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# Comparative study of safety of Propranolol Versus Amitriptyline for prophylaxis of Migraine

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**Abstract** **Original Research Article**

Migraine headache is a common, disabling condition. When migraine episodes are frequent, treatment can be challenging. Prophylactic therapy for migraine remains one of the more difficult aspects. Although, all of the medications used in treatment have incomplete efficacy, and most produce adverse effects. ***Material and methods:*** The study was conducted in Patients with symptoms of Migraine attending Department of Medicine, Santosh Medical College & Hospital, after the approval of the Institutional Ethics Committee. This was a prospective, comparative, parallel, open-label, randomized clinical trial. As per the ICHD III beta diagnostic criteria for migraine. The ADRs related to Propranolol and Amitriptyline were monitored and documented in suitably designed ADR documentation form after initial notification of the suspected ADR by physicians. Severity and causality of the ADRs were assessed by using Modified Hartwig and Siegel scale and Naranjo's Algorithm, respectively. ***Result:*** Mean age in group 1 patients were 27.21±7.71 years and in Group 2 patients were 28.01±7.65. There was no statistically significant difference in mean between both groups. As per the modified Hartwig and Siegel's scale maximum number of ADRs was mild category and lowest in sever type of reaction was observed in this study. No ADRs were found in lethal type of reaction. Most common adverse drug reaction reported in two groups were includes. In the Group 1: In period 1 maximum ADR was Dizziness and least one constipation whereas in during period 2 highest incidence of ADR was Somnolence and least was Dizziness and constipation. On the other hand, in group 2 during period 1 maximum ADR was Xerostomia and least constipation. Moreover, in during period 2 more ADR were dizziness and followed by weight gain and xerostomia, somnolence and constipation. ***Conclusion:*** This trial shows that propranolol is well tolerated as compared with amitriptyline in migraine prophylaxis. The ideal drug for migraine prophylaxis is propranolol has few side effects compared with Amitriptyline. When migraine with depression, anxiety disorders, irritable bowel syndrome and epilepsy are comorbidities of migraine for amitriptyline. When migraine and hypertension and/or angina occur together, propranolol might be drug of choice.

**Keywords:** Migraine headache, Prophylactic therapy, migraine prophylaxis.



## INTRODUCTION

Although migraine is one of the commonest reasons for patients to consult their doctor and despite its enormous impact, it is still under-recognized and under-treated [1]. This has various reasons. On the one hand, there are no biological markers to confirm the diagnosis and many doctors lack knowledge, time, interest, or all three, to manage migraineurs [2]. On the other hand, there is no cure for migraine and, although effective therapies do exist, they have only partial efficiency or are not accessible to all. As a result, a proportion of affected individuals do not seek (anymore) medical help [3]. We hope that this article, in which we will focus on migraine in adulthood, will help to convince that migraineurs should certainly accept their disorder and cope with it, but not resign themselves.

**Before starting Prophylaxis**

Patients for whom prophylactic therapy is indicated have the following migraine features:

- More than 2 headaches per month, but fewer than 8 (>8 attacks per month usually indicate overuse of abortive therapy)

- Headaches less frequent but more prolonged (>2 days' duration) or severe attacks leading to substantial disability
- Migraines are refractory to abortive treatment measures
- Therapies for acute attacks are intolerable, contraindicated, or overused (>2 per week)2-4
- Migraines are predictable in occurrence
- The patient has other migraine conditions such as migraine with prolonged aura or hemiplegic migraine [4].

**Drugs with an Established Role in Migraine Prophylaxis**

**First-line agents**

The first-line agents with the greatest efficacy are β-blockers, tricyclic antidepressants, and divalproex sodium or valproic acid [5]. I have not considered agents unavailable in the India, such as lisuride, and pizotifen. 1 I have also excluded agents that have proved to be ineffective or for which proof of efficacy is limited.

**β -Blockers**

The scientific and clinical evidence supports -blockers as the drugs of choice for the prevention of migraines [6]. The most commonly used agent is propranolol hydrochloride. Generally, if 1 agent fails, another in its class may be tried, and this change may prove to be effective. It is imperative that abrupt stoppage of therapy is avoided [6]. β–Blockers are not effective in reducing aura [7]. In general, response to these agents is gradual, and it may take at least a month to see an effect [8]. The use of β -blockers with intrinsic sympathomimetic activity (such as pindolol) should be avoided [9]. The daily dose range for -blockers in migraine prophylaxis, together with their side effects, precautions, and special indications [10].

**Tricyclic Antidepressants**

Tricyclic antidepressants are another class of medication considered as first-line treatment in migraine prophylaxis. Even without the presence of depression, these agents are effective in preventing migraines, and the response is usually more rapid (within 4 weeks) than with β-blockers [11]. Combined use with β -blockers does not reduce the incidence of migraines, but it may reduce that of tension- type headaches [12]. Although the entire class is considered useful in prophylaxis, tertiary amines, such as amitriptyline, are more effective than the secondary amines, such as nortriptyline [13]. Amitriptyline hydrochloride is the first-line agent of choice among the tricyclic antidepressants [14]. Physicians need to consider the differences in side effect profiles of the various drugs when deciding which one to use [15].

Hence, this study was undertaken 1. To find out a prophylactic drug for migraine having better efficacy and minimal side effects and thereby safety of these drugs 2. To compare the efficacy of Propranolol Vs. Amitriptyline as prophylactic agent for migraine and 3. To compare the safety of Propranolol Vs Amitriptyline as prophylactic agent for migraine. The study was intending to probe into the best medication for prophylaxis of migraine in terms of safety and efficacy with careful and well-planned design which can be translated into clinical settings for benefit of migraine patients.

## MATERIAL AND METHODS

The study was conducted in Patients with symptoms of Migraine attending Department of Medicine, Santosh Medical College & Hospital, after the approval of the Institutional Ethics Committee. This was a prospective, comparative, parallel, open-label, randomized clinical trial.

As per the International Classification of Headache Disorders 3rd edition-Beta version (ICHD III beta) diagnostic criteria for migraine were followed as [16]:

| Migraine without aura | Migraine with aura | Migraine in children | Chronic migraine |
|---|---|---|---|
| A. At least five attacks 1 fulfilling criteria B-D | A. At least two attacks fulfilling criteria B and C | A. At least five attacks fulfilling criteria B-D | A. Headache (tension-type-like and / or migraine-like) on 15 days per month for > 3 months 2 and full-filling criteria B and C |
| B. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated) | B. One or more of the following fully reversible aura symptoms:<br>1. Visual<br>2. Sensory<br>3. Speech and / or language<br>4. Motor<br>5. Brainstem<br>6. Retinal | B. Headache attack lasting: 1-72 hours | B. Occurring in a patient who has had at least five attacks fulfilling criteria B-D for 1.1 Migraine without aura and / or criteria B and C for 1.2 Migraine with aura |
| C. Headache has at least two of the following four characteristics:<br>1. Unilateral location<br>2. Pulsating quality<br>3. Moderate or severe pain intensity<br>4. Aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs) | C. At least two of the following characteristics:<br>1. At least one aura symptom spreads gradually over 5 minutes, and / or two or more symptoms occur in succession<br>2. Each individual aura symptom lasts 5-60 minutes<br>3. At least one aura symptom is unilateral<br>4. The aura is companied, or followed within 60 minutes, by headache | C. has at least two of the following four characteristics:<br>1.Unilateral<br>2. Pulsating quality<br>3. Moderate to severe pain intensity<br>4. Aggravation by routine physical activity | C. On 8 days per month for > 3 months, fulfilling any of the following 3:<br>1. Criteria C and D for 1.1 Migraine without aura<br>2. Criteria B and C for 1.2 Migraine with aura<br>3. Believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative |
| D. During headache at least one of the following:<br>1. Nausea and / or vomiting<br>2. Photophobia and phonophobia | D. Not better accounted for by another ICHD-3 diagnosis, and transient ischemic attack has been excluded. | D. During headache at least one of the following:<br>1. Photophobia and phonophobia<br>2. Nausea or vomiting | D. Not better accounted for by another ICHD-3 diagnoses. |
| E. Not better accounted for by another ICHD-3 diagnosis | | | |

Subject aged between 5-65 years.

The following categories of patients were excluded from the study:

- Patients <5 years & >65 years.
- Patients having chronic incapacitating illness e.g. AIDS, cancer, TB.
- Patients whose primary headaches are other than migraine headaches.

The patients meeting the inclusion criteria were explained in detail about the nature of the trial, its purpose, procedures, and follow-up. They were provided with detailed trial information in case report form. Written informed consent was obtained from those who volunteered to participate in the trial. Current medical history and diagnosis were noted during the first visit.

A total of 126 patients were enrolled in the study, diagnosed cases of migraine were randomly allocated using random number table to either Group 1 (Period 1: To receive tablet Propranolol 4–16 weeks and Period 2: Amitriptyline 20–32 weeks) or Group 2 (Period 1: To receive tablet Amitriptyline 4–16 weeks and Period 2: Propranolol 20–32 weeks). During the first 4 weeks, the run-in period, the patients do not receive prophylactic treatment and have to record in a headache diary the number of migraine attacks, the duration of attacks in hours and the severity. The severity shall be graded on 1–3 scale:

1. Able to work throughout the attack;
2. Unable to work, but not staying in bed;
3. Staying in bed.

- Follow-up visits shall be 4, 16, 20, and 32 after start of study.
- Evaluations done by a psychiatrist blind to the treatment given.

**Adverse Drug reaction (ADR) monitoring**

The ADRs related to Propranolol and Amitriptyline were monitored and documented in suitably designed ADR documentation form after initial notification of the suspected ADR by physicians.

Additional details were collected by review of the patient case records and interview with patients. Severity and causality of the ADRs were assessed by using Modified Hartwig and Siegel scale and Naranjo's Algorithm, respectively. The Modified Hartwig and Siegel scale grades ADRs as Mild, Moderate, and

Severe. Naranjo's Algorithm scale grades causality of ADRs as Definite, Probable, Possible and Unlikely.

## STATISTICAL ANALYSIS

All values were displayed as mean ± SD. Categorical variables were compared by chi-square test. Quantitative data on adverse-effects were analyzed by using the students unpaired 't'-test for difference between means. *P*-value <0.05 was taken as significant and *P*-value <0.001 was taken as highly significant, while *P* >0.05 was considered as insignificant.

## RESULTS

In both the groups, maximum number of patients were in the age group of 5-25 years and least number of patients were 46-65 years of age. Mean age in group 1 patients were 27.21±7.71 and in Group 2 patients were 28.01±7.65. There was no statistically significant difference in mean age of patient from Group 1 and Group 2 patients with Unpaired t test.

**Table-1: Comparison of Mean Age in Groups**

| Age-Group | Group 1 | | Group 2 | |
|---|---|---|---|---|
| | No | Percentage | No | Percentage |
| **5-25 years** | 37 | 61.6% | 34 | 56.6% |
| **26-45** | 20 | 33.3% | 25 | 41.6% |
| **46--65** | 3 | 5.0% | 1 | 1.6% |
| **Total** | 60 | 100 | 60 | 100 |
| **Mean±SD** | 27.21±7.71 years | | 28.01±7.65 years | |
| **p-value** | 0.609 | | | |

**Table-2: Gender difference between Group 1 and Group 2**

| | Group 1 | | Group 2 | | Chi-Square test p=value |
|---|---|---|---|---|---|
| | n=60 | (%) | n=60 | (%) | |
| **Male** | 19 | 31.6 | 21 | 35.0 | 0.112 |
| **Female** | 41 | 68.3 | 39 | 65.0 | |
| **Total** | 60 | 100 | 60 | 100 | |

The Table-2 reflects that 120 migraine patients in Group 1: 19 were male (31.6%) while 41 were female patients (68.3%). In Group 1 consisted of 21 male patients (35%) and 39 female patients (65%). There was no statistically significant difference in number of patient from Group A1and Group 1 patients (0.112) when we applied with Chi-square test.

**Table-3: WHO causality assessment of ADRs**

| Type of reaction | Group 1 | | Group 2 | |
|---|---|---|---|---|
| | Period 1 (Propranolol) | Period 2 (Amitriptyline) | Period 1 (Amitriptyline) | Period 2 (Propranolol) |
| Certain | 3 | 2 | 4 | 4 |
| Probable/ likely | 4 | 11 | 9 | 5 |
| Possible | 6 | 8 | 6 | 2 |
| Unlikely | 1 | 1 | 1 | 1 |
| Conditional/ unclassified | - | 1 | - | - |

**Table-4: Severity of reported ADRs by modified Hartwig & Siegel scale**

| Type of reaction | Group 1 | | Group 2 | |
|---|---|---|---|---|
| | Period 1 (Propranolol) | Period 2 (Amitriptyline) | Period 1 (Amitriptyline) | Period 2 (Propranolol) |
| Lethal | - | - | - | - |
| Severe | 1 | 3 | 4 | 1 |
| Moderate | 6 | 9 | 7 | 5 |
| Mild | 7 | 11 | 9 | 6 |

In Table-4 As per the modified Hartwig and Siegel's scale maximum number of ADRs was mild category and lowest in sever type of reaction was observed in this study. No ADRs were found in lethal type of reaction.

**Table-5: Comparison of ADRs during treatment with Group 1 and Group B**

| Type of reaction | Group 1 | | Group 2 | | |
|---|---|---|---|---|---|
| | Period 1 (Propranolol) | Period 2 (Amitriptyline) | Period 1 (Amitriptyline) | Period 2 (Propranolol) | p=value |
| Xerostomia | 2 | 6 | 7 | 1 | 0.02 |
| Dizziness | 6 | 3 | 2 | 7 | 0.03 |
| Weight gain | 3 | 4 | 3 | 2 | 0.09 |
| Somnolence | 2 | 7 | 6 | 1 | 0.01 |
| Constipation | 1 | 3 | 2 | 1 | 0.04 |

In Table-5 most common adverse drug reaction reported in two groups were includes. In the Group 1: In period 1 maximum ADR was Dizziness and least one constipation whereas in during period 2 highest incidence of ADR was Somnolence and least was Dizziness and constipation. On the other hand, in group 2 during period 1 maximum ADR was Xerostomia and least constipation. Moreover, in during period 2 more ADR were dizziness and followed by weight gain and xerostomia, somnolence and constipation.

## DISCUSSION

None of patients abandoned the study due to side effects of drugs. Propranolol was very well tolerated. The most frequent side effect to this drug, Dizziness, was significantly more frequent than in the other groups. Amitriptyline was also very well tolerated. In groups 1 and 2 the frequency of xerostomia was significantly higher. There was also a higher frequency of weight gain, but it has not reached statistical significance. These findings were already expected considering the profile of side effects of amitriptyline. This drug did not result in more side effects than monotherapy. This is encouraging in the sense of carrying out further studies of combination of drugs.

All β-blockers can produce behavioural adverse events, such as drowsiness, fatigue, lethargy, sleep disorders, nightmares, depression, memory disturbance, and hallucinations [17]. Other potential adverse events include gastrointestinal symptoms, decreased exercise tolerance, hypotension, bradycardia, and impotence [18]. Although stroke has been reported to occur after patients with migraine with aura were started on beta-blockers, neither an absolute nor a relative contraindication to their use by patients with migraine, either with or without aura, exists [19]. Contraindications to the use of beta blockers for the treatment of migraine include asthma and chronic obstructive lung disease, atrioventricular conduction defects, Raynaud disease, peripheral vascular disease, and severe diabetes mellitus [20]. Patients with coexistent hypertension, anxiety, mitral valve prolapses, or benign essential tremor could benefit from its use.

Adverse events are common with tricyclic antidepressant use. Antimuscarinic adverse events include dry mouth, a metallic taste, epigastric distress, constipation, somnolence, dizziness, mental confusion, tachycardia, palpitations, blurred vision, and urinary retention [21]. Other adverse events include weight gain, orthostatic hypotension, reflex tachycardia, palpitations, QT interval prolongation, decreased seizure threshold, and sedation [22]. Antidepressant treatment may change depression to hypomania or frank mania (particularly in bipolar patients). Older patients may develop confusion or delirium [23]. The antimuscarinic and antiadrenergic effects of these agents may pose increased risks for cardiac conduction abnormalities, especially in the elderly, and these patients should be carefully monitored or other agents considered [24]. TCAs can cause the syndrome of inappropriate ADH secretion (SIADH), and precipitate mania in bipolar patients [25]. It can be particularly useful when comorbid depression, peripheral neuropathy, or insomnia is present. TCAs can lower the seizure threshold.

This study has several limitations. The number of patients who completed the study in two groups was too small, so that the conclusions on the effectiveness of these treatments must be interpreted very cautiously. In addition, the follow-up time of patients in the therapy phase was only of 32 weeks for titration of doses. Future studies evaluating the association of drugs in patients with migraine and patients with chronic migraine should include a larger number of patients and should follow patients for at least six months using the drugs. Another limitation is that the symptomatic medications were not registered in the pretreatment and treatment phases. However, despite these limitations, this study points to some data that should be taken into account in future drugs studies. First, the use of beta blockers, at doses below those used in previous therapeutic trials that used 80 to 160 mg per day of propranolol, was effective. Therefore, low beta blockers doses in combination with antidepressants or other types of drugs may be used in future studies. Second, the combination of these drugs did not result in higher intolerance or more frequent side effects, suggesting that further studies with combination of drugs can be safely carried out.

## CONCLUSION

Pharmacological preventive treatment of migraine and chronic migraine is a major challenge. The use of a single drug has been widely studied, but the combination of drugs could theoretically have advantages, since different substances act on different targets of the pathophysiology of the disease. Although this study has provided evidence of the therapeutic efficacy of Propranolol and amitriptyline, these substances showed to be safe and well tolerated. Further studies using this and other combinations of substances, in larger groups of patients, in higher doses, and for a longer period of time, may help to clarify the role of combined therapy in the treatment of migraine.

This trial shows that propranolol is well tolerated as compared with amitriptyline in migraine prophylaxis. The ideal drug for migraine prophylaxis is propranolol has few side effects compared with Amitriptyline. When migraine with depression, anxiety disorders, irritable bowel syndrome and epilepsy are comorbidities of migraine for amitriptyline. When

migraine and hypertension and/or angina occur together, propranolol might be drug of choice.

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