001$). On comparing the pain score from day 60 to day 0, it was observed that the pain scores of trapezius myalgia treated by Onabotulinum toxin A and Incobotulinum toxin A significantly differed ($P = 0.003$). **Conclusions:** Incobotulinum toxin A had the same efficacy but a longer lasting effect for the trapezius size contouring and a higher efficacy for trapezius myalgia treatment compared with Onabotulinum toxin A.

Keywords: Incobotulinum toxin A, Onabotulinum toxin A, trapezius hypertrophy, trapezius myalgia, ultrasound-guided injection

Introduction

Trapezius myalgia and trapezius hypertrophy are conditions usually occurring together among middle-aged women; many women are concerned about the thickness of their neck and shoulders pertaining to their appearance, resulting in a loss of confidence.

Trapezius myalgia is characterized by symptoms such as stiffness, pain, and tightness of the upper trapezius muscle, which could present as acute or chronic neck and shoulder pain.[1]

In addition, trapezius myalgia could be definitely diagnosed when muscle tightness, neck pain, and trigger point are presented without tension neck syndrome or cervical syndrome presentation.[2] Usually, the upper trapezius muscle thickness is approximately 5 mm.[3] The hypertrophic process of the trapezius muscle increases the size of the muscle beyond normal thickness; trapezius hypertrophy could affect women, as it makes them appear more masculine than feminine.

Botulinum toxin A not only relieves myofascial pain but also improves shoulder and neck contouring. The efficacy

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Address for correspondence: Ms. Napamon Supornpun, 36/87-88 School of Anti-aging and Regenerative Medicine, Asoke Road, Sukhumvit 21, Wattana, Bangkok 10110, Thailand.
E-mail: dr.napamon@gmail.com

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of Botulinum toxin A for trapezius myofascial pain has also been reported for five years in Thailand.[4] Moreover, it could be used in cosmetic applications, such as facial rhytids, brow lifting,[5] and masseteric hypertrophy for lower facial contouring.[6] In the past, Botulinum toxin type A,which had a component of complex proteins, was believed to contribute greater stability and effectiveness, but presently, one study has demonstrated no difference in outcome between with and without complex proteins.[7]

Botulinum toxin A could interfere with the releasing of many mediators of pain transmission, for example, substance P, calcitonin gene-related peptide (CGRP), and ATP. Simultaneously, noradrenaline and dopamine provide pain relief.[8] Three Botulinum toxin formulations that have been approved by the US Food and Drug Administration and that are well known consist of Onabotulinum toxin A, Abobotulinum toxin A, and Incobotulinum toxin A.[9] All three preparations have similar mechanisms and are produced from *Clostridium botulinum*, a gram-positive, anaerobic bacterium serotype A. The active neurotoxin is pure 150 kDa; however, the nontoxic accessory proteins (NAPs) bonding with the toxin differ in size, creating various molecular weights of Botulinum toxin complex.[10] The complex size of Onabotulinum toxin A is 900 kDa, Abobotulinum toxin A is 500–900 kDa, and Incobotulinum toxin A is pure 150 kDa without any complex proteins included.[11] *In vivo* potency between Onabotulinum toxin A and Incobotulinum toxin A also differed as reported.[12] All unopened vials have a shelf life of approximately three years, Incobotulinum toxin A could be stored at room temperature (below 25°C), and others require a storage at 2°C–8°C. However, all products should be stored for only 24 h at 4°C after reconstitution.[13]

Also, differences of pharmacological details have been reported between Onabotulinum toxin A and Incobotulinum toxin A, such as quantities of neurotoxin (ng/100 U), the specific potency of neurotoxin,[14] the median effective dose (ED50) potency,[15] and the median lethal dose (LD50).[16] Further, Onabotulinum toxin A is prepared under a process of repeated precipitation under low pressure or vacuum-dried,[17] whereas Incobotulinum toxin A is stabilized in the lyophilization process.[18]

Saad and Gourdeau demonstrated the noninferiority of Incobotulinum toxin A to Onabotulinum toxin A for benign essential blepharospasm (BEB).[7] Mastromauro *et al.* described an earlier onset of Incobotulinum toxin A compared with that of Onabotulinum toxin A.[11] Chundury *et al.* reported that Incobotulinum toxin A had a shorter effective period compared with Onabotulinum toxin A in treating patients with BEB,[19] whereas Roggenkämper *et al.* described the same duration of effect between both products.[20] However, Rappl *et al.* reported a longer lasting effect of Incobotulinum toxin A in treating glabellar frown lines, compared with Onabotulinum toxin A and Abobotulinum toxin A.[21] Further, reports have revealed that some patients receiving Botulinum toxin A with complex proteins could develop neutralizing antibodies, resulting in antibody-induced therapy failures.[22,23]

The differences between Incobotulinum toxin A and Onabotulinum toxin A still need to be determined due to disparity in previous reports of the differences in the onset, efficacy, complex proteins, molecular weights, manufacturing process, LD50 dosage, and also the quantity of neurotoxin. Consequently, the relationship between the dose and clinical effects of Incobotulinum toxin A (Xeomin) and Onabotulinum toxin A (Botox) should be studied.

This clinical study aimed at evaluating the therapeutic equivalence in the efficacy of Incobotulinum toxin A compared with Onabotulinum toxin A in the treatment of trapezius hypertrophy contouring and other outcomes, such as the efficacy of Botulinum toxin A for trapezius myalgia without considering the trigger point, the period of effectiveness from the treatment and safety of trapezius contouring with Botulinum toxin A under the secured injection design. Further, other serious complications, such as shoulder drop or limited ranges of neck motions due to accessory nerve injury, were observed in this study.[24]

Materials and Methods

Study design

The study comprised a one-year, prospective, split-shoulder, double-blind, randomized controlled trial conducted between May 2019 and May 2020. Twenty patients with trapezius muscle hypertrophy and trapezius myalgia, matching the inclusion and exclusion criteria, were included. The patients comprised newly diagnosed subjects and subjects who had not previously been injected with Botulinum toxin A. The study protocol was approved by the Mae Fah Luang University Ethics Committee on Human Research (approval no. 200/2561) and conformed to the guidelines of the 1975 Declaration of Helsinki. Written informed consent was obtained from all participants. All patients were treated with Botulinum toxin A in one session, with two-month and one-year follow-up periods. Single injections of 30 U of Onabotulinum toxin A and 30 U of Incobotulinum toxin A were administered to all participants in a randomized, double-blind, split-shoulder manner.

Population and sample

In examining related studies, none had compared the efficacy of Incobotulinum toxin A and Onabotulinum toxin A on trapezius contouring effectiveness. However, one related study had recorded the thickness decrease of the muscles after being treated with a Botulinum toxin A injection,[25] which was calculated as two dependent

mean formulations for the sample size in this study, and the sample size should be at least 19. Hence, with the probability of a 5% dropout, 20 subjects were enrolled. Twenty female patients with trapezius hypertrophy concerns, aged from 20 to 45 years, at an outpatient clinic, were randomly enrolled in the study from May 1, 2019 to May 1, 2020.

Symptoms such as muscle spasm, limited ranges of shoulder motions, and myalgia were reported, of which the average trapezius thickness was around 5 mm.[26] Consequently, the inclusion criteria overarched the myofascial pain at the shoulders and neck according to the neck and shoulder thickness. The trapezius thickness was greater than or equal to 6 mm, which was confirmed by ultrasonography and subjects were available for the follow-up at the hospital on day 60 and at one year. In this regard, all participants agreed to sign an informed consent form, approving their photographs to be published.

The exclusion criteria included allergic reactions to Botulinum toxin, medical illnesses in contraindicated diseases, such as myasthenia gravis, Eaton-Lambert syndrome, and amyotrophic lateral sclerosis; current medication, such as aminoglycoside antibiotics, cyclosporine, muscle relaxants, magnesium sulfate, lincosamide, history of cervical injury or cervical spondylolisthesis, lactation or pregnancy, history of Botulinum toxin injection at the trapezius area; and medical illnesses, such as cervical dystonia.

Procedure

Preparation

In all, 100-U vials of crystallized Onabotulinum toxin A and Incobotulinum toxin A were reconstituted with 2 mL of 0.9% of preservative-free saline to yield 5 U/0.1 mL.

Injection design

Trapezius muscle is the largest complex scapulothoracic muscle consisting of three parts: descending part, transverse part, and ascending part.[27] The descending part of the trapezius muscle is clinically associated with neck pain and aesthetic applications.[28] In clinical applications, the injection site is confined to the upper portion connecting the neck (C7, spinous process of vertebra prominence) and shoulders (acromion). The main trunk of the accessory nerve is distributed from the foramen ovale down to the trapezius and sternocleidomastoid muscle, while perforating the branch innervated descendant part of the trapezius muscle about 2 cm medial to the trapezius muscle.[29] Injury to this nerve can cause wasting of the shoulder muscles, winging of the scapula, and weakness of shoulder abduction and external rotation.[30] Therefore, considering nerve distribution and homogenous outcome, six injection points were designed at the middle area of an imaginary line [Figure 1] from the C7 to the acromion process; the interval between each point of the injection was 1 inch [Figure 1].

This design of the injection technique was safe for both the patients and physicians due to its proper area of injection to minimize the size of the trapezius muscle without nerve injury. In addition, the pattern of the injection points, which were aligned along the trapezius muscles, was useful for homogenous contouring related to the equal spreading of Botulinum toxin A at each point of the injection that Botulinum toxin A generally diffuses 2–4 cm from the injection site.[31]

Ultrasound-guided injection technique

Onabotulinum toxin A and Incobotulinum toxin A were randomly injected in the trapezius muscle. An ultrasound-guided injection of the trapezius muscle was administered with a 1.5-inch 30-G needle. Thirty units of Onabotulinum toxin A and Incobotulinum toxin A were randomly injected to each side at the prominent portions of the upper trapezius muscle and 5-unit dosage of Botulinum toxin A per one point; in total six points on each side according to the study design and using the ultrasound guided injection technique [Figure 2]. This would be useful only for an injection placed precisely in the muscle that would not accidentally mislead the needle in the subcutaneous fat layer.

Outcomes and methods of assessment

The primary outcome was the thickness of the trapezius size, which was measured by ultrasonography. The secondary outcome was the visual analogue scale (VAS) of the pain scores using a 10-point pain scale (0 = no pain to 10 = severe pain) and other complications, such as bruising, muscle fatigue, and pain after treatment based on the provided questionnaires. A photograph of the shoulder area was taken before the treatment and on day 60 [Figures 3 and 4].

Ultrasonography of the trapezius size was performed on day 0, day 60 and at one year at the most prominent

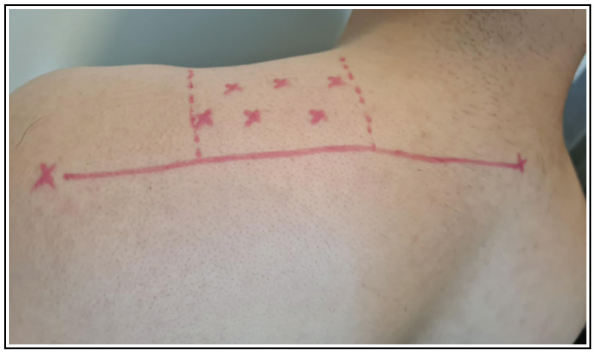

Figure 1: Six points of injection in the middle part of an imaginary line from the cervical spine level 7 to the acromion process

portions of the upper trapezius muscle. Moreover, the pain of the trapezius myalgia was assessed by the VAS of pain scores at the shoulder area before and 60 days after treatment.

Statistical analyses

The reduced thickness of the trapezius was reported by ultrasonography, and the mean trapezius thickness decreased after the treatment was calculated. The paired t-test was used to compare the decreasing muscle thickness and regaining of the trapezius hypertrophy within the group. The student t-test was used to compare the mean of the decreasing muscle thickness and regaining between Onabotulinum toxin A and Incobotulinum toxin A. Significant levels for all analyses were set at P value <0.05. The pain assessment by VAS of the shoulder area was recorded before and after treating trapezius hypertrophy with Onabotulinum toxin A and Incobotulinum toxin A. The mean of the trapezius myalgia VAS pain score was calculated. The paired t-test (normal distribution) was used to compare the VAS pain score of the trapezius myalgia within the group, and the student t-test was used to compare the mean pain score between Onabotulinum toxin A and Incobotulinum toxin A.

Results

The participants' demographic details are provided in Table 1.

Figure 2: Ultrasound-guided injection technique

All the enrolled subjects were measured for their trapezius thickness by using ultrasonography to obtain more precise data of the thickness. This was performed on day 0, day 60 and at one year after the treatment [Figure 5].

From the results of the Onabotulinum toxin A injection compared with the baseline of trapezius thickness, the size had significantly decreased after 60 days (95% CI = 2.30; $P < 0.001$) and at one year; however, the difference was not significant (95% CI = 0.04; $P = 0.585$). In contrast, when comparing the trapezius thickness of one year with day 60, the muscle had regained at a significant level (95%

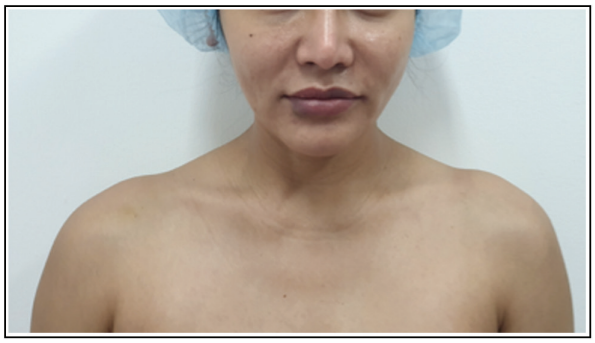

Figure 3: Before treatment

Figure 4: After treatment

Table 1: Participants' demographics

Data characteristics	Subject, n (%)
Gender	
Female	20 (100)
Male	0
Age	
Mean ± SD	36.15 ± 5.62
Minimum–maximum	28–45
Occupation	
Housekeeper	4 (20)
Therapist	5 (25)
Office employee	5 (25)
Nurse	6 (30)
Underlying disease	
Dyslipidemia	1 (5)
Allergic rhinitis	1 (5)

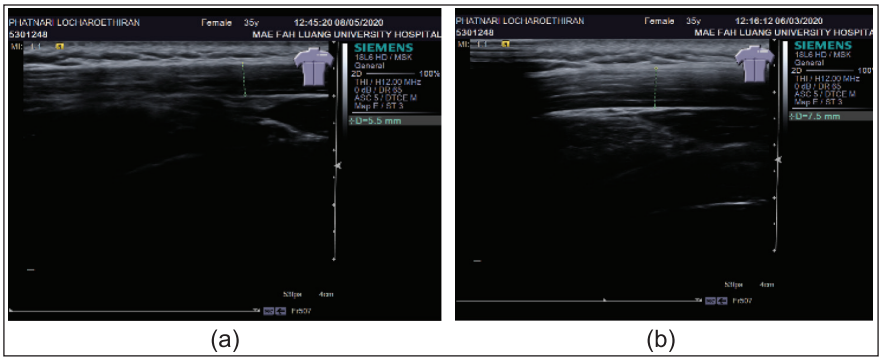

Figure 5: Trapezius thickness from ultrasonography: (A) before; (B) after

Table 2: Results of trapezius thickness from ultrasonography before and after treatment with onabotulinum toxin A

Time of evaluation of onabotulinum toxin A				Mean difference (95% CI)	*P* value
Time	**Mean ± SD**	**Time**	**Mean ± SD**		
Baseline	9.66 ± 2.07				
		60 days	7.35 ± 1.11	2.31 (1.56 to 3.06)	<0.001
		12 months	9.62 ± 1.97	0.04 (−0.10 to 0.1)	0.585
60 days	7.35 ± 1.11				
		Baseline	9.66 ± 2.07		
		12 months	9.62 ± 1.97	−2.27 (−2.99 to −1.56)	<0.001

CI = −2.27; $P < 0.001$) [Table 2]. For the Incobotulinum toxin A injection compared with the baseline trapezius thickness, the size had significantly decreased after 60 days (95% CI = 2.30; $P < 0.001$) and at one year (95% CI = 0.74; $P < 0.001$). Nonetheless, comparing the trapezius thickness between one year and day 60, the muscle size had regained at a significant level (95% CI = −1.56; $P < 0.001$) [Table 3].

Comparing the muscle size on day 0 with that at one year, the thickness of the trapezius muscle, treated by Onabotulinum toxin type A, had regained a larger size compared with that treated by Incobotulinum toxin A, which was at a significant level (95% CI = −0.70 ± 0.44; $P < 0.001$) [Table 4; Figure 6]. Therefore, Incobotulinum toxin A was equally effective in reducing the trapezius muscle thickness compared with Onabotulinum toxin A on day 60 after treatment. Nevertheless, after four months, the period of the reversible effect of every type of Botulinum toxin A, the trapezius muscle, which was treated by Incobotulinum toxin A, was still smaller than baseline thickness and had regained less muscle mass compared with Onabotulinum toxin A. The differences between the products might be the result of being free from complex proteins in the Incobotulinum toxin A structure, which might have caused a longer lasting effect due to a lack of reactions from the immune system to complex protein,[32] which did not contain Incobotulinum toxin A.

In this regard, the pain scores decreased significantly in both products ($P < 0.001$) after Botulinum toxin A injection [Table 5]. The differences in the pain score (0–10) of trapezius myalgia between Onabotulinum toxin A and Incobotulinum toxin A were at a significant level (95% CI = −1.5; $P = 0.003$). Incobotulinum toxin A had a higher efficacy in treating trapezius myalgia compared with Onabotulinum toxin A [Figure 7], which might be related to the smaller molecular size of Incobotulinum toxin A, which could cause greater distribution to the muscle and create a higher effect for muscle relaxation and higher efficacy in treating trapezius myalgia.

Discussion

Both types of Botulinum toxin A were effective in reducing the trapezius muscle in the same way, as proved by a related study in which the calf was reduced using Onabotulinum toxin A.[33] Other studies also reported the effectiveness of Incobotulinum toxin A for the reduction of masseter muscle.[34] This study reported the effective treatment of Botulinum toxin type A for both trapezius contouring and myalgia. Incobotulinum toxin A had a superior outcome for muscle myalgia compared with Onabotulinum toxin A, which may be related to the smaller molecular size, resulting in easier distribution to the muscle and an earlier onset of the efficacy.[6] Incobotulinum toxin A also had a longer lasting effect for reducing the muscle size, similar to a related study.[21] Further, this might be related to the condition of being free from complex proteins in the preparation of Incobotulinum toxin A.

Even though Botulinum toxin A has been used for the myofascial trigger point in treating myofascial pain syndrome for a while, this study performed the procedure without detecting any trigger points in the treatment area. In addition, a positive result was observed of gradual pain relief in two weeks along with reduced size of the trapezius

Table 3: Results of trapezius thickness from ultrasonography before and after treatment with incobotulinum toxin A

Time of evaluation of incobotulinum toxin A				Mean difference (95% CI)	*P* value
Time	Mean ± SD	Time	Mean ± SD		
Baseline	9.63 ± 1.58				
		60 days	7.33 ± 1.21	2.30 (1.76 to 2.85)	<0.001
		12 months	8.89 ± 1.52	0.74 (0.52 to 0.96)	<0.001
60 days	7.33 ± 1.21				
		Baseline	9.63 ± 1.58		
		12 months	8.89 ± 1.52	−1.56 (−2.07 to −1.06)	<0.001

Table 4: Paired differences of mean trapezius thickness

	Onabotulinum toxin A	Incobotulinum toxin A	Mean difference ± SD	*P* value
	Mean ± SD	Mean ± SD		
Day 60+	2.31 ± 1.59	2.30 ± 1.16	0.01 ± 1.30	0.991
1 year++	0.04 ± 0.28	0.74 ± 0.48	−0.70 ± 0.44	<0.001
1 year+++	−2.27 ± 1.53	−1.56 ± 1.07	−0.71 ± 0.30	0.027

[+]Day 0–60
[++]Day 0–1 year
[+++]Day 60–1 year

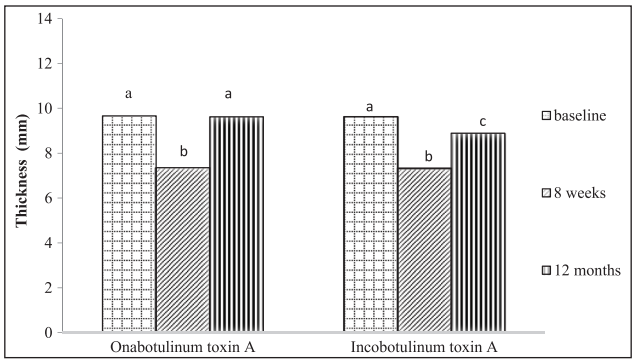

Figure 6: Comparison of trapezius thickness within the group at different points of time: The different letters indicate significance

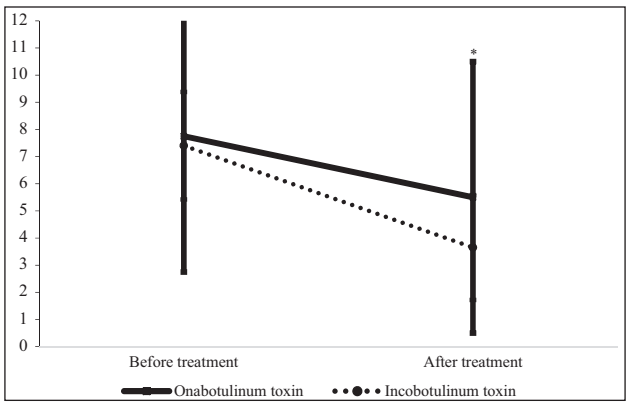

Figure 7: Pair differences of mean pain scores in trapezius myalgia (* indicating a significant difference, $P = 0.003$)

muscle, in which the effectiveness for trapezius myalgia treatment could be related to the muscle relaxation effect of Botulinum toxin A, which was supplied to the whole trapezius muscle mass, causing an affirmative result of the trapezius myalgia treatment.

Considering the injection technique, the ultrasound-guided injection at the injection landmarks in this study was safe. Satisfaction with the shoulder contouring was achieved without any irregularity of the trapezius area. In addition, the ultrasound-guided injection was useful for injecting Botulinum toxin in the muscle, which was related to a previous study reporting that instrumental guidance was found to be superior to a manual needle injection.[35]

Conclusions

Botulinum toxin type A is the treatment of choice for trapezius hypertrophy and trapezius myalgia. The ultrasound-guided along injection technique in this study and 30-unit dosage were recommended for practical trapezius contouring because no serious side effects were found, and this contributed to the satisfactory outcomes for all patients. Incobotulinum toxin A had a superior outcome for trapezius myalgia compared with Onabotulinum toxin A, and it had a longer lasting effect for reducing the size of the trapezius muscle.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Table 5: Pain scores of trapezius myalgia before and after treatment

Group	VAS, day 0	VAS, day 60	Mean differences (95% CI)	*P* value
Onabotulinum toxin A	7.75 ± 1.65	5.50 ± 1.79	2.25 ± 0.79 (1.88 to 2.63)	<0.001
Incobotulinum toxin A	7.40 ± 1.98	3.65 ± 1.93	3.75 ± 1.97 (2.83 to 4.67)	<0.001

Conflicts of interest

There are no conflicts of interest.

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