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Original Article

Efficacy of Combined Topiramate and Nortriptyline Over Monotherapy of Topiramate or Nortriptyline for Migraine Prophylaxis

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ABSTRACT

Introduction: *Migraine is a chronic disabling disease that often requires prophylaxis to achieve control over the frequency, duration, and intensity of headaches. Different single or combination drugs are used for prophylaxis.* ***Aims of the Study:*** *This study aimed to evaluate the efficacy of combined of Topiramate plus Nortriptyline and monotherapy of Topiramate or Nortriptyline for migraine prophylaxis.* ***Methods & Materials:*** *A one-year, Randomized Controlled Trial was done at Department of Pharmacology and Therapeutics, Dhaka Medical College, Dhaka, Bangladesh. A total of 63 migraine patients were enrolled by block random sampling block of 9, 1:1:1 design. The patients were divided into three groups. In Group A, 21 patients were treated with Topiramate, in Group B, 21 patients were treated with Nortriptyline and in Group C, 21 patients were treated with Topiramate plus Nortriptyline.* ***Result:*** *After 3 months of treatment, frequency of headache reduced from median (IQR) 6.0 (2.5-11.0) to 0.0(0.0-1.0) in Group A, 12.0 (6.0-16.0) to in Group B and 6.0(3.5-12.00 to 0.0(0.0-0.0) in Group C. Duration of headache reduced from median (IQR) 6.0 (5.5-12.0) to 6.0(4.0-10.0) in Group A, 4.0(3.5-8.0) in Group B and 6.0 (4.0-12.0) to 5.0(3.0-10.0) in Group C. Intensity of Headache (Visual Analogue*

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Scale score) reduced from median (IQR) 8.0 (7.0-9.0) to 3.0(2.0-3.5) in Group A, from 8.0(7.0-9.0) to 3.0(2.0-4.0) in Group B and 8.0(7.0-9.0) to 2.0(2.0-3.0) in Group C. ***Conclusion:*** *The combined Topiramate plus Nortriptyline in the headache treatment compared to monotherapy of topiramate or nortriptyline group, the frequency, duration, severity of the headache and HIT-6 score, all were reduced most by the combined group.*

Keywords: *Migraine, Migraine Prophylaxis, Topiramate, Nortriptyline, Combination Therapy*

INTRODUCTION

Migraine is a primary headache disorder and a complex neurological disease[1]. It manifests as episodic attacks of headache and associated symptoms[2,3]. The disability of migraine can be severe enough to impose a considerable burden on the sufferer and society[4,5,6]. It is a neurovascular disorder. It affects over one billion people worldwide[7]. Global migraine prevalence was 11.6% (95% CI 10.7 - 12.6%; random effects); 10.4% in Africa, 10.1% in Asia, 11.4% in Europe, 9.7% in North America, 16.4% in Central and South America[8]. Among the all-neurologic conditions, migraine ranks second worldwide due to years lost to disability[9,10]. Migraine has a substantial burden of illness which might be widespread. The one-year prevalence is 18% in women and 6% in men in the US population[11,12]. The prevalence peaks between the ages of 25 and 55 years. Migraine attacks can significantly impaired functional ability at work or school, at home, and in social situations. Migraine is associated with a considerable financial burden. The annual total cost is estimated at $27 billion in the United States. Due to this financial burden, there is an increased risk for a range of common health conditions, including anxiety, depression, asthma, epilepsy, and stroke[13]. The International Headache Society defines migraine as a recurrent primary headache disorder resulting in attacks that last for 4 to 72 hours. Typically, the headache is unilateral pulsating and moderate or severe in intensity, aggravated by routine physical activity, and associated with at least one of the two; (I) nausea and/or vomiting (II) photophobia and phonophobia (Headache Classification Committee of the International Headache Society (IHS), 2018). Migraine is characterized by five phases. The phases are prodromal or premonitory, aura, headache, postdrome and interictal[14]. A premonitory phase, often lasting hours to days, almost always precedes the aura or headache (Headache Classification Committee of the International Headache Society (IHS), 2018; Russo, 2015). Symptoms that occur during the premonitory phase varied. The most common symptoms are fatigue, neck discomfort, yawning, gastrointestinal disturbances, and mood changes[15,16]. In approximately one-third of migraine sufferers, some attacks are associated with an aura phase which might be comprised of visual, sensory and language, or brainstem disturbances. The disorder may be categorized

according to the frequency of attacks. The episodic migraine is defined as a headache occurring on 1-14 days per month and the chronic migraine is diagnosed in those who experienced a headache on ≥15 per month, at least 8 days after fulfilling the criteria for migraine with or without aura[17,18]. The basic principle in the management of migraine is avoiding the trigger factors, blocking the mediator, and splinting the end organ. Pharmacological treatment is divided into acute and preventive modalities because migraine resembles both acute and chronic conditions[19]. Preventive treatment is recommended for patients with frequent or disabling attacks[4]. The first choice of medications are Beta-blockers, Tricyclic antidepressants, Calcium channel antagonists, and Neuromodulators[20,21]. The Calcitonin gene-related peptide antagonists have opened new scopes for prophylactic treatment options. Botulinum toxin A has been introduced in the treatment of chronic migraine. Various data are emerging with combination therapy. Indications for preventive treatments differ. The American Migraine Prevalence & Prevention expert advisory group recommends preventive treatment for those who experience two or more monthly headaches accompanied by disability and those who experience four or more monthly attacks with or without disability[22]. Some guidelines recommend preventive treatments for patients who have five or more migraine attacks per month but others suggest it only for those who experience headaches on most days of the month[23]. Preventive treatment is often recommended for only 6 to 9 months. But very limited research has examined migraine frequency after the discontinuation of preventive treatment[24]. Preventive treatments aim to reduce headache frequency by at least 50% without intolerable harm[25,26]. In clinical practice, physicians choose preventive treatments based primarily on FDA approval and drug tolerability[27,28]. When properly used, preventive medications are associated with improvement in the quality of life and decreased disability. But a portion of the population of migraineurs in need of preventive therapy does not significantly benefit from monotherapy or experience side effects. Clinical experience and limited evidence suggest that combination preventive therapy benefits individuals with poor responses to monotherapy. Combination therapy of Topiramate and Nortriptyline is effective in migraine patients with incomplete benefits using Topiramate or Nortriptyline in monotherapy[29]. In recent years, Topiramate was tested prospectively. Topiramate showed statistically significant efficacy in migraine prevention. Topiramate appeared as a safe drug with an acceptable safety profile. Tricyclic antidepressants such as Nortriptyline has been a mainstay in the prophylactic therapy of migraine[30]. This study aimed to evaluate the efficacy of combination therapy of Topiramate plus Nortriptyline and monotherapy of Topiramate or Nortriptyline for migraine prophylaxis. In our country, no such study has been performed yet. The study will help to improve the

prophylactic use of migraine and guide future physicians.

METHODS & MATERIALS

Trial design: The Randomized controlled trials were carried out from January 2022 to December 2022. A total of 63 migraine patients were enrolled by block random sampling block of 9, 1:1:1 design in the headache clinic of Dhaka Medical College Hospital. Eligible patients were randomly assigned to the treatment Group A, Group B and Group C on day 1 of the trial. The allocation schedule was created with a list of random numbers generated using a generated program by the Assistant Professor Department of Neurology, Dhaka Medical College, Dhaka. Both the investigators and the patients were blinded to treatment options. All participants in this research provided consent or waived it. ERC-DMC/ECC/2022/194 (R) was approved by the Dhaka Medical College, Dhaka, Bangladesh. The study, titled " Efficacy of Combined Topiramate and Nortriptyline Over Monotherapy of Topiramate or Nortriptyline for Migraine Prophylaxis," was carried out in a tertiary healthcare facility and was approved by the IRB's scientific and ethical committees.

Patients: Patients were enrolled between 1 July 2022 & 30 September 2022. The inclusion criteria for enrollment were as follows: adult migraine patient aged between 18 & 55 years. Exclusion criteria were patients with known comorbid diseases like Ischemic Heart Diseases, Peripheral Vascular Diseases, Coronary Artery Diseases, Uncontrolled Hypertension, Diabetes Mellitus, Asthma, Chronic Obstructive Pulmonary Diseases, Hepatic Failure, Renal Failure, Patients with complicated migraine, like hemiplegic or basilar migraine, Female patients with pregnancy and Lactating mother. Patients, satisfying the inclusion criteria, were enrolled in the study after obtaining their informed written consent from the patients/patient's caregiver.

Sample size calculation: Statistical studies (surveys, quasi-experimental studies, etc.) are always better when they are carefully planned. The problems were carefully defined and operationalized. Quasi-experiments were selected from the appropriate population. The study was randomized correctly. The procedures were followed carefully. Reliable instruments were used to obtain measurements. Finally, the study was adequate size, relative to the aim of the study. Sample size is 21 for each group. Sample size for hypothesis testing of the different between two proportions. $n = \frac{P1(100-p1)^2+P2(100-P2)}{(P1-P2)^2} x(Z\alpha + Z\beta)^2$.

According to this formula sample size was 19. Here the number of participants enrolled after the sample size calculation was 19, and with 10% attrition the sample size was 21.1111≈ 21. That is n=21 participants were enrolled with 10% dropout to finally include 19 participants in the study.

Study intervention: In the headache clinic of DMCH the diagnosed migraine patients who were prescribed

Topiramate were included in Group A, the patients who were prescribed Nortriptyline were included in Group B and the patient who were prescribed Topiramate plus Nortriptyline where included in Group C.

Experimental procedure: The initial assessment of diagnosed patients was done by the investigators with the help of HIT 6 score and headache characteristic. The patients were advised to maintain headache diary. The patients' record with relevant data was reviewed and necessary data was collected according to the objective of the study. These patients were reassessed after 3 months with the help of the HIT-6 score and headache characteristics. The efficacy of Group A and Group B were compared to Group C.

Outcome measures: A specially designated form was used and prescriptions of the patients were collected to collect data. The co-investigators assessed the outcome and documented adverse reactions.

Measures about adverse effects: This study observed the late adverse effects, if any, assessed by doing liver function test (SGPT), kidney function test (S. Creatinine), and bone marrow function test (CBC). Female patients of reproductive age were screened for pregnancy by doing pregnancy test. We provided Counseling of the female patient of reproductive age, not to be pregnant during this study period. In case of accident pregnancy, the participant advised to stop the medication and informed. The spectrum of adverse effects of Group A and Group B were compared to Group C.

RESULTS

Sample characteristic: Of 95 screened patients, 73 were enrolled and randomly assigned to the treatment with Topiramate group (Group A), Nortriptyline group (Group B) and combined Topiramate plus Nortriptyline group (Group C). The 24 patients allocated in Group A and Group B 3 from both groups loss to follow-up and from Group C patients 25 patients allocated in the group 4 were loss to follow-up. Twenty-One patients were completed follow-up analyzed in all three groups. Demographic data, consumption of Oral Contraceptive Pill (OCP) and frequency, duration, intensity (Visual Analogue Score) and HIT-6 score were measured at baseline and 3 months after treatment in each group. These data were compared between three groups.

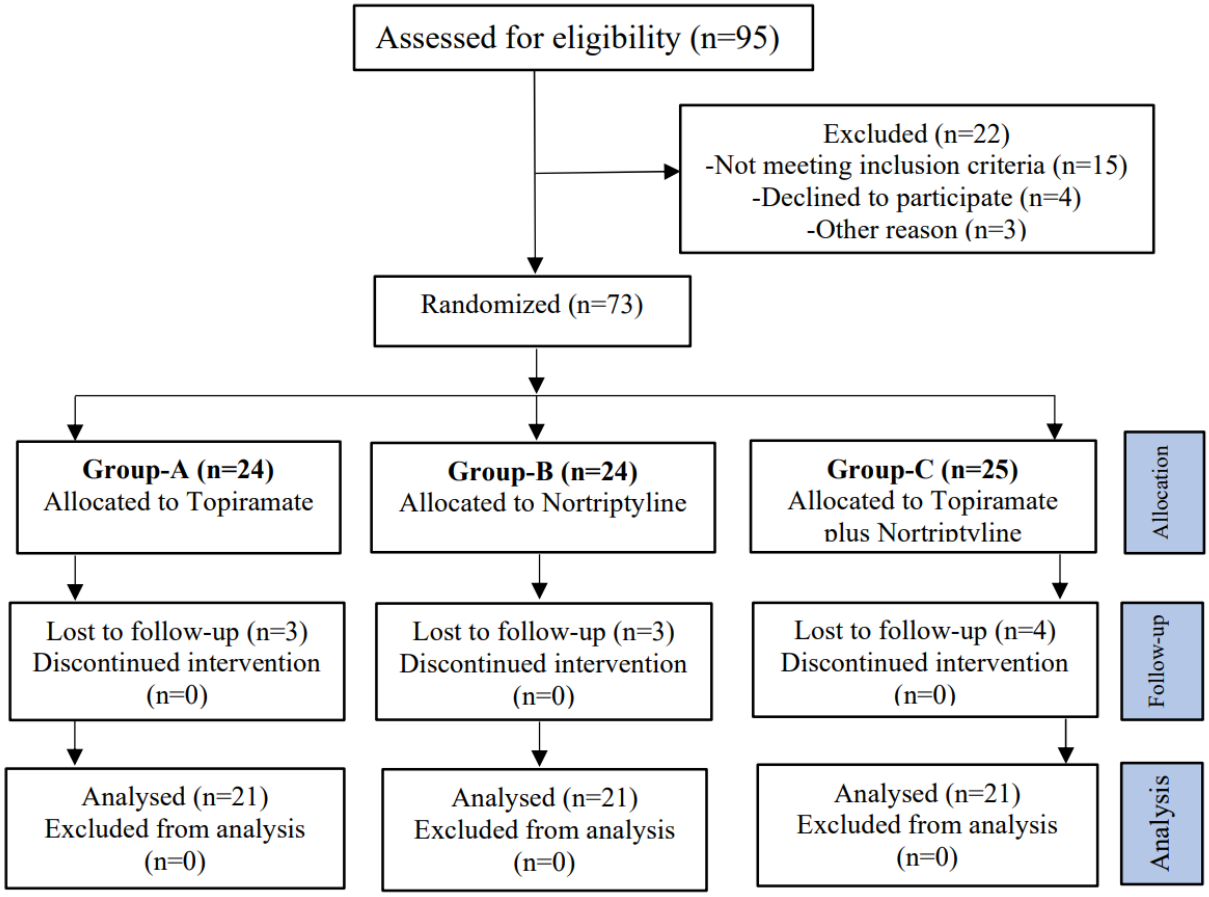


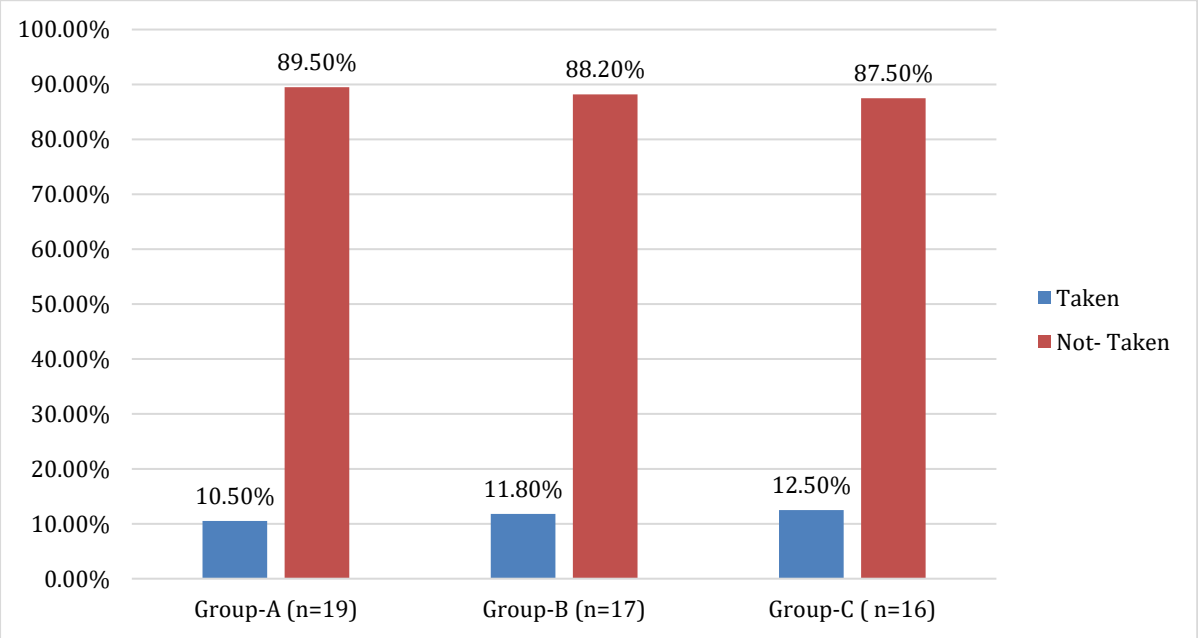
Figure – 1: Enrolment, Randomization, Follow-up and Analysis of Patients According to the CONSORT 2010 Flow Diagram

Distribution of the study patients by their age in years. In Group A, highest patients in age group 30-39 years which occupied (42.9%), in Group B, highest patients in age group 20-29 years which occupied (33.3%) and in Group C, highest patients in age group 20-29 years which occupied (42.9%). Sex distribution in Group A (90.5%), in Group B (81.0%) and Group C (76.2%) of study patients were female. Female gender was predominant in each Group. Male: Female ratio was 1:9, 1:4, 1:3 respectively in Group A, Group B and Group C (**Table I**).

Table – I: Demographic Distribution of the Study Patients (*n*=63)

Age Distribution (year)	Group A	Group B	Group C	*p*-value
<20	0.0	14.3	0.0	0.327
20-29	38.1	33.3	42.9	
30-39	42.9	28.6	28.6	
40-49	14.3	19.0	28.6	
>50	4.8	4.8	0.0	

Sex Distribution				
Male	9.50	19.0	23.80	0.463
Female	90.50	81.0	76.20	



p-value obtained by Chi-square test (P=0.983)

Figure – II: Distribution of the Female Patients by Consumption of Oral Contraceptive Pill Among Three Groups (*n*=52)

In each group, the consumption history of OCP was almost similar. Frequency, duration and intensity of headache of the study patients (**Figure II**). Comparison of per months frequency, duration and intensity (VAS score) of headache among three Groups of study patients. Headache frequency in headache days/ month was highest in Group B 12.0(2.0-20.0), duration of headache in hours was highest in Group A and Group B6.0 (2.0-24.0). Intensity of headache which was expressed by visual analogue scale (VAS) score were same in Group A, Group B and Group C 8.0 (7.0-9.0.) (**Table II**).

Table II: Baseline headache status of study patients (N=63)

	Group A (*n*=21)	**Group B (*n*=21)**	**Group C (*n*=21)**	***p*-value**
Headache frequency (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.

Comparison of after three months of treatment, headache frequency expressed as headache days/month among three groups of study patients at the end of 1st, 2nd, 3rd months. At the end of 1st month, median headache frequency was the same in all three groups (3.0 days/month). At the end of 2nd month, headache frequency was highest in Group B (2.0 days/month). At the end of 3rd month, headache frequency was same in all three groups (0.0day/month). Post Hoc Bonferroni test (3rd month) Group A vs Group B p value is 0.730, Group A vs Group C p value is 0.487 and Group B vs Group C p value is 0.036. Wilcoxon Signed Ranks test 1st month vs 2nd month of Group A, Group B and Group C p value are 0.011, 0.004 and <0.001 respectively. 2nd month vs 3rd month of Group A, Group B and Group C p value are 0.001, 0.004 and <0.0022 respectively and 1st month vs 3rd month are <0.001, <0.001 and <0.001 respectively (**Table III**).

Table – III: Comparison of after treatment headache frequency per month among three Groups (*n*=63)

-	**Group A (*n*=21)**	**Group B (*n*=21)**	**Group C (*n*=21)**	***p*-value**
1st month				
Median (IQR)	3.0 (2.0-4.0)	3.0 (2.0-4.0)	3.0 (2.0-5.0)	0.654
2nd month				
Median (IQR)	1.0 (0.65-2.0)	2.0 (1.0-3.0)	1.0 (0.0-2.5)	0.562
3rd month				
Median (IQR)	0.0 (0.0-1.0)	0.0 (0.0-1.0)	0.0 (0.0-0.0)	0.022*

Data were expressed in Median and Range p-value obtained by Kruskal Wallis test and Wilcoxon Signed Ranks test p<0.05 was considered significant throughout the study.

Comparison of headache frequency before treatment and 3 months of treatment among three Groups of study patients. Headache frequency significantly decreased in all Groups. Headache frequency before treatment and after 3 months of treatment among the groups. Mann-Whitney test after 3 months of treatment of Group A vs Group B p value is 0.307, Group A vs Group C p value is 0.050 and Group B vs Group C p value is 0.006 respectively. Comparison of duration of headache before treatment and 3 months of treatment among three Groups of study patients. Median duration of headache decreased in all Groups. Maximum decreased in Group C compared to Group A and Group B. Comparison of duration of headache before treatment and 3 months of treatment among three Groups of study patients. Median

duration of headache significantly decreased in Group A and Group C. Maximum decreased in Group C compared to Group A and Group B. VAS score before and after three months of treatment among the groups. VAS score before treatment and 3 months of treatment among three Groups of study patients. Median VAS score significantly decreased in all Groups. Maximum decreased in Group C compared to Group A and Group B. VAS score before and after three months of treatment within the same groups. VAS score before treatment and 3 months of treatment among three Groups of study patients. Median VAS score significantly decreased in all Groups. Maximum decreased in Group C compared to Group A and Group B. Association of pain status before and after three months of treatment (**Table VI**).

Table – IV: Comparison of Baseline and After 3 Months Treatment Headache Characteristic (*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*
p-value	<0.001*	<0.001*	<0.001*	
Duration of Headache (hours)				
Before Treatment				
Median	6.0	4.0	6.0	0.061
IQR	5.5-12.0	3.0-8.0	4.0-12.0	
After 3 Months of Treatment				
Median	6.0	4.0	5.0	0.366
IQR	4.0-10.0	3.5-8.0	3.0-10.0	
p-value	0.011*	0.371	<0.001*	
VAS score				
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 Wilcoxon Signed Ranks Test. p<0.05 was considered significant. *Significant

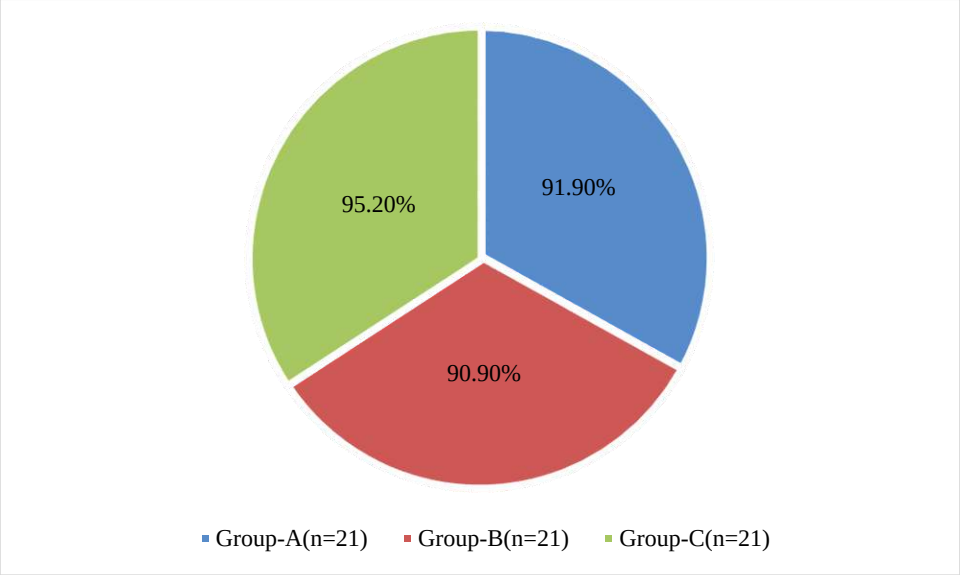


Figure – III: Pie Diagram Showing the Percentage of Headache Frequency Reduction After Three Months of Treatment from Baseline Among Three Groups of Study Patients (*n*=63)

Percentage of headache frequency reduction after three months of treatment form baseline among three Groups of study patients. There was highest reduction of headache frequency (95.20%) in Group C, followed by (91.90%) in Group A and lowest reduction in Group B (90.70%) (**Figure III**).

Comparison of VAS scores before treatment and 3 months of treatment among three Groups of study patients. After three months of treatment, proportion of VAS scores significantly decreased in all Groups. Maximum decreased in Group C compared to Group A and Group B (**Table V**).

Table – V: Association of Pain Status (According to VAS Score) During Enrolment 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(%)	
	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)	3(14.3)	0(0.0)	2(9.5)	0(0.0)
p-value	0.567		0.466		0.007*	

Comparison of HIT-6 score before treatment and 3 months of treatment among three Groups of study patients. There was the highest reduction of HIT-6 score in Group C (64.3±5.2 to 45.0±5.2). HIT-6 Score before and after three months of treatment among the Groups of the patients. After treatment, mean HIT-6 score significantly decreased in all Groups. Post Hoc Bonferroni test of HIT-6 score before and after three months of treatment. After treatment, Group A vs Group C and Group B vs Group C showed statistically significant results. Post Hoc Bonferroni test of HIT-6 score during enrollment of Group A vs Group B p value is 1.000, Group A vs Group C p value is 0.830 and Group B vs Group C p value is 1.00 respectively. Post Hoc Bonferroni test of HIT-6 score follow-up visits 3 months later of Group A vs Group B p value is 1.000, Group A vs Group C p value is 0.012 and Group B vs Group C p value is 0.032 respectively (**Table VI**).

Table – VI: Comparison of HIT-6 Score During Enrolment and Follow-up Visits 3 Months Later Among Three Groups (*n*=63)

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

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

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 VII**).

Table – VII: Adverse Effects Profile Among the Three Groups of Study Patients (*n*=63)

Groups	Adverse effects	n=63	%
Group A (*n*=21)	Yes	5	23.8
	Sedation	4	19.0
	Weakness	1	4.8
Group B (*n*=21)	Yes	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)	Yes	12	57.1
	Sedation	3	14.3
	Dry mouth	3	14.3
	Blurring of vision	3	14.3
	Weakness	3	14.3

Data were expressed in frequency and percentage.

DISCUSSION

This study was carried out to compare the efficacy and safety between combination therapy of Topiramate plus Nortriptyline and monotherapy of Topiramate or Nortriptyline for migraine patient. Using the VAS score, HIT-6 score, and the frequency, duration, and intensity of headaches, the groups medication efficacy was compared. During the research period, adverse symptoms including sedation, dry mouth, blurred vision, weakness, and palpitations were measured to evaluate safety. Age is most prevalent between the ages of 25 and 55 in the majority of research[31]. We found that the age group of 30-39 years old had the greatest study patient occupancy (42.9%) in Group A; the age group of 20-29 years old had the highest study patient occupancy (33.3%) in Group B; and the age group of 20-29 years old had the highest study patient occupancy (42.9%) in Group C. This coincides well with the age range that is generally acknowledged as the most common for migraines. According to epidemiological research, there is a notable global majority of migraine in women (52% versus 37%). According to a recent population-based study conducted in Turkey, women are far more likely than males (12%) to get migraine headaches (24%)[32]. We observed, Group A (19.5%), in Group-B (81.0%) and in Group C (76.2%) of study patients were female. Male to female ratio was 1:9 in Group A, 1:4 in Group B and 1:3 in Group- C. The study showed female gender was predominant in each to which was supported by a study[33]. where stated that 18% female and 6% male in US were affected yearly by migraine headache. 83Precipitating drug for headache Oral Contraceptive

Pill (OCP) consumption among three groups of the study patients showed (10.5%) patients in Group A, (11.8%) patients in Group B and (12.5%) patients in Group C had taken OCP. In each group, consumption history of OCP was almost similar. In this study baseline headache frequency was 6.0 in headache days/month in Group A, 12.0 headache days/month in Group B and 6.0 headache days/month Group C which was near about the study[34]. where headache frequency was 8.1 headache days/month in Group I, 8 headache days/month Group II and Group III. In this study, duration of headache in hours was highest in Group A 6.0, in Group B 4.0 and in Group C 6.0 and baseline intensity of headache, which was expressed by Visual Analogue Scale (VAS) score was similar in Group A, Group B and Group C (8.0). In this study, the percentage of headache frequency reduction after 3 months of treatment from baseline among there group of study patients were (95.20%) in Group C, (91.90%) in Group A and (90.70%) in Group B which was similar to a study[34]. Where 78.3% patients of combination group, 47.0% patients of Topiramate group and 37.0% patients of Notriptyline group had at least 50% reduction in headache frequency reduction. This study showed that, after treatment headache frequency expressed as headache days per month among there groups of study patients at the end of 1st month was 3.0 in Group A, Group B and Group C; at the end of 2nd month was 1.0 in Group A, 2.0 in Group B and 1.0 in Group C; at the end of 3rd month headache days/month was 0.0 in all three groups. We observed, duration of headache in hours expressed by median (IQR), 6(4.0-12.0) to 5(3.0-10.0) indicated that highest reduction by the Group C compared to Group A and Group B. The intensity of headache expressed by VAS score, reduced maximum in Group C (8.0 to 2.0) compared to Group A and Group B. In this study, comparison of HIT-6 score before treatment and 3 months of treatment among three groups of study patients showed that there was highest reduction of HIT- 6 score in Group C 64.3 to 45.0 (p-value<0.001) followed (p-value <0.001) and there after 64.8 to 50.1 in Group B (p-value<0.001). From overall findings, it can be concluded that the combination of Topiramate plus Nortriptyline (Group C), provided best improvement in prophylactic management of migraine. The Group C, achieved control over the all characteristics of migraine headache such as headache frequency, duration of headache, intensity of headache which expressed as VAS score. HIT-6 score was also reduced most by Group C.

Managing migraine patients can be challenging, especially when they are referred from a neurologist to a headache specialist. According to guidelines, the goal of preventative treatment should be to reduce headache frequency by at least 50%, with the premise that this reduction is clinically relevant[35,36]. When a patient does not respond as expected to suitable therapy, or declares at the initial consultation that he or she has tried everything and nothing works, it is critical to discover the reason for treatment failure. Inadequate pharmacotherapy is one of

numerous probable causes[37]. Inadequate pharmacotherapy can occur when inappropriate treatments are chosen, excessive initial doses are used, final doses are insufficient, treatment duration is too short, combination therapy is required, the patient fails to absorb the drug, or the patient is noncompliant[37]. As a result, while monotherapy is normally suggested, sensible combination therapy is sometimes required.

In this study period, it was observed that in 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.

There are numerous and significant barriers to adequate migraine care[38]. With advancements in recognition and diagnosis, as well as improved access to effective acute treatments, recent focus has shifted to the impediments to proper preventative medication use[39]. A significant number of migraineurs using preventative monotherapy are dissatisfied with its efficacy.

Limitation of the Study

The present study was conducted in a very short period due to time constraints and funding limitations. The small sample size was also a limitation of the present study.

Conclusion and recommendation

The combined Topiramate plus Nortriptyline in the headache treatment compared to monotherapy of topiramate or nortriptyline group, the frequency, duration, severity of the headache and HIT-6 score, all were reduced most by the combined group. This study can serve as a pilot to much larger research involving multiple centers that can provide a nationwide picture, validate regression models proposed in this study for future use and emphasize points to ensure better management and adherence.

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Conflict of Interest

The authors declare no conflict of interest.

Ethical Approval

The study was approved by the Institutional Ethics Committee.

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