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Original Article

Comparison of Efficacy of Botulinum Toxin Injection and Conventional Oral Drugs for Treatment of Refractory Migraine

Anusha Pervaiz[1]*, Wasim Alamgir[1], Babar Khan[1], Khurram Haq Nawaz[1], Imran Ahmad[1], Saima Shafait[2], Fawad Ahmad[1]

[1]Pak-Emirates Military Hospital, Rawalpindi

[2]Fauji Foundation Hospital, Lahore

Corresponding Author: Anusha Pervaiz; Email: anushapervaiz@gmail.com

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ABSTRACT

Background: Migraine, a debilitating neurological condition, significantly impacts quality of life. Despite various treatments, some cases remain refractory to conventional therapies. This study explores the efficacy of Botulinum Toxin Type A (BOTOX) injections compared to Conventional Oral Drugs (CODs) in treating refractory migraines, offering potential advancements in migraine management.

Objectives: This single-center retrospective cohort study compared the efficacy and safety of Botulinum toxin (BOTOX) injection and Conventional Oral Drugs (COD) for treating the refractory migraine.

Methods: Between May and August of 2023, 78 adults with refractory migraine were enrolled at tertiary care center in Islamabad. Their demographic data revealed the mean age of 46.5 years (SD=10.09), gender distribution of 28 males (35.90%) and 50 females (64.10%), and distribution of 27 employed (34.61%) and 51 unemployed (65.30%).

Results: Average duration of refractory migraines was 9.72 years and average number of migraines per month was 22. The number of headache days per month decreased from 22 at baseline to 19 after two months and to 12 after three months ($p=0.239$) as the primary outcome measure ($p>0.05$). The VAS scores decreased substantially from 7.6 to 5.5 ($p=0.049$), indicating decrease in headache severity ($p<0.05$). Scores on Migraine-Specific Quality of Life (MSQ) increased from 43 to 73% ($p>0.05$). The Migraine Disability Assessment (MIDAS) scores decreased from 66 to 48 ($p=0.047$) and Headache Impact Test (HIT-6) scores decreased from 69 to 40 ($p=0.025$), indicating an improvement in disability and quality of life ($p<0.05$). Injection site pain (n=35), nausea (n=25), dizziness (n=15), fatigue (n=12), parched mouth (n=5), and muscle weakness (n=5) were reported as adverse effects.

Conclusion: While BOTOX treatment significantly improved measures of headache severity, disability, and quality of life, patient tolerability and potential distress must be considered when selecting this treatment.

Keywords: BOTOX; Headache; Migraine; NSAIDs; OnabotulinumtoxinA, Refractory migraine

INTRODUCTION

Refractory migraine, a complex neurological disorder resistant to standard treatment modalities, has a devastating impact on affected health and comfort. These are resistant, necessitating the use of more specialized and frequently intensive treatment methods (1-2). Despite comprehensive, appropriate intervention, these migraines persist in frequency and intensity and typically manifest on 15 or more days per month for at least three months (3).

There are two primary manifestations of this condition: Refractory Chronic Migraine (RCM) and Refractory Episodic Migraine (REM). With the pathogenesis that is complex and not entirely understood, both types can cause significant pain and impairment (4). Researchers believe that family predisposition, environmental factors, and concomitant medical and psychiatric conditions all play a role in their development (5).

Given the resistance of refractory migraines to conventional therapeutic approaches, their management presents a formidable challenge. As a result, the discipline has shifted its focus to innovative, multidisciplinary approaches to treat this condition. Current research seeks to develop more effective treatments and discover the enigmatic causes and mechanisms underlying migraines that are resistant to treatment (6).

Life with refractory migraine is fraught with challenges, including chronic pain, disturbed sleep, impaired physical abilities, and diminished capacity for daily activities. Equally profound are the societal ramifications of this condition, as it generates considerable economic strain through rising healthcare costs and decreased productivity. Awareness and comprehension of refractory migraines are essential for both patients and healthcare providers responsible for their care (7).

The administration of BoNT-A injections and use of conventional oral medications have emerged as the two most effective treatments for refractory migraines at present. Although BoNT-A was initially recognized for its cosmetic applications, it has shown promise in the treatment of intractable migraines (8-9). Numerous studies attest to its efficacy and safety, resulting in FDA approval for the treatment of chronic migraines. Despite its demonstrated efficacy, precise mechanism of BoNT-A in migraine prophylaxis is still a subject of active investigation (10). Conventional oral medications, a broad category that includes triptans, nonsteroidal anti-inflammatory drugs (NSAIDs), beta-blockers, antiepileptic drugs, and antidepressants, primarily seek to prevent migraines or reduce their severity. Although essential to the treatment of refractory migraines and effective in most patients, a significant proportion do not respond or cannot tolerate adverse effects, necessitating the investigation of alternative therapies (11).

Comparative investigations of BoNT-A injections and conventional oral medications have produced contradictory findings. Some claim that BoNT-A is preferable in managing migraines by reducing their frequency and severity, others indicate that two methods are equally effective. However, factors such as adverse effect profiles, patient preferences, cost, and accessibility frequently influence the selection of a treatment (12-13).

The lifestyle of the patient, their personal preferences, and economic implications of treatment also play the crucial role (14). While progress has been made in understanding and treating refractory migraine, this investigation between BoNT-A injections and conventional oral medications would provide healthcare professionals with clearer guidelines, enabling them to make more informed judgments regarding optimal treatment options, thereby enhancing the overall management of this challenging condition.

MATERIAL AND METHODS

The study was a single-center retrospective cohort investigation conducted at the Neurology Outpatient Department of a tertiary care center in Islamabad, Pakistan. It enrolled 78 adult participants aged between 18 and 65 years who were diagnosed with refractory migraine according to the International Classification of Headache Disorders (ICHD-3) criteria. This enrolment occurred from May to August 2023.

Participants in the study, all of whom had refractory migraine that did not respond to Conventional Oral Drugs (CODs), were chosen based on the ICHD-3 criteria. The refractoriness of their condition was determined in line with the European Headache Federation's guidelines for refractory migraine. The study employed OnabotulinumtoxinA injections (BoNT-A/BOTOX) as per the protocol outlined in the PREEMPT study. These injections were administered at multiple sites using the "FDFS" and "FTP" injection paradigms, with a dosage of 195 U across 39 sites. The injections were scheduled at the start (day 0) and then at three-month intervals (plus or minus one week). The efficacy of the treatment was evaluated through the frequency of headaches, number of migraine days, and acute pain medication intake. Baseline data were captured using patients' headache diaries from the month prior to the initiation of OnabotulinumtoxinA treatment. Follow-up evaluations were conducted every three months in conjunction with each injection session. Additionally, the Headache Impact Test (HIT-6) was completed by patients after three months to further assess efficacy. The outcomes were then juxtaposed with the initial scores. During this three-month period, all adverse effects associated with the treatment were meticulously recorded, serving as indicators of safety (15).

The study's primary aim was to ascertain whether the BOTOX dosage had a differential impact on efficacy and tolerability compared to COD. To this end, the outcomes were compared with the baseline scores of the investigated population. The clinical evaluation regimen for these patients was rigorously adhered to throughout the study period.

The primary outcome measure was the change from baseline in the number of headache days per month, assessed after three months. Secondary outcome measures included changes in headache severity, measured using the Visual Analogue Scale (VAS); disability, determined by the Migraine Disability Assessment (MIDAS) questionnaire; and quality of life, evaluated through the Migraine-Specific Quality of Life Questionnaire (MSQ).

For the statistical evaluation, the data were analyzed with the intent-to-treat approach, using the ANOVA test for categorical data. A p-value of 0.05 or less was considered statistically significant. All analyses were performed using version 26.0 of the SPSS Statistics software.

To account for potential confounding variables, factors such as age, sex, employment status, duration of migraine history, headache frequency and types, and the presence of comorbidities were recorded at baseline and controlled for during the statistical analysis. Adverse events were closely monitored and recorded throughout the study to ensure a comprehensive safety assessment.

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RESULTS

Comprehensive overview of baseline characteristics and demographic data for the BOTOX group indicated that the participants' average age was 46.5 years, with a standard deviation (SD) of 10.09 years (p>0.05). In terms of gender, this cohort consisted of 28 men (35.90%) and 50 women (64.10%). The gender distribution within the group did not manifest a statistically significant difference (p>0.05). It was also determined that 27 participants (34.61%) were employed while 51 participants (65.39%) were unemployed (p>0.05), indicating that the employment status distribution within the sample was not statistically significant. Mean duration of refractory migraines among the study's participants was 9.72 years (standard deviation = 2.40 years) (p>0.05). The average number of migraine days per month for participants was 22 (standard deviation = 2), and there was no statistically significant variation within the group (F- value = 0.0007, p-value = 0.97). The participants' average (HIT-6) score was 69.35 (SD = 3.01) (p>0.05). In terms of these demographic characteristics and baseline characteristics, BOTOX group was statistically indistinguishable among the participants (Table 1).

There were 32 participants (41.02%) who reported experiencing imploding migraines. Statistical analysis demonstrated that the incidence of imploding headaches within the group does not differ substantially (p>0.05). Twenty-one participants (or 26.92%) reported experiencing exploding migraines (p>0.05). Twelve participants (15.38%) of the cohort, reported having equal-type headaches (p>0.05). 13 participants (16.66%) reported ocular migraines as a final symptom. The variance in the incidence of ocular migraines within the group was not statistically significant, as indicated by an F-value of 2.165 and a p-value of 0.141. None of the four headache types – imploding, explosive, equal, and ocular – showed the statistically significant difference in their incidence within the group, indicating a heterogeneous distribution of headache types among the participants (Table 2).

The outcomes of treatment modalities of the participants were keenly recorded and throughout the treatment duration, participants reported fewer headaches per month. Initially, at baseline, participants experienced 22 migraines per month on average. This average decreased to 19 headaches per month after two months, and further decreased to 12 headaches per month after three months of treatment. Nevertheless, this decrease in headache frequency over time was not statistically significant with p-value of 0.239. In contrast, the VAS scores for headache intensity decreased significantly over the course of treatment (p<0.05). At the beginning of this research, average VAS score of the participants was 7.6. This average score decreased to 6.8 after two months and to 5.5 by the conclusion of the three-month period with a p-value of 0.049, the decline in VAS scores during the treatment period was statistically significant (p<0.05). The participants' MSQ scores increased from 43% at baseline to 56% after two months and then to 73% after three months (p>0.05). Scores on MIDAS and HIT-6 also improved significantly (p<0.05). The MIDAS scores decreased from 66 at baseline to 58 after two months and to 48 after three months (F-value = 4.041, p-value = 0.047). Similarly, the HIT-6 scores decreased from 69 at baseline to 59 after two months and from 59 to 40 after three months (F-value = 4.348, p-value = 0.025). Over the duration of three months, BOTOX treatment significantly improved VAS scores for headache intensity, MIDAS, and HIT-6 scores, indicating its potential efficacy in managing refractory migraine. Despite being observed, the decrease in the number of migraines per month and the improvement in MSQ scores were not statistically significant (Table 3). The presented data provided an overview of the adverse effects participants experienced after receiving BOTOX treatment for refractory migraines. 35 participants reported experiencing discomfort at the injection site as the most common adverse effect. This was followed by nausea, which was reported by 25 people. 15 participants reported dizziness, and 12 participants reported fatigue, indicating that these were uncommon but evident side effects of the treatment. Five participants reported dry mouth and muscle weakness as the adverse effects that occurred the least frequently. While the evidence suggested the potential efficacy of BOTOX in treating the refractory migraines, these side effects emphasized the importance of considering patient tolerability and potential discomfort when choosing this treatment option (Figure 1).

Table 1 Baseline characteristics and demographic features of randomized trial participants

S. No	Characteristics	BOTOX group (n=78)	F-value	p-value
1	Age (Mean + SD) years	46.5+10.09	0.0005	0.9826
2	Gender n(%) Male Female	 28 (35.90) 50 (64.10)	 0.5027 0.1567	 0.4783 0.6922

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S. No	Characteristics	BOTOX group (n=78)	F-value	p-value
3	Working status n(%) Employed Unemployed	 27 (34.61) 51 (65.39)	 0.5038 0.2720	 0.4778 0.6020
4	Duration of refractory migraine (years)	9.72+2.34	0.0029	0.9568
5	Monthly migraine days (n)	22+2	0.0007	0.9793
6	Mean HIT-6 scores	69.35+3.01	0.0004	0.9831

Table 2 Types of headaches in participating individuals

S. No	Type of headache	BOTOX group (n=78)	F-value	p-value
1	Imploding	32 (41.02)	0.025	0.874
2	Exploding	21 (26.92)	0.375	0.540
3	Equal	12 (15.38)	1.610	0.204
4	Ocular	13 (16.66)	2.165	0.141

Table 3 Outcome of treatment modalities

S. No	Outcome measures	BOTOX group (n=78)	F-value	p-value
1	No. of headache per month Baseline months months	22 19 12	1.389	0.239
2	VAS score for headache Baseline months months	7.6 6.8 5.5	4.281	0.049*
3	MSQ score (%) Baseline months months	43 56 73	1.234	0.267
4	MIDAS Baseline 2 months 3 months	66 58 48	4.041	0.047*
5	HIT-6 Scores Baseline months months	69 59 40	4.348	0.037*

*indicated that the value is significant at p<0.05

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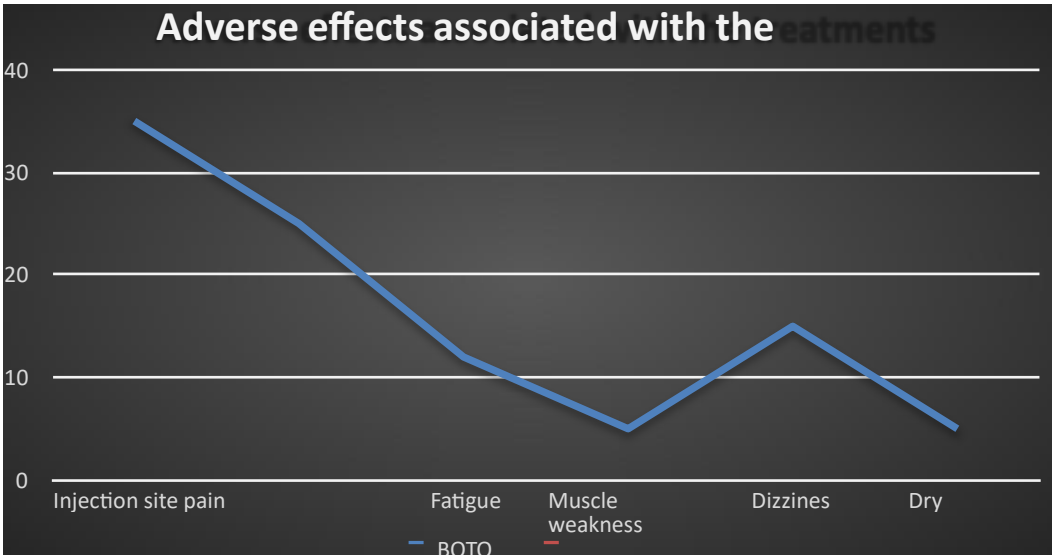

Figure 1 Recorded adverse events during the trial

DISCUSSION

The objective of this retrospective cohort study was to compare the efficacy of botulinum toxin injection (BOTOX) and CODs for treating refractory migraine. Significant improvements in headache severity, migraine-related disability, and quality of life were observed in 78 participants non-responsive to CODs after receiving BOTOX injections for three months. A crucial finding was the significant decrease in VAS scores for headache intensity from 7.6 at baseline to 5.5 after three months ($p<0.05$), suggesting that BOTOX injections may effectively treat patients with refractory migraine attacks.

Moreover, MIDAS and HIT-6 scores improved significantly after three months of BOTOX treatment ($p<0.05$), indicating an enhancement in the quality of life by decreasing migraine-related disability. Our research revealed a diverse distribution of imploding, exploding, equal, and ocular migraines. Adverse effects associated with BOTOX use included pain at the injection site and vertigo, while dizziness, fatigue, dry mouth, and muscle weakness were less frequent. Despite these effects, the health improvements in participants were notable. Supporting our findings, a retrospective analysis of 33 patients receiving Botox® injections every three months according to the PRE-EMPT protocol for up to 33 months showed a significant decrease in HIT-6 scores (mean reduction =-5.45, p = 0.000920), with 21% of patients exhibiting a sustained decrease to below 60 (16). This indicated the effectiveness of Botox® therapy for chronic migraines resistant to relief.

Although limited randomized, double-blind, placebo-controlled studies exist, our study aligns with previous research suggesting the efficacy of Botulinum toxin A in migraine prevention. In one study, 30% of patients in both botulinum toxin A treatment groups experienced a 50% or greater reduction in migraine frequency in the third month relative to baseline, compared to 25% in the placebo group (P = 0.921) (17).

Our findings also align with a study evaluating headache days, migraine days, acute pain medication ingestion days, and HIT-6 score reductions in 172 patients treated with OnabotulinumtoxinA 195 U over two years. This study demonstrated the efficacy, safety, and tolerability of OnabotulinumtoxinA 195 in treating chronic migraine patients (15). Our investigation concurred with a report stating BoNT-A injections significantly reduced headache frequency and migraine disability assessment scores in Refractory Chronic Migraine patients. Approximately 40% of patients experienced at least a 30% reduction in headache frequency twelve weeks after injection. Patients with ocular-type headaches had a higher response rate, suggesting a predictor of favorable treatment outcomes. Despite some adverse events like lateral eyebrow elevation and neck discomfort, these were mostly transient and manageable, confirming the safety of BoNT-A in migraine treatment. These results underscore the potential of BoNT-A as a viable treatment option for Refractory Chronic Migraine, especially in patients with ocular-type migraines (18, 20).

CONCLUSION

This study provided compelling evidence for efficacy of BOTOX injections in the treatment of refractory migraine. Over a three-month period, BOTOX injections significantly decreased headache severity and improved migraine-related disability and health of patients. Even though the reduction in headache days per month was not statistically significant, the overall improvement of patients who did not respond to conventional oral medications was remarkable. However, potential adverse effects such as injection site pain and nausea have been reported, highlighting the importance of considering patient tolerance and potential discomfort when deciding on this treatment. This study added to the increasing body of evidence supporting BOTOX as a potential treatment for refractory migraine; however, additional research is required to confirm these findings and investigate their long-term effects.

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ETHICAL APPROVAL

Before enrolment, informed consent was obtained from all participants. Institutional ethics committee endorsed the study protocol, and it was conducted in accordance with the Declaration of Helsinki.

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