Sodium Valproate versus Amitriptyline in the Prophylactic Treatment of Migraine

Shahjada Mohammad Dastegir Khan1, Salma Akhtar Wali2, Abul Kalam Mohammed Shoab3, Muhammad Abdul Momen Khan1, Sakhawat Hossain1, Md. Shaheen Wadud4, Khan Md. Muzammel Hossain5

1Assistant Professor, Department of Neurology, Sir Salimullah Medical College, Dhaka, Bangladesh; 2Assistant Professor, (Obs & Gynae), Department of Gynae Oncology, National Institute of Cancer Research and Hospital, Dhaka, Bangladesh; 3Assistant Professor, Department of Neurology, Sylhet MAG Osmani Medical College, Sylhet, Bangladesh; 4Assistant Professor, Department of Neurology, National Institute of Neurosciences & Hospital, Dhaka, Bangladesh; 5Professor and Head, Department of Neurology, Sir Salimullah Medical College, Dhaka, Bangladesh; 6Associate Professor(CC), Department of Neurology, Dhaka National Medical College, Dhaka, Bangladesh; 7Associate Professor, Department of Pharmacology, MAG Osmani Medical College, Sylhet, Bangladesh

[Received on: 22 April 2021; Accepted on: 12 May 2021; Published: 1 July 2021]

Abstract

Background: Drug prophylaxis of migraine is a safe and effective way of reducing the attack of headache frequency and the economic burden of migraine. Several drugs have been shown to be efficacious in double-blind placebo-controlled trials. Many patients avoid the regular intake of prophylactic drugs because of fear about the side effects, tolerance and addiction. Another reason for the low acceptance of migraine prophylaxis is that the efficacy of most drugs is limited and the burden of treatment cost. In this study two effective drugs, Amitriptyline and Sodium valproate are evaluated regarding their safety and efficacy. This study shows the comparative effectiveness, safety of both drugs and withdraw all the misconception about the prophylactic treatment of migraine among the patients and improve their life style adjustment and reduce the economic burden of the society. Objective: The purpose of the present study was to observe and compare the efficacy of Sodium Valproate and Amitriptyline in the prophylactic management of migraine patients.

Methodology: This experimental study was carried out in the Department of Neurology at Sir Salimullah Medical College & Mitford Hospital, Dhaka, Bangladesh during the period from January 2013 to December 2013. A total of 120 patients with migraine were selected of which 60 were treated with Amitriptyline (Group-A) and another 60 were treated with Sodium Valproate (Group-B). Both groups were observed for 6 months and the improvement of headache regarding frequency, severity and duration of episodes of headache was recorded in every 2 months follow up. Adverse effect of the drugs also monitored in both group. Result: Out of 120 patients the mean age was 32±8.64 years and 34.23±8.09 in group-A and group-B respectively (p=0.147). There were 23 (38.3%) male and 37 (61.7%) female in group-A; whereas 17 (28.3%) male and 43 (71.7%) female in group-B (p=0.245). Thus the study was an age and sex matched study. It was observed that one third 20(33.3%) patients were house wife’s in group-A and 24(40.0%) in group-B. The difference was not statistically significant (p>0.05) between two groups. Frequency of attack per month before treatment was 6.25±5.21 in group-A and 7.80±4.1 in group-B. Frequency of attack per month after 2 months treatment was 4.30±4.14 and 6.19±4.10 in group-A and group-B respectively. Frequency of attack per month after 4 months treatment was 3.78±2.53 in group-A and 4.89±2.83 in group-B. Frequency of attack per month after 6 months treatment was 1.70±1.42 in group-A and 3.1±1.98 in group-B. Frequency of attack per month after 2, 4 and 6 months treatment was statistically significant (p<0.05) between two groups. It was observed that majority (88.3%) patients were improved headache in group-A and 23(38.3%) in group-B. The difference was statistically significant (p<0.05) between two groups. Conclusion: The pain intensity score is significantly decline in patients who received amitriptyline after treatment and almost similar in patients who received sodium valproate. Improved headache most of the patients who received Amitriptyline and less adverse effects developed in this group. Amitriptyline is more effective, seems to be safer than Sodium Valproate. [Journal of National Institute of Neurosciences Bangladesh, July 2021;7(2):126-131]

Keywords: Headache; migraine; sodium valproate; amitriptyline
Introduction

Migraine is one type of primary headache presenting with episodic headache that is usually unilateral, pulsating in quality, moderate to severe in intensity and exacerbated by physical activity, associated with nausea or vomiting, photophobia and phonophobia. The disorder is classified as migraine with aura and migraine without aura, according to the presence or absence; respectively of premonitory neurological symptoms. It is the second most common cause of childhood and adolescence headache and about 16% of all primary headaches. It is annually affecting 18.0% of women, 6.0% of men and 4.0% of children and common in people who are in lower socioeconomic groups. Migraine is now ranked by the World Health Organization as number 19 among all diseases causing worldwide disability. A pharmaco-economic study of migraine in the USA calculated that the annual loss of productivity due to migraine cost more than USD 13 billion per year and some studies have suggested that the cost might be as much as $17 billion per year.

The management of Migraine involves non pharmacological strategies, abortive and prophylactic drugs. Prophylactic treatment is necessary when the migraine attack is unacceptably frequent, prolonged, severe, and unresponsive to acute medication, associated with hemiparesis or aura. So management is designed to reduce the frequency, duration and/or severity of the attack. In addition, prophylactic treatment makes migraine attack more responsive to acute migraine therapies, reduces migraine associated disability, improves the patient’s ability to maintain normal lifestyle and decreases healthcare costs.

A variety of drugs are used in the prophylaxis of migraine. The basic principle in management of migraine is avoiding the trigger factors and blocking the mediator like serotonin, substance P, histamine and prostaglandin. Amitriptyline is the most frequently used drug in migraine prophylaxis, it was first used in the treatment of migraine in 1964, and in study on 27 patients, and resulted in significant improvement in 56.0% patients. Anticonvulsant drugs have been used for migraine prophylaxis since 1970 with carbamazepine as the first drug of this group. Publication of four RCTs on sodium valproate for migraine prophylaxis has shown that there is reduction in the number of migraine attacks or days with migraine by about 50.0% cases. In this context, Sodium valproate can be used in the prophylaxis of migraine.

The mechanism of action of sodium valproate in migraine prevention might be related to the facilitation of GABA-mediated neurotransmission. Valproate enhances GABA activity within the brain by inhibiting its degradation, stimulating its synthesis and release and directly enhancing postsynaptic effects. Active metabolites (e.g. 2-en-valproic acid) accumulates in the brain have an anticonvulsant effect. Most important adverse effects are nausea, alopecia, vomiting, tremor, weight gain, hair loss, drowsiness, ataxia, hepatotoxicity, pancreatitis are most serious adverse effects. It carries a high risk of congenital abnormality. Both amitriptyline and sodium valproate have class I recommendation for migraine prophylaxis. There are few studies, comparing the relative efficacy and tolerability of Sodium valproate and amitriptyline. In Bangladesh perspective no similar study was done previously. So this study was revealed the efficacy of sodium valproate and amitriptyline in migraine prophylaxis.

Methodology

This experimental study was conducted in Department of Neurology at Sir Salimullah Medical College & Mitford Hospital, Dhaka, Bangladesh from January 2013 to December 2013 for a period of one year. All attended patients of both sexes between 12-45 years who presented with migraine in the Out Patient Department of Neurology, Sir Salimullah Medical College and Mitford Hospital, fulfilling the inclusion criteria were considered as study population. Informed written consent was taken from each patient or his/her attendant. All information regarding history and
physical findings and other risk factors and relevant physical examination like nervous system examination, selected general and systemic examination recorded. Everyday all patients attending in the outdoor were divided into even number and odd number. Even number given Amitriptyline and odd number given Sodium Valporate with doses, Sodium Valporate: 400-1200 mg/d & Amitriptyline: 10-50 mg/d. for 6 months. All patients collected till the required number of sample size of 120 was reached. Then total patients divided into group A and group B. Even number patients considered as group A and odd number considered as group B. Then both groups were observed for 6 months and the improvement of headache regarding frequency, severity and duration of episodes of headache was recorded in every 2 months follow up. Adverse effect of the drugs also monitored in both group. In terms of nausea, dyspepsia, sedation, drowsiness, dry mouth, dizziness, increased appetite, weight gain, and ataxia. The data gathered was expressed by descriptive statistical methods (average, frequency distribution, percentage, mean & standard deviation) as applicable. Statistical analyses related with this study were performed by use of SPSS 17.0 package program. Comparison between groups was done by standard statistical test e.g. Chi-square test. A probability value (p) of <0.05 was considered as significant.

Results
One hundred and twenty (120) migraine patients were selected from which 60 patients of group-A (Amitriptyline treated group) and 60 patients of group-B (Sodium Valproate treated group) were analyzed. The mean age was found 32±8.64 years in group A and 34.23±8.09 years in group B. The mean age difference was not statistically significant (p>0.05) between two groups. Two third 37(61.7%) patients were female in group-A and 43(71.7%) in group-B. The difference was not statistically significant (p>0.05) between two groups. One third 20(33.3%) patients were house wife’s in group-A and 24(40.0%) in group-B. The difference was not statistically significant (p>0.05) between two groups (Table 1).

Frequency of attack per month before treatment was 6.25±5.21 in group-A and 7.80±4.1 in group-B. Frequency of attack per month after 2 months treatment was 4.30±4.14 and 6.19±4.10 in group-A and group-B respectively. Frequency of attack per month after 4 months treatment was 3.78±2.53 in group-A and 4.89±2.83 in group-B. Frequency of attack per month after 6 months treatment was 1.70±1.42 in group-A and 3.1±1.98 in group-B. Frequency of attack per month after 2, 4 and 6 months treatment was statistically significant (p<0.05) between two groups (Table 2).

Table 1: Distribution of the patients according to age, sex and duration

| Parameters     | Group A          | Group B          | P Value |
|----------------|------------------|------------------|---------|
| Age (Mean±SD)  | 32±8.64          | 34.23±8.09       | 0.147ns |
| Age Range (min-max) | 13 to 45       | 19 to 45         |         |
| Gender         |                  |                  |         |
| Male           | 23 (38.3%)       | 17 (28.3%)       | 0.245ns |
| Female         | 37 (61.7%)       | 43 (71.7%)       |         |
| Occupation     |                  |                  |         |
| Student        | 14 (23.3%)       | 8 (13.3%)        |         |
| House wife     | 20 (33.3%)       | 24 (40.0%)       |         |
| Service        | 15 (25.0%)       | 17 (28.3%)       | 0.491ns |
| Farmer         | 0 (0.0%)         | 2 (3.3%)         |         |
| Teachers       | 3 (5.0%)         | 3 (5.0%)         |         |
| Others         | 8 (13.3%)        | 6 (10.0%)        |         |

ns= not significant. P value reached from chi square test; Group-A (n=60)=Amitriptyline; Group-B (n=60); Sodium Valproate

Table 2: Distribution of the study patients by frequency of migraine (n=120)

| Group     | Frequency of attack per month |
|-----------|-------------------------------|
|           | Before treatment | 2 Months | 4 Months | 6 Months |
| Group A   | 6.25±5.21      | 4.30±4.14 | 3.78±2.53 | 1.70±1.42 |
|           | (2-25)         | (1-18)    | (1-12)    | (1-8)     |
| Group B   | 7.80±4.1      | 6.19±4.10 | 4.89±2.83 | 3.1±1.98  |
|           | (3-24)         | (2-20)    | (1-15)    | (1-13)    |
| P value   | 0.072ns       | 0.013s    | 0.025s    | 0.001s    |

s=significant; ns=not significant, P value reached from unpaired t-test

It was observed that majority (88.3%) patients were improved headache in group-A and 23(38.3%) in group-B. The difference was statistically significant (p<0.05) between two groups. Follow up in terms of frequency, intensity and duration had been shown in the table (Table 3).

In group A, nausea 5.0%, dyspepsia 6.7%, sedation 13.3%, drowsiness 11.7%, dry mouth 13.3%, dizziness 8.3%, increase appetite 5.0%, weight gain 6.7% and ataxia 3.3% cases. In group B, nausea 25.0%,...
Amitriptyline is the most frequently used drug in migraine. The basic principle in management of migraine attack more responsive to acute migraine attack. In addition, prophylactic treatment makes by physical activity, associated with nausea or vomiting, drugs. Prophylactic treatment is necessary when the migraine prevention might be related to the facilitation of GABA activity within the brain by inhibiting its active degradation, stimulating its synthesis and release and directly enhancing postsynaptic effects. Active

dyspepsia 16.7%, sedation 6.7%, drowsiness 8.3%, dry mouth 5.0%, dizziness 18.3%, increase appetite 20.0%, weight gain 16.7% and ataxia 13.3% cases. In conclusion adverse effects are mild in group-A than group-B users which gradually decreasing throughout the period of study (Table 4).

Table 3: Distribution of study patients according to follow up considering headache (n=120)

| Headache   | Group-A | Group-B | P value |
|------------|---------|---------|---------|
| Improved   | 53(88.3%) | 23(38.3%) | 0.001s |
| Not improved | 7(11.7%)  | 37(61.7%) |         |

s= significant, P value reached from chi square test

Table 4: Distribution of Study Patients According To Adverse Effect (n=120)

| Adverse Effect | Group A | Group-B |
|----------------|---------|---------|
| Nausea         | 3(5.0%)  | 15(25.0%)|
| Dyspepsia      | 4(6.7%)  | 10(16.7%)|
| Sedation       | 8(13.3%) | 4(6.7%)  |
| Drowsiness     | 7(11.7%) | 5(8.3%)  |
| Dry mouth      | 8(13.3%) | 3(5.0%)  |
| Dizziness      | 5(8.3%)  | 11(18.3%)|
| Increase appetite | 3(5.0%) | 12(20.0%)|
| Weight gain    | 4(6.7%)  | 10(16.7%)|
| Ataxia         | 2(3.3%)  | 8(13.3%) |

Discussion
This comparative prospective study was carried out with an aim to observe and compare the efficacy of Sodium valproate and Amitriptyline in the prophylactic management of migraine patients. A total of 120 were included in this study and among them 60 patients received Amitriptyline and rest 60 patients received Sodium valproate were considered as group A and group B respectively, in patients age belonged to 12 to 45 years presenting with migraine as per criteria fixed by the International Headache Society (IHS).

The mean age was 32±8.64 years varied from 13 to 45 years in group A and 34.23±8.09 years varied from 19 to 45 years in group B. The mean age was almost alike between two groups no statistical significant (p=0.05) difference was found between two groups, and no relationship of headache in migraine with age found. Similarly, Kalita et al.12 and Rao et al.8 showed mean age of their migraine patients were 32 years varied from 16 to 49 years and 28.6 years varied from 16 to 53 years respectively. Almost similar age range observed by another study13 where they found age range varied from 12 to 50 years. In this study it was observed that migraine is more common in female subject, where almost two third (61.7%) of the patients were female in group A (Amitriptyline) and 71.7% in group B (Sodium valproate). Male to female ratio were 1:1.2 and 1.25 in group A and group B respectively. The difference was not statistically significant (p=0.05) between two groups, and females are predominant in both groups. Similarly, two studies12,13 have observed identical incidence of female predominant of their study patients having migraine and thus, support the present study, where they found almost male to female ratio was 1:4. In a cross sectional study4 showed the crude prevalence of migraine was 18.2% and 6.5% in female and male respectively. As regards to the incidence of migraine, a number of investigators4-9 found in their studies that migraine was predominant in female subject.

Regarding the occupation it was observed that one third (33.3%) patients were housewives in group-A (Amitriptyline) and 40.0% in group-B (Sodium valproate); statistically not significant (p=0.05). It was observed by study13 that housewife 51.4%, student 21.6%, service 18.9%, business 2.7% and others 5.4%, which are comparable with the current study.

The present study found that frequency of attack per month before treatment was 6.25±5.21 in group-A and 7.80±4.1 in group B. Frequency of attack per month after 2 months treatment was 4.30±4.14 and 6.19±4.10 in group A and group B respectively. Frequency of attack per month after 4 months treatment was 3.78±2.53 in group-A and 4.89±2.83 in group-B. Frequency of attack per month after 6 months treatment was 1.70±1.42 in group-A and 3.1±1.98 in group-B. Frequency of attack per month after 2nd, 4th and 6th months of treatment were significantly (p<0.05) decline in both groups but more decline in group-A.

Regarding the pain intensity scale it was observed that pretreatment period, all patients had severe pain intensity in both groups and their mean pain intensity score was 8.98±0.83 varied from 8 to 10 in group A (Amitriptyline) and 8.67±0.9 varied from 8 to 10 in group B (Sodium valproate). After treatment received during 6th months of follow-up 86.7% patients had mild pain intensity in group A, whereas in group-B, moderate intensity was found 43.3% and severe intensity found 50% of the patients. In addition the mean pain intensity score was 2.78±0.71 varied from 2 to 5 in group A and 7.10±1.92 varied from 3 to 10 in group B. The pain intensity score after 6 months of treatment was significantly (p<0.05) decline from pretreatment period in group-A but almost similar between pretreatment period with after 6 months of treatment in group B, which is similar with a study13, where it found the mean...
Amitriptyline is the most frequently used drug in preventing attacks of migraine, improving the patient's ability to maintain normal life and productivity due to migraine cost more than USD 13 billion per year. Some studies have suggested that the pharmacological management of migraine patients. The most common cause of headache, functional disability, and overcrowding of rescue medications, which have lead to a more comprehensive evaluation.

In this study it was observed during follow up majority (88.3%) of the patients improved headache in group-A (Amitriptyline) and 38.3% in group-B (Sodium valproate), which was significantly (p<0.05) higher in group A. In the divalproate extended release (DVA-ER) group, 74.7% patients had improved with respect to the headache frequency, whereas in the amitriptyline (AMT) improvement at 3 months and 69.3% at 6 months in DVA-ER group. In the AMT group, these were 64.0% and 56.0%, respectively. In a small double blind crossover study done by Couch et al on 27 subjects treated with amitriptyline and placebo, 56.0% were more than 50.0% improved. In an uncontrolled study of 110 subjects reported that 72% were improved by ≥50% with amitriptyline.

In this present study it was observed that in group-A nausea 5.0%, dyspepsia 6.7%, sedation 13.3%, drowsiness 11.7%, dry mouth 13.3%, dizziness 8.3%, increase appetite 5.0%, weight gain 6.7% and ataxia 3.3% cases. In group B nausea 25.0%, dyspepsia 16.7%, sedation 6.7%, drowsiness 8.3%, dry mouth 5.0%, dizziness 18.3%, increase appetite 20.0%, weight gain 16.7% and ataxia 13.3% cases. In conclusion adverse effects are mild in group-A than group-B users which gradually decreasing throughout the period of study. Dodick et al. obtained that treatment-emergent adverse events (TEAEs) were reported in 85.9% in the topiramate group and 88.8% in the amitriptyline group. Adverse effects of amitriptyline include drowsiness, weight gain, and atypical effects such as dry mouth and also adverse effect of sodium valproate are nausea, vomiting, tremor, drowsiness, ataxia, weight gain, hepatotoxicity, and pancreatitis.

**Conclusion**

This study was undertaken to observe and compare the efficacy of Amitriptyline and Sodium Valproate in the prophylactic management of migraine patients. The pain intensity score was significantly lower in patients who received Amitriptyline after treatment and almost similar in patients who received Sodium Valproate. Improved headache most of the patients who received Amitriptyline and less adverse effects developed in this group. Amitriptyline is more effective, seems to be safer than Sodium Valproate.

**References**

1. Lipton RB, Bigal ME. The epidemiology of migraine. The American Journal of Medicine Supplements. 2005;118:3-10
2. Lipton RB, Bigal ME. Migraine: epidemiology, impact, and risk factors for progression. Headache: The Journal of Head and Face Pain. 2005;45:S3-13
3. Powers SW, Coffey CS, Chamberlin LA, Ecklund DJ, Klingner EA, Yankey JW, et al. Trial of amitriptyline, topiramate, and placebo for pediatric migraine. New England Journal of Medicine. 2017;376(2):115-24
4. Lipton RB. ‘Menstrually related migraine: Implications for employers and managed care’. 2005; 9: S800-S804
5. Mennini FS, Gitto L, Martelletti P. Improving care through health economics analyses: cost of illness and headache. J headache and pain. 2008; 9(4): 199–206
6. Leonardi M, Steiner TJ, Scher AT, Lipton RB. The Global Burden of migraine: measuring disability in headache disorders with WHO’s Classification of Functioning, Disability and Health (ICF). J Headache Pain. 2005; 6(6): 429–40
7. Dodick DW, Freitag F, Banks J, Saper J, Xiang J, Rupnow M et al. Topiramate Versus Amitriptyline in Migraine Prevention: A 26-Week, Multicenter, Randomized, Double-Blind, Double-Dummy, Parallel-Group Noninferiority Trial in Adult Migraineurs. Clin Ther. 2009; 31: 542-559
8. Rao BS, Das DG, Taraknath VR, Sarma Y. ‘A double blind controlled study of propranolol and cyproheptadine in migraine prophylaxis’, Open access journal indexed with Index Medicus. 2000; 48(3): 223-6
9. Yu S, Han X. Update of chronic tension-type headache. Current pain and headache reports. 2015;19(1):469
10. Sadeghian H, Motiei-Langrudi R. Comparison of Levetiracetam and sodium valproate in migraine prophylaxis: A randomized placebo-controlled study. Annals of Indian Academy of Neurology. 2015;18(1):45
11. Freitag FG, Collins SD, Carlson HA. A randomized trial of divalproex sodium extended-release tablets in migraine prophylaxis. Neurology. 2002; 58: 1652–9
12. Kalita J, Bhoi SK, Misra UK. ‘Amitriptyline vs divalproex in migraine prophylaxis: a randomized controlled trial’. Acta Neurol Scand. 2013; 128(1): 65-72
13. Chowdhury MI, Anwar Ullah AKM, Omar Hassan KM & Majumder S. ‘Sodium Valproate in Migraine Prevention Efficacy is the Same as Propranolol’. JAMC Bangladesh. 2012; 8(2): 32-38
14. Amanat M, Togha M, Agah E, Ramezaniz M, Tavassoli AR, Azizi Malamiri R, et al. Cinnarizine and sodium valproate as the preventive agents of pediatric migraine: A randomized double-blind
placebo-controlled trial. Cephalalgia. 2020;40(7):665-74
15. Shaygannejad V, Janghorbani M, Ghorbani A, Ashtary F, Zakizade N, Nasr V. ‘Comparison of the effect of topiramate and sodium valproate in migraine prevention: a randomized blinded crossover study’. Headache. 2006; 46: 642–8
16. Yurekli VA, Akhan G, Kutluhan S, Uzar E, Koyuncuoglu HR, Gultekin F. The effect of sodium valproate on chronic daily headache and its subgroups. The journal of headache and pain. 2008;9(1):37-41
17. Evers S. Treatment of migraine with prophylactic drugs. Expert opinion on pharmacotherapy. 2008;9(15):2565-73
18. Fernández-de-las-Peñas C, Schoenen J. Chronic tension-type headache: what is new?. Current opinion in neurology.
2009;22(3):254-61
19. Couch JR. Amitriptyline Versus Placebo Study Group. Amitriptyline in the prophylactic treatment of migraine and chronic daily headache. Headache: The Journal of Head and Face Pain. 2011;51(1):33-51
20. Snow V, Weiss K, Wall EM, Mottur-Pilson C. ‘American Academy of Family Physicians; American College of Physicians-American Society of Internal Medicine. Pharmacologic management of acute attacks of migraine and prevention of migraine headache’. Ann Intern Med. 2002;137: 840-9
21. Silberstein SD. Preventive Migraine Treatment. Neurol Clin 2009; 27:429–443.