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Results of treating Patients with Chronic Migraine with OnabotulinumtoxinA alone Versus Its Combination with Other Prophylactic Drugs

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ABSTRACT

Background: Chronic migraine [CM] is a severe neurological disorder characterized by pulsating unilateral or bilateral headache episodes. In people with chronic migraine, onabotulinumtoxinA could reduce the frequency and severity of migraines. Patients report that the treatment is well tolerated.

The Aim of The Work: The aim of this study was to evaluate the efficacy of onabotulinumtoxinA injection compared with the efficacy of onabotulinumtoxinA injection in combination with other oral prophylactics.

Materials and Methods: This observational study included one hundred five patients with chronic migraine attending the neurology clinic at Almoosa Specialized Hospital in Saudi Arabia, and was conducted from November 2019 to January 2021. Forty-five patients [42.9%] received an injection of onabotulinumtoxinA alone [group A], and 60 patients [57.1%] received a combined injection of onabotulinum-toxinA plus oral prophylaxis [group B].

Results: The study included 105 patients. The mean age of participants was 41.2 ± 5.7 years and ranged from 35 to 55 years. Seventy women [66.7%] and 35 men [33.3%] were affected. The mean frequency of migraine days showed a significant reduction from 17.6±10.3 days per month to 7.2±4.3 days after treatment in patients receiving onabotulinum toxin-A in combination with oral prophylactic medication, whereas it showed a less significant reduction from 16.4 ± 10.4 days per month to 9.1 ± 2.4 days in patients receiving onabotulinum toxin-A alone. Mean treatment frequency per month and mean duration of migraine attacks per hour were also significantly reduced after treatment in both groups.

Conclusion: Onabotulinum toxin-A toxin injection is highly effective in treating patients with chronic daily migraine, reducing the number and severity of migraine attacks per month and improving the quality of life of migraine patients. However, it is even more effective when combined with other prophylactic medications depending on the patients' concomitant diseases.

Keywords: Chronic Migraine; OnabotulinumtoxinA; Headache.

INTRODUCTION

Chronic migraine [CM] is a subtype of chronic daily headache that is distinct from others and has only recently been described. Chronic migraine is defined as more than fifteen headache days per month in a three-months period, of which more than eight are migraine-like, without medication overdose, and affecting less than 1% of the population, according to the International Headache Society [IHS] [1].

More than 20% of the population suffers from migraine at some point in their lives. According to epidemiological studies, 4.5% of the Western European populations suffer from headaches at least 15 days per month [2], while global studies estimated that approximately 1% of the world's populations suffer from chronic migraine [3].

In Saudi Arabia, the prevalence of all types of headaches is estimated at 77.2 percent, with migraine headaches accounting for about 25 percent of the populations. Saudi Arabia has a higher rate of migraine headaches [14%] than the rest of the world [4].

To ensure effective treatment, an evaluation of migraine headaches must be comprehensive and cover the patient's mental health, well-being, and real-life impact. According to one study, migraine has a significant impact on all elements of quality of life [5].

Migraine can lead to other comorbidities if you are affected by migraine for a significant portion of your life, including later in life, depression, anxiety and panic disorders, stroke, and other cardiovascular diseases such as coronary artery disease and hypertension. visual disturbances with aura can lead to Parkinson's disease or restless legs syndrome. High-risk patients are 50 years of age or older [6]. Gudmundsson *et al*. found that men and women suffering from migraine with aura had a higher risk of cardiovascular and all-cause mortality than those without headache [7].

Patients with CM had lower socio-economic status than those with less frequent headaches. They have lower annual incomes, are less likely to work part-time or full-time, and are more likely to be unable to work [8]. Patients with CM are more likely to need to visit general practitioner [GP], specialists, and emergency rooms and are more likely to be hospitalized. Chronic migraine has a significant negative impact on quality of life, which is not surprising [9].

Both acute treatments [used during an attack or exacerbation of chronic pain] and preventive treatments [used before an attack or exacerbation of chronic pain] are used to treat CM [medications or other measures to reduce the tendency to attack]. It can be difficult to identify specific triggers in patients who suffer from chronic severe headache. Surprisingly, triggers usually become clearer as the chronic headache improves with treatment. Meals, hydration, sleep, and stress should be part of a normal daily routine to prevent migraines [10, 11].

To increase the benefit of migraine medications, comorbid conditions such as depression, anxiety, and other pain syndromes such as fibromyalgia must be adequately treated [12].

Treat an acute attack as soon as possible with a simple analgesic [acetaminophen, aspirin, ibuprofen, and naproxen] and gradually increase the dose to the maximum acceptable dose unless the headache is severe or worsens from the start. In such cases, take a triptan in addition to the above medications to increase effectiveness. Stay away from opiates if possible. Any associated side effects, such as nausea, should be treated. Transcranial magnetic stimulation and transcutaneous supraorbital nerve stimulation are two alternative treatment options to be considered [13].

According to the American Academy of Neurology and American Headache Society guidelines, the following medications have been shown to be effective and should be offered for migraine prevention [recommendation grade A]: antiepileptic drugs [AEDs] [divalproex sodium, sodium valproate, topiramate], β-blockers [metoprolol, propranolol, timolol] and triptans [frovatriptan] [13].

The goal of preventive treatment is to reduce the frequency of headaches. Beta-blockers, angiotensin blockers, tricyclic antidepressants, anticonvulsants, injections of onabotulinumtoxinA, and calcitonin gene-related peptide [CGRP] are examples of preventive therapy [14, 15].

Botulinum toxin has been shown to relieve pain in a variety of situations, but its mechanism of action is unknown. Botulinum toxin is thought to relieve pain by suppressing the production of neuropeptides that play a role in triggering migraine, such as calcitonin gene-related peptide and substance P [16].

OnabotulinumtoxinA has been shown to be effective and should be provided to increase the number of days without headache. It is likely to be beneficial and should be studied to improve health-related quality of life in chronic migraine patients [17].

Compared with the anticonvulsant topiramate, treatment with onabotulinumtoxinA is more effective, more tolerable, and results in greater functional improvement in the prevention of chronic migraine [18]. However, its value alone in comparison to its combination with oral medications is not well studied.

THE AIM OF THE STUDY

The aim of this study was to compare the efficacy of onabotulinumtoxinA injection as a sole treatment with the efficacy in combination with other oral prophylactics.

PATIENTS AND METHODS

This cross-sectional observational study was conducted from November 2019 to January 2021 in one hundred five patients with chronic migraine attending the neurology clinic at Almoosa Specialized Hospital in the Eastern KSA. This study was approved by the Almoosa Hospital Ethics Committee. All patients gave verbal informed consent. Data collection was performed by information technologist [IT] at our hospital using the YASSI system. Data collected included final diagnosis, age, sex, family history, comorbidities, brain imaging, Migraine Disability Assessment Test [MDAT] score, and frequency of migraine during monthly follow-up.

The inclusion criteria included all adult patients [over 18 years of age] who met the criteria for chronic migraine and had not received prophylactic medications or onabotulinumtoxinA, only analgesics, in the previous 3 months.

Chronic migraine was defined by the International Headache Society [IHS] as more than fifteen headache days per month over a 3-months period, of which more than eight are migraine-like, without medication overdose. This definition was used in the current work [1].

Exclusion criteria were: [1] Patients with other forms of primary or secondary headache, [2] planned or actual pregnancy or lactation, [3] any type of substance use disorder and patients with medication overuse [simple analgesics, narcotic analgesics, and benzodiazepines], [4] prior exposure to botulinum toxin-A [BTX-A], neuro-muscular disease, or treatment with medications that affect the neuromuscular junction, [5] previous injection of an anesthetic or steroid into the muscles to be injected in the month before study entry, [5] patients who have missed a follow-up examination, [6] skin diseases such as chickenpox or herpes zoster, no ability to communicate or inability to follow instructions, and fever of 38.5°C, and [7] severe physical or psychiatric illness or disease of the cervical spine, such as cervical spondylosis or herniated disk, or neurological disease, such as hemiplegia or paresis.

All patients underwent a detailed physical and neurological examination. Further investigations were performed to rule out secondary causes of headache in case of doubt. Hematology, blood chemistry tests consisting of liver function tests, thyroid function tests, blood urea nitrogen, creatine, electrolytes, vitamin B12, folic acid, and ferritin. In addition, a magnetic resonance image [MRI] of the brain without contrast was requested for patients with "red flag" signs [persistent headache unresponsive to analgesics, waking headache, change in type of pain].

Patients were divided into two groups. The first group received onabotulinumtoxinA alone [group A] and the second group received onabotulinumtoxinA in combination with other prophylactic medications [group B], depending on other comorbidities. The patients with insomnia received amitriptyline, which was started at a low dose of 10 mg before night and gradually increased to 75 mg depending on tolerability. Sedation and dry mouth were the most common pharmacologic adverse effects. However, topiramate has been prescribed for the prevention of migraine headache in overweight subjects with normal renal function and normal cognitive ability. The exact mechanism of action is not yet known. The most common side effects of topiramate were upper and lower limb paresthesias and memory impairment at a dose of 25 mg before bedtime for one week, then 25 mg bid for one week, up to 50 mg bid. In patients who reported chronic migraine in addition to palpitations and hypertension, a beta-blocker [propranolol] was used at a dose of 10 mg per day for one week and titrated to 40 mg depending on patient tolerance. Propranolol is approved for the prevention of migraine. The dose can be gradually increased to achieve optimal migraine prophylaxis. Patients were selected for treatment with the toxin onabotulinumtoxinA. After an explanation of the indication, the mode of action of the toxin, and possible side effects, an appointment was made for an injection session and, finally, a written informed consent was obtained for high-risk treatments according to the guidelines of our hospital. Patients come to their appointments for injection sessions and we used the protocol PREEMPT [The Protocol for the Use of Botox-A Injection Therapy for the Treatment of Chronic Migraine], which was based on the clinical research studies that earned the FDA approval and subsequent FDA guidelines. Each treatment includes 31 injections [5 Botox A units per injection, for a total of 155 units]. The injection protocol PREEMPT, ie, injection of 155 U-195 U at 31-39 sites every 12 weeks, set the standard for onabotulinumtoxinA treatment in CM. It has been argued that an injection paradigm tailored to the individual patient would be preferable [19].

Headache severity was assessed with the Migraine Disability Assessment Test [MIDAS]. MIDAS is the most commonly used disability assessment tool in studies of migraine; a test to determine how severely migraine affects a patient's life. Patients were asked questions about the frequency and duration of their headaches and how often these headaches limit their ability to participate in activities at work, school, or home [20].

Patients were asked to complete a questionnaire about headaches in the past 3 months. Select the answer in the box next to each question. MIDAS Score I- Little or no disability [0-5], II - Mild disability [6-10], III - Moderate disability [11-20], IV-Severe disability [21+]. This questionnaire was completed before and after monthly treatment over a 3-months period [21, 22].

The primary efficacy variables of BOTOX-A were headache days per month and headache severity. All patients were re-viewed 30 and 90 days after injection.

Adverse Events: Any adverse events such as redness, bruising, infection, and pain at the injection site. Dizziness, mild dysphagia, respiratory infections, nausea, headache and muscle weakness, double vision, drooping

or swollen eyelids, eye irritation, dry eyes, tearing, decreased blinking, and increased sensitivity to light have been reported

Statistical analysis: It was conducted using the computer package, statistical package for social sciences [SPSS] version 25.0 [IBM SPSS Statistics for Windows. Armonk, NY: IBM Corp., USA]. For descriptive statistics, mean ± SD [standard deviation] were used for quantitative variables, while frequency and percentage were used for qualitative variables. Chi-square test or Fisher's Exact test were used to evaluate the differences in frequency of qualitative variables, while Mann-Whitney test, Wilcoxon test or Kruskal-Wallis tests were used to evaluate the differences in means of quantitative non-parametric variables with Bonferroni post-hoc correction to determine where significance differences exist. Statistical methods were reviewed assuming a significant level of $p < 0.05$.

RESULTS

The study included 105 patients who met the inclusion criteria. Forty-five patients [42.9%] received an injection of onabotulinumtoxinA only [group A] and 60 patients [57.1%] received a combined injection of onabotulinum toxin-A plus oral prophylactic medication [group B]. The mean age of the participants was 41.2±5.7 years and ranged from 35 to 55 years. Seventy women [66.7%] and 35 men [33.3%] were affected. A positive family history of migraine was reported by 58 patients [55.2%] and comorbidities were present in only 11 patients [10.5%], with no significant differences between the two groups [Table 1]. Neuroimaging was performed in 66 patients [62.9%] and showed positive findings in the form of nonspecific ischemic foci in 45 patients [68.2%], while 21 patients were negative [31.8%]. MDAT grading before treatment showed grade III in 64.8% of patients, grade IV in 27.6%, and grade II in 7.6%, with no patient having grade I. After treatment, about half of the patients had grade I, with significant improvement in both groups. Grade II increased in about 21% of patients, with a significant increase in group B. Grade III decreased in about 21% of patients, with a significant decrease in both groups. Grade IV decreased in about 7.6% of patients, with no patient in group B [Table 2]. The mean frequency of migraine days showed a significant reduction from 17.6±10.3 days per month to 7.2 ± 4.3 days after treatment in group B, while it showed a less significant reduction from 16.4 ±10.4 days per month to 9.1±2.4 days in group A. The mean frequency of seeking treatment per month and the mean duration of migraine attacks per hour were also significantly reduced in both groups after treatment, with a greater reduction in the mean duration of migraine attacks per hour in Group B. When comparing the effect of treatment on migraine frequency in both groups, patients in group B showed a significant improvement in mean frequency of migraine days per month and mean duration of migraine attacks per hour than patients in group A, but no significant difference in mean frequency of the use of acute treatment per month [Table 3]. In group B, 21 patients [35%] received amitriptyline alone, 15 patients [25%] received beta-blockers alone, 11 patients [18.3%] received topiramate alone, and 13 patients [21.7%] received a combination of two oral prophylactic medications. A significant reduction in the 3 outcome variables [the mean frequency of migraine days per month, the mean frequency of seeking acute treatment per month, and the mean duration of migraine attacks per hour] was observed in patients who received a combination of two oral prophylactic agents, followed by those who received amitriptyline [Table 4]. Only two patients developed transient ptosis [1.9%] and 6 patients had localized pain and numbness at injections [5.7%], while 10 patients had transient neck pain [9.5%] [Figure 1].

Table [1]: Demographics and comorbidities of the studied groups.

Variable		Total n=105 [%]	Group A n=45 [%]	Group B n=60 [%]	P-value
Age [years]	Mean ±SD	41.2 ± 5.7	40.8 ± 5.5	41.5 ± 5.9	0.375
Gender	Male	35 [33.3]	17 [37.8]	18 [30.0]	0.412
	Female	70 [66.7]	28 [62.2]	42 [70.0]	
Family history	Positive	58 [55.2]	26 [57.8]	32 [53.3]	0.695
	Negative	47 [44.8]	19 [42.2]	28 [46.7]	
Comorbidities	Positive	11 [10.5]	8 [17.8]	3 [5.0]	0.052
	Negative	94 [89.5]	37 [82.2]	57 [95.0]	

Values presented as the mean ± SD were analyzed by the Mann-Whitney U test; Values presented as numbers and percentages were analyzed by Fisher's exact test.

Table [2]: Migraine disability assessment test before and after treatment.

MDAT grade	Before treatment n=105 [%]	After treatment			P-value
		Group A n=45 [%]	Group B n=60 [%]	Total n=105 [%]	
I	0 [0.0]	17 [37.8] a	36 [60.0] a b	53 [50.5]	<0.001*
II	8 [7.6]	7 [15.5]	15 [25.0] a	22 [21.0]	0.009*
III	68 [64.8]	13 [28.9] a	9 [15.0] a	22 [21.0]	<0.001*
IV	29 [27.6]	8 [17.8]	0 [0.0] a b	8 [7.6]	<0.001*

Values presented as numbers and percentages were analyzed by Qui-square test; *: Significant, a: Significant with "before treatment", b: Significant with "Group A".

Table [3]: Migraine frequency before and after treatment.

	Group A		P-value a	Group B		P-value [a]	P-value [b]
	Before treatment	After treatment		Before treatment	After treatment		
Migraine [days/month]	16.4±10.4	9.1±2.4	<0.001*	17.6±10.3	7.2±4.3	<0.001*	0.009*
Using acute treatment/month	9.2±2.8	5.8±2.9	<0.001*	11.3±4.7	5.6±3.1	<0.001*	0.737
Duration of migraine attack /hour	18.1±6.6	10.5±4.6	<0.001*	18.4±5.7	8.3±4.8	<0.001*	0.020*

a: Comparing means within the same group before and after treatment were analyzed by Wilcoxon test; b: Comparing means between both groups after treatment were analyzed by Mann-Whitney U-test; *: Significant.

Table [4]: The use of oral prophylactic drugs and migraine incapacity test and migraine frequency.

Variable	Before treatment n=60	After treatment by				P-value
		Amitriptyline n=21	Beta blocker n=15	Topiramate n=11	> one oral prophylactic medication n=13	
Migraine [days/month]	17.6±10.3	6.6±4.2 a	8.2±4.1 a	10.2±4.9 a	4.5±2.1 a	<0.001*
Using acute treatment /month	11.3±4.7	5.2±3.0 a	5.6±2.1 a	8.3±4.1	3.8±1.9 a	<0.001*
Duration of migraine attack/hour	18.4±5.7	7.4±4.0 a	11.0±5.7 a	9.5±4.5 a	5.6±3.2 a	<0.001*

*: Significant, a: Significant with "before treatment".

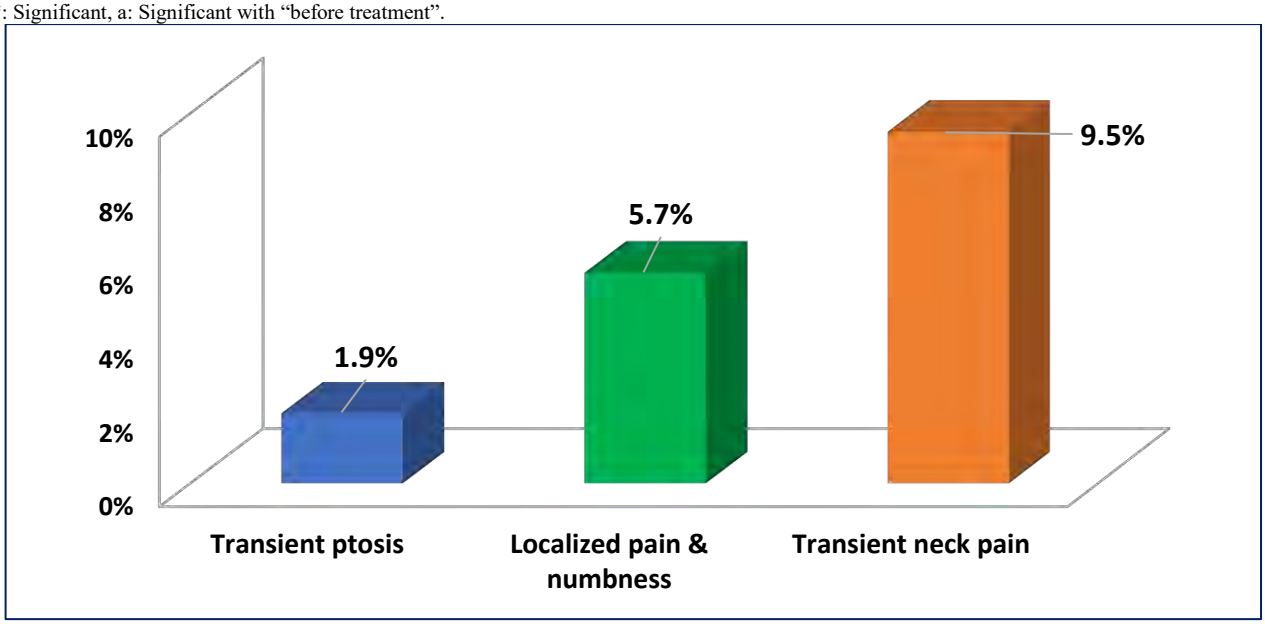

Figure [1]: Side effects of medications among the studied patients.

DISCUSSION

Chronic migraine can have a negative impact on quality of life, similar to cancer and arthritis. Chronic migraine patients are much more likely than patients with episodic migraine to miss work, school, leisure, household chores, and social activities. Chronic migraine also impairs performance, resulting in more than 50% loss of productivity at work or school. Chronic migraine is more disabling than blindness, paraplegia, angina, or rheumatoid arthritis and is on par with dementia and quadriplegia [18].

The mean age of participants in this study was 41.2±5.7 years, and 66.7 percent of them were female.

This is consistent with many studies showed that women are more likely to suffer from chronic migraine than men [24, 25]. Chronic migraine affects 1.89 percent of the demographic subgroup with the highest adjusted prevalence [women aged 40-49 years] [26].

In this study, neuroimaging was performed for 66 individuals [62.9 percent] and yielded positive results. This is consistent with the American Headache Society Systematic Review [10 studies examined the benefit of CT only, 9 examined MRI only, and 4 examined both for migraine]. On CT and MRI scans, the most common abnormalities were chronic ischemia or atrophy and nonspecific white matter lesions. Clinically severe abnormalities requiring intervention were rare [27].

This was one of the unique studies [may be the first study] in our field evaluating the efficacy of onabotulinum toxin-A injections as stand-alone prophylaxis and to compare it with the efficacy of other prophylactic drugs. Patients receiving onabotulinumtoxinA in combination with oral prophylactic medications had a significant reduction in the number of migraine days after treatment, whereas patients receiving onabotulinumtoxinA alone had a less significant reduction. After therapy, the mean number of migraine episodes per month and the mean duration of migraine attacks per hour were significantly reduced in both groups.

Many studies evaluating the efficacy of onabotulinum toxinA injections as a prophylactic medication for CM have found that onabotulinumtoxinA is not 100 percent effective in migraine prophylaxis. Many patients require other medications in addition to onabotulinumtoxinA to prevent migraine attacks [16,24,28,29]. OnabotulinumtoxinA was administered as prophylactic therapy to 77 of the 106 patients. Therapeutic benefit was assessed by patient self-report. Overall, 51% of those classified as true migraineurs showed a complete response, whereas 28% showed a partial response [30]. Treatment with 25 MU onabotulinumtoxinA reduced the number of monthly migraine attacks more effectively than placebo [31].

A statistically significant difference in the number of headaches during a 30-day period was found in a subgroup analysis of 228 people who were not receiving preventive medication at the time of enrollment in the study. The authors concluded that onabotulinumtoxinA was beneficial in treating patients with persistent daily headache who were not taking other associated prophylactic drugs [32]. OnabotulinumtoxinA was found to have a statistically significant effect in reducing migraine episodes in 86 individuals with chronic migraine who were not abusing medications [33].

On the other hand, an Italian double-blind study of 68 people with chronic migraine found no difference in headache days between onabotulinumtoxinA and placebo, but those treated with onabotulinumtoxinA used fewer acute analgesics [34]. To date, only two studies have compared onabotulinumtoxinA with other drugs that are useful in the prevention of chronic migraine. Magalhes *et al*. [35] found that onabotulinumtoxinA was as effective as amitriptyline in the prevention of chronic migraine, whereas Cady *et al*. [36] found that onabotulinumtoxinA was as effective as topiramate in the preventive treatment of CM. In addition, onabotulinumtoxinA has been shown to be effective in the treatment of chronic migraine in numerous studies [37, 38]. Several other studies in subsequent years have failed to show beneficial effects on chronic migraine, and the results of controlled clinical trials have been inconsistent [39, 40].

There is good evidence of efficacy for several medications. There is weak evidence for the superiority of amitriptyline over some other medications. Selection of prophylactic medications should be tailored to patient preferences, characteristics, and side effect profile. Patients with migraine and hypertension should consider a trial of a beta-blocker. Patients with depression may benefit from either a selective serotonin reuptake inhibitor [SSRI] or a tricyclic antidepressant [TCA]. Patients with restless leg syndrome or another indication for an anticonvulsant may benefit from topiramate or valproate. This has not been confirmed in the limited number of direct comparative effectiveness studies that have been conducted [41].

In this study, when comparing the effect of treatment on migraine frequency in both groups, patients in group B showed a significant improvement in the mean frequency of migraine days per month and the mean duration of migraine attacks per hour compared with patients in group A, but no significant difference in the mean frequency of use of acute treatment per month. Oral drug therapy or the combination of oral drug therapy and BOTOX-A injection improved both the Dizziness Handicap Inventory score and the Migraine Disability Assessment Scale and significantly reduced attack frequency in vestibular migraine patients. In addition, BTA use along with oral drug therapy significantly improved the Migraine Disability Assessment Scale and seizure frequency compared with oral drug therapy alone. The type of oral medication [propranolol, flunarizine, or amitriptyline] did not differ in terms of frequency of vestibular migraine attacks, increase in DHI score, and increase in MIDAS score [42].

Transient ptosis [2 cases], local discomfort and numbness on injection [6 cases], and transient neck pain [10 cases] were reported as side effects of onabotulinum toxinA injection in this study. Botulinum toxin-A side effects are almost always related to the injection; systemic side effects are extremely rare [43]. Injection-related side effects are usually moderate and transient and rarely lead to discontinuation of therapy. Neck pain [4.3 %], injection site pain [2.1 percent], eyelid spasms [1.9 percent], and muscle weakness [1.6 percent] were the most commonly reported side effects in studies [24]. Several clinical trials have demonstrated that onabotulinumtoxinA therapy is safe and effective [43, 44].

Study limitations: A single cross-section and small study population size without comparison of results with other approved medications for chronic migraine. These are limitations of this study that should be considered when interpreting the results.

Conclusion: OnabotulinumtoxinA injection is beneficial in the treatment of patients with chronic daily migraine. It improves quality of life by reducing the number and severity of migraine attacks per month. When combined with other preventive medications that are matched to patients' concurrent conditions, the effect is even greater.

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