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Original Research Article

Subcutaneous Injection of Botulinum Toxin A Is Beneficial in Postherpetic Neuralgia

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Abstract

Objective. To assess the benefits of subcutaneous injection of botulinum toxin A (BTX-A) for the treatment of postherpetic neuralgia (PHN).

Design. We investigated the therapeutic benefits of BTX-A in subjects with PHN in a randomized, double-blind, placebo-controlled study. Sixty subjects with PHN were randomly and evenly distributed into BTX-A, lidocaine, and placebo groups.

Measures. After randomization, one of the following solutions was injected subcutaneously in the affected dermatome: 5 u/mL BTX-A, 0.5% lidocaine, or 0.9% saline (placebo). Visual analog scale (VAS) pain and sleeping time (hours) were evaluated at the time of pretreatment, day 1, day 7, and 3 months posttreatment. Opioid usage was calculated at day 7 and 3 months posttreatment.

Results. Compared with pretreatment, VAS pain scores decreased at day 7 and 3 months posttreatment in all three groups ($P < 0.01$). However, the VAS pain scores of the BTX-A group decreased more significantly compared with lidocaine and placebo groups at day 7 and 3 months posttreatment ($P < 0.01$). Sleep time (hours) had improved at day 7 and at 3 months compared with pretreatment in all three groups, but the BTX-A group improved more significantly compared with lidocaine and placebo groups ($P < 0.01$). The percent of subjects using opioids posttreatment in the BTX-A group was the lowest (21.1%) compared with the lidocaine (52.6%) and placebo (66.7%) groups ($P < 0.01$).

Conclusions. Subcutaneous administration of BTX-A significantly decreased pain in PHN and reduced opioid use compared with lidocaine and placebo at day 7 and 3 months post-treatment. It also increased subjects' sleep times.

Key Words. Botulinum Toxin A (BTX-A); Postherpetic Neuralgia (PHN); Subcutaneous Injection

Introduction

Postherpetic neuralgia (PHN) is a debilitating disease characterized by continued, intense pain following an outbreak of herpes zoster. The risk of developing PHN after shingles increases with age. In a large population-based study, the rate of PHN increased from 5% in those younger than 60 years to 10% in those aged 60–69 years and to 20% in those aged 80 years or older [1]. As PHN is associated with substantial impairment of both quality of life and activities of daily living [2], it is a significant health care problem. Although topical lidocaine, anticonvulsants, or antidepressants are recommended as first-line medication [3–5], these treatments have limited efficacy [3,5,6]. While many procedures have been tried, no single best treatment for PHN has been identified. Therefore, we desperately need more effective treatments for this condition.

Botulinum toxin is a neurotoxic protein produced by the bacterium *Clostridium botulinum* in seven different serotypes [7]. It is a two-chain polypeptide including a protease unit that cleaves SNAP-25, the fusion protein critically involved in the release of acetylcholine in synapses. This mechanism allows clinicians to commonly use botulinum toxin A (BTX-A) in the treatment of myofascial diseases and neuromuscular hyperactivity diseases,

particularly dystonia or spasticity [8–10]. It has also been used successfully to treat several different types of headaches, including tension-type headaches, cervicogenic headaches, and migraine [11–14]. Additional information from animal experiments demonstrates that BTX-A can inhibit not only the exocytosis of acetylcholine but also other neurotransmitters such as glutamate [15], substance P [16], and calcitonin gene-related peptide [17]. As these latter neurotransmitters are involved in pain transmission, inhibition of their release has been proposed to explain the relief of neuropathic pain symptoms [18–24]. Human experimental studies have demonstrated the antinociceptive effects of BTX-A in pain models with associated reduction in pain and neurogenic inflammation [25,26]. Recently, some clinical trials have suggested that BTX-A might be useful in treating neuropathic pain, such as trigeminal neuralgia and chronic neuropathic pain, diabetic neuropathy, and CRPS [27–31].

The aim of this study was to investigate the potential direct analgesic effects of one-time, single-use BTX-A in the painful area, especially the allodynia area in subjects with PHN, via a double-blinded, placebo-controlled clinical trial. We hypothesized that subcutaneous administration of BTX-A would significantly decrease pain in PHN, reduce opioid use, and improve quality of life compared with lidocaine and placebo at day 7 and 3 months posttreatment.

Methods

This study was conducted at Shenzhen Nanshan Hospital, Guangdong Medical School, Shenzhen, China, and approved by the Human Ethics Review Committee of Guangdong Medical School. Subjects were recruited between January 2006 and January 2009.

Subjects

Subjects with PHN confirmed by clinical examination and who had failed medication trials and physiotherapy were enrolled in the study. All subjects were hospitalized in the wards of the Pain Management Department of Shenzhen Nanshan Hospital. Criteria for inclusion were: 1) confirmed diagnosis of PHN according to the diagnosis of pain 3 months after rash healing [32]; 2) daily pain of at least 5 out of 10 on the visual analog scale (VAS) pain scale for greater than 3 months; and 3) failure or troublesome side effects from non-opioid pharmacotherapy. Exclusion criteria included: 1) contraindications to BTX-A (e.g., myasthenia gravis or other diseases of the neuromuscular junction); 2) hypersensitivity to the BTX-A formulation; 3) coagulation disorders; 4) localized infection; 5) current major depressive or anxiety disorder; 6) history of serious drug or alcohol abuse; or 7) ongoing litigation. This procedure of subcutaneous injection and associated potential complications were explained to the subjects, and informed consent was obtained after the subject agreed to attend the project before treatment. No other medications were used except transcutaneous electrical nerve stimulation (TENS) therapy.

Protocol

We used a prospective, randomized, placebo-controlled, double blind (subjects, those providing injections, and observers were blind) parallel group design. Subjects were randomized into one of three parallel groups according to the last number of addition of their medical record number: The subjects were recruited 1) to the BTX-A group with the last number of 1, 4, or 7; 2) to the lidocaine group with the last number of 2, 5, or 8; and 3) to the saline placebo group with the last number of 3, 6, or 9. Subjects with the last number of 0 were recruited into the three groups one by one. The lidocaine group (0.5% lidocaine) acted as an active control. Non-preserved saline (0.9%) was used for the placebo group. For the BTX-A group, aliquots of 100 IU/vial of BTX-A (Lanzhou Institute of Biological Products, Lanzhou, China) were reconstituted with 20 mL of saline (0.9% NaCL) as recommended by the nurse.

Subjects received subcutaneous injections into the affected area, specifically the area demonstrating evidence of tactile allodynia, with single-use tuberculin syringes (1 mL) within 1.0–2.0 cm radius of skin (Figure 1)

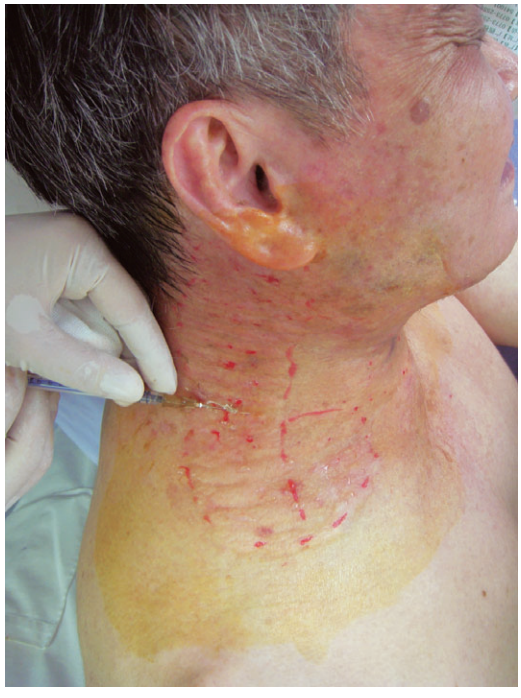

Figure 1 Photograph showing the botulinum toxin A subcutaneous injection technique for the affected area (marked in red lines) in a male patient with cervical postherpetic neuralgia. Subcutaneous injections were performed with single-use tuberculin syringes within 1.0–2.0 cm radius of skin for 1-mL volume.

Table 1 Baseline characteristics of cases

Group	N	Duration of pain (months) (mean ± SD)	Gender (M/F)	Age (years) (mean ± SD)	VAS score (mean ± SD)
Botox A	20	12.2 ± 9.1	11/9	70 ± 15.4	7.6 ± 2.1
Lidocaine	20	11.3 ± 8.8	8/12	65 ± 14.2	7.9 ± 1.5
Saline (placebo)	20	12.8 ± 9.3	9/11	67 ± 12.1	8.1 ± 1.7

VAS = visual analog scale; SD = standard deviation.

from fixed pain physicians. The affected area with tactile allodynia was mapped with a marker for all subjects before injection. The contents of the solutions were 5 u/mL in the BTX-A group, 0.5% lidocaine in the lidocaine group, and 0.9% saline in the placebo group. Subjects and observers were blinded to the contents of solutions during the entire study. Volumes of administration vary according to the area of tactile allodynia, but less than 40-mL volumes (200 units for the maximum BTX-A dose) were used. Opioid medications were administrated on the seventh day if subjects' pain intensity reported VAS pain scales ≥5 after subcutaneous injection in all three groups.

Sixty volunteers (28 males and 32 females, aged 42–84, averaged 68 ± 12.2) diagnosed with PHN were enrolled in this study according to the above criteria from 2006 to 2009. This population was composed of 13 subjects with hypertension, 15 with diabetes, and 9 with both hypertension and diabetes. The specific areas affected with PHN included 11 with oro-facial PHN, 14 with cervical and upper extremity PHN, 18 with thoracical area PHN, and 17 with lumbar and lower extremity PHN. There were no differences in baseline characteristics between the three groups ($P > 0.05$) (Table 1).

Evaluation and Data Analysis

Assessment of Pain

Pain intensity was measured according to a digital VAS. The bottom of the scale (0) was marked "no pain," and the top (10) was marked "maximum pain." The data were sampled in the morning and afternoon by the same observers at the time of pretreatment, day 1, day 7, and 3 months after treatment. The average scale was used to measure overall pain for each group.

Assessment of Quality of Life

The quality of life was evaluated by the sleeping time (hours), daily activity, diets, and stance in a day at the time of pretreatment, day 1 and day 7 after treatment, and after 3 months.

Percent of Opioid Use

None of the patients took opioids for at least 3 months prior to the study. Opioid medications, such as sustained release morphine, morphine, or transdermal fentanyl patch, were administered to the subjects when pain was not sufficiently relieved (VAS scales ≥5) after subcutaneous injections in all three groups by the seventh posttreatment day. The percent of opioid use was assessed at day 7 and after 3 months.

Data Analysis

Any preexisting allergies to medication or other side effects in all three groups were reported prior to the study.

All data in the text, tables, and figures are means ± standard deviation (SD). VAS values and sleep time (hours) were performed by the *t*-test. Total opioid use was calculated by an analysis of variance. P value <0.05 was considered statistically significant.

Results

Sixty subjects fulfilling the inclusion criteria were randomly assigned to the BTX-A, lidocaine, and placebo groups. Four subjects dropped out of this study during this process—two subjects because of the intolerable pain during the subcutaneous injection (one from the BTX-A group and one from saline group) and another two subjects due to the limited effect at day 3 after treatment (one from the lidocaine group and one from the saline group). The mean (±SD) volumes of injection in the three groups were similar for the BTX-A (15.4 ± 3.7 mL), lidocaine (14.6 ± 4.1), and saline placebo (15.7 ± 2.9 mL) groups.

The Assessment of Safety

There were no allergic reaction in any of the three groups, and no complaints of shortness or breath, or weakness of muscles. Most subjects reported that the subcutaneous injections were painful, with no significant difference among the three groups. The severity of pain caused by the subcutaneous injections was related to the site of affected area, being worse at the facial, cervical areas, and extremities. No other local or systemic side effects were reported during the injections or at any other time during the trial.

The Assessment of Pain Intensity

VAS pain decreased in all three groups at day 7 and after 3 months as compared with pretreatment pain scores (Figure 2A). The improvement of the BTX-A group was

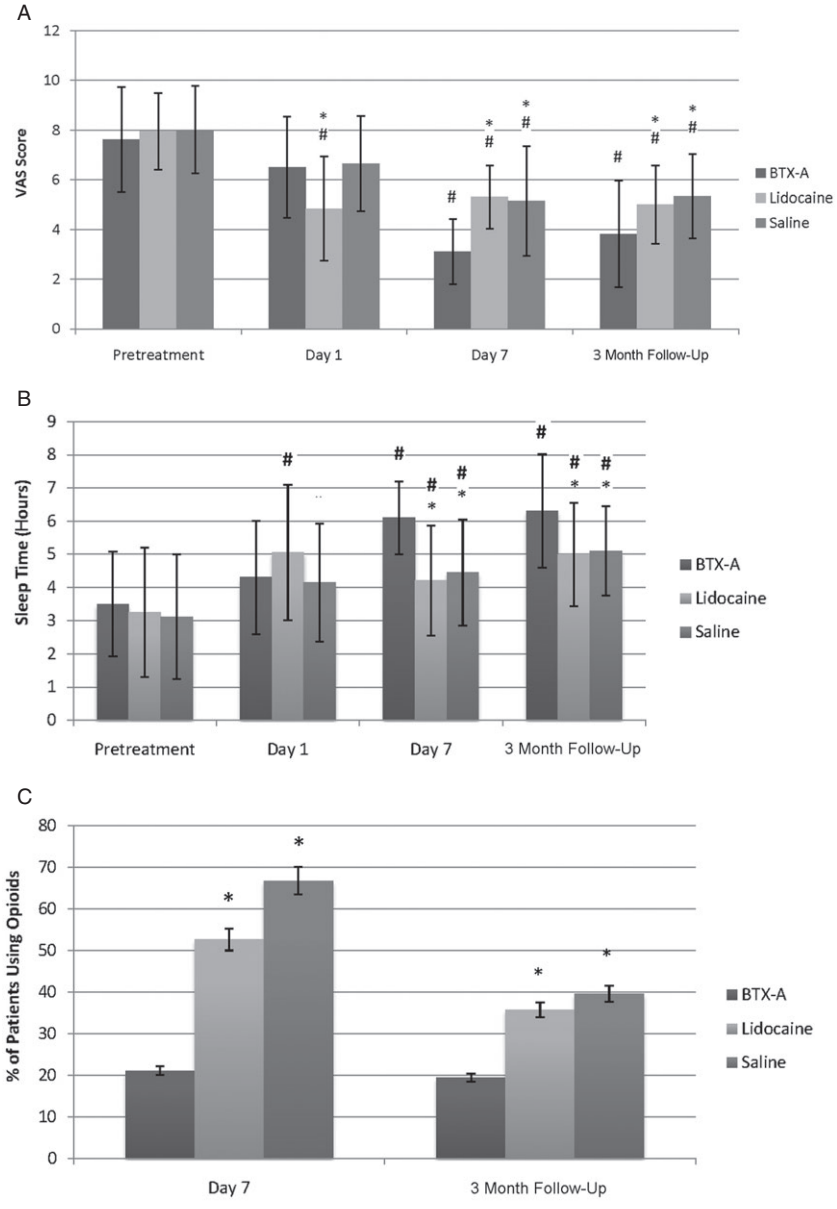

Figure 2 (A) Pain VAS scores in all three groups demonstrated significant reduction in the BTX-A compared with the lidocaine group and placebo group at day 7 and after 3 months. VAS scores in the lidocaine group were reduced significantly at day 1 compared with pretreatment ($P < 0.01$). *Compared with the BTX-A group, $P < 0.01$; #compared with pretreatment, $P < 0.01$. (B) Sleep time (hours) showed significantly improved sleep in the BTX-A group compared with the other two groups at day 7 and after 3 months ($P < 0.01$). *Compared with the BTX-A group, $P < 0.01$; #compared with pretreatment, $P < 0.01$. (C) The percentage of subjects using opioids posttreatment were reduced significantly in the BTX-A group compared with the lidocaine and placebo groups at day 7 and after 3 months ($P < 0.01$). *Compared with the BTX-A group, $P < 0.01$. VAS = visual analog scale; BTX-A = botulinum toxin A.

more significant compared with the lidocaine and saline placebo ($P < 0.01$) groups at day 7 and after 3 months. We found that the improvement of pain started from days 3 to 5 after BTX-A injection and increased to maximum effect at day 7, and then remained stable for up to 3 months. While we monitored pain in some patients beyond 3 months, we did not perform this systematically in all patients. The mean pain scores decreased by 4.5 with the BTX-A as compared with the lidocaine (decreased by 2.6) and saline placebo (by 2.9) ($P < 0.05$) at the time of day 7 posttreatment. Lidocaine significantly decreased the pain intensity after subcutaneous injection with peak effectiveness at day 1. Lidocaine provided better analgesia at only day 1 compared with BTX-A and saline placebo ($P < 0.01$).

The Assessment of Quality of Life

Quality of life was assessed by recording the sleep time (hours) (Figure 2B). The subjects' sleep time (hours) in the three groups continually increased from day 1 through 3 months posttreatment ($P < 0.01$). The improvement in sleep time of BTX-A was significantly greater compared with the other two groups ($P < 0.01$).

The Assessment of Opioid Usage Percent

Opioid medications were administered to subjects who reported that their pain was not sufficiently relieved (VAS scales ≥ 5) on day 7 after treatment. All subjects who received opioids, regardless of the type, were assessed at day 7 and 3 months (Figure 2C). The percentage of subjects using opioids in the BTX-A group (day 7: 21.1%, after 3 months: 19.4%) was significantly less than the lidocaine (day 7: 52.6%, after 3 months: 35.7%) and saline (day 7: 66.7%, after 3 months: 39.6%) groups. However, the percentage after 3 months is a little less than that at day 7 in each group, but this was not significant.

Discussion

This randomized controlled trial (RCT) is the first to examine the effectiveness of subcutaneous injection of BTX-A in reducing the symptoms of PHN. Overall symptom severity (pain, opioid use, sleep interference) was significantly reduced in the BTX-A condition at day 7 and lasted at least 3 months as compared with the lidocaine and saline placebo groups. Furthermore, the long-lasting effects of BTX-A were accompanied by a low incidence of side effects. Indeed, the only significant side effect was transient pain during subcutaneous injections in a few subjects, notably those subjects with PHN in facial and cervical areas. We noted no serious adverse effects. The results of this trial suggest that subcutaneous BTX-A may be an effective and well-tolerated treatment option for patients suffering from PHN.

Several subjects in our BTX-A group also reported analgesic effects lasting 6 months or more. Unfortunately, we did not evaluate all the subjects at the time of 6 months after treatment. This long duration of analgesic benefit from BTX-A in patients with neuropathic pain is in line with a previous clinical study by Ranoux et al. that found that one-time intradermal injection of BTX-A had direct analgesic effects in subjects with focal chronic neuropathic pain with allodynia. In their study, Ranoux et al. noted that the analgesic effects lasted more than 24 weeks in some subjects [29]. Similarly, we had a very long-lasting duration from a single injection in more homogenous PHN patient population.

In addition to long-lasting improvements in pain, we found that the subjects' quality of life improved significantly at day 7 after intradermal administration of BTX-A. These effects were measured by self-assessment of daily life, such as sleep time (hours), mood, activity, diets, stance, and showers. While these improvements in quality of life are presumably due to the analgesic benefits, we did not perform daily sampling of data that would allow us to determine if the analgesic benefits preceded or followed the improvements in quality of life.

Results of our trial also demonstrated that subcutaneous injection of lidocaine relieved the pain of PHN and improved sleep time at day 1 compared with pretreatment ($P < 0.01$). The effects of lidocaine did not persist beyond day 1, which is consistent with lidocaine's duration of action. The lack of improvement of BTX-A on day 1 is consistent with BTX-A requiring several days for initial analgesic benefit.

The percent of opioid use, starting at day 7, in the BTX-A group was the lowest among the three groups and remained so up to 3 months posttreatment. There was a general reduction in opioid use in all three groups at 3 months compared with day 7. Possible explanations for the reduction of opioid use in all groups includes: 1) improvement of some patients' symptoms over time in all three groups; 2) cessation of opioids due to side effects; 3) cultural avoidance of taking long-term opioids; and 4) costs associated with long-term opioid management.

How can the long-lasting analgesic effects of single-use BTX-A by subcutaneous injection be explained? Both peripheral and central mechanism may play a role. Investigators have shown that peripheral effects of BTX-A in reducing neuropathic pain may be due to inhibition of neuropeptide releases from peripheral nociceptive nerve endings [25,26]. This mechanism could also account for the early effect of BTX-A on subjects with PHN observed in this study within 1 week after subcutaneous injection. Central mechanism may also have a role [18]. A recent study offered a novel pathway of BTX-A trafficking in neurons. Antonucci et al. [33] have demonstrated that BTX-A undergoes retrograde axonal transport and is transcytosed to afferent neurons, in which it cleaves its substrate, SNAP-25. These findings were observed in the contralateral hemisphere after unilateral BTX-A delivery to the hippocampus, and cleaved SNAP-25 also appeared in the facial nucleus after injection of BTX-A into rat whisker muscles. Current evidence suggests that BTX-A may exert central nervous system (CNS) effects through axonal

transport to the CNS after a peripheral application [34,35]. Future work is needed to elucidate the peripheral and central analgesic mechanisms resulting from subcutaneous injection of BTX-A.

There are a few methodological limitations of this study that are associated with the exploratory nature of our project. First, the specific opioid used by patients was not fixed. They were placed on either extended release morphine or a transdermal fentanyl patch. This makes direct comparison of equal analgesic conversions to a milligram opioid basis challenging. Nonetheless, the choice and dose of opioids were relatively random among the three groups, and there was a clear and significant reduction in opioid use in the BTX-A group. Second, the form of BTX-A (Lanzhou Institute of Biological Products) has not been as well characterized as other formulations of BTX-A reported in clinical studies. There are differences in these formulations, and this fact must be considered in attempting to generalize these results. Third, we relied on self-report for pain and quality of life data. Future studies should also characterize changes in mechanical allodynia and more detailed reported of symptoms. Fourth, more exploration of dose–response relationships are needed. In this initial signal-detecting study, we chose a dose of BTX-A that has been used for other chronic pain studies. Future studies should characterize the dose–response relationship to analgesia and duration of benefit. Additionally, dose–response relationships should be determined for different neuropathic pain conditions (e.g., PHN vs focal neuropathies).

Conclusion

PHN is a particularly challenging neuropathic pain condition to treat with a tremendous toll on the individual and society. While there are a small number of FDA-approved therapies, many subjects continue to suffer. Furthermore, current anticonvulsant therapies for PHN are problematic due to limited efficacy and untoward side effects, particularly on cognition, which may be intolerable in the elderly population [36,37]. Consequently, there is a strong need for an efficacious and safe therapy for this debilitating disease.

We conclude that subcutaneous injection of BTX-A attenuates the chronic pain of PHN associated with mechanical allodynia. Large-scale studies and long-term follow-up are warranted to further confirm the analgesic effects of BTX-A for patients suffering from the pain of PHN.

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