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Is Botulinum Toxin A safe and effective for the treatment of trigeminal neuralgia in adults?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

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Abstract

Objective: The objective of this evidence based medicine review is to determine whether or not Botulinum Toxin A is safe and effective for the treatment of trigeminal neuralgia in adults.

Study Design: Three double blind, randomized controlled trials were reviewed and selected based on their relevance to the clinical question and their inclusion of patient oriented outcomes (POEMS).

Data Sources: Each study was obtained by searching NCBI and PubMed database.

Outcome measures: The outcomes were measured using the Visual Analog Scale (VAS), Quality of Life (QoL), Patient Global Impression of Change Scale (PGIC), Last Observation Carried Forward (LOCF), and detected adverse effects.

Results: The results Shehata et al. study showed that the VAS and LOCF showed significant decrease in daily pain, use of acute medications, daily paroxysms, and increase in QoL using Botulinum Toxin A vs. normal saline. These results were shown by pain had a decrease by 6.5 with Botulinum Toxin A vs. 0.3 with normal saline, paroxysms with a score of 0.88 to 7.12, acute medications with a score of 3.69 to 5.71, and QoL with a score of 8.35 to 9.65, and these all had p values of <0.0001 and CO of 95% respectively utilizing simple descriptive analysis, ANCOVA model, and Pearson correlation coefficient. This study also showed adverse effects of facial asymmetry utilizing ARI and NNH which showed for every 3 participants, 1 participant experienced facial asymmetry³. The results of Wu et al. study showed that the VAS and PGIC showed significant decrease in daily pain and daily paroxysms. By utilizing the Fisher exact test, RBI, ABI, and NNT, PGIC showed for every 3 participants, 1 participant experienced improvement and p values of <0.05 and by utilizing the Wilcoxin rank sum test, VAS showed improvement with daily pain and paroxysms with a p value <0.05 . This study also showed adverse effects of facial asymmetry utilizing ARI and NNH which showed for every 2 participants, 1 participant experienced facial asymmetry⁴. The Zuniga et al. showed that the VAS showed significant decrease in daily pain and paroxysms. Utilizing the T-test and paired t-test, VAS showed improvement with pain and paroxysms with a p value of <0.001 . This study also showed adverse effects of facial asymmetry utilizing ARI and NNH which showed for every 10 participants, 1 participant experienced facial asymmetry⁵.

Conclusions: All three RCTs demonstrated positive outcomes with Botulinum Toxin A in the treatment of trigeminal neuralgia with low risk of detected adverse effects.

Keywords: trigeminal neuralgia, Botulinum Toxin A

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Introduction

Trigeminal neuralgia is a chronic pain condition caused by inflammation of the trigeminal nerve which is the most widely distributed nerves in the head. This nerve has three branches which supplies sensation to the scalp, eyes, eyelids, forehead, cheeks, jaw, lips, teeth, and gums. Trigeminal neuralgia affects 150,000 people every year where it can affect any age group. Trigeminal neuralgia can be triggered by just any daily task like touching one's face, washing one's face, shaving, brushing one's teeth, blowing one's nose, drinking hot/cold beverages, applying make-up, smiling and even talking which all these things people do on a daily basis so it can really have a negative impact on a patients quality of life¹. About 8,000 patients with trigeminal neuralgia undergo surgical intervention each year which costs are estimated over \$100 million per year. The exact cause of TN is unknown. Trigeminal neuralgia could be caused by many things. Some are compression of the nerve by a blood vessel exiting the brain stem, multiple sclerosis, trauma, stroke, tumor on the nerve, and/or rarely arteriovenous malformation. There is no exact cure of trigeminal neuralgia but there are many treatments which vary from oral medications to surgical intervention to help decrease symptoms and pain. The usual methods used to treat trigeminal neuralgia are anticonvulsant medications (i.e. carbamazepine, phenytoin, gabapentin, topiramate), microvascular decompression, percutaneous stereotactic rhizotomy, percutaneous glycerol rhizotomy, percutaneous balloon compression, stereotactic radiosurgery, motor cortex stimulation². This method of treatment (Botulinum Toxin A) is being proposed because the treatment options mentioned above all can play a role in

treating trigeminal neuralgia, but most of the treatment options consist of surgical intervention which are invasive and not guaranteed effective and the use of Botulinum Toxin A has been shown to be effective in the treatment of trigeminal neuralgia.

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Objective

The objective of this evidence based medicine review is to determine whether or not Botulinum Toxin A is safe and effective for the treatment of trigeminal neuralgia in adults.

Methods

The population consists of men and women over 21 years of age with a diagnosis of trigeminal neuralgia. The intervention is Botulinum Toxin A and the comparison is normal saline. The outcomes consist of the reduction of daily pain of trigeminal neuralgia using Botulinum Toxin A, daily paroxysms of trigeminal neuralgia using Botulinum Toxin A, and adverse effects of Botulinum Toxin A for the treatment of trigeminal neuralgia. The studies that are included in this review consist of three randomized controlled trials (RCTs). The keywords used in the searches were “Botulinum Toxin A” and “trigeminal neuralgia”. All articles were published in English. All articles were published in peer reviewed journals and found via NCBI and PubMed. The articles were selected based on relevance and that the outcomes of the studies mattered to the patients (POEMS). The inclusion criteria consisted of studies that were RCTs published after 1996 and topics not used by prior students in our program, and patients over the age of 21 with a diagnosis of trigeminal neuralgia. The exclusion criteria consisted of patients who responded to usual medical to usual medical therapy, pregnant women, patients with history

of trigeminal neuralgia from secondary causes, or hypersensitivity reaction to Botulinum Toxin

A. The summary of statistics reported or used were p-value, RRI, RBI, ABI, ARI, NNH, NNT.

Table of demographics and characteristics of included studies (Table 1)

Study	Type	# Pts	Age (yrs)	Inclusion criteria	Exclusion criteria	W/D	Interventions
Shehata2013 (1)	RCT	20	27-72	Subjects had idiopathic TN according to HIS criteria, all patients elicited sensory stimulation in different skin area, and failure in reduction of pain last 3 months	Patients who responded to medical treatments, pregnant women, symptomatic trigeminal neuralgia (abnormal neurological examination or demonstrable structural lesion by MRI), patients with possibility of lack of coherence during follow up	0	Botulinum Toxin A- 100 U in 2mL preservative- free normal saline resulting in a concentration of 5 u/1mL vs. Visually matched placebo- 2 mL of 0.9% NaCl saline
Wu 2012 (2)	RCT	42	30-88	Failure of recent treatment for TN at baseline and understanding the information given relative to the trial, particularly with regard to possible complications such as transient facial weakness	Pts with any medical condition or use of agent that puts them at increased risk if exposed to Botulinum Toxin A or skin infection at injection site, women of child bearing age, nursing, or planning pregnancy	2	Botulinum Toxin A 75U/ 1.5 mL (saline) vs. Visually matched placebo- 1.5 mL of normal saline

Zuniga 2013 (3)	RCT	36	42-93	Men and women greater than 18 y/o with diagnosis of TN, brain MRI r/o secondary causes, subjects who had not responded to usual treatment prior	Subjects with hx of TN from secondary causes, who responded to usual treatment, change in their medications 2 months before study, women of child bearing potential, hypersensitivity to Botulinum Toxin A, or concomitant conditions where invasive procedures are contraindicated	0	Botulinum Toxin A- 50U/ 1mL vs. Visually matched placebo- 0.9% saline 1mL
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Outcomes Measured

The outcomes were measured by Visual Analog Scale (VAS), Quality of Life (QoL), Patient Global Impression of Change Scale (PGIC), Last Observation Carried Forward (LOCF), Detected adverse effects.

Results

All three articles reviewed were randomized controlled trials and all assessed the efficacy of Botulinum Toxin A in the treatment of trigeminal neuralgia. All three studies used a placebo of normal saline as the comparative group. All three studies randomized their sample population and matched them to the experimental and control groups. The Shehata et al. study consisted of 20 Egyptian men and women (10 BTX/10 placebo) between the ages of 27-72 years of age with a diagnosis of intractable trigeminal neuralgia³. The Wu et al. study consisted of 42 men and women (22 BTX/20 placebo) between the ages of 30-88 year of age with a diagnosis of trigeminal neuralgia⁴. The Zuniga et al. study consisted of 36 men and women (20 BTX/16 placebo) older than 18 years of age with a diagnosis of trigeminal neuralgia⁵. All of these studies

were 12 weeks in duration. The withdrawal rate of Shehata et al. and Zuniga et al. were 0%, while Wu et al. had a withdrawal rate of 0.5%. Only one study noted non compliance, Wu et al., where two participants were withdrawn from the study⁴.

The results Shehata et al. study showed that the VAS and LOCF results were statistically significant by participants having a daily decrease in pain, use of acute medications, paroxysms, and increase in QoL using Botulinum Toxin A vs. normal saline. These results were shown by that pain had a decrease by 6.5 with Botulinum Toxin A vs. 0.3 with normal saline, paroxysms with a score of 0.88 to 7.12 with 95% CI, acute medications with a score of 3.69 to 5.71 with 95% CI, and QoL with a score of 8.35 to 9.65 with 95% CI at the end of 12 weeks, and these all

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had p values of <0.0001 respectively utilizing simple descriptive analysis, ANCOVA model, and Pearson correlation coefficient. This study also showed adverse effects of facial asymmetry utilizing ARI and NNH which showed for every 3 participants, 1 participant experienced facial asymmetry³. The results of Wu et al. study showed that the VAS and PGIC showed a statistically significant decrease in daily pain and daily paroxysms. By utilizing the Fisher exact test, RBI, ABI, and NNT, PGIC showed for every 3 participants, 1 participant experienced improvement in daily paroxysms with a p value of <0.05, and by utilizing the Wilcoxin rank sum test, VAS showed improvement with daily pain intensity with a score of 1 with the Boltulinum Toxin A vs. a score of a 5 with the placebo at the end of the 12 weeks which shows a p value <0.05. This study also showed adverse effects of facial asymmetry utilizing ARI and NNH which showed for every 2 participants, 1 participant experienced facial asymmetry⁴. The Zuniga et al. showed that the VAS showed significant decrease in daily pain and paroxysms. Utilizing the T-test and

paired t-test, VAS showed to be statistically significant by improvement with pain from 4.75 to 6.94 from those treated with Botulinum Toxin A vs. placebo and paroxysms showing a decline from 29.1 daily to 7.1 with a p value of <0.001 by the end of 12 weeks. This study also showed adverse effects of facial asymmetry utilizing ARI and NNH which showed for every 10 participants, 1 participant experienced facial asymmetry⁵.

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Table 2- Comparison and statistical significant outcomes measured by included studies

	Outcome measured	Scoring System	Mean scores	p-value	Statistically significant
Shehata 2013 ³	pain, paroxysms, acute meds, QoL	VAS, LOCF, QoL	VAS/LOCF- Pain- 6.5 vs. 0.3 Paroxysms- 0.88-7.12 Acute Meds- 3.69-5.71 QoL- 8.35 to 9.65	all p<0.0001	YES, all 95% CI

Wu 2012 ⁴	Pain, paroxysms	VAS, PGIC	Paroxysms- PGIC= RBI- 100%, ABI- 40%, NNT- 3 Pain- VAS- 1 (BTX) vs. 5 (placebo)	All P<0.05	YES
Zuniga 2013 ⁵	Pain, paroxysms	VAS	VAS- Pain- 4.75 (BTX) vs. 6.94 (placebo) Paroxysms- 29.1(beginning) vs. 7.1 (end)	Pain- p<0.01 Paroxysms - p<0.001	YES

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Table 3: Efficacy of Botulinum Toxin A in the treatment of trigeminal neuralgia

Study	CER	EER	RRI	ARI	NNH
Shehata 2013 ³	0	40%	0	40%	3
Wu 2012 ⁴	0	50%	0	50%	2
Zuniga 2013 ⁵	0	10%	0	10%	10

Discussion

After reviewing the results in the studies of this systematic review, several limitations must be considered when interpreting the results. First of all, different amounts of Botulinum Toxin A were used in the studies. The placebo visually matched the amount of Botulinum for each study, but each study used a different amount of Botulinum Toxin A. Secondly, in Shehata et al., the study only consisted of Egyptian participants, participants had different branches of the trigeminal nerve affected, and participants were on different medications for pain prior to study and kept on the same regimen throughout the study.³ Thirdly, in Wu et al., participants were on different medications for pain prior to study and kept the same regimen throughout the study, and two participants one from each group withdrew because of lack of efficacy.⁴ Lastly, in Zuniga et al., participants had different branches of the trigeminal nerve affected, and participants were on different medications for pain prior to study and kept on same regimen throughout the study.⁵

As of now, Botulinum Toxin A is not covered under insurance, but if this problem continues to rise and affect the general population more and more, it may become FDA approved and considered to be a treatment option and be covered under insurance in the future.

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Conclusions

All three RCTs have shown that Botulinum Toxin A is safe and effective for the treatment of trigeminal neuralgia in adults. All three RCTs demonstrated positive outcomes with Botulinum Toxin A in treating trigeminal neuralgia. The studies showed significant improvements in daily pain, paroxysms, quality of life, and the use of acute medications. The

studies also showed to have low risk of harmful adverse effects like facial asymmetry. The participant age, race, sample size, withdrawal rate, study length, and experimental design should all be considered in future studies. There should be also more research done for Botulinum Toxin A as a singular treatment instead of adjunctive therapy with oral medications for trigeminal neuralgia.

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