



## ORIGINAL ARTICLE

### Comparison of Propranolol and Amitriptyline as Monotherapy for Migraine Prophylaxis

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#### Abstract

**Background:** Several drugs are used individually for migraine prophylaxis. **Objective:** The purpose of the present study was to compare the propranolol and amitriptyline as monotherapy for the prophylaxis of migraine. **Methodology:** This randomized control trial was conducted in headache clinic at Banghabandhu Sheikh Medical University (BSMMU), Dhaka, Bangladesh from July 2012 to June 2014 for a period of two (02) years. Migraine patients with or without aura of 16 to 50 years of age, patients not on any prophylactic medication were included for this study. Patients meeting all the criteria was randomized group A who were treated with Amitriptyline and group B who were treated with propranolol. Patients was followed for a three months period during which they was instructed to maintain a headache diary. The primary outcome evaluated was the proportion of patients in each group that achieved a 50% reduction in the number of days with headache. **Result:** A total 80 adult patients were selected. During 1<sup>st</sup> visit among the patients duration of pain 1 to 4 hours (2.5.0%), 5 to 8 hours (13.3%) 9 to 12 hours (35.0%) and above 13 hours (22.5%) in group A were recorded; however, in group B, duration of pain 1 to 4 hours 1(2.5), 5-8 hours 16(13.3%), 9-12 hours 19(47.5) and above 13 hours 4(10.0) (p>0.05). In group A, no adverse effect was found 26(65.0%), drowsiness 6 (15.0%), dryness of mouth 6(15.0%), constipation 2(5.0%), fatigue and bradycardia were not found. In group B, no adverse effect was found 29(72.5%), drowsiness, dryness of mouth and constipation were not found, fatigue and bradycardia were 7(17.5%) and 4(10.0%). **Conclusion:** In conclusion number of attack and headache before treatment gradually decrease in subsequent follow up in both groups. [*Journal of Current and Advance Medical Research* 2019;6(2):77-82]

**Keywords:** Propranolol; Amitriptyline; monotherapy; Migraine Prophylaxis

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**Contributions to authors:** Islam MA, Sultana D, have contributed in protocol preparation, data collection, data analysis upto the report writing; Shahi MS, Hassan MS have prepared & have revised the manuscript.

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## Introduction

Migraine headache are usually characterized by pain on one or both sides of the head<sup>1</sup>. Migraine headaches are often accompanied by photophobia, phonophobia and vomiting. 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<sup>2</sup>. Different elements need to be considered in migraine management. These include avoidance of trigger factors, lifestyle modifications, non-pharmacological therapies and medications<sup>3</sup>.

Pharmacological treatment is traditionally divided into acute or symptomatic treatment, and preventive treatment or prophylaxis<sup>4</sup>. 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<sup>5</sup>. A variety of drugs from diverse pharmacological classes are in use for migraine prevention. Adrenergic receptor blockers like propranolol, tricyclic antidepressants like amitriptyline, anticonvulsants like topiramate and valproate and serotonergic drugs like methysergide are most commonly administered for this purpose<sup>6-7</sup>. Currently, topiramate was tested prospectively and proved effective<sup>8</sup> based on the prior success of certain anticonvulsants, despite acknowledged differences between migraine and epilepsy. Beta-adrenergic blockers, such as propranolol, are among the most prescribed drugs for migraine prophylaxis<sup>9-10</sup>.

There is clear evidence that propranolol is more effective than placebo in the treatment of migraine<sup>9</sup>. The usual propranolol doses for migraine prevention in clinical trials have ranged from 80 to 160 mg a day<sup>9-12</sup>. Adverse events most commonly reported with beta-blockers are fatigue, depression, nausea, dizziness, and insomnia<sup>11</sup>. These symptoms are fairly well tolerated and are seldom the cause of premature withdrawal. Antidepressants, especially tricyclic agents such as amitriptyline and nortriptyline, have also been a mainstay in the prophylactic therapy of migraine<sup>14</sup>. Amitriptyline is a mixed serotonergic and noradrenergic reuptake inhibitor with well-established efficacy in chronic pain relief and migraine prophylaxis<sup>15-16</sup>. It is useful for the treatment of patients with migraine and comorbid depression<sup>17</sup>. Common side effects of amitriptyline include dry mouth, constipation, and sedation. They

may also cause slowing of atrioventricular conduction and orthostatic hypotension.

Most studies have evaluated the efficacy of such drugs alone; however, there are some studies with propranolol<sup>18,19</sup> and tricyclic agents<sup>20</sup> in association with other drugs. The clinical experience with combination therapy for migraine seems to be a rational approach when monotherapy fails and when migraine is refractory<sup>21</sup>. This clinical trial study was carried out to see safety and efficacy of propranolol and amitriptyline as monotherapy in migraine prophylaxis.

## Methodology

**Study Settings and Population:** This study was designed as single centre, parallel, randomized control trial. This study was conducted in headache clinic at Banghabandhu Sheikh Medical University (BSMMU), Dhaka, Bangladesh from July 2012 to June 2014 for a period of two (02) years. Migraine patients with or without aura of 16 to 50 years of age, patients not on any prophylactic medication and patients willing to take part in the study were included for this study. Age less than 16 years or more than 50 years, patients with chronic migraine, complicated migraine, ophthalmoplegic migraine, basilar migraine, catamenial migraine, 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. Informed written consent was taken from all patients. Migraine was diagnosed according to the criteria of the Headache Classification Committee of the International Headache Society<sup>22</sup>. Detailed history, general examination, neurological examination including fundoscopy and relevant systemic examination was done. Before the commencement of the study, the protocol for the following study was approved by ethical authority.

**Randomization and Blinding:** Patients meeting all the criteria was randomized for two (02) treatment groups designated as the group A who were treated with amitriptyline and the group B who were treated with propranolol. Blinding was not performed.

**Intervention:** The doses of propranolol was 20 mg BD for the first two weeks, 20 mg TDS for the next

two weeks and finally 40 mg BD for the consecutive 8 weeks. The doses of amitriptyline was 10 mg in the first two weeks and 25 mg during second two weeks once at bedtime and 50 mg at bed time in the next 8 weeks. The doses of each of these drugs was the same when given alone or in combination.

**Follow up and Outcome Measures:** Patients was followed for a three months period during which they was 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 include the need for analgesic for headache. Patients was asked to return on days 30, 60 and 90. 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 was 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. The causes of noncompliance and side effects was individually registered.

**Statistical Analysis:** After collection all the data were checked and edited. Then data were entered into the computer with the help of software SPSS for windows programmed version 16.0. After frequency run, data were cleaned and frequencies were checked. An analysis plan was developed keeping in view with the objectives of the study. Cross tabulation was prepared and a comparison had been made between, Data was presented as means (SD) and analyzed with 2-tailed *t* tests when

normally distributed. Every data was kept confidential.

**Results**

This study was carried out to see the efficacy of propranolol and amitriptyline as monotherapy for migraine prophylaxis. A total 80 adult patients were selected according to selection criteria. The patients were categorized in to 2 groups. Group A received Amitriptyline, Group-B received Propranolol. They were interviewed with a specific pre-designed and pre-tested questionnaire and some information were gathered by document review. Collected data were cleaned, edited and analyzed with the help of software SPSS. The analyzed data have been presented in this chapter through tables and appropriate graphs.

**Table 1: Distribution of age among the patient**

Age group	Group A	Group B
16 to 25 Years	24 (60.0%)	20(50.0%)
26 to 35 Years	14(35.0%)	15(37.5%)
≥36 Years	2(5.0%)	5(12.5%)
<b>Total</b>	<b>40(100.0%)</b>	<b>40(100.0%)</b>

P value=0.208

Table 1 shows that distribution of age among the patient. In group A, 16-25 age group were 24 (60.0%), 26-35 age group were 14 (35.0%), 36 and above age group were 2 (5.0%). In group B, 16-25 age group were 20 (50.0%), 26-35 age group were 15 (37.5%), 36 and above age group were 5 (12.5%). The association was not statistically significant.

**Table 2: Duration of pain found in First follow up among the patients**

Duration	Group A		Group B	
	1 <sup>st</sup> FU	Final FU	1 <sup>st</sup> FU	Final FU
1-4hours	1(2.5%)	24 (60.0%)	1(2.5%)	20(50.0%)
5-8 hours	16(13.3%)	14(35.0%)	16(13.3%)	15(37.5%)
9-12hours	14(35.0%)	2(5.0%)	19(47.5%)	5(12.5%)
>13hours	9(22.5%)	0(0.0%)	4(10.0%)	0(0.0%)
<b>Total</b>	<b>40(100.0%)</b>	<b>40(100.0%)</b>	<b>40(100.0%)</b>	<b>40(100.0%)</b>

Gr-A Amitriptyline; Gr-B Combination

Table 2 shows that duration of pain found in during 1<sup>st</sup> visit among the patients. In group A, duration of pain 1 to 4 hours 1 (2.5.0%), 5 to 8 hours 16(13.3%) 9 to 12 hours 14(35.0%). Above 13 hours 9(22.5%) In group B, duration of pain 1 to 4

hours 1(2.5), 5 to 8 hours 16(13.3%), 9 to 12 hours 19(47.5) and above 13 hours 4(10.0). The difference were not statistically significant. The duration of pain in final follow up was recorded among the patients. In group A, duration of pain 1

to 4 hours 24 (60.0%), 5 to 8 hours 14 (35.0%), 9 to 12 hours 2 (5.0%). In group B, duration of pain 1 to 4 hours 20 (50.0%), 5 to 8 hours 15 (37.5%), 9 to 12 hours 12 (30.0%). The difference was not statistically significant.

**Table 3: Distribution of patients by side effects of drugs**

Adverse effects	Group A	Group B
No AD	26(65.0%)	29(72.5%)
Drowsiness	6(15.0%)	0(0.0%)
Dry mouth	6(15.0%)	0(0.0%)
Constipation	2(5.0%)	0(0.0%)
Fatigue	0(0.0%)	7(17.5%)
Bradycardia	0(0.0%)	4(10.0%)
<b>Total</b>	<b>40(100.0%)</b>	<b>40(100.0%)</b>

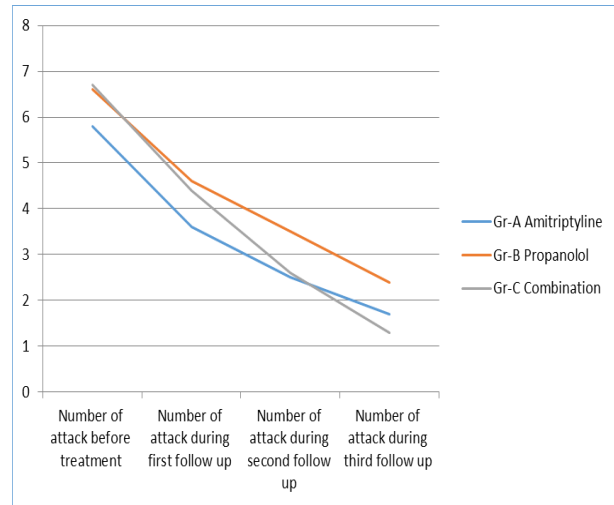
P value=0.000; AD= adverse effect

In group A, no adverse effect was found 26 (65.0%), drowsiness 6 (15.0%), dryness of mouth 6 (15.0%), constipation 2 (5.0%), fatigue and bradycardia were not found. In group B, no adverse effect was found 29 (72.5%), drowsiness, dryness of mouth and constipation were not found, fatigue and bradycardia were 7 (17.5%) and 4 (10.0%) (Table 3).

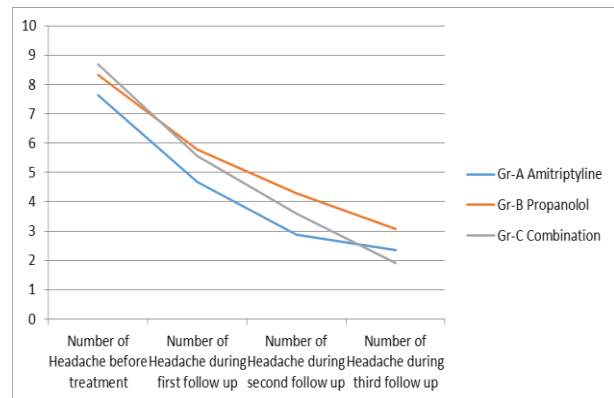
**Table 4: Number of attack and headache before treatment and subsequent follow up**

Number of	Group A	Group B	P value
Attack Before Treatment	5.825±2.18	6.575±1.87	0.085
Attack During 1st Follow Up	3.625±1.89	4.575±1.29	0.013
Attack During 2nd Follow Up	2.475±1.67	3.5±1.13	0.002
Attack During 3rd Follow Up	1.675±1.09	2.375±1.39	0.0001
Headache Before Treatment	7.625±2.50	8.325±2.03	0.094
Headache During 1st Follow Up	4.675±2.23	5.775±2.09	0.037
Headache During 2nd Follow Up	2.875±2.11	4.275±1.35	0.001
Headache During 3rd Follow Up	2.35±1.64	3.075±1.65	0.005

Number of attack and headache before treatment and subsequent follow up with medication it was found that number of attack and headache gradually decrease. The differences are statistically significantly (Table 4).



**Figure I: Number of Attack before treatment and final, second and third follow up**



**Figure II: Number of Headache before treatment and final, second and third follow up**

**Discussion**

Propranolol and amitriptyline are two commonly used drugs for migraine prophylaxis<sup>3</sup>. Both drugs are cheap, 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.

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, unresponsive 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<sup>13</sup>. This study is intended to compare the efficacy and safety of propranolol and amitriptyline in prevention of migraine attack when used alone or in combination.

In this present study a total of 120 patients were studied and were divided into three groups, total 120 adult patients were selected and according to selection criteria divided into three groups, Group A received Amitriptyline, Group B received Propranolol. In group A, 16 to 25 age group were 24(60.0%), 26 to 35 age group were 14(35.0%), 36 and above age group were 2(5.0%). In group B, 16 to 25 age group were 20(50.0%), 26 to 35 age group were 15(37.5%), 36 and above age group were 5(12.5%). The mean age of study population was  $27.22 \pm 7.85$  and their minimum and maximum age were 16 years and 60 years respectively. Similar result was reported by Peterlin et al<sup>21</sup> and mentioned that migraines usually develop in childhood, adolescence or early adulthood. Chowdhury<sup>13</sup> 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.

Duration of pain found during 1st visit among the patients in group A, duration of pain 1-4 hours 1 (2.5.0%), 5-8 hours 16 (13.3%), 9-12 hours 14 (35.0%) and above 13 hours 9 (22.5%). In group B, duration of pain 1-4 hours 1 (2.5), 5-8 hours 16 (13.3%), 9-12 hours 19 (47.5) and above 13 hours 4 (10.0). In group C, duration of pain 1-4 hours 0 (0.0), 5-8 hours 18 (15.0) 9-12 were 21 (52.5), above 13 hours pain duration were 1(2.5%). Duration of pain found in final follow up among the patients; in group A, duration of pain 1-4 hours 24 (60.0%), 5-8 hours 14 (35.0%), 9-12 hours 2 (5.0%). In group B, duration of pain 1-4 hours 20 (50.0%), 5-8 hours 15 (37.5%), 9-12 hours 12 (30.0%). In group C, duration of pain 1-4 hours 28 (70.0%), 5-8 hours 12 (30.0%), 9-12 hours were not found. There was no significant relationship between pain and migraine ( $p > 0.05$ ). Similar result has been reported by Bordini et al<sup>18</sup>.

Distribution of patients by side effects of drugs, in group A, no adverse effect was found 26 (65.0%),

drowsiness 6 (15.0%), dryness of mouth 6 (15.0%), constipation 2 (5.0%), fatigue and bradycardia were not found. In group B, no adverse effect was found 29 (72.5%), drowsiness, dryness of mouth and constipation were not found, fatigue and bradycardia were 7 (17.5%) and 4 (10.0%). In group C, no adverse effect was found 22 (55.0%), drowsiness 8 (20.0%), dryness of mouth 6 (15.0%), constipation 2 (5.0%), fatigue 2 (5.0%) and bradycardia were not found. In conclusion side effects are no adverse effect throughout the period of study.

Number of attack and headache before treatment and subsequent follow up with medication it was found that number of attack and headache gradually decrease. The differences are statistically significantly.

Although optimum care had been tried by the researcher in every steps 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.

## Conclusion

The study findings of this study shown that the efficacy of Propranolol and Amitriptyline in combination is more effective than monotherapy of Amitriptyline in migraine prophylaxis. The side effects are minimum than monotherapy. A large scale and multicenter study should be done to evaluate efficacy of Propranolol and Amitriptyline in combination is more effective than monotherapy of either drug in migraine prophylaxis.

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