A comparative study of effect of sodium valproate & flunarizine on psychomotor performance in patients of common migraine: A randomized, parallel, open label, prospective observational study

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Abstract
Introduction: Psychomotor performance results from the coordination of sensory and motor system through the integrative and organizational process of brain and central nervous system. Psychotropic drugs may adversely affect work performance which depends on psychomotor activities. Both valproate and flunarizine are widely used drugs in prophylaxis of migraine and they are known to have effect on psychomotor performance. Hence this study was carried out to evaluate the effect of valproate & flunarizine on psychomotor performance in patients of migraine with the help of battery of subjective & objective psychomotor tests over a period of 8 weeks.

Materials and Methods: Patients were allocated to one of the two groups on first day of examination. Baseline psychomotor tests were measured using battery of tests including critical flicker fusion test (CFFT), hand steadiness test (HST), arithmetic ability test & reaction time monitoring. At the end of 4 weeks & 8 weeks, again tests using same methods employed previously were performed. Efficacy was calculated by using Migraine dairy template (0, 4, 8 weeks) & CGI Scale (end). A total of 44 patients were recruited with 22 patients in each arm.

Results: Flunarizine (n=20) & valproate (n=20) significantly increased CFFT, AAT scores at the end of 8 weeks compared to baseline and significantly reduced HST, RT, Frequency, Duration and severity at the end of 8 weeks compared to baseline. When flunarizine was compared to valproate no statistical significance was found in scores of CFFT, AAT, HST, RT, Frequency, duration, severity, global improvement and efficacy index.

Conclusion: Flunarizine & Valproate were found to be equally efficacious to improve psychomotor performance.

Keywords: Sodium valproate, Flunarizine, Psychomotor, Migraine, Prophylaxis, Performance.

Introduction
Migraine, the second most common cause of headache, and the most common headache - related and indeed neurologic cause of disability in the world, afflicts approximately 15% of women and 6% of men over a 1-year period. It is usually an episodic headache associated with certain features such as sensitivity to light, sound, or movement; nausea and vomiting often accompany the headache. Classically, it is categorized as migraine with aura (classic migraine) and migraine without aura (common migraine).1

The drugs that have been approved by the FDA for the prophylactic treatment of migraine includes propranolol, timolol, sodium valproate, topiramate, flunarizine and methysergide.1

Valproate is one of the most frequently prescribed antiepileptic drugs worldwide. The number of patients treated with valproate is growing since it has been shown to be effective in the management of prophylaxis of migraine. Most frequent adverse effects include nausea, sedation, tremor, dyspepsia & weight gain. Some studies suggest that valproate might also induce other motor deficits like decreased alternate motion rates, rigidity, abnormalities of posture and gait.2,3

Flunarizine was developed as a calcium channel blocker to treat brain hypoxia, but when applied to migraine, it is certainly effective. It has a number of adverse effects such as sedation, weight gain, depression & extrapyramidal symptoms.3

Psychomotor performance results from the coordination of sensory and motor system through the integrative and organizational process of brain and central nervous system. Central, sensory and motor components of psychomotor performance can be evaluated by standard validated battery of psychomotor function tests 4

Quantitative assessment of motor function of valproate done by Farkas z et al suggested significant irregularity of repetitive hand movements & finger tapping even in patients with no motor complaints. Objective methods might help to recognize valproate-induced motor performance deterioration5

For flunarizine, in many studies like Shurks M et al hyperkinesias, tremors, Parkinson-like symptoms are main side effects 3,6

Both valproate and flunarizine are widely used drugs in prophylaxis of migraine and they are known to have effect on psychomotor performance

There are studies comparing efficacy of both these drugs but hardly any studies on psychomotor performance

Hence the present study was planned with the objective to evaluate the effect of valproate & flunarizine on psychomotor performance in patients of migraine with the help of battery of subjective & objective psychomotor tests over a period of 8 weeks.
Materials and Methods

The study was randomized, open label, parallel arm, prospective observational study. Patients visiting psychiatry OPD of Government medical college Nagpur were interviewed by psychiatrist and those who were suffering from moderate to severe migraine were included into the study. Study was carried out after approval from institutional ethics committee (No. 961 EC/Pharmac/GMC/NGP). A written informed consent was taken from each subject after explaining them the nature of the study. Study duration was from January 2017 to May 2018.

Baseline psychomotor tests were measured using battery of tests including Critical Flicker Fusion test (CFFT), Hand Steadiness Test (HST), Arithmetic Ability Test & Reaction time monitoring. At the end of 4 weeks & 8 weeks, again tests using same methods employed previously were performed. Baseline headache characteristics including frequency, duration & severity of migraine were noted on migraine diary. At the end of 4 weeks & 8 weeks, patient submitted migraine diary giving details of their migraine attacks since the last visit (i.e., every 4 weeks).

At the end of the treatment other parameters assessed were Global improvement using Clinical Global Impression scale (CGI) & Efficacy index using Clinical Global Impression scale (CGI).

There were 2 Follow up visits where in every visit patients were given medicines for 4 weeks. Patient & person accompanying were explained dosing schedule in detail & were instructed to follow it strictly. If only one visit was completed, last observation was carried forward. At the end of study treatment was continued or modified as per decision of Psychiatrist.

Observation and Results

A total of 74 patients were screened, out of which 30 did not meet the eligibility criteria; hence were not included in the study. A total of 44 patients were randomized and allocated to two treatment groups, out of which 40 patients completed the study according to the protocol. There were 4 drop-outs who were lost to follow-up: Two in sodium valproate, group two in flunarizine group. There were two patients in sodium valproate group and one patient in flunarizine group who completed only one visit and there last observation was carried forward according to study protocol.

Comparison of demographic characteristics & clinical parameters of patients at baseline In sodium valproate & flunarizine groups (Table 1) for parameters like mean age, gender, weight, height, CFFT, AAT, RT, HST, Frequency, duration & severity showed both the groups were comparable and there was no statistically significant difference in demographic data & clinical parameters between two groups at baseline.

Intragroup analysis in sodium valproate group was done (Table 2) where Repeated measures Anova followed by Post hoc Tukey’s multiple comparison Test showed Statistically significant increase at 8 weeks (P <0.001) When compared with baseline on critical flicker fusion test. In this test more the frequency threshold better is the psychomotor performance. On Arithmetic ability test statistically significant increase at 4 weeks (p <0.01) & 8 weeks (P <0.001) When compared with baseline. In this test also more the score better is the psychomotor performance. On Reaction time statistically significant decrease at 4 weeks (p <0.001) & 8 weeks (P <0.001) When compared with baseline. That means participant took less time to touch the screen after the appearance of green light. On Hand Steadiness Test Statistically significant decrease at 4 weeks (p <0.01) & 8 weeks (P <0.001) When compared with baseline. Which means participants either required less time or less errors were done which is indicated by number of contact of stylus with the surface of the holes.

As far as efficacy in migraine is concerned our observation in sodium valproate group on Frequency showed statistically significant decrease at 4 weeks (p <0.05) & 8 weeks (P <0.001) When compared with baseline. On Duration Statistically significant decrease at 4 weeks (p <0.05) & 8 weeks (P <0.001) When compared with baseline. On severity statistically significant decrease at 4 weeks (p <0.05) & 8 weeks (P <0.001) When compared with baseline.

Intragroup analysis in flunarizine group was done (Table 3) where Repeated measures Anova followed by Post hoc Tukey’s multiple comparison Test reveals Statistically significant increase at 4 weeks (p <0.01) & 8 weeks (P <0.001) on Critical Flicker Fusion Test When compared with baseline. In this test more the frequency threshold better is the psychomotor performance. On Arithmetic Ability Test Statistically significant increase at 4 weeks (p <0.01) & 8 weeks (P <0.001) When compared with baseline. In this test also more the score better is the psychomotor performance. On Reaction Time: Statistically significant decrease at 4 weeks (p <0.001) & 8 weeks (P <0.001) When compared with baseline. That means participant took less time to touch the screen after the appearance of green light. On Hand Steadiness Test Statistically significant decrease at 4 weeks (p <0.01) & 8 weeks (P <0.001) When compared with baseline. Which means participants either required less time or less errors were done which is indicated by number of contact of stylus with the surface of the holes.

As far as efficacy in migraine is concerned our observation in flunarizine group on Frequency showed statistically significant decrease at 4 weeks (p <0.01) & 8 weeks (P <0.001) When compared with baseline. On Duration Statistically significant decrease at 4 weeks (p <0.001) & 8 weeks (P <0.001) When compared with baseline. On severity statistically significant decrease at 4 weeks (p <0.01) & 8 weeks (P <0.001) When compared with baseline.

On Intergroup analysis when comparison of change of values of sodium valproate and flunarizine was done (table 4) at the end of treatment from baseline, here the difference in each parameter was taken as the value of 8 weeks minus
the value at baseline of both the groups and then both the
groups were compared using Unpaired t-test. No statistical
significance was seen in between the groups on critical
flicker fusion test, hand steadiness test, arithmetic ability
test, reaction time, frequency, duration, severity, global
improvement. On efficacy Index Statistical significant
decrease (p < 0.05) was seen in between the groups which
was lesser in flunarizine group. Lesser the score more the
efficacy.

Table 1: Baseline demographic characteristic & clinical parameters

<table>
<thead>
<tr>
<th></th>
<th>Valproate group</th>
<th>Flunarizine group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean age</strong></td>
<td>33.15 ± 7.68</td>
<td>33.25 ± 11.85</td>
<td>0.97*</td>
</tr>
<tr>
<td><strong>Gender (M:F)</strong></td>
<td>5:15</td>
<td>7:13</td>
<td>0.73*</td>
</tr>
<tr>
<td><strong>Weight</strong></td>
<td>50 ± 7.86</td>
<td>52.40 ± 10.05</td>
<td>0.40*</td>
</tr>
<tr>
<td><strong>Height</strong></td>
<td>160.8 ± 5.51</td>
<td>162.1 ± 7.03</td>
<td>0.51*</td>
</tr>
<tr>
<td><strong>CFFT</strong></td>
<td>38.42 ± 2.84</td>
<td>37.71 ± 2.93</td>
<td>0.32*</td>
</tr>
<tr>
<td><strong>AAT</strong></td>
<td>6.95 ± 1.35</td>
<td>7.75 ± 1.97</td>
<td>0.14*</td>
</tr>
<tr>
<td><strong>RT</strong></td>
<td>595.8 ± 110.2</td>
<td>580.9 ± 152.6</td>
<td>0.72*</td>
</tr>
<tr>
<td><strong>HST</strong></td>
<td>328.5 ± 99.32</td>
<td>317 ± 96.30</td>
<td>0.94*</td>
</tr>
<tr>
<td><strong>Frequency</strong></td>
<td>2.80 ± 0.61</td>
<td>2.40 ± 0.68</td>
<td>0.05*</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>2.40 ± 0.59</td>
<td>2.57 ± 0.69</td>
<td>0.34*</td>
</tr>
<tr>
<td><strong>Severity</strong></td>
<td>2.20 ± 0.61</td>
<td>1.80 ± 0.61</td>
<td>0.05*</td>
</tr>
</tbody>
</table>

Values are expressed as Mean ± SD ; # - Unpaired t test ; ^ - Fisher’s Exact test ; $ - Mann Whitney Test ; CFFT : Critical Flicker Fusion Test ; AAT: Arithmetic ability test ; RT: Reaction Time ; HST : Hand steadiness test

Table 2: Intragroup analysis of effect of Valproate on CFFT (Critical flicker fusion test), AAT (Arithmetic ability test), RT (Reaction time), HST (Hand steadiness test), Frequency, Duration, Severity :

<table>
<thead>
<tr>
<th>Parameter</th>
<th>0 week</th>
<th>4 week</th>
<th>8 week</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFFT</td>
<td>38.42 ± 2.84</td>
<td>38.56 ± 2.81</td>
<td>38.78 ± 2.70***</td>
</tr>
<tr>
<td>AAT</td>
<td>6.95 ± 1.35</td>
<td>7.60 ± 1.63**</td>
<td>8.30 ± 1.78***</td>
</tr>
<tr>
<td>RT</td>
<td>595.8 ± 110.2</td>
<td>578.6 ± 111.4***</td>
<td>568.7 ± 113***</td>
</tr>
<tr>
<td>HST</td>
<td>328.5 ± 99.32</td>
<td>314.6 ± 105.9**</td>
<td>303.3 ± 106***</td>
</tr>
<tr>
<td>Frequency</td>
<td>2.80 ± 0.61</td>
<td>2.45 ± 0.60*</td>
<td>1.85 ± 0.67***</td>
</tr>
<tr>
<td>Duration</td>
<td>2.40 ± 0.60</td>
<td>2.15 ± 0.52*</td>
<td>1.70 ± 0.64***</td>
</tr>
<tr>
<td>Severity</td>
<td>2.20 ± 0.62</td>
<td>1.90 ± 0.55*</td>
<td>1.75 ± 0.55***</td>
</tr>
</tbody>
</table>

Values are expressed as Mean ± SD; *** = P <0.001; ** = p <0.01; * =p <0.05 When compared to baseline by Repeated measures ANNOVA followed by Post hoc Tukey’s multiple comparison Test

Table 3: Intragroup analysis of effect of flunarizine on CFFT (Critical flicker fusion test), AAT (Arithmetic ability test), RT (Reaction time), HST (Hand steadiness test), frequency, duration, severity

<table>
<thead>
<tr>
<th>Parameter</th>
<th>0 week</th>
<th>4 week</th>
<th>8 week</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFFT</td>
<td>37.71 ± 2.93</td>
<td>38.05 ± 2.85**</td>
<td>38.30 ± 2.83***</td>
</tr>
<tr>
<td>AAT</td>
<td>7.75 ± 1.97</td>
<td>8.5 ± 2.14**</td>
<td>9.95 ± 2.48***</td>
</tr>
<tr>
<td>RT</td>
<td>580.9 ± 152.6</td>
<td>564.7 ± 152.6***</td>
<td>552 ± 151.5***</td>
</tr>
<tr>
<td>HST</td>
<td>317 ± 96.30</td>
<td>301.5 ± 99.60**</td>
<td>282 ± 104***</td>
</tr>
<tr>
<td>Frequency</td>
<td>2.40 ± 0.68</td>
<td>2.00 ± 0.79**</td>
<td>1.60 ± 0.82***</td>
</tr>
<tr>
<td>Duration</td>
<td>2.57 ± 0.69</td>
<td>1.90 ± 0.74***</td>
<td>1.80 ± 0.80***</td>
</tr>
<tr>
<td>Severity</td>
<td>1.80 ± 0.62</td>
<td>1.50 ± 0.51*</td>
<td>1.30 ± 0.47***</td>
</tr>
</tbody>
</table>

Values are expressed as Mean ± SD; *** = P <0.001; ** = p <0.01; * =p <0.05 When compared to baseline by Repeated measure One way ANNOVA followed by Post hoc Tukey’s multiple comparison Test
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Table 4: Comparison of change at end of treatment of Valproate and Flunarizine on CFFT (Critical flicker fusion test), AAT (Arithmetic ability test), RT (Reaction time), HST (Hand steadiness test), Frequency, Duration, Severity, Morisky scale, Global improvement, Efficacy index:

<table>
<thead>
<tr>
<th>Test</th>
<th>Valproate</th>
<th>Flunarizine</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFFT</td>
<td>0.36 ± 0.28</td>
<td>0.59 ± 0.59</td>
<td>0.25</td>
</tr>
<tr>
<td>HST</td>
<td>27.30 ± 20.98</td>
<td>34.95 ± 29.82</td>
<td>0.35</td>
</tr>
<tr>
<td>AAT</td>
<td>1.35 ± 0.93</td>
<td>1.75 ± 1.11</td>
<td>0.27</td>
</tr>
<tr>
<td>RT</td>
<td>27.10 ± 19.03</td>
<td>28.90 ± 17.25</td>
<td>0.46</td>
</tr>
<tr>
<td>Freq</td>
<td>0.95 ± 0.51</td>
<td>0.80 ± 0.61</td>
<td>0.38</td>
</tr>
<tr>
<td>Duration</td>
<td>0.70 ± 0.47</td>
<td>0.77 ± 0.59</td>
<td>0.85</td>
</tr>
<tr>
<td>Severity</td>
<td>0.45 ± 0.51</td>
<td>0.50 ± 0.51</td>
<td>0.76</td>
</tr>
<tr>
<td>Global improv</td>
<td>3.30 ± 0.92</td>
<td>2.95 ± 0.82</td>
<td>0.13</td>
</tr>
<tr>
<td>Efficacy index</td>
<td>9.95 ± 3.25</td>
<td>7.45 ± 2.83**</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Values are expressed as Mean ± SD; ** = P <0.01 Change at the end of treatment by Mann Whitney test

Discussion

In our study baseline demographic characteristics & clinical parameters were comparable in both the treatment groups. In present study, sodium valproate & flunarizine showed statistically significant improvement in Critical flicker fusion test at the end of 8 weeks suggesting improvement in information processing and overall integrative capacity though it may not be clinically relevant. Scores of Arithmetic ability test were significantly improved by sodium valproate & flunarizine which suggests improvement in central processing mechanism of perception which may be clinically relevant. The present study found significant decrease in errors during hand steadiness test with sodium valproate & flunarizine suggesting improvement in the tasks involving motor coordination and could be clinically relevant. Sodium valproate & flunarizine had significantly decreased reaction time at the end of 8 weeks which suggests improved sensorimotor performance and it is clinically relevant.

A number of studies like Sun et al. 2008; Donati et al. 2007; McKee et al. 1992; Gillham et al. 1991 have indicated that sodium valproate exerts little detrimental impact on cognitive function in patients of epilepsy.5,7,8,10

Ristic et al. 2006 showed small minority of patients (5 of 364 adults) can develop parkinsonism with associated memory problems and psychomotor slowing in patients of epilepsy receiving sodium valproate.9 Prevey et al. 1996 reported no decline in tasks assessing coordination, memory, concentration.11 Luo et al in a randomized trial reported adverse events of flunarizine which included dizziness, unsteady gait, rashes, paresthesia, and drowsiness symptoms.12

B. holmes et al mentioned the most common side effect with flunarizine alone, or flunarizine associated with other drugs, was drowsiness occurring in 7% of 2894 patients or mental flexibility in patients of epilepsy receiving sodium valproate. In our study when sodium valproate was compared with flunarizine for the effect of psychomotor performance no statistical significance was found showing that both the drugs are equally efficacious in improving psychomotor performance.13

Our in-depth search and review of literature failed to retrieve any data comparing effect of psychomotor performance on sodium valproate and flunarizine in the prophylaxis of migraine headache.

Migraine Prophylaxis Efficacy Parameters Including Frequency, Duration and Severity of Migraine Attack:

In present study Sodium valproate & flunarizine significantly reduced frequency, duration & severity of migraine headache. Other studies comparing the migraine prophylactic effect of sodium valproate and flunarizine (at various doses for various treatment durations) have reported similar results.

Hering and Kuritzky (1992) performed a 8 week, double-blind study and compared sodium valproate with placebo. The study revealed that sodium valproate significantly reduced the frequency, severity and duration of migraine headache compared with placebo.14

Afshari D et al. (2012) performed a 12 week, randomized, double-blind, parallel group clinical trial, comparing low-dose topiramate and sodium valproate. A significant decrease in monthly frequency, duration, and intensity of headache occurred in both the groups.15

Bostani A et al. (2013) performed a 12 week, randomized, double-blind, parallel-group study, comparing low-dose cinnarizine and sodium valproate. A significant decrease in monthly frequency, duration, and intensity of headache occurred in both the groups.16

Kegang Cao et al (2016) double-dummy, double-blind, multicenter, positive drug (flunarizine), parallel randomized controlled, non-inferior clinical trial. A significant decrease in monthly frequency, duration, and intensity of headache occurred in both the groups.17

Frenkeneta1. (1984) a 12-week randomized double-blind study in which After a 1-month starting period the difference between flunarizine and placebo in reducing the frequency of the migraine attacks became statistically significant in favour of flunarizine.18

In our study when sodium valproate was compared with flunarizine for the headache parameters no statistical significance was found showing that both the drugs are...
equally efficacious in improving migraine headache parameters.

A. Bostani et al. (2013) a randomized, double-blind, parallel-group study comparing sodium valproate with calcium channel blocker cinnarizine showed both cinnarizine and valproate could significantly decrease headache frequency, intensity and duration, but the reduction in the valproate group was significantly more than in the cinnarizine group. Fenyé Liu et al. (2017) single-blinded randomized trial of 3 months comparing efficacy of venlafaxine, flunarizine & valproic acid in prophylaxis of vestibular migraine showed Venlafaxine & valproic acid to be preferable to flunarizine in decreasing the number of vertiginous attacks, but valproic acid was shown to be less effective than venlafaxine & flunarizine to decrease vertigo severity.

**Efficacy Index**

In our study when sodium valproate was compared with flunarizine taking the efficacy index of CGI scale under consideration in which efficacy and safety parameters are considered together through which an objective score is given it was found that flunarizine was more efficacious than sodium valproate as evaluated by psychiatrist.

It may be due to more side effects caused by Sodium valproate in comparison with flunarizine as efficacy index which is taken from clinical global impression scale is based upon overall improvement which also takes side effects into consideration.

Further studies comparing side effects of both these drugs will be useful in deciding which among these both drugs should be preferred for migraine prophylaxis.

**Global Improvement**

In our study when sodium valproate was compared with flunarizine taking global improvement of CGI scale under consideration no statistical significance was found showing that both the drugs are equally efficacious in improving migraine headache parameters.

**Adherence**

In our study when sodium valproate was compared with flunarizine taking Morisky scale under consideration no statistical significance was found and both the drugs were in the range of medium adherence.

**Limitations**

This is an open label study. The effects on psychomotor performance obtained are for particular dose of the drug, studies with different doses of the drug will be more useful.

**Conclusion**

Sodium valproate & flunarizine are found to be equally efficacious to improve psychomotor performance. Both drugs equally reduced frequency, duration & severity of migraine headache. Flunarizine has better efficacy index as compared with sodium valproate the efficacy index takes into consideration both efficacy & safety simultaneously to yield a score, so further studies comparing side effects of both these drugs would be desirable.

**Conflict of Interest:** None.

**References**


