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# Comparative Study to Evaluate the Efficacy and Safety of Propranolol versus Amitriptyline for Prophylaxis of Migraine

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## ABSTRACT

**Aim:** To find out a prophylactic drug for migraine having better efficacy and minimal side effects. To compare the efficacy of Propranolol Vs. Amitriptyline as prophylactic agent for migraine.

**Material and Methods:** This was a prospective, comparative, parallel, double blind, randomized clinical trial. As per the ICHD III beta diagnostic criteria for migraine. Included subject aged between 5-65 years. 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). Patients were recorded in a headache diary the number of migraine attacks, the duration of attacks in hours and the severity.

**Result:** 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. The mean Frequency of Attack of migraine in Group 1 at period 1 was 4.41±1.22 and period 2 was 4.01±0.92. In Group 2 during period 1 was 3.93 ±0.97 and in period 2 mean 4.21 ±1.02. The mean severity of Attack of migraine in Group 1 at period 1 was 2.91 ±0.84 and period 2 was 2.11 ±0.64. In Group 2 during period 1 was 2.03 ±0.71 and in period 2 mean 2.76 ±0.81. The mean duration of Attack of migraine in Group 1 at period 1 was 16.01 ±2.60 hours and period 2 was 13.51 ±2.22. In Group 2 during period 1 was 13.63 ±1.56 and in period 2 mean 15.83 ±2.00. These were statistically significant difference in Group 1 and Group 2.

**Conclusion:** This trial shows that Amitriptyline is superior effective compare with propranolol but propranolol is well tolerated as compared with amitriptyline in migraine prophylaxis.

**Keywords:** Migraine, Amitriptyline, Propranolol.

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## INTRODUCTION:

A migraine is a primary headache disorder characterized by recurrent headache that are moderate to severe. Typically, the headaches affect one half of the head, are pulsating in nature, and last from two to 72 hours.(1) Associated symptoms may include nausea, vomiting, and sensitivity to light, sound, or smell.(2) The pain is generally made worse by physical activity. Up to one-third of people have an aura: typically, a short period of visual disturbance that signals that the headache will soon occur. (3) Occasionally, an aura can occur with little or no headache following it. (4)

Migraines are believed to be due to a mixture of environmental and genetic factors.(5) About two-thirds of cases run in families.(6) Changing hormone levels may also play a role, as migraines affect slightly more boys than girls before puberty and two to three times more women than

men.[7] The risk of migraines usually decreases during pregnancy.[8] A number of psychological conditions are associated, including depression, anxiety, and bipolar disorder, as are many biological events or triggers.[9]

Whereas, the underlying mechanisms involve the nerves and blood vessels of the brain.[10] Some evidence supports a primary role for central nervous system structures (such as the brainstem and diencephalon), while other data support the role of peripheral activation (such as sensory nerves that surround blood vessels of the head and neck).[11,12] The potential candidate vessels include dural arteries, pial arteries and extracranial arteries such as those of the scalp. The role of vasodilatation of the extracranial arteries, in particular, is believed to be significant. [13]

Furthermore, Classification of these migraine disorders is included in the International Classification of Headache Disorders (ICHD), third edition, published in 2013. [14] Headaches are classified into primary and secondary types. Migraines are tension-type headaches are the most common of the primary headache disorders. [15] Migraine disorders are further classified into migraine without aura, migraine with aura, familial or sporadic hemiplegic migraine, and basilar-type migraine. Complications of migraines include chronic migraine, status migrainosus, and persistent aura without infarction, migrainous infarction, and migraine-triggered seizures. [16]

Treatments of migraines include medications, nutritional supplements, lifestyle alterations, and surgery. Prophylaxis is recommended in those who have headaches more than two days a week, cannot tolerate the medications used to treat acute attacks, or those with severe attacks that are not easily controlled.[17] The goal is to reduce the frequency, painfulness, and/or duration of migraines, and to increase the effectiveness of abortive therapy.[18]Another reason for prevention is to avoid medication overuse headache. This is a common problem and can result in chronic daily headache.[19]Prophylaxis of migraine medications are considered effective if they reduce the frequency or severity of the migraine attacks by at least 50%.[20] Guidelines are fairly consistent in rating Topiramate, Sodium Valproate, Propranolol, and Metoprolol as having the highest level of evidence for first-line use.[21]

Beta-adrenergic blockers, such as propranolol, are among the most prescribed drugs for migraine prophylaxis. [22] The usual propranolol doses for migraine prevention in clinical trials have ranged from 80 to 160 mg a day. [23] The possible mechanisms of action of propranolol in the prophylactic treatment of migraine are listed below:

1. Blockade of these beta-adrenergic receptors results in inhibition of arterial dilatation.
2. The drug may block the sticky elements of the blood, the platelets, from adhering together and thus releasing substances which cause blood vessels to constrict and dilate.
3. There may be a central mechanism of action in the brain "turning off" the generators that cause migraine. [24]

In addition to its effects on the adrenergic system, there is evidence that indicates that propranolol may act as a weak antagonist of certain serotonin receptors, namely the 5-$HT_{1A}$, 5-$HT_{1B}$, and 5-$HT_{2B}$ receptors. The latter involved in the effectiveness of propranolol in the treatment of migraine at high doses. [25]

Antidepressants, especially tricyclic agents such as amitriptyline has been a mainstay in the prophylactic therapy of migraine. It can be particularly useful when co-morbid conditions such as depression, peripheral neuropathy, or insomnia is present. [26] Amitriptyline inhibits histamine, 5-HT, and acetylcholine, Norepinephrine and serotonin uptake and is the only antidepressant of this class with established efficacy in migraine prevention. [27] Diffuse noxious inhibition may be enhanced through this mechanism. Other possible mechanisms in migraine could be explained by its ability to block sodium-channels; enhance GABA-mediated inhibition; potentiate endogenous opioids; and intensify descending inhibition on nociceptive pathways. [28]

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:

| 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<br>fulfilling criteria B-D | A. Headache (tension-type-like and / or migraine-like) on 15 days per month for > 3<br>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<br>lasting: 1-72 hours | B. Occurring in a patient who has had at least five attacks fulfilling criteria B-D for 1.1<br>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<br>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<br>of the following four characteristics:<br>1.Unilateral<br>2. Pulsating quality<br>3. Moderate to severe<br>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<br>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<br>ischemic attack has been excluded. | D. During headache<br>at least one of the<br>following:<br>1. Photophobia and<br>phonophobia<br>2. Nausea or vomiting | D. Not better accounted for by another ICHD-<br>3 diagnoses. |
| E. Not better accounted for by another ICHD-3<br>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.

**Statistical analysis**

All values were displayed as mean ± SD. Categorical variables were compared by chi-square test. Quantitative data on adverse-effects were analysed 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: Comparison of Frequency of Attack of migraine between Group 1 and Group 2**

| | Group 1 Mean±SD | | Group 2 Mean±SD | | p-value |
|---|---|---|---|---|---|
| Frequency of Attack | Period 1 (Propranolol) | Period 2 (Amitriptyline) | Period 1 (Amitriptyline) | Period 2 (Propranolol) | P=0.016 |
| | 4.41±1.22 | 4.01±0.92 | 3.93±0.97 | 4.21±1.02 | |

In **Table 3**, the mean Frequency of Attack of migraine in **Group 1** at period 1 was 4.41 with SD of 1.22 and period 2 was 4.01 with SD 0.92. In **Group 2** during period 1 was 3.93 with SD of 0.97 and in period 2 mean 4.21 with SD 1.02. These was statistically significant difference in **Group 1 and Group 2** (p=0.016) with **Unpaired t test**.

**Table 4: Comparison of severity of Attack of migraine between Group 1 and Group 2**

| | Group 1 Mean±SD | | Group 2 Mean±SD | | p-value |
|---|---|---|---|---|---|
| Severity of Attack | Period 1 (Propranolol) | Period 2 (Amitriptyline) | Period 1 (Amitriptyline) | Period 2 (Propranolol) | P=0.023 |
| | 2.91±0.84 | 2.11±0.64 | 2.03±0.71 | 2.76±0.81 | |

In **Table 4**, the mean severity of Attack of migraine in **Group 1** at period 1 was 2.91 with SD of 0.84 and period 2 was 2.11 with SD 0.64. In **Group 2** during period 1 was 2.03 with SD of 0.71 and in period 2 mean 2.76 with SD 0.81. These was statistically significant difference in **Group 1 and Group 2** (p=0.023) with **Unpaired t test**.

**Table 5: Comparison of Duration of Attack of migraine between Group 1 and Group 2**

| | Group 1 Mean±SD | | Group 2 Mean±SD | | p-value |
|---|---|---|---|---|---|
| | Period 1 (Propranolol) | Period 2 (Amitriptyline) | Period 1 (Amitriptyline) | Period 2 (Propranolol) | P=0.038 |
| **Duration of Attack (hours)** | 16.01±2.60 | 13.51±2.22 | 13.63±1.56 | 15.83±2.00 | |

In **Table 5**, the mean duration of Attack of migraine in **Group 1** at period 1 was 16.01 hours with SD of 2.60 and period 2 was 13.51 hours with SD 2.22. In **Group 2** during period 1 was 13.63 hours with SD of 1.56 and in period 2 mean 15.83 hours with SD 2.00. These was statistically significant difference in **Group 1 and Group 2** (p=0.038) with **Unpaired t test**.

## DISCUSSION

In this study, we compared Propranolol and amitriptyline. Although these two drugs are first choice drugs for migraine prophylaxis, they are commonly used and have been shown to be effective. [29] In our study reduced mean frequency of migraine attack by Amitriptyline compared with Propranolol. This is somewhat similar results of Peikert et al. who found that Propranolol reduced the mean frequency attack [30] and Taubert who achieved a reduction of using an Amitriptyline. [31]

Mean severity of attack of migraine was reduced higher with Amitriptyline compared with Propranolol in our study, leading us to the conclusion that Amitriptyline was superior to Propranolol in reducing attack severity. Similar results have been reported in other studies. Peikert et al. [30] also reported that statistical significance. This was also the fact in the study of Taubert where there was significant difference in Amitriptyline reducing attack severity, [31] though the results were in favour of Amitriptyline.

We found that drug regimens, Propranolol and amitriptyline, are superior in reducing attack frequency and severity when compared with each other. The reduction in frequency and severity of migraine attacks was statistically significance when compared to each other. This trial shows that both drug is equally effective and well tolerated as Propranolol and amitriptyline in migraine prophylaxis. It could be a new treatment option, especially for patients in whom other established drugs are contraindicated, not tolerated or ineffective. As this is the only comparative trial of Propranolol in migraine prophylaxis so far and our numbers are small, more and larger comparative trials with Propranolol and amitriptyline, also comparing first choice drugs like beta-blockers, are needed. The ideal drug for migraine prophylaxis however, a drug that is highly effective in reducing attack frequency but has few side effects. [32]

The mechanism of antimigraine prophylactic effects of amitriptyline and propranolol: Evidence indicated a relationship between serotoninergic or adrenergic system and migraine. [33] A preventive migraine drug could raise threshold to activation of migraine process either centrally or peripherally. Drug could decrease activation of migraine generator, enhance central antinociception, rise threshold for spreading depression, or stabilize sensitive migrainous nervous system by changing serotonergic or sympathetic tone. [34] Some have suggested that down-regulating the 5HT2 receptor or modulating discharge of serotonergic neurons involved in migraine prevention. [35] Amitriptyline down-regulates both 5HT2 and β-adrenergic receptors. [36] Propranolol can also bind to 5HT2 receptors and exert site-selective vasoconstrictive effects via serotonergic blockade. [37] This drug is also believed to reduce stress-induced release of serotonin from platelets. [38] It should be considered that undoubtedly there are more than one mechanism involved in migraine attacks and preventive drug also most likely work by more than one mechanism of action. [39]

Different profile of results in two phases of propranolol and amitriptyline, might be related to different mechanisms of actions of these two drugs. [40] It has been claimed that prevention of migraine attacks by early treatment of acute migraine headaches or prophylactic management of headaches might minimize headache recurrence. [41] This hypothesis is strengthened by results of propranolol and amitriptyline. However, the frequency, severity and duration of migraine attacks in both groups were statistically significant compared to the intergroup and intragroup comparison. These results approve hypotheses that prevention of migraine attacks reduces headache recurrence with Amitriptyline. Propranolol drug has fewer side effects as may consider this drug as a preferred drug for migraine treatment.

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 Amitriptyline is superior effective

compare with propranolol but propranolol is well tolerated as compared with amitriptyline in migraine prophylaxis. The ideal drug for migraine prophylaxis is Amitriptyline, highly effective in reducing frequency, severity and duration of attack but propranolol has few side effects. 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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