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A comparison between amitriptyline and divalproex in prophylactic treatment of episodic migraine: An open label study from Nepal

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Abstract

Background & Objective: Migraine is one of the most common types of headache that presents in clinical practice. Both amitriptyline and divalproex are commonly used for migraine prophylaxis. We aimed to compare the efficacy of these drugs longitudinally over a 16-week period in patients with episodic migraine. *Methods:* This is an open label trial done at a headache clinic of Tribhuvan University Teaching Hospital, Kathmandu, Nepal. Patients were categorized into two groups; those receiving amitriptyline (group A) and divalproex (group D). The efficacy of drugs was assessed by headache frequency (headache days/month), duration (hours/headache episode), and severity (visual analogue scale). Both within group and between group comparisons were done at baseline, 4, 8, and 16 weeks. *Results:* The mean age of the patients was 33±11.7 and 36.6±15.3 years in group A and D (p=0.465). The majority of patients were females (94.3% and 84.8% in group A and D, respectively; p=0.201), and were married (71.4% and 75.8% in group A and D; p=0.624). In both the groups there was significant improvement in all the outcome measures (headache frequency, duration, and severity) from baseline to week 4 to week 8 and week 16 ($p<0.001$). In between group comparisons, the two treatment groups did not differ significantly in measures of headache frequency, duration and severity at all points of observation.
Conclusion: Both Amitriptyline and divalproex are effective drugs for migraine prophylaxis in Nepalese population. There was no significant difference in efficacy of these two drugs assessed at different time points.

Keywords: Episodic migraine, prophylaxis, Nepal, amitriptyline, divalproex

INTRODUCTION

Headache is one of the most common presentations in both out-patient and emergency settings. The general prevalence of headache is high and headache disorders are a major cause of disability worldwide.[1,2] Migraine alone ranks second highest in terms of years lived with disability on a global scale.[3] Globally, the percentage of the adult population with an active headache disorder is 46% for headache in general and 11% for migraine.[2] In USA 14.2% of adults above 18 years of age have reported having migraine or severe headache in previous 3 months in a 2012 National Health Interview Survey.[4] It is estimated that the prevalence of migraine in Asia is in the range of 8.4% to 12.7%.[5] Recently there is a rise in the prevalence of migraine to be as high as 1 in 10 persons, with a higher incidence in females, students and urban residents globally.[6] The goals of migraine preventive therapy are threefold: reduce attack frequency, severity, and duration; improve responsiveness to treatment of acute attacks; and improve function and reduce disability.[7,8] Epidemiologic studies suggest that approximately 38% of patients of migraine need prophylaxis but that only 3%–13% receive it.[9]

There are different pharmacological classes of prophylactic anti-migraine drugs. The five most common of these are β-adrenergic blockers (metoprolol, propranolol, atenolol, bisoprolol, nadolol, timolol), anti-epileptic drugs

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(valproic acid, topiramate), calcium channel antagonists (flunarizine), tricyclic antidepressants (amitriptyline) and serotonin antagonists (pizotifen, methysergide).[10] The choice of prophylactic therapy for migraine depends on existing comorbidities, contraindications, reported efficacy, and adverse effect profiles. Amitriptyline and divalproex are both effective in migraine prophylaxis. At least 6 clinical studies, reviewed in the recent American Headache Society (AHS) and American Academy of Neurology (AAN) guidelines, provide consistent evidence for the effectiveness of valproate in reducing headache frequency at a dose of 500 to 1000 mg per day.[11] Similarly, with a target dose of 10-100 mg per day, amitriptyline has been given strong recommendation in migraine treatment.[12] Both the AAN and AHS have published revised guidelines for effective use of drugs in different forms of primary headaches including episodic migraine and have recommended divalproex as a drug with level A recommendation and amitriptyline as a drug with level B recommendation.[11] Divalproex is a comparatively newer drug than amitriptyline but has received United States Food and Drug Administration (FDA) approval for prophylactic treatment of episodic migraine as early as 1996.[13] However, amitriptyline, a tricyclic antidepressant, although used for migraine prophylaxis for a long time has no FDA approval to date. Considering the routine use of both molecules in clinical practice in Nepal we planned a study to compare effectiveness of these two drugs at 4, 8, and 16 week- follow ups.

METHODS

This study was designed as an open label trial. The aim of this study was to evaluate the efficacy of two drugs, amitriptyline and divalproex, when used as prophylaxis in episodic migraine. The study was conducted over a period of 6 months from January 2015 to June 2015. It was carried out in a headache clinic run once a week by the Department of Psychiatry and Mental Health at Tribhuvan University Teaching Hospital, Kathmandu, Nepal. The study was designed where all patients visiting the headache clinic were considered for the study and inclusion criteria were applied. The inclusion criteria were: patients between the age of 16- 65 years and fulfilling the diagnostic criteria for episodic migraine with or without auras as per the diagnostic criteria of the International Classification of Headache Disorders second revision (ICHD II)[14] for at least 6 months before screening. The exclusion criteria were: patients with headache other than episodic migraine such as medication overuse headache, tension headache or refractory migraine. Refractory migraine was defined as patients with migraines causing significant interference with function and quality of life even after making necessary lifestyle modifications despite 2 months of treatment with preventive medicines with good efficacy. Those with comorbid psychiatric or medical conditions such as coronary heart disease, diabetes, hypertension, substance use disorders (except for nicotine) were also excluded along with pregnant women, lactating mothers and those not willing to participate in the study. Considering the potential teratogenecity of both amitriptyline (Category C), and divalproex (Category D), contraception was advised at the time of inclusion to all women of child-bearing age.

A serial number was given to each patient upon enrollment into the study. Those with odd numbers received amitriptyline (group A) and those with even numbers received divalproex (group D) as prophylaxis. Patients in the amitriptyline group received a starting dose of 25 mg per day with a maximum dose reaching 100 mg per day (dose increments done in every two weeks, as needed). Patients in the divalproex group received an initial dose of 250 mg per day with a maximal dose of 1000 mg per day (dose increments every two weeks, as needed). The average dose of amitriptyline was 50 mg per day while that of divalproex was 500 mg per day.

A semi-structured proforma was designed to collect essential information from the patients on socio-demographic variables like age, gender, religion, occupation, address etc. The primary outcome measure was the frequency of headache days per month, duration of each headache episode (hours) and severity of headache using visual analogue scale (VAS) with 0 as minimum and 10 as maximum. The measures were taken at four different points: at baseline, 4 weeks, 8 weeks, and 16 weeks after the initiation of treatment. We also assessed adverse effects for both the groups using Udvalg for Kliniske Undersogelser (UKU) side effect rating scale.

Informed written consent was obtained from the patients prior to inclusion in the study. The identity of the patients in the study was kept confidential to respect their privacy. The decision to participate in the study solely depended on participant's choice. Patients had the right to withdraw their consent from participation at any time after inclusion in the study. No incentive was given to participants

upon their participation. Ethical approval for the study was also taken from the Institutional review committee of Institute of Medicine (Reference number 124 (6-11-E)^2/071/072). The data were analyzed using SPSS version 26 ((IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp.). Mann-Whitney U testing was used to compare mean differences of the two treatment groups at different time points, and the Kruskal Wallis H test was used to compare intra-group efficacy of the intervention at different time-points. Chi-square tests were utilized for categorical variables. Data are presented as mean±SD, and percentage, where appropriate.

RESULTS

A total of 68 patients were enrolled in the study. Thirty-five patients received amitriptyline (Group A), and 33 patients received divalproex (Group D). Sociodemographic profiles were similar in both groups A and D (Table 1). The majority of the patients were in their early to mid-thirties, with a female preponderance (94% in group A, and 85% in group D). The majority of the patients were married, homemakers, had an educational attainment of secondary level or above, and followed Hinduism as their religion.

The headache frequency at baseline, week 4, week 8, and week 16 was 7.8 ±3.4, 4.9 ±2.8, 4.3±2.1, 2.6 ±1.4 days/month, respectively in group A ($p<0.001$), and 6.5±3.2, 4.3 ± 2.3, 4.1 ± 2.0, 2.5 ± 1.6 days/month, respectively in group D ($p<0.001$). Comparison between the two groups at each time interval did not show any significant difference in the headache frequency (Table 2). The headache duration at baseline, week 4, week 8, and week 16 was 5.9 ± 2.5, 3.9 ± 1.6, 3.8 ± 1.5, 2.9 ± 1.2 hours, respectively in group A ($p<0.001$), and 6.0 ± 2.8, 3.9 ± 2.4, 3.5 ± 2.0, 2.5 ± 1.3 hours, respectively in group D ($p<0.001$). Comparison between the two groups showed a similar headache duration at each time interval (Table 2). Headache severity assessed by VAS at baseline, week 4, week 8, and week 16 was 6.9 ± 1.5, 5.4 ± 1.3, 3.9 ± 0.9, 3.1 ± 1.1, respectively in group A ($p<0.001$), and 6.9 ± 1.7, 5.5 ± 1.5, 4.2 ±

Table 1: Sociodemographic profile

	Group A (n=35)	Group D (n=33)	P value
Age, years (mean±SD)	33.3±11.7	36.6±15.3	0.465
Gender, n (%)			0.201
Male	2 (5.7%)	5 (15.2%)	
Female	33 (94.3%)	28 (84.8%)	
Marital Status, n (%)			0.624
Single	7 (20%)	7 (21.2%)	
Married	25 (71.4%)	25 (75.8%)	
Divorced/separated/widowed	3 (8.6%)	1 (3%)	
Address, n (%)			0.309
Kathmandu Valley	18 (51.4%)	21 (63.6%)	
Outside	17 (48.6%)	12 (36.4%)	
Religion, n (%)			0.536
Hindu	28 (80%)	29 (87.8%)	
Buddhist	5 (14.3%)	2 (6.1%)	
Others	2 (5.7%)	2 (6.1%)	
Occupation, n (%)			0.556
Employed	13 (37.1%)	14 (42.4%)	
Homemaker	17 (48.6%)	12 (36.4%)	
Student	5 (14.3%)	7 (21.2%)	
Education, n (%)			0.658
Illiterate	4 (11.4%)	8 (24.2%)	
Primary	4 (11.4%)	2 (6.1%)	
Secondary	10 (28.6%)	9 (27.3%)	
Higher secondary	12 (34.3%)	9 (27.3%)	
University	5 (14.3%)	5 (15.1%)	

Footnotes: n=number of patients, SD=standard deviation

Table 2: Effect of Amitriptyline and Divalproex in headache frequency, duration and severity (between and within group comparisons)

Domains	Group A (n=35)	Group D (n=33)	P value (Mann-Whitney U)
Headache (days/month), Mean±SD			
Baseline	7.8 ±3.4	6.5± 3.2	0.072
Week 4	4.9 ±2.8	4.3 ± 2.3	0.532
Week 8	4.3±2.1	4.1 ± 2.0	0.763
Week 16	2.6 ±1.4	2.5 ± 1.6	0.531
Intra-group Kruskal-Wallis H	p<0.001	p<0.001	
Headache duration (hours), Mean±SD			
Baseline	5.9 ± 2.5	6.0 ± 2.8	0.833
Week 4	3.9 ± 1.6	3.9 ± 2.4	0.549
Week 8	3.8 ± 1.5	3.5 ± 2.0	0.358
Week 16	2.9 ± 1.2	2.5 ± 1.3	0.215
Intra-group Kruskal-Wallis H	p<0.001	p<0.001	
Headache Severity (VAS), Mean±SD			
Baseline	6.9 ± 1.5	6.9 ± 1.7	0.586
Week 4	5.4 ± 1.3	5.5 ± 1.5	0.686
Week 8	3.9 ± 0.9	4.2 ± 1.2	0.169
Week 16	3.1 ± 1.1	3.1 ± 1.2	0.745
Intra-group Kruskal-Wallis H	p<0.001	p<0.001	

Footnotes: n=number of patients, SD=standard deviation

1.2, 3.1 ± 1.2, respectively in group D (p<0.001). Comparison between the two groups for headache severity at each time interval showed similar scores (Table 2). The trend of headache frequency, duration, and severity over the course of treatment for both the groups is shown in Figure 1. Over the

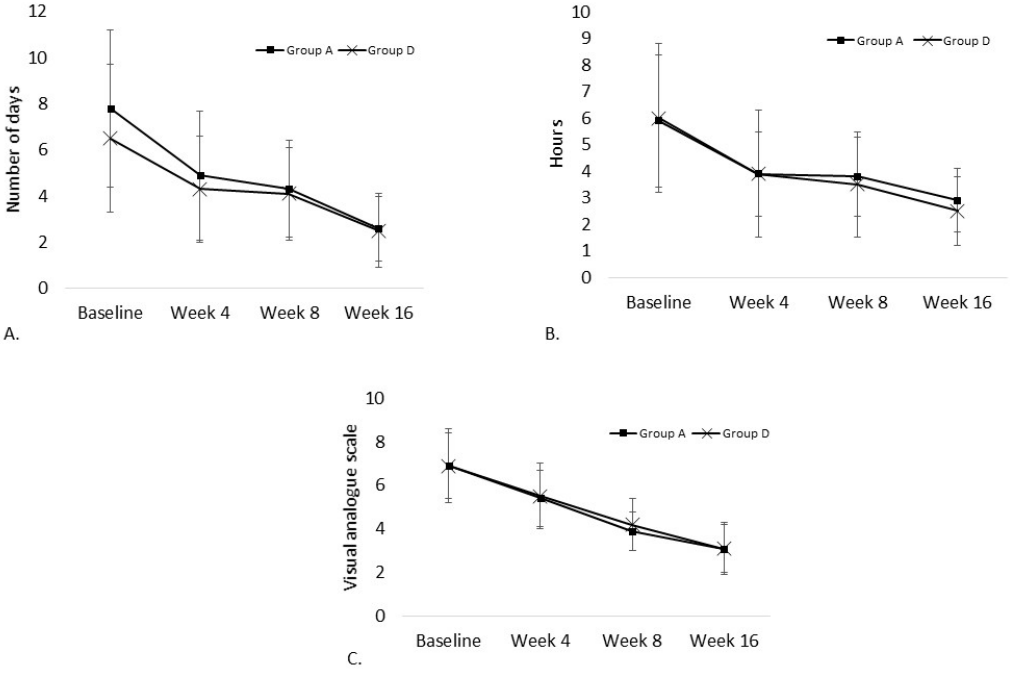

Figure 1. A. Trends of headache frequency (days of headache/month), B. trends of headache duration (hours), C. trends of headache severity (visual analogue scale) over the course of treatment in groups A and D.

period of 16 weeks, no subject dropped out of the study. In terms of adverse effects, most patients who were prescribed amitriptyline complained of sedation, dry mouth and constipation, and those on divalproex complained of tremors, sedation and dizziness. There were no patients in both groups A and D requiring discontinuation of the drug due to disabling side effects.

DISCUSSION

The higher rate of female participants seen in our study is similar to the epidemiological studies of UK, USA and Denmark.[4,15,16] The mean age seen in our study is comparable to other studies where migraine is common among those aged 30-40 years.[17] Our study found significant improvements in all the outcome measures, namely headache frequency, headache duration and headache severity from baseline to 16 weeks' measurement in both the treatment groups. The efficacy of amitriptyline in migraine treatment in terms of duration, frequency and severity has been established by many other studies.[18,19] A meta-analysis that looked into the efficacy of tricyclic antidepressants found amitriptyline to be an effective drug for migraine prophylaxis.[20] Divalproex is also regarded as a very effective drug for the prophylactic management of migraine.[21-24]

Most of the studies that have studied the efficacy of migraine prophylaxis have compared the drug under study with placebo. There are very few head to head comparisons between different drugs. Among those studies we could find only one study that compared efficacy of amitriptyline and divalproex. In the study done by Kalita *et al*. in 300 patients of migraine, it was seen that valproate extended release was more effective at 3 months than amitriptyline; however, at 6 months both were equally effective in migraine prophylaxis.[25] Even though the end point of outcome measures in our study was 16 weeks, the results of our study are comparable. A recent meta-analysis showed both amitriptyline and divalproex to be effective in migraine prophylaxis.[26] We found 6 randomized placebo-controlled trials (RCTs) for valproate and a greater than 50% improvement in headache was seen in 5 trials. Similarly, there were 5 trials for amitriptyline and all except one trial reported more than 50% improvement in headache. So, evidence from direct head to head comparison and placebo control comparison shows efficacy of both the drugs for migraine prophylaxis to be similar. Our study is therefore in line with results from published literature worldwide.

The major strength of this study is that there were no dropouts over three follow-up visits over 16 weeks in both treatment groups. However, this study is not without limitations. The major limitation is that this is not a blinded study. Neither the patients nor the treating doctors were blinded to the treatment received by the patients. We conducted this study among adults, so we do not know if the results hold true for other age groups of migraine headache. The sample size was small, so the generalizability of the study may be questionable. We only included patients with episodic migraine and therefore we do not know if the results hold true for chronic migraine. In most cases, patients with migraine have medical comorbidities which we have totally excluded. However, it is interesting to note that in Nepal, the cost of divalproex is four-fold the cost of amitriptyline for any comparable dosage. A cost effectiveness analysis done by Hunter and Rouff has also shown amitriptyline to be the most cost-effective prophylactic drug for migraine.[27] Furthermore, amitriptyline has been kept under the list of essential drug list by the Government of Nepal making it easily available even in remote areas.

We conclude that both amitriptyline and divalproex are effective drugs for migraine prophylaxis in the Nepalese population. Both drugs are well tolerated. There was no significant difference in their effects on headache frequency, duration, and severity. We recommend large-scale studies in migraine patients with better methodology for robust conclusions to be drawn.

DISCLOSURE

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Conflict of Interest: None

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