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Efficacy of Scalene Muscle Botulinum Toxin Injection for the Treatment of Neurogenic Thoracic Outlet Syndrome

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Abstract

Background: Neurogenic thoracic outlet syndrome (nTOS) is a disease process caused by the compression of neurovascular structures passing through the anatomical thoracic outlet. This compression can manifest as pain, paresthesia, progressive muscle weakness and subsequent muscle loss of the effected limb. Current mainstay treatment for patients with nTOS is conservative therapy and surgical decompression. However, in recent years, botulinum toxin, which is a neuromuscular junction blocking agent has been effective as a short-term treatment.

Method: A literature search using the following search engines CINAHL, MEDLINE-OVID, EBMR Multifile and Web of Science was conducted using the following search terms: thoracic outlet syndrome, botulinum toxin and Botox. Inclusion criteria were: adults diagnosed with thoracic outlet syndrome who were being treated with botulinum toxin injections alone, studies in English, dates from 2000-2012. Studies excluded if patients had previous surgical intervention for TOS and evaluated using the GRADE system.

Results: Three studies met inclusion criteria. A double-blind, randomized, controlled trial involving 38 patients used ultrasound-guided Botox injections in the scalene and pectoralis minor muscles for treatment of patients with nTOS. Results showed no clinical difference in treatment and placebo groups when compared on a visual analog scale. A prospective longitudinal study involving 27 patients receiving CT-guided low dose Botox injections to the anterior scalene muscle, resulted in as much as 47% reduction in pain. Lastly, a prospective study that enrolled 22 subjects examined nTOS patients response to electrophysiologically and fluoroscopically guided Botox injections in the anterior scalene, middle scalene and pectoralis minor muscles, demonstrated a greater than 50% reduction of pain in 64% of the cohort.

Conclusion: Two quasi-experimental studies demonstrated Botox injections in the scalene muscles and pectoralis minor muscle to be effective in symptomatic treatment of nTOS but results of a recent randomized controlled trial show no clinical significance. All relevant articles revealed limitations, with each of the studies needing a larger sample size, better randomization, blinding techniques and a more specific and well defined inclusion criteria.

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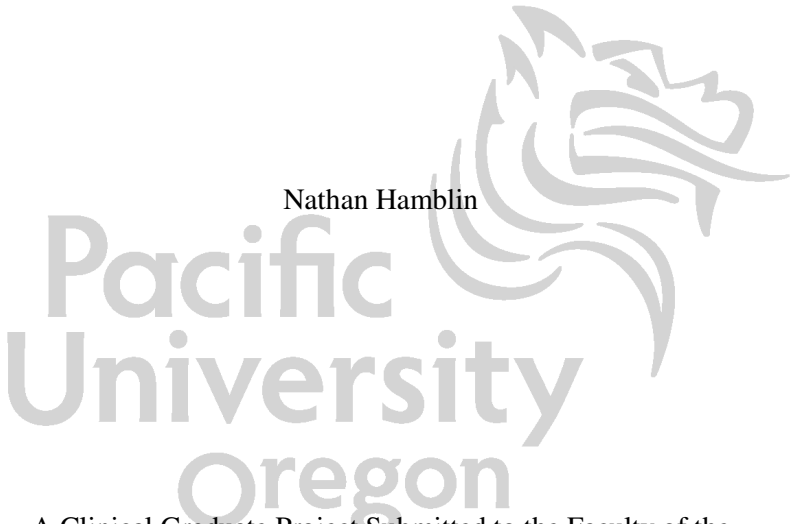

A Clinical Graduate Project Submitted to the Faculty of the

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Faculty Advisor: Eric Foote, PA-C, MS

Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS

Biography

Nathan Hamblin was born and raised on the Central Coast of California. After high school he served in the Navy as an Aviation Electrician, which afforded him and his wife Laurie the opportunity to experience Japan, the east coast and the entire west coast. After the Navy, Nathan started his college career at the University of Washington, continued at Cal State San Marcos and received a Bachelor of Science in Human Biology from Cleveland Chiropractic College Los Angeles. When Nathan isn't spending time with Laurie and his two daughters Taylor and Haley, you can usually find him surfing, swimming, trail running or in the kitchen.

Abstract

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Keywords: Botulinum toxin, Botox, Thoracic Outlet Syndrome, Botulinum toxin type A, Neurogenic Thoracic Outlet Syndrome,

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To *my wife:* I want to thank you and share this moment with you because ultimately my success is your success. I would not have been able to accomplish such an achievement without your love, support and understanding.

To *my daughter:* Taylor, you have been by my side since before you could even remember and you have shared me so graciously with my studies and I am so proud to share this moment with you.

To *my parents, sister, family and friends*: Thank you for all of your years of support, love and endless words of encouragement.

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List of Abbreviations

aTOS.....Arterial Thoracic Outlet Syndrome

ASM.....Anterior Scalene Muscle

BOTOX.....Botulinum Toxin

BTX-A.....Botulinum Toxin Type A

CT.....Computed Tomography

MRI.....Magnetic Resonance Imaging

MSM.....Middle Scalene Muscle

nTOS.....Neurogenic Thoracic Outlet Syndrome

TOS…….....Thoracic Outlet Syndrome

VAS.....Visual Analog Scale

vTOS.....Vascular Thoracic Outlet Syndrome

Efficacy of Scalene Muscle Botulinum Toxin Injection for the Treatment of Neurogenic Thoracic Outlet Syndrome

BACKGROUND

Thoracic outlet syndrome (TOS) is considered to be a spectrum of symptoms caused by compression of neurovascular structures that pass through the thoracic outlet.[1] The term "Thoracic Outlet Syndrome" was first given by Peet et al[2] in 1956, to describe a condition caused by the compression of neurovascular structures in the upper extremity.[3,4] The Thoracic Outlet is an anatomical space defined by the superior edge of the first rib, posterior border of the clavicle, lateral border of the mediastinum and the bony landmarks of the spinal column to the fifth cervical rib.[5] Within the Thoracic Outlet, the scalene triangle is most commonly involved in the compression of the brachial plexus.[6] There are three main subtypes of TOS that are categorized by the principally affected structure involved in symptoms[3]. The three subtypes are neurogenic (nTOS) due to brachial plexus compression, arterial (aTOS) due to subclavian artery compression, and venous (vTOS) due to subclavian vein compression.[7] Neurogenic TOS is the most common subtype, making up 95% of cases.[7] The brachial plexus, subclavian artery and vein are particularly susceptible to injury and compression when passing through either the costoclavicular space, scalene triangle or pectoralis minor space.[8] The "space problem" as proposed by Brantigan and Roos[5] can arise from congenital or post-traumatic bony and soft tissue anomalies such as a cervical rib, first rib deformities, displaced fractures, scalene muscle fibrosis, scalene muscle hypertrophy and scalene muscle insertion anomalies. The anterior scalene muscle (ASM) and middle scalene muscles (MSM) originate from the transverse processes of cervical vertebrae 2-7 and

insert on the first rib. Both the ASM and MSM, function as an accessory muscle to respiration by elevating the first rib.[9] The brachial plexus along with the subclavian artery and vein traverse through the scalene triangle that is created by the origin and insertion of the ASM and MSM.

Standard imaging techniques and testing is generally not effective at assisting in the diagnosis of TOS. This burden is then passed on to patients who are left with an incapacitate disease that is largely unrecognizable by most clinicians. Along with the difficulty of diagnosing TOS, it is just as difficult to know where to start treatment.[3] To date, one of the most reliable methods to diagnose nTOS is by a neuromuscular blocking agent injection to the anterior scalene muscle at its insertion on the first rib.[3] As reported through multiple studies[4,10,11], lidocaine or bupivicaine injected in the ASM under computed tomography (CT) guidance or ultrasound guidance has been shown to successfully alleviate symptoms caused by compression of the neurovascular structures in the scalene triangle. The lidocaine and bupivacaine injections however, are only effective for a few hours. Furthermore, these studies[4,10-12] demonstrated that imaging guided botulinum toxin injections in the ASM provided the same relief as lidocaine and bupivacaine, but Botox lasted for a duration of approximately 3 months. With limited options for management of nTOS, patients who have not benefited from conservative treatment, such as physical therapy, exercise and massage therapy, have often found botulinum toxin injections to be a useful approach for those not able to tolerate surgical intervention or as a bridge to surgical treatment[4,10,11]. The question remains, how effective is the use of botulinum toxin injected into the scalene muscles for short-term and/or long-term symptomatic relief of neurogenic thoracic outlet syndrome.

METHODS

A literature search using the following search engines CINAHL, Medline-OVID, EBMR Multifile and Web of Science was conducted using the following search terms: thoracic outlet syndrome, botulinum toxin and Botox. Inclusion criteria were: adults diagnosed with thoracic outlet syndrome who were being treated with botulinum toxin injections alone, studies in English, dates from 2000-2012. Studies were excluded if patients had previous surgical intervention for TOS. The quality of evidence for all relevant articles was then evaluated using the grades of recommendation, assessment, development and evaluation (GRADE) system.[13]

RESULTS

The search using keywords, Thoracic Outlet Syndrome, Botulinum Toxin, Botox and a timeline of 2000-2012, yielded a total of 24 articles. After reviewing all eligible articles, only 3 met the inclusion criteria. The articles included were a double-blind, randomized, controlled trial by Finlayson et al[12], a prospective longitudinal study by Christo et al[4] and a prospective study by Jordan et al[11].

Finlayson et al study

This double-blind, randomized, controlled trial[12] was performed in Canada and is the first of its kind to evaluate the efficacy of EMG-guided botulinum toxin injections for the treatment of TOS. Thirty-eight patients were selected and randomized to receive an injection to the scalene muscles of either 75cc of botulinum toxin type A (BTX-A) reconstituted with 0.75cc of normal saline or 0.75cc of normal saline alone to the scalene muscles. Patients were followed for a total of 6 months. The primary outcome of the

study was pain using a 100-mm horizontal visual analog scale (VAS) with scores in a range of 0-100. Secondary scores were paresthesias measured by VAS, Disability of the Arm, Shoulder, and Hand (DASH) questionnaire, SF-36 Health Survey physical and mental scores. Pain scores were noted at baseline, 6 weeks, 3 months, and 6 months post injection, with the primary outcome of interest being evaluated at 6 weeks.[12]

Criteria for eligibility in the study included patients with a clinical diagnosis of TOS presenting with symptoms for a minimum of 6 months, 19 years of age or older, medically stable, mentally and physically sound to give informed consent, prior electromyography (EMG) and a magnetic resonance imaging (MRI) or a computed tomography (CT) of the cervical spine for ruling out bony abnormalities or anomalies. Patients were excluded from the study if they had prior BTX-A therapy; BTX-A allergy; history of botulism; scalenectomy; TOS surgery scheduled in the upcoming 6 months; current anticoagulant therapy; diagnosis of myasthenia gravis or Eaton-Lambert syndrome; were pregnant; unable to complete follow up at 6 weeks, 3 months, and 6 months post injection. Subjects were randomized to each group using a computer random number generator carried out by a statistician who was not a co-investigator. As soon as a subject was enrolled into a group, a first study investigator confirmed treatment for that individual, prepared the solution and presented it to a second investigator who would perform the injection. The treatment plan was concealed in a locked filing cabinet and only known to the first investigator. Contents in both the BTX-A and placebo syringe were identical in appearance and quantity to ensure the injector and subject could not identify which group they were associated with.[12]

According to the VAS, botulinum toxin type A treatment did not have significant changes in average pain scores from baseline when compared to placebo according to the VAS. The difference in pain scores between the two groups was measured at 5.03 mm in favor of the treatment group (95% CI -15.7 to 5.69, P = 0.36). At 6 weeks follow up, 6 of the 20 patients in the BTX-A group (30%) and 2 of the 18 patients in the placebo group (11%) reported a 30% or greater reduction in pain when compared to baseline (difference = 19%, 95% CI: -8% to 42%, P = 0.24). Secondary outcomes were not averaged and varied from subject to subject.[12]

Finlayson et al[12] reported no clinical or statistical significance between the BTX-A and the placebo groups. They did however, point out several limitations to the study. The average duration of symptoms in the BTX-A group before being enrolled in the study was found to be 6 years; in comparison those in the placebo group had been symptomatic for an average of 3 years despite efforts at randomization. They also did not identify or assess patients for chronic pain syndrome, which may not be successfully treated with a single intervention. Although needle placement was confirmed using EMG guidance, other studies[4,11] that have reported significant reduction in pain post BTX-A injection used CT-guidance[4] and flouroscopic guidance.[11] This may suggest that EMG guidance is not as accurate as other imaging techniques. The authors[12] also felt that their methods of blinding "were suboptimal". Findlayson et al concluded that the lack of pain reduction in BTX-A subjects could be attributed to patients with long standing symptoms who potentially have chronic pain syndrome. They suggest future studies should involve patients with a shorter duration of TOS symptoms.[12]

Christo el al study

This prospective longitudinal study[4] looked at the efficacy of low dose, CT-guided, single botulinum toxin injection of the anterior scalene muscle for symptomatic relief of neurogenic thoracic outlet syndrome. Twenty-seven patients were followed over a period of 3 months. The primary outcome was pain relief as measured by the Short-form McGill Pain Questionnaire (SF-MPQ). Selected patients with a diagnosis of TOS received 1cc of 0.25% bupivicaine to the anterior scalene under CT-guidance. Those who had a greater than 50% reduction in pain and improved ability to perform an elevated arm stress test (EAST) were considered for botulinum toxin injection. From there, each eligible subject was given 20 units of Botox in the anterior scalene. Pain scores were recorded at 4 intervals; baseline, 1 month, 2 months, and 3 months post injection.[4]

Eligibility criteria for subjects were age 18 or older, no prior TOS surgical intervention, radiographic confirmation of normal cervical spine anatomy and positive elevated arm stress test (EAST). The procedure was carried out with patients in the supine position and a 25-guage needle was placed into the ASM that was confirmed with radiographic contrast. Once needle placement was confirmed, 20 units of Botox was injected without any repositioning of the needle. In order to confirm proper placement and spread of Botox in the ASM, a focal-scan was performed.[4]

Results of SF-MPQ convey a marked reduction in pain during the three months post injection as indicated by the four components; sensory ($P = 0.02$), total ($P = 0.05$), VAS ($P = 0.04$), and present pain intensity (PPI) score ($P = 0.06$). Median score of pain as suggested by the above four components decreased by 30-42% during the first month, 29-47% during the second month, and 14-33% during the third month. According to the

present pain intensity (PPI) score, more intense pain is given a score of 3, 4, or 5. Pre-Botox, approximately 75% of participants reported their pain as "more intense". After treatment, less than 50% of subjects reported "more intense" pain during the three month follow up. Side effects reported by subjects were few, with neck weakness being the most prevalent.[4]

Christo et al[4] reported significant decreases in pain as measured by SF-MPQ. The researchers[3] also stated that they used a lesser amount of Botox at 20 cc in comparison to at least 100 cc used in similar trials[10-12] and this yielded comparable results. They concluded that due to complication of surgical intervention and large-scale resultant disability (30% and 60% respectively), it is vital that alternative treatments such as the one examined here be pursued and perfected.[14]

Jordan et al study

In this prospective study,[11] researchers examined the effects of botulinum toxin as a bridge therapy for patients diagnosed with TOS who were being evaluated for surgery. Twenty-two patients were selected and followed for 6 months. Each patient was to receive a total of 100 units of botulinum toxin dissolved in 1mL of saline, delivered to the anterior scalene muscle, middle scalene muscle and trapezius muscle. All injections were to be electrophysiologically and fluoroscopically guided to ensure precision at each injection site. Primary outcomes were pain and symptomatic relief as measured by a 101-point analog scale.[11]

In order for participants to meet eligibility criteria they needed to have a clinical diagnosis of nTOS and a minimum of 2 years with stable clinical symptoms. A cervical

MRI for all subjects was obtained to rule out bony abnormalities or anomalies. Each patient had already attempted and failed at more conservative therapy. During the 6 month trial, patients were still being treated with physical therapy, medications and workplace ergonomic adjustments.[11]

Accurate placement of the needle was confirmed with iodinated contrast injected into the anterior scalene muscle. A 2mL mixture of 2% lidocaine and 1.5 mg of betamethasone sodium phosphate was injected into the anterior scalene as an anesthetic blockade. Patients were then reexamined to identify their degree of pain. If a subject reported > 50% pain relief on the 101-point analog scale, they were considered for Botox injections. Botox injections were then carried out in the same fashion with 12 units injected into the ASM, 12 units injected into the MSM, and the remaining 76 units injected into the ipsilateral trapezius muscle.[11]

Follow up results demonstrated a significant decrease in pain scores with 64% of patients reporting > 50% pain relief for longer than 1 month. As reported by Jordan et al[11] "the mean duration of improvement after botulinum injection was 88 days with a range of 30 - 180 days". Similar to other researchers,[4,10] Jordan et al[11] found botulinum toxin to be a valuable treatment for patients awaiting surgery but not a long-term definitive treatment.[11]

DISCUSSION

Surgery is the current mainstay treatment for patients that have failed conservative management. For patients who are not surgical candidates, Botox injection may provide an alternative treatment option to more invasive procedures such as

scalenectomy or rib resection. Furthermore, long-term success rates for surgical interventions, range from 40-65% but have been shown to diminish over time.[14,15] In two of the studies, [4,11] botulinum toxin used as therapy for nTOS has been shown to be a safe, effective, short-term, non-surgical approach to treatment for patients who have failed conservative therapy or not considered to be a good candidate for surgery. However, the one RCT reviewed,[12] failed to demonstrate efficacy. There are several limitations in all of these studies which makes it difficult to truly know the effects of scalene muscle Botox injections and whether or not they should be considered by clinicians with patients looking to defer or avoid surgery.

Aside from BTX-A as a treatment for TOS, it has also been suggested that botulinum toxin can be an effective bridge therapy for patients who are waiting for elective surgery.[11] This idea of a bridge therapy could benefit from a study that looks at patients preparing for non-expeditious surgery to correlate success of BTX-A treatment results with surgical results. For all of these aforementioned reasons further research is warranted on this non-surgical approach to treatment.

One of the largest flaws of the Finlayson et al study[12] that the authors did not address is the small population size, which may be a reason as to why they interpret there to be no significant difference between the treatment and placebo groups. While a 19% difference in pain reduction between BTX-A and placebo may not seem significant in a population of 38, a 19% difference would be more meaningful in a population of 1,000 or greater. It has been recognized that using VAS scores to measure pain can be subjective and may not be as valid a measurement when comparing a group of individuals as it would if it was used to identify changes in an individual.[16]

An even more significant limitation to the Findlayson et al study,[12] involved the randomization of the two groups. The authors concluded after randomization that the patients in both groups had a significantly long duration of symptoms prior to entry into the study, but the BTX-A group had an average duration that was double the placebo group. Patients in the BTX-A group averaged 6 years of symptoms, while the patients in the placebo group averaged 3 years. With nTOS being described as a chronic and progressive disease,[8] it would be difficult to understand how such a difference in duration of symptoms would not dramatically affect the results. It could also be assumed that a longer duration of symptoms is accompanied by a later stage of disease progression, which could change the approach to treatment. Presumably, a patient with a much greater duration of symptoms may not benefit from a single BTX-A injection, rather multiple injections or simply a more aggressive treatment. In accordance with GRADE system,[13] this randomized controlled trial could be given a quality score of low. See Table I.

In the Christo et al[4] and Jordan et al study,[11] the results seemed to suggest that Botox could be successful short-term treatment for TOS or successful as a bridge therapy for patients considering surgery. These studies however, were prospective longitudinal studies and of quasi-experimental design that did not use a control group or account for the possibility of placebo effect. The inclusion criteria for both studies could have been better defined. For example, the pre-enrollment duration of symptoms for patients in both studies[4,11] were broad and allowed for patients who may have had a significantly longer progression of the disease. This potential longer duration of symptoms however, would only make the results more valid considering that a great majority of subjects had

relief of symptoms. Also, in both studies the sample sizes used were small. In terms of accuracy or injection placement, Christo et al[3] performed their treatment under CT guidance, using a significantly smaller amount of botulinum toxin than in previous studies[10,11] to reproduce a similar outcome. This would suggest that other methods for confirmation of needle placement such as ultrasound and electromyography, which are using 3-5 times as much BTX-A,[10,11] are lacking precision. The results of these studies[4,11] suggest a benefit for nTOS patients but need further refinement in order to be considered of higher quality according to the GRADE system. Seeing that both studies are quasi-experimental studies, according to GRADE, they would be downgraded to a very low. Both studies would have a more profound outcome if reproduced using a double-blind, randomized controlled trial with a larger sample size.

CONCLUSION

Research to date on treatment of thoracic outlet syndrome with botulinum toxin, is lacking in quantity and quality. The population sizes for all current studies have been very small and could significantly distort treatment effect. There has also been imprecision in determining inclusion criteria, which allows for confounders such as severity and progression of disease. However, two studies that have been performed show a significant improvement of symptoms.[4,11]

For most patients, nTOS can interfere with normal daily activities and can be debilitating to patients suffering from this diagnosis. Also, the proper diagnosis and classification of TOS can be a controversial entity to clinicians due to its complex symptoms and lack of consistent clinical presentation.[3,5]

Although two studies[4,11] have demonstrated evidence of successful botulinum toxin treatment, more effort should be put into controlling the primary outcome measure by using a larger sample size, better randomization and blinding techniques and a more specific and well defined inclusion criteria.

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Table I. Characteristics of Reviewed Studies

Quality Assessment							
		Downgrade Criteria					*Quality*
Studies	*Design*	*Limitations*	*Indirectness*	*Imprecision*	*Inconsistency*	*Publication bias likely*	High; Moderate; Low; Very Low
Finlayson et al[12]	RCT	Serious limitations[a]	No serious indirectness	No serious imprecision	Serious inconsistencies[b]	No bias likely	Low
Christo et al[4]	Prospective Longitudinal Study	Very serious limitations[c]	No serious indirectness	Serious imprecision[d]	No inconsistencies	No bias likely	Very low
Jordan et al[11]	Prospective	Very serious limitations[c]	No serious indirectness	Serious imprecision[d]	No inconsistencies	No bias likely	Very low

a Small sample size demonstrating non-significant confidence intervals
b Failure of randomization with the treatment group having symptoms for an average of 6 years compared to 3 years in the control group
c Quasi-experimental design lacking control group, randomization, and placebo. Also, broad inclusion criteria.
d Small sample size