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A study on comparison of efficacy of sodium valproate and amitriptyline in the management of migraine

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Abstract

Introduction: Migraine is a common disabling neurological disorder that affects men and women equally. Frequently recurring, severe, disabling and long-lasting migraine attacks requires long term prophylaxis. The two most common alternatives that are used in the prophylactic therapy is Amitriptyline and Sodium valproate. Hence it is thought worthwhile to study the efficacy and tolerability of sodium valproate vs. Amitriptyline in migraine prophylaxis and find out the best treatment option between the two.
Material & Methods: This Prospective observational study was done in 200 patients; they were enrolled on the basis of inclusion and exclusion criteria. The baseline characteristics of the patients were recorded, along with headache frequency and migraine pain severity before and after treatment were recorded using VAS score. Efficacy was assessed by noting the reduction in number of migraine attacks per month, severity of pain corresponding to the baseline at the end of 3 months and 6 months of treatment. The adverse drug reactions were recorded in ADR form and causality was assessed using WHO Causality assessment.
Results: At the end of 3 and 6 months of treatment, patients in both the groups showed significant improvement in migraine symptoms. Improvement in VAS score at the end of 3 months, 50% and 70% patients showed > 50% improvement in Amitriptyline and sodium valproate group respectively. At the end of 6 months, it was 63% and 82%. Only 40% in Amitriptyline group had developed ADR, whereas in sodium valproate group 67% developed ADR. Maximum number of ADR associated in both groups had possible causal association as per WHO causality assessment scale.
Conclusion: Sodium valproate had better efficacy at the end of 3 months and 6 months of prophylactic therapy. In terms of tolerability profile, amitriptyline was superior in comparison with sodium valproate, during the study period.
Keywords: Migraine, Prophylaxis, Amitriptyline, Sodium Valproate.

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1. Introduction

Migraine is a common disabling neurological condition that affects men and women equally. Population based studies suggests that about 10-12% of the general population suffer from migraine. [1] Migraine is listed as the 3rd most prevalent disorder and 7th highest specific cause of the disability across the world. Migraine also has a negative impact on quality of life. Patients suffering from migraine attacks tend to reject sports, social events or holidays, in order to minimize the risk of painful episode of migraine attack. William Gower stated that migraine and epilepsy are the common disorders that might coexist in a same individual. Migraine also aggravates the epileptic seizure. [2] Thus migraine management is an important healthcare issue. Treatment modalities for migraine include pharmacological and non-pharmacological methods. Non-pharmacological mode of management includes behavioral and lifestyle changes that includes avoidance of triggering factors, assurance and patient follow-up. Therapeutic options for migraine consist of prophylactic treatment and symptomatic treatment. Symptomatic management of migraine ranges

from simple analgesics like non-steroidal anti-inflammatory drugs or acetaminophen to triptans or the less commonly used dihydroergotamine. But the frequently recurring, severe, disabling and long-lasting migraine attack requires long term prophylaxis.

The prophylactic therapy for migraine with aura and without aura consists of Beta-blockers, Calcium-channel blockers like partials erotonin agonists, Tricyclicanti-depressants, anti-epileptics like gabapentin, valproate, topiramate. All the above mentioned drugs are mostly effective in the prophylactic management of migraine. Apart from their efficacy, they also tend to have relevant adverse effects and contraindications and may also interfere with other concurrent medical conditions and treatment. Though wide varieties of drugs are available, the two most common alternatives that are used in the prophylactic therapy is Amitriptyline and Sodium valproate. There are only limited studies comparing the efficacy and safety profile of Amitriptyline and Sodium valproate in migraine prophylaxis. Hence it is thought worthwhile to study the efficacy and tolerability of sodium valproate vs Amitriptyline in migraine prophylaxis and find out the best treatment option between the two. The main objectives of the study are to compare the efficacy of Sodium valproate and Amitriptyline in the prophylaxis of migraine and to compare the safety profile of the two drugs used for migraine prophylaxis and assess causality of ADR using WHO Causality assessment scale.

2. Methodology

This study was a Prospective observational one conducted at Government Dharmapuri Medical College, Dharmapuri. Study was done for one year from April 2020 to March 2021. Patients diagnosed with migraine based on international headache society criteria of age above 18 years having more than 4 migraine attacks per month, who were on sodium valproate or amitriptyline prophylactic therapy were included in the study.

Patients on other medication for migraine prophylaxis and who were not willing to participate in the study and with history of severe drug allergy, hypertension, coronary heart disease, pregnancy, malignancy, glaucoma, papilledema, epilepsy were also excluded. The study proposal was approved by the Institutional Human Ethics Committee Written informed consent was obtained from every participant before enrolling them in to the study. Data were collected from 200 migraine patients taking amitriptyline or sodium valproate prophylactically who were recruited during study period. The baseline characteristics, symptom duration, headache frequency, neurological examination and also migraine pain severity before and after treatment were recorded using VAS score, Efficacy was assessed by noting the reduction in number of migraine attacks per month. The adverse drug reactions were recorded in ADR form, causality was assessed using WHO Causality assessment scale.

The severity of pain, frequency of headache and functional disability at baseline, 3 months and 6 months following treatment within the group were compared using ANOVA, Chi-square test. The variables were considered significant if P-value was less than 0.05. The statistical analysis was performed using SPSS version 22.

3. Results

A prospective, observational study was conducted in 200 patients with migraine who were prescribed with Amitriptyline and sodium valproate, age distribution of the study population was from 18-70 years. Most common age group of study population in amitriptyline and sodium valproate group was 21-40 years. (Amitriptyline group n=88, 88% and Sodium valproate group n=87, 87%) The usage of both drugs was found to be higher among females (amitriptyline n=61, 61% and sodium valproate group n=62, 62%)

The study population had migraine symptoms for a period of 1-6 years and headache frequency per month was found to be 4-12 attacks per month. Severity of Migraine attack among the encounters in both the group was assessed using MIDAS score. In amitriptyline group 70% (n=70) patients had migraine attack with mild disability, 28 % (n=28) with moderate disability and only one patient had severe disability.

Among sodium valproate group, 20% (n=20) had migraine attack with mild disability, 58% (n=58) with moderate disability, 22% (n=22) with severe disability and disability was graded as II, III and IV respectively using MIDAS score.

The severity of pain among the patients was assessed using VAS score. 98% of migraine encounters in Amitriptyline group had VAS score ranging from 6-9. In sodium valproate group, 95% of patients had severe migraine pain with VAS score ranging from 7-10.

The patients were followed at the end of 3 months and 6 months. Their pain severity and overall improvement in headache frequency were assessed, at the end of 3 months, 60% patients (n=60) in amitriptyline group and 91% patients (n=91) in sodium valproate had > 50% improvement in overall headache frequency. (P value=0.067), whereas at the end of 6 months, 64% (n=64) patients in amitriptyline group and 87% (n=87) in sodium valproate had>50%improvement in overall headache frequency. (P value<0.001)

Table1: Improvement in VAS score, Severity of headache at the end of 3 months and 6 months

Outcome parameter	Improvement/ no improvement	Amitriptyline Group	Sodium valproate Group	P value	
				Amitriptyline	Sodium Valproate
VAS score					
Attheendof3 months	>50% improvement	50(50%)	70(70%)	<0.0001	<0.0001
	<50% improvement	50(50%)	30(30%)		
At the end of 6 months	>50% improvement	63(63%)	82(82%)	0.0086	<0.0001
	>50% improvement	37(37%)	14 (14%)		
Severity of headache improvement					
At the end of 3 months	Improvement No improvement	82(82%) 18(18%)	91(91%) 9(9%)	<0.0001	<0.0001
At the end of 6 months	Improvement No improvement	88(88%) 12 (12%)	95(95%) 5(5%)	0.0092	<0.0001

In Amitriptyline group, 50 (50%) patients at the end of 3 months and 63(63%) patients at the end of 6 months had > 50% improvement in VAS score. In sodium valproate group 70(70%) patients and 82 patients (82%) had improvement in VAS score at the end of 3 months and 6 months respectively (p value<0.0001 for both the groups and was statistically significant).

The severity of headache decreased in both the groups at 3 and 6 months when compared with the baseline. 82 (82%) patients had improvement at 3 months and 88 (88%) at the end of 6 months in amitriptyline group, whereas in sodium valproate group, these were 91 (91%) and 95 (95%) respectively (P Value <0.0001in both the groups).

Out of 200 migraine subjects, only 40 patients in Amitriptyline group had developed ADR, whereas in sodium valproate group 67 patients developed ADR during the study period. Maximum number of patients who had ADR in Amitriptyline group (53%) developed sedation, followed by menstrual irregularities (13%) and weight gain (13%) at the end of 3 months. At the end of 6 months majority of the patients had sedation (58%) as the most common ADR, followed by weight gain (15%), dry mouth (13%) and 10% of the female developed menstrual irregularities.

At the end of 3 months, in sodium valproate group 26% of patients had significant weight gain, 18% of the female had menstrual irregularities, and 15% developed sedation as the ADR. At the end of 6 months, 54% of patients developed significant weight gain, 20% of the female encounters had menstrual disturbance and 12% of the subjects had sedation as the most common ADR in sodium valproate group.

At the end of 3 months, causality of ADR associated with Amitriptyline was assessed using WHO-UMC causality assessment scale, 88% of ADR had possible causal association, 10% with probable association, 2% of ADR were found to have unlikely association**.** At the end of 6 months, 81% of ADR had possible causal association, 15% of ADR had probable relationship and 4% of ADR were found to have unlikely causal association as per WHO-UMC causality assessment scale.

Similarly, at the end of 3 months, causality of ADR associated with sodium valproate was assessed. 79% of ADR had possible association, 12% with probable causal relationship, 5% of ADR were found to have certain and 4% of ADR had unlikely causal association as per WHO-UMC causality assessment scale. At the end of 6 months, causality of ADR associated with sodium valproate was assessed, 81%of ADR had possible causal association, 15% of ADR with probable causal association and 4% of ADR were found to be unlikely as per WHO-UMC causality assessment scale.

4. Discussion

In our study prevalence of usage of Amitriptyline and Sodium valproate was found to be higher among females, which is in line with the study of Kalita *et al*.[3] Susceptibility of migraine is higher among females especially during active reproductive period due to hormonal changes which is predominant during this period. Some studies suggest that it is due to genetic influence. (Male to female relation is 1:3)[4]

The commonest age group receiving above mentioned drugs lie between21to 40 years, (which is comparable with the study done by Bigal *et al*[5] Migraine is common at this age group because they are exposed to variety of triggering factors like stress, hormonal imbalance, high fat diet, fasting, nutritional deficiency, sunlight exposure, etc.[6] There is an overall improvement in headache frequency and VAS pain score comparing the baseline with 3 months and 6 months of treatment for both the drugs.

At the end of 3 months, Sodium valproate group showed significant reduction in severity of pain (n=70, [70%] p value <0.001). The group also had greater than 50% improvement in headache frequency (p value <0.001) when compared with Amitriptyline. This replicates a comparative study on migraine prophylaxis done by Kalita *et al*[3] At the end of 6 months, difference in response between the two

alternatives were quiet significant. Sodium valproate had better efficacy even at the end of 6months.Thisstudy result was different from the study by Kalita *et al*[3], which showed no significant difference between the two alternatives in VAS score and other outcome parameters. This observed difference between our study and the study done by Kalita *et al* [3] might have occurred due to genetic differences, pharmaceutical variation also due to difference in dosing schedule. In our study Amitriptyline and Sodium valproate were prescribed in a dose range of 10-25mg/day and 200-400mg/day respectively. In their study, Amitriptyline and Sodium valproate was prescribed with a higher dose range of 25-50mg/day and 200-1000mg/day respectively.

In our study we included efficacy as the primary endpoint and causality of ADR associated with both amitriptyline and sodium valproate were assessed using WHO-UMC causality assessment scale, which have led to more detailed comprehensive evaluation.

On comparing the tolerability profile of both drugs at 3 months and 6 months, Amitriptyline had a better tolerability profile. Out of 100 migraine patients in Amitriptyline group only 40 patients developed ADR. The most common ADR reported with amitriptyline usage was sedation (53%) followed by menstrual irregularities (13%), weight gain (13%) and dry mouth (10%) at 3 months and 6months. These results were similar to the study done by Goncalves *et al*.[7] No serious adverse events were reported. In sodium valproate group 67 patients developed ADR. Out of 100 patients, 26% of them suffered from weight gain, 18% of the females had menstrual irregularities, 15% had sedation, 7% had hair loss followed by increased skin pigmentation, acne and GIT upset at the end of 3 months and 6 months of treatment. These results were comparable with the study done by Mansoureh *et al*.[8] No hematological or hepatic side effects were seen in the patients of both groups.

In this study, the causality of ADR associated with amitriptyline and sodium valproate was assessed using WHO-UMC causality assessment scale. Majority of ADR in the amitriptyline and sodium valproate group had possible causal association at the end of 3 months and 6 months. None of the previous studies had assessed the causality of ADR associated with usage of migraine prophylactic drugs. Assessment of causality helps to strengthen the relationship between exposure and outcome.

5. Conclusion:

Sodium valproate had better efficacy at the end of 3 months and 6 months of prophylactic therapy. In terms of tolerability profile, amitriptyline was superior in comparison with sodium valproate, during the study period. Hence in cases of planning a prophylactic drug for migraine patients sodium valproate can be better drug based on its efficacy, furthermore studies are required in larger population to evaluate the tolerability of both drugs.

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