Botulinum toxin and/or Greater Occipital Nerve Block for Patients with Chronic Migraine

Thesis Submitted for Partial Fulfillment of Master Degree in Neurology

Prepared by

Rakia Mohamed Taha Basiouny

(M.B.B.CH)

Faculty of Medicine - October 6 University

Under supervision of

Dr. Amr Hassan Al Sayed

Professor of Neurology

Kasr Al Ainy Faculty of Medicine – Cairo University

Dr. Mona Hussein Tawfik

Professor of Neurology

Faculty of Medicine - Beni-Suef University

Dr. Mona Ali Abosrea

Lecturer of Neurology

Faculty of Medicine - Beni-Suef University

Faculty of Medicine

Beni-Suef University

2026

Official Title: Botulinum Toxin and/or Greater Occipital Nerve Block for Patients With Chronic Migraine

Protocol ID: RakiaBasiouny97$

Date: April 2026

NCT Number: Not yet assigned

Introduction

Chronic migraine (CM) is a highly disabling neurological disorder affecting approximately 1–2% of the global population and about 8% of individuals with migraine **(Global Burden of Disease Collaborators, 2017; Karaoğlan et al., 2022).** The consequences of CM extend beyond pain, imposing substantial functional, psychological, and socioeconomic challenges. Individuals with CM usually experience significant impairments in daily functioning, reduced health-related quality of life, and diminished productivity **(Serrano et al., 2013; Ford et al., 2021).** The condition contributes to considerable healthcare costs, emphasizing the need for effective preventive therapeutic strategies **(Bonafede et al., 2018).**

Management of CM is multifaceted, encompassing acute, preventive, and non-pharmacologic strategies. Acute therapies, including triptans and nonsteroidal anti-inflammatory drugs (NSAIDs), are often limited by medication overuse, which itself is a risk factor for chronification **(Bigal & Lipton, 2009)**. Preventive pharmacotherapy includes beta-blockers, anticonvulsants (e.g., topiramate), tricyclic antidepressants, and more recently, monoclonal antibodies targeting the CGRP pathway **(Schwedt, 2018).** Non-pharmacologic strategies such as cognitive-behavioral therapy (CBT), biofeedback, and relaxation training are increasingly recognized as essential adjuncts in CM management. Lifestyle modifications including avoidance of migraine triggers, adequate sleep hygiene, good hydration, and dietary regulation further support headache prevention (**Meise et al., 2022**).

OnabotulinumtoxinA (BoNT-A) is an established prophylactic therapy for CM. Its proposed mechanism involves inhibition of peripheral nociceptive input and attenuation of central sensitization **(Gazerani et al., 2006).** The PREEMPT clinical trials demonstrated significant reductions in headache frequency and sustained improvement in quality of life following treatment with BoNT-A,

leading to regulatory approval of BoNT-A for CM prevention **(Diener et al., 2010; Aurora et al., 2011).**

Greater occipital nerve block (GONB) is another therapeutic approach used in chronic migraine and other headache disorders. By targeting the sensory innervation of the occipital region, GONB can provide rapid pain relief and short-term reduction in migraine burden **(Diener et al., 2012).** However, the duration of benefit is often limited to days or weeks, and standardized protocols remain lacking due to scarce high-quality randomized trials **(Ashkenazi & Levin, 2007; Sun-Edelstein et al., 2016).**

Despite strong evidence supporting BoNT-A and emerging evidence for GONB in chronic migraine, no high-quality randomized controlled trials have directly compared combination therapy versus BoNT-A alone and GONB alone. Existing studies focus on each treatment independently, and the potential synergistic effect of the two therapeutic approaches remains insufficiently evaluated. This creates an important clinical gap regarding whether combination therapy offers superior benefit to monotherapy.

Given the rapid but transient effect of GONB and the slower onset but sustained effect of BoNT-A, we hypothesize that combination therapy with BoNT-A and GONB will result in immediate and prolonged reduction in monthly migraine days and improved patient-reported outcomes compared with either BoNT-A alone or GONB alone.

Aim of the work:

The main objective of this study is to compare the efficacy, patient-reported outcomes, and safety of three therapeutic approaches for treatment of chronic migraine, Onabotulinumtoxin A (BoNT-A) combined with a greater occipital nerve block (GONB), BoNT-A monotherapy, and GONB monotherapy.

Patients and Methods

Study design:

This prospective, randomized, assessor-blinded, controlled trial will include 90 patients diagnosed with chronic migraine. Participants will be randomly assigned to one of three treatment groups: Group 1 (n = 30) will receive BoNT-A combined with GONB; Group 2 (n=30) will receive BoNT-A alone; and Group 3 (n = 30) will receive a GONB alone.

Randomization will be performed using a computer-generated allocation sequence. Block randomization will be employed to ensure balanced allocation across the groups throughout the enrollment period. Randomization sequence will be generated by an independent investigator who is not involved in participant recruitment, clinical evaluation, intervention administration, or data analysis. Allocation concealment will be maintained using sequentially numbered, opaque, sealed envelopes (SNOSE), This procedure minimizes selection bias and preserves the integrity of the randomization process.

Given the nature of the study, blinding of participants and treating clinicians is not feasible. However, to minimize detection bias, all outcome assessments will be performed by an independent investigator who will remain blinded to group allocation. In addition, the data analyst will be blinded to treatment assignments until completion of the primary statistical analysis, thereby preserving objectivity in data interpretation.

The patients will be recruited from Neurology Clinic Beni-Suef University hospital during the period from January 2026 to January 2027.

Inclusion criteria:

1. Diagnosis of chronic migraine according to the International Classification of Headache Disorders, 3rd edition (ICHD-3): headache occurring on ≥15 days per month for more than three months, with at least 8 days per month exhibiting migraine features. **(International Headache Society, 2013)**
2. Age > 18 years
3. Stable preventive migraine regimen for at least two months prior to recruitment

Exclusion criteria:

1. Co-morbid other
2. Prior treatment with BoNT-A or GONB for headache within the previous 3 months.
3. Known hypersensitivity to BoNT-A or local anesthetics.
4. Cervical anatomical abnormalities that hinder proper localization of injection sites or compromise the safety of the procedure
5. Neuromuscular junction disorders (e.g., myasthenia gravis).
6. Coagulation disorders or anticoagulant therapy that contraindicates nerve block.
7. Significant psychiatric comorbidity that would impair proper pre and post treatment assessment.
8. Pregnancy.

Clinical assessment

The patients will be subjected to a comprehensive headache assessment through face-to-face interviews with a neurologist who will be blinded to the type of intervention:

1) **History taking focusing on:** age, sex, disease duration, the presence of aura, allodynia, autonomic manifestations, and the current preventive migraine medications.
2) **Headache diary (at baseline and at one and three months after receiving treatment):** It includes monthly migraine days (MMD) and monthly days with acute analgesics.
3) **The Arabic version of Headache Impact (HIT-6) (Hussein et al., 2024):** It will be performed for all included patients at baseline and at one and three months after receiving treatment. It is a six-item scale that assesses the impact of headache on daily activities, psychological well-being, and social life, in addition to assessment of severity of pain, attention, and fatigue. Each item is rated using five responses (always, very often, sometimes, never, or rarely) **(Kosinski et al., 2003).** The total score ranges from 36 to 78, with higher scores indicating more severe headache **(Gandek et al., 2003).**

4) **The 12-item Allodynia Symptom Checklist (ASC-12):** It will be performed for all included patients at baseline and at one and three months after receiving treatment. It is a validated instrument used to assess the presence and severity of cutaneous allodynia in patients with migraine. It includes 12 questions that evaluate the frequency with which patients experience pain or unpleasant sensations during everyday activities such as brushing hair, wearing glasses, resting the head on a pillow, exposure to heat or cold, or light touch. Each item is scored based on how often the symptom occurs, allowing calculation of a total score that classifies allodynia as absent, mild, moderate, or severe **(Lipton et al., 2008)**.

5) **The Migraine interictal burden scale (MIBS-4):** It will be performed for all included patients at baseline and at one and three months after receiving treatment. It is a brief, validated tool designed to assess the burden experienced by patients between migraine attacks, capturing the often-overlooked interictal impact of the disorder. The scale evaluates four key domains: the effect of headaches on work or school performance, difficulties in planning or participating in social and leisure activities, the overall interference of migraine with daily life, and the emotional or affective toll experienced during headache-free intervals. Each of the four items is self-administered and scored based on frequency of impact, providing a clear and concise measure of interictal disability. The minimum score that can be obtained from the scale is 0, scores of 1–2 indicate mild burden, scores of 3–4 indicate moderate burden, and scores above 5 indicate severe interictal burden **(Buse et al., 2007).**

6) **The patient's global impression of change (PGIC):** It will be performed for all included patients at one and three months after receiving treatment. It is a widely used, outcome measure that provides a holistic assessment of perceived improvement or deterioration following treatment. It consists of a single, straightforward question in which patients rate the overall change in their condition compared with a specified baseline. It captures multiple dimensions of health, including symptom severity, functional limitations, emotional well-being, and overall quality of life, making it a valuable complement to more domain-specific scales. It is typically scored using a 7-point Likert scale, where patients rate the overall change in their condition compared with baseline. The response options range from "very much improved" to "very much worse" **(Diener et al., 2019).**

7) **Short Assessment of Patient Satisfaction (SAPS) scale:** It will be performed for all included patients at one and three months after receiving treatment. It consists of the following seven items: satisfaction with treatment, explanation of the treatment outcome, medical care, respect by the physician, participation in medical decision making, time with the physician, and satisfaction with clinic/ hospital care. Responses scales are 5-point scales. SAPS scores were interpreted as follows: 0 -10 = very dissatisfied, 11 - 18 = dissatisfied, 19 - 26 = satisfied, and 27 - 28 = very satisfied **(Yellen et al., 2002).**

Interventions

- **Group (1): Combination therapy (BoNT-A + GONB)**

BoNT-A:

- ✓ Administered following the PREEMPT protocol for migraine **(Aurora et al., 2010).**
- ✓ Total dose: 155–195 units, distributed across standard injection sites including the frontal, temporal, occipital, cervical, and trapezius regions.
- ✓ Injection technique: Intramuscular, as per established PREEMPT guidelines.

GONB:

- ✓ Administered bilaterally immediately after BoNT-A injections at baseline.
- ✓ Medication: Lidocaine 1% - 2%, 1- 2 mL per side.
- ✓ Technique: Targeted infiltration at the greater occipital nerve region, ensuring accurate delivery while minimizing risk of local complications.

- **Group (2): BoNT-A monotherapy**

  BoNT-A injections as above (at baseline).

- **Group (3): GONB monotherapy**

  Bilateral GONB with Lidocaine as above (at baseline).

Outcome

- **Primary outcome**

1. **Responder rate:** Proportion of participants achieved a ≥50% reduction in MMDs at one and three months after receiving treatment.

- **Secondary outcomes**

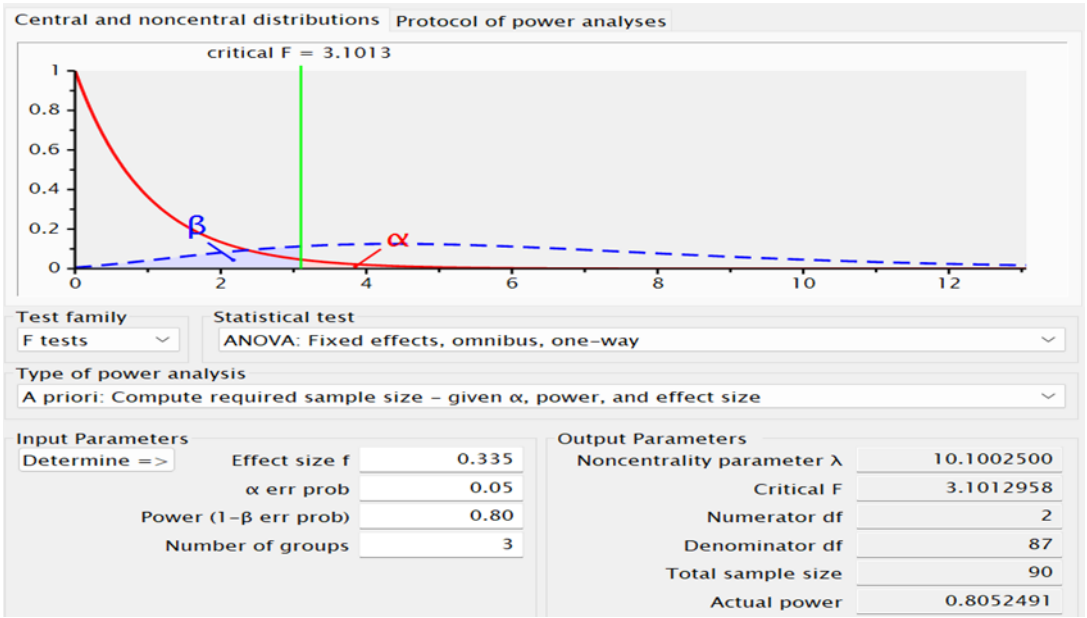
1. **Time to first clinically meaningful response:** Duration until participants achieve 30% decrease in MMDs. This threshold aligns with established IMMPACT recommendations for defining clinically meaningful improvement in chronic pain and migraine trials **(Dworkin et al., 2008).**
2. **Changes in patient-reported outcomes:** Differences from baseline in the total scores of HIT-6, ASC-12, and MIBS at one and three months after receiving treatment.
3. **Acute medication use**: Variation in frequency and dosage of acute migraine treatments at one and three months after receiving treatment compared to baseline.
4. **Patient-perceived improvement:** Assessment of overall improvement using PGIC and SAPS scales at one and three months after receiving treatment.
5. **Safety and tolerability:** Incidence and severity of adverse events, both local and systemic.

Ethical considerations

Written informed consent will be obtained from the participants. Data will be confidential and anonymous. Administrative approvals will be sought from the head of selected facilities. Ethical approval will be sought from ethics committee, faculty of medicine, Beni-Suef University.

Sample Size

The sample size for this randomized controlled trial was calculated using GPower. A one-way ANOVA (fixed effects, omnibus) was selected to compare the primary outcome across the three study groups. Using an effect size of f = 0.335, a significance level of α = 0.05, and statistical power of 80%, with three parallel groups, the minimum required total sample size was 90 participants. This corresponds to 30 participants per group, as shown by the GPower output (noncentrality parameter λ = 10.10, numerator df = 2, denominator df = 87, actual power = 0.805). This sample size ensures adequate power to detect clinically meaningful differences between the intervention arms.



Statistical analysis

IBM SPSS (Statistical Package of Social Science) Version 25 will be used to analyze the data. Kolmogorov–Smirnov test will be used to test the normality of data. Categorical variables will be expressed as numbers and percentages. Non-normally distributed quantitative variables will be expressed as median and inter quartile range (IQR). Normally distributed quantitative variables will be expressed as mean and standard deviation. Chi-squared test will be used for comparison between groups in categorical variables. Independent sample t test will be used for comparison between quantitative normally distributed variables, whereas Mann- Whitney test will be used for comparison between quantitative non-normally distributed variables. Correlations between quantitative variables will be done using Spearman or Pearson correlation test. P-value ≤ 0.05 was considered statistically significant. All tests will be two-tailed.

References

- **Ashkenazi, A., & Levin, M. (2007).** Greater occipital nerve block for migraine and other headaches: Is it useful? *Current Pain and Headache Reports, 11*, 231–235.

- **Aurora, S. K., & Brin, M. F. (2017).** Chronic migraine: An update on physiology, imaging, and the mechanism of action of two available pharmacologic therapies. *Headache, 57*(1), 109–125.

- **Aurora, S. K., Winner, P., Freeman, M. C., et al. (2011).** OnabotulinumtoxinA for treatment of chronic migraine: Pooled analyses of the 56-week PREEMPT clinical program. *Headache, 51*, 1358–1373.

- **Bigal ME, Lipton RB.** Overuse of acute migraine medications and migraine chronification. Curr Pain Headache Rep. 2009 Aug;13(4):301-7. doi: 10.1007/s11916-009-0048-3. PMID: 19586594.

- **Blumenfeld, A. M., Stark, R. J., Freeman, M. C., et al. (2018).** Long-term study of the efficacy and safety of onabotulinumtoxinA for the prevention of chronic migraine: COMPEL study. *Journal of Headache and Pain, 19*, 13.

- **Bonafede, M., Sapra, S., Shah, N., et al. (2018).** Direct and indirect healthcare resource utilization and costs among migraine patients in the United States. *Headache, 58*(5), 700–714.

- **Buse, D. C., Bigal, M. B., Rupnow, M., Reed, M., Serrano, D., & Lipton, R. B. (2007).** Development and validation of the Migraine Interictal Burden Scale (MIBS): A self-administered instrument for measuring the burden of migraine between attacks. *Neurology, 68*(Suppl 1), A89.

- **Buse, D. C., Bigal, M., Rupnow, M., Reed, M., Serrano, D., & Biondi, D., et al. (2007).** The Migraine Interictal Burden Scale (MIBS): Results of a population-based validation study [abstract F64]. *Headache, 47*(7), 778.

- **Chowdhury, D., & Mundra, A. (2020).** Role of greater occipital nerve block for preventive treatment of chronic migraine: A critical review. *Cephalalgia Reports, 3*, 2515816320964401.

- **Diener, H. C., et al. (2019).** Guidelines of the International Headache Society for controlled trials of acute treatment of migraine attacks in adults: Fourth edition. *Cephalalgia, 39*(6), 687–710.

- **Diener, H. C., et al. (2010).** OnabotulinumtoxinA for treatment of chronic migraine: Results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 2 trial. *Cephalalgia, 30*, 804–814.

- **Diener, H. C., et al. (2012).** Chronic migraine—classification, characteristics and treatment. *Nature Reviews Neurology, 8*, 162–171.

- **Dworkin, R. H., Turk, D. C., Farrar, J. T., Haythornthwaite, J. A., Jensen, M. P., Katz, N. P., et al. (2008).** Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain, 137*(3), 255–266.

- **Dworkin, R.H., et al., (2008).** Interpreting the Clinical Importance of Treatment Outcomes in Chronic Pain Clinical Trials: IMMPACT Recommendations. *The Journal of Pain*, 9(2): p. 105-121.

- **Ford, J. H., Stauffer, V. L., McAllister, P., et al. (2021).** Functional impairment and disability among patients with migraine: Evaluation of galcanezumab in a long-term, open-label study. *Quality of Life Research, 30*(2), 455–464.

- **Freitag, F. G., Diamond, S., Diamond, M., & Urban, G. (2008).** Botulinum toxin type A in the treatment of chronic migraine without medication overuse. *Headache, 48*(2), 201–209.

- **Gandek, B., Ali, M., Gertman, P., et al. (2003).** Translating the short-form Headache Impact Test (HIT-6) in 27 countries: Methodological and conceptual issues. *Quality of Life Research, 12*(8), 975–979.

- **Gazerani, P., Staahl, C., Drewes, A. M., & Arendt-Nielsen, L. (2006).** The effects of botulinum toxin type A on capsaicin-evoked pain, flare, and secondary hyperalgesia in an experimental human model of trigeminal sensitization. *Pain, 122*(3), 315–325.
- **Global Burden of Disease Study 2016. (2017).** Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries, 1990–2016: A systematic analysis. *The Lancet, 390*, 1211–1259.

- **Hussein, M., Hassan, A., & Nada, M. A. F. (2024).** Reliability, validity, and responsiveness of the Arabic version of HIT-6 questionnaire in patients with migraine indicated for preventive therapy: A multi-center study.

- **International Headache Society. (2013).** *The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia, 33*(9), 629–808.

- **Karaoğlan, M., et al. (2022).** A comparison of the clinical efficacy of greater occipital nerve block at the C2 level and at the classical distal occipital level in the treatment of migraine. *Clinical Neurology and Neurosurgery, 220*, 107282.

- **Kosinski, M., Bayliss, M. S., Bjorner, J. B., Ware, J. E., Jr., Garber, W. H., Batenhorst, A., Cady, R., Dahlöf, C. G., Dowson, A., & Tepper, S. (2003).** A six-item short-form survey for measuring headache impact: The HIT-6. Quality of Life Research, 12(8), 963–974.

- **Lipton, R. B., Bigal, M. E., Ashina, S., et al. (2008).** Cutaneous allodynia in the migraine population. *Annals of Neurology, 63*(2), 148–158.

- **Meise, R., Schwarz, A. & Luedtke, K (2022)**. Effectiveness of Patient Education and Cognitive Behavioural Treatment as a Non-Pharmacological Intervention for Migraine in Adults – a Systematic Review. *SN Compr. Clin. Med.* **4**, 197.

- **Schwedt TJ.** Preventive Therapy of Migraine. Continuum (Minneap Minn). 2018 Aug;24(4, Headache):1052-1065. doi: 10.1212/CON.0000000000000635. PMID: 30074549.

- **Serrano, D., Manack, A. N., Reed, M. L., et al. (2013).** Cost and predictors of lost productive time in chronic migraine and episodic migraine: Results from the American Migraine Prevalence and Prevention (AMPP) Study. *Value in Health, 16*(1), 31–38.

- **Sun-Edelstein, C., et al. (2016).** Update on the pharmacological treatment of chronic migraine. *Current Pain and Headache Reports, 20*(1), 3.

- **The International Classification of Headache Disorders. (2018).** *Cephalalgia, 38*(1), 1–211.

- **Yellen, E. A., Davis, G. C., & Ricard, R. J. (2002).** The measurement of patient satisfaction. *Journal of Nursing Care Quality, 16*, 2