



Efficacy Comparison of Nortriptyline and Topiramate 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 topiramate can be effective in prophylaxis of migraine.

Objective: Our aim was to compare the efficacy of nortriptyline and topiramate 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 out patient clinic, Neurology department, Sir Ganga Ram hospital Lahore from August 2019 to March 2020. Data was collected from 120 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 40 patients each. Group A received nortriptyline, group B topiramate and group C combination of both drugs.

Results: In group A after three months 16 patients (40%), and after 6 months 24 patients (60%), in group B after three months 14 patients (35%) and after 6 months 22 patients (55%) and in group C at three months 24 patients (60%), at 6 months 32 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 topiramate 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, topiramate

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 arteries. 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 headaches.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. Topiramate is an antiepileptic drug also used in the prophylaxis of migraine. Guidelines from the American Academy of Neurology, the American Headache Society, and the Canadian Headache Society list topiramate as a

INTRODUCTION:

Headache disorders are among the most common disorders of nervous system.¹ There are three types of primary headaches, namely migraine, tension-



first-line agent to prevent episodic migraine. Other first-line agents are beta blockers (metoprolol, propranolol, and timolol); the antiepileptic valproate.¹¹

The exact mechanism of topiramate is unknown, but several activities are theorized to contribute to its efficacy for migraine prophylaxis. Since migraine and epilepsy are thought to share various pathophysiologic properties, it is thought that topiramate exhibits similar mechanisms of action in both disorders. During both migraine and epilepsy, topiramate is predicted to exhibit its action through the blockade of sodium channels, L-type calcium channels, and also blockade of α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) and kainate currents.¹² Topiramate is proposed to inhibit carbonic anhydrase.¹³ The dose of topiramate in migraine prophylaxis is 100 mg per day which is build up in 4 weeks. Paresthesias, fatigue, gastrointestinal side effects, memory difficulty, and taste perversion are common side effects with topiramate therapy.¹⁴

Anti depressants i.e amitriptyline 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 topiramate used as monotherapy, and in combination for the prophylaxis of migraine.

MATERIALS AND METHODS:

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

Study design: Cross sectional observational study

Duration: August 2019 to March 2020 .

Sample Size: 120 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 Renal stones, under weight, cognitive problems, Active liver disease, bladder outlet obstruction, hypersensitivity to these drugs, pregnant women, lactating mothers

Data Collection Procedure Patients were allocated to nortriptyline group A, topiramate 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 Topiramate 25 mg daily at night for 7 days, then 25 mg twice daily for next 7 days, then 25mg in morning and 50 mg at night for next 7 days and then 50 mg twice 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 vomiting, 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(Topiramate)	GroupC (Nortriptyline+ Topiramate)
15-25	28(70%)	20(50%)	24(60%)
26-36	8(20%)	12(30%)	14(35%)
37 and above	4(10%)	8(20%)	2(5%)
Total	40(100%)	40(100%)	40(100%)

Mean±SD 26.5±7.6

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		Group B		Group C	
	1 st FU	2 nd FU	1 st FU	2 nd FU	1 st FU	2 nd FU
1-4	4(10%)	20(50%)	6(15%)	22(55%)	6(15%)	26(65%)
5-8	16(40%)	12(30%)	14(35%)	10(25%)	20(50%)	12(30%)
9-12	12(30%)	8(20%)	14(35%)	8(20%)	12(30%)	2(5%)
>13	8(20%)	0(0%)	6(15%)	0(0%)	2(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**

1 st FU	Group A		Group B		Group C	
	2 nd FU	1 st FU	2 nd FU	1 st FU	2 nd FU	
16(40%)	24(60%)	14(35%)	22(55%)	24(60%)	32(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 120 patients were chosen that fulfilled the diagnostic criteria of migraine and divided into three groups. Group A, B and C was given nortriptyline, topiramate and combination of both respectively. In group A, 15-25 years of age patients were 28(70%), 26-36 years of age were 8(20%) and 37 years and above were 4(10%). In group B, 15-25 years of age patients were 20(50%), 26-36 years of age were 12(30%) and 37 years and above were 8(20%). In group C, 15-25 years of age were 24(60%), 26-36 years of age were 14(35%) and 37 years and above was 2(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 16 patients(40%), and after 6 months 24 patients (60%), in group B after three months 14 patients (35%) and after 6 months 22 patients(55%) and in group C at three months 24 patients(60%), at 6 months 32 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 topiramate 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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