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Efficacy and Safety of Topiramate for Prophylactic Treatment of Children Suffering from Moderate Migraine: A Randomized Controlled Trial

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Abstract

Background: Paediatric migraine is the most common cause of recurrent headache in children. **Objective:** The purpose of the study was to assess the efficacy and tolerability of topiramate for prophylactic treatment of children suffering from moderate migraine. **Methodology:** This randomized controlled trial was done in the outpatient department of Paediatric Neurology at National Institute of Neurosciences, Dhaka, Bangladesh from January to July, 2018. Children of 5 to 15years with migraine of moderate intensity were randomized into study group (TPM treatment group) and control group (FNZ treatment group). The efficacy and safety of TPM was assessed after 4 months of treatment. **Results:** There was significant reduction of frequency of headache /month in both groups after treatment (within group, 4.65 ± 1.59 vs1.70 ± 0.73, p <0.001 for FNZ, 5.20 ± 1.73 vs 1.75 ± 0.71, p <0.001 for TPM). The efficacy of two drugs was not different in moderate intensity of migraine p being 0.304 and 0.828. **Conclusion:** Topiramate is effective as well as safe in prophylaxis of children suffering from moderate migraine. *[Journal of National Institute of Neurosciences Bangladesh, January 2022;8(1): 19-22]*

Keywords: Moderate migraine; topiramate; efficacy

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Introduction

Migraine headaches are common in children but often not recognized and misdiagnosed[1]. Prevalence of migraine increases steadily through childhood, occurring in up to 10.6% of children and adolescents between the ages of 5 and 15 years[2-4]. Migraine in children increases school absenteeism, impairs school performance, and reduces interactions with family and friends[1,5].

Migraine in children causes high burden to society but significant relief is possible with appropriate intervention. Flunarizine (FNZ) is safe and effective as preventive treatment in children with migraine and was recommended as a probable effective treatment in the American Academy of Neurology (AAN) practice parameter in 2004[6].Topiramate is the only FDA-approved preventive therapy for adolescents in migraine. Several clinical case series and a prospective open-label trial[7-9] suggest that topiramate may be an effective migraine preventive therapy in children, No study has compared TPM with FNZ as a prophylactic treatment of pediatric migraines in real clinical practice settings. The purpose of this study was to observe the efficacy of

topiramate and also perform a comparison of TPM (Topiramate) and FNZ (Flunarizine) in children with migraine from a single centre.

Methodology

Study Settings and Population: This randomized controlled trial was conducted at the outpatient Department of Paediatric Neurology in National Institute of Neurosciences, (NINS), Dhaka, Bangladesh from January to July, 2018 for a period of 6 months. 40 Children of 5 to 15 years who were diagnosed as Migraine with/without aura (ICHD-3 beta) with moderate intensity (PedMIDAS) and who had no history of taking any prophylactic drug for migraine, other type of recurrent headache who were intended to be enrolled were randomized either as Intervention group (TPM treatment group) and Control (FNZ treatment group). Prior to beginning of the study, the research protocol was accepted by ethical review committee of NINS & H (ERC: NINS letter number: 34) and informed written consent was taken from parents.

Randomization and Blinding: Randomization of study children were done among moderate Migraine with/without aura by lottery method i.e. the mother or father of each child was given a chance to pick up an opaque brown colored envelope containing the name of the drug from groups of 10 envelops, 5 envelopes containing the name of TPM and another 5 containing the name of FNZ. Once the first set of envelope was exhausted after picking up by parents, a second set was introduced. In this way enrollment was continued till desired sample size of 40 was achieved. The allocation concealment was done by opaque sealed envelope, so that both the treating physician and the parents of the children will remain blinded to the group of allocation.

Allocation: Initially Intervention group received TPM 25 mg and Control group received FNZ 5 mg at night. Patients were assessed at 1 month if response was not satisfactory, then TPM was increased to 50 mg/d in two divided doses and FNZ was increased to 10mg at night.

Follow up and Outcomes Measures: Follow up was done at 1, 2 and 4 month of starting treatment. Primary end point of the study was 4 months after starting of treatment to find out the efficacy and safety of both TPM and FNZ. Side effects of drugs were also recorded. Headache diary was maintained throughout the study period. Tolerability of the drugs and its adverse effects were evaluated by means of parental interview at each visit including dizziness, weight gain, anorexia, weight loss, fatigue, somonolence, memory/language dysfunction, abnormal vision, paresthesia, abnormal pain, constipation. Patients enlisted into the study were treated and followed up even after the study period at OPD of NINS as part of routine follow up like other general patients.

Statistical analysis: Statistical analysis of the study was done by using the Statistical Package for Social Science (SPSS) version 22.0. The result was presented in tables, figures and diagrams. Confidence interval was

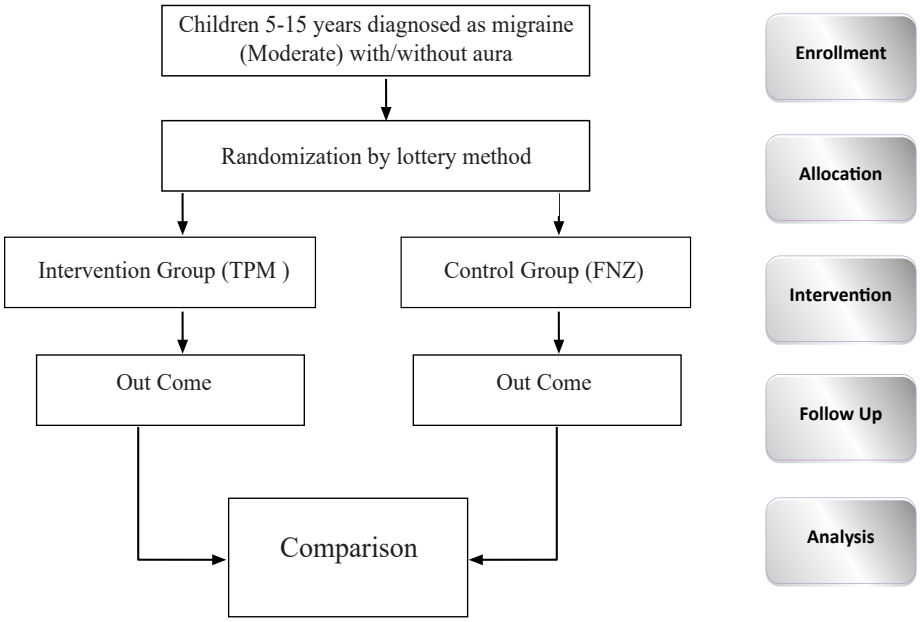

Figure I: Algorithm of the Randomized Controlled Trial

considered at 95% level. The qualitative data was expressed as frequency and percentage and the quantitative data was expressed as mean with standard deviation. Chi-square test and Fisher's Exact test was performed to compare between qualitative variables Probability value less than 0.05 was taken as statistically significant.

Results

A total of 40 children were included in the study. There was no significant difference between groups in terms of age and sex. There were more children in 10-14 years age group (60-85%) in both the groups (Table 1).

Table 1: Demographic Characteristics among Intervention group (TPM) And Control group (FNZ) Having Moderate Migraine (n=40)

Variables	Intervention Group	Control Group	P value
Age Group			
• 5 to 10 Years	3 (15.0%)	8 (40.0%)	
• 10 to 14Years	17 (85.0%)	12 (60.0%)	
Mean±SD	11.35 ± 1.81	10.53 ± 1.94	**0.173
Gender			
• Male	11(55.0%)	8(40.0%)	**0.342
• Female	9(45.0%)	12(60.0%)	
Age of onset of migraine (years)	8.55±1.74	9.60±1.54	*0.051
Age at diagnosis (years)	11.35±1.81	10.53±1.94	*0.173
Age at treatment (years)	11.35±1.81	10.53±1.94	*0.173

*Unpaired t test was performed to see the level of significance;
**Chi-square was done to measure the level of significance

Significant reduction of post-treatment frequency of headache /month in both groups within group,4.65 ± 1.59 vs1.70±0.73, p <0.001 for FNZ, 5.20 ± 1.73 vs 1.75 ± 0.71, p <0.001 for TPM but inter group analysis demonstrated no significant difference in the two treatment groups(p being 0.304 and 0.828)which pointout both drugs were equally effective (Table 2).

Table 2: Comparison of Pre and Post Treatment Frequency of Headache among Intervention group (TPM) And Control group (FNZ)

Frequency of Headache /Month	Intervention Group	Control Group	P value
Pre treatment	5. 20 ±1.73	4.65 ± 1.59	0.304
Post treatment	1.75 ± 0.71	1.70 ± 0.73	0.828
P value	<0.001	<0.001	

Unpaired t test was performed to see the level of significance

After treatment severity of migraine decreased but there was no significant difference between intergroup (Table 3).

Table 3: PEDMIDAS Score among Intervention group (TPM) And Control group (FNZ)

PEDMIDAS Score	Intervention Group	Control Group	P value
Base score	39.00±3.86 (32to48)	39.20±3.88 (32 to48)	0.869
1 month	23.75±5.15 (16to32)	27.8±5.55 (18to36)	0.118
2 month	25.30±5.877 (16to36)	15.65±5.29 (8to26)	0.122
4 month	11.15±6.12 (4to22)	12.50±6.31 (5to30)	0.672

Unpaired t test was performed to see the level of significance

Adverse events were present in 5.0% in FNZ group and 10% in TPM in moderate migraine. Adverse events were not significantly differing between the groups (Table 4).

Table 4: Adverse Events of Drugs among Intervention Group And Control Group

Adverse Events	Intervention Group	Control Group	P value
Weight loss	1 (5.0%)	0 (0.0%)	0.387
Fatigue	0(0.0%)	1 (5.0%)	
Abnormal vision	1 (5.0%)	0 (0.0%)	

Chi-square test was done to measure the level of significance

Discussion

Mean age of study population was 10.53±1.94 years for FNZ and 11.35±1.81 years for TPM. In this study, the comparison of TPM and FNZ for migraine prophylaxis in paediatric patients revealed that the efficacy of TPM were not different from those of FNZ. Responder rates was 80.0% for both drugs in moderate which was similar to a previous study that evaluated drug efficacy and showed responder rates of 81.0% for FNZ and 80.0% for TPM[10]. It was also reported in a recent study in adult patients that responder rates of 66.7% in the FNZ group and 72.7% in the TPM group for prophylaxis of migraines[11]. But this findings does not correlate with the Childhood and Adolescent Migraine Prevention (CHAMP) trial which showed no significant difference in the efficacy between the prescription drugs and placebo group which was 52.0% for amitriptyline vs 55.0% for topiramate vs 61.0% for placebo group[12]. Dissimilarity may be due to the

present study focused only on episodic migraine but CHAMP trial included both episodic and chronic migraine.

Topiramate had been studied in several open-label and placebo-controlled randomized trials in paediatric migraine showed effectiveness and tolerable side-effect profile[5,13]. A larger double-blind, placebo-controlled study on topirmate in children age 6 to 15 years, showed equivocal results; not statistically significant reduction of headache[5]. A subsequent smaller randomized, double-blind, placebo-controlled trial of adolescents age 12 to 17 years showed topiramate has statistically significant effectiveness in headache reduction compared to placebo at doses of 100 mg/day but not at doses of 50 mg/day[2].

Baseline pain intensity (PedMIDAS) decrease significantly after four months treatment with both drugs which correlates with a Bangladeshi study[13]. Baseline headache days has reduced significantly after four months treatment with Topiramate ($p < 0.001$).This findings is consistent with study done by Luo et al[11].

Common adverse events were fatigue, weight gain in FNZ group and weight loss, abnormal vision, anorexia, fatigue in TPM group. The adverse events rates found here was not similar with the randomized controlled trails[14-15] which reported a 15.0 to 25.0% incidence of adverse events. Another study showed that topiramate had mild to moderate side effects with favorable tolerability in children[5]. All patients that were included the study ultimately continued medicine because of low dose, tolerable side effects and was also similar in both treatment group ($p=0.387$).

Conclusion

The study has documented that topiramate was found to be effective as flunarizine in reducing headache burden in children with migraine and well tolerated in the studied children. Only few adverse effects have been observed during study period. Multi-centered, double blinded, larger sample size, longer duration study from various ethnic group should be carried out.

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