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COMPARISON OF EFFICACY OF NORTRIPTYLINE AND PROPRANOLOL USED AS MONOTHERAPY AND IN COMBINATION FOR MIGRAINE PROPHYLAXIS

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Abstract:

Background: *Migraine headache is one of the most common and disabling disorders of nervous system that impairs the quality of life. Combination of nortriptyline and propranolol can be effective in prophylaxis of migraine.*

Objective: *Our aim was to compare the efficacy of nortriptyline and propranolol used as monotherapy and in combination in terms of reduction of number of attacks and duration of pain of migraine.*

Subjects and Methods: *This cross-sectional study was carried out at outpatient clinic, Neurology department, Sir Ganga Ram hospital Lahore from May 2018 to December 2018. Data was collected from 60 patients (15-50 years of age) who fulfilled the diagnostic criteria of migraine using non-probability consecutive sampling technique. They were divided into three groups of 20 patients each. Group A received nortriptyline, group B propranolol and group C combination of both drugs.*

Results: *In group A after three months 8 patients (40%), and after 6 months 12 patients (60%), in group B after three months 7 patients (35%) and after 6 months 11 patients (55%) and in group C at three months 12 patients (60%),at 6 months 16 patients(80%) have 50% or more reduction in number of migraine attacks per month. Similarly, there was significant reduction in duration of pain in group C as compared to group A and B.*

Conclusion: *The efficacy of nortriptyline and propranolol in combination is significantly greater than used as monotherapy in terms of reduction of number of migraine attacks and duration of pain.*

Keywords: *Migraine prophylaxis, nortriptyline, propranolol.*

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INTRODUCTION:

Headache disorders are among the most common disorders of nervous system. [1] There are three types of primary headaches, namely migraine, tension-type headache and cluster headache. Among these, migraine headache is disabling, extremely painful and prevailing resulting in poor life quality. [2,3]. Migraine headache is characterized by recurrent episodes lasting for 4-72 hours, unilateral, pulsatile quality, moderate to severe intensity, aggravated by or causing hindrance in routine physical activity and associated with nausea/vomiting, photophobia/phonophobia. [4] The etiology of migraine is not known , but it is commonly familial and polymorphic genetic condition probably. [5] Different theories were proposed regarding etiology of migraine. The vascular theory was proposed by Thomas Willis, in which he said that "all pain is an action violated" and he gave reasons regarding pain from headache is due to vasodilatation of cerebral and meningeal ateries. The other, neurogenic theory suggested that migraine pain is associated with activation of trigeminovascular system. [6] The cortical spreading depression theory suggested that neuronal hyperactivity wave is followed by an area of cortical depression, which is responsible for aura and headache is caused by activation of trigeminovascular pain pathway. [7] 18% of females and 6% of males experience migraines. Out of these only 50% receive the diagnosis of migraine, others being treated as tension type headaches/sinus headache [5]. Mollaoglu M.2012 carried out a study which reveals that most common triggers for migraine are emotional stress(79%), sleep disturbance (64%) and dietary factors (44%). [8]

The worldwide prevalence of migraine is 10-12% of adult population.9 No local data on migraine prevalence is available in Pakistan, to the best of our information. [10]. Different drugs are being given in the prophylaxis of migraine attacks. Beta-adrenergic blocking agents like propranolol is one of the most commonly prescribed for prophylaxis of migraine. [11,12] Propranolol has been used for prophylaxis since 1966,when Rabkin et al. discovered its usefulness in migraine headache patients who were using it for angina pectoris. [11] There is evidence that propranolol is more useful than placebo for migraine treatment. [11] The propranolol dose used for prophylaxis of migraine in clinical trials ranged from 80-160 mg/day. [11-14] Most commly reported adverse effects with beta-adrenergic blockers are bradycardia, hypotension, depression, fatigue, insomnia, nausea, hyper/hypoglycemia. Anti depressants i-e amytriptyline and nortriptyline have also been used in the prophylaxis of migraine. [15] Nortriptyline is a mixed serotonergic and noradrenergic reuptake inhibitor. It has established efficacy in relief of chronic pain and prophylaxis of migraine. [16,17] It is quite effective in the treatment of patients having migraine and depression. [18] The most common side effects of tricyclic agents e.g nortriptyline are sedation, dry mouth, constipation, blurred vision, nausea, vomiting. They may cause delay in atrioventricular conduction and orthostatic hypotension.

The study was carried out to compare the efficacy of nortriptyline and propranolol used as monotherapy, and in combination for the prophylaxis of migraine.

SUBJECTS AND METHODS:

Setting: Out patient clinic,Neurology department Sir Ganga Ram hospital Lahore

Study design: Cross sectional observational study

Duration: May 2018 to December 2018.

Sample Size: 60 patients of migraine

Sampling Technique: Non-probability consecutive sampling.

Sample Selection:

Inclusion Criteria Males and females having age 15 to 50 years fulfilling the diagnostic criteria of migraine(as defined in operational definition), not taking any treatment of migraine prophylaxis before, willing to take part in study.

Exclusion Criteria patients having bronchial asthma/COPD, cardiac arrhythmia,ischemic heart disease, uncontrolled hypertension, diabetes mellitus, bladder outlet obstruction, hypersenstivity to these drugs, pregnant women, lactating mothers.

Data Collection Procedure Patients were allocated to nortriptyline group A, propranolol group B and combination of both drugs as group C using computer generated random number table**.**

Intervention: Group A was given Nortriptyline 25 mg once daily for seven days and then 50 mg once at night time, Group B was given Propranolol 40 mg twice daily for 14 days, then 40 mg thrice daily and Group C was given combination of these two drugs in same doses as prescribed in group A and B.

Instructions and Follow up : Patients were followed up after three and six months. They were advised to maintain a headache diary with following

information: number of migraine attacks per month and duration of attacks in hours.

Data Analysis Data was entered and evaluated using SPSS version 20. Chi-square test was applied to find out any significant impact of drug groups taking $p \leq 0.05$ as significant.

Operational Definitions:. According to International Headache Society Criteria19 **Migraine without aura** is defined as patients having at least five attacks, lasting for 4-72 hours(unless successfully treated) plus at least two of following pain characteristics, pulsating quality, unilateral location, moderate to severe in intensity, aggravated by or causing hindrance of routine physical activity. One among the following should be present: nausea or vomitting, phonophobia or photophobia. Migraine with aura is defined as patients having same features as described in migraine without aura plus any of the following: visual symptoms including positive features like flickering spots, lights or lines or negative features like loss of vision, blind spots or both. Sensory symptoms including positive features like pins and needles or negative features like numbness or both. Speech disturbance (dysphasia), symptoms of aura that develop over at least five minutes and last less than one hour: headache, if present, that follows within the hour.

RESULTS:

Table I: Distribution of age groups of patients

Age group(years)	Group A(Nortriptyline)	Group B(Propranolol)	GroupC (Nortriptyline+ Propranolol)
15-25	14(70%)	10(50%)	12(60%)
26-36	4(20%)	6(30%)	7(35%)
37 and above	2(10%)	4(20%)	1(5%)
Total	20(100%)	20(100%)	20(100%)

Mean±SD 26.52±7.64

Table II: Comparison of duration of migraine attacks after first(three months) and second(six months) follow up

Duration of pain attack(hours)	Group A 1st FU	2ndFU	Group B 1st FU	2ndFU	Group C 1st FU	2ndFU
1-4	2(10%) 10(50%)		3(15%) 11(55%)		3(15%) 13(65%)	
5-8	8(40%)	6(30%)	7(35%) 5(25%)		10(50%)	6(30%)
9-12	6(30%)	4(20%)	7(35%) 4(20%)		6(30%)	1(5%)
>13	4(20%)	0(0%)	3(15%)	0(0%)	1(5%)	0(0%)

Table III**: Comparison of patients of groups in terms of 50% or more reduction of migraine attacks after first(three months) and second(six months) follow up**

Group A 1st FU	2ndFU	Group B 1st 2ndFU	FU	Group C 1st FU	2ndFU
8(40%) 12(60%)		7(35%) 11(55%)		12(60%) 16(80%)	

DISCUSSION:

The migraine treatment includes both abortive and prophylactic drugs and non- pharmacological options. Prophylactic treatment is essential when the attacks of migraine are unacceptably prolonged, frequent, severe, impairing the quality of life, not responding to abortive medication or associated with prolonged aura and hemiparesis. That is why, it is desired to reduce the duration ,frequency and/or severity of attacks. Moreover, the prophylactic treatment makes attacks of migraine more responsive to abortive treatment, decreases disability associated with it, improves the ability of patients to live better life and cause reduction of health care costs. [20]

In this study, total 60 patients were chosen that fulfilled the diagnostic criteria of migraine and divided into three groups .Group A,B and C was given nortriptyline, propranolol and combination of both respectively. In group A, 15-25 years of age patients were 14(70%), 26-36 years of age were 4(20%) and 37 years and above were 2(10%). In group B. 15-25 years of age patients were 10(50%), 26-36 years of age were 6(30%) and 37 years and above were 4(20%). In group C, 15-25 years of age were 12(60%), 26-36 years of age were 7(35%) and 37 years and above was 1(5%). Similar results were described and reported that migraine usually develop in childhood, adolescence and early adulthood. [21]

In this study, we stratified the patients that have 50% or more reduction in number of migraine attacks per month. In group A after three months 8 patients(40%), and after 6 months 12 patients (60%) , in group B after three months 7 patients (35%) and after 6 months 11 patients(55%) and in group C at three months 12 patients(60%),at 6 months 16 patients(80%) have 50% or more reduction in number of migraine attacks. Similarly there was significant reduction in duration of pain in group C as compared to group A and B.

Although maximum care was tried by the research team in each step of the study, but some limitations existed. The study was carried out in limited number of people of selected area. So the study population might not be representative of whole community. Budget and time limitation were the important reasons. Despite of maximum effort by research team, due to time and resources limitations, sample size was small. A larger sample size would result in better results.

CONCLUSION:

The results of this study showed that the use of nortriptyline and propranolol in combination is more effective than use of these drugs as monotherapy in migraine prophylaxis. A multicenter and large scale study should be carried out to evaluate the efficacy of these drugs in combination and as monotherapy for migraine prophylaxis.

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