

Botulinum Toxin Type A (BOTOX®) Therapy for Intractable Headache

Poster: #123

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ABSTRACT

Objective: In an open-label trial 187 refractory headache (HA) patients were treated with botulinum toxin type A (BTX-A: BOTOX®; Allergan, Inc.). The vast majority of these patients had previously failed 3 or more pharmacologic therapies.

Methods: Data for initial analyses were available for 134 patients (101 females, 33 males) who received 1 to 4 treatment cycles. Five patients were excluded for missing data and the remaining 48 patients had not yet had their first visit. Patients were divided into 5 categories by IHS criteria: chronic daily HA (CDH), n=97; migraine with aura, n=9; migraine without aura, n=24; episodic tension-type HA (ETTH), n=2; and unknown (n=2). CDH was defined as occurring >15 days/month. Patients were treated with intramuscular injections of BTX-A variously in the forehead, temples, neck, and shoulders. Doses of BTX-A ranged from 30 to 200 U for CDH (mean 102 U) and 15 to 240 U for migraine (mean 117 U). Patients were asked to return 2 months after treatment and evaluate the treatment effect on their HA via a 5-point categorical scale where 1=no improvement; 2=mild improvement; 3=moderate improvement; 4=good improvement; and 5=excellent improvement.

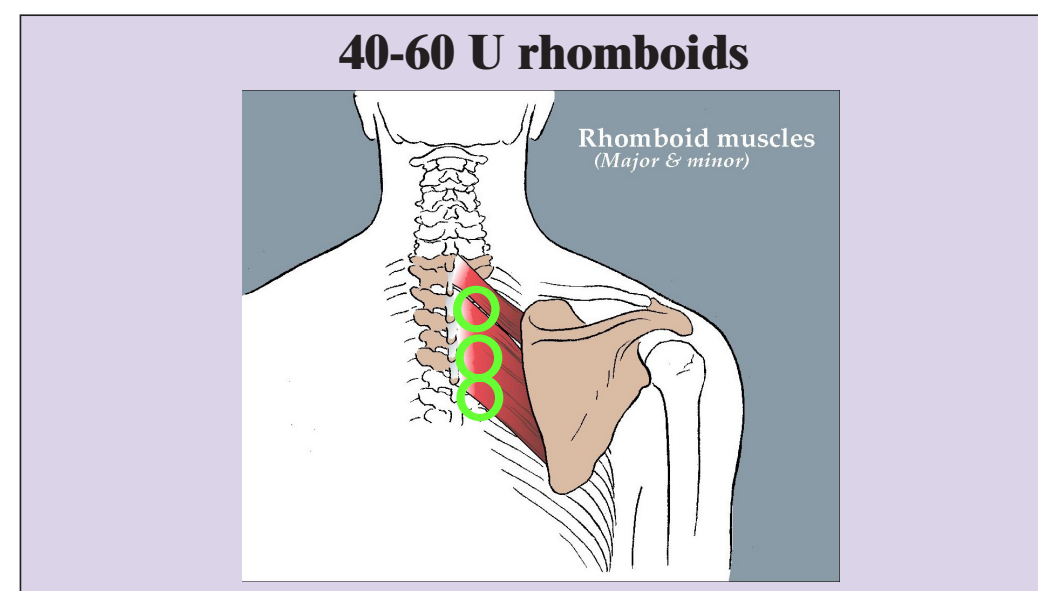
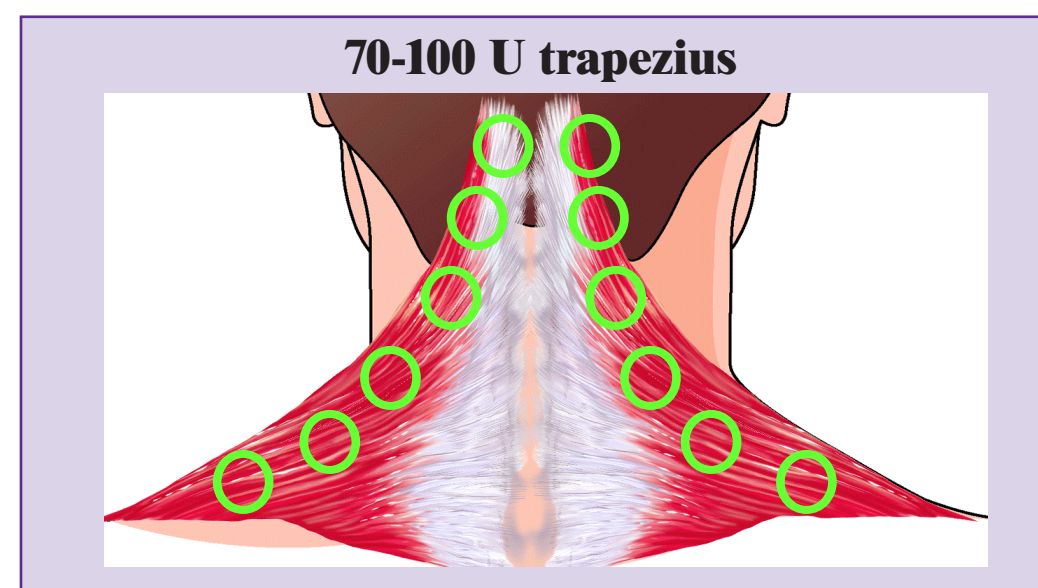
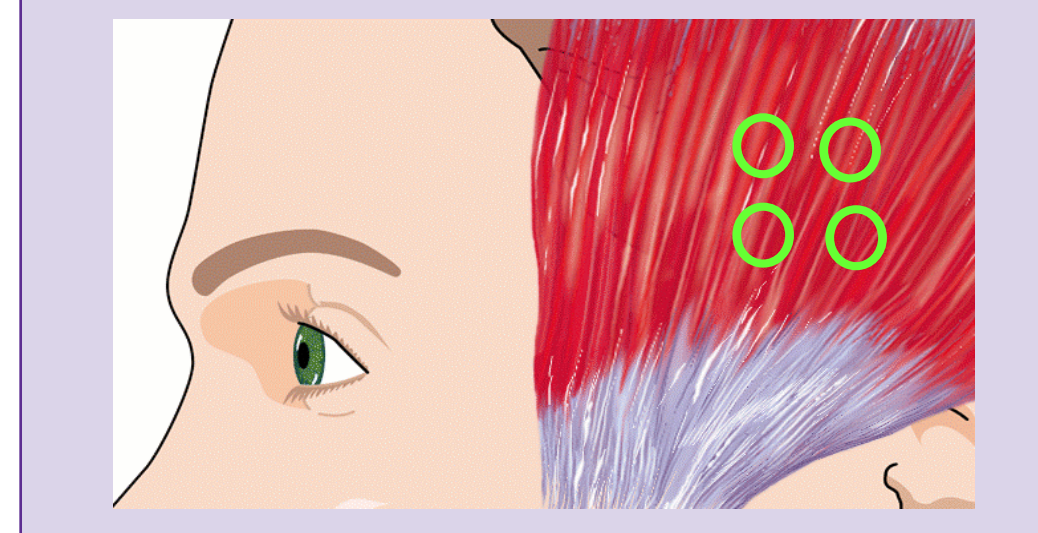
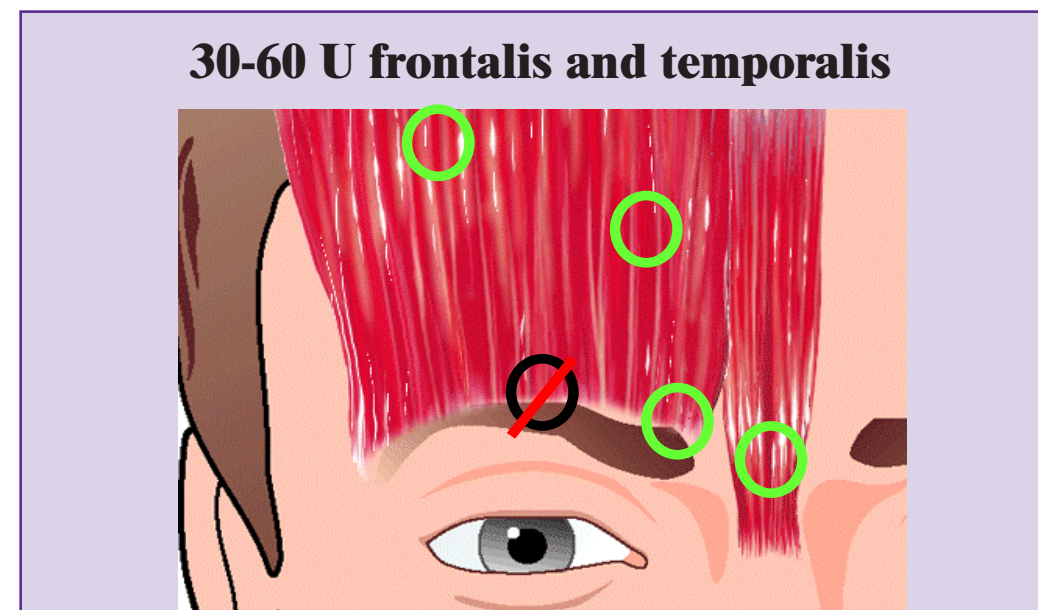
Results: Mean scores by treatment cycle were 3.3, 3.8, 4.1, and 4.3 for the first to fourth treatments, respectively. Across all treatments, improvement was reported by 84% of patients, and 16% reported no improvement. Improvement rates rose with multiple treatments. Clinical improvement was seen in 77%, 94%, 90%, and 92% of patients for treatments 1 to 4, respectively. Treatment effect was evaluated as excellent in cycles 1 to 4 by 33%, 42%, 61%, and 67% of patients, respectively; as good improvement by 16%, 22%, 10%, and 8%, respectively; as moderate improvement by 17%, 10%, 13%, and 17%, respectively; as mild improvement by 11%, 19%, 6%, and 0%, respectively; and no improvement by 23%, 6%, 10%, and 8%, respectively. No gender differences were seen. Median dose per treatment was 100 U BTX-A with exceptions of the third cycle for migraine (median 145 U) and the fourth cycle for CDH (median 140 U). Safety was assessed by spontaneous reports of adverse events by the injecting physician. No adverse events were reported across BTX-A doses and treatment cycles.

Discussion: In the group of 134 refractory HA patients treated with BTX-A for which data were available, there were significant improvements observed that appear to be progressive and may also be cumulative. This high response rate may be due to the fact that each injection was individually tailored to the specific patient, dependent on factors such as pain, location, muscle spasm, and patient weight. These data are based on a preliminary analysis, with additional results anticipated from further interpretation of the data.

- 100 U BTX-A was diluted in 2 cc of 0.9% saline solution.
- Injection sites used in this study are shown in Figure 1.
- Patients returned 2 months after initial treatment for evaluation of HA treatment effect and subsequent BTX-A treatment. Up to 4 treatment cycles were administered according to patient need.

Fixed-Site Approach	"Follow the Pain" Approach	Combined Approach
Injection sites predetermined	Injections given where pain/tenderness reported	Inject in fixed + follow-the-pain sites

Figure 1. Injection sites used in study.



Outcome Measures

- The primary outcome measure was evaluation of BTX-A treatment effect:
 - Patients self-evaluated BTX-A treatment effect using a 5-point categorical scale developed for the purpose of this study (Table 2)

1=no improvement
2=mild improvement
3=moderate improvement
4=good improvement
5=excellent improvement

- Safety was assessed by spontaneous reports of adverse events (AEs) by patient

RESULTS

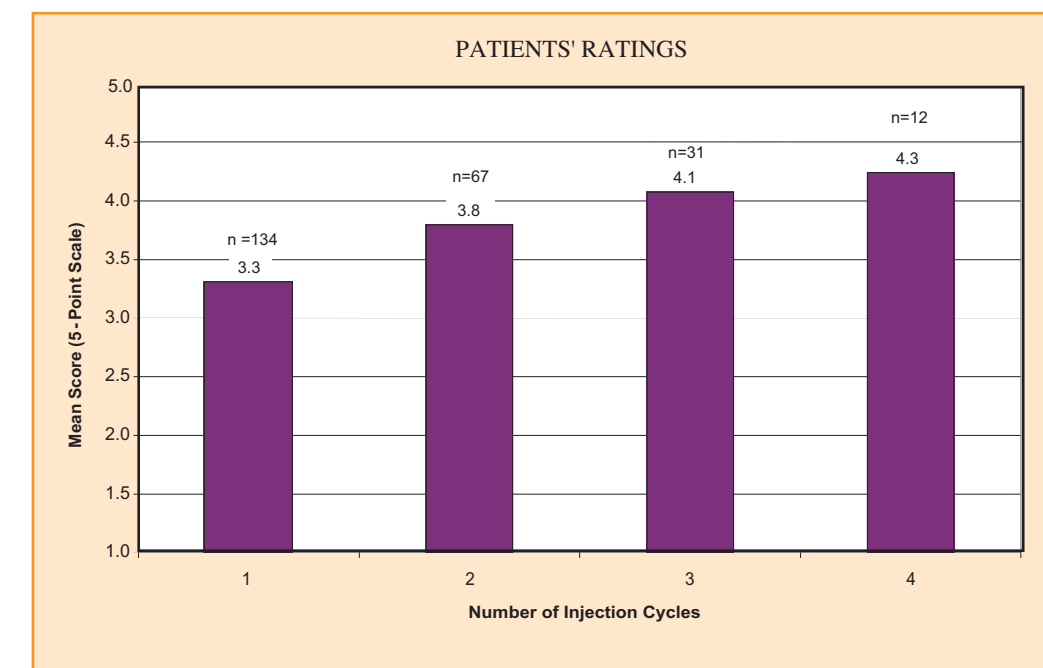
Study Population

- Data for initial analysis were available for 134 patients (101 females and 33 males)
 - 97 patients - CDH
 - 9 patients - migraine with aura
 - 24 patients - migraine without aura
 - 2 patients - ETTH
 - 2 patients - unknown cause
- The majority of these patients had failed 3 or more pharmacologic treatments, including:
 - Over-the-counter analgesics
 - Prescription analgesics
 - Triptans
 - Migraine preventive therapy
- Excessive use of analgesics was observed in the majority of patients.

Efficacy

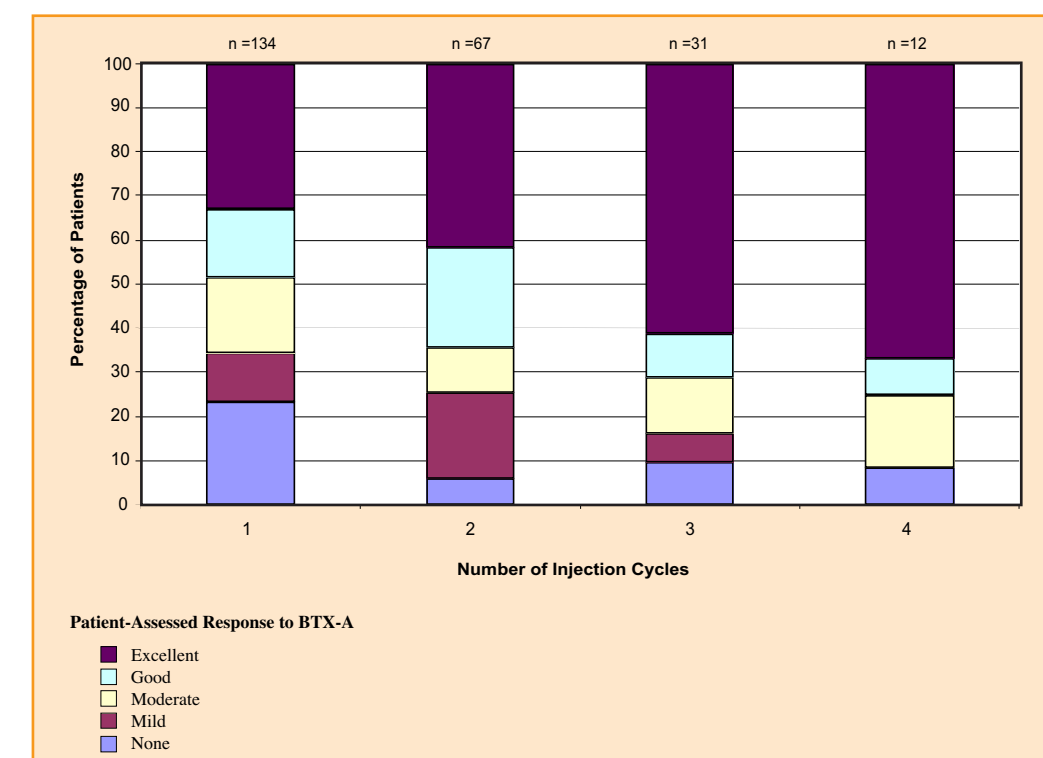
- Mean scores (5-point categorical scale) by cycle were 3.3, 3.8, 4.1, and 4.3 for the first to fourth treatment, respectively (Figure 2).

Figure 2. Mean patient scores per injection cycle.



- Improvement rates increased with multiple cycles (Figure 3).

Figure 3. Improvement rates per injection cycle.



- After the first injection cycle, 49% (65/134) reported good or excellent improvement.
- Of the patients returning for the second treatment cycle, 64% (43/67) reported good or excellent improvement.
- After treatment cycles 3 and 4, 71% (22/31) and 75% (9/12) reported good or excellent improvement, respectively.
- Clinical improvement (including excellent, good, moderate, and mild improvement) was reported by 77%, 94%, 90%, and 92% of patients after treatment cycles 1, 2, 3 and 4, respectively.

BTX-A Dose

- BTX-A doses ranged from 30 to 200 U (mean 120 U) and 15 to 240 U (mean 117 U) for CDH and migraine, respectively.
- The median dose per treatment was 100 U BTX-A, with the exception of the third cycle for migraine (145 U) and the fourth cycle for CDH (140 U).

Safety/Tolerability

- No adverse events were reported across BTX-A doses and treatment cycles.

CONCLUSION

- Refractory HA patients who failed conventional HA therapy showed good improvement of their HA following BTX-A treatment.
- Of those patients who returned for follow-up injections, a greater proportion showed excellent or good improvement.
- BTX-A showed sustained efficacy over a period of >8 months.
- These results suggest that repeated BTX-A treatment and/or potential increases in dose are associated with a progressive reduction in HA-related pain.
- The observed improvements are possibly due to injection regimens tailored to patient need.
- Further studies to support these findings will be needed.
- Since this abstract has been submitted, a total of 350 refractory HA patients has been treated with BTX-A (corresponding to approximately 1000 injection cycles) and similar results have been observed. These results will be presented at a later date.
- The results of this study are based on the BOTOX® formulation (Allergan, Inc.) of BTX-A and cannot be generalized to other formulations of BTX-A or to other BTX serotypes.

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Disclosure

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INTRODUCTION

- Substantial numbers of the population suffer from debilitating headaches (HA); migraine, for example, affects about 17% of women and 6% of men in the US,¹ and chronic daily headaches (CDH), where HA occurs >15 days/month, affect 4% to 5% of the population.²
- Some HA patients are refractory to acute medication, which can lead to analgesic overuse. Overuse of systemic HA medication, for example, has been observed in up to 80% of CDH patients.³ Refractory HA patients should be considered for prophylactic therapy.
- There is emerging evidence that botulinum toxin type A (BTX-A: BOTOX®, Allergan, Inc.) is a safe and effective prophylactic treatment for CDH, migraine, and tension-type HA.^{4,7}
- The aim of this study was to investigate the safety and efficacy of BTX-A injections in a largely CDH population.
- This study allowed some tailoring of injection protocols according to patient need.

SUBJECTS AND METHODS

Subjects

- This study enrolled patients with refractory HA.
- Where appropriate, patients were divided into 5 "proposed" IHS criteria:
 - CDH (>15 HA days/month)
 - Migraine with aura
 - Migraine without aura
 - Episodic tension-type HA (ETTH)
 - Unknown cause

- Subjects were treated at the Wake Forest University School of Medicine.

Study Design

- This was a prospective, open-label study.
- Patients received 1 to 4 BTX-A treatment cycles.
- Initial injections were given following a fixed-site protocol:
 - Frontalis and temporalis: 30 to 60 U
 - Posterior: (trapezius) 70 to 100 U
- Before receiving the next BTX-A treatment, patients were re-examined and subsequent injections were given following a fixed-site or "follow the pain" or combined approach, according to patient need (Table 1). Additional injection sites included the upper back:
 - Rhomboids: 40 to 60 U