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Assessing Prophylactic Therapies for Migraine: A Headache Impact Test-6 Score Comparison in Bangladesh

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ABSTRACT
Background: *Migraine is a prevalent and disabling neurological disorder characterized by recurrent headaches, often accompanied by nausea, vomiting, and sensitivity to light and sound. This study aimed to evaluate the efficacy of Topiramate, Nortriptyline, and their combination in reducing migraine frequency, duration, and severity, as measured by the Headache Impact Test-6 (HIT-6) score.*
Methods: *A quasi experimental was conducted with 63 adult migraine patients, divided into three groups: Group A (Topiramate), Group B (Nortriptyline), and Group C (combination therapy). The study spanned was one year, with HIT-6 scores, headache frequency, and duration recorded at baseline and at the end of the study period. Adverse effects were also monitored.*
Results: *All treatment groups showed significant reductions in headache frequency, duration, and HIT-6 scores. The combination therapy in Group C demonstrated the most substantial improvement, with HIT-6 scores decreasing from 64.3±5.2 to 45.0±5.2 ($p < 0.001$). Group C also reported the highest percentage of patients with little or no impact from migraines (85.7%). Adverse effects were noted across all groups, but the incidence was relatively low and comparable between groups.*
Conclusion: *The combination of Topiramate and Nortriptyline was more effective in reducing the overall impact of migraines than either drug alone. These findings suggest that combination therapy may be a superior option for migraine prevention, particularly for patients who do not achieve adequate relief with monotherapy. However, further research is needed to assess the long-term efficacy and safety of this treatment approach.*
Keywords: *Quasi experimental study, migraine prophylaxis, topiramate, nortriptyline, combination therapy.*

I. INTRODUCTION:

Migraine is a prevalent and incapacitating neurological condition characterized by recurring headaches, frequently accompanied by nausea, vomiting, and heightened sensitivity to light and sound. Migraine is the second leading cause of years lost to disability worldwide among all neurologic disorders [1]. Migraine is accompanied

by a substantial and potentially prevalent burden of illness. The frequency of the US population after one year is 6% for males and 18% for females. The age span between 25 and 55 is the period of highest occurrence [2]. Migraine episodes can significantly hinder an individual's ability to perform tasks at home, work, or in social situations. Migraine is associated with a substantial financial burden. The annual estimated overall cost in the United States amounts to $27 billion. Anxiety, depression, asthma, epilepsy, and stroke are common health issues that are more likely to be caused by the burden of financial stress [3]. Migraine attacks may significantly affect the overall quality of life, impacting both personal and professional endeavors. Efficient management of migraine is crucial in order to decrease the frequency and intensity of attacks, therefore enhancing the overall quality of life for individuals experiencing them.

The disease can be categorized according to the frequency of attacks. A migraine is categorized as episodic if it happens between one and fourteen days per month, and as chronic if it happens between fifteen and twenty-five days per month, at least eight days after satisfying the criteria for migraine with or without aura [4]. Due to the combination of acute and chronic features in migraines, the pharmacological treatment is divided into acute and preventative methods. Individuals who frequently encounter debilitating bouts are encouraged to undergo preventive therapy. Preferred medications include neuromodulators, beta-blockers, tricyclic antidepressants, and calcium channel antagonists [5]. The antagonists of the calcitonin gene-related peptide have broadened the spectrum of available options for preventative treatment. Botulinum toxin A has been introduced as a treatment for chronic migraine [6]. Preventive treatments have varying indications. The expert recommends preventive medication for persons who experience two or more monthly headaches along with a disability, as well as those who have four or more monthly episodes, independent of disability [7]. While some guidelines only recommend preventive medicines for people who get headaches on most days of the month, others recommend them for patients who encounter five or more migraine attacks each month [8]. The goal of preventive care is to reduce the frequency of headaches by at least 50% without inflicting severe harm. When choosing preventative medication, doctors primarily take into account FDA approval and the patient's capacity to tolerate the drug. When used as intended, preventive medicine is associated with enhanced quality of life and decreased disability [9]. Nevertheless, not all individuals suffering from migraines who need preventive medicine have significant advantages from using a single remedy, and a portion of them do not encounter any adverse effects. Combining multiple preventive therapies may be beneficial for individuals who do not show a good response to a single therapy, based on limited evidence and clinical experience.

Migraine pharmacotherapy can be roughly classified into acute and preventive treatments. Acute therapies are given to relieve the symptoms of a migraine attack once it has started, whereas preventive treatments are used regularly to prevent or decrease the frequency of migraine attacks [10]. Patients who experience frequent or severe migraine attacks, especially those that do not respond well to immediate treatment or cause significant disability, are advised to undergo prophylactic treatment. The aim of preventative medication is to decrease the frequency, intensity, and duration of migraine attacks, therefore decreasing the overall impact on patients' quality of life [11].

Among the various prophylactic treatments available, Topiramate and Nortriptyline have emerged as effective options for migraine prevention [5]. Topiramate, an anticonvulsant drugs, has been proven to decrease the occurrence of migraine attacks by affecting many processes in the brain, such as regulating the release of neurotransmitters and blocking certain ion channels [12]. Nortriptyline, a tricyclic antidepressant, is believed to exert its prophylactic effects on migraines by enhancing serotonergic and noradrenergic neurotransmission, as well as modulating pain pathways [5]. In recent years, a prospective examination of topiramate was conducted. Topiramate showed a considerable effectiveness in avoiding migraines. Topiramate appeared to have a drug with a satisfactory level of safety [13]. Nortriptyline is one of the tricyclic antidepressants that has long been a mainstay in the treatment of migraine avoidance [14]. Although these drugs are effective when used alone, there is increasing interest in the possible advantages of combining them for the prevention of migraines. The reason for utilizing combination therapy is that the use of two drugs with distinct modes of action may result in greater effectiveness compared to using a single medication, perhaps leading to a synergistic impact. Nevertheless, the effectiveness of using a combination of therapies for preventing migraines have not been thoroughly investigated. Patients suffering from migraines who do not get complete improvement from either topiramate or nortriptyline alone can derive benefits from a combination of both medications [5].

The Headache Impact Test-6 (HIT-6) is a commonly employed and validated instrument for evaluating the effects of headaches on an individual's everyday activities. The study conducted by Pradela et al. (2021) assesses the intensity and frequency of headaches, as well as their impact on physical, social, and emotional well-being [15]. The HIT-6 score serves as a valuable metric in clinical research aimed at assessing the effectiveness of migraine medications, as it offers a thorough evaluation of the impact of migraine on patients. This study is designed to examine the effectiveness of Topiramate, Nortriptyline and a combination of Topiramate and Nortriptyline therapy in patients with migraines. The primary outcome measure will be the HIT-6 score. This study aims to assess the effect of these treatment methods on the level of disability caused by migraines. Its goal

is to offer evidence-based recommendations to doctors when choosing preventive treatments for patients with migraines.

II. METHODOLOGY:

Study design: This study was designed as a quasi-experimental to evaluate and compare the effectiveness of Topiramate, Nortriptyline, and a combination of Topiramate-Nortriptyline therapy in reducing the impact of migraines, as measured by the Headache Impact Test-6 (HIT-6) score. The trial was conducted at the Department of Pharmacology and Therapeutics, Dhaka Medical College, Dhaka, between January 2022 and December 2022. Patients aged 18 to 55 years, clinically diagnosed with migraine according to the International Classification of Headache Disorders (ICHD-3) criteria, were recruited from the Neurology Department's Outpatient Headache Clinic. Exclusion criteria included patients with significant comorbidities (e.g., ischemic heart disease, peripheral vascular disease, coronary artery disease, uncontrolled hypertension, diabetes mellitus, asthma, chronic obstructive pulmonary disease, hepatic or renal failure), complicated migraines (e.g., hemiplegic or basilar migraines), and female patients who were pregnant or lactating. All participants provided written informed consent before enrollment. A total of 63 participants were randomly assigned in a 1:1:1 ratio to one of three groups: Group A received Topiramate, Group B received Nortriptyline, and Group C received a combination of Topiramate and Nortriptyline. Randomization was carried out using block random sampling with a block size of 9 to ensure equal allocation among groups. Out of the 95 patients initially screened, 73 were enrolled and randomized. Ultimately, 63 patients were allocated to Group A (Topiramate), Group B (Nortriptyline), or Group C (combined therapy). A total of 21 participants completed the study across all three groups after accounting for losses to follow-up. The primary outcome, HIT-6 score, along with secondary outcomes including the frequency, duration, and intensity of migraines (assessed using the Visual Analogue Scale), were measured at baseline and after three months of treatment.

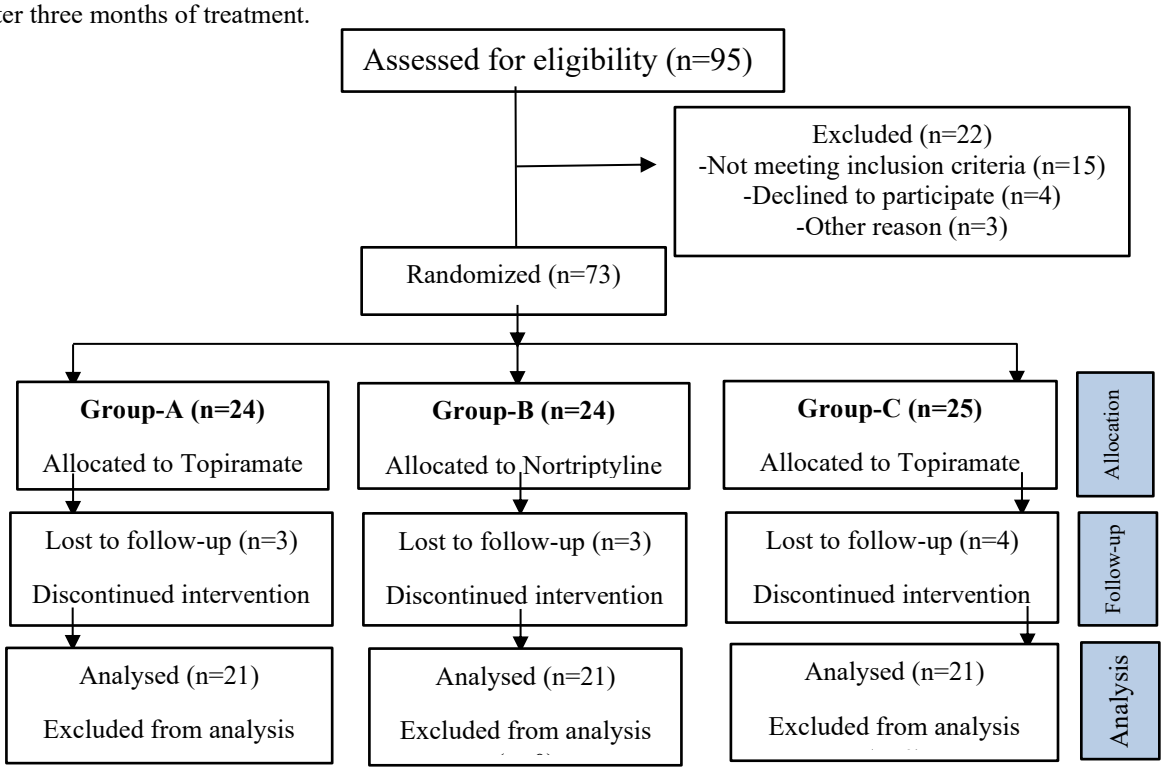

Figure 1: Enrolment, randomization, follow up and analysis of patients according to the CONSORT 2010 flow diagram.

Sample size calculation: The sample size for each group was 21. This calculation was based on hypothesis testing for the difference between two proportions. The formula used for the sample size determination is:

$$n = \frac{P1(100-p1)^2+P2(100-P2)}{(P1-P2)^2} \times (Z\alpha + Z\beta)^2$$

According to this formula, the required sample size was determined to be 19 participants. To account for a potential attrition rate of 10%, the initial sample size was increased to 21 participants. This adjustment ensures

that, even with a 10% dropout rate, the study would still have 19 participants. Thus, 21 participants were enrolled, anticipating a 10% dropout, to ultimately include 19 participants in the study.

Study interventions: Participants in Group A received Topiramate, those in Group B received Nortriptyline, and those in Group C received both Topiramate and Nortriptyline. The treatment regimen and dosing were based on established guidelines for migraine prophylaxis. The HIT-6 score and headache characteristics were assessed at baseline, with a follow-up assessment conducted after three months using the HIT-6 score and a headache diary. Data collection was managed via a secure electronic data capture system, ensuring anonymity and compliance with data protection regulations. Regular monitoring ensured adherence to the study protocol and data accuracy.

Statistical analysis: Data analysis was conducted according to the intention-to-treat (ITT) principle. Baseline characteristics were summarized using descriptive statistics. Continuous variables were analyzed using analysis of variance (ANOVA) or the Kruskal-Wallis test, depending on the distribution, while categorical variables were analyzed using chi-square tests. The primary outcome, change in HIT-6 score, was analyzed using mixed-effects linear regression models adjusted for baseline HIT-6 scores and other relevant covariates. Secondary outcomes were analyzed similarly, using mixed-effects models for continuous variables and logistic regression for categorical outcomes. Adverse events were summarized descriptively. All analyses were performed using Stata version 16.0, with a significance level set at $p < 0.05$.

Ethical clearance: The study adhered to the Declaration of Helsinki and Good Clinical Practice guidelines. Ethical approval was obtained from the Ethical Review Committee of Dhaka Medical College, Dhaka, Bangladesh (ERC-DMC/ECC/2022/194.R). All participants provided written informed consent and were informed that they could withdraw from the study at any time without affecting their standard medical care.

III. RESULTS

Demographic characteristics:

The demographic characteristics of the study participants are summarized in Figures I and II. The study population consisted predominantly of females across all three groups. Specifically, Group A had 90.5% female participants, Group B had 81.0%, and Group C had 76.2% (Figure II). The male-to-female ratios in Groups A, B, and C were approximately 1:9, 1:4, and 1:3, respectively.

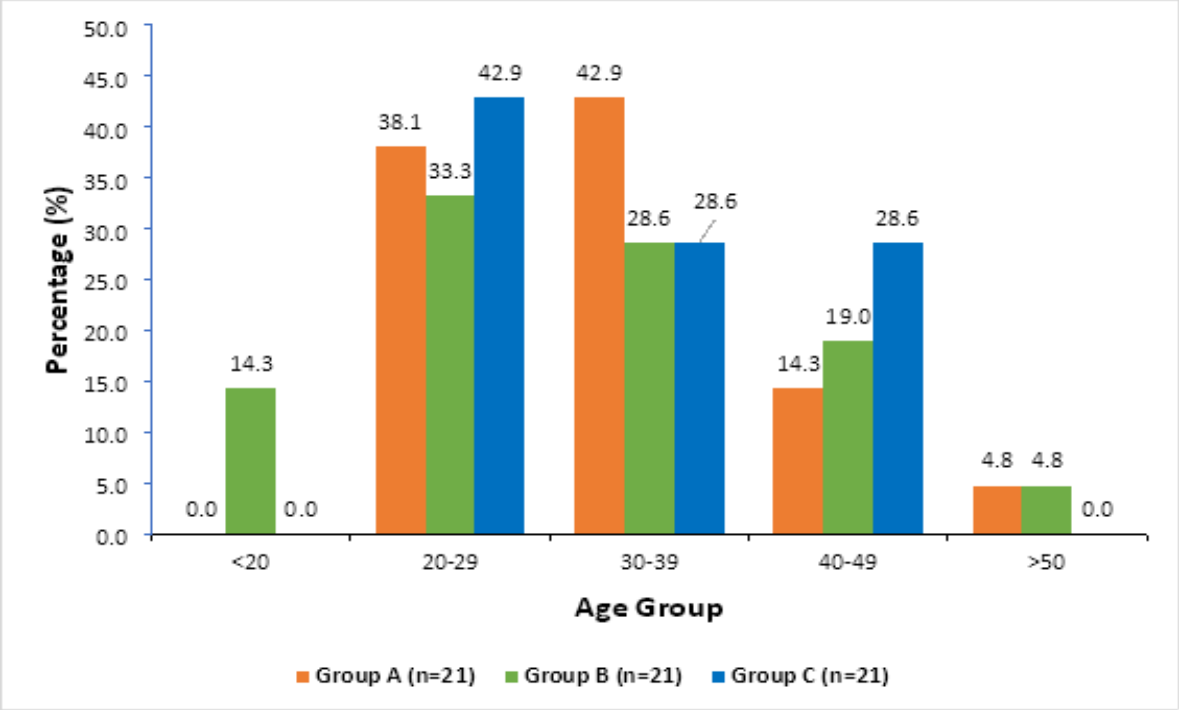

Figure I: Age distribution of the study patients among three Groups (N=63)

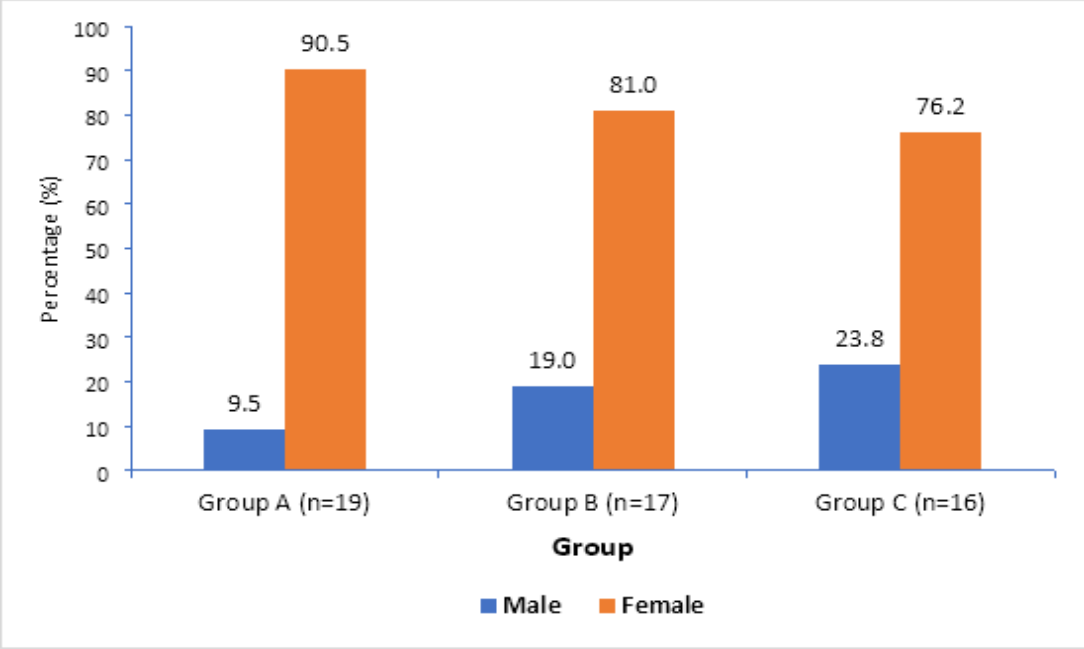

Figure II: Gender distribution of the study patients among three Groups (N=63)

Baseline characteristics:

Table 1 presents a comparison of baseline headache characteristics among the three groups, including frequency, duration, and intensity (VAS score) of headaches. At baseline, Group B exhibited the highest median frequency of headaches at 12.0 days per month (IQR: 2.0-20.0), followed by Groups A and C, both with a median of 6.0 days per month. The duration of headaches was highest in Groups A and C, with a median duration of 6.0 hours (IQR: 2.0-24.0). The intensity of headaches, as measured by the Visual Analogue Scale (VAS), was comparable across all groups, with a median score of 8.0 (IQR: 7.0-9.0). The Kruskal-Wallis H test showed no statistically significant differences among the groups at baseline for any of these variables, indicating that the groups were comparable at the start of the study.

Table 1: Comparison of per month baseline frequency, duration and intensity (VAS) of headache among three Groups of study patients (N=63)

Variable	Group A (n=21)	Group B (n=21)	Group C (n=21)	*p*-value
Headache days / month	6.0 (1.0-20.0)	12.0 (2.0-20.0)	6.0 (2.0-20.0)	0.079
Duration of headache (hours)	6.0 (2.0-24.0)	4.0 (2.0-12.0)	6.0 (2.0-24.0)	0.061
VAS score	8.0 (7.0-9.0)	8.0 (7.0-9.0)	8.0 (7.0-9.0)	0.967

Data were expressed median and IQR
p-value obtained by Kruskal-Wallis H test
$p<0.05$ was considered significant.

Changes in headache frequency and duration:

Table 2 shows there was a significant reduction in headache frequency across all three groups after three months of treatment. The median headache frequency reduced to 0.0 days per month (IQR: 0.0-1.0) in all groups. The Kruskal-Wallis H test indicated a significant overall reduction in headache frequency ($p = 0.022$). Post-hoc analysis using the Mann-Whitney test revealed significant differences between Group B and Group C ($p = 0.006$) and between Group A and Group C ($p = 0.050$), suggesting that the combined therapy (Group C) was more effective than monotherapy with either Topiramate (Group A) or Nortriptyline (Group B) alone. These findings highlight the potential synergistic effect of the combination therapy in reducing migraine frequency.

Table 2: Comparison of headache frequency during enrollment and follow-up visits 3 months later among three Groups (N=63)

Headache Frequency (days/month)	Group A (n = 21)	Group B (n = 21)	Group C (n = 21)	p-value
Before treatment				
Median (IQR)	6.0 (2.5–11.0)	12.0 (6.0–16.0)	6.0 (3.5–12.0)	0.079
After 3 months of treatment				
Median (IQR)	0.0 (0.0–1.0)	0.0 (0.0–1.0)	0.0 (0.0–0.0)	0.022*
Pairwise comparisons after 3 months (Mann–Whitney U test)				
Group A vs Group B	—	—	—	0.307
Group A vs Group C	—	—	—	0.050*
Group B vs Group C	—	—	—	0.006*

Data were expressed in Median and IQR.
p-value obtained by Kruskal-Wallis test and Mann-Whitney test.
p<0.05 was considered significant.
*Significant

Table 3 outlines the changes in headache duration before and after three months of treatment. Although the duration of headaches decreased in all groups, the most substantial reduction was observed in Group C. The median duration of headaches in Group C decreased from 6.0 hours (IQR: 4.0-12.0) at baseline to 5.0 hours (IQR: 3.0-10.0) after treatment, with a statistically significant p-value of <0.001. Group A also showed a significant reduction in headache duration (p = 0.011), while Group B did not show a significant change (p = 0.371). The results suggest that the combination therapy was more effective in reducing the duration of migraines compared to the monotherapy options.

Table 3: Comparison of duration of headache during enrollment and follow up visits 3 months later among three Groups (N=63).

Duration of Headache (hours)	Group A (n = 21)	Group B (n = 21)	Group C (n = 21)	Between-Group p-value
Before treatment				
Median (IQR)	6.0 (5.5–12.0)	4.0 (3.0–8.0)	6.0 (4.0–12.0)	0.061
After 3 months of treatment				
Median (IQR)	6.0 (4.0–10.0)	4.0 (3.5–8.0)	5.0 (3.0–10.0)	0.366
Within-group p-value†	**0.011***	**0.371**	**<0.001***	—

Data were expressed in Median and IQR.
p-value obtained by Wilcoxon Signed Ranks Test.
p<0.05 was considered significant.
*Significant

Pain status and pain intensity (VAS scores):

Table 4 presents the comparison of Visual Analogue Scale (VAS) scores for pain intensity before and after three months of treatment among the three study groups. At baseline, the median VAS score was 8.0 (IQR: 7.0-9.0) across all groups, with no significant difference between them (p = 0.967). After three months of treatment, a significant reduction in median VAS scores was observed in all groups, with the greatest reduction seen in Group C, where the median VAS score decreased to 2.0 (IQR: 2.0-3.0), compared to 3.0 (IQR: 2.0-3.5) in Group A and 3.0 (IQR: 2.0-4.0) in Group B. Although the difference in post-treatment VAS scores between the groups did not reach statistical significance (p = 0.066), the trend suggests that the combined therapy in Group C may be more effective in reducing pain intensity. These results indicate that the treatment interventions in all groups effectively reduced pain intensity, with the combination therapy in Group C showing the most substantial improvement. The statistical significance of the reductions in VAS scores within each group further supports the effectiveness of these treatments in managing migraine-related pain.

Table 4: Comparison of VAS score during enrollment and follow-up visits 3 months later among three Groups (N=63).

VAS score	Group A (n=21)	Group B (n=21)	Group C (n=21)	*p*-value
Before treatment				
Median	8.0	8.0	8.0	0.967
IQR	7.0-9.0	7.0-9.0	7.0-9.0	
After 3 months of treatment				

Median	3.0	3.0	2.0	0.066
IQR	2.0-3.5	2.0-4.0	2.0-3.0	
p-value	<0.001*	<0.001*	<0.001*	

Data were expressed in Median and IQR.
p-value obtained by Kruskal-Wallis test.
p<0.05 was considered significant.

Table 5 illustrates the changes in pain status, categorized by VAS scores, before and after three months of treatment. Before treatment, the majority of patients in Group A (95.2%) and Group C (85.7%) experienced severe pain (VAS score 7-9), while Group B had a slightly lower proportion of patients with severe pain (71.4%). Notably, Group C also had 9.5% of patients experiencing the worst pain possible (VAS score of 10). Following three months of treatment, the proportion of patients experiencing mild pain (VAS score 1-3) increased dramatically, especially in Group C, where 95.2% of patients reported mild pain compared to 76.2% in Group A and 66.7% in Group B. None of the patients in Group C reported severe or worst pain after treatment. The Chi-square test showed that the reduction in severe and worst pain was statistically significant in Group C (p = 0.007), whereas the changes in Groups A and B did not reach statistical significance (p = 0.567 and p = 0.466, respectively).

Table 5: Association of pain status (according to VAS score) during enrollment and follow-up visits 3 months later among three Groups (N=63).

VAS score	Group A (n=21), n (%)		Group B (n=21), n (%)		Group C (n=21), n (%)	
	Before	After	Before	After	Before	After
Mild pain (1-3)	0(0.0)	16(76.2)	1(4.8)	14(66.7)	0(0.0)	20(95.2)
Moderate pain (4-6)	1(4.8)	5(23.8)	2(9.5)	7(33.3)	1(4.8)	1(4.8)
Severe pain (7-9)	20(95.2)	0(0.0)	15(71.4)	0(0.0)	18(85.7)	0(0.0)
Worst pain possible (10)	0(0.0)	0(0.0)	3(14.3)	0(0.0)	2(9.5)	0(0.0)
p-value	0.567		0.466		0.007*	

Data were expressed in frequency and percentage.
p-value obtained by Chi-square test.
p<0.05 was considered significant.
*Significant

Impact on Headache Severity (HIT-6 scores) Before and After Treatment:

Table 6 illustrates the comparison of HIT-6 scores before treatment and after three months of treatment among the three study groups. The mean HIT-6 score at baseline was comparable across the groups, with no statistically significant differences (p = 0.534). However, after three months of treatment, there was a substantial reduction in HIT-6 scores across all groups, with the most significant reduction observed in Group C, where the mean HIT-6 score decreased from 64.3±5.2 to 45.0±5.2 (p = 0.012). The statistically significant p-values across the groups (p < 0.001) confirm that the treatments were effective in reducing the impact of headaches, with Group C showing the most pronounced improvement. These findings suggest that the combination therapy in Group C is potentially more effective in reducing the overall impact of migraines, as measured by the HIT-6 score, compared to the monotherapies used in Groups A and B.

Table 6: Comparison of HIT-6 score during enrollment and follow-up visits 3 months later among three Groups (N=63).

HIT-6 score	Group A (n=21) Mean±SD	Group B (n=21) Mean±SD	Group C (n=21) Mean±SD	*p*-value
Before treatment	65.9±3.6 (61.0-72.0)	64.8±5.0 (56.0-75.0)	64.3±5.2 (52.0-76.0)	0.534
After 3 months of treatment	50.8±6.8 (36.0-60.0)	50.1±6.7 (38.0-62.0)	45.0±5.2 (36.0-56.0)	0.007*
p-value	<0.001*	<0.001*	<0.001*	
Before treatment				
Group A vs Group B	-	-	-	1.000

Group A vs Group C	-	-	-	0.830
Group B vs Group C	-	-	-	1.00
After 3 months of treatment				
Group A vs Group B	-	-	-	1.00
Group A vs Group C	-	-	-	0.012*
Group B vs Group C	-	-	-	0.032*

Data were expressed in mean±SD (Range).
p-value obtained by ANOVA test.
p<0.05 was considered significant.
*Significant

Table 7 details the association between headache severity (as measured by the HIT-6 score) and its impact on patients' lives before and after treatment. Prior to treatment, the majority of patients in all groups experienced severe impact (HIT-6 score 60-78). After three months, Group C demonstrated the most significant improvement, with 85.7% of patients reporting little or no impact (HIT-6 score ≤49), compared to 38.1% in Group A and 42.9% in Group B. This significant shift suggests that the combination therapy used in Group C not only reduces the frequency and duration of migraines but also significantly mitigates their overall impact on daily functioning.

Table 7: Association of headache severity (according to HIT-6 score) during enrollment and follow-up visits 3 months later among three Groups (N=63).

HIT-6 score	Group A (n=21), n (%)		Group B (n=21), n (%)		Group C (n=21), n (%)	
	Before	After	Before	After	Before	After
Little or no impact (≤49)	0(0.0)	8(38.1)	0(0.0)	9(42.9)	0(0.0)	18(85.7)
Some impact (50-55)	0(0.0)	7(33.3)	0(0.0)	7(33.3)	1(4.8)	2(9.5)
Substantial impact (56-59)	0(0.0)	4(19.0)	5(23.8)	4(19.0)	3(14.3)	1(4.8)
Severe impact (60-78)	21(100.0)	2(9.5)	16(76.2)	1(4.8)	17(81.0)	0(0.0)
p-value	-		0.935		0.771	

Data were expressed in frequency and percentage
p-value obtained by Chi-square test.
p<0.05 was considered significant.

Table 8 shows the baseline mean±SD HIT-6 scores for each group, with no significant differences observed among them (p = 0.534). This indicates that the groups were comparable at the beginning of the study. Table 9 reveals that after three months, the mean follow-up HIT-6 score for Group C was significantly lower (45.0±5.20) than those in Groups A and B (50.76±6.77 and 50.09±6.68, respectively), with a statistically significant difference (p = 0.007). This further supports the conclusion that the treatment regimen in Group C is more effective at reducing migraine severity and its impact on patients' quality of life.

Table 8: Association of Initial Visit HIT-6 score among three Groups (N=63).

Initial Visit HIT score group	Groups			p-value
	Group A (n=21). n (%)	Group B (n=21), n (%)	Group C (n=21), n (%)	
Little or no impact (<=49)	0(0.0)	0(0.0)	0(0.0)	
Some impact (50-55)	0(0.0)	0(0.0)	1(4.8)	
Substantial impact (56-59)	0(0.0)	5(23.8)	3(14.3)	
Severe impact (60-78)	21(100.0)	16(76.2)	17(81.0)	0.534
Total	21(100.0)	21(100.0)	21(100.0)	
Mean±SD	65.90±3.58	64.81±5.01	64.33±5.16	

Data were expressed in frequency and percentage
p-value obtained by Unpaired t-test.
p<0.05 was considered significant.

Table 9 shows the mean±SD of the follow-up visit HIT-6 scores for each group. The mean follow-up visit HIT-6 score for Group A was 50.76±6.77, for Group B was 50.09±6.68, and for Group C was 45.0±5.20. There is a statistically significant difference in the mean follow-up visit HIT-6 scores among the three groups (p 0.007). The mean follow-up visit HIT-6 score for Group C was significantly lower than Groups A and B. The

mean follow-up visit HIT-6 score for Group C was significantly lower than Groups A and B by a statistically significant margin.

Table 9: Association of Follow-up Visit HIT score among three Groups (N=63).

Follow up Visit HIT score group	Groups			p-value
	Group A (n=21), n (%)	Group B (n=21), n (%)	Group C (n=21), n (%)	
Little or no impact (<=49)	8(38.1)	9(42.9)	18(85.7)	0.007*
Some impact (50-55)	7(33.3)	7(33.3)	2(9.5)	
Substantial impact (56-59)	4(19.0)	4(19.0)	1(4.8)	
Severe impact (60-78)	2(9.5)	1(4.8)	0(0.0)	
Total	21(100.0)	21(100.0)	21(100.0)	
Mean±SD	50.76±6.77	50.09±6.68	45.0±5.20	

Data were expressed in frequency and percentage
p-value obtained by Unpaired t-test.
p<0.05 was considered significant.
*Significant

Tables 10 and 11 explore the relationship between HIT-6 scores and gender at both the initial visit and follow-up. Table 10 shows a significant association between gender and initial HIT-6 scores (p = 0.033), suggesting that female patients might experience a greater impact from migraines at baseline. However, Table 11 indicates that after three months of treatment, there was no significant association between gender and HIT-6 scores (p = 0.752), implying that the treatment effectiveness was consistent across genders.

Table 10: Association of Initial Visit HIT-6 score group with gender (N=63).

Gender	Initial Visit HIT-6 score group			p-value
	Some impact (50-55), n (%)	Substantial impact (56-59), n (%)	Severe impact (60-78), n (%)	
Male	0(0.0)	4(50.0)	7(13.0)	0.033*
Female	1(100.0)	4(50.0)	47(87.0)	
Total	1(100.0)	8(100.0)	54(100.0)	

Data were expressed in frequency and percentage
p-value obtained by Chi-square test.
p<0.05 was considered significant.
*Significant

Table 11: Association of Follow-up HIT-6 score group with gender (N=63).

Gender	Follow-up Visit HIT-6 score group				p-value
	Little or no impact (<=49), n (%)	Some impact (50-55), n (%)	Substantial impact (56-59), n (%)	Severe impact (60-78), n (%)	
Male	7(20.0)	2(12.5)	1(11.1)	1(33.3)	0.752
Female	28(80.0)	14(87.5)	8(88.9)	2(66.7)	
Total	35(100.0)	16(100.0)	9(100.0)	3(100.0)	

Data were expressed in frequency and percentage
p-value obtained by Chi-square test.
p<0.05 was considered significant.

Table-12 Shows the adverse effects profile among the three Groups of study patients during this study period. It was observed that Group B and Group C 12(57.1%) had the highest experience of adverse effects. Highest 4(19.0%) patients had experienced sedation in Group A, followed by 3(14.3%) patients in Group C and the lowest 1(4.8%) patient in Group B. Highest 7(33.3%) patients had experienced dry mouth and lowest 3(14.3%) patients in Group C. Blurring of vision 3(14.3%) patients in Group B and Group C. Palpitation 1(4.8%) patients Group B, weakness 3(14.3%) patients in Group C and 1(4.8%) patient in Group A.

Table-12: **Adverse effects profile among the three Groups of study patients (N=63).**

Group	Adverse Effect	No. of Patients (n)	Percentage (%)
Group A (n = 21)	Any adverse effect	5	23.8
	Sedation	4	19.0
	Weakness	1	4.8
Group B (n = 21)	Any adverse effect	12	57.1

	Sedation	1	4.8
	Dry mouth	7	33.3
	Blurring of vision	3	14.3
	Palpitation	1	4.8
Group C (n = 21)	Any adverse effect	12	57.1
	Sedation	3	14.3
	Dry mouth	3	14.3
	Blurring of vision	3	14.3
	Weakness	3	14.3

IV. DISCUSSION:

In this study, female predominance is consistent with existing literature, which indicates that migraines are more common in females, with a prevalence of 18% compared to 6% in males in the United States [3]. Additionally, a population-based study in Turkey reported a higher prevalence of migraines among women (24%) compared to men (12%) [16]. Regarding age distribution, the study revealed that the majority of participants were within the 20-39 age range, aligning with the age group typically affected by migraines [17]. In Group A, the highest proportion of patients (42.9%) was within the 30-39 age group. In contrast, Groups B and C had the highest number of patients in the 20-29 age group, accounting for 33.3% and 42.9% of participants, respectively. This distribution reflects the global epidemiological trends, where migraines predominantly affect individuals aged 25-55, a period often associated with high productivity and significant life responsibilities.

The demographic findings of this study underscore the well-documented trend of migraines being more prevalent among females, particularly those in their reproductive years. The observed gender distribution supports the notion that hormonal fluctuations, particularly those related to estrogen, play a significant role in the pathophysiology of migraines [3,17]. The female predominance in this study, with a male-to-female ratio skewed heavily towards females, further corroborates the existing literature that suggests gender as a critical factor in migraine prevalence. The age distribution data also align with global patterns, where the peak incidence of migraines occurs between the ages of 20 and 39. This is a period characterized by a high level of stress and hormonal changes, factors known to trigger migraines [17]. The results from this study, with the highest incidence observed in the 20-39 age group, are consistent with these established patterns. The demographic profile of the study participants, particularly the predominance of females and the concentration in the 20-39 age range, aligns with global epidemiological data on migraines. These findings are crucial for tailoring migraine management strategies, as they highlight the need for gender-specific approaches and age-targeted interventions to effectively mitigate the impact of migraines on patients' lives.

The results of this study demonstrate that both Topiramate and Nortriptyline are effective in reducing the frequency and duration of migraines, but the combination therapy offers a superior outcome, particularly in reducing headache duration. The significant reduction in headache frequency and duration in Group C aligns with the hypothesis that combining medications with different mechanisms of action can provide a synergistic effect, thereby enhancing therapeutic efficacy. This study's findings are consistent with previous research, which suggests that combination therapy may be more effective than monotherapy in managing complex conditions like migraines, where multiple pathways contribute to symptom manifestation [5]. The significant improvement observed in Group C, especially in terms of headache duration, highlights the potential of combination therapy as a first-line treatment for patients who do not respond adequately to monotherapy.

The results from this study clearly indicate that the combined therapy (Topiramate and Nortriptyline) in Group C offers superior benefits in reducing both the intensity and severity of migraine-related pain, as evidenced by the significant improvements in VAS scores and pain status categories. While all three treatment regimens were effective, the combination therapy demonstrated the greatest impact, reducing the median VAS score more significantly and increasing the proportion of patients experiencing only mild pain after three months. These findings are consistent with existing literature suggesting that combination therapies targeting multiple mechanisms in migraine pathophysiology can provide more comprehensive pain relief than single-agent treatments [5]. The significant improvements observed in Group C further underscore the importance of a multifaceted approach in managing chronic migraines, particularly for patients who do not respond adequately to monotherapy.

The baseline headache frequency was comparable across the groups, with Group A and Group C reporting a median of 6.0 headache days per month, while Group B had a higher median of 12.0 days. These values align with findings from Krymchantowski et al. (2012), where headache frequency ranged between 8.0 to 8.1 days per month across different treatment groups. After three months of treatment, the percentage of patients experiencing a reduction in headache frequency was notably high: 95.2% in Group C, 91.9% in Group A, and 90.7% in Group B. These results are consistent with Krymchantowski et al.'s study, which reported a reduction of at least 50% in headache frequency in 78.3% of patients in the combination therapy group, compared to 47.0% in the Topiramate group and 37.0% in the Nortriptyline group [5].

Over the treatment period, the frequency of headaches decreased progressively in all groups. By the end of the first month, the number of headache days had reduced to 3.0 per month in all groups. This reduction continued, with Group A reporting 1.0 headache day, Group B reporting 2.0, and Group C reporting 1.0 by the end of the second month. Remarkably, by the end of the third month, all three groups reported no headache days, underscoring the efficacy of the treatments.

The Headache Impact Test-6 (HIT-6) scores further corroborate these findings. Group C showed the most significant reduction in HIT-6 scores, decreasing from 64.3 to 45.0 ($p < 0.001$). Group A also demonstrated a substantial reduction, from 65.9 to 50.8 ($p < 0.001$), followed by Group B, with a reduction from 64.8 to 50.1 ($p < 0.001$). These results suggest that the combination therapy in Group C was particularly effective in mitigating the impact of migraines.

Regarding adverse effects, 57.1% of participants in Groups B and C, and 23.8% in Group A, reported experiencing side effects during the study. Sedation was the most commonly reported side effect, with the highest incidence in Group A (19.0%), followed by Group C (14.3%), and Group B (4.8%). Dry mouth was most frequently reported in Group B (33.3%), with Group C reporting the lowest incidence (14.3%). Blurred vision was reported by 14.3% of patients in both Groups B and C. Notably, one patient in Group B (4.8%) experienced palpitations, and weakness was reported by 14.3% of patients in Group C and by one patient (4.8%) in Group A.

Migraine is the second most common cause of headaches and the leading cause of disability worldwide among neurological conditions. It has a lifetime prevalence of approximately 20% in women and 6% in men, with the onset occurring before the age of 30 in over 80% of cases [18]. Globally, migraine impacts around 15% of women and 6% of men annually, contributing significantly to disability [19]. According to the Global Burden of Disease Survey 2010, migraine was the third most common and seventh leading cause of disability worldwide [20].

V. LIMITATIONS

While this study provides valuable insights into the effectiveness of Topiramate, Nortriptyline, and their combination in the prevention of migraines, several limitations should be acknowledged. Firstly, the study's sample size was relatively small, with only 63 participants across three treatment groups. Although the results were statistically significant, a larger sample size would provide more robust data and enhance the generalizability of the findings. Secondly, the study's follow-up period was limited to three months. While significant improvements were observed during this time, a longer follow-up period is necessary to assess the long-term efficacy and safety of the treatment regimens, particularly for chronic migraine management. The short duration may also limit the ability to observe potential late-onset side effects or changes in treatment efficacy over time. Thirdly, the study did not explore the underlying mechanisms that might contribute to the superior efficacy of the combination therapy. Understanding these mechanisms could offer insights into why certain patients respond better to combination therapy, guiding more personalized treatment approaches in clinical practice. Additionally, the study was conducted at a single medical center, which may introduce site-specific biases and limit the external validity of the findings. Conducting a multicenter trial could help mitigate this limitation and provide a more comprehensive understanding of the treatment effects across different populations and healthcare settings.

VI. CONCLUSION

This study demonstrates that the combination therapy of Topiramate and Nortriptyline is more effective in reducing the frequency, duration, and severity of migraines compared to monotherapy with either drug alone. The combination therapy not only resulted in the greatest reduction in HIT-6 scores, indicating a substantial decrease in the overall impact of migraines on patients' lives, but also maintained a relatively low incidence of adverse effects, making it a promising option for the preventive treatment of chronic migraines. While all treatment groups showed significant improvements over the three-month period, the combination therapy group consistently outperformed the monotherapy groups, suggesting that a multifaceted approach targeting different mechanisms of migraine pathology may offer enhanced therapeutic benefits. However, given the limitations of this study, including its short follow-up period and small sample size, further research is needed to confirm these findings and evaluate the long-term efficacy and safety of combination therapy in diverse patient populations. Overall, this study supports the use of combination therapy as a potentially superior treatment strategy for patients with chronic migraines, particularly those who have not responded adequately to monotherapy. This approach may lead to improved quality of life for migraine sufferers and represents an important step forward in the management of this debilitating condition.

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