Pediatric Neurology 147 (2023) 68–71

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Research Paper

Botulinum Toxin for Pediatric Migraine: A Retrospective Multisite Cohort Study

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ARTICLE INFO

Article history:
Received 27 October 2022
Accepted 7 July 2023
Available online 13 July 2023

Keywords:
Onabotulinum toxin A
Migraine
Pediatric
Incobotulinum toxin A
Botulinum toxin

ABSTRACT

Background: Onabotulinum toxin A is effective in adult chronic migraine, but the efficacy is not well established in adolescent patients. The objective of this study is to describe the safety and efficacy of onabotulinum toxin A and incobotulinum toxin A for adolescent chronic migraine headache.
Methods: We performed a chart review of adolescents who received onabotulinum toxin A or incobotulinum toxin A for headache prevention. Demographic information and baseline headache characteristics were collected. The primary end point was a 50% reduction in headache frequency. Secondary outcome measures included reduction in headache frequency, repeat appointments for injections, reduction in other migraine medications, and adverse events.
Results: We included 51 adolescents who received at least one injection of either incobotulinum toxin A or onabotulinum toxin A for chronic migraine. Mean age at first dose was 16.0 (1.1; 13 to 17), (S.D. and range). Patients averaged 24.0 headache days per month (7.6; 4 to 28), (S.D. and range) before injection. In addition, 36 of the 51 adolescents (71%) were experiencing continuous headaches. Thirty-five (69%) adolescents had experienced 50% reduction in headache days by the time of first follow-up, which occurred on average at 16.6 weeks from initial injection (11.5; 2 to 55.7) (S.D. and range). Adolescents reported an average decrease of 13.1 headaches days per month. Only two adolescents reported side effects (4%), which were neck soreness and headache following injection.
Conclusions: Botulinum toxin had better efficacy in our adolescent migraine population than has been demonstrated in other studies.

Introduction/background

Pediatric migraine is a common and debilitating condition. Despite its importance, there is a lack of clear evidence favoring a particular treatment for prophylaxis. Topiramate demonstrated successful migraine prevention in a double-blind placebo trial and in 2014 became the only US Food and Drug Administration-approved preventive treatment for adolescent migraine.[1] Amitriptyline and propranolol were both found to be superior to placebo in a double-blind study in 2012 when combined with non-pharmacologic therapy.[2] Despite extensive clinical use and prior studies supporting their use, there is conflicting evidence for amitriptyline and topiramate use in adolescent migraines. In 2017,

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Author contributions: D.E.H. and P.G.E. conceived and designed the study and collected the data. J.M.S. and W.W.C.Y. contributed data and analysis tools. D.E.H. and P.G.E. performed the analysis. D.E.H. and P.G.E. wrote the paper. J.M.S. and W.W.C.Y. edited the paper before submission.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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https://doi.org/10.1016/j.pediatrneurol.2023.07.005
0887-8994/

the Childhood and Adolescent Migraine Prevention (CHAMP) trial showed no significant differences in reduction in headache frequency or disability between amitriptyline, topiramate, and placebo.[3] The CHAMP trial emphasized that there was not a consensus best prophylactic medication for adolescent migraine.

Owing to a paucity of data assessing botulinum toxin use in pediatric patients, most of the supporting data are extrapolated from the adult population. In adult patients, onabotulinum toxin A (OBA) improves chronic migraine headaches but not other headache types. Early studies investigating the use of OBA in adult migraine were successful but did not follow a consistent injection pattern.[4] Subsequently, the injection techniques that demonstrated the most consistent efficacy in migraine are based on the technique elucidated by Blumenfeld and further established by the Phase III Research Evaluating Migraine Prophylaxis Therapy (PREEMPT) trials.[4]

The PREEMPT I trial was a phase 3, placebo-controlled study assessing the efficacy of OBA in migraine headache. Patients were given 155 U OBA in a standardized 31-injection site pattern with an elective 40 U applied in a "follow-the-pain" approach at physician discretion. There was no difference between OBA and placebo for the primary outcome measure, reduction in the number of headaches. However, OBA had statistically significant reduction in the number of headache and migraine days, cumulative hours of headache on headache days, and frequency of moderate/severe headache days.[5] The PREEMPT II trial was performed similarly to the PREEMPT I trial except that the primary outcome measure was changed to number of headache days per 28-day period. OBA demonstrated a statistically significant reduction in headache days, and all secondary end points favored the OBA group.[6] Pooled results from PREEMPT I and II confirmed the superiority of OBA over placebo with all outcome measures.[7]

The authors were unable to find any studies reviewing incobotulinum toxin A (IBA) use in either pediatric or adult migraines. Although OBA and IBA have slightly different protein structures, they both contain the same neurotoxin component. Providers in the Department of Defense have used IBA in addition to OBA due to decreased administrative and handling requirements. IBA neither requires refrigeration nor requires gentle handling during reconstitution. Since we use IBA within our treatment facilities, it was included in the study.

There are few studies assessing botulinum toxin as a treatment in pediatric migraines. One small prospective, randomized, double-blind study of OBA in pediatric patients found a statistically significant difference in migraine days per month.[8] The largest pediatric retrospective study to date is an analysis of 45 patients who had failed two prior migraine prophylactic agents and demonstrated a statistically significant reduction in headache frequency without statistically significant change in headache severity or a reduction in Pediatric Migraine Disability Assessment score, a scoring system designed to assess migraine disability in children.[9] Another retrospective study by Ahmed et al.[10] assessed 10 pediatric patients with medication-refractory migraine headaches and demonstrated meaningful migraine relief in four of them with minimal adverse effects. A third study assessed 12 adolescent patients aged 14 to 18 years and demonstrated effectiveness in six long-term patients who received multiple series of injections. Adverse effects included ptosis, hematoma with transient paresthesia in an arm, blurred vision, and burning sensation at all injection sites.[11]

With limited data on preventive treatments for pediatric migraine, this study further examines and augments the current body of evidence supporting the role for botulinum toxin in pediatric migraine treatment.[12]

TABLE 1.
Demographic and Baseline Data for 51 Patients Treated With at Least One Dose of OBA or IBA

Age at first dose, mean (S.D.); range	16.0 (1.1); 13-17
Female sex; number (%)	44 (86%)
Headache frequency per month; average; median (S.D.); range	24.0; 28 (7.6); 4-28
Patient with continuous headache; n (%)	36 (71%)
Number of preventive medications tried; average (S.D.); median; range	2.16 (2.34); 1.00; 0-14

Methods

This is a retrospective multisite cohort study of patients aged 13 to 17 years who were treated in the military health care system with OBA or IBA as preventive treatment for chronic migraine headaches.

Permissions

This study was exempt from review by the Institutional Review Boards at Walter Reed National Military Medical Center and Tripler Army Medical Center. Both institutions approved sharing of data.

Inclusion criteria

Patients were included if they met the following criteria: (1) received OBA or IBA for chronic migraine diagnosed by a pediatric neurologist between January 1, 2008, and December 31, 2020; (2) aged seven to 17 years when receiving treatments; and (3) at least one clinical follow-up appointment with pediatric neurology after OBA or IBA injections. Exclusion criteria included patients subsequently diagnosed with a secondary headache disorder.

Data collection

We obtained patient names and medical record numbers by searching for pediatric encounters with a headache or migraine diagnosis and OBA or IBA injection or chemodenervation procedure codes. From this list, encounters were reviewed and analyzed for inclusion and exclusion criteria. Patient charts that qualified were deidentified and then reviewed for relevant clinical data including patient demographics, headache frequency, headache severity, type of botulinum toxin administered, number of units given, injection pattern, current and previous preventive medications, missed school days, emergency room evaluations, and any adverse effects. We assessed follow-up appointments and repeat injections in the pediatric neurology clinic for subsequent number of units given, subsequent selected injection pattern, changes to preventive medications, change in headache frequency, change in headache severity, follow-up emergency department evaluations, missed school days, and whether the patient elected to continue with OBA or IBA injections.

Outcome measures

The primary end point was a 50% reduction in headache frequency. Secondary outcome measures included an absolute reduction in headache frequency, repeat appointments for botulinum toxin injections, reduction in other headache prophylactic agents, and adverse events limiting subsequent injections.

Results were stratified based on injection patterns in one of three broad classifications. Patients received an injection pattern based on the location of the headache ("follow the pain"), the full

TABLE 2.
Efficacy and Outcomes

Time to first follow-up in weeks; average (S.D.); range			16.6 weeks (11.5); 2-55.7
50% Reduction; n (%) (95% confidence interval)			35 (69%) (54%-81%)
Patients presenting for repeat injections; n (%)			39 (76%)
Type of Toxin		OBA	IBA
N (%)		32 (62.7%)	19 (37.3%)
50% Reduction; n (%) (95% confidence interval)		22 (69%) (51%-82%)	13 (68%) (45-84%)
Injection Pattern			
	"Follow the Pain"	Modified PREEMPT	Full PREEMPT
N (%)	16 (31%)	27 (53%)	8 (16%)
50% Reduction; n (%) (95% confidence interval)	11 (69%) (44%-85%)	16 (59%) (39%-78%)	8 (100%) (74%-100%)
Headache frequency per month pretreatment; average; median (S.D.); range			24.0; 28 (7.6); 4-28
Headache frequency per month post-treatment; average; median (S.D); range			9.1; 4 (11.3); 0-28
Change in headache frequency (days per month); mean (S.D,); median, *P* value			−13.1 (12.2); −13, <0.000001
Participants reporting resolution of daily headache after treatment; n (%)			28/36 (78%)
Patients on additional preventive medications at time of OBA/IBA; n (%)			32 (63%)
Patients requiring additional preventive medication at follow-up; n (%)			17 (33%)

Abbreviations:
IBA = Incobotulinum toxin A
OBA = Onabotulinum toxin A
PREEMPT = Phase III Research Evaluating Migraine Prophylaxis Therapy

injection pattern with 155 U as utilized in the PREEMPT trial, or a 100-U version of the PREEMPT pattern without injection into the cervicalis or trapezius.

Side effect data

Any side effect documented in charts was recorded and reported as a secondary outcome measure.

Statistical analysis and plan

Descriptive statistics for continuous variables include mean, S.D., and median. Proportions are reported for categorical variables. Student *t* tests were used to compare changes in absolute values of continuous variables.

Results

This retrospective cohort study included 51 patients. Patients' ages ranged from 13 to 17 years, and all patients received at least one injection of OBA or IBA for migraine headache. Baseline data are shown in Table 1. The patient population had chronic migraines with an average of 24.0 headache days per month. Thirty-six of 51 (71%) had continuous headaches. Our patient population had trialed an average of 2.16 preventive medications before OBA or IBA injections with a range of 0 to 14 medications.

Post-treatment outcomes at first follow-up are demonstrated in Table 2. IBA was utilized in 37.3% and OBA was utilized in 62.7% of the patients. Our data show that 69% of patients who received IBA and 68% of patients who received OBA obtained a 50% reduction in headache frequency. Thirty-nine patients (67%) returned for repeat injections. A dose-response curve is shown in Fig.

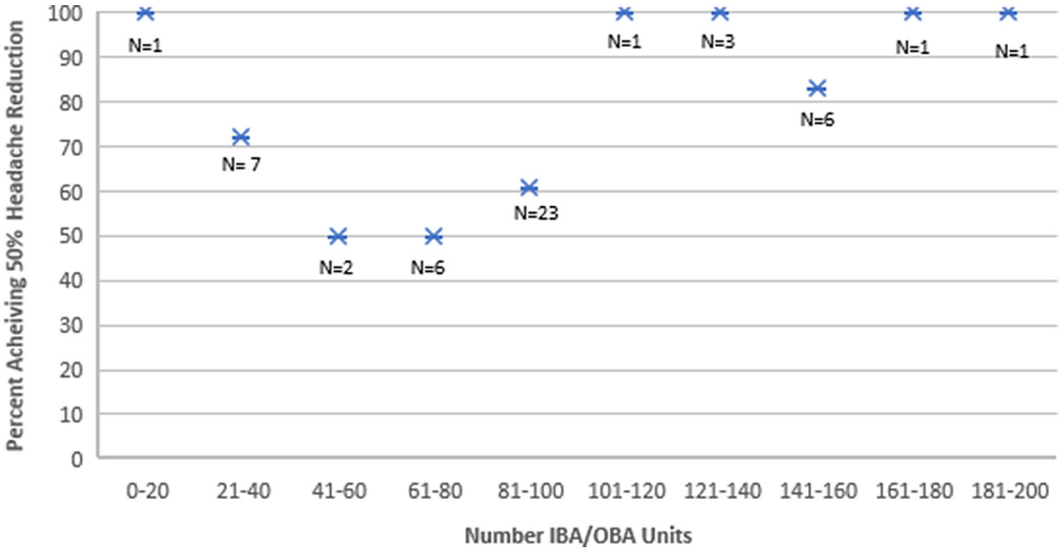

FIGURE. Dose-response curve for patients achieving 50% reduction in monthly headache days by number of units injected. The color version of this figure is available in the online edition.

TABLE 3.
Adverse Effects

Adverse Outcome	Number Reporting n (%)
Any side effect	2 (4)
Neck soreness	1 (2)
Headache following injection	1 (2)

The modified PREEMPT pattern was the most common injection pattern (27 patients, 53%). Sixteen patients (31%) received the "follow-the-pain" regimen, and eight patients (16%) received the full PREEMPT pattern. Sixteen patients (59%) injected with the modified PREEMPT pattern achieved a 50% reduction in headache frequency. The "follow-the-pain" protocol achieved 50% headache reduction in 11 patients (69%). The full PREEMPT pattern had 100% of patients meet the 50% reduction.

There was an average decrease of 13.1 headache days per month ($P < 0.000001$). These benefits were maintained when specifically examining patients with daily headaches. Of the 36 patients who had continuous headaches at the time of injection, 28 (78%) had complete resolution of their headaches at their first follow-up encounter.

Thirty-two patients (63%) were on additional prophylactic therapies at the time of injection. At the first follow-up, 17 patients remained on additional preventive medications.

Only two patients in the cohort had mild adverse effects (Table 3). One patient had postinjection neck soreness. This patient received the full PREEMPT pattern with cervical paraspinal injections. This same patient had complete resolution of headaches and continued to get injections despite this complaint. Another patient reported a headache following the injections and no improvement in headache days.

Discussion

Our retrospective multicenter cohort study is the largest retrospective study of botulinum toxin for adolescent migraines and supports its effectiveness and tolerability. The data suggest that more severe patient populations will have a more robust response to therapy, as 69% of patients with chronic migraine and 72% of patients with daily headache met the primary end point. This rate exceeded the response rates in the CHAMP trial (52% to 61%) and compared similarly to a study by Aurora et al.[13] that assessed adult patients who completed all five treatment cycles of OBA.

The patients who received OBA or IBA in our group had severe headaches based on the number of previously trialed preventive medications and number of headache days per month. This finding suggests that patients more severely disabled by headache who failed prior treatments can be successfully managed with OBA or IBA.

Our cohort included patients suffering from medication overuse headache in addition to migraines. It is common for patients with severe and medication-refractory migraine headaches to have some component of medication overuse headache. Our inclusion criteria were designed to limit nonmigraine headaches, and our methodology was unable to exclude medication overuse headaches. This study indicates that botulinum toxin therapy may have a role in the management of patients with more severe migraine headaches regardless of medication overuse.

This study supports the general safety and tolerability of OBA and IBA. Compared with other migraine therapies including calcitonin gene-related peptide antagonists, OBA and IBA appear to have a better side effect profile.[14]

This study suggests that botulinum toxin can reduce migraine frequency and severity in adolescents with severe headaches and failure of multiple prophylactic medications. Although the results are retrospective, this study provides justification for a large-scale prospective study. Botulinum toxin is a safe and viable alternative to conventional second-line prophylactic agents in adolescents with chronic migraine headache.

Declaration of competing interest

The authors declare no potential conflicts of interest with respect to the authorship and/or publication of this article.

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