Efficacy of Botulinum Toxin for Treating Cramps in Peripheral Neuropathy

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ABSTRACT

Introduction: Muscle cramps are a common occurrence in patients with peripheral neuropathy and are known to cause significant distress and decrease the quality of life. Although several drug formulations have been used in the management of cramps, there is significant variability in terms of efficacy and tolerability in patients with peripheral neuropathy. This study aims to assess the efficacy of botulinum toxin A in the management of lower limb cramps in patients with peripheral neuropathy.

Methods: This retrospective chart review included a total of ten patients with peripheral neuropathy with cramps. Relevant data such as age, gender, race, pain score and cause of peripheral neuropathy were documented. Statistical analyses to compare the variables were done using the Wilcoxon Test. The pain score before the administration, at 3-month, 6-month and 9-month follow up were compared.

Results: All patients enrolled in the study showed improvement of pain assessed by visual pain analog scale. An improvement of 1.60 (95%CI, $p<0.05$), 2.70 (95%CI, $p<0.05$) and 3.50 (95%CI, $p=0.05$) was noted between test scores from before administration of botulinum toxin to 3-month, 6-month and 9-month follow up respectively.

Conclusion: Local BTX-A infiltration is likely an efficacious and safe procedure for improving pain associated with cramps in patients with peripheral neuropathy.

Keywords: *cramps, peripheral neuropathy, botulinum toxin, lower limb, efficacy*

Introduction

Muscle cramps are paroxysmal, painful and involuntary contraction of a muscle group or a single muscle.[1] They may occur spontaneously or be triggered by the contraction of muscle. It can manifest as a part of physiological conditions such as pregnancy, muscle fatigue and aging or be a symptom of pathological conditions affecting the neurological, metabolic or endocrinological disorders.[2] They occur frequently in general adult population and may range from mild and infrequent to severe.[3,4] The severity and frequency of cramps has been reported to affect the quality of life of several patients due to the acute pain and soreness which may last for several days and has been known to affect sleep as well.[5,6] To manage the distressing and disabling effects of cramps, several agents such as quinine, anti-epileptic drugs and magnesium have been used but have been reported to provide insufficient relief and in some cases are poorly tolerated.[7-10]

Theorized to occur as a result of abnormal hyperexcitation of terminal branches of motor axons and the hyper excitability of motor neurons at the spinal level, the exact mechanism of cramp origin and initiation remains a mystery.[11-13] Lambert *et al*. in 1969 reported the inability of muscle cramps to be evoked in curarized muscles.[14] This finding led to the realization that a long-standing block at the neuromuscular junction may prove to be useful in managing cramps. Botulinum toxin A (BTX-A) is known to reduce hyperactivity of a muscle by blockade of acetylcholine release at neuromuscular junction thereby leading to muscle relaxation[14,15] This property of botulinum toxin has been used successfully to manage cramps in patients with diabetic neuropathy and patients with benign fasciculation syndrome.[16,17]

Our study aims to assess the efficacy of botulinum toxin A (BTX A) in a well-defined cohort of patients with peripheral neuropathy who suffered from cramps due to various etiologies.

Methods

This study is a retrospective chart review of patients attending a University based hospital approved by the Institutional review board (IRB). The study population included patients with peripheral neuropathy aged more than 18 years who were undergoing care at the University hospital for peripheral neuropathy.

These patients had undergone BTX A administration for managing cramps by the same physician. Only patients with lower limb cramps and at least a 12-month follow up during the study period were included in the study. All patients in this study had tried and failed two oral medications for cramps (either reached maximum dose with no benefit or had side effects resulting in discontinuation or dose limitation). The standardized injection sites for botulinum toxin included bilateral gastrocnemius and intrinsic muscles of the foot. 100 units for each limb bilaterally was administered for each patient with 75 units injected to gastrocnemius and 25 units into intrinsic muscles of the foot. A total of 10 patients fulfilled the criteria and were made a part of the study.

Information including age, gender, race, cause of peripheral neuropathy and visual analog pain score were collected for these 10 patients. The 10-point visual analog pain score was used to record the pain level at baseline before the administration of botulinum toxin and was followed up at 3-month, 6-month and 9-month intervals from the first injection by the physician.

The analysis of the data included summarizing patient demographics and pain scores in form of descriptive statistical variables including mean, standard deviation, ranges and percentages. Comparison of the pain scale at different intervals was done by using Wilcoxon signed rank test and a correlation between them was done. All statistical analyses were done using SPSS v22 software (IBM, Armonk, NY).

Results

The subjects of our study had a mean age of 64.3 ± 6.9 years. The study population belonged to Caucasian ethnicity and with 80% men. The cause of peripheral neuropathy in the majority of these patients (60%) was diabetic neuropathy followed by bortezomib induced peripheral neuropathy (20%). Monoclonal gammopathy of undetermined significance (MGUS) and Tri sulfate disaccharide IdoA2S-GlcNS6S (TS-HDS) neuropathy each constituted 10 % of the total study population (Table 1). For all patients, botulinum toxin was well tolerated and no side effects were reported.

The data analyzed reported a significant change in pain scores from before administration and at 3-month and 6-month intervals. The average pain score of patients reported before the administration of botulinum toxin and at 3-month, 6-month and 9-month intervals were 8.50±0.97, 6.90±0.73, 5.70±1.15 and 5.00±0.66 respectively. Figure 1 demonstrates the change in average pain scores at different time intervals. The improvement of pain score from before and at 3-month, 6-month and 9-month follow up was 1.6 (95%CI, $p<0.05$), 2.7 (95%CI, $p<0.05$) and 3.50 (95%CI, $p = 0.05$) with ranges of 4, 6 and 6, respectively.

Table 1. Patient demographics.

Characteristics of the patient	Detail of the patient
Age (years)	64.3 ± 6.9
Gender (female/male)	2/8
Ethnicity (Caucasians)	10
Cause of peripheral neuropathy	
Diabetes mellitus	6
Bortezomib induced peripheral neuropathy	2
MGUS	1
TS-HDS	1

Discussion

This study shows that patients with peripheral neuropathy of varying causes having cramps showed an improvement of pain due to cramps at 3-month, 6-month and 9-month intervals when compared to that before administration of botulinum toxin. Majority of the patients in our study (6 patients out of 10) suffered from diabetic neuropathy which is a common cause of neuropathy and of cramps.[18] Other causes of peripheral neuropathy in our study included MGUS (1 patient), TS-HDS (1 patient) and chemotherapy induced peripheral neuropathy (2 patients). The agent used in both these patients was Bortezomib, a potent proteasome inhibitor which has been used as a cornerstone for the treatment of newly diagnosed or relapsing multiple myeloma.[19] Our study showed improvement in their pain score with no issues with tolerability. This can be owed to the less adverse effect profile with botulinum toxin and its administration after several weeks in comparison to the regular use of other medications which often have a higher chance of developing adverse effects and issue with tolerability.

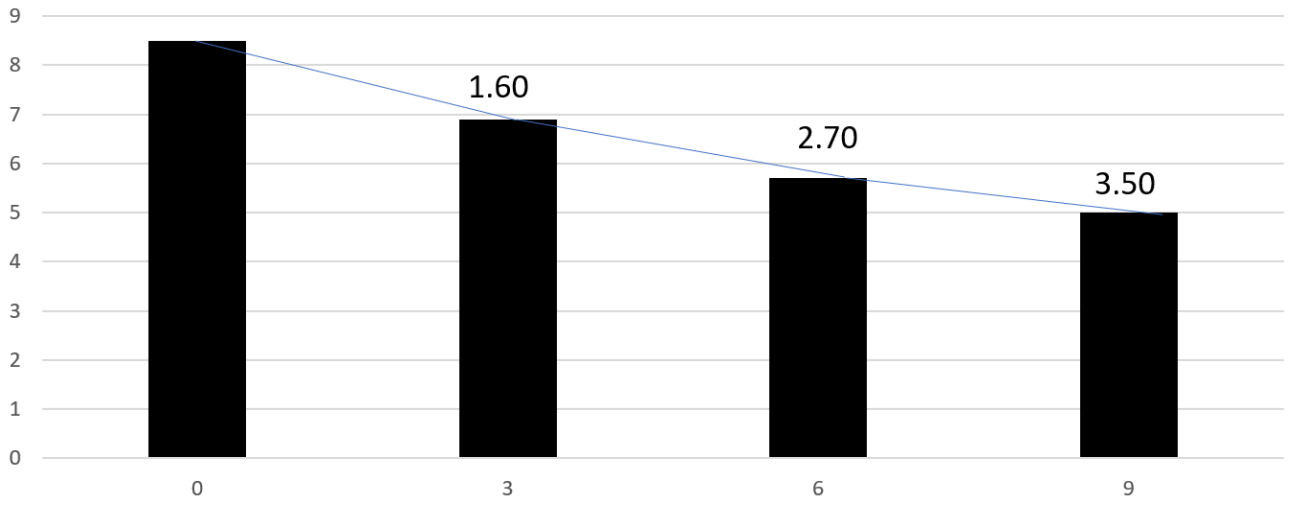

Figure 1. Chart depicting change in average pain score over different intervals during a 9-month period. The digits on the top of the graphs show the improvement in pain score from before the administration of botulinum toxin to that particular interval of time. The x axis depicts the months and the y axis depicts the pain score.

Our study reported significant improvement in pain scores from before to the 3-month and 6-month intervals. The improvement noted was 1.60 at the 3-month interval and 2.70 at the 6-month interval. This significant improvement in pain score is comparable to the results of the study conducted in 1997 by Bertolasi et al where they used botulinum toxin to manage cramps in 5 patients with benign cramps — fasciculation syndrome.[16] The study used clinical and neurophysiological variables collected before and after the administration of botulinum toxin to assess its effects. A significant lowering of clinical cramp severity scores and a significant increase in cramp threshold frequencies was noted. However, the muscle strength remained unchanged in these patients.[18] This pilot study showed that intra muscular injection of botulinum toxin is a safe, effective and long-lasting treatment of muscle cramps and fasciculations.

A recent study by Restivo et al also depicted the efficacy of botulinum toxin in management of cramps due to diabetic neuropathy.[17] The placebo controlled, double blind, perspective study assigned fifty diabetic patients randomly to each of the arms with variables including change in pain intensity, cramp frequency and cramp threshold frequency noted for all patients at different intervals of time. Significant improvements in all outcome measures were reported by patients who were administered botulinum toxin. Twenty of these twenty-five patients responded positively reporting improvements as early as 1 week after the administration and effects lasting up to 14 weeks. The remaining five patients were non responders.[17] Our study, while being retrospective in nature, included patients with peripheral neuropathy due to different causes and showed the efficacy of botulinum toxin in managing cramps due to peripheral neuropathy irrespective of its cause. Table 2 summarizes the studies where botulinum toxin was used to manage cramps and are contrasted with our study.

Costa et al in 2005 reported a case of 56-year-old man with S1 radiculopathy who presented with painful right calf hypertrophy, fasciculations and cramps which were aggravated by long standing and walking.[20] Administration of botulinum toxin led to marked subjective improvement in pain, cramp, fasciculation and calf hypertrophy within 15

Table 2. A comparison of studies conducted to assess the efficacy of botulinum toxin for managing cramps

Study reference number	Type of study	Number of subjects	Cause of cramps	Variables used to assess efficacy	Result
16	Prospective	5	Benign cramp fasciculation syndrome	Cramp severity score, Cramp threshold frequency	Significant decrease in cramp severity score and increase in cramp threshold frequency
17	Placebo controlled, double blind prospective	25 in placebo group and 25 in botulinum toxin group	Diabetic neuropathy	Patient diary, cramp severity score, cramp threshold frequency	Decreased pain intensity and cramp severity score, increase in cramp threshold frequency in 20 patients
20	Case report	1	S1 radiculopathy	Subjective clinical benefit, calf diameter, side effects if any, muscular electrical activity.	Marked subjective improvement, decreased spontaneous muscular activity, no change in calf diameter
21	Randomized clinical trial	45 (21 from the conservative treatment with gabapentin and 24 from botulinum toxin group)	Lumbar spinal stenosis	Pain numeric rating scale, Oswestry disability index, subjective grading of cramps, Insomnia severity index	Leg pain, cramp severity, cramp frequency and insomnia improved.
Our study	Retrospective chart review	10	Diabetic neuropathy, chemotherapy induced neuropathy, MGUS and TS-HDS	Visual analog pain scale	Decrease in average pain scale score in all patients

days of administration. This time frame of feeling relieved by the action of botulinum toxin is comparable to studies mentioned above showing the average time of action to be similar.

A randomized clinical trial conducted Korean researchers involving fifty patients with lumbar spinal stenosis (LSS) suffering from nocturnal cramps aimed to assess the clinical effectiveness of botulinum toxin.[21] The patients were randomly assigned to the treatment arms – conservative management with gabapentin and botulinum toxin alone. Patients administered with botulinum toxin reported decreased leg pain intensity, cramp frequency and cramp severity. Insomnia in these patients improved as well. The study showed the superiority of botulinum toxin in managing nocturnal cramps.

Our study, however, has notable limitations including a small sample size and the changes in electrophysiological parameters to back the subjective assessment of improvement in cramp pain. Larger studies including randomized clinical trials should be conducted to have a definitive conclusion about the efficacy and tolerability of using botulinum toxin in the management of cramps due to peripheral neuropathies from different etiologies.

Conclusion

Local BTX-A infiltration is likely an efficacious and safe procedure for improving pain associated with cramps in patients with peripheral neuropathy.

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