

Onabotulinumtoxin A improves psychological aspects in chronic migraine patients

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Abstract

Background: Chronic migraine (CM) affects 5.4% of the Kuwaiti population. It is associated with significant headache-related disability, psychiatric comorbidity and reduces quality of life. The aim of this study is to assess the efficacy of OnabotulinumtoxinA on psychological aspects of chronic migraine patients.

Methods: 113 chronic migraineurs were identified in a tertiary headache center. Eligible patients met International Classification of Headache Disorders disorders-third edition, beta version (ICHD-III)Revision criteria for chronic migraine. They received 155 units of Onabotulinumtoxin A quarterly according to the Phase III Research Evaluating Migraine Prophylaxis Therapy Trail (PREEMPT) protocol. Patients received less than 4 injections cycles were excluded. Quality of life, the seven-item Generalized Anxiety Disorder (GAD-7) scores, the nine-item Patient Health Questionnaire (PHQ9), The Pittsburgh Sleep Quality Index (PSQI) were collected before injection and at last visit. Mean comparison tests were performed using the independent sample t test to assess the effects of onabotulinumtoxin A on quality of life, comorbid symptoms of anxiety, depression, and quality of sleep.

Results: This is retrospective study included 113 chronic migraine patients, with a mean age of 44.92+9.47years, mean disease duration 12.20 +10.10 years and a mean treatment duration 33.72 +43.14 months. At last visit, most of our cohort showed improvement in quality of life (81%), GAD-7 (81%), PHQ9 (79%), and PSQ1 (76%). The mean score of patient satisfaction was 7.21 +2.21. OnabotulinumtoxinA treatment for CM improved Quality of life significantly (72.92 +17.34 versus103.62 +15.62;P< 0.0001). It was also associated with significant reduction in GAD-7 (12.00 +4.40 versus 6.61 +4.40; P< 0.0001); PHQ-9 (17.91 +8.43 versus12.52 +8.77; P< 0.0001) scores and PSQI (12.60 +5.66 versus 6.66 +5.04; P< 0.0001) at last visit.

Conclusion: Prophylactic OnabotulinumtoxinA treatment for CM was associated with significant improvement of quality of life, reduction in symptoms of anxiety and depression, and improved associated symptoms of poor sleep.

Background

Migraine, a primary type of headache, is a common disabling disorder that can be divided into episodic and chronic migraine [1]. Global prevalence of migraine is 14.4%, 18.9% for females, and 9.8% (9.4–10.2) for males [2]. Global studies show that approximately 1.4–2.2% of the world's population may have chronic migraine [2]. One-year prevalence of migraine in Kuwait was 23% [3]. According to the latest Global Burden of Disease Study, headaches, including migraines, ranked second in the leading causes of disability showing the large burden of the disorder [4]. Migraine majorly affects the everyday lives of its sufferers, productivity, and schooling [5]. This burden is also increased by the comorbid psychiatric conditions that occur in association with it, including depression, anxiety, and sleep disorders. Large scale population-based studies showed that patients with migraine are 2.2 to 4.0 times more likely to have

depression [6]. Moreover, in those who have episodic migraine, depression was associated with an increased risk of developing chronic migraine [7]. The diagnosis of generalized anxiety disorder was significantly more prevalent in migraineurs than those without migraine [8]. Generalized anxiety disorder is often comorbid with major depressive disorder (MDD), and when taken into consideration, its presence attenuates the association between MDD and migraine, further increasing the burden [8].

Sleep also has been demonstrated to have a clear relationship with migraine. Chronic migraine patients reported shorter nightly sleep periods than those with episodic migraine, and they were more likely to exhibit trouble initiating sleep, staying asleep, and sleep triggering headache; Complaints of those insomnia-like symptoms were at least threefold greater in those patients than the incidence in the general population [9]. This shows the importance of management in migraine patients in the hope of decreasing this socioeconomic and medical burden. Therefore, patients with migraine and psychiatric co-morbidities may benefit from preventive therapy to reduce the attacks.

OnabotulinumtoxinA was approved as a prophylactic therapy in adult patients with chronic migraine by the United State Food and Drug Administration (FDA) in 2010 [10]. OnabotulinumtoxinA has been proven to reduce not only headache frequency but also meaningfully reduce symptoms of depression, anxiety, as well as poor sleep quality in migraine patients [11].

While OnabotulinumtoxinA is known to cause muscle paralysis, the exact mechanism by which it relieves chronic migraine is not clear, however, some evidence suggest it does so by reducing local nerve sensitization by local inhibition of neuropeptide release thus resulting in indirect reduction of central sensitization [12]. Neuropeptide calcitonin gene-related peptide (CGRP), which is known to be a major player in migraine, might be involved in regulating sleep maintenance at night [13, 14]. Therefore, OnabotulinumtoxinA treatment may help to improve sleep in migraine patients by repressing CGRP from activated sensory neurons and by directly decreasing the amount of CGRP released from trigeminal neurons [15].

Although we previously studied the socioeconomic burden of migraine in the Kuwaiti population, psychiatric comorbidities were not assessed [3]. And to our knowledge, no study to date has assessed those psychiatric co-morbidities in patients suffering from migraine in Kuwait. In this report, we hope to show the treatment effect on those conditions in chronic migraine patients who received OnabotulinumtoxinA injections.

Method

Study Design:

This A cross-sectional, questionnaire-based study was conducted in specialized headache clinic in tertiary hospital in Kuwait.

A total of four questionnaires were used to interview patients in order to collect the data for the study. The questionnaires used in the study include The Quality of Life (QOL) [16], Generalized Anxiety Disorder-7 (GAD-7) [17] The Pittsburgh Sleep Quality Index (PSQI) [18] and The Patient Health Questionnaires-9 (PHQ-9) questionnaires [19].

Participants:

Both males and females patients aged 18–65 years who are diagnosed with chronic migraine (CM) with or without medication over use headache (MOH). Diagnosis was confirmed by headache specialist according to International Classification of Headache Disorders III (ICHD-III) [1]

Patients with diagnosis of another headache disorder, pregnancy or breast feeding, previous use of any OnabotulinumtoxinA for treatment of any headache (at any time) or non-headache indication in the last year, and patients who not had completed at least three treatment cycles were excluded from the study.

Patients were injected intramuscularly with OnabotulinumtoxinA according to the PREEMPT protocol, 155 units injected into 31 injection sites around the head and neck every 3 months [10].

Outcomes:

Outcome measures included change in PHQ-9, GAD-7, PSQI and QOL from baseline. The patients were asked to answer abovementioned questionnaires twice, first before their treatment and the second after their treatment. The changes in the answers were compared to determine the effectiveness of the onabotulinumtoxinA treatment.

Improvement by ≥ 1 in severity category in the PHQ-9 or GAD-7 score from baseline was considered clinically meaningful improvement [20, 21]. Reduction by ≥ 3 -point in the total PSQI score was considered a clinically meaningful improvement [22].

Treatment satisfaction was assessed by numerical scale, 0 means no satisfaction at all and 10 means full satisfied.

The study was performed in observation of the latest version of the declaration of Helsinki [23] and all data were protected in accordance with the ethical guidelines of the Council for International Organizations of Medical Sciences [24].

Statistical Analysis:

Statistical analyses were performed with IBM SPSS Statistics 25.0 software for Mac (SPSS Inc., Chicago, IL, USA). All continuous variables were expressed as mean \pm SD, categorical ones were expressed as proportions and percentages. Paired sample t test was used to compare between PHQ-9, GAD-7, PSQI and QOL before and after treatment with OnabotulinumtoxinA. A significant difference was set to be at $p < 0.05$.

Results

This is cross-sectional study included 113 chronic migraine patients. Table 1 shows demographic and clinical characters of our cohort. The participants had mean age of 44.92 ± 9.47 years, mean disease duration 12.20 ± 10.10 years and a mean treatment duration 33.72 ± 43.14 months. At last visit, most of our cohort showed improvement in quality of life (81%), GAD-7 (81%), PHQ9 (79%), and PSQI (76%). Mean of treatment satisfaction was high.

The mean score of patient satisfaction was 7.21 ± 2.21 . OnabotulinumtoxinA treatment for CM improved QOL significantly (72.92 ± 17.34 versus 103.62 ± 15.62 ; $P < 0.0001$). It was also associated with significant reduction in GAD-7 (12.00 ± 4.40 versus 6.61 ± 4.40 ; $P < 0.0001$); PHQ-9 (17.91 ± 8.43 versus 12.52 ± 8.77 ; $P < 0.0001$) scores and PSQI (12.60 ± 5.66 versus 6.66 ± 5.04 ; $P < 0.0001$) at last visit (Table 2).

Table 1
Demographic and clinical Characters of chronic migraine patients (N = 131).

Variable	Mean \pm SD/No(%)
Age Range	44.92 ± 9.47 23–65
Gender • Female • Male	116 (88.5) 15 (11.5)
Disease Duration in years	12.20 ± 10.10
Disease Treatment in months	33.72 ± 43.14
Improvement of Psychological aspects with Onabotulinumtoxin A • QOL • GAD-7 • PHQ9 • PSQI	81 (61.8) 81 (61.8) 79 (60.3) 76 (58)
Satisfaction	7.21 ± 2.21

Quality of Life: QOL; Seven-item Generalized Anxiety Disorder: GAD-7, Patient Health Questionnaire: PHQ9, The Pittsburgh Sleep Quality Index: PSQI.

Table 2
Impact of Onabotulinumtoxin A on psychological aspect in
chronic migraine patients (N = 113)

Variables	Before treatment Mean ± SD	After treatment Mean ± SD	P
QOL	72.92 ± 17.34	103.62 ± 15.62	0.0001*
GAD-7	12.00 ± 4.40	6.61 ± 4.40	0.0001*
PHQ9	17.91 ± 8.43	12.52 ± 8.77	0.0001*
PSQI	12.60 ± 5.66	6.66 ± 5.04	0.0001*

Quality of Life: QOL; Seven-item Generalized Anxiety Disorder: GAD-7, Patient Health Questionnaire: PHQ9, The Pittsburgh Sleep Quality Index: PSQI.

Discussion

Migraine is a common neurological disease that can be very disabling to the patient and their families. It is associated with reduced quality of life and other psychiatric comorbidities [25]. Migraine primarily managed through three approaches: lifestyle and behavioral modification, acute therapy, and prophylactic therapy to reduce the frequency, severity, and duration of the attack and thus reducing the risk of medication overuse [26]. The United States FDA has approved onabotulinumtoxinA for the prophylactic treatment of chronic migraine in 2010 [10]. Its efficacy, safety and tolerability, proved by the largest migraine therapeutic trial PREEMPT [27].

Our analysis concluded that the majority of participants with chronic migraines were aged 45 years old on average, which is consistent with previous studies that people in this age group are most likely to be affected by chronic migraine [25,28]. It was also concluded that the majority of the participants were satisfied with their treatment. In addition, the study showed a significant improvement in the quality of life of patients with chronic migraine, which can be attributed to the successful migraine relief. This finding is similar to previous studies [27, 29]. The mechanism by which OnabotulinumtoxinA decrease the burden of the disease is not entirely known but it is theorized that OnabotulinumtoxinA works on the central and peripheral sensitization and injections in the trigeminally innervated craniofacial cervical region will block the peripheral sensitization by inhibiting the release of pain mediating peptide specifically at calcitonin gene related protein (CGRP) [30].

Also of note, anxiety and mood disorders have been shown to be closely associated with migraine [31, 32]. It is found that anxiety is 2–10 times more likely to affect migraineurs than the general population [31–33]. These psychiatric comorbidities may influence the prognosis of migraine as they have been associated with poorer quality of life, increased suicide risk, and a risk factor for progression of migraine from episodic to chronic [19, 31, 33]. These results showed that OnabotulinumtoxinA used for the

treatment of migraine helped with depression and anxiety in these patients as there was a significant improvement in the PHQ-9 and GAD questionnaires for depression and anxiety, respectively. This result was consistent with previous published studies [11, 34] that found that OnabotulinumtoxinA is associated with a reduction in the frequency and impact of migraine attacks and an improvement in the symptoms of depression and anxiety, for which the exact mechanism is not entirely clear; however, it may be attributed to either the placebo effect on headache and mood disturbances, or it can be due to the reduction of headaches, with a secondary reduction in depression and anxiety[34]. On the other hand there is some evidence that OnabotulinumtoxinA also can help in depression and anxiety independent of its effect of improvement of migraine [35, 36]. Therefore using OnabotulinumtoxinA in patient with chronic migraine and other psychological comorbidity maybe an excellent choice.

Moreover, Previous Studies have shown a significant association between migraine and sleep disturbances [37, 38]. As sleep disruption is common among migraine patients and can trigger a migraine attack [39]. The results of this study showed a significant reduction in the last visit compared to the first in the PSQI used to measure the quality and patterns of sleep. This is similar to the finding in a previous cross-sectional case control study that found PSQI scores increased with the increase in the frequency of migraine[39].

Conclusion

The study concluded that Onabotulinumtoxin A improves psychological aspects in chronic migraine patients, leading to improvements in the quality of life, anxiety symptoms, as well as sleep disturbances.

Strengths

First study has been conducted in Kuwait to study the association between Onabotulinumtoxin A use for treatment of chronic migraines and psychological aspects and symptoms in patients. Another strength is the appropriate sample size. Nevertheless, some limitations were identified.

Limitations

The limitations of the study are as follows: (1) the sample was chosen from the patient list in Ibn-Sina hospital, which may not completely represent all chronic migraines patients in Kuwait; (2) in addition, the study studied symptoms of psychiatric symptoms, whereas future studies can study specific diagnoses concluded by psychiatrists by applying Diagnostic and Statistical Manual of Mental Disorders (DSM-5), and then studying the specific improvements in the symptomatology and relating the improvements to the specific diseases.

Abbreviations

Calcitonin gene related protein
CGRP
Chronic migraine
CM
Diagnostic and Statistical Manual of Mental Disorders
DSM-5
Food and Drug Administration
FDA
International Classification of Headache Disorders III
ICHD-III
Major depressive disorder
MDD
Medication over use headache
MOH
Patient Health Questionnaire
PHQ9
Phase III Research Evaluating Migraine Prophylaxis Therapy Trial
PREEMPT
Quality of Life
QOL;
Seven-item Generalized Anxiety Disorder
GAD-7
The Pittsburgh Sleep Quality Index
PSQI.

Declarations

Our research was carried out according to ethical guidelines of Kuwait Ministry of Health.

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data

Data are available at administrative section, neurology department, Ibn Sina hospital, Kuwait.

Competing interests

No competing interests.

Funding

The study is not funded.

Authors' contributions

JA-H designed the study and reviewed the manuscript. HKh, OA, FAB, SM, SA performed data collection

and drafted the manuscript, DY and RA reviewed the manuscript performed data collection and drafted the manuscript. SFA performed statistical analysis, criticized and reviewed the manuscript. All authors read and approved the final manuscript.

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Conflicts of Interest

None declared.

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