

Efficacy of Topiramate as Prophylactic Treatment of Severe Migraine in Children attending OPD of a Tertiary Care Hospital in Bangladesh- a Randomized Control Trial

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Abstract

Background: Migraine is the most common cause of severe recurrent headache in children. Flunarizine (FNZ) is safe and effective drug for prevention of migraine in children. Topiramate (TPM) is also successful as a preventive drug for migraine in children on randomized, double-blind, placebo-controlled trials.

Objective: This study was done to observe the efficacy of Topiramate and also perform a comparison TPM and FNZ in patients with migraine of severe intensity in our situation.

Materials & Methods: This was a randomized controlled trial done from January to July, 2018. This study was carried out in the OPD of Paediatric Neurology department, National Institute of Neurosciences, (NINS) Dhaka. Forty Children, 5-15 years old diagnosed as migraine with/without aura with severe intensity were randomized either as in study group (TPM treatment group) and control group (FNZ treatment group). Primary end point of the study was to find out the efficacy and safety of both TPM and FNZ after 4 months of treatment.

Result: Post-treatment frequency of headache/month was significantly decreased in both groups (within group, $p < 0.001$). There was no significant difference considering pre and post-treatment frequency of headache/month between two treatment groups. (pre-treatment $p = 0.333$ and post-treatment $p = 0.401$). Adverse events were not significantly different between the groups $p < 0.387$.

Conclusion: Topiramate is equally efficacious as Flunarizine in prophylactic treatment of severe migraine in children.

Keywords: Severe Migraine, Flunarizine (FNZ), Topiramate (TPM), Prophylaxis.

Introduction:

Migraine is the most common cause of severe recurrent headache in children. Prevalence of migraine ranges from 3% at 5 years of age to 14% at 15 years of age.¹ Children who suffer from frequent attack and/or severe intensity of migraine that interfere with daily

activity may benefit from an effective preventive drug. Preventive therapy for migraine in children would be indicated if headache frequency is ≥ 4 headache days per month, failure or poor tolerance of abortive therapies, or significant disability from less frequent headaches.²⁻⁴ Medications used for prevention of migraine include antiepileptic agents, antidepressants, anti-hypertensives, antihistamines, and nutraceuticals. Topiramate (TPM) is efficacious for prevention of migraine in adult patients. It was found in several open-label and small controlled studies.⁵⁻⁸ A randomized controlled trial showed significant efficacy ($p < .05\%$) of TPM in prevention of migraine within the first month of treatment.⁹ FDA approved TPM only for adolescents as preventive drug for migraine. Flunarizine (FNZ) is a calcium channel blocker which was assessed in several trials for the prevention of migraine in children. An open

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long-term, multicenter trial revealed that FNZ had an excellent result in 69.5% of the patients suffering from migraine.¹⁰

Materials & Methods:

This was a randomized controlled trial done from January to July, 2018 in the OPD of Paediatric Neurology department, National Institute of Neurosciences, (NINS) Dhaka. After taking approval from ethical review committee of NINS, forty children aged 5 to 15 years diagnosed as Migraine with/without aura (ICHD-3 beta) with severe intensity Pediatric Migraine Disability Assessment (PedMIDAS) who were not receiving any prophylactic drug for migraine, have not other types of recurrent headache or any serious illness were enrolled and randomized by lottery method either as study group (TPM treatment group=20) or control (FNZ treatment group=20).

PedMIDAS is scored by summing the answers across the 6 questions. The score range is little to none (0 to 10), mild (11 to30), moderate (31 to 50), severe (Greater than 50). Before being finally included into the study, parents were explained about the purpose of the study including advantages and disadvantages of drug. Ethical approval from local ethical review board was taken.

FNZ was initiated as 5mg and TPM was started as 25 mg at night and at 1 month follow up if patient did not respond, dose of FNZ was increased to 10mg at night and TPM was increased to 50mg/d in two divided dose. Clinical assessment was done at 1 month, 2 month and 4 month of starting treatment. Tolerability of the drugs and its adverse effects were evaluated by means of parental interview at each visit. Then statistical analysis was performed by SPSS.

Results:

There was no significant difference between the two treatment groups in terms of age and sex. Mean age among FNZ group was 10.08± 2.50 years and in TPM group 11.03 ± 2.24 years. No significant difference was found between two groups considering age of onset, age of diagnosis of migraine. Post-treatment frequency of headache / month was significantly decreased in both the groups (within group p<0.001) but not significant in intergroup (p=0.333, p=0.401) indicating equal effectiveness of both drugs in severe migraine. Common adverse events were fatigue, weight gain in FNZ group and weight loss, abnormal vision, anorexia, fatigue in TPM group. There was no serious event in any group to discontinue drug.

Table I
Demographic & Headache Characteristic of study population (n=40).

	Control (FNZ) (n=20)	Case (TPM) (n=20)	p-value
Age (years)			
5 - <10	8 (40%)	4 (20%)	
10 - 14	12 (60%)	16 (80%)	
Mean±SD	10.08 ± 2.50	11.03 ± 2.24	^a 0.214
Gender			
Male	11 (55%)	11 (55%)	^b 1.000
Female	9 (45%)	9 (45%)	
Age of onset of migraine (yrs)	8.70 ± 2.63	8.58 ± 2.01	^a 0.873
Age at diagnosis (yrs)	10.08 ± 2.50	10.88 ± 2.25	^a 0.294
Age at treatment (yrs)	10.08 ± 2.50	10.88 ± 2.25	^a 0.133

^aUnpaired t test ^bChi-square was done to measure the level of significance

Table II
Comparison of Pre and Post Treatment Frequency of Headache (n=40)

Frequency of Headache/Month (Mean±SD)	FNZ Group (n=20)	TPM Group (n=20)	p-value
Pre treatment	6.30 ± 2.12	5.65 ± 2.05	0.333
Post treatment	2.25 ± 1.91	1.85 ± 0.87	0.401
p-value (within group)	<0.001	<0.001	

* Unpaired t test was done to measure the level of significance

Table III
Treatment Response of Studied Children

	Control (FNZ) (n=20)	Case (TPM) (n=20)	p-value
>50%	17 (85%)	19 (95%)	0.348
<50%	1 (5%)	1 (5%)	
No change	2 (10%)	0	

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

Table IV
PedMIDAS Score of Studied Children (N=40).

PedMIDAS Score	Case (TPM) n=20	Control (FNZ) n=20	p-value
Base score	57.50±3.81 (52-67)	57.55±3.76 (52-67)	0.967
1 month	24.55±6.01 (17-40)	26.45±13.01 (14-61)	0.461
2 month	14.70±5.85 (8-36)	19.00±15.85 (8-61)	0.149
4 month	7.15±5.16 (4-28)	13.65±17.27 (2-61)	0.0533

Table V
Adverse Effects of Drugs in Studied Children (N=40).

	Control (FNZ) (n=20)	Case (TPM) (n=20)	p-value
Weight gain	1	0	
Weight loss	0	1	
Anorexia	0	1	
Fatigue	1	1	0.387
Memory/language dysfunction	0	1	
Abnormal vision	0	1	

Discussion

In this study, basic demographic data such as age, sex, were comparable both in study and control group. Here frequency of headache before and after administration of drugs were compared and found that frequency decreased significantly in both the studied groups (within group $p < 0.001$) which was compatible with other study where they also found significant decrease in headache frequency ($p < 0.001$).¹¹ Significant decrease in headache frequency ($p < 0.001$) was also reported after treatment with TPM on chronic migraine by Lakshmi CV¹² and Unalp A et al.¹³ When the efficacy was looked in terms of reduction of > 50% headache days/month, 85% reduction was observed in FNZ group, 95% in TPM group which

was consistent with a previous report that showed 69.4% of patients treated with TPM had > 50% reduction of headache and 75-100% reduction in headache in FNZ treated group.¹⁴ But this findings differs from The recent Childhood and Adolescent Migraine Prevention (CHAMP) trial that showed no significant difference in the efficacy between the prescription drugs and placebo group (52% for amitriptyline vs 55% for topiramate vs 61% for placebo group). Diversity of results may be due to fact that CHAMP trial included both episodic and chronic migraine whereas the present study focused only on episodic migraine.¹⁵⁻¹⁷

Baseline pain intensity (PedMIDAS) score was decreased significantly after four months treatment with both drugs which correlates with a Bangladeshi study where baseline headache days has reduced significantly after three months treatment with FNZ ($p < 0.001$).¹⁸ In this current study, side effects of drugs were mild and comparable in both treatment group ($p = 0.387$) which was similar with different randomized controlled trials.^{12,16,19}

Conclusion:

TPM (Topiramate) is as efficacious and tolerable as FNZ (Flunarizine) in the prophylactic treatment of paediatric migraine. Further large scale, longer duration, double-blinded study should be carried out to observe the long-term outcome.

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