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Comparison of Propranolol versus Amitriptyline as monotherapy for migraine prophylaxis

Dr Deepthi Rao Gorukanti
Associate Professor, Department of General Medicine, Surabhi Institute of Medical Sciences, Mittapally village, Siddipet MDL & Dist, Telangana State

Dr Vallakoti Rajneesh
Assistant Professor, Department of General Medicine, Surabhi Institute of Medical Sciences, Mittapally village, Siddipet MDL & Dist, Telangana State

Dr N Sumalatha
Assistant Professor, Department of General Medicine, RIMS, Adilabad, Telangana State

Dr Ch Karunakar
Professor, Department of Medicine Surabhi Institute of Medical sciences, Mittapally village, Siddipet MDL & Dist, Telangana State
Corresponding Author: Dr Ch Karunakar

***Abstract*---**Introduction: Several drugs like Beta Blockers, SSRIs etc., are used for migraine prophylaxis. Objectives: The purpose of the present study was to compare the efficacy of propranolol and amitriptyline as monotherapy for the prophylaxis of migraine. Materials and Methods: This was a comparative, double-blinded, Prospective, randomized controlled study conducted at Department of General Medicine at Surabhi Institute of Medical Sciences. A total of 140 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. Similarly during 16 to 20 weeks patient didn't receive any prophylactic treatment to wear of the drug effects. Results: The mean Frequency of Attack of migraine in Group 1 at period 1 was 5.69±2.13 and period 2 was 5.69±1.97. In Group 2 during period 1 was 4.69 ±1.83 and in period 2 mean 5.64 ±2.13. The mean severity of Attack of migraine in Group 1 at period 1 was 3.82 ±1.63 and period 2 was 3.34

±1.41. In Group 2 during period 1 was 3.10 ±1.69 and in period 2 mean 3.61 ±1.73. The mean duration of Attack of migraine in Group 1 at period 1 was 18.24 ±3.54 hours and period 2 was 14.69 ±3.17. In Group 2 during period 1 was 14.53 ±2.15 and in period 2 mean 16.72 ±3.09. There was statistically significant difference in Group 1 and Group 2. Conclusion: Our analysis suggested that amitriptyline is more effective than propranolol, in terms of the number of migraine attacks, the duration of attacks in hours and the severity. Patients with migraine headaches and hypertension should consider with a beta blocker. Patients with depression may benefit from either SSRI or TCA.

***Keywords*---**Propranolol, Amitriptyline, Migraine Prophylaxis, Migraine.

Introduction

Migraine headaches are usually characterized by recurrent episodes of pulsatile headaches on one or both sides of the head. [1] Migraine headaches are often accompanied by photophobia, phonophobia and vomiting usually called aura. It is a common condition which is annually affecting 12.0% of the United states population, including 18% of women, 6.0% of men and 4.0% of children. [2] Different elements need to be considered in migraine management. These include avoidance of trigger factors, lifestyle modifications, medications and non-pharmacological therapies. [3]

Pharmacological treatment is traditionally divided into acute or abortive treatment, and preventive treatment or prophylaxis. [4] Many migraine patients can be treated using only acute treatment that is, prescribing medications that are used only during headache attacks to abort an ongoing attack or to stop its progression to severe pain and associated symptoms. Patients with severe and/or frequent migraines require long-term preventive therapy. [5] A variety of drugs from diverse pharmacological classes are in use for migraine prevention. Beta blockers like propranolol, tricyclic antidepressants like amitriptyline, anticonvulsants like topiramate and valproate and serotonergic drugs like methysergide are most commonly administered for this purpose. [6] Beta-adrenergic blockers, such as propranolol, are among the most prescribed drugs for migraine prophylaxis. [7]

There is clear evidence that propranolol is more effective than placebo in the treatment of migraine. [8] The usual propranolol doses for migraine prevention in clinical trials have ranged from 80 to 160 mg a day and Amitriptyline was 0.5 to 50 mg. [9] Adverse events most commonly reported with beta-blockers are fatigue, depression, nausea, dizziness, and insomnia. [10] These symptoms are fairly well tolerated and are seldom the cause of premature withdrawal. Antidepressants, especially tricyclic agents such as amitriptyline and nor triptyline, have also been a mainstay in the prophylactic therapy of migraine. [11] Amitriptyline is a mixed serotonergic and noradrenergic reuptake inhibitor with well-established efficacy in chronic pain relief and migraine prophylaxis. [12] It is useful for the treatment of

patients with migraine and comorbid depression. [13] Common side effects of amitriptyline include dry mouth, constipation, and sedation.

Most studies have evaluated the efficacy of such drugs alone; however, there are some studies with propranolol and tricyclic agents in association with other drugs. [14] The clinical experience with combination therapy for migraine seems to be a rational approach when monotherapy fails and when migraine is refractory. [15] This clinical study was carried out to see safety and efficacy of propranolol and amitriptyline as monotherapy in migraine prophylaxis.

Materials and Methods

This is a prospective, double-blinded, randomized, comparative, with a parallel group design and single center study conducted at Department of General Medicine at Surabhi Institute of Medical Sciences.

Inclusion criteria:

- Patients between 18 and 70 years of age, of either sex (male/female) with a diagnosis of Migraine either with or without aura as per The International Classification of Headache Disorders (ICHD) criteria were recruited in the study.
- Patients had more than two attacks of headache per month, each episode lasting for more than 2 days > 2 episodes/months.

Exclusion criteria:

- Patients with other known causes of headache in addition to migraine.
- Patients with known hypersensitivity to or contraindication to the use of Amitriptyline were excluded from the study.

A total of 140 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. Similarly no drug was given between 16-20 weeks to wear of drug effect.

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.

Statistical analysis

The statistical analysis was done by using SPSS software. Two-factor repeated measures Analysis of variance (ANOVA) was done to find statistical significance in difference between the headache scores at recruitment through follow-up,

between the two groups and also within each group. P-value less than 0.001 was considered statistically significant at 95% confidence interval.

Result

In both the groups, maximum number of patients were in the age group of 18-30 years and least number of patients were 51-70 years of age. Mean age in group 1 patients were 31.45±9.37 and in Group 2 patients were 30.28±9.79. There was no statistically significant difference in mean age of patient from Group 1 and Group 2 patients.

Table 1
Comparison of Mean Age in Groups

Age-Group (Years)	Group 1		Group 2	
	No	Percentage	No	Percentage
18-30	41	58.5%	38	54.3%
31-50	24	34.2%	29	41.4%
51-70	5	7.3%	3	4.3%
Total	70	100	70	100
Mean±SD	31.45±9.35 years		30.28±9.79 years	
p-value	0.821			

Table 2
Gender difference between Group 1 and Group 2

	Group 1		Group 2		Chi-Square test p=value
	n=70	(%)	n=70	(%)	
Male	24	34.2	26	37.1	0.209
Female	46	65.8	44	62.9	
Total	70	100	70	100	

The table 2 reflects that 140 migraine patients in Group 1: 24 were male (34.2%) while 46 were female patients (65.8%). In Group 2 consisted of 26 male patients (37.1%) and 44 female patients (62.9%). There was no statistically significant difference in number of patient from Group 1and Group 2 patients (0.209) 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
	Period 1 (Propranolol)	Period 2 (Amitriptyline)	Period 1 (Amitriptyline)	Period 2 (Propranolol)	P=0.018
Frequency of Attack	5.69±2.13	5.09±1.97	4.69±1.83	5.64±2.13	

In Table 3, the mean Frequency of Attack of migraine in Group 1 at period 1 was 5.69 with SD of 2.13 and period 2 was 5.09 with SD 1.97. In Group 2 during period 1 was 4.69 with SD of 1.83 and in period 2 mean 5.64 with SD 2.13. These was statistically significant difference in Group 1 and Group 2 (p=0.018) 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
	Period 1 (Propranolol)	Period 2 (Amitriptyline)	Period 1 (Amitriptyline)	Period 2 (Propranolol)	P=0.038
Severity of Attack	3.82±1.63	3.35±1.41	3.10±1.69	3.61±1.73	

In Table 4, the mean severity of Attack of migraine in Group 1 at period 1 was 3.82 with SD of 1.63 and period 2 was 3.35 with SD 1.41. In Group 2 during period 1 was 3.10 with SD of 1.69 and in period 2 mean 3.61 with SD 1.73. These was statistically significant difference in Group 1 and Group 2 (p=0.038) 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
Duration of Attack (hours)	Period 1 (Propranolol)	Period 2 (Amitriptyline)	Period 1 (Amitriptyline)	Period 2 (Propranolol)	P=0.023
	18.24±3.54	14.69±3.17	14.53±2.15	16.72±3.09	

In Table 5, the mean duration of Attack of migraine in Group 1 at period 1 was 18.24 hours with SD of 3.54 and period 2 was 14.69 hours with SD 3.17. In Group 2 during period 1 was 14.53 hours with SD of 2.15 and in period 2 mean 16.72 hours with SD 3.09. These was statistically significant difference in Group 1 and Group 2 (p=0.031) with Unpaired t test.

Discussion

This study is intended to compare the efficacy and safety of propranolol and amitriptyline in prevention of migraine attack. Propranolol and amitriptyline are two commonly used drugs for migraine prophylaxis. Both drugs are cheap, easily available and effective and have been in use for a long time in prevention of migraine. In clinical practice these drugs can be used alone or in combination with other abortive medication.

The treatment of migraine involves both acute and preventive drugs and non-pharmacological strategies. Preventive treatment is necessary when the migraine attacks are unacceptably frequent, prolonged, severe, unrespeonsive to acute

medication or associated with hemiparesis or prolonged aura. It is therefore designed to reduce the frequency, duration and/or severity of the attacks. In addition, preventive treatment often makes migraine attacks more responsive to acute migraine therapies, reduces migraine associated disability, improves the patients' ability to function and decreases health care costs and use of healthcare resources. [16]

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. Some have suggested that down-regulating the 5HT2 receptor or modulating discharge of serotonergic neurons involved in migraine prevention. [17]

Amitriptyline down-regulates both 5HT2 and β-adrenergic receptors. [18] Propranolol can also bind to 5HT2 receptors and exert site-selective vasoconstrictive effects via serotonergic blockade. [19] This drug is also believed to reduce stress-induced release of serotonin from platelets. [20] 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. [21]

In this present study, a total of 140 patients were studied and were divided into two groups, total 70 adult patients were selected and according to selection criteria. The mean age of study population was 31.45±9.35 and their minimum and maximum age were 18 years and 70 years respectively. Similar result was reported by Peterlin et al and mentioned that migraines usually develop in childhood, adolescence or early adulthood. [22] Chowdhury documented that prevalence peak of migraine is at about age 40 and then prevalence declines progressively which is not headache intensity declined from 40 years to 74 years without change in headache frequency or headache duration which is consistent with the present study. [23]

In our study, the mean Frequency of Attack of migraine in Group 1 at period 1 was 5.69 with SD of 2.13 and period 2 was 5.09 with SD 1.97. In Group 2 during period 1 was 4.69 with SD of 1.83 and in period 2 mean 5.64 with SD 2.13. These was statistically significant difference in Group 1 and Group 2 (p=0.018) with Unpaired t test. Similar result has been reported by Bordini et al. [24]

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. Ashina M et al. [25] also reported that statistical significance of reducing severity of attack of migraine with Amitriptyline compared with Propranolol. This was also the fact in the study of Ferrari where there was significant difference in Amitriptyline reducing attack severity, though the results were in favour of Amitriptyline. [26]

Different profile of results in two phases of propranolol and amitriptyline, might be related to different mechanisms of actions of these two drugs. 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. [27] The mechanism of antimigraine prophylactic effects of amitriptyline and propranolol:Evidence indicated a relationship between serotoninergic or adrenergic system and migraine. [28]

Number of attacks of headache before treatment and subsequent follow up with medication it was found that number of attacks of headache gradually decrease. The differences are statistically significantly. Although optimum care had been tried by the researcher in every step of this study, still some limitations existed: The study was conducted in a selected area. So, the study population might not represent the whole the people. Time and budget constraints were also an important limitation of this study. In spite of maximum effort by the researcher due to time and resource limitation sample size was small; a larger sample size would have given a better result.

Educational efforts have been helpful in improving the quality of care and quality of life for migraine sufferers. Perhaps the education and basic headache management skills provided in the education program equipped patients with enough knowledge and basic skills that worry and anxiety about headaches were reduced. This idea is supported that those with high worry at the beginning of the study reported the greatest amount of improvement on ratings of disability and quality of life. It is possible that the educational materials distributed to the patients resulted in their becoming more knowledgeable about migraine and, in turn, more satisfied with their care.

Conclusion

Our data suggests that the current practice of tailoring prophylactic medication according to patient characteristics and expected side effects is a good approach. Patients with depression may benefit from either SSRI or TCA. Our analysis suggests that amitriptyline is more effective than the other medications, this has not been confirmed in the limited number of direct comparative effectiveness study that have been conducted. Propranolol cannot be postulated as more effective as little number of patients and depending on other comorbidities.

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