Comparison between flunarizine and levetiracetam in paediatric migraine prophylaxis
SM Rahman1, GK Kundu2, K Fatema3, S Akhter4, MM Rahman5

Abstract
Background: Migraine hampers child’s life through school absence, limitation of home and social activities. The goal of prophylactic (preventive) therapy is to reduce headache frequency, headache days, and headache severity with minimum side effects.

Objective: To evaluate the efficacy and tolerability of levetiracetam compared to flunarizine as prophylactic treatment of Migraine in children.

Methods: This prospective study was carried out in the outpatient department of a tertiary care hospital in Bangladesh. A total of 105 children aged 6-15 years, diagnosed as migraine without aura, were enrolled. Patients were treated with flunarizine or levetiracetam for three months. Headache disabilities were evaluated at baseline and at the end of three months.

Results: In flunarizine group, 54 children and in levetiracetam group, 51 children were enrolled. Among them thirty nine children in flunarizine group and 36 children in levetiracetam group completed the study. Headache frequency, headache days, VAS (Visual Analogue Scale) score and PedMIDAS (Paediatric Migraine Disability Assessment Score) score were evaluated at baseline and during the follow up. After three months, headache frequency, headache days, pain severity (Visual Analogue Scale score) reduced significantly compared to baseline (p<0.05). PedMIDAS score was also reduced from 60.35(±16.36) to 30.13(±14.28) in flunarizine group and from 64.25(±19.63) to 25.91(±18.6) in levetiracetam group (p<0.05). Some minor side effects were also reported by both groups, but were well tolerated by the patients and need not withdrawal of medication.

Conclusion: Levetiracetam is as effective as flunarizine in paediatric Migraine Prophylaxis.

Key words: Migraine, Flunarizine, Levetiracetam, Paediatric, Prophylaxis.

Introduction
According to World Health Organization, Global Burden of Disease Survey 2010, migraine headache was ranked as the 3rd most prevalent disorder and 7th highest specific cause of disability worldwide.1 It occurs with prevalence rates of 3.2% to 10.6%.2 Once the diagnosis is established, a balanced, flexible, and individually tailored treatment plan should be started.3 A diverse group of medications is used to prevent attacks of migraine. Preventive medications are used to reduce headache frequency, duration of pain, severity of individual attack, mean headache days, migraine related disabilities and also to reduce acute medication overuse. However their use should be limited to those patients whose headaches occur with sufficient frequency or severity as to warrant preventive treatment. Once preventive treatment is initiated, patients must be encouraged to continue treatment for at least 8-12 Weeks for the beneficial effects.4 Flunarizine has established its efficacy for preventive treatment of migraine in children. Encouraging data are emerging from several antiepileptic agents, such as topiramate, sodium valproate and levetiracetam.5-8 Flunarizine, a long acting calcium channel blocker was introduced in the 1970s. The Children’s Headache Clinic at Great Ormond Street Hospital, London, is a national referral centre and flunarizine has been

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used in this clinic since 1998. Flunarizine has been an established drug used in migraine prevention both in adult and pediatric age group. Levetiracetam is a molecule studied and proposed in the 1980s as having anxiolytic action and later an antiepileptic action too. It has excellent pharmacokinetic profile, no drug interaction and good safety profile. Levetiracetam’s efficacy in migraine prophylaxis has been proved in several studies and also recommended by paediatric text books. Miller showed in a retrospective study, levetiracetam reduced headache frequency significantly after treatment. Pakalnis et al. and Pizza et al. showed efficacy of levetiracetam in migraine headache. Levetiracetam might be well suited as a prophylactic agent for long duration and can be utilized for migraine prevention.

Migraine was previously thought to be a vascular event, presently it is established that it is a neurogenic event. Levetiracetam could reduce migraine headache frequency by neuromodulation. Flunarizine and levetiracetam are both safe and can be given in pediatric age group. Both the drugs showed good results with least side effects in their clinical trials. The objective of the efficacy was to evaluate the efficacy and tolerability of levetiracetam compared to flunarizine as prophylactic treatment of migraine headache in children.

Materials and method

The prospective study was carried out in the Outpatient Department (OPD), of Pediatric Neurology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, in the capital of Bangladesh from October 2013 to December 2014. All children diagnosed as migraine without aura according to International Classification of Headache Disorders (ICD-3) attending in the outpatient department during the study period were enrolled.

A total of 105 patients fulfilled the inclusion criteria. Among them 75 patients completed the study. Inclusion criteria were: 1) Children diagnosed as migraine without aura between 6 years to 15 years of age. 2) Attack frequency >4 per month. 3) Suffering from migraine attacks for at least one year before study entry. Exclusion criteria were: 1) Previous prophylactic treatment with other medications had failed, or was discontinued due to adverse events. 2) Patients / attendants unwilling to give informed consent to make part in the study. 3) If the patient required medication for other medical conditions. Outcome variables was to measure frequency of headache per month, mean headache days per month, pain intensity (VAS score), Pediatric Migraine Disability Assessment Score (PedMIDAS). Prior to the commencement of this study the research protocol was approved by the Institutional Review Board of BSMMU. A signed informed consent described in Bengali language was taken from the parents after explaining them about the nature, objective, procedure, risks and benefits and implications of the study.

Complete history, general, physical and neurological examinations was done for all enrolled patients. One hundred five (105) patients met the inclusion criteria to be selected as study subjects out of 821 headache patients during the study period. Study subjects were randomly selected for preventive treatment with flunarizine 5 mg daily or levetiracetam 20 mg/kg/day in 2 divided doses. Randomization had been done by lottery method. Each patient committed 3 visits: a baseline visit and follow up visit after 1 month and at the end of 3 months of drug treatment. Assessment was done regarding headache frequency, headache days per month, VAS score and PedMIDAS before starting treatment. Parents were asked to maintain a headache diary to note headache frequency, headache days (headache lasting <24 hours=1 day, >24 hours to <48 hours = 2 days, >48 hours to <72 hours = 3 days). During the treatment period parents/patient filled up headache diary at home as per instruction and came for follow up according to his/her child’s follow up schedule along with headache diary. Incomplete headache diaries were filled up by the researcher with the help of parents and patients. During follow up headache diary was interpreted and assessment was done regarding headache frequency, headache days/month, VAS score and pedMIDAS. Any side effects of the drugs were also recorded.

Data were processed and analyzed using computer software SPSS (Statistical Package for Social Science) version 21. Data presented on categorical scale are expressed as frequency and corresponding percentage, while the quantitative data are presented as mean and standard deviation (±SD). By applying paired t test intra group headache related disabilities were measured at the end of 3 months compared to baseline and by applying unpaired ‘t’ test inter group headache related disabilities were also measured. The level of significance was set at 5%. All comparisons were made two-sided and a p-value <0.05 (2-tailed) was considered as significant.
Results

Thirty nine patients in flunarizine group and 36 patients in levetiracetam group completed the study. Mean age was 10.64 (±2.31) years in flunarizine group and 10.77 (±2.35) years in levetiracetam group; mean total headache duration was 2.80 (±2.14) years in flunarizine group and 2.46 (±1.60) years in levetiracetam group (p>0.05). In flunarizine group, females were 51% and males were 49%. In levetiracetam group, females were 61% and males were 39%. Family history of migraine was positive in 89% children in flunarizine group and 73% in levetiracetam group.

Table I
Baseline data of two groups of patients

<table>
<thead>
<tr>
<th></th>
<th>Flunarizine n=39</th>
<th>Levetiracetam n=36</th>
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</thead>
<tbody>
<tr>
<td>Headache frequency</td>
<td>10.17(±3.26)</td>
<td>9.41 (±3.12)</td>
</tr>
<tr>
<td>Headache days</td>
<td>10.92 (±3.93)</td>
<td>10.69 (±4.30)</td>
</tr>
<tr>
<td>VAS score</td>
<td>7.97(±1.13)</td>
<td>7.94(±1.06)</td>
</tr>
<tr>
<td>PedMIDAS score</td>
<td>60.35(±16.36)</td>
<td>64.25(±19.63)</td>
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Table I, II, III and IV shows, at the end of three months preventative treatment, both flunarizine and levetiracetam could reduce >50% of baseline headache frequency, headache days, VAS score, PedMIDAS score compared to baseline (p < 0.05). Headache disabilities were not significantly different between the groups at baseline, and after three months of preventive therapy (p > 0.05).

Table II
Headache disabilities at the start and after 3 months of Flunarizine

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>After 3 months</th>
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<tbody>
<tr>
<td>Headache frequency</td>
<td>10.17(±3.26)</td>
<td>2.76(±2.37)</td>
</tr>
<tr>
<td>Headache days</td>
<td>10.92 (±3.93)</td>
<td>3.41(±3.42)</td>
</tr>
<tr>
<td>VAS score</td>
<td>7.97(±1.13)</td>
<td>2.74(±1.95)</td>
</tr>
<tr>
<td>PedMIDAS score</td>
<td>60.35(±16.36)</td>
<td>30.13(±14.28)</td>
</tr>
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</table>

Table V shows, side effects reported by the patient/parents during the study period in both flunarizine and levetiracetam group. Those side effects were well tolerated in both the groups and none discontinue the drug due to adverse events. There was no significant difference between two groups regarding adverse events (p > 0.05).

Table III
Headache disabilities at the start and after 3 months of Levetiracetam

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>After 3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache frequency</td>
<td>9.41(±3.12)</td>
<td>2.41(±2.41)</td>
</tr>
<tr>
<td>Headache days</td>
<td>10.69 (±4.30)</td>
<td>2.77(±3.02)</td>
</tr>
<tr>
<td>VAS score</td>
<td>7.94(±1.06)</td>
<td>2.36(±1.85)</td>
</tr>
<tr>
<td>PedMIDAS score</td>
<td>64.25(±19.63)</td>
<td>25.91(±18.6)</td>
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Table IV
Difference in disability severity between the group of patients after three months prophylactic treatment

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Table V
Frequency of Adverse events among the study population

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<th>Levetiracetam n=36</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedation/ drowsiness</td>
<td>05(12.8)</td>
<td>03(8.33)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>02(5.1)</td>
<td>01(2.7)</td>
</tr>
<tr>
<td>Increased appetite</td>
<td>03(7.6)</td>
<td>0(0)</td>
</tr>
<tr>
<td>Irritability</td>
<td>01(2.5)</td>
<td>01(2.7)</td>
</tr>
<tr>
<td>Vertigo</td>
<td>02(5.1)</td>
<td>01(2.7)</td>
</tr>
</tbody>
</table>

Discussion
In this study, efficacy and tolerability of flunarizine and levetiracetam has been compared in pediatric migraine patients. Headache related...
disabilities were significantly reduced compared to baseline in both the group after three months preventive therapy.

Demographic and clinical characteristic e.g mean age, mean duration of headache of the study population were almost similar in both the group (p<0.05). These similarities enabled the study to have a valid comprehensive statistical analysis. Females were more in both the groups. Ashkenazi et al. and Young et al. also found high percentage of female in pediatric Migraine patients.16

Flunarizine, a long acting calcium channel blocker with selective effects on cerebrovascular smooth muscle and neurons, has antihistaminic, anti-dopaminergic action and raises excitatory threshold in cortical spreading depression. In this study, baseline headache frequency was reduced significantly after three months treatment with flunarizine (p<0.001). Kim et al. and Luo et al. found, flunarizine could reduce headache frequency compared to baseline over twelve months period.12,13 Thus efficacy of flunarizine, regarding reduction of headache frequency is consistent with previous studies.

Recently Levetiracetam has been shown to exert inhibitory effects on neuronal type calcium channels and appear to inhibit burst firing and hyper synchronization of neurons.19 In this study, baseline headache frequency also reduced significantly after three months treatment with levetiracetam (p<0.001). Previous levetiracetam treated paediatric patients also showed significant reduction in headache frequency after treatment. Pakalnis et al., Miller and Brigbina, et al. showed a significant reduction in headache frequency in the sixth month of treatment with levetiracetam.2,14,19 Pizza et al. and Rapoport et al. also showed reduction of headache frequency after one month and three months treatment with levetiracetam.15-18

Baseline headache days has reduced significantly after three months treatment with levetiracetam (p<0.001). This finding is consistent with Pizza et al.15 Baseline pain intensity (VAS score) has reduced significantly after three months treatment with levetiracetam (p<0.001). However Young et al. also found, headache severity reduced significantly after treatment with levetiracetam in relation to baseline after three Months.16

This study shows, there was significant reduction of baseline PedMIDAS score after 3 months treatment with levetiracetam. (p<0.001). Pakalnis et al. found that, baseline PedMIDAS was also reduced significantly after three months treatment with levetiracetam.2

There was no significant difference of adverse events in flunarizine and levetiracetam treated patients. Among flunarizine treated patients, reported adverse events are: drowsiness, dizziness, vertigo, increased appetites and irritability. However none of the effect caused withdrawal of medication. Flunarizine side effects were- dizziness, lethargy and headache.3 Diener et al. reported depression in maximum patients treated with flunarizine.11 In this study, in levetiracetam treated patients, reported adverse events were drowsiness, dizziness, irritability and vertigo. These side effects were not severe enough to cause withdrawal of Medication. In this regard Pizza et al found, levetiracetam treated patients had somnolence, lack of concentration, vertigo and a moderate gastralgia.15 None of the patients withdrew the study due to adverse events. Pakalnis et al. also showed, levetiracetam was well tolerated and no patients discontinued drug due to side effects.2 Levetiracetam was also well tolerated and reported adverse events were somnolence, dizziness, and nervousness.19

Limitation of the study was mainly very small sample size. So the study findings are not generalizable in large scale. Drop out were high in both the groups and it was an open label study.

Conclusion

It can be concluded that levetiracetam is as effective as flunarizine in paediatric migraine prophylaxis on three month therapy. Some minor side effects were reported by both groups, but were well tolerated by the patients.

Reference


