Original Article

Efficacy of Topiramate Over Nortriptyline as Monotherapy — Migraine Prophylaxis

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Nargis Akter [1*], Ahmed Imran [2], Khatun-E-Zannat [3], Rozina Afroz [4], Sk Humayun Kabir [5], Shahina Parvin [6], Ishrat Jahan Shammy[7], Md Mahbubur Rahman[8], Ripa Biswas [9] Tania Alam [10]

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*Corresponding Author

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ABSTRACT

Introduction: *Migraine is a chronic neurologic disease characterized by attacks of throbbing, often unilateral headaches that are exacerbated by physiological activity and associated with photophobia, phonophobia, nausea and vomiting.* ***Objective:*** *The aim of the study was to assess the efficacy of Topiramate over Nortriptyline as monotherapy for migraine prophylaxis.* ***Methods and Materials:*** *A Randomized controlled trial was done at department of Pharmacology and Therapeutics, Dhaka Medical College, Dhaka, Bangladesh. The total duration of the study was from January 2022 to December 2022. A total of 42 migraine patients were enrolled by block random sampling block of 3, 1:1 design. The patients were divided into two groups. In Group A, 21 patients were treated with Topiramate and in Group B, 21 patients were treated with Nortriptyline for consecutive 3 months.* ***Results:*** *In Group A, highest patients in group30-39 years which occupied (42.9%), in Group B, highest patients in group 20-29 years which occupied (33.3%). Male: Female ratio was 1:9 and 1:4 respectively in Group A and Group B.*

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1. *Lecturer, Department of Pharmacology, Chandpur Medical College, Chandpur, Bangladesh.*
2. *Phase B Resident, Dhaka Medical College, Dhaka, Bangladesh.*
3. *Assistant Professor, Department of Pharmacology, Diabetic Association Medical College, Faridpur, Bangladesh*
4. *Lecturer, Department of Pharmacology, Khulna Medical College, Khulna, Bangladesh.*
5. *Lecturer, Department of Pharmacology, Shaheed Tajuddin Ahmad Medical college, Gazipur, Bangladesh.*
6. *Lecturer, Department of Pharmacology, Sheikh Sayera Khatun Medical College, Gopalgonj, Bangladesh.*
7. *Lecturer, Department of Pharmacology, Dhaka Medical College, Dhaka, Bangladesh.*
8. *Assistant Professor, Department of Pharmacology, Bashundhara Ad-din Medical College, Dhaka, Bangladesh*
9. *Lecturer, Department of Pharmacology, Dhaka Medical College, Dhaka, Bangladesh.*
10. *Assistant Professor, Department of Physiology, Chandpur Medical College, Chandpur, Bangladesh.*

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 6.0(2.0-24.0). Intensity of headache which was expressed by visual analogue scale (VAS) score were same in Group A and Group B 8.0 (7.0-9.0). After treatment, at the end of 1st month, median headache frequency was the same (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 between two groups (0.0day/month). The reduction of headache frequency was higher (92.90%) in Group A than (90.70%) in Group B. Median duration of headache significantly decreased in two Groups. Maximum decreased in Group A compared to Group B. Regarding comparison of VAS scores before treatment and 3 months of treatment, Proportion of VAS scores significantly decreased in two Groups. Maximum decreased in Group A compared to Group B. The adverse effects profile among the three Groups of study patients during this study period. It was observed that Group B 12(57.1%) had the highest experience of adverse effects. Highest 4(19.0%) patients had experienced sedation in Group A and the lowest 1(4.8%) patient in Group B. Blurring of vision 3(14.3%) patients in Group B. Palpitation 1(4.8%) patients Group B, weakness 1(4.8%) patient in Group A. ***Conclusion:*** *In migraine patient prophylactic management, the patients who were treated with the Topiramate in the Headache Clinic of Dhaka Medical College showed the statistically significant results in this study with the best efficacy after 3 months of treatment compared Nortriptyline group.*

Keywords*: Topiramate, Nortriptyline, Migraine Prophylaxis.*

INTRODUCTION

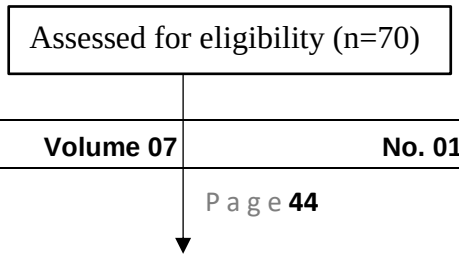
Migraine is a chronic neurologic disease characterized by attacks of throbbing, often unilateral headaches that are exacerbated by physiological activity and associated with photophobia, phonophobia, nausea, vomiting [1] and frequently cutaneous allodynia [2-4]. About one-third of those with migraine have migraine with aura and approximately three-quarters experience a premonitory phase before the onset of the headaches [5]. Initially, it was thought that migraine occurs only due to vascular events. But now it is referred as a neural as well as vascular phenomenon [6]. Migraine headaches and headache-related disabilities affect approximately 15% of women and 6% of men over one year worldwide [7]. Forty percent of adults with episodic migraine and all patients with chronic migraine might benefit from preventive medications; yet, only about 12 percent of adults with frequent migraines take preventive medications [8,9]. The U.S. Food and Drug Administration (FDA) has approved five drugs for episodic migraine prevention in adults: The Beta Blockers; Propranolol and Timolol, and the antiepileptic drugs; Topiramate and Sodium Valproate and Methysergide, Flunarizine is commonly used for adults in Europe [10]. Topiramate is an antiepileptic drug. Recently approved by the U.S. Food and Drug Administration (FDA) for the prevention of migraine headaches in adults. The exact mechanism of action of Topiramate in migraine prophylaxis is uncertain. It is known to affect neuronal hyperexcitability, which is one probable factor in the development of migraine [11]. Though it was initially introduced as an antidepressant, it is also very effective as a pain reliever. It is used for migraines and other headaches as well as other pain conditions such as back pain [12]. Nortriptyline was initially introduced as an antidepressant. It is also very effective as a pain reliever. It is used for migraines and other headaches as well as other pain conditions such as back pain. During a migraine attack, there's a drop-in serotonin level [13]. Nortriptyline is usually used to that depression. But there are some evidences that it is also beneficial in treating migraine [14].

METHODS AND MATERIALS

Patients: Of 70 screened patients, 48 were enrolled and randomly assigned to the treatment with Topiramate and to the treatment with Nortriptyline group. Among the 24 patients in the allocated 3 were loss to follow-up and 21 were completed follow-up in both groups. **Trial design:** The Randomized controlled trials were carried out from January 2022 to December 2022. A total of 42 migraine patients were enrolled by block random sampling block of 3, 1:1 design in the headache clinic of Dhaka Medical College Hospital. **Inclusion and Exclusion:** Adult migraine patients aged between 18 & 55 years were included. 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. **Study intervention:** In the headache clinic of DMCH the diagnosed migraine patients who were prescribed Topiramate were included in group A and the patients who were prescribed Nortriptyline group B. **Experimental procedure:** The initial assessment of diagnosed patients was done by me 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 were compared to Group B. **Outcome measures:** A specially designated form was used and prescriptions of the patients were collected to collect data. **Statistical methods:** Continuous data were expressed in mean ± SD (standard deviation) and nominal data were expressed in percentages. Differences in baseline character between groups were assessed by unpaired t-test or Mann-Whitney U-test for continuous variables and Chi square test for categorical variables. Paired t-test or Wilcoxon signed Rank Sum test for comparison of pre-and post-treatment was done. The p-values were obtained from these tests. A p-value of <0.05 was considered statistically significant at 95% CI (confidence interval). Analysis of data was carried out by using Statistical Package for Social Sciences (SPSS) 26 version.

RESULTS

This study was conducted to compare the efficacy between Topiramate and Nortriptyline for migraine prophylaxis. The data was collected from the Neurology Outpatient Department (Headache Clinic) of Dhaka Medical College Hospital from July to December, 2022, 42 patients were enrolled. The patients were divided into two groups. A total of 42 migraine patients were enrolled by block random sampling block of 3, 1:1 design. Demographic data, consumption of Oral Contraceptive Pill (OCP) and frequency, duration, severity (Visual Analogue Scale score) and HIT-6 score were measured at baseline and 3 months after treatment in each group. These data were compared between two groups. During study period, sedation, dry mouth, blurring of vision, palpitation, weakness were searched for in each groups. Results were calculated by using different statistical tests. The findings were presented with tables and diagrams.



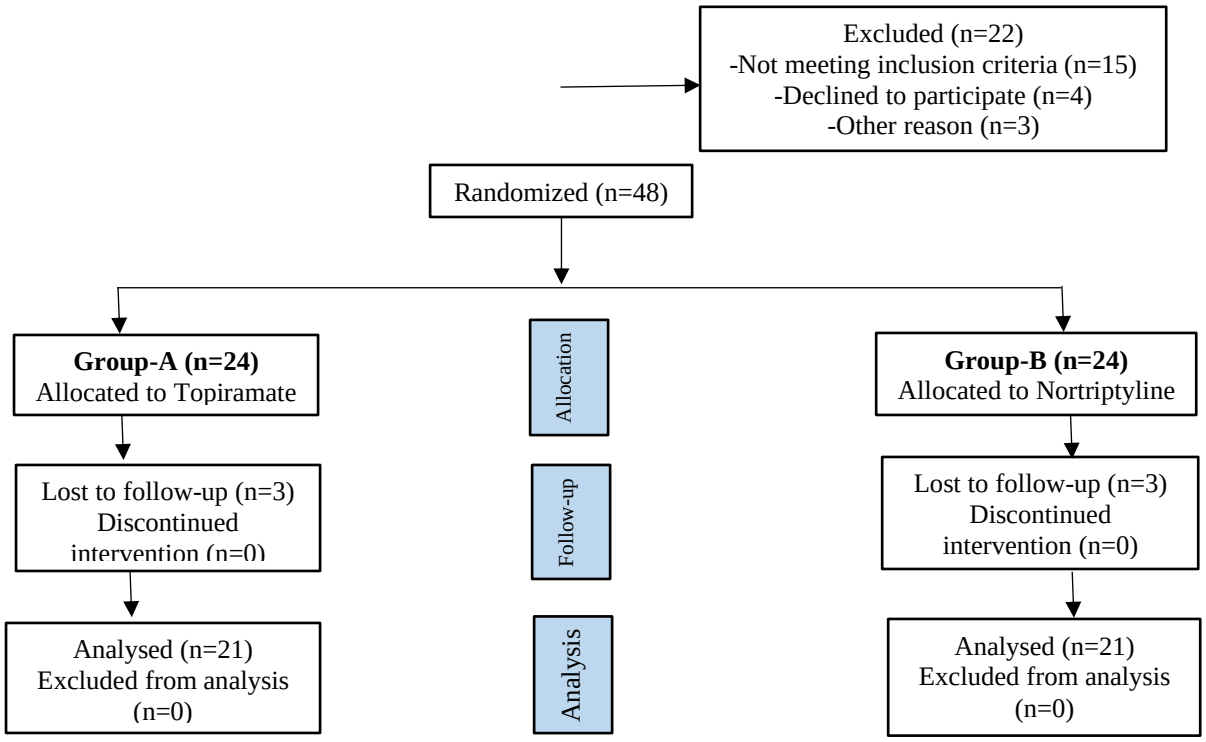


Figure 1: Enrollment, randomization, follow up and analysis of patients according to the CONSORT 2010 flow diagram.

Table I: Demographic distribution of the study patients. (n=42)

	Group-A		Group=B		P value
Age group	N=21	%	N=21	%	
<20	0	0	3	14.30	0.327
20-29	8	38.10	7	33.30	
30-39	9	42.90	6	28.60	
40-49	3	14.30	4	19.0	
>50	1	4.80	1	4.80	
Gender					
Male	2	9.50	4	19	0.463
Female	19	90.50	17	81	

p-value obtained by Chi-square test

Table I Shows distribution of the study patients by their age in years. In Group A, highest patients in group30-39 years which occupied (42.9%), in Group B, highest patients in group 20-29 years which occupied (33.3%). (P= 0.327) Regarding gender, ***Table I*** Shows in Group A (90.5%), in Group B (81.0%) of study patients were female. Female gender was predominant in each Group. Male: Female ratio was 1:9, 1:4 respectively in Group A, Group B. (P= 0.463).

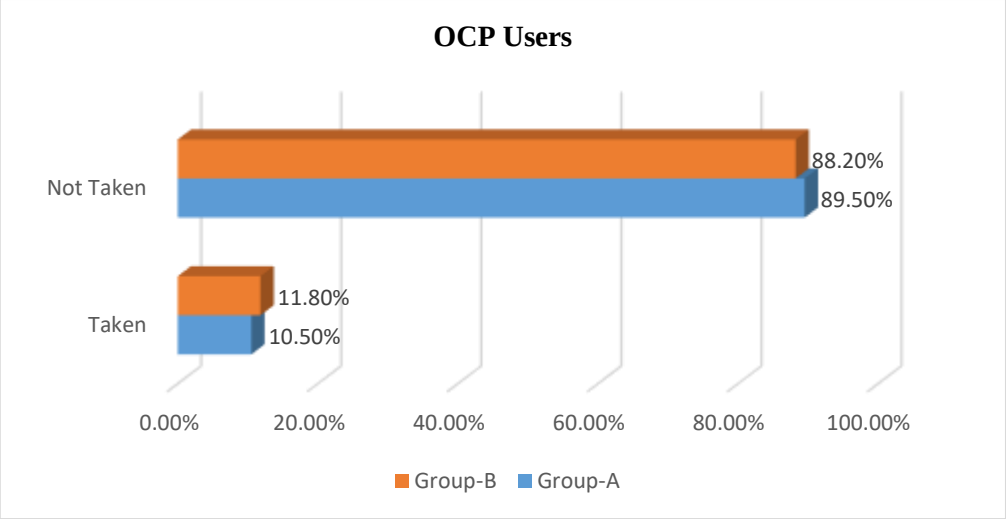


Figure II: Distribution of the female patients by consumption of oral contraceptive pill

Figure II Shows in each group, the consumption history of OCP was almost similar.

Table II: Headache among of study patients. (n=42)

	Group A (n=21)	Group B (n=21)	*p*-value
Headache frequency (days/month)	6.0 (1.0-20.0)	12.0 (2.0-20.0)	0.079
Duration of headache (hours)	6.0 (2.0-24.0)	4.0 (2.0-12.0)	0.061
VAS score	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 throughout the study.

Table II shows comparison of per months frequency, duration and intensity (VAS) between two 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 6.0(2.0-24.0). Intensity of headache which was expressed by visual analogue scale (VAS) score were same in Group A and Group B 8.0 (7.0-9.0).

Table III: Comparison of after-treatment headache frequency per month between two Groups

Headache frequency (days/month)	Group A (n=21)	Group B (n=21)	*p*-value
1st Month			
Median	3.0	3.0	0.654
IQR	2.0-4.0	2.0-4.0	
2nd Month			

Median	1.0	2.0	0.562
IQR	0.0-2.5	1.0-3.0	
3rd Month			
Median	0.0	0.0	0.022*
IQR	0.0-1.0	0.0-1.0	
Wilcoxon Signed Ranks test			
1st month vs 2nd month	<0.001*	0.004*	
2nd month vs 3rd month	0.001*	0.004*	
1st month vs 3rd month	<0.001*	<0.001*	

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. *Significant

Table III Shows comparison after treatment headache frequency expressed as headache days/month between two groups of study patients at the end of 1st, 2nd, 3rd months. At the end of 1st month, median headache frequency was the same (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 between two groups (0.0day/month).

Table IV: Comparison of headache frequency during enrollment and follow-up visits 3 months later

Headache frequency (days/month)	**Group A (n=21)**	**Group B (n=21)**	***p*-value**
Before treatment			
Median	6.0	12.0	0.079
IQR	2.5-11.0	6.0-16.0	
After 3 months of treatment			
Median	0.0	0.0	0.022*
IQR	0.0-1.0	0.0-1.0	
P-value	<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 throughout the study. *Significant

Table IV shows the comparison of headache frequency before treatment and 3 months of treatment. Headache frequency significantly decreased in groups.

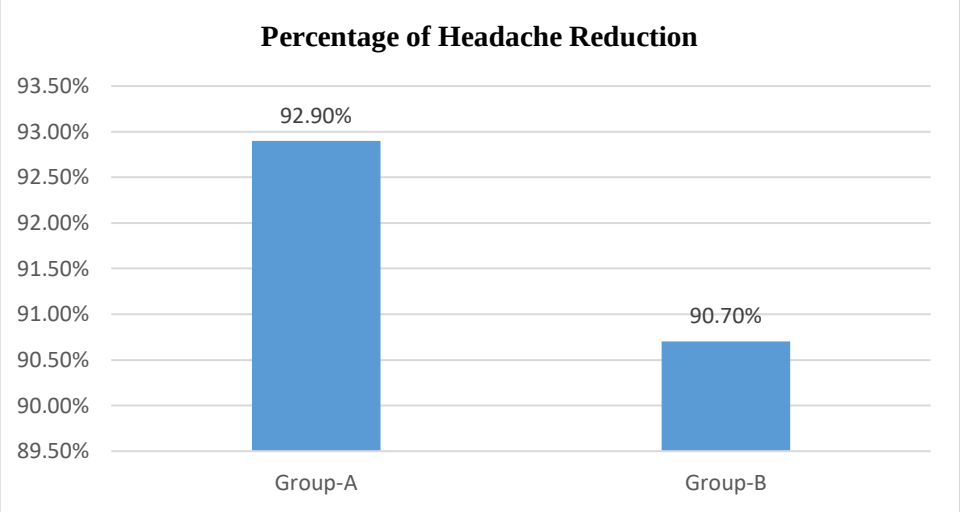


Figure III: Diagram showing the percentage of headache frequency reduction after three months of treatment from baseline

Figure III Shows percentage of headache frequency reduction after three months of treatment form baseline. The reduction of headache frequency was higher (92.90%) in Group A than (90.70%) in Group B.

Table V: Comparison of duration of headache during enrollment and follow up visits 3 months later

Duration of headache (hours)	Group A (n=21)	Group B (n=21)	*p*-value
Before treatment			
Median	6.0	4.0	0.061
IQR	4.0-12.0	3.0-8.0	
After 3 months of treatment			
Median	5.0	4.0	0.366
IQR	3.0-10.0	3.5-8.0	
P Value	0.011*	0.371	

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

Table V Shows comparison of duration of headache before treatment and 3 months of treatment. Median duration of headache significantly decreased in two Groups. Maximum decreased in Group A compared to Group B.

Table VI: Comparison of VAS score during enrollment and follow-up visits 3 months later

VAS score	Group A (n=21)	Group B (n=21)	*p*-value

Before treatment			
Median	8.0	8.0	0.967
IQR	7.0-9.0	7.0-9.0	
After 3 months of treatment			
Median	2.0	3.0	0.066
IQR	2.0-3.0	2.0-4.0	
p-value	<0.001*	<0.001*	

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

Table VI Shows comparison of VAS score before treatment and 3 months of treatment. Median VAS score significantly decreased in two Groups. Maximum decreased in Group A compared to Group B. VAS score before treatment and 3 months of treatment among three Groups of study patients. Median VAS score significantly decreased in two Groups. Maximum decreased in Group A compared to Group B.

Table VII Association of pain status (according to VAS score) during enrollment and follow-up visits 3 months later

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

Data were expressed in frequency and percentage. p-value obtained by Chi-square test.

Table VII Shows comparison of VAS scores before treatment and 3 months of treatment Proportion of VAS scores significantly decreased in two Groups. Maximum decreased in Group A compared to Group B.

Table VIII: Comparison of HIT-6 score during enrollment and follow-up visits 3 months later among two groups (N=42).

HIT-6 score		Group A (n=21)	Group B (n=21)	*p*-value
Before treatment	Mean±SD	65.9±3.6	64.8±5.0	0.534
	Range	(61.0-72.0)	(56.0-75.0)	
After 3 months of treatment	Mean±SD	50.8±6.8	50.1±6.7	0.007*

	Range	(36.0-60.0)	(38.0-62.0)	
p-value		<0.001*	<0.001*	

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

Table VIII Shows a 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 A 65.9±3.6 to 50.8±6.8.

Table IX Adverse effects profile among the two groups of study patients (N=42).

Groups	Adverse effects	No. of patients	Percentage
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%

Data were expressed in frequency and percentage.

The adverse effects profile among the three Groups of study patients during this study period. It was observed that Group B 12(57.1%) had the highest experience of adverse effects. Highest 4(19.0%) patients had experienced sedation in Group A and the lowest 1(4.8%) patient in Group B. Blurring of vision 3(14.3%) patients in Group B. Palpitation 1(4.8%) patients Group B, weakness 1(4.8%) patient in Group A ***[Table IX]***.

DISCUSSION

This was a randomize control trial. The study was carried out from January 2022 to December 2022. The sample size was 21 each group, 21 patients, who were treated with Topiramate (Group-A) for consecutive 3 months and 21 patients, who were treated with Nortriptyline (Group-B) for consecutive 3 months. Efficacy of drugs among the groups were compared by frequency, duration, intensity of headache (VAS score) and HIT-6 score.

Age is most prevalent between the ages of 25 and 55 in the majority of studies [15]. According to my research, the age group of 30-39 years old had the most study patient occupancy (42.9%) in Group A, whereas the age group of 20-29 years old had the highest study patient occupancy (33.3%) in Group B. This fits well with the age range that is generally acknowledged as the most common for migraineurs. According to epidemiological research, there is a notable global majority of migraine in women (52% versus 32%). According to a recent population-based study conducted in Turkey, women are substantially more likely than men (12%) to get migraine headaches (24%) [16].

In my research, there were more female study participants in Group B (81.0%) than in Group A (19.5%). Group A's male to female ratio was 1:9, whereas Group B's ratio was 1:4. The study found that women predominated in all categories, which was corroborated by research by Ailani et al. [17]

that found that 6% of men and 18% of women in the US suffer from migraine headaches annually. In this study medication that precipitates headaches the three study patient groups' intake of oral contraceptive pills (OCP) revealed that 10.5% of Group A patients and 11.8% of Group B patients used OCP. The OCP consumption histories of each group were essentially identical. In this study baseline headache frequency was 6.0 in Group A, 12.0 headache days/month in Group B which was near about the study done by Krymchantowski et al. [18] where headache frequency was 8.1 headache days/month in Group I, 8 headache days/month Group II. In this study, duration of headache in hours was highest in Group A 6.0, in Group B 4.0 and baseline intensity of headache, which was expressed by Visual Analogue Scale (VAS) score was similar in Group A, Group B (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 (92.90%) in Group A and (90.70%) in Group B which was similar to study done by Krymchantowski et al [18] where 47.0% patients of Topiramate group and 37.0% patients of Notriptyline group. This study showed that, after treatment headache frequency expressed as headache days per month between two groups of study patients at the end of 1st month was 3.0 in both Group A and Group B; 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 between two groups (0.0day/month). In my study, duration of headache in hours expressed by median (IQR), 6(4.0-12.0) to 5(3.0-10.0) indicated that Maximum decreased in Group A compared to Group B. The intensity of headache expressed by VAS score, reduced maximum in Group A (8.0 to 2.0) compared to Group B.

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 12(57.1%) had the highest experience of adverse effects. Highest 4(19.0%) patients had experienced sedation in Group A and the lowest 1(4.8%) patient in Group B. Blurring of vision 3(14.3%) patients in Group B. Palpitation 1(4.8%) patients Group B, weakness 1(4.8%) patient in Group A.

From overall findings, it can be concluded that the Topiramate (Group A), provided best improvement in prophylactic management of migraine than Nortriptyline (Group-B).

CONCLUSION

In migraine patient prophylactic management, the patients who were treated with the Topiramate in the Headache Clinic of Dhaka Medical College showed the statistically significant results in this study with the best efficacy after 3 months of treatment compared Nortriptyline group. The frequency, duration, severity of the headache, all were reduced most by the Topiramate group.

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