Original Research Article

Efficacy of Amitriptyline Versus Propranolol for prophylaxis of Migraine: A Comparative study

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Abstract

Introduction: Migraine headaches may be preceded by aura symptoms lasting 4 to 72 hours; unilateral location; pulsating quality; moderate to severe intensity; aggravated by physical activity; and associations with nausea, vomiting, phonophobia or photophobia. **Material and Methods:** This is prospective, comparative, parallel, randomized and single centre study. This study was conducted in Medicine NC Medical College & Hospital, Israna, Panipat over a period of one year. **Inclusion Criteria:** Migraine patients either gender of 18 to 60 years of age according to International Headache Society Criteria for Migraine with and without Aura. **Results:** The mean Frequency of Attack of migraine in Amitriptyline group before treatment was 5.73±1.32 and after treatment was 3.74±0.94. In Propranolol group before treatment was 5.68±1.18 and after treatment was 4.03±0.98. There was statistically significant difference between Amitriptyline and Propranolol after treatment (p=0.023) with Unpaired t test. The mean duration of Attack of migraine Amitriptyline group before treatment was 9.37±6.74 hours and after treatment was 3.43± 0.38 hours. In Propranolol group before treatment was 9.72±6.84 hours and after treatment was 7.84±0.47 hours. There was statistically significant difference between Amitriptyline and Propranolol after treatment (p=0.029) with Unpaired t test. ***Conclusion:*** 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 decreasing frequency, severity and period of attack but propranolol has few side effects.

Keywords: Migraine, Aura, Amitriptyline, Propranolol.

Introduction

Migraines are distinguished from other headache types by the following attributes: lasting 4 to 72 hours; unilateral location; pulsating quality; moderate to severe intensity; aggravated by physical activity and associations with nausea, vomiting, phonophobia or photophobia. Migraine headaches may be preceded by aura symptoms. [1] Episodic and chronic migraines are part of a spectrum of migraine disorders but are distinct clinical entities. [2] Chronic migraines are less common (1% to 5% of patients with migraines) and are defined as having headaches at least 15 times a month for at least three months. [3] Preventive therapy for episodic migraines may decrease headache frequency, severity, and prevent progression to chronic migraines.

Amitriptyline, a Tricyclic Antidepressant (TCAs) is a first-line agent for migraine prophylaxis and is the only antidepressant with consistent evidence supporting its effectiveness for this use. Whereas amitriptyline is more beneficial for patients with mixed migraine and tension features. [4] Amitriptyline inhibits serotonin transporter (SERT) uptake and norepinephrine transporter (NET) uptake and is the only antidepressant of this class with recognised efficiency in migraine prevention. [5] 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. [6] Amitriptyline is also useful in patients with comorbid insomnia or when used in higher dosages for depression. Adverse effects of amitriptyline include drowsiness, weight gain and anticholinergic symptoms such as dry mouth. [7]

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Evidence consistently supports the use of the beta blocker propranolol in migraine prophylaxis. Propranolol diminishes central catecholaminergic activity by inhibiting norepinephrine release, reduces neuronal activity and excitability, has membrane-stabilizing properties and inhibits nitric oxide production. These effects may contribute to the antimigraine action. [8] Adverse effects associated with beta blockers include fatigue, reduced exercise tolerance, nausea, dizziness, insomnia and depression. In trials, these side effects were well tolerated and rarely prompted discontinuation of therapy. [9]

Contraindications for beta-blocker use include asthma, hypoglycemia associated with diabetes treatment, heart block and hypotension. Beta blockers may be especially useful in patients with concomitant cardiovascular disease. [10]

The goal of preventive therapy is to improve patient's quality of life by reducing migraine frequency, severity and duration and by increasing the responsiveness of acute migraines to treatment. Therapy should be initiated with medications that have the highest levels of effectiveness and the lowest potential for adverse reactions; these should be started at low dosages and titrated slowly. Factors that should prompt consideration of preventive therapy include the occurrence of two or more migraines per month with disability lasting three or more days per month; failure of, contraindication for, or adverse events from acute treatments; use of abortive medication more than twice per week; and uncommon migraine conditions (e.g., hemiplegic migraine, migraine with prolonged aura, migrainous infarction). Patient preference and cost also should be considered. [11]

Limited data guide treatment for chronic migraines, which are associated with a poor quality of life. This clinical study was carried out to see which drug is having more efficacy as monotherapy in migraine prophylaxis.

Materials and Methods

This is prospective, comparative, parallel, randomized and single centre study. This study was conducted in Medicine NC Medical College & Hospital, Israna, Panipat over a period of one year.

Inclusion Criteria

Migraine patients either gender of 18 to 60 years of age according to International Headache Society Criteria for Migraine with and without Aura. Patients not on any prophylactic medication and patients willing to take part in the study were included for this study.

Exclusion criteria

Age less than 18 years or more than 60 years, patients on prophylactic medication, pregnant women, lactating mother, patients having history of bronchial asthma, cardiac arrhythmia, ischemic heart disease, bladder outlet obstruction or any known hypersensitivity to these drugs, patients with any serious co morbid condition such as uncontrolled hypertension, heart failure, hepatic or renal impairment, diabetes mellitus were excluded from this study.

Migraine was diagnosed according to the criteria of the Headache Classification Committee of the International Headache Society. [12] Detailed history, general examination, neurological examination including funduscopic and relevant systemic examination was done.

Intervention

The doses of amitriptyline were 25 mg for the 1 month once a day. The doses of propranolol were 40 mg BD for the 1 month.

Follow up and Outcome Measures

Patients were followed for a one month period during which they were instructed to maintain a headache diary with the following information: presence of headache and intensity of headache by Visual Analogue Pain Scale. This was also including the need for analgesic for headache. Patients were asked to return on day 30. The primary outcome evaluated was the proportion of patients in each group that achieved a 50% reduction in the number of days with headache. Secondary outcomes were reduction of visual analogue pain scale score, the number of days with headache per month, frequency of side effects, and the proportion of patients abandoning the study before the end of medication.

Statistical Analysis

The data were entered into the computer with the help of software SPSS for windows programmed version 25.0. Cross tabulation was prepared and a comparison had been made between, Data was presented as means and Standard devation (SD) and analyzed with Unpaired t tests when two different variables.

Results

In both the groups, maximum number of patients were in the age group of 18-20 years and least number of patients were 41-60 years of age. Mean age in Amitriptyline group patients were 29.34±6.27 years and in Propranolol Group patients were 30.64±6.49 years. There was no statistically significant difference in mean age of patient between Amitriptyline and Propranolol Group patients with Unpaired t test.

Table 1: Comparison of Mean Age between Amitriptyline and Propranolol

Age-Group (Years)	Amitriptyline		Propranolol	
	n=70	(%)	n=70	(%)
18-20	41	58.57%	44	62.85%
21-40	27	38.57%	24	34.3%
41-60	2	2.85%	2	2.85%
Total	70	100	70	100
Mean±SD	29.34±6.27 years		30.64±6.49 years	
p-value	0.583			

Table 2: Gender difference between Amitriptyline and Propranolol

	Amitriptyline		Propranolol		Chi-Square test p=value
	n=70	(%)	n=70	(%)	
Male	24	34.3	0.243	31.5	0.243
Female	46	65.7	48	68.5	
Total	70	100	70	100	

Table 2 reflects that 70 migraine patients in each group. In Amitriptyline group 24 were male (34.3%) while 46 were female patients (65.7%). Propranolol Group consisted of 22 male patients (31.5%) and 48 female patients (68.5%). There was no statistically significant difference in number of patient between Amitriptyline and Propranolol group patients (0.243) when we applied with Chi-square test.

Table 3: Comparison of Frequency of migraine Attack between Amitriptyline and Propranolol

Frequency of migraine Attack	Amitriptyline (Mean±SD)	Propranolol (Mean±SD)	p=value
Before treatment	5.73±1.32	5.68±1.18	p=0.839
After treatment	3.74±0.94	4.03±0.98	p=0.023

In Table 3, the mean Frequency of Attack of migraine in Amitriptyline group before treatment was 5.73±1.32 and after treatment was 3.74±0.94. In Propranolol group before treatment was 5.68±1.18 and after treatment was 4.03±0.98. There was statistically significant difference between Amitriptyline and Propranolol after treatment (p=0.023) with Unpaired t test.

Table 4: Comparison of severity of Attack of migraine between Amitriptyline and Propranolol

Severity of migraine Attack	Amitriptyline Mean±SD	Propranolol Mean±SD	p=value
Before treatment	2.84±0.82	2.84±0.79	p=0.683
After treatment	1.73±0.03	2.04±0.98	p=0.037

In Table 4, the mean severity of Attack of migraine in Amitriptyline group before treatment was 2.84±0.82 and after treatment was 1.73±0.03. In Propranolol group before treatment was 2.84±0.79 and after treatment was 2.04±0.98. There was statistically significant difference between Amitriptyline and Propranolol after treatment (p=0.037) with Unpaired t test.

Table 5: Comparison of Duration of Attack of migraine between Amitriptyline and Propranolol

Duration of Attack (Hours)	Amitriptyline Mean±SD	Propranolol Mean±SD	p=value
Before treatment	9.37±6.74	9.72±6.84	p=0.596
After treatment	3.43±0.38	7.84±0.47	p=0.029

In **Table 5**, the mean duration of Attack of migraine Amitriptyline group before treatment was 9.37±6.74 hours and after treatment was 3.43±0.38 hours. In Propranolol group before treatment was 9.72±6.84 hours and after treatment was 7.84±0.47 hours. There was statistically significant difference between Amitriptyline and Propranolol after treatment (p=0.029) with Unpaired t test.

Table 6: Comparison of ADRs during treatment with Amitriptyline and Propranolol

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

In table 6: Most common adverse drug reaction reported in two groups were includes. In Amitriptyline group, maximum adverse drug reaction (ADR) was **Somnolence,** Xerostomia and least constipation and dizziness. In Propranolol Group, maximum ADR was Dizziness and least one constipation, Somnolence and Xerostomia.

Discussion

Migraine is a chronic disabling disease accompanied with recurrent headache. Patients with migraine often suffer from throbbing headache and preventative therapies have been introduced to reduce the risk of migraine onset. Several medications have been applied to migraine patients as prophylaxis and most of these medications are able to reduce the monthly attack frequency by 50%. [13] This study is conducted in order to determine the relative efficacy, safety and tolerability of two popular prophylactic migraine interventions: propranolol and amitriptyline. Results of this study indicated that two drugs may be particularly efficacious for reducing the corresponding symptoms of migraine: propranolol and Amitriptyline. In this study, Amitriptyline ranked the highest with respect to the reduction of monthly headache days whereas propranolol appeared to be the most preferable intervention for reducing headache frequency. Moreover, in this study also suggested that Amitriptyline superior performance with respect to at least 50% reduction in headache attacks. Another study conducted by Kaniecki et al. revealed that Amitriptyline significantly reduced headache frequency and the number of headache days compared to placebo, however, there was significant difference in the efficacy between the two interventions. [14]

Amitriptyline is a mixed serotonin-norepinephrine reuptake pump inhibitor and thereby thought to facilitate descending noxious inhibition, i.e., endogenous pain control mechanisms descending from the brainstem to the trigeminal nucleus caudalis and the spinal cord. Alpha2-adrenoceptor blockade has been shown to block the antinociceptive effect of amitriptyline and hence at least part of amitriptyline's efficacy is thought to be mediated by α2-agonism, but multiple other channel and receptor effects of amitriptyline are known. [15] As such, amitriptyline is thought to act as a sodium channel blocker and also has antimuscarinic and antihistaminic effects. There is also an interaction with the endogenous adenosine system and it has also been shown to suppress cortical spreading depression. [16] As with other preventive migraine medications, it remains unclear which mechanism is key and probably the multiplicity of synergistic effects in multiple pathways explains the clinical efficacy (as well as the broad side-effect profile).

The mechanisms of action of Propranolol is Inhibition of β1-mediated receptor effects on the target site. Indeed, blockade of β1 receptors could inhibit noradrenaline (NA) release and tyrosine hydroxylase activity, the rate-limiting step in NA synthesis. [17] Moreover, propranolol reduces the neuronal firing rate of noradrenergic neurons of the locus coeruleus. [18] Interestingly, Beta-adrenergic blockers also regulate the firing rate of periaqueductal gray matter (PAG) neurons via a GABA-mediated action. [19] Both these effects may contribute to the antimigraine action of Beta-adrenergic blockers. Recent findings in an animal model of trigeminovascular activation showed that propranolol exerts its prophylactic action, at least in part, by interfering with the chronic sensitization processes in the rostral ventromedial medulla and locus coeruleus, and by counteracting the facilitation of trigeminovascular transmission within the trigeminocervical complex. [20]

Finally, it has also been hypothesized that Beta-adrenergic blockers exert some of their therapeutic effects in migraine through an action at the ventroposteromedial thalamic nucleus, which represents a relay of trigeminal sensory input to the primary somatosensory cortex. Considering the complex and widespread nature of the sensory disturbance in migraine, and neurophysiological findings, a possible thalamic involvement in the mechanisms of action of Beta-adrenergic blockers represents a fascinating hypothesis. [21]

The efficacy of Amitriptyline in reducing migraine attacks has been verified by several studies, for instance, Sørensen et al. was the first one who suggested that Amitriptyline exhibited a noteworthy effect on patients with severe migraine with respect to migraine prophylaxis. [22, 23] Although this study suggested that patients with Amitriptyline were more likely to experience at least 50% reduction in migraine attacks than those with Propranolol, the wide confidence interval resulted from potential inconsistency or inadequate evidence should be addressed by conducting large-scale studies in order to verify the above conclusions.

Apart from efficacy, the safety of migraine medication is another predominating factor that must be considered by physicians when selecting an appropriate intervention. As suggested by previous studies, migraine patients treated by Amitriptyline drugs may experience several side-effects, including Somnolence, Xerostomia, constipation and dizziness. [24] One significant result produced in this study is that patients with Amitriptyline exhibited a significantly increased risk of Somnolence, Xerostomia compared to those with Propranolol. Apart from that, one meta-analysis discovered that patients with Amitriptyline were associated with a significantly increased risk of Somnolence, Xerostomia compared to those with Propranolol. [25,26]

Conclusion

This study 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 decreasing frequency, severity and period of attack but propranolol has few side effects. When migraine with depression, anxiety disorders are comorbidities, amitriptyline is drug of choice. When migraine and hypertension and/or angina occur together, propranolol might be drug of choice.

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