Original Article

Combined Effectiveness of Nortriptyline and Topiramate in Comparison to Nortriptyline Alone as Migraine Prophylaxis

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Abstract:

Background: Migraine is a chronic neurological illness characterized by recurrent episodes of headache and other related symptoms. Patients who experience severe headaches frequently need to use both acute and preventive medication treatments for migraine. Prophylactic treatment is intended to improve the patient's capacity to function normally, to increase the benefits of acute treatments, and to lessen the frequency, duration, or severity of attacks. **Objective:** The aim of this study was to compare the combined effectiveness of Nortriptyline and Topiramate in comparison to Nortriptyline alone as migraine prophylaxis. **Methods:** The Randomized controlled trail was conducted in the department of Pharmacology and Therapeutics, Dhaka Medical College, Dhaka, from January 2022 to December 2022. A total of 42 patients were enrolled by block random sampling block of 3, 1:1 design. The Participants were divided into two groups. The 21 patients treated with Nortriptyline were in group A and the 21 patients treated with Nortriptyline-Topiramate were in group B. **Result:** In this study, in both Group, highest patients in age group 20-29 years. Male: Female ratio was 1:4 and 1:3 respectively in Group A and Group B. At the end of 3rd month, headache frequency was same between two groups (0.0day/month). Median duration of headache and VAS score significantly decreased in two groups. Maximum decreased in Group B compared to Group A. There was the highest reduction of HIT-6 score in Group B (64.3±5.2 to 45.0±5.2). **Conclusion:** Both drugs were effective in reducing headache. Between them, Nortriptyline-Topiramate provided the best improvement.

Key words: Migraine, Prophylaxis, Topiramate, Nortriptyline.

J Com Med Col Teachers Asso July 2024; 28(2): 48-52

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Introduction:

Migraine is a chronic neurologic illness, include periodic bouts of headaches and related symptoms[1]. The estimated prevalence and potential prevalence of migraine in our nation was found to be 28.8% in a year and only 4.9% of patients received prophylactic treatment[2]. Only 13% of patients in the American Migraine Prevalence and Prevention Study were receiving prophylactic treatment, despite the fact that 38% of migraine patients needed prophylactic treatment[3]. The objective is to enhance the effectiveness of acute attack management, enhance functional status and reduce headache-related impairment through preventive treatment[4].

DOI:https://doi.org/10.3329/jcomcta.v28i2.77977

Pharmacological treatment for migraine is frequently separated into acute and preventative modalities[5]. Pharmacological agents such as beta-blockers, tricyclic antidepressants, calcium channel antagonists, and neuromodulators are often prescribed as first-choice for the prevention of migraine[6]. Preventive drugs have been linked to improved quality of life[7] and reduced disability[8].

Globally, it impacts more than one billion people[9]. 11.6% (95% CI 10.7 - 12.6%; random effects) of people worldwide had migraines; the prevalence was 10.4% in Africa, 10.1% in Asia, 11.4% in Europe, 9.7% in North America, and 16.4% in Central and South America[10]. When it comes to years lost to disability, migraine ranks second globally among all neurologic disorders[11]. There is a significant and possibly widespread sickness burden associated with migraine. In the US population, the one-year prevalence is 6% for men and 18% for women[12]. Between the ages of 25 and 55 is when the prevalence peaks. According to the Headache Classification Committee of the International Headache Society (IHS), 2018: (I) nausea and/or vomiting (II) photophobia and phonophobia are the two most common causes of unilateral pulsating headaches. The headaches are usually aggravated by routine physical activity[13].

Migraine is classified as episodic if it occurs one to fourteen days a month and as chronic if it occurs fifteen days or more a month and at least eight days after meeting the criteria for migraine with or without aura[14]. The three main strategies for managing migraines are splinting the end organ, inhibiting the mediator, and avoiding trigger factors[15]. According to 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 Nortriptyline in monotherapy[16].

Methodology:

Study design: This was a randomized controlled trail study on combined effectiveness of Nortriptyline and Topiramate in comparison to Nortriptyline alone as migraine prophylaxis. **Place of study:** This randomized controlled trail study was conducted by the department of Pharmacology & Therapeutics, Dhaka Medical College, Dhaka, Bangladesh. **Duration of the study:** The duration of the study was one year from January 2022 to December 2022. An extensive literature review process was done from the beginning of the study. **Population:** This randomized controlled trail study was carried out in the Headache Clinic, Neurology outpatient department, Dhaka Medical College Hospital, Dhaka, Bangladesh. Of 71 screened patients, 49 were enrolled and they were randomized to receive either Nortriptyline treatment (group A) or Nortriptyline-Topiramatetreatment (group B). Out of 24 patients in Group A, 3 were lost to follow-up and 21 had finished the follow-up. Out of the 25 patients in Group B, 4 patients were lost to follow-up and 21 patients finished the follow-up. **Inclusion criteria:** Adult migraine patients who aged between 18 years to 55 years were included. **Exclusion criteria:** Patients with known comorbid diseases like Ischemic Heart Disease, Coronary Artery Disease, Uncontrolled Hypertension, Diabetes Mellitus, Asthma, Chronic Obstructive Pulmonary Disease, Hepatic Failure, Renal Failure, Patients with complicated migraine, like hemiplegic or basilar migraine, female patients with pregnancy and lactation. Patients fulfilled the selection criteria after obtaining their informed written consents from the patients or their caregiver. **Randomization:** The block random sampling method was maintained by inclusion and exclusion criteria in the Headache clinic of above mentioned hospital, block of 3, 1:1 design. **Study intervention:** At first, assessment of all migraine patients was done with the help HIT-6 score and headache characteristics. All the migraine patients were advised to maintain headache diary. Face to face interview was done to collect data with a semi-structured questionnaire. After collection, the data were checked and cleaned, followed by editing, compiling, coding, and categorizing according to the objectives and variable to detect errors and to maintain consistency, relevancy and quality control. These patients were assessed again after completing 3 months of treatment with the help of HIT-6 score and headache characteristics. Patients treated with Nortriptyline included in group A andpatients treated with To Nortriptyline-Topiramate included in group B. **Outcome:** A specially designated form was used and prescriptions of the patients were collected to collect data. The efficacy of group A was compared to group B. **Statistical methods:** The p-values were obtained from these tests. A p- value of <0.05 was considered statistically significant at 95% CI (Confidence Interval). Evaluation of the results used to be obtained via the use of a window-based computer software program devised with Statistical Packages for Social Sciences (SPSS) 26 version.

Result:

Sample characteristic: Of the 71 patients assessed, 49 were enrolled and randomly assigned to two groups:

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Topiramate (Group A) and Nortriptyline -Topiramate (Group B). Of the 24 patients assigned to Group A, 3 were lost to follow-up, whereas of the 25 patients assigned to Group B, 4 were lost to follow-up. 21 patients completed follow-up in both groups. Headache parameters such as frequency, duration, intensity (Visual Analogue Score), and HIT-6 score were evaluated at baseline and three months after treatment. These results were compared across two groups.

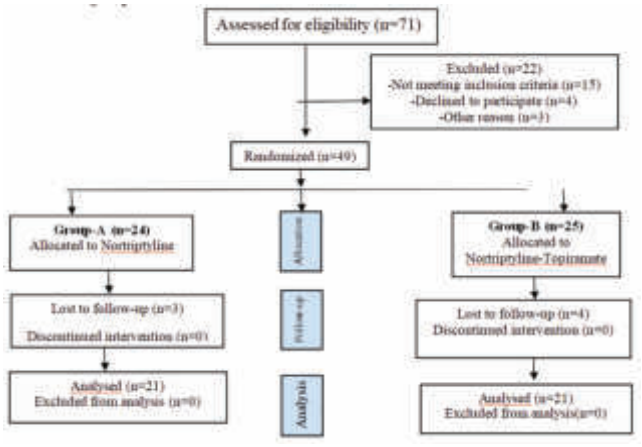

Figure-1: Enrollment, randomization, follow up and analysis of patients according to the CONSORT 2010 flow diagram.

Table-I: Distribution of the patients according to age (n = 42)

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

Table I shows that, the distribution of study patients based on their age in years. In both groups, the majority of patients were between the ages of 20 and 29 years.

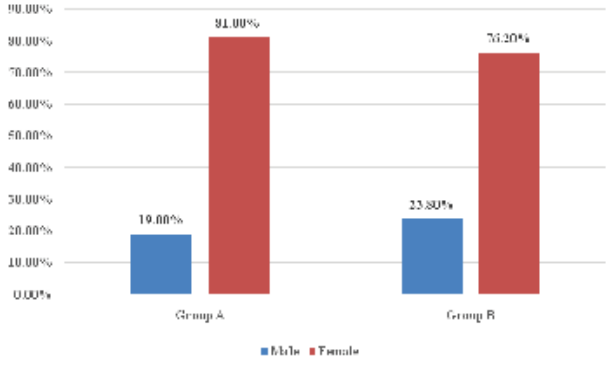

Figure-II: Distribution of the patients according to gender (n = 42)

According to Figure II, the majority of the patients in both groups were female, with 17 (81.00%) and 16 (76.20%) respectively. Male: female ratios were 1:4 and 1:3, respectively, in Groups A and B.

Table-II: Baseline headache status of study patients (n = 42)

	Group A (n=21)	Group B (n=21)	*p*-value
Headache frequency (days/ month)	12.0 (2.0-20.0)	6.0 (2.0-20.0)	0.079
Duration of headache (hours)	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)	0.967

The Kruskal-Wallis H test yielded median and IQR values, with p-values <0.05 considered significant. Table II compares the monthly frequency, duration, and intensity (VAS score) of headaches in two groups of study subjects.

Table-III: Comparison of Baseline and after 3 months treatment headache characteristic (n=42)

Headache characteristic	Group A (n=21)	Group B (n=21)	*p*-value
Headache frequency (days/month)			
Before treatment			
Median (IQR)	12.0 (6.0-16.0)	6.0 (3.5-12.0)	0.711
After 3 months of treatment			
Median (IQR)	0.0 (0.0-1.0)	0.0 (0.0-0.0)	0.012*
p-value	<0.001*	<0.001*	
Duration of headache (hours)			
Before treatment			
Median	4.0	6.0	0.358
IQR	3.0-8.0	4.0-12.0	
After 3 months of treatment			
Median	4.0	5.0	0.366
IQR	3.5-8.0	3.0-10.0	
p-value	0.371	<0.001*	
VAS score			
Before treatment			
Median	8.0	8.0	0.046
IQR	7.0-9.0	7.0-9.0	
After 3 months of treatment			
Median	3.0	2.0	0.079
IQR	2.0-4.0	2.0-3.0	
p-value	<0.001*	<0.001*	

Table-III shows that the headache frequency reduced in both groups. The median duration of headache and VAS scrore maximum reduced in Group B.

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Table-IV: Comparison of HIT-6 score during enrollment and follow-up visits 3 months later between two groups

HIT-6 score		Group A (n=21)	Group B (n=21)	*p*-value
Before treatment	Mean±SD	64.8±5.0	64.3±5.2	0.564
	Range	(56.0-75.0)	(52.0-76.0)	
After 3 months of treatment	Mean±SD	50.1±6.7	45.0±5.2	0.084
	Range	(38.0-62.0)	(36.0-56.0)	
	P value	<0.001*	<0.001*	

Table IV shows the HIT-6 score before and after three months of treatment among the three groups of study patients. Group B experienced the greatest reduction in HIT-6 score (64.3±5.2 to 45.0±5.2).

Discussion:

A randomized controlled trail was conducted in the Department of Pharmacology & Therapeutics, Dhaka Medical College, Dhaka, from January 2022 to December 2022. A total of 42 patients were enrolled and analyzed in this study. This study compared the efficacy of Nortriptyline- Topiramateversus Nortriptyline as migraine prophylaxis. The groups' pharmaceutical efficacy was assessed using the VAS score, HIT-6 score, monthly frequency and duration in hours. The majority of study focuses on people aged 25 to 55[17]. We discovered that the majority of patients in both groups were between the ages of 20 and 29 years which occupied 33.3% in Group A and 42.9% in Group B. According to a recent population-based study conducted in Turkey, women are significantly more likely than men (12%) to get migraine headaches (24%)[18]. We found that Group A (19.5%) and Group B (76.2%) of study participants were female. The study found that the female gender was prevalent in both, which was corroborated by a study conducted by[19], which claimed that 18% of females and 6% of males in the United States were affected by migraine headaches each year. In this study, the baseline headache frequency was 6.0 headache days/month in Group A and 6.0 headache days/month in Group B, which was similar to the study conducted by[20]. The proportion of headache frequency decrease after 3 months of treatment from baseline among the study participants was (95.20%) in Group B and (90.90%) in Group A, which was similar to the study conducted by[21]. Whereas 78.3% of patients in the combined group, 47.0% in the Topiramate group and 37.0% in the Nortriptyline group experienced at least a 50% reduction in headache frequency. Overall results showed that Group B obtained control over all migraine headache features including headache frequency, duration, and intensity, measured by the VAS score. Group B also experienced the greatest reduction in HIT-6 scores.

Limitations of the study: The study could not perform in multi-centric set-up and sample size was relatively small. There were also funding and time constraints.

Recommendations:

This study can act as a test run for much larger studies including several centers that will provide a more valid picture of the country.

Conclusion:

The Nortriptyline-Topiramategroup showed greatest reduction in compared to Nortriptyline group in headache characteristics and HIT-6 score reduction.

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