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Do Injections of Onabotulinumtoxina Reduce Migraine Attack Frequency in Adults?

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Do injections of OnabotulinumtoxinA reduce migraine attack frequency in adults?

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ABSTRACT

OBJECTIVE: The objective of this selective evidence based medicine (EBM) review is to determine whether or not "Do injections of OnabotulinumtoxinA reduce migraine attack frequency in adults?"

STUDY DESIGN: A systematic review of three peer-reviewed studies published between 2015 and 2017.

DATA SOURCES: One randomized controlled trial; one randomized, double-blind, placebo-controlled clinical trial; and one observational, open-label, cohort study comparing frequency of migraine in adults when injected with OnabotulinumtoxinA (OBT-A). Based on their ability to answer the clinical question, articles were selected from PubMed and Cochrane Library.

OUTCOME(S) MEASURED: All articles were based on patient oriented outcomes and focused on mean change from baseline in number of migraine attacks per month. Self-reported questionnaires and diaries kept by patients were used to track number of attacks.

RESULTS: One study conducted (Ranoux D, Martiné G, Espagne-Dubreuilh G, et al. *The journal of headache and pain*. 2017;18(1): 75. doi:10.1186/s10194-017-0781-7) revealed a large treatment effect and high response rate with 41 of 63 having ≥ 50% reduction in headache days per month with OBT-A injection versus baseline (experimental event rate (EER)= 65.1%). In another study (Naderinabi B, Saberi A, Hashemi M, et al. *Caspian J Intern Med*. 2017; 8(3): 196-204. doi:10.22088/cjim.8.3.196) patients receiving OBT-A injections experienced a mean change from baseline of 12.4 and clinically significant improvement (P=0.0001) versus a control group of 5.2 during a three month period. In a third clinical trial (Hou M, Xie JF, Kong XP, et al. *Toxins*. 2015; 7(11): 4442-54. doi:10.3390/toxins7114442) patients were injected with OBT-A during a four month interval revealing a mean change in baseline of 7.2 to 3.5 headaches per month, and the study was clinically significant with a p-value of <0.01.

CONCLUSIONS: This review provides evidence from three separate studies that prophylactic injections with OBT-A greatly reduce the number of migraine attacks per month. Further research is warranted to provide more accurate time frames for efficacy and adverse effects (AE) compared to traditional prophylactic methods.

KEY WORDS: OnabotulinumtoxinA, Botox®, migraine

INTRODUCTION

Migraine is a common, primary headache disorder with debilitating consequences affecting approximately 15% of the population world-wide.[1,2] In 2016, the Global Burden of Disease Study classified migraine as the second leading cause of disability in patients less than 50 years of age.[2] Many patients are unable to carry on normal daily activities due to the symptoms associated with this neurovascular disorder which includes throbbing head pain, nausea, vomiting, photophobia, phonophobia, allodynia, fatigue, increased agitation, along with aura in many patients.[1] Episodic attacks are common, but some patients may be diagnosed with chronic migraine (CM) when attacks frequently occur and pain is relentless to the point that prophylactic drugs are needed to function in normal daily activities.[2] With a disease process affecting and interfering with so many across the globe, a definite need for preventative measures exists that allow patients to carry on their lives as normal without AE commonly seen with the most frequently used preventative medications on the market to date.

Currently, the most widely accepted theory of migraine etiology is overstimulation of trigeminal ganglion nerves and a resultant release of neuropeptides.[3] Overflow of neuropeptides ultimately leads to neurogenic inflammation and is believed to result in the neuronal overstimulation which causes the throbbing head pain associated with migraines and its associated symptoms.[3] The mechanism of action with injections of OBT-A is thought to be an inhibition of trigeminal nerve overstimulation blocking the release of neuropeptides, therefore preventing the neurogenic inflammation that would have ultimately occured.[1]

The most common, current therapies used for migraine prophylaxis are drugs used for other comorbid conditions. Use of these therapies for migraine is dependent on factors such as age, sex, current status of premorbid conditions, and is reliant on classes and medications such as beta blockers (e.g., propranolol and metoprolol), antidepressants (e.g., amitriptyline and venlafaxine), anticonvulsants (e.g., topiramate and valproate), or CGRP (calcitonin gene-related

peptide) antagonists (e.g., galcanezumab, fremanezumab, and/or erenumab).[4] Inclusion or exclusion of patient conditions, current dosages, and AE must all be taken into consideration when prescribing these for migraine. Most of these must be taken on a daily basis while injections of OBT-A can be administered every 3 months,[4] and many of the AE seen with traditional therapies have not been experienced in OBT-A injection trials to date.[1,5]

In 2017, there were an estimated 1.2 million emergency department (ED) visits as a result of migraine,[6] compounding the issue of long ED wait times seen around the globe. It has also been estimated that migraine costs are in excess of $20 million United States dollars (USD) annually.[7] An opportunity exists for healthcare providers to introduce new methods of migraine prophylaxis that not only allow patients a better quality of life (QOL) but also reduces healthcare costs and cuts back on emergency department overcrowding. OBT-A injections have shown to be effective in multiple trials at a range of three to six months.[8] This provides a possible solution to both of these issues along with far less AE, leading to better patient-oriented outcomes. This systematic review evaluates the use of OBT-A injections to reduce the frequency of attacks many migraine sufferers experience.

OBJECTIVE

The objective of this selective evidence based medicine (EBM) review is to determine whether or not "Do injections of OnabotulinumtoxinA reduce migraine attack frequency in adults?".

METHODS

This paper assesses the effectiveness of OBT-A injections ability to produce a mean change in baseline of migraine attack frequency as measured by diaries kept by patients and self-reported questionnaires in adults ages 17-75 suffering from migraine. The following studies were used in this review: 1) a randomized controlled trial; 2) a randomized, double-blind, placebo-controlled clinical trial; 3) an observational, open-label, cohort study. All three studies were used to address the proposed clinical question and focused on patient-oriented

outcomes.

Keywords, "OnabotulinumtoxinA, Botox®, and migraine" were used searching PubMed and Cochrane Library Database for articles published in English. All articles were published in peer-reviewed journals over the last 10 years, and statistics were reported using p-values or experimental event rate (EER). Inclusion criteria for article selection included: randomized controlled trial (RCT), articles published within the last 10 years, and those published in English; exclusion criteria included studies involving: only pediatrics, only acupuncture, and only Botox®.

Table 1 - Demographics and Characteristics of included studies[5,8,1]

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/ D	Intervention
Ranoux[5] (2017)	observational, open-label, cohort study	63	44.3	Considered eligible by fulfilling IHS criteria for chronic migraine	Patients not fulfilling IHS criteria for chronic migraine	6	Injection with 150U of OBT-A
Naderinabi[8] (2017)	Randomized controlled trial	162	37.2	Patients with chronic migraine previously diagnosed with ICHD-3 criteria by a neurologist, ages 20-60, with normal liver function/ coag. studies	Patients with prior use of OBT-A; prior headache medication overuse; opioid abuse; prophylactic headache medication use in prior 3 months; pregnant or lactating	12	Injection with OBT-A with a total of 155U

Hou[1] (2015)	Randomized, double-blind, placebo-controlled clinical trial	102	40.7	Patients male (21) and female (81) with both chronic and episodic HIS-defined migraine, ages 18-57, with or without aura from one to 16 years	Patients with: any medical or neurological condition which may be in contact with OBT-A; diseases that could interfere with neuromuscular function; uncontrolled systemic disease; pregnant or breast feeding	0	Injection with 2.5U at each site, total of 25U per subject

OUTCOMES MEASURED

The outcomes measured were all patient-oriented and focused on a mean change from baseline in the number of migraine attacks individuals suffered during a predetermined time interval. Quantities of OBT-A injected and time periods observed all varied between trials. Details such as injection techniques, site of injections, intensity and duration of headaches, and associated symptoms were some specifics measured but attack frequency with a mean change from baseline in number of migraine attacks per month, measured by diaries kept by patients and self-reported questionnaires collected at pre-determined times, was the subject investigated from each article for this review.

Ranoux et al. injected up to 150U of OBT-A per session during a two month span and considered patients responsive if having $\geq$ 50% reduction of headache days per month after two consecutive, efficacious injection cycles.[5] In the trial completed by Naderinabi et al., a total of 155U were injected in test subjects and compared number of headache days with a control group using a placebo during a three month interval.[8] Hou et al. injected a total of 25U per session and recorded the number of headache days per month over a four month interval and compared this

with a control group which was given a placebo.[1]

RESULTS

Ranoux et al. conducted an observational, open-label, cohort study through the Teaching Hospital of Limoges, France.[5] Sixty-three patients were considered eligible and selected based on the International Headache Society (IHS) criteria for CM.[5] Once selected, patients underwent an adaptive phase where the most appropriate injection site was determined based on the pain experienced by an individual during a CM attack.[5] Patients then underwent an observation period which began eight weeks before the first effective dose, and ended eight weeks after the second, consecutive effective or ineffective dose.[5] During both of these phases, patients kept a headache diary and recorded days which they had an attack.[5] Patients were allowed to continue use of abortive medications, e.g., triptans, as needed.[5]

Patients were injected to the corrugator, temporalis, and/or trapezius muscles with 70U of OBT-A if their pain was determined to be limited to the myofascial muscles during the adaptive phase and 150U if muscle groups of both the head and neck were involved.[5] Patients were considered to be responsive to treatments if they had ≥50% reduction of headache frequency after two consecutive injection cycles.[5] Of the 63 patients with intention to treat (ITT), 57 were able to complete the trial and 41 of those were considered responsive to treatment while 16 patients reported that they were non-responsive to treatment (EER = 65.1%).[5]

Table 2: Primary Outcome Results[5]

Initial Test Subjects	Responders	Non-Responders	Dropped Out	EER
63	**41**	**16**	**6**	**65.1%**

In 29 of the 41 responders, ≥ 70% reduction in headache day frequency was achieved and 9 patients reported having ≤1 headache day per month.[5] Among responders, 28 of the 41 were

accustomed to triptan abortive therapy and 81% reported reduced need of such drugs during the three to four month duration of action OBT-A injections provided.[5] Patient satisfaction was particularly high, reported as being an 8.6 on a 0-10 scale.[5] The only AE subjects reported was myalgia to the trapezius muscle which was described as being severe with the initial injection but subsequent doses were described as being minimally noticeable.[5] In contrast to this, the site found to be most responsive to injections was the trapezius muscle with 38 of 41 (92.7%) responders finding efficacy at this site.[5]

Table 3: Secondary Outcome Results[5]

	Responders (N=41 Total)	Percentage
≥ 70% reduction of headache day frequency	29 of 41	71%
Reporting ≤ 1 headache per month	9 of 41	22%
Reduced need of abortive therapy (Triptans)	28 of 41	81%
Patient satisfaction (0-10 scale)	Lowest 6.5, Highest 10	86%
Most effective injection site (Trapezius muscle)	38 of 41	92.7%

This study provides data to support the proposed claim that OBT-A injections prophylactically reduce the number of headache days suffered by those diagnosed with migraines because of the large number of patients claiming response to treatment. Limitations of this trial include: generalizability being limited due to the small number of patients used in the trial, a lack of control or placebo being used, individual ages of patients are not detailed, and too little information is given to calculate the treatment effect. Based on outcomes of this study, there is evidence to support the use of OBT-A injections to reduce the number of headache days per month for those diagnosed as migraine sufferers.

In the study piloted by Naderinabi et al., a randomized controlled trial (RCT) was held at the Guilan Pain Clinic, North of Iran.[8] One hundred sixty-two patients were found eligible based on the International Classification and of Headache Disorders 3rd edition (ICHD-3) and selected

based on inclusion and exclusion criteria shown in Table 1.[8] This study focused on comparing the treatment effects of patients injected with OBT-A, acupuncture techniques of traditional Chinese medicine (TCM), and a control group given sodium valproate 500mg/day for three months.[8] Fifty patients were randomly placed into each group for a total of 150, leaving 12 who dropped out due to compliance issues unrelated to AE.[8] All 150 patients completed the three month trail and were allowed to abortively treat their acute attacks with Novafen.[8] All 50 patients who were injected with OBT-A were injected by the same injector who followed protocol of the phase III Research Evaluating Migraine Prophylaxis Therapy I (PREEMPTI).[8] Each patient was given a total dose of 155U injected to the facial and peri-cranial muscle trigger zones.[8] A physician who was blinded to treatment types per group completed an evaluation of each patient in each group at one month intervals for three months. Evaluations included the number of headache days per month, abortive medication use, and AE.[8] By excluding patients who had taken traditional prophylactic medications within the past three months,[8] a higher degree of validity could possibly be attributed to statistics analyzed during this trial.

At baseline (T0), the group receiving OBT-A injections had an average of 23.6 headache days per month.[8] The changes trended in the OBT-A group from 10.8 at the end of month one (T1), 9.7 after month two (T2), and 13.1 at the end of month three (T3)[8] with the mean change from baseline at 10.5. This reveals a large treatment effect and a greater mean change from baseline than the control group which was 6.2 and trended at 19.3 (T0), 15.8 (T1), 13.4 (T2), and 13.1 (T3).[8] The p-values between groups at T0 was insignificant at ($p= 0.072$), with $p < 0.05$ being statistically significant, but were significant at T3 ($p=0.0001$) and indicates the estimate of treatment effect is precise.[8]

Table 4: Headache Days/Month and Trends in Mean Change from Baseline[8]

Test Group	T0	T1	T2	T3	Mean Change from Baseline
OBT-A	23.6	10.8	9.7	13.1	12.4

Control Group (Sodium Valproate)	19.3	15.8	13.4	13.1	5.2
Significance of Mean Change	P=0.072			P=0.0001	

The average number of times patients needed acute abortive therapy per month was also reduced among patients injected with OBT-A from an average of 17.76 (T0) to 6.32 (T3), although this patient group had the greatest increase for drug therapy at T3.[8] Nausea and vomiting was found to be insignificant ($p > 0.05$) among groups at T2 but at T3 those injected with OBT-A had a significantly higher rate ($p=0.027$).[8] Both of these facts provide evidence for the half-life and therapeutic effects of OBT-A being limited to this period of time. The most common AEs reported with OBT-A were ptosis and facial asymmetry although this study regarded treatments as safe with very low complication rates, agreeing with prior studies.[8]

Table 5: Comparison of Side Effects[8]

Test Group	T2	T3
OBT-A	$p > 0.05$	$p=0.027$
Control Group (Sodium Valproate)	$p > 0.05$	$p > 0.05$

This study provides evidence of clinical importance supporting the claim that OBT-A injections do prophylactically reduce the number of headache days per month in migraine sufferers. The statistical analysis provided indicates the estimate of treatment effect is precise and strengthens this study. Generalizability is limited while adding validity to the study due to patients suffering from medication overuse, opioid abuse, a past history of prophylactic drug use in the past three months, or a past history of OBT-A injections being excluded.

In the randomized, double-blind, placebo-controlled clinical trial carried out by Hou et al. at the Department of Neurology and Pain Treatment, Gansu Province People Hospital in China, subjects (n=102) were enrolled according to inclusion and exclusion criteria documented in Table 1 and examined to determine the effects of OBT-A injections on migraine attacks at

baseline and the following four month period.[1] It involved investigating effects among three groups: 1) 25U of OBT-A injected at fixed-site locations in the most common muscular trigger zones (n=41); 2) acupuncture that included OBT-A injections in common sites used in traditional Chinese medicine (n=42); and 3) a placebo group injected with 0.9% normal saline (n=19).[1] The trial focused on attack frequency but also included other factors such as intensity, duration, and associated symptoms.[1] Attacks were self-recorded by patients for one month prior to the first injection and four months afterward in a detailed diary reviewed monthly by investigators who had no awareness of the type of injection used per group.[1]

Hou et al. provided data to support the claim that OBT-A injections produce a large decrease in frequency of migraine attacks during a four-month interval when compared with placebo, regardless if fixed-site or acupuncture injections were used.[1] At baseline, the group injected with OBT-A at fixed-site locations suffered a mean of 7.5 migraine attacks per month, 4.0 at the end of month one, 3.8 after month two, 3.6 after month three, and 3.7 after month four.[1] This reveals a p-value of clinical significance ($p < 0.01$) compared with placebo which reported 7.5 attacks per month at baseline, 7.4 after month one, 7.1 after month two, 7.2 after month three, and 7.4 after month four.[1]

Table 6: Headache Frequency/Month and Trends in Mean Change from Baseline[1]

Test Group	Baseline	Month 1	Month 2	Month 3	Month 4	Mean change from baseline
OBT-A	7.2	4.0	3.8	3.6	3.7	3.5
Placebo	7.5	7.4	7.1	7.2	7.4	0.2
Significance of mean change						P<0.01

While three of 41 (7%) injected with OBT-A at fixed-sites experienced AEs involving self-resolving, unilateral eye ptosis lasting from three to five days, 35 of the 41 subjects (85%) with fixed-site injections recorded reductions in migraine frequency during the four month period and nine of those reported to be attack free (22%).[1] One patient complained of injection

site discomfort that dissipated in less than 24 hours.[1] This study concurs with previous studies that OBT-A injections are safe, tolerable, and effective in the prophylaxis of migraine attacks with far fewer AE when compared to other drugs more commonly used.

Table 7: Ratio of Migraine Frequency in OBT-A and AE[1]

Test Group	Ratio of Patients	Percentage of Patients
Fixed-site (OBT-A) Injections with Reduction in Frequency	35 of 41	85%
Fixed-site (OBT-A) Injections Headache Free	9 of 41	22%
AE (Eye ptosis)	3 of 41	7%

Several factors may have affected the outcome of this study including the small number of subjects investigated and the disproportionate number of females to males; such factors should be taken into consideration when referencing this study. Generalizability of the trial is limited due to excluding patients who: may be at risk with exposure to OBT-A, have a pre-existing medical condition interfering with neuromuscular function, pathological conditions which may contribute to migraine, current drug or alcohol abuse, and/or patients who were pregnant or breastfeeding.[1] Taking these factors into consideration, this trial does relate to and provide evidence answering the clinical question that OBT-A injections do reduce migraine attack frequency in adults.

DISCUSSION

Although rare, the most common AEs with OBT-A injections for CM include neck pain (9%) at injection sites and headache (5%).[4] The only contraindication to OBT-A injection is current infection at injection site and hypersensitivity to previous administration; a black-box warning does exist in the United States for botulinum toxin effects which could spread from the

site of injection to distant locations.[4] Total dosage recommended is up to 155U administered every 12 weeks.[4]

To date, the most common prophylactic drugs used for migraine attacks include prescription drugs such as beta blockers, antidepressants, and anticonvulsants, each having many more AE than studies have found OBT-A injections result in, and pre-existing comorbidities requiring use of such drugs must be factored in when prescribing these medications.[1,7,9] Compounding this issue is the fact that many migraine sufferers struggle with many of the AEs produced by the current preventative therapies prior to beginning treatments.[6] The AE produced by OBT-A injections in all three studies were temporary and self-resolved, aligning with previous research.[1,5,8]

The studies reviewed in this article provide evidence supporting the use of OBT-A injections to prophylactically reduce the frequency of migraine while promoting effective patient-oriented outcomes with far less AE seen with currently approved medications. Whether episodic or chronic in nature, migraine headaches place a burden on and alter daily activities in millions of sufferers world-wide annually.[6] These facts provide healthcare providers and researchers the opportunity to investigate and intervene with more effective treatments such as OBT-A injections.

CONCLUSION

The three articles reviewed provide sufficient data supporting the use of OBT-A injections to provide prophylaxis in both episodic and CM attacks in adults. The use of a placebo and a control group in the studies by Hou et al.[1] and Naderinabi et al.,[8] respectively, provide clinical and statistical evidence that there is significant reduction in frequency of migraine headaches per month. While the research conducted by Ranoux et al.[5] does not use a placebo or control group, their use of responders versus non-responders to treatment may in fact yield a more accurate figure due to the exclusion of the possibility of a placebo effect.

With regards to improvement among the trials, all three would benefit from having

larger numbers of subjects studied over longer time periods of time. A more recent study by Santoro et al.[10] makes use of smartphone technology which may improve outcomes with both of these factors. By selecting a larger subject field and including a greater variety of race and ethnicity, more concrete evidence would be obtained in regards to OBT-A's half-life, therapeutic effects, and AE.

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