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Botulinum Toxin type A injections for patients with painful hallux valgus: a double-blind, randomized controlled study

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KEYWORDS

Adductor hallucis
Botulinum toxin type A
Disability
Hallux valgus angle
Pain

ABSTRACT

Hallux valgus (HV) related pain and disability remains a medical challenge to date. We have evaluated the therapeutic effect of intramuscular Botulinum Toxin type A (BTX-A) injection on painful HV in a double-blind randomized controlled trial. Sixteen patients having painful HV in at least one foot from the Department of Physical Medicine and Rehabilitation at a medical center in northern Taiwan have participated. Patients were randomized into two groups to receive intramuscular injections of either BTX-A or normal saline (NS) to the oblique and transverse heads of the adductor hallucis, flexor hallucis brevis and extensor hallucis longus muscles. Primary outcome measurements were selected from the Taiwan Chinese version of the Foot Function Index subscales on pain (questions 1-6, 9) and disability (question 10-18). The secondary outcome measurement was the HV angle. Patients were assessed at baseline and at 1, 2, 3, and 6 months after treatment. The demographic data and measurements were comparable between the two groups at baseline ($p>0.05$). BTX-A and NS reduced pain and disability one month after injection. Pain reduction induced by BTX-A injection lasted for at least 6 months while that induced by NS lasted for only 1 month. In addition, patients in the BTX-A group showed greater improvement in pain score ($p<0.001$), disability score ($p<0.05$), and HV angle ($p<0.05$) than patients in the NS group. The results reflected that HV-related muscle injection of BTX-A resulted in a marked reduction in pain for up to 6 months.

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1. Introduction

Hallux valgus (HV) is a frequently seen abnormality of the first metatarsophalangeal joint. HV affects foot appearance, choice of footwear [1], and causes functional disability, including foot pain [2,3], impaired gait patterns [4], poor balance [5], falls in older adults [6,7] and impaired quality of life [8]. Although HV affects approximately 23% of adults [9], effective conservative interventions are limited [10]. Patients with a mild (<30°) HV angle are generally managed with conservative treatment [11]. For example, night splints are often used to balance the pull of the surrounding ligaments, foot exercises are used to increase muscle strength, and orthotic applications such as inserts, are used to correct foot biomechanics [12-14]. However, Ferrari et al. suggested that orthotic devices and night splints have no superiority over no treatment for mild-to-moderate HV [15]. Furthermore, padding, orthotic devices, and larger shoes are patient-dependent and can be inconvenient [10].

Intramuscular Botulinum toxin type A (BTX-A) injections induce muscle paralysis by blocking the release of presynaptic acetylcholine at the neuromuscular junction [16]. BTX-A injections have been proved useful in treating muscle imbalance, muscle spasms [10], and spastic toes [17,18] and in providing significant pain reduction [19] in patients with recalcitrant plantar fasciitis at six months as compared to one month post-injection [19]. In a case study, Radovic et al. showed that BTX-A injection not only reduced HV-induced pain, but also reduced hallux abducto valgus deformity induced by HV [10].

In this double-blind, randomized controlled trial, we examined the effectiveness of intramuscular BTX-A injections in patients with painful HV who did not respond to chronic medication, splinting or surgical intervention. The therapeutic approach for managing such patients included injecting BTX-A into the oblique and transverse heads of the adductor hallucis, the flexor hallucis brevis, and the extensor hallucis longus muscles.

2. Methods

2.1. Participants

A total of 23 patients were enrolled after obtaining approval from the institutional review board of the Chang Gung Memorial

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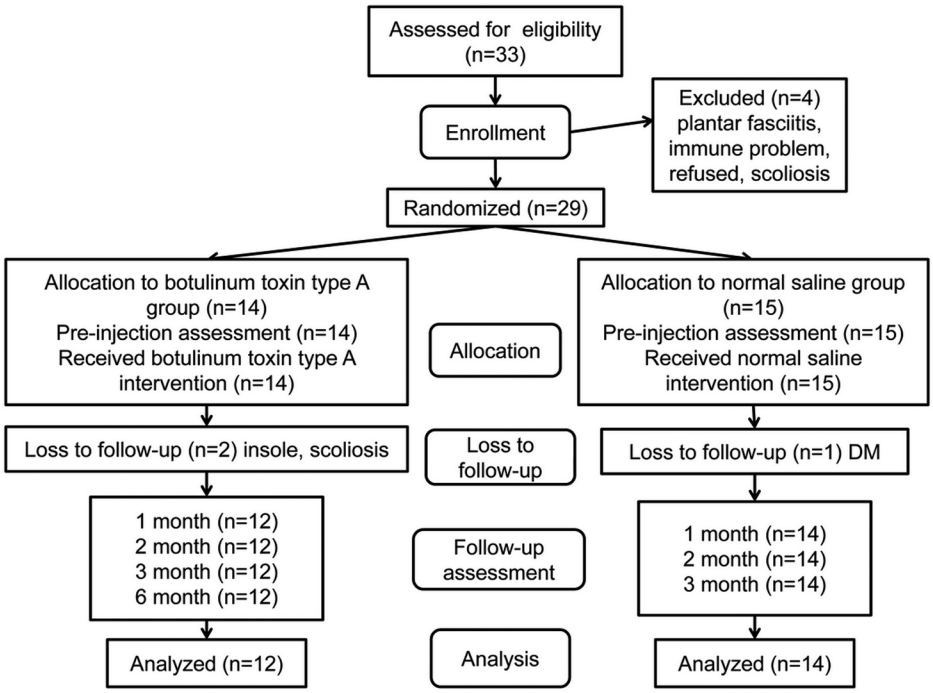


Fig 1. The CONSORT flow chart of the study. Abbreviation: DM, diabetes mellitus.

hospital. Diagnosis of HV was made based on evidence of lateral deviation of the great toe. Inclusion criteria included an HV angle of at least 20° in either great toe. Exclusion criteria include an HV angle of less than 20°, cognitive impairment, inability to walk unassisted, history of ankle or foot surgery, evidence of coagulopathy, pregnant women and women expecting to become pregnant within 2 years, any adverse reaction to BTX-A, myasthenia gravis or Eaton Lambert syndrome, and concurrent infection. Of the 33 eligible HV feet (23 patients) , 29 feet (19 patients) were recruited after the first eligibility assessment and were then randomized to receive either BTX-A injections (BTX-A group) or normal saline injections (NS group) using a computer program. The BTX-A group comprised 10 patients (14 feet) and the NS group comprised nine patients (15 feet) (Fig. 1). A total of two feet were excluded from the BTX-A group: one candidate (1 foot) was excluded because she had been wearing insoles for an extended time and had not informed the research assistant during the initial screening and one candidate (1 foot) was excluded due to scoliosis. One candidate (1 foot) was excluded from the NS group because of chronic diabetes mellitus with poor glucose control. Therefore, the final number of patients included in the study included eight patients (12 feet) in the BTX-A group and eight patients (14 feet) in the NS group.

2.2. Interventions

Patients in the BTX-A group received intramuscular injections of BTX-A into the oblique head (40 U) and transverse head (30 U) of the adductor hallucis muscle, the flexor hallucis brevis (30 U) muscle, and the extensor hallucis longus muscle (30 U). The BTX-A solution was diluted with NS to a concentration of 100 U/ml. The dosage of BTX-A was chosen according to clinical guidelines [20]. Patients in the NS group received equal volume injections of NS into the same four muscles. NS was used as a control agent because it is safe and has been widely used in control groups [21,22]. Each foot in each group received a total volume of 1.3 ml of reconstituted BTX-A with normal saline or only normal saline. The BTX-A or saline vials were prepared and reconstituted by the research assistant and the physiatrist who performed the injection and assessed outcome measurements was blinded to the content of each syringe.

A peripheral electrical stimulator was used to locate the muscles in the lower extremity. A Teflon-coated, 21-gauge, open-lumen needle (Allergan, Irvine, USA) was used to stimulate the targeted muscle once per second (repetitive square wave pulses, 0.25 ms in duration). The same needle was used for injection of either BTX-A or NS to the selected muscles. Injection was performed when either a continuous or stretch of muscle had been induced by the electromyographic stimulator (Stimuplex® HNS12, B.Braun, Melsungen, Germany).

2.3. Outcome measurement

2.3.1. Primary outcome measurements: subscales on pain and disability of the Taiwan Chinese version of the Foot Function Index

The Taiwan Chinese version of the Foot Function index has been shown to be a reliable and valid tool for assessing foot-related pain, disability and limitation [23]. The Taiwan Chinese version of the Foot Function Index consists of three subscales: pain (questions 1-9), disability (questions 10-18) and activity limitation (question 19-23). However, several questions were not applicable to our subjects and thus were not used, namely questions 7 and 8 in the pain subscale, which evaluate the extent of pain induced by walking and standing with orthotics and questions 19-23, which reflect activity limitations. Both pain intensity and disability severity were measured on an 11-point numerical rating scale, where 0 denoted no pain or no disability and 10 denoted the worst possible pain or disability. In the BTX-A group, measurements were performed at baseline and at 1, 2, 3, and 6 months after treatment, while in the NS group, measurements were performed at baseline and at 1 and 2 months after treatment but not at 3 and 6 months post treatment because the therapeutic effect was expected to wear off 2 months after treatment.

2.3.2. Secondary outcome measurement: hallux valgus angle (HV angle)

HV angle was measured directly on weight-bearing anterior-posterior radiographs, in which the X-ray beam was inclined 15° in an anteroposterior direction centered on the second tarsometatarsal joint at a distance of 100 cm [22]. Images were taken by the same radiology technician and angle measurements were performed by the same research assistant. Roentgenographs were taken at baseline and at 1, 2, 3, and 6 months after treatment.

2.4. Statistics

The statistical analyses were performed using the Statistical Package for Social Science Version 18 (SPSS Inc., IL, USA). The Student t-test was used to compare differences in demographic data and outcome measurements between the two groups at baseline. The gender difference between the two groups was compared using the chi-squared test. Repeated measures ANOVA was used to compare the temporal changes in pain, disability, and HV angle between the two groups. Specifically, the between-subject effect defines the group difference, the within-subject effect the difference between two assessments, and the interaction effect the difference in temporal changes between groups. Significant variables were analyzed using the Fisher's Least Significant Difference methods. An α-value of 0.05 was considered statistically significant.

3. Results

3.1. Demographic data and baseline measurements

The BTX-A and NS groups did not differ significantly in age, body weight, body height, or body mass index ($p<0.05$ in all tests) (Table 1). In addition, there were no differences between the two groups in baseline measurements of pain, disability, or HV angle ($p<0.05$ in all tests) (Table 1).

3.2. Pain

The degree of pain at baseline was comparable between the two groups (Fig. 2). An immediate reduction in pain intensity was noted in the BTX-A group. The reduction in pain reached plateau after the second month but persisted for up to six months post intervention. On the other hand, NS treatment resulted in temporary pain reduction. The reduction in pain peaked one month after injection; however, pain levels in patients who received NS were similar to baseline levels at two-month follow-up.

Repeated measure ANOVA showed that pain decreased over time in both groups ($F(2.48) = 13.98$, $p<0.001$). The between-group effect showed no group differences ($F(1.24) = 0.005$, $p=0.94$). Importantly, a significant interaction effect was noted ($F(2.48) = 8.07$, $p<0.01$), indicating that the pain decrease was stronger in the BTX-A group than in the control group (Table 2).

3.3. Disability

The degree of disability at baseline did not differ between the two groups (Fig. 3). The BTX-A group showed a continuous improvement in disability until three-month follow-up and the improvement lessened at six-month follow-up. NS on the other hand resulted in a temporary improvement in disability, peaking at one-month follow-up but falling to baseline levels at two-month follow-up.

The within-group effect showed that disability decreased over time in both groups ($F(2.48) = 5.96$, $p<0.01$). The between-group effect showed no group differences ($F(1.24) = 0.05$, $p=0.83$). The improvement in disability was stronger in the BTX-A group than in the control group, as evidenced by a borderline interaction effect ($F(2.48) = 3.13$, $p=0.05$) (Table 2).

Table 1
Demographic data and baseline measurements

Demographic data	BTX-A group (N=12)	NS group (N=14)	p value
Age (year)	42.8 ± 11	42.9 ± 13.6	0.996
Gender (F:M)	12/0	13/1	0.365
Body height (cm)	158.3 ± 3.4	158.6 ± 9.1	0.913
Body weight (kg)	56.6 ± 9.7	53.8 ± 6.9	0.420
BMI (kg/m²)	22.6±3.6	21.5±2.7	0.390
Pain	33.5 ± 14.2	27.0 ±17.0	0.325
Disability	32.2 ± 16.1	32.6 ±17.3	0.953
HV angle (°)	26.3 ± 4.9	29.3 ± 8.0	0.279

BTX-A: Botulinum Toxin Type A; F: female; M: male. BMI: body mass index; HV: hallux valgus.
The data is presented as mean ± standard error of mean.

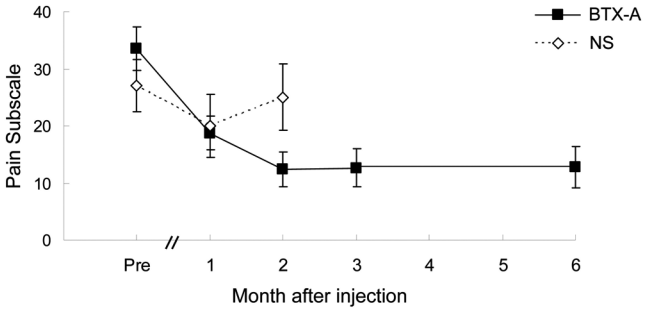


Fig 2. The temporal changes in pain score in the BTX-A and NS groups. The error bar denotes standard error of mean. BTX-A: Botulinum Toxin Type A; NS: normal saline group.

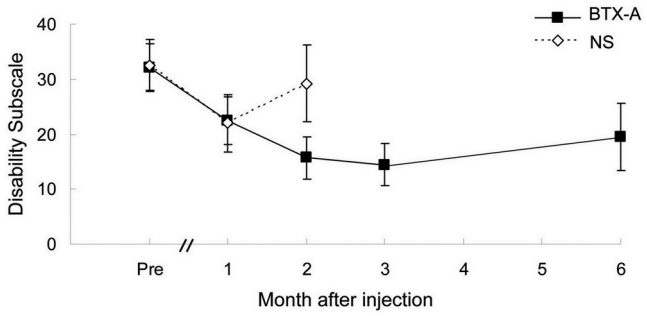


Fig 3. The temporal changes on disability score in the BTX-A and NS groups.

3.4. HV angle

Baseline HV angle did not differ between the two groups (Fig. 4). The BTX-A group showed a continuous reduction in HV angle until the third month but the HV angle returned to near its baseline value at three- and six-month follow-up; the NS group showed a temporary HV angle improvement that peaked at one month and rebounded near its baseline level at two-month follow-up.

The within-group effect showed that the HV angle decreased over time in both groups ($F(2.48) = 5.23$, $p<0.01$). The between-group effect showed no group differences ($F(1.24) = 1.69$, $p=0.21$). The interaction effect was non-significant ($F(2.48) = 1.31$, $p=0.28$), indicating that the decrease in HV did not differ between the two groups (Table 2).

Table 2
Temporal change in outcome measurements following intervention in the two study groups

	BTX-A group (N=12)			NS group (N=14)			p value		
	Baseline	1 month	2 month	Baseline	1 month	2 month	Assessment	Group	Interaction
Pain (score)	33.5±3.8	18.8±3.0	12.4±3.0	27.0±4.5	20.0±5.5	25.0±5.9	<0.001†	0.702	<0.001†
Disability(score)	32.2±4.3	22.4±4.3	15.8±3.9	32.6±4.6	22.0±5.2	29.2±7.0	<0.05*	0.515	0.05
HV angle (deg.)	26.3±1.3	25.0±1.4	24.3±1.5	29.3±2.1	28.4±2.1	28.7±2.2	<0.05*	0.208	0.269

BTX-A: Botulinum Toxin Type A; NS: normal saline; HV: hallux valgus.
*p<0.05; †p<0.001

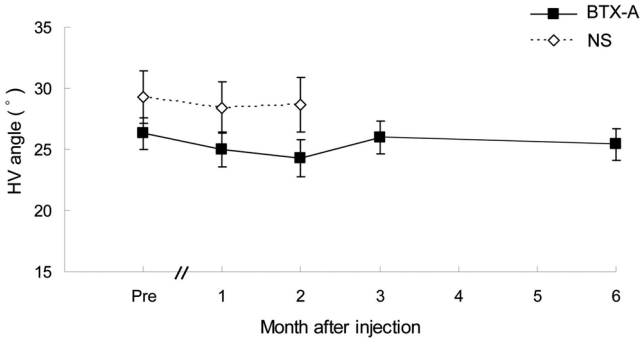


Fig 4. The temporal changes on HV angle in the BTX-A and NS groups.

4. Discussion

Surgical osteotomy is an effective means to treat painful HV [13]. However, orthoses are known to provide only temporary relief [13], and are limited to patients with an HV angle <30° [11]. Medication can reduce muscle spasm and control pain; however, medication does not have a direct effect on the anatomy or function of the foot. Perera et al. suggested that the first ray is inherently unstable and that its alignment relies on both static (such as capsule, ligaments, and plantar fascia) and dynamic stabilizers (such as peroneus longus and small muscles of the foot) [24].

To date, there are no non-surgical treatment options that can alter the static stabilizers. Several studies [24-27] have compared HV subjects with their normal counterparts and found pathologic and electromyographic evidence of HV-related muscle degeneration. These findings imply that it is possible to manage HV-related pain in the muscle group that acts on the first metatarsophalangeal joint. Normally, the abductor hallucis muscle can resist the valgus force exerted on the proximal phalanx [26]; however, when the abductor hallucis is dysfunctional, the adductor hallucis takes over and pulls the phalanx into pronation [24]. The muscles that coordinate the movement of the first metatarsophalangeal joint consist of the abductor hallucis, adductor hallucis, extensor hallucis longus, and flexor hallucis brevis [27,28]. In patients with HV, early onset of stance phase activities was found in these four muscles [25,27]. Also, electromyographic studies have demonstrated a marked decrease in abductor hallucis activities as compared to those of the adductor hallucis in patients with HV [28,29]. Hoffmeyer et al. examined the relationship between muscle pathology and HV and found not only enlarged mitochondria with paracrystalline inclusions but also myogenic and neurogenic alterations in patients with HV [29]. An ultrasonic evaluation of the abductor hallucis muscle in patients with hallux valgus also suggested that morphological changes may occur early in the development of the deformity. These findings suggest that a treatment strategy focused on HV-related muscle groups may provide pain and disability relief, and can even suppress the progression of HV angle. To the best of our knowledge, the present study is the first randomized controlled trial to demonstrate the effect of BTX-A injections into HV-related muscles to treat painful HV.

Agents such as dry needling and NS injections are chemically neutral and can exert an effect on a local muscular spasm through mechanical disruption instead of biochemical alternations [30]. BTX-A, on the other hand, reduces pain chemically, blocking excess acetylcholine release and directly inhibiting the release of pain mediators. We found that injection of a chemically neutral agent can exert a temporary effect, evidenced by the fact that both BTX-A and NS injections induced comparable pain and disability reduction at one-month follow-up; however, the effect of BTX-A and NS started to diverge at two-month follow-up. Specifically, while levels of pain and disability in the NS group returned to baseline levels at two-month follow-up, patients in the BTX-A group showed further reduction in pain and disability and the effect was maintained for up to six months post treatment.

Our results show that BTX-A intramuscular injection to HV-related muscles is more effective than NS at reducing pain and disability. The effect of intramuscular NS injection to painful HV cannot be underestimated. In a double-blind study conducted by Frost et al., patients receiving NS tended to have more pain relief than those who received four local injections of mepivacaine [31]. According to our data, NS intramuscular injection alone provided a magnitude of pain and disability reduction similar to that of BTX-A treated group for up to one month; however, NS only had a short-term effect. BTX-A provides an alternative treatment option for patients with HV-related pain who are not eligible for surgery. The therapeutic effect of BTX-A intervention peaked at two to three months but persisted for up to six months post treatment. Our results are similar to those reported in Babcock MS et al.'s randomized, double-blinded, placebo-controlled study of 27 patients (43 feet) on plantar fasciitis. They found that BTX-A treatment resulted in significant improvements in pain and overall foot function in patients with painful plantar fasciitis between three and eight weeks after treatment [19]. Moreover, Radovic PA et al. found that BTX-A had resulted in a reduction in HV angle from 20° to 7° 6 weeks after the injection and that the effect lasted for up to 69 weeks [10]. On the contrary, we observed only temporary prevention in HV angle progression in the BTX-A group, which peaked around two months post treatment. The effect wore off three months post treatment. In the NS group, HV angle did not change during the two-month follow-up period. Further studies are needed to elucidate the effects of dosage, target muscles and concurrent therapeutic exercises on HV-related pain and disability.

4.1. Study limitations

The present study has several limitations. First, the data obtained in this study were preliminary and the sample size was very small. Second, a six-month follow-up time is not long enough to accurately measure the long-term effect of BTX-A injection. Third, the effect of repetitive injections BTX-A injections was not explored.

5. Conclusion

Our results suggest that intramuscular BTX-A injection to muscle groups that act on the first metatarsophalangeal joint can reduce pain and disability in patients with painful HV up to six months.

Acknowledgments

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Conflict of Interest Statement

The authors declared no potential conflicts of interests with respect to the authorship and/or publication of this article.

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Ethical approval

This study was approved by the Institutional Review Boards for Human Studies at the Chang Gung Memorial Hospital. All participants provided informed consent.

IRB approval/Research Ethics Committee: Institutional Review Board of Chang Gung Medical Foundation IRB 98-3883A3 and IRB 100-2040A3

Clinical Trial Registration

NCT01501500

The device(s) is/are FDA approved for the indicated usage in the United States.

Author contributions

Study concept and design: Katie Pei-Hsuan Wu, Simon FT Tang.

Acquisition of subjects and/or data: Katie Pei-Hsuan Wu, Simon FT Tang, Shih-Cherng Lin, Ruei-Heng Lin, Chih-Kuang Chen, Yu-Cheng Pei, Wen-Chung Tsai

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Interpretation of data: Katie Pei-Hsuan Wu, Yu-Cheng Pei, Wen-Chung Tsai

Preparation of manuscript: Katie Pei-Hsuan Wu, Chih-Kuang Chen

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