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Retrospective Review Investigating the Efficacy of the Gray/Campbell Migraine Injection Protocol for OnabotulinumtoxinA (A Modified PREEMPT Injection Paradigm for Chronic Migraine Treatment)

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Abstract

Chronic migraine is a potentially debilitating condition that can be detrimental to someone's quality of life. Clinical data has proven OnabotulinumtoxinA (BoNT-A) to be an effective prophylactic treatment for chronic headache types, and it is now regularly employed by headache treatment centers. The PREEMPT injection protocol has become the standard treatment regimen surrounding Botox injections for chronic migraine treatment since it was granted approval by the FDA in 2010. This retrospective chart review of patients treated for chronic migraine at Maine Comprehensive Pain Management in Scarborough, Maine, presents an alteration to the standard PREEMPT injection paradigm that reinforces the efficacy of Botox for chronic migraine treatment. We will discuss our Modified PREEMPT injection paradigm, which yields a positive clinical response rate of 95% of patients achieving at least 50% improvement in their migraine headaches. This appears to be the highest established response rate in the literature to date.

Keywords

OnabotulinumtoxinA, Botox Injection

1. Introduction

Migraine is a highly disabling primary headache disorder that affects 6% - 10% of the adult male population and 17% - 25% of the adult female population [1]. Migraine is characterized by both painful symptoms, including attacks of intense throbbing headache that are often accompanied by nausea, vomiting, and sensitivity to light and sound, and other sensory symptoms, such as tiredness, numbness, and allodynia (experiencing pain from a stimulus that normally would not induce pain) [2]. The symptoms of chronic migraine cause a level of functional and emotional impact in people with migraine that ranks the disease second among worldwide causes of disability [3]. The most important modifiable risk factors for chronic migraine include overuse of acute migraine medication, ineffective acute treatment, obesity, depression, and stressful life events [4]. Moreover, age, female sex, low educational and socioeconomic status, respiratory disorders such as asthma, and cardiac risk factors like hypertension have all shown statistically significant associations with the development of chronic migraine [4] [5].

Chronic migraine (CM) is defined by the current ICHD-3 as part of the International Headache Society as a headache occurring on ≥ 15 days per month for 3 months with features of migraine on ≥ 8 days/month. The exact pathophysiology of chronic migraine is unknown [6]. There are some preclinical and clinical data pointing out the impact of altered brain structures and metabolism, cortical hyperexcitability, and the central sensitization of the TS in the pathogenesis of CM. Neuroimaging studies revealed the reduction of cerebral gray matter in the pain matrix, such as that of the anterior cingulate cortex, the reduction of which showed a positive correlation with migraine attack frequency [7]. Additionally, positron emission tomography (PET) has demonstrated that, during a spontaneous migraine attack, specific-brainstem nuclei (e.g., periaqueductal gray matter (PAG), locus coeruleus and raphe nuclei) showed increased activity [8]. Iron accumulation in the PAG was observed in migraine, which showed a correlation with disease duration [9]. Finally, human PET studies concerning brain metabolism and hyperexcitability have also suggested that the orbitofrontal and temporal cortices might play a role in the initiation of chronic migraine [7].

There are many treatment options available to help manage the pain of migraine. Pharmacologic management for primary headaches includes both acute and prophylactic treatment strategies. However, considerable side effects are often observed with these therapies, which, unfortunately, limits their usefulness. In patients who take medications too often to treat their headaches, MOH—Medication Overuse Headache—may occur. It is also known as a rebound headache. These can cause migraine episodes to occur more frequently and become more severe. Instead of alleviating symptoms, the medications increase the intensity and frequency of headaches [10].

BoNT is a neurotoxin produced by the bacteria Clostridium botulinum. This neurotoxin is responsible for botulism. It inhibits the release of the acetylcholine neurotransmitter from axon endings at the neuromuscular junction. There are eight

types of BoNT: from A to H. Types A and B are used in headache treatment [10].

In 1989, the FDA approved the use of the Botulinum toxin for the treatment of blepharospasm and hemifacial spasm. One year later, a facial plastic surgeon, Dr. Binder, observed that some patients who received botulinum toxin for cosmetic purposes reported reduced headache frequency. Prospective open-label observational studies confirmed the acceptable safety and tolerability profile of BoNT-A in chronic migraine prophylaxis [11]. In 2010, BoNT-A was reported as effective for the treatment of chronic migraine in the Phase 3 Research Evaluating Migraine Prophylaxis Therapy (PREEMPT) trials [12] [13]. Next, it was approved by the European Medicines Agency (EMA) and by the US Food and Drug Administration (FDA) for the prophylaxis of chronic migraines. Its use was endorsed by the National Institute for Health and Care Excellence (NICE) in 2012. The pathophysiological mechanism underlying the efficacy of BoNT-A in CM is not clearly understood, but blockade of SNAP-25 mediated exocytosis of proinflammatory neuropeptides, including CGRP and Substance P, as well as excitatory neurotransmitters including glutamate, may be one plausible mechanism [14].

The PREEMPT injection paradigm involves a minimum of 31 injections to 7 specific head and neck muscle areas (frontalis, corrugator, temporalis, cervical paraspinal, occipitalis, trapezius, and procerus). The protocol calls for injections of the botulinum toxin in 12-week intervals for a minimum of 36 weeks (3 complete cycles). When deciding on the dose and location of additional onabotulinumtoxinA, physicians take into consideration the location of the patient's predominant pain and the severity of palpable muscle tenderness—a strategy known as "follow the pain" [10] [15]. Although "follow the pain" injections are frequently administered, it is not fully established whether they provide additional benefits [16].

2. Objectives

The purpose of this study was to conduct a retrospective chart review concerning the real-world effectiveness of our revised version of the PREEMPT injection paradigm for onabotulinumtoxinA treatment of chronic migraine and to discuss these results relative to those obtained in the onabotulinumtoxinA PREEMPT pivotal trials.

3. Methods

We conducted a retrospective chart review of all patients treated for chronic migraine at Maine Comprehensive Pain Management in Scarborough, Maine. The clinic's electronic health records were searched using the Sevocity software, which the practice relies on for medical scheduling/record keeping. The following codes were leveraged from the International Classification of Disorders (ICD-10) to filter out all patients diagnosed with migraine who had arrived at the practice for treatment: G43.709 (migraine without aura, not intractable, without status migrainosus), G43.101 (migraine with aura, not intractable, with status migrainosus), and G43.109 (migraine with aura, not intractable, without status migrainosus). Only those patients who adhered to our advised PREEMPT injection protocol

(Gray/Campbell Migraine Injection Protocol), receiving a minimum of three cycles of Botox injection in three-month intervals, were included in the study.

4. Patient Disposition

Our study cohort consisted of 140 patients (114 females, 81% female) with a mean age of (54.3 ± 14.6) years (range 24 - 93). Each patient's symptomatology satisfied the diagnostic criteria established by the International Headaches Society (ICHD-3) in their 3rd edition of the "International Classification of Headache Disorders". According to the ICHD-3, patients qualifying as chronic migraine patients must have had headaches on ≥ 15 days/month for > 3 months, with each episode lasting anywhere from 4 to 72 hours when untreated or unsuccessfully treated. Additionally, headaches must have at least two of the following four criteria: unilateral location, pulsating quality, moderate or severe pain intensity, aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs). Also, during a headache, the patient must have at least one of the following: nausea and/or vomiting, or photophobia (sensitivity to light) and phonophobia (sensitivity to sound) [17].

5. Procedure

The sevocity software was accessed using employer credentials at Maine Comprehensive Pain Management's medical practice. A list of patients who had received the ICD-10 diagnostic labels discussed above was formulated in alphabetical order, and student researchers went down the list, investigating each patient's specific case. Our researchers accessed the patient's treatment history at the clinic and identified whether they received Botox injections for treatment of their migraines. If the patient did undergo Botox treatment, the researcher ensured they did so in a manner that conformed to our modified PREEMPT injection paradigm (Gray/Campbell Migraine Injection Protocol). If the patient did not undergo the minimum of three cycles established in the protocol, or if they were more than two weeks off schedule (from the suggested 3-month intervals between injections), they were not included in the study.

Of the 182 patients whose clinical presentation satisfied the diagnostic criteria for chronic migraine and who also had undergone at least one round of BoNT-A treatment, 42 were excluded from this study. **Figure 1**, seen below, illustrates the five most common reasons for discontinuation of the BoNT-A treatment, and thus exclusion, of these patients. Other less common reasons for exclusion included Patient Moving out of State (1 patient), Insurance Complications (2 patients), and Post-Injection Side Effects (Ptosis, 1 patient) (Post-Injection Discomfort, 1 patient).

It should be noted that, in general, patients who had either been "Lost to Follow-Up" or had "…Neglected to Schedule a Repeat Injection Appointment Within Scheduling Guidelines" still demonstrated positive responses to treatment. Those who were "Lost to Follow-Up" had undergone only one or two injection cycles and still demonstrated a positive response rate of 92%, with an

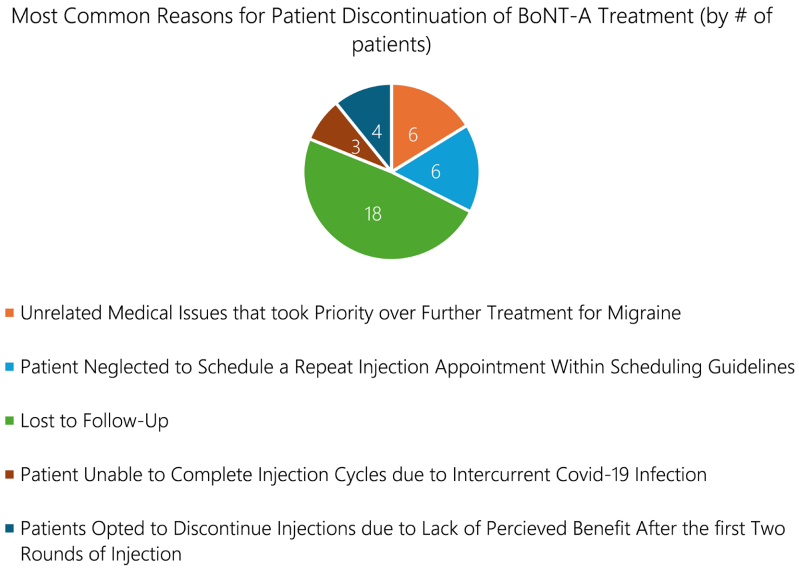

Figure 1. The most common reasons for discontinuation of BoNT-A treatment among qualifying chronic migraine patients at Maine Comprehensive Pain Management. Patients "Lost to Follow-Up" [18] constituted the greatest proportion of those excluded from the study, while "Patient Neglected to Schedule a Repeat Injection Appointment Within Scheduling Guidelines" [6] and "Unrelated Medical Issues that took Priority over Further Treatment for Migraine" [6] represented the next largest populations of subjects excluded from the study.

average percent improvement of 85%. Those patients who "…Neglected to Schedule a Repeat Injection Appointment Within Scheduling Guidelines" did end up undergoing the minimum of three injection cycles, but they did so in a manner that deviated from the time parameters our investigators laid out in the inclusion criteria. Although these patients were more than two weeks off schedule between two or more of their injection cycles, they still demonstrated a positive response rate of 96%, as well as an average self-reported improvement of 87% in their migraine symptoms.

All patients who were selected for Botox injections had either tried and failed or had incomplete treatment benefits with pharmacotherapy. Some of these patients had unwanted side effects from pharmacotherapy, which limited their use. Other patients tried pharmacotherapy without adequate response. All patients were tried on at least three pharmacotherapeutic options prior to initiating Botox injections unless prior side effects or contraindications limited their use. Pharmacotherapy classes included anticonvulsants (*i.e.*, Topiramate, Gabapentin, Valproic Acid), Selective Serotonin Reuptake Inhibitors (SSRIs) (*i.e.*, Fluoxetine, Sertraline, Paroxetine, Citalopram, Fluvoxamine), Serotonin Norepinepherine Repuptake Inhibitors (SNRIs) (*i.e.*, Duloxetine or Venlafaxine), Beta Blockers (*i.e.*, Propranolol) or Calcium Channel Blockers (*i.e.*, Amlodipine or Verapamil).

Once the patients who were classified as chronic migraine patients were appropriately identified via an investigation into their medical records, the doctor's notes of their most recent visit were analyzed. First off, our researchers checked

to see if they exhibited a response to the Botox injections after having received a minimum of three rounds of injection. For those patients who did demonstrate a positive response to the Botox treatment regimen, their self-reported percent improvement was recorded.

6. Statistical Analyses

All patients who satisfied both the criteria for chronic migraine (as established by the ICHD-3), had either failed or had incomplete pharmacotherapeutic treatment, and who underwent ≥ 3 injection cycles no more than 2 weeks off schedule were pooled together. All analyses were conducted using the most recent version of the Microsoft Excel Software. No statistical power calculations were conducted, and all available data were used for this analysis. Due to the retrospective nature of this study, no formal statistical testing was performed.

7. Efficacy

A positive patient-rated response to the Botox treatment regimen constitutes a ≥ 50% reduction in migraine days (Hull criteria), with at least 100 hours and 7 days fewer headaches per month [18]. These two criteria were employed in the PREEMPT pivotal trials, allowing for easy interpretation of our findings.

The overall improvement in headache symptoms was captured via a self-reported "percent improvement" score on a scale from 0 - 100%. In context, a self-report score of 0% implies the patient considers themselves no better off than they were when arriving at the practice for their initial consultation. A self-report score of 100% implies that the patient has realized complete relief in their headache symptoms and that they are now symptom-free.

8. Results

In general, the distribution of percent improvement in migraine symptoms is heavily skewed to the left, with most patients landing in the "90% - 100%" improved group. (**Figure 2**)

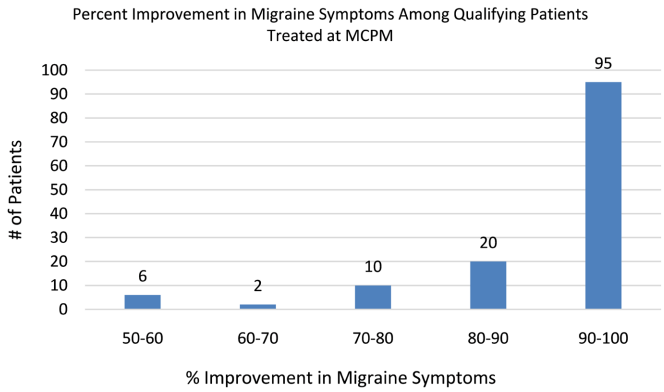

Figure 2. The distribution of self-reported percent improvement scores among qualifying migraine patients who exhibited a positive response (n = 133) after having received ≥ 3 injection cycles, with roughly 3 months between each injection.

95% of patients treated for chronic migraine at the practice demonstrate a positive clinical response. (Figure 3)

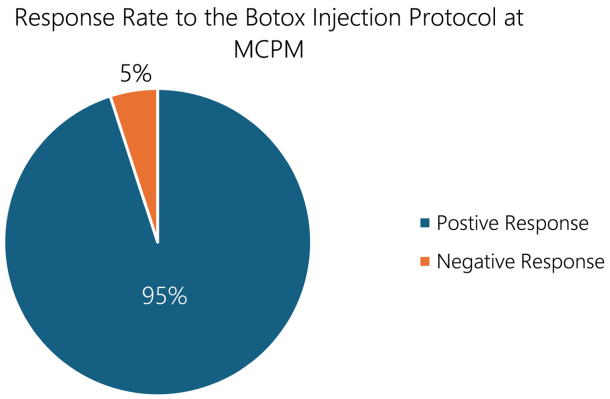

Figure 3. The response rates to the revised version of the PREEMPT injection protocol administered at Maine Comprehensive Pain Management.

9. Discussion

This retrospective chart review demonstrates that 95% of Botox patients treated at Maine Comprehensive Pain Management for symptoms of chronic migraine exhibit a positive response to the revised version of the PREEMPT injection paradigm. Further, the average improvement in headache symptoms among those who demonstrated a patient self-reported positive response to the Botox treatment was 89.13%. (Table 1)

Table 1. Descriptive statistics of the self-reported percent improvement scores.

Average (%)	89.13
Standard Deviation (%)	12.43
Relative Standard Deviation (%)	13.95
Median (%)	90
Mode (%)	90
Interquartile Range (%)	14
Range (%)	50

Following the revised version of the PREEMPT paradigm (≥3 injection cycles, with ≈ 12 weeks between each cycle) at our practice, the recorded response rate was 95%. This number corresponds to the percentage of patients who realized a 50% reduction from baseline in headache days/month after receiving at least 3 rounds of injection cycles. The national average response rate after just two injection cycles reported by Allergan is 51% [14]. Silberstein *et al.* report a response rate of roughly 70% after three injection cycles [19]. We believe the glaring difference between these reported numbers and our practice is attributed to the slight revisions made to the PREEMPT injection paradigm, which targets the etiology of

splenius capitis syndrome. Figure 4, seen below, illustrates the standard injection protocol for the administration of onabotulinumtoxinA in 31 injection sites in the head and neck among chronic migraine patients. Figure 5 illustrates the revised injection protocol that clinicians at Maine Comprehensive Pain Management routinely adhere to when treating patients. The revised approach (Gray/Campbell Migraine Injection Protocol) calls for our clinicians to make a total of 33 injections among muscles in the head and neck.

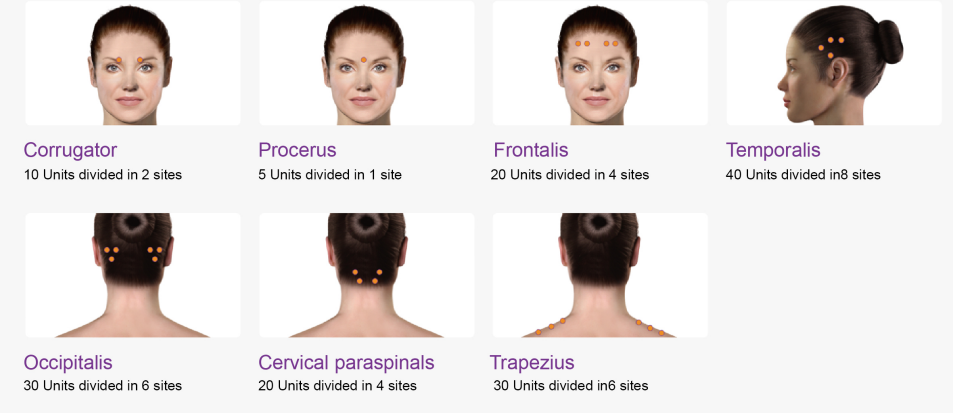

Figure 4. The proven PREEMPT* paradigm means an established administration process. (https://www.botoxone.com/chronic-migraine/dosing)

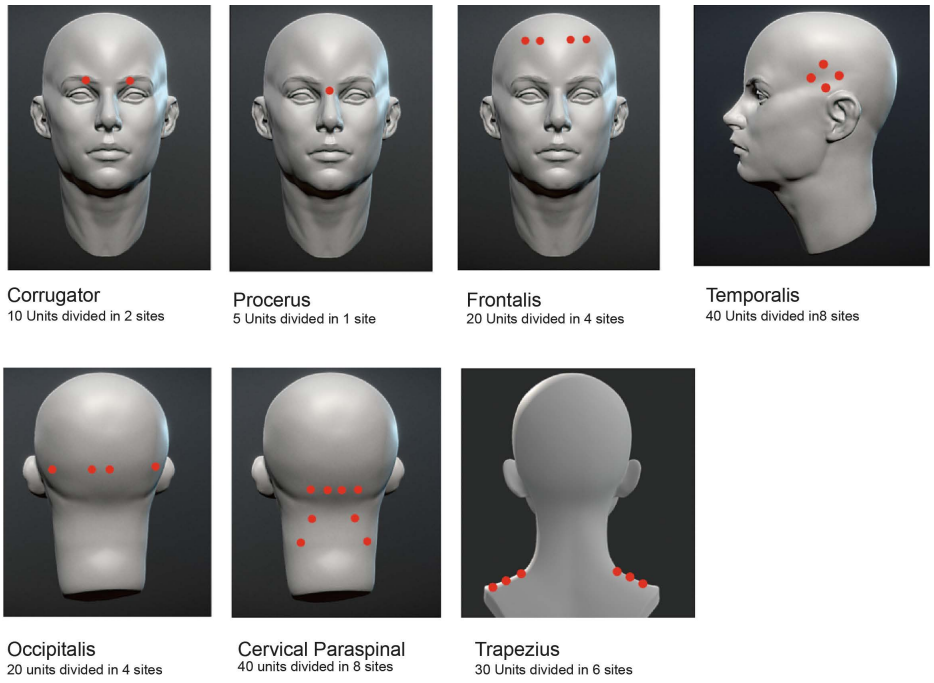

Figure 5. The "follow the pain" strategy used at Maine Comprehensive Pain Management employs a strategic approach. The proven PREEMPT paradigm is slightly adjusted at our clinic as follows: Injection site at the corrugator muscle bilaterally, moving the injection for the procerus inferiorly by a couple of millimeters, 2 millimeters superiorly for the four frontalis injection sites, four temporalis injection sites (on both sides), four occipitalis injection sites, eight cervical paraspinal injections, and six trapezius injections.

In the revised approach to the PREEMPT injection paradigm, clinicians make changes to the injection sites at the following five muscle groups: procerus, frontalis, temporalis, occipitalis, and cervical paraspinal. When injecting at the procerus under the revised version of the injection paradigm, clinicians will move a few millimeters inferiorly to the standard injection site, probing the muscles as they go until finding the most tender area. For the frontalis injections, clinicians will move 2 millimeters superiorly for all four injection sites. The temporalis injections realize just one small alteration: the top right injection is dropped a few millimeters inferiorly to make a rough "diamond shape" of injections in the muscle group.

The occipitalis and cervical paraspinal muscle groups realize the greatest degree of revision to their injections. We believe these revisions are largely responsible for the marked difference in response rate between the nationally established administration process and our revised version of the protocol. As is seen in **Figure 5**, the occipitalis muscle receives only 4 injections under the revised administration protocol. In our treatments, we propose that the superior fibers of the trapezius and the fibers of the splenius capitis play a key role in the symptoms of migraine headaches. This may, in part, be due to the spasm in the Splenius Capitis, which leads to the condition already described in the literature, Splenius Capitis Syndrome.

We believe the marked difference in the reported positive response rate in our Gray/Campbell injection protocol compared to the national positive response rate is because of its impact on treating splenius capitis syndrome. To understand splenius capitis syndrome, it is important to understand the muscle function and location. Splenius capitis is in the rear of the neck and is a member of the splenius muscle group, which also includes the splenius cervicis muscle. The splenius capitis muscle helps to rotate and extend the cervical spine and helps keep the head and neck in a neutral position. Trigger points may result from tense, worn-out, or overused muscles, which may contribute to headaches or pain in the upper part of the head. One study has shown that this muscle can contribute to chronic tension-type headaches, in addition to the muscles of the suboccipital, temporalis, upper trapezius, and splenius cervicis [20].

Typically, temporal tendinitis and migraine headache pain reference patterns are mimicked by Splenius Capitis Muscle Syndrome. The unpleasant headache begins medially with the mastoid process and at the lateral edge of the superior nuchal line [21]. In adults, the headache occurs most often at the attachment of the Splenius Capitis and Semispinalis Capitis Muscles. As inflammation develops, entrapment and irritation of the Greater Occipital Nerve result. The typical symptom complex results from muscle spasms as well as from neuralgia [22]. Pain is frequently brought on by trauma, such as falls, physical trauma, and motor vehicle accidents. Muscle stress causes microtrauma to the muscle attachment, which leads to swelling and the development of myalgia or neuralgia [23]. Pain that is piercing, throbbing, or lancinating in the upper neck, back of the head, and behind

the eyes is the most prevalent symptom of occipital neuralgia. The issue is often unilateral, and because eye discomfort is frequent, it is mistakenly diagnosed as "migraine." With referred pain behind the eye, Splenius Capitis Syndrome (SCS) discomfort starts in the neck and moves throughout the brain [22].

Splenius capitis syndrome is commonly undiagnosed among patients but can cause the same symptoms of a common migraine, so if palpating along the superior nuchal line between the trapezius and sternocleidomastoid muscles yields any hypertonicity, it would indicate the presence of splenius capitis syndrome. Most of the patients at our clinic yield positive for this syndrome, so BoNT injections are placed where it is more hypertonic, typically around the superior nuchal line. Treating the symptoms of Splenius Capitis Syndrome at its origin helps the patient treat their migraine symptoms [21].

Every patient is different, and medicine is expected to care for each specific difference in patients and appease their respective problems. The difference in the response rate at our clinic may be explained by the fact that we take the patient's perspective into account when injecting BoNT-A. Before administering the injection, the doctor palpates each muscle (bilaterally if necessary) to confirm muscle tenderness and to identify any sore spots or regions of discomfort that need attention. The idea behind this approach is that the palpation for tenderness in a muscle can be at different locations patient by patient, and this approach helps take the patient's perspective of the pain into account before the injection. The emphasis on a patient-centered approach will regularly yield positive results for the patient and help improve the physician-patient outlook.

10. Limitations

We'd like to recognize several limitations that are inherent in this study:

1) The pain being reported by patients is inherently subjective. There are pain tolerance discrepancies from patient to patient, thus imposing a limitation when measuring the pain a patient is experiencing. This phenomenon is not unique to this research—a completely objective pain measurement does not exist and will never be able to exist because pain is a subjective entity. Even pain scales like VIS, which are regularly utilized by clinicians, are, at the end of the day, a subjective measure. Not only do patients interpret their pain experiences in their own unique ways, but they also engage with clinical measurements of pain in varying ways, as well.

2) There is an inherent bias in the patient's personal assessment of their headaches and response to Botox injections. It is possible that some patients went into treatment thinking they would not realize any benefit from the injections, so any benefit they did realize could have been diluted. On the flip side, patients could have gone in over-confident in the efficacy of the injections and over-dramatized the benefit they gained from their treatment.

3) The pain and experiences are self-reported by the patients. Many of the patients suffering from migraine headaches are only reporting the highest severity

of headaches they experience, a phenomenon we refer to as "the iceberg effect." These patients are dismissing the day-to-day headaches they are experiencing, limiting the assessment of the patient and, therefore, limiting the treatment.

4) Reporting bias is possible within the study as the findings are presented by Maine Comprehensive Pain Management clinicians after being self-reported by each patient. However, the reporting clinicians held to strict reporting of each patient's personal rating of their perceived personal improvement.

5) There is no control group within the treatment done at Maine Comprehensive Pain Management.

6) The study success rate is limited to a single clinical practice and geographical location, which can impose limitations when applying the findings to larger populations within different clinical practices.

With undergraduate pre-medical students and medical students, under the direction and guidance of the lead investigator, spearheading the research for this study, resources like time and money were inherently insufficient for a larger study design. It is thus our hope that future studies are conducted to further examine the efficacy of the Gray/Campbell Migraine Injection Protocol (the revised version of the PREEMPT injection paradigm). Ideally, a longitudinal meta-analysis of clinics throughout the country that would compare the Gray/Campbell Migraine Injection Protocol to the standard PREEMPT injection paradigm, along with the presence of a control group, would work to expand on the findings presented here.

11. Conclusion

This retrospective chart review of chronic migraine patients treated with the Gray/Campbell Migraine Injection Protocol (a revised version of the PREEMPT injection paradigm) presents unparalleled efficacy results in the literature to date. We hope this paper serves as an impetus for future research into this injection approach and that, one day, migraine patients throughout the country can realize the same benefits as the patients treated at our practice.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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