

SODIUM VALPROATE IN MIGRAINE PREVENTION: EFFICACY IS THE SAME AS PROPRANOLOL

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Introduction: Migraine is the most important cause of severe headache and headache related disability. Many time tested old drugs like propranolol and amitriptyline are in use as prophylactic agents but recently antiepileptic drugs like sodium valproate and topiramate have opened the new door for its treatment.

Objective: This study was carried out to observe and to compare the efficacy of Sodium Valproate versus Propranolol in preventive treatment of migraine.

Methods: This is a cross sectional study and a total of 77 migraine cases were included in the study of which 40 were treated with Propranolol and 37 were treated with Sodium Valproate. They were followed up for 3 months to observe the frequency, duration & severity of each headache and migraine related disability.

Result: After 3 months it was seen that in Propranolol treated cases there were 53.17 percent decline in headache frequency, 64.81 percent decline in headache duration, 15.16 percent decline in headache severity and 60.54 percent decline in migraine disability assessment score (MIDAS). Whereas in Sodium Valproate treated cases there were 48.98 percent decline in headache frequency, 62.84 percent decline in headache duration, 18.15 percent decline in headache severity and 61.49 percent decline in MIDAS.

Conclusion: We have found that Sodium Valproate

is effective and there is no significant difference between the efficacy of Propranolol and Sodium Valproate in prevention of migraine.

Key-words: Propranolol, Sodium valproate, MIDAS.

Introduction

Headache is one of all symptoms that frequently brings a man to a physician. As many as 90 percent of the individuals have at least one attack of headache per year. Severe disabling headache is reported to occur at least annually in 40 percent of individual worldwide¹. Migraine is an important cause of headache and headache related disability. It is an episodic primary headache characterized by episodic, usually unilateral headache of pulsating quality, moderate to severe in intensity aggravated by routine physical activity and often associated with nausea, vomiting, photophobia or phonophobia. Sometimes migraine is preceded by visual or sensory aura symptom².

The impact of migraine on the sufferers and his productivity at work is innumerable. Migraine is now ranked by World Health Organization (WHO) as number 19 among all diseases worldwide causing disability³. In United States prevalence of migraine was 18.2 percent among females and 6.5 percent among males. Approximately 23 percent of the households contained at least one member suffering from migraine. Prevalence increases from age 12 years to about age 40 years and declines thereafter in both sexes.

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In 53 percent of migraineurs severe headache causes substantial impairment of activities or required bed rest. Approximately 31 percent missed at least one day of work or school in previous 3 months because of migraine and 51 percent of migraineurs had 50 percent reduction of productivity at school or at work⁴. The median frequency of migraine attack is 1.5 per month and median duration of an attack is 24 hours; at least 10 percent have weekly attacks and 20 percent attacks lasted 2 or 3 days⁵. Life time prevalence of migraine is at least 18 percent⁶.

Pharmacological treatment of migraine can be abortive or preventive. Patients with frequent severe headache often require both approaches. Abortive treatment is used for reliving headache of individual attack. Preventive treatment is used to reduce the frequency, duration and severity of each attack. Additional benefit of preventive treatment includes improvement of responsiveness to abortive treatment, improvement of function and reduction of headache related disabilities⁷. Preventive treatment may preclude the progression of episodic migraine into chronic migraine⁸. Many medication groups are used for preventive treatment of migraine. The choice of preventive medication is influenced by efficacy, adverse effects and patients' coexisting and co-morbid conditions⁹. β -blocker (propranolol) has been prescribed for migraine since 1966¹⁰. It is cheaper and well tolerated medicine and is about 50 percent effective at producing more than 50 percent reduction in migraine frequency, duration and severity of individual attack. The efficacy of propranolol is so well established by dozens of randomized case control study that it can be used as a comparator drug when new agents are tested for migraine prevention¹¹.

Anticonvulsant drugs for migraine prevention have been tested since 1970 with carbamazepine as the first drug in this group¹². In 1988 Sorensen showed that Sodium Valproate is effective in migraine prevention¹³. Since then multiple clinical trials have been published showing the efficacy of Valproate with placebo.

Consistent evidence supports that Sodium Valproate is at least as effective as Propranolol^{14,15,16}. No study has been published comparing the efficacy of Propranolol versus Sodium Valproate among Bangladeshi population.

With this background this study was carried out to see the efficacy of sodium valproate and to compare its efficacy with propranolol in prophylaxis of migraine.

Materials and Methods

This comparative study was carried out among migraine cases attended in Headache Clinic of Department of Neurology in BSMMU from 1 Nov 2005 to 31 Dec 2006. Both male and female aged 10 years and above were included in the study. Migraine was diagnosed according to diagnostic criteria of International Classification of Headache Disorder-II (ICHD-II)-2004. Patients having 3 or more attacks of migraine in the previous month were included in the study. Patients having suspicion of headache other than migraine, having pregnancy or wants to have pregnancy in next 6 months, having bronchial asthma, heart block, active liver disease and who were already on any migraine preventive treatment were excluded from the study. During study period a total of 400 fresh headache cases were screened. Of them 163 patients met the diagnostic criteria of migraine. Out of them 100 patients were selected as subjects who fulfilled the inclusion-exclusion criteria. They were randomly selected for migraine preventive treatment with either Propranolol or Sodium Valproate. Every patient was interviewed in detail for recording frequency of headache (in number), headache duration (in days), pain intensity (in number in a visual analogue scale of 0 to 10) and Migraine Disability Assessment Score (MIDAS).

Headache attack duration lasting for less than 24 hours was recorded as one day, more than 24 hours to 48 hours was recorded as 2 days and more than 48 hours to 72 hours was recorded as 3 days. Pain intensity was recorded in a visual Analogue Scale of 0 to 10, where 0 is no pain and 10 is severe pain ever experienced.

MIDAS is a scoring system from five item questionnaire to assess the influence of headache on three domains of activity of a person that is designed to assess the impact of migraine on school/paid work, household work and family/social/leisure activity for previous 3 months. Each domain can have possible score of 0 to 90. Maximum total MIDAS is thus can be 270^{17,18}. 50 patients were randomly selected for treatment with Propranolol and 50 patients were thus selected for treatment with Sodium Valproate. Abortive medications when required were prescribed for each case. Selected study population were followed up monthly for 3 months. Their pulse, blood pressure were recorded monthly. Serum ALT and Serum valporic acid level were tested at the end of first month in sodium valproate treated patients. At the end of 3 months every patient's headache frequency,

total headache days, pain intensity and MIDAS were calculated. The obtained results were compared with pretreatment values as well as with Propranolol versus Sodium Valproate groups.

Results

We started our study with 100 cases, 23 cases failed to come for regular follow up so they were discarded from the study. Ultimately 77 cases completed the study; 40 from Propranolol group and 37 from Sodium Valproate group.

Among the patients who completed the study 21 (27.3%) were male and 56 (72.7%) were female. Average age of the study subjects were 25.5 years, ranging from 12 to 50 years. Demographic characteristics and pretreatment headache related disabilities had no significant difference between the study groups (Table-I&II).

Table-I: Socio-demographic characteristics of study subjects

Parameter	Propranolol (n=40)	Sodium Valproate (n=37)	p value
Age	Mean±SD 24.55±11.20	Mean±SD 26.51±7.72	>0.10
Sex			
Male	8	13	>0.10
Female	32	24	
Migraine Type:			
With Aura	3	05	>0.10
Without Aura	37	32	
Duration of Migraine(years)	Mean±SD 2.69±2.38	Mean±SD 3.64±3.14	>0.10
Occupation:	No	No	
Housewife	18	19	>0.10
Student	16	8	
Service	5	7	
Business	1	1	
Others	0	2	

Chi-square test/Unpaired Student's 't' test

Table-II : Pretreatment migraine related disabilities of study subjects

Migraine Parameter	Propranolol (n=40) Mean±SD	Sodium Valproate (n=37) Mean±SD	P value
Frequency (No per 3 months)	12.68±4.10	12.89±3.86	>0.10
Duration (Days per 3 months)	19.95±9.50	20.19±8.74	>0.10
Pain severity (in a scale of 0 to 10)	6.73±0.60	6.95±0.62	>0.10
MIDAS (Per 3 months)	47.73±25.07	49.62±29.53	>0.10

Unpaired Student's 't' test, MIDAS= migraine disability assessment score.

Table-III: Assessment of patient after 3 months of preventive anti-migraine treatment

Parameter /Group	Pretreatment Mean±SD	Posttreatment Mean±SD	Percent Change	P Value
Freq of attack (no per 3 month):				
Propranolol	12.68±4.10	5.65±1.87	-53.17	<0.001
Valproate	12.89±3.86	6.30±2.12	-48.98	<0.001
Duration of migraine (days per 3 month)				
Propranolol	19.95±9.50	6.20± 2.19	-64.81	<0.001
Valproate	20.19±8.74	7.03±2.88	-62.84	<0.001
Pain severity (in 0 to 10 scale)				
Propranolol	6.73±0.60	5.65±0.53	-15.16	<0,001
Valproate	6.95±0.62	5.65±0.59	-18.15	<0.001
MIDAS Score				
Propranolol	47.73±25.07	16.08±5.94	-60.54	<0.001
Valproate	49.62±29.53	17.41±8.41	-61.49	<0.001

Paired Student's 't' test, MIDAS= migraine disability assessment score.

After 3 months of preventive anti-migraine treatment with propranolol there were reduction of 53.17 percent in headache frequency; 64.81 percent in headache duration; 15.16 percent in headache severity and 60.54 percent in MIDAS score. By comparing with pretreatment values the reductions were highly significant ($p < 0.001$) (Table-III).

On the other hand after 3 months of preventive anti-migraine with Sodium Valproate there were reduction of 48.98 percent in headache frequency,

Discussion

Migraine is an important cause of recurrent headache and headache related disability in general population affecting children, adolescents and adult. There is no curative treatment. Abortive treatment is more or less successful and have many options including newer generation Triptan group of drugs. But prevention is not an easy task. So far, no drug has shown any remarkable outcome. Preventive medications are used to reduce headache frequency, duration and severity of each attack. The major medication groups are β -blockers, anti-depressants, anticonvulsants and serotonin antagonists.

Table-IV : Post treatment migraine related disabilities of the study subjects

Migraine Parameter	Propranolol (n=40) Mean \pm SD	Sodium Valproate (n=37) Mean \pm SD	P value
Frequency (No per 3 months)	5.65 \pm 1.87	6.30 \pm 2.12	>0.10
Duration (Days per 3 months)	6.20 \pm 2.19	7.03 \pm 2.88	>0.10
Pain severity (in a scale of 0to10)	5.65 \pm 0.53	5.65 \pm 0.59	>0.10
MIDAS (Per 3 months)	16.08 \pm 5.94	17.41 \pm 8.41	>0.10

Unpaired Student's 't' test

62.84 percent in headache duration, 18.15 percent in headache severity and 61.49 percent in MIDAS score. By comparing with pretreatment values the reductions were highly significant ($p < 0.001$) (Table-III).

By applying unpaired students t test the outcome reductions of headache related disabilities found to have no significant difference ($p > 0.10$) among Propranolol and Sodium Valproate treated groups.(Table-IV).

Physicians are on a hunt for a better and effective drug for prevention of migraine. For last decade anticonvulsant like Sodium Valproate is in use for preventive treatment of migraine. Its efficacy is established by various randomized placebo controlled study. The present study is a hospital based prospective cross sectional study, carried out to see whether there is any difference in efficacy of Sodium Valproate with that of Propranolol for migraine prevention. In our study we found no difference in efficacy of Propranolol versus Sodium valproate.

In this study majority (95%) of the study subjects were between 12 and 45 years of age. Female occupied 72.7 percent and male 27.3 percent of the study population.

Female to male ratio is of 2.67:1; which was near to ratio of 3:1 shown by Lipton et al 2001⁴. According to Lipton et al most of the migraineurs were between 12 and 40 years of age and according to Roper and Brown¹⁹ more than 80% of the migraineurs were under 30 years of age. 10.4 percent of our study subjects were having migraine with aura and 89.6 percent were having migraine without aura. Rasmussen⁶ has shown that 15% of the migraineurs were having migraine with aura and 85 % migraineurs without aura. Difference in our study is likely due to age limit and small sample size. Pretreatment difference in headache related disability eg. headache frequency, duration, severity and MIDAS score between propranolol and Sodium Valproate groups were not statistically significant ($P>0.10$). Post treatment outcome were significantly different and were in favor of treatment by both the drugs. But when outcome were compared with each other the difference in efficacy between the drugs were not statistically significant ($p>0.5$). Ashrafi et al¹⁶ who studied Sodium valproate versus propranolol in pediatric patients of 5 to 15 years of age for migraine prevention also found 50% reduction in headache frequency and mean headache duration. They also found no difference between the efficacy of Propranolol and Sodium Valproate.

Conclusion

Propranolol is a time tested drug for migraine prevention. Its efficacy is established. It is cheaper and easily available in the market. Sodium Valproate is having same efficacy as Propranolol. It is effective in lower dose than that used for epilepsy. It has no added advantage over Propranolol. It is relatively costlier than Propranolol. It has an established side effect of hepatotoxicity in children under 3 years, though we have not come across any adverse effect of Sodium Valproate in our study population.

However it can be recommended to use in migraine cases where Propranolol failed to have effect or where Propranolol is contraindicated e.g. in bronchial asthma, heart block and heart failure.

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