Botulinum Toxin for the Treatment of Lower Limb Cramp Pain in Patients with Amyotrophic Lateral Sclerosis

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ABSTRACT

Background. Muscle cramps and pain associated with them can be seen in patients with amyotrophic lateral sclerosis (ALS) and are known to reduce the quality of life. Pharmacological treatment may not benefit all patients in treating these cramps. We assess the efficacy of Onabotulinum toxin A (BTX-A) in the treatment of lower limb cramps in patients with ALS.

Methods. This retrospective chart review included a total of ten patients with ALS who suffered from pain due to lower limb cramps and were managed with BTX-A. Data including patient demographics, visual analog pain scale at different intervals during follow up, ALS functional rating scale and site of onset of ALS symptoms were documented. The pain score at baseline (before administration), at 3 months follow up and at 6 months follow up were compared using Wilcoxon test to assess BTX-A's efficacy.

Results. A significant improvement in average pain score due to cramps from baseline to the 6-month interval with a change of 3.1±0.7 ($p<0.05$,95%CI) was seen on the pain scale. No adverse events were noted during administration or post injections.

Conclusion. Local BTX-A administration is an efficacious and safe procedure for improving pain associated with cramps in patients with ALS.

Introduction

Muscle cramps are involuntary contractions of an individual muscle or muscle group which can range from mild to severe, and is known to reduce a patient's quality of life by negatively affecting sleep and causing pain lasting for days. [1,2] Various physiological states are commonly associated with cramps, including pregnancy and fatigue. [3-7]. There are two main theories describing the origin of a cramp - the unusual arousal of terminal branches of motor axons, and hyperactive motor neurons in the spine. [3,7-14] These two processes can occur simultaneously thereby leading to muscle hyperactivity presenting as a cramp.[9]

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder characterized by degeneration of anterior horn cells. Cramps are one of the most commonly reported symptoms with up to 90% of the patients diagnosed with ALS having them during the course of the disease.[15,16,17] A study reported that about 56% patients with cramp require treatment for the same.[18] They have also been reported to be the presenting symptom and may precede weakness and wasting by several months.[19,20] Cramps in ALS patients are caused by excitation of glutamate, triggering the random release of motor nerves, which eventually progress to muscle fibers.[4]

Currently, treatment for ALS is centered around symptom management.[21-23] Typical treatments for cramps and the pain associated with it include antiepileptic drugs, quinine, and magnesium supplements, which are known to have unpleasant effects and are not efficacious.[24-27] The use of vitamin E, gabapentin, and quinidine have been investigated for the relief of cramps in ALS patients, but none were successful in alleviating cramps.[28-31] Mexiletine, a sodium channel blocker has been demonstrated to reduce cramp and cramp induced pain without affecting the progression of the disease.[32] Another effective management modality which has proved to be efficacious is the use of onabotulinum toxin A (BTX-A) which works by preventing acetylcholine release at the neuromuscular junction thereby relaxing the muscle and ceasing the pain caused due to cramps.[33,34,35]

The purpose of our study is to assess the efficacy of botulinum toxin in reducing lower limb cramp pain in ALS patients.

Materials and Methods

Our study is a retrospective chart review of patients that attended a University based hospital approved by the Institutional review board (IRB) and the IRB waived the need to collect informed consent for this study. The study population included patients with ALS aged more than 18 years who were undergoing care our hospital for the same.

These patients had undergone BTX-A administration for managing pain due to cramps by the same physician. Only patients with lower limb cramps and at least 6 months follow up during the study period were included. All patients in this study had tried and failed two or more 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 BTX-A included bilateral gastrocnemius (50 units each), quadriceps (50 units each) and intrinsic muscles of the foot (50 units each). They received injections every three months to coincide with their regular clinic visit. A total of 10 patients fulfilled the criteria and were made a part of the study.

Information including age, gender, race, site of onset of ALS, ALS functional rating scale score and visual analog pain score was collected for these 10 patients. The visual analog pain score was recorded at baseline before the administration of botulinum toxin and was followed up at 3-month and 6-month intervals from the first injection.

Results

Out of the 10 patients seven were males. Table 1 summarizes the patient demographics of our study. Our study showed the average ALS functional rating scale score amongst these patients to be 36.5±5.01. The average pain score due to cramps at baseline (before the administration of BTX-A), at 3 months follow up and at 6 months follow up were 8.8±0.7 (8-10), 6.8±1.5 (4-9) and 5.7±1.4 (4-8) respectively.

The change in average pain score from baseline to 3 months follow up was 2±0.8 (p=0.05,95%CI) with correlation coefficient of 0.782. However, a significant improvement in the score from baseline to the 6-month interval with a change of 3.1±0.7 (p<0.05,95%CI) was noted. Figure 1 demonstrates the change in pain scores from before administration to 3 month and 6-month intervals. No adverse either during the procedure or during interval between injections were reported.

Table 1: Patient demographics

Characteristics of the patients	Detail
Age (years)	64.1± 5.48
2.Gender (M/F)	7/3
Ethnicity	
• Caucasians	9
• African American	1
Site of onset of ALS	
• Lower limb	8
• Upper limb	2

Statistics

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

Discussion

ALS is characterized by progressive weakness in absence of pain and sensory loss. Although not a cardinal symptom in ALS, pain is bound to occur to patients at some point during their illness. Cramps are a leading cause of pain in patients with ALS and have been reported to affect 92% of ALS patients in the USA. Occurring on an average of 5.3 cramps per day, they do not correlate with the disease severity or duration.[16] They have been reported to occur most commonly in the calf and thigh followed by hand and foot. Cramps were reported to trend down from the first year of the disease to the second and third year although its prevalence appears to be stable from the first to the third years of ALS and increase during months of illness prior to diagnosis.[16] This was one of the rationales why we chose the specific sites for injecting BTX-A in these patients.

Our study assessed the efficacy of BTX-A which has been reported to effectively manage cramps in other conditions including benign fasciculation syndrome and diabetic neuropathy. [33,36,37] The property of relaxing the muscle by preventing acetylcholine release at the neuromuscular junction has been utilized in ALS patients to manage spasticity, sialorrhea and dysphagia. [38,39,40] Table 2 summarizes the different studies that used medications to manage pain as a result of cramps in patients with ALS.

A relatively recent trial by De Carvalho in 2010 aimed to assess the efficacy of Memantine when compared to placebo in 63 participants of the study reported the failure of Memantine as a cramp relieving agent.[47]

A study in 2016 involving 60 patients from 10 centers randomized 1:1:1 to placebo, mexiletine 300mg/d or mexiletine 900mg/d and followed for 12 weeks. Mexiletine 300 mg/d was found to be safe and well tolerated whereas Mexiletine 900mg/d was associated to more discontinuations. Large dose dependent reductions in muscle cramps frequency and intensity were reported in patients who were on Mexiletine. A dose dependent reduction in pain intensity was also noted when compared to placebo (300

Table 2: Summary of studies conducted with different medications that were targeted to provide relief to ALS patients with cramps.

Authors	Reference	Year of study	Medication used	Outcome
Norris et al	41	1979	Baclofen	Diminution of cramps in placebo arm and Baclofen arm
Blin et al	42	1989	L-threonine	No improvement in cramps
Blin et al	43	1992	L-threonine	No improvement in cramps
Gil et al	44	1992	L-threonine alone, L-threonine + L-isoleucine and L-valine combination	No change in cramps
Desnuelle et al	45	2001	Riluzole, Riluzole + Vit E	No significant difference in cramps between treatment and placebo group
Miller et al	30	2001	Gabapentin	No difference between treatment and placebo group.
Meininger et al	46		Xaliproden	No significant change in cramp characteristics.
Weber et al	48	2010	THC	No significant change in cramp characteristics.
De Carvalho et al	47		Memantine	No significant difference between two groups.
Weiss et al	32	2016	Mexiletine - 300mg/d and 900mg/d	Dose dependent reduction in pain intensity
Oskarsson et al	49	2018	Mexiletine	13 out of 18 patients had significant reduction in cramps due to administration of drug.
Our study		2019	Onabotulinum toxin A	Significant reduction in average pain score from before administration to 6-month interval

mg Mexelitine: 37% placebo, p=0.058; 900mg mexiletine: 16% of placebo, p=0.025%). There was a decrease in ALS FRS-R that was observed and was not different from that seen in the placebo group.[32] A multi-center, double blinded, placebo control cross over trial of Mexiletine involving reported the reduction of cramp frequency in 18 of 20 patients out of which 13 reductions were attributed to the treatment ($p<0.05$). One of the patients discontinued the study due to dizziness while the other initiated an open label mexiletine therapy.[49] As compared to Mexiletine, the adverse effect profile of BTX-A is less severe which is reflected in our study. None of our patients complained of any adverse effects and all patients continued using this option. The improvement in average pain score from before administration to follow up at 3 months was insignificant while that from before administration to at 6 months follow up was significant implying that approximately 6 months were needed to get significant improvement in pain due to cramps. This implied that BTX-A may be a good option to manage pain due to cramps in a long-term setting.

Our study however has notable limitations including a small sample size and the use of a subjective pain scale to

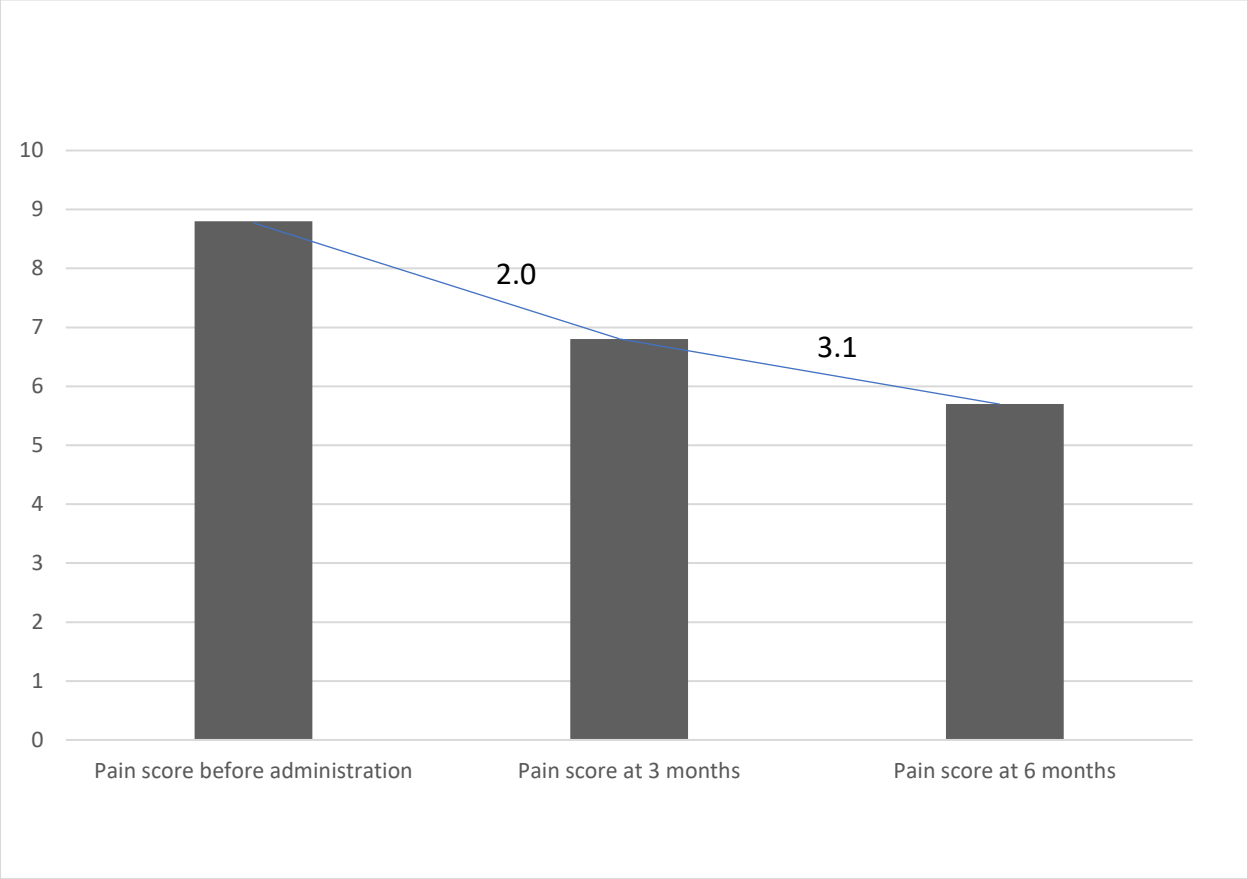

Figure 1: Graph showing the change in average pain score at different intervals of time during the patient's follow up. The number on top of the graph denotes the decrease in average pain score from the score noted before administration of botulinum toxin to that time interval.

assess the change in pain from last visit. We also lacked objective cramp measures. 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 pain due to cramps in patients with ALS.

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