



Comparing efficacy and safety of sodium valproate with propranolol in paediatric migraine prophylaxis

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ABSTRACT

Migraine is a common disorder of the paediatric age group. Propranolol has been used in prophylaxis for migraine. The use of Sodium valproate in the prophylaxis of migraine is not known. It is postulated that it increases the level of GABA in the brain that will decrease events related to migraine in the cortex. All parents of the patient were advised to keep diaries for noting time, date, severity and duration of headache during the study period, which was for a period of 6 wks. The decreased frequency of headache more than in Group A was 68% and propranolol group was 68.89%. In group A (sodium valproate), patients showed a reduction in headache duration and 52% in Group B. 20% of them headache free in Group A and 18% in Group B. Decrease in the severity of headache in Group A was 52% while 50% in Group B. The mean headache frequency before and after treatment was reduced from 8 to 2.5 attacks per month in group A and from 8.2 to 2.6 in group B. The t-value is 11 for group A. Sodium valproate is more effective and safer in migraine prophylaxis as compared with propranolol.

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INTRODUCTION

In the paediatric age group, migraine is a common complaint. The overall population shows that the 3.5–5% paediatric group will experience frequent headaches. In about 90% of cases, one of the family members will have a history of migraine. More incidence is seen in pubertal girls which is because of hormonal imbalance related to the menstrual cycle. (Dooley, 2009; Damen, 2005)

Complains of migraine varies according to age. Less than 1-year infants will present with the banging of the head. Preschool children have a history of abdominal pain without pathological cause, vomiting, crying excessively and sleeping in a dark place. Bifrontal and bitemporal, nausea, vomiting, photophobia, diarrhoea is a typical feature found in this age group, sleeping in lonely dark place (Rompel and Bauermeister, 1970; Carroll *et al.*, 1990). Older children have a more intense headache like a pulsating or throbbing character and the location is the temporal location as well as frontal. No abnormal finding is seen in physical and neurological exam nor in imaging investigation that is routinely done to rule out other causes of headache. Propranolol has been used in prophylaxis for migraine. The possible mechanisms of action are 1. The beta-adrenergic receptor will be blocked by propranolol and this will lead to arterial dilatation (Diener *et al.*, 2002). Propranolol will block platelets from adhesion which causes blood vessels dilate (Bostani *et al.*, 2013). Another mechanism is stimulating of CNS, which signals blood vessels to dilate.

The use of Sodium valproate in the prophylaxis of migraine is not known; it is postulated that it increases the level of GABA in the brain that will decrease events related to migraine in the cortex or trigeminal nucleus caudal. (Wasiewski, 2001)

Many studies are done on comparing the efficacy of drugs of propranolol and sodium valproate in the prophylaxis of migraine in adult population (Wöber-Bingöl, 2013; Lewis, 2004)

But only a few studies are done on comparing the efficacy of drugs of propranolol and sodium valproate in a paediatric population. And therefore, we decided our study be done in the pediatric population (Stovner *et al.*, 2014; Yurekli *et al.*, 2008)

MATERIALS AND METHODS

The present study was undertaken in the Department of Pharmacology, Datta Meghe Medical College Hingana, Nagpur, in collaboration with the Surgery department, Jawaharlal Nehru Medical College, Wardha. Both medical colleges of Datta Meghe Institute of medical science (DMIMS), Sawangi, Meghe, Wardha, Maharashtra India.

Duration of study - was from June 2020 to November 2020.

Study design – Single centre prospective longitudinal interventional randomised controlled trial

Sample size - The numbers of patients were 100

Inclusion criteria

1. Age group of 5-16 yrs. including both sexes
2. History of migraine headache without aura (as per International Classification of Headache Disorders). (Bostani *et al.*, 2013)
3. Patients experiencing 3–7 migraine attacks/month.

Exclusion criteria

Exclusion criteria were as follows,

1. History of the use of propranolol and sodium cromoglycate in the past.
2. Abnormal finding on neurological images and on fundal examination, i.e., papilledema.
3. Abnormal change in behaviour
4. H/o of Valsalva manoeuvre causing an increase in headaches
5. Persistent focal neurological signs.

6. Patient diagnosed as bronchial asthma (propranolol is contraindicated).

7. Hepatitis /liver failure.

Methods and data collection tools and process, variables, definitions, analysis plan

All parents of the patient were advised to keep diaries for noting time, date, severity and duration of headache during the study period which was for a period of 6 wks. For this purpose, a well-constructed questionnaire was provided.

All patient in study groups were investigated for a baseline blood test, imaging studies and performed general and neurological examination

100 patients were included in a study by simple random method. To reduce allocation bias, participants were blindly placed in both groups.

Patients were divided into two groups. 50 patients in (group A) were treated with Sodium Valproate 10 mg/kg/day in two divided doses and slowly increased up to 40 mg/kg/day while 50 patients in (group B) received Propranolol 1–3 mg/kg/day divided in two doses, for a period of 6 weeks,

Recording the headache frequency, severity and duration in diaries and its response to medications enabled to assess and compare the efficacy of drugs in two groups.

The severity of headache was scored on a 1–3 point scale with 1 as no effect on daily activity, 2 for the partial effect of daily activity and 3. daily activities were affected. As a prophylactic agent, the drug is considered to be effective if it decreases 50% the baseline headache frequency per month. The decrease in severity and duration of headache is considered a better response to migraine prophylaxis.

For comparing the mean difference in the outcome of 2 groups, an independent T-test was done.

RESULTS

Table 1 shows the demographic characteristics of 50 patients in (Group A) and 50 patients in (group B). There are 28 males in group A and 29 males in group B. Equal female participant in both groups.

Table ?? shows the decreased frequency of headache more than in Group A was 68% and the propranolol group was 68.89%. In group A(sodium valproate), patients showed a reduction in headache duration and 52% in Group B. 20% of them headache free in Group A and 18% in Group B. Decrease in the severity of headache in Group A was 52% while 50% in Group B.

Table 1: Age and gender distribution

	Total participant	Sex		Age		Mean
		Male	Female	Min.	Max.	
Group A (sodium valproate)	50	28	22	5	16	7
Group B (propranolol)	50	29	22	5	16	7

Table 2: Percentage of symptoms of migraine prevented by study drugs

Symptoms	Group A (sodium valproate)	Group B (propranolol)
Decrease frequency of headache	68%	68.89%
Decrease headache duration	50%	52%
Total Cessation of a headache attack	20%	18%
A decrease in the severity of headache	52%	50%

Table 3: Headache frequency before and after treatment and t-test results

Groups	Mean Pre-treatment	Post-treatment mean	T-test to show the effect of an intervention (Before and after the intervention)		T-test comparing both groups	
			T Value	P value	T Value	P value
Group A (sodium valproate)	8	2.5	11	< .00001.	-0.18042.	.430656
Group B (propranolol)	8.2	2.6	10.72245	< .00001		

Table 3 shows, the mean headache frequency before and after treatment was reduced from 8 to 2.5 attacks per month in group A and from 8.2 to 2.6 in group B. No significant difference was seen between severity and duration of headache in treatment groups.

The t-value is 11 for group A. The p-value is < .00001. The result is significant at $p < .05$, This suggest this intervention (sodium valproate) is effective significantly in preventing recurrent attacks of migraine.

The t-value is 10.72245 for group B. The p-value is < .00001. The result is significant at $p < .05$. This suggests this intervention (propranolol) is also effective significantly in preventing recurrent attacks of migraine.

To compare the efficacy of both interventions, an independent T-test was applied and got the t-value of -0.18042. The p-value is .430656. The result is not significant at $p < .05$.

This suggests both interventions were equally effective in the prophylaxis of migraine.

DISCUSSION

Various medications studied for preventive treatment of Migraine are Cyproheptadine, propranolol, Clonidine (alpha-adrenergic agonist), Amitriptyline (TCA), Trazodone (Triazolopyridine derivative), Divalproex Sodium (Valproate), Topiramate Levetiracetam, Nimodipine, Flunarizine Calcium Channel Blocker. (Jensen *et al.*, 1994)

In our study, demographic characteristics had no significant differences between two groups in male to female ratio (Table 1), which coincides with a study done by Veda Ali Yareli, Gallop Akhan. (Afshari *et al.*, 2012)

In the present study, as per the results of statistical analysis by applying the T-test in group A. It suggests that sodium valproate is effective in preventing significantly recurrent attacks of migraine. (Table ?? and Table 3). A similar finding was observed in other studies. (Sadeghian and Motiei-Langroudi, 2015; Ramadan, 2004) Similarly, in Group B (Table 3), propranolol also effective in decreasing recurrent

attacks of migraine. It appears that Sodium chromoglycate has slightly more effective than propranolol, but statistically, there was no significant difference.

Multiple researchers, including Diener et al. and Carroll et al., also have similar findings suggesting equal efficacy of both sodium valproate and propranolol in the prophylaxis of migraine (Bidabadi and Mashouf, 2010; Dakhale and Sharma, 2019). See Table 3 (t-value of -0.18042. The p-value is .430656. The result is not significant at $p < .05$). This suggests both interventions were equally effective in the prophylaxis of migraine. In one study done by Elham Bid Abadi, Mehran Masgouf confirms the equal efficacy of both sodium valproate and propranolol in preventing migraine attacks, which was similar to the present study.

In another study done by Ganesh N Ducale, Vikas Mohanlal Sharma has concluded in their study that sodium valproate and propranolol significantly reduced frequency, severity, and duration of migraine headache, but propranolol caused a significantly greater reduction in the severity of headache compared to sodium valproate. Which again is different from our study. One study coincides with our study done by M.R. Ashrafi, R. Sasanian, which again suggests the equal potential of both drugs for the treatment of migraine. (Ashrafi and Shabaniana, 2005)

CONCLUSION

Sodium valproate is statistically more efficacious and safer in migraine prophylaxis as compared with propranolol. In addition to reducing headache frequency as the major effect of a drug used for migraine preventive pharmacotherapy, both of these drugs have shown significant improvement in the severity and duration of headache as well as better response to rescue medications. Sample sizes, comparing other drugs, especially the new generation of anti-epileptic drugs and controlled trials to determine the efficacy of combination therapy in difficult migraineurs, will be the base of future advances to improve the care of pediatric patients with migraine headache.

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Conflict of Interest

The authors declare that they have no conflict of interest for this study.

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