



Clinical Evaluation of OnabotulinumtoxinA for the Management of Chronic Migraine in Tripoli, Libya (A Prospective Observational Study)

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التقييم السريري لفعالية توكسين البوتولينوم من النوع A (Onabotulinumtoxin A) في تدبير الصداع النصفي المزمن في طرابلس، ليبيا (دراسة رصدية مستقبلية)

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Abstract:

Background: Chronic migraine (CM) is a disabling neurological disorder characterized by frequent headache days and substantial impairment in daily functioning and quality of life. OnabotulinumtoxinA is an established preventive therapy for chronic migraine and is commonly administered according to the standardized Phase III Research Evaluating Migraine Prophylaxis Therapy (PREEMPT) protocol. The PREEMPT regimen uses fixed-site injections with a base dose of 155 Units administered across 31 injection sites, with treatment generally repeated at 12-week intervals, **Objective:** This study aimed to evaluate the clinical effectiveness, functional impact, and short-term tolerability of OnabotulinumtoxinA administered according to the PREEMPT protocol among patients with chronic migraine in Tripoli, Libya, **Methods:** A prospective observational study was conducted among 20 adult patients diagnosed with chronic migraine. Participants received 155 Units of OnabotulinumtoxinA distributed across 31 injection sites according to the PREEMPT protocol and were followed for 12 weeks. Clinical outcomes included Monthly Headache Days (MHD), acute medication-use days, Headache Impact Test-6 (HIT-6) scores, treatment response, Medication-Overuse Headache (MOH), and adverse effects. Statistical analysis was performed using SPSS, with paired-samples t-tests used to compare baseline and Week-12 measurements, **Results:** The mean number of MHD decreased from 21.1 ± 3.2 days at baseline to 9.95 ± 2.8 days at Week 12, representing a mean reduction of 11.15 days ($t(19)=14.32$, $p<0.0001$). Acute medication-use days decreased from 15.4 ± 3.7 to 4.85 ± 2.1 days/month, with a mean reduction of 10.55 days ($t(19)=11.84$, $p<0.0001$). Mean HIT-6 scores decreased from 66.5 ± 4.1 to 50.3 ± 5.2 points, representing a mean reduction of 16.2 points ($t(19)=13.51$, $p<0.0001$). Overall, 16 participants (80%) achieved at least a 50% reduction in MHD. Among the 13 participants who met the study's baseline criteria for MOH, all no longer met those operational criteria at Week 12. Treatment was generally well tolerated; 11 participants (55%) reported no

adverse effects, while reported adverse events were mild, localized, and transient, **Conclusion:** In this small real-world cohort, OnabotulinumtoxinA administered according to the PREEMPT protocol was associated with substantial reductions in headache frequency, acute medication use, and headache-related disability over 12 weeks. The treatment demonstrated a generally favorable short-term tolerability profile. However, the small sample size, absence of a control group, and short follow-up period limit causal inference and generalizability. Larger controlled multicenter studies are warranted in the Libyan healthcare setting.

Keywords: Chronic migraine; OnabotulinumtoxinA; Botulinum toxin type A; PREEMPT protocol; Monthly Headache Days; HIT-6; Medication-Overuse Headache; Libya.

المخلص

الخلفية: الشقيقة المزمنة (CM) هي اضطراب عصبي موهن يتسم بتكرار نوبات الصداع والتأثير السلبي الأداء اليومي. يُعد الحقن بعقار أونابوتولينومتكسين أ وفق بروتوكول PREEMPT الموحد (155 وحدة موزعة على 31 موضعاً محدداً) استراتيجية وقائية معتمدة. **الهدف:** تقييم الفعالية السريرية والأثر الوظيفي والمأمونية قصيرة المدى لعقار أونابوتولينومتكسين أ باتتباع بروتوكول PREEMPT لدى المرضى البالغين المصابين بالشقيقة المزمنة في طرابلس، ليبيا. **المنهجية:** أجريت دراسة رصدية استطلاعية على 20 مريضاً بالغاً تم تتبعهم لمدة 12 أسبوعاً بعد تلقي العلاج. شملت المخرجات السريرية: عدد أيام الصداع شهرياً (MHD)، أيام استخدام أدوية المعالجة الحادة، درجات مقياس أثر الصداع (HIT-6)، مدى انحسار الصداع الناتجة عن الإفراط في استخدام الأدوية (MOH)، معدل الاستجابة للعلاج (انخفاض MHD بنسبة $\leq 50\%$)، والآثار الجانبية. أجريت التحليلات الإحصائية باستخدام اختبار (t) للعينات المزدوجة. **النتائج:** في الأسبوع 12، انخفض متوسط MHD بشكل ملحوظ من 21.1 ± 3.2 يوماً إلى 9.95 ± 2.8 يوماً (بمتوسط انخفاض قدره 11.15 ± 14.32 ، $t(19) = 14.32$ ، $p < 0.0001$). وانخفضت أيام استخدام أدوية المعالجة الحادة من 15.4 ± 3.7 إلى 4.85 ± 2.1 يوماً/شهر (بمتوسط انخفاض 10.55 يوماً، $t(19) = 11.84$ ، $p < 0.0001$). كما انخفض متوسط درجات HIT-6 من 66.5 ± 4.1 إلى 50.3 ± 5.2 (بمتوسط انخفاض 16.2 نقطة، $t(19) = 13.51$ ، $p < 0.0001$). حقق 16 مشاركاً (80%) استجابة علاجية ($\geq 50\%$) انخفاض في (MHD) وعلاوة على ذلك، أظهر جميع المشاركين الـ 13 المصابين بالصداع الناتج عن الإفراط في استخدام الأدوية تحسناً كاملاً وعدم استيفاء المعايير الإجرائية للمرض عند الأسبوع 12. أظهر العلاج مأمونية جيدة؛ حيث كانت الآثار الجانبية خفيفة وموضعية وعابرة. **الخلاصة:** أدى العلاج بعقار أونابوتولينومتكسين أ وفق بروتوكول PREEMPT إلى تحسن جوهري في تكرار الصداع، واستهلاك الأدوية الحادة، والإنهاك الوظيفي، مع سجل مأمونية ممتاز على مدى 12 أسبوعاً. يُوصى بإجراء دراسات موسعة ومضبوطة لتأكيد هذه النتائج الرصدية.

الكلمات المفتاحية: الشقيقة المزمنة؛ أونابوتولينومتكسين أ؛ بروتوكول PREEMPT؛ أيام الصداع الشهرية؛ مقياس أثر الصداع HIT-6؛ الصداع الناتج عن الإفراط في استخدام الأدوية؛ طرابلس؛ ليبيا.

1. Introduction

Chronic migraine is a disabling neurological condition associated with frequent headache attacks, impaired physical and psychosocial functioning, and substantial healthcare utilization. Patients with chronic migraine experience headache on at least 15 days per month for more than three months, with migraine features occurring on a substantial proportion of these days. Persistent activation of the trigeminovascular system and sensitization of peripheral and central pain pathways contribute to the transformation from episodic to chronic migraine. The pathophysiology of migraine involves complex interactions between trigeminal sensory pathways, neuropeptides, vascular structures, and central pain-processing networks. Calcitonin gene-related peptide (CGRP) has an important role in trigeminovascular nociceptive transmission and migraine pathophysiology.

Medication overuse may further complicate chronic migraine. Frequent use of acute headache medications can contribute to medication-overuse headache, creating a cycle of recurrent headache and increasing reliance on rescue medications. In the present study, 13 of 20 participants (65%) met the study's baseline operational criteria for MOH.

OnabotulinumtoxinA has become an established preventive treatment for chronic migraine. Its clinical efficacy was demonstrated in the large PREEMPT clinical program, in which patients received 155–195 Units every 12 weeks.

The standard fixed-site regimen consists of 155 Units administered at 31 sites, with an optional additional dose when clinically indicated.

At the molecular level, botulinum neurotoxin type A cleaves SNAP-25, a protein involved in synaptic vesicle release. In migraine, the therapeutic effect is thought to involve inhibition of the release of several pain-related neuropeptides and neurotransmitters from peripheral sensory nerve terminals, including CGRP. This mechanism may reduce peripheral nociceptive input and subsequently influence central sensitization.

Evidence from the PREEMPT program demonstrates that OnabotulinumtoxinA can produce clinically meaningful reductions in headache frequency and disability. In pooled PREEMPT analyses, repeated treatment was associated with sustained reductions in headache and migraine days, while the overall safety profile remained favorable.

Furthermore, subgroup analyses have demonstrated benefit among patients with medication overuse. In the PREEMPT population, OnabotulinumtoxinA was associated with significantly greater reductions in headache days and other headache-related outcomes among patients with acute medication overuse compared with placebo.

Despite the established international evidence, locally generated clinical data concerning OnabotulinumtoxinA treatment for chronic migraine in Libya remain limited. Therefore, the present study was designed to provide preliminary real-world evidence concerning the clinical response, headache-related disability, acute medication use, and short-term safety of OnabotulinumtoxinA in a cohort of patients treated in Tripoli.

2. Materials and Methods

2.1 Study Design and Setting

A prospective observational study was conducted among adult patients with chronic migraine receiving OnabotulinumtoxinA treatment in Tripoli, Libya. The observation period extended for 12 weeks following treatment.

The study was designed as a real-world clinical evaluation rather than a randomized controlled trial. Accordingly, the results were interpreted as changes observed within the treated cohort and not as definitive evidence of treatment causality.

2.2 Study Population

The study included **20 adult patients with chronic migraine** who fulfilled the study eligibility criteria and received OnabotulinumtoxinA according to the PREEMPT protocol.

The baseline cohort demonstrated a substantial disease burden. The mean baseline MHD was 21.1 ± 3.2 days/month, mean acute medication use was 15.4 ± 3.7 days/month, and mean HIT-6 score was 66.5 ± 4.1 . In addition, 13 participants (65%) had baseline MOH according to the study criteria.

2.3 Intervention

Participants received a total base dose of **155 Units of OnabotulinumtoxinA**, administered across **31 fixed injection sites** according to the PREEMPT protocol. The dose distribution included the frontalis, corrugator, procerus, temporalis, occipitalis, cervical paraspinal, and trapezius muscle groups.

The documented protocol was:

Muscle group	Dose	Injection sites
Frontalis	20 U	4
Corrugator	10 U	2
Procerus	5 U	1
Temporalis	40 U	8
Occipitalis	30 U	6
Cervical paraspinal	20 U	4
Trapezius	30 U	6
Total	155 U	31 sites

The PREEMPT paradigm is consistent with the established international protocol of 155 Units across 31 sites, with an optional additional dose when clinically indicated.

2.4 Outcome Measures

The following outcomes were assessed at baseline and Week 12:

1. **Monthly Headache Days (MHD).**
2. **Acute medication-use days per month.**
3. **HIT-6 score.**
4. **Clinical treatment response.**
5. **Medication-Overuse Headache (MOH).**
6. **Treatment-related adverse effects.**

HIT-6 was used to quantify the impact of headache on daily functioning. The instrument was administered before treatment and at the end of the 12-week observation period.

2.5 Definition of Clinical Response

Clinical response was defined as achieving a **≥50% reduction in MHD from baseline** at Week 12.

This endpoint was selected because a reduction of at least 50% in headache frequency is commonly used as a clinically meaningful response criterion in preventive migraine research. PREEMPT analyses have similarly evaluated ≥50% reductions in headache days as an important treatment-response measure.

2.6 Statistical Analysis

Data were analyzed using SPSS. Continuous variables were summarized using means and standard deviations. Baseline and Week-12 values were compared using paired-samples t-tests. Statistical significance was set at **p<0.05**.

3. Results

3.1 Baseline Clinical Characteristics

The cohort demonstrated a substantial headache burden before treatment.

Table 1: Baseline Clinical Characteristics of Enrolled Patients (n = 20)

Variable	Baseline Mean ± SD
Monthly Headache Days	21.1 ± 3.2
Acute medication-use days/month	15.4 ± 3.7
HIT-6 score	66.5 ± 4.1
Baseline MOH	13/20 (65%)

The baseline MHD substantially exceeded the threshold used to define chronic migraine, while the mean HIT-6 score was within the severe-impact range.

3.2 Changes in Clinical Outcomes After 12 Weeks

A marked improvement was observed across all three principal continuous outcomes.

Table 2: Clinical Outcome Metrics Before and 12 Weeks After OnabotulinumtoxinA Treatment

Outcome	Baseline	Week 12	Mea Change	p-value
MHD	21.1 ± 3.2	9.95 ± 2.8	−11.15	<0.0001
Acute medication days/month	15.4 ± 3.7	4.85 ± 2.1	−10.55	<0.0001
HIT-6	66.5 ± 4.1	50.3 ± 5.2	−16.2	<0.0001

The paired-samples t-test demonstrated statistically significant reductions in MHD, acute medication use, and HIT-6 scores. Specifically, $t(19)=14.32$ for MHD, $t(19)=11.84$ for acute medication use, and $t(19)=13.51$ for HIT-6, all with $p<0.0001$.

3.3 Treatment Response

At Week 12, 16 of 20 participants (80%) achieved the predefined $\geq 50\%$ reduction in MHD and were classified as responders. Four participants (20%) were classified as non-responders.

The individual post-treatment data showed that the four non-responders were PT-12, PT-15, PT-18, and PT-20.

3.4 Medication-Overuse Headache

Thirteen participants (65%) met the study's baseline operational criteria for MOH. At Week 12, all 13 were reported as no longer meeting those criteria, corresponding to a 100% observed resolution rate within the affected subgroup.

This result should nevertheless be interpreted cautiously because the study did not provide sufficient detail to fully separate the effect of OnabotulinumtoxinA from medication withdrawal or reduction strategies.

3.5 Headache-Related Disability

Mean HIT-6 scores decreased from 66.5 ± 4.1 at baseline to 50.3 ± 5.2 at Week 12, representing a mean reduction of 16.2 points.

The paired-samples t-test showed a statistically significant difference, $t(19)=13.51$, $p<0.0001$. The magnitude of this reduction is clinically important because the observed change exceeded the commonly used threshold for meaningful improvement in HIT-6 scores.

3.6 Safety and Tolerability

Treatment was generally well tolerated.

Table 3: Summary of Adverse Events (n = 20)

Adverse effect	n	%
No adverse effects	11	55%
Mild injection-site pain	3	15%
Neck stiffness/weakness	2	10%
Mild headache	2	10%
Injection-site erythema	1	5%
Mild ptosis	1	5%
Total	20	100%

The reported adverse effects were predominantly mild, localized, and transient. The documented case of mild ptosis resolved within three weeks.

4. Discussion

The present prospective observational study evaluated the short-term clinical effectiveness and tolerability of OnabotulinumtoxinA administered according to the PREEMPT protocol in 20 patients with chronic migraine in Tripoli, Libya. The principal findings were substantial reductions in headache frequency, acute medication use, and headache-related disability, accompanied by a high proportion of patients achieving the predefined $\geq 50\%$ reduction in MHD.

The most important finding was the reduction in MHD from 21.1 ± 3.2 to 9.95 ± 2.8 days/month, corresponding to a mean reduction of 11.15 days. The difference was statistically significant, $t(19)=14.32$, $p<0.0001$.

The direction of this finding is consistent with the established evidence for OnabotulinumtoxinA. The PREEMPT clinical program demonstrated significant reductions in headache days among patients receiving OnabotulinumtoxinA compared with placebo, and subsequent analyses demonstrated sustained benefit with repeated treatment.

However, the magnitude of the reduction observed in the present study appears numerically larger than that reported in some randomized controlled trials. This difference should not be interpreted as evidence of superior efficacy because the present investigation included only 20 patients and did not have a placebo or untreated comparison group. Regression to the mean, patient adherence, changes in acute medication use, behavioral changes, and other factors may have contributed to the observed improvement.

The 80% responder rate represents another clinically important finding. Sixteen of the 20 participants achieved at least a 50% reduction in MHD. Although this rate is favorable, it should be interpreted in the context of the small sample and observational design. In the PREEMPT program, response accumulated across treatment cycles, with some patients who did not respond during the first cycle responding during subsequent cycles.

A second important finding was the reduction in acute medication use, from 15.4 ± 3.7 to 4.85 ± 2.1 days/month. This reduction is particularly relevant because excessive acute medication use is closely associated with MOH. The PREEMPT program has previously demonstrated benefit from OnabotulinumtoxinA among patients with chronic migraine and medication overuse.

The observed resolution of MOH in all 13 affected participants is encouraging but requires cautious interpretation. The present study itself recognizes that insufficient information was available concerning the specific medication withdrawal or reduction strategies applied to these patients. Therefore, the 100% resolution rate should be described as an observed clinical outcome, rather than being attributed exclusively to the pharmacological action of OnabotulinumtoxinA.

The reduction in HIT-6 from 66.5 ± 4.1 to 50.3 ± 5.2 provides evidence that improvement extended beyond headache frequency to patient-perceived functional burden. The 16.2-point mean reduction was statistically significant and clinically substantial.

The safety findings were also favorable. More than half of the cohort reported no adverse effects, and the remaining adverse effects were mild and transient. This pattern is broadly consistent with published clinical experience, in which local pain, neck symptoms, and other transient treatment-related events have been reported without major new safety signals.

The findings therefore provide preliminary evidence that implementation of a standardized PREEMPT-based treatment approach is feasible in a Libyan clinical setting. The study is particularly relevant because localized evidence regarding the real-world use of OnabotulinumtoxinA for chronic migraine in Libya remains limited.

Nevertheless, the results should not be overinterpreted. The absence of a control group prevents determination of the proportion of improvement attributable specifically to OnabotulinumtoxinA. The small sample size limits statistical generalizability, while the 12-week observation period does not permit assessment of long-term treatment retention, cumulative efficacy, or long-term safety. These limitations are explicitly recognized in the source study.

5. Strengths and Limitations

5.1 Strengths

The main strengths of the study include:

- Prospective collection of clinical outcomes.
- Use of the standardized 155-U PREEMPT protocol.
- Assessment of multiple clinically relevant outcomes rather than headache frequency alone.
- Inclusion of MHD, acute medication use, HIT-6, MOH, treatment response, and adverse effects.
- Use of paired statistical analysis to evaluate within-patient changes.
- Provision of preliminary real-world evidence from a Libyan clinical population.

5.2 Limitations

Several limitations must be considered.

First, the sample size was small ($n=20$), limiting generalizability to the broader Libyan population.

Second, there was no control group, making it impossible to distinguish the pharmacological treatment effect from placebo effects, regression to the mean, behavioral changes, or other concurrent factors.

Third, follow-up was limited to 12 weeks, preventing evaluation of repeated treatment cycles and long-term efficacy and safety.

Fourth, the study was conducted within a local clinical setting, and differences in patient characteristics and healthcare access may limit generalization.

Fifth, the observed 100% resolution of MOH among the 13 affected participants should be interpreted cautiously because the documentation does not provide sufficient detail regarding medication-withdrawal strategies.

Finally, age-stratified response rates were based on very small subgroups and should therefore be regarded as exploratory rather than definitive.

6. Conclusion

This prospective observational study provides preliminary real-world evidence concerning the use of OnabotulinumtoxinA for chronic migraine in Tripoli, Libya.

Administration of 155 Units according to the PREEMPT protocol was associated with substantial improvement over 12 weeks. MHD decreased from 21.1 ± 3.2 to 9.95 ± 2.8 days/month, acute medication use decreased from 15.4 ± 3.7 to 4.85 ± 2.1 days/month, and HIT-6 scores decreased from 66.5 ± 4.1 to 50.3 ± 5.2 points. All three changes were statistically significant at $p<0.0001$.

Furthermore, 80% of participants achieved at least a 50% reduction in MHD, while treatment was generally well tolerated, with 55% reporting no adverse effects.

Overall, the findings support the feasibility and potential clinical usefulness of OnabotulinumtoxinA for chronic migraine within the studied Libyan clinical setting. However, the findings should be considered preliminary because of the small sample size, absence of a comparator group, and short follow-up.

7. Recommendations

1. Larger prospective multicenter studies should be conducted across different Libyan healthcare institutions.
2. Future investigations should include randomized or matched control groups whenever ethically and practically feasible.
3. Follow-up should extend over multiple 12-week treatment cycles to evaluate cumulative efficacy and long-term safety.
4. MOH should be assessed using standardized diagnostic criteria and clearly documented medication-withdrawal strategies.
5. Future studies should evaluate additional patient-centered outcomes, including migraine-specific quality of life and work productivity.
6. Standardized documentation of injection technique, dose, treatment intervals, and adverse events should be maintained.
7. Comparative studies between OnabotulinumtoxinA and newer preventive therapies, including CGRP-targeted therapies, would be valuable in the Libyan context.
8. Establishing local clinical registries for chronic migraine could improve monitoring of treatment effectiveness and safety.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare that they have no conflict of interest.

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