Onabotulinumtoxin Type A reconstitution with preserved versus preservative-free saline in chronic migraine (B-RECON). A randomized, double-blind trial.

I. BACKGROUND AND SIGNIFICANCE

Chronic migraine (CM) is a complex, progressive headache disorder affecting approximately 1.3-2.4% of the general adult population. Onabotulinumtoxin type A (BoNTA) is considered an effective, FDA-approved, prophylactic treatment. Injections are administered at 31 sites of the head and neck, and treatment is repeated every 3 months. [2]

BoNTA is manufactured as powder that requires reconstitution with normal saline prior to injection. The manufacturer of botulinum A exotoxin (Allergan Inc) has historically encouraged reconstitution with unpreserved saline. [3] However, the use of preserved saline (i.e. bacteriostatic) is common among practitioners to lengthen the shelf life of BoNTA (Botox ®) after reconstitution.

A growing body of literature on the cosmetic use of BoNTA has suggested that preserved saline exerts a local anesthetic effect, and reduces the procedure discomfort when used in reconstitution in lieu of preservative-free saline. [3,4,5,6] However, this has never been studied in chronic migraine, and while reducing discomfort is a desirable target in all procedures, it has a special importance for the use of BoNTA in chronic migraineurs due to the numerous injection locations each session (31 sites) and the ubiquity of scalp tenderness in this population. [7] In addition, the pain during procedure is a known migraine trigger for many of these patients. In fact, one study showed that up to 5% report migraine attacks lasting more than 5 days as a side effect of BoNTA injection. [8]

II. STUDY OBJECTIVES

We hypothesize that bacteriostatic saline (a.k.a preserved saline) produces lower procedure-related discomfort when used as a

dissolving solution for BoNTA injections in individuals with chronic migraine as opposed to using preservative-free saline.
In addition, we hypothesize that reduction of procedure-relate pain during BoNTA injection will also result in reduced migraine/headache attacks in the week immediately following the procedure.

III. METHODS

A. Study Design

The study is a prospective, randomized, double-blind trial.
Subjects will be enrolled consecutively at UHCC headache clinic from the practice of the two lead authors; AZ and LM who will be performing the injections.
Two of the investigators, SH or AF, will perform the randomization through simulated, web-generated, coin toss.

B. Study Materials

Our preservative-free saline is a 0.9% sodium chloride injection. Each milliliter contained 9 mg of sodium chloride. The solution is supplied in 25-mL, single-dose vials.
Our preservative-containing saline is a bacteriostatic 0.9% sodium chloride injection. Each milliliter contained 9 mg of sodium chloride and 9 mg of benzyl alcohol added as a bacteriostatic preservative. The solution is also supplied in 25-mL, single-dose vials.
Both preserved saline and preservative-free saline are identical-appearing, colorless solutions.
BoNTA (Botox ® Allergan Inc) is a powder vial containing 200 u. Powder is reconstituted with 4 ml of normal saline and then drawn in four 1 ml syringes. All four syringes are used in a single patient in one session.

C. Study Population

- Patients with diagnosis of chronic migraine receiving FDA-approved treatment with BoNTA injection as per standard protocol used in PREEMPT study [2]. Standard protocol consists of 31 injection sites, with total dose ranging from 155 u to 195u.
- Exclusion criteria:

  1. Age < 18, or > 79
  2. Subjects whom BoNTA injections deviate from standard protocol for any reason, such as head/neck infection, head deformity, recent surgery…etc.
- Study population will be randomized into two groups; preserved saline and preservative-free saline

D. Study Procedures

UHCC headache clinic performs 20-25 BoNTA injections a week on average. Enrollment plan is as following: on weekly basis, one of the investigators, either SH or AF, will contact all patients scheduled for BoNTA injections and explain the study's objectives and details. If the subject agrees to enroll, he/she will be assigned a study serial number and will be randomized to one of the two groups. Randomization will be done through a simulated "coin flipper" website; www.random.org. Heads will be assigned to the preserved saline group, and tails will be assigned to the preservative-free saline group. SH and AF will keep the assignment sheet in a password-protected excel file that only they have access to.

On the day of the procedure, informed consent will be confirmed and singed. Then, each subject will receive 10-15 minute session on the appropriate use of headache diary.

Same randomizing investigator will reconstitute BoNTA vial (Allergan Inc) using one of the two identical solutions, and then hand it to the principal investigators; AZ or LM, who will be

performing the procedure using 30G 1/2’ needles. AZ ,LM, and the subject will all be blinded to which solution is used for reconstitution.
Following the injections, subjects will be asked to rate procedure-related pain using verbal pain rating scale (0 to 10). They will asked to maintain a 7-day headache diary (see supplementary). Prepaid mail envelopes will be provided to ensure the return of the diaries following their completion.

IV. DATA COLLECTION

Collected data will include age, gender, race, ethnicity, verbal pain rating scale, headache/migraine frequency and use of headache symptomatic medications.

V. DATA ANALYSIS

Sample size determination was calculated based on a minimally significant mean difference in verbal pain score of 1.5. To detect this difference with 90% power, alpha = .05; a total of 70 subjects (35 per group) will be required (SD=1.9). T-tests will be used to compare outcome of both groups. Statistical analysis will be carried by GB.

VI. ETHICAL CONSIDERATIONS

A. Informed Consent
Informed consent will be obtained by investigators SH or AF at the time of the visit. Refusal of participation will not affect the treatment plan, and the subject will continue to receive BoNTA injections as scheduled, using the standard preservative-free saline.

B. Risks and Side Effects
Both solutions of normal saline are widely used in practice, and there are no known risks or side effects from using either.

Alerting subjects to the painful nature of the procedure and asking them to report that pain may exaggerate the resulting discomfort. Yet, we do not anticipate the discomfort to be sufficient to produce a significant clinical distress. The study carries inherent inconvenience related to filling headache diaries.

C. Benefits to Subjects
None

D. Costs to Subjects
None

E. Compensation to Subject
None

F. Provisions for vulnerable subjects
BoNTA injections is contraindicated in children <18 year-old, and in pregnancy. UHCC headache clinic does not participate in prisoners care. Thus, the study will not include vulnerable subjects.

G. Subject Privacy and Data Confidentiality
Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA).
A regulatory binder will be maintained for this study. This will include items such as this protocol, the letter of approval from the IRB, the consents, and all other information pertinent to this study. The investigators will permit study-related monitoring, audits, and inspections by the SUNY Upstate IRB, the sponsor and government regulatory bodies of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.).

VII. REFERENCES

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VIII. APPENDICES