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Original Research Article.

Observation of Adverse Effect of Topiramate & Propranolol in Migraine Prophylaxis

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ABSTRACT

Background: Migraine headache is a common neurological episodic condition originating from the central nervous system that can significantly impair the lives of otherwise normally functioning people. Pharmacologic options for migraine prophylaxis include beta blockers, calcium channel blockers, antidepressants and anticonvulsants; all of which have varying degrees of adverse effects that may significantly limit their use in this disease.

Objectives: To observe whether low dose Topiramate is more effective compared to Propranolol in migraine prophylaxis.

Methods: This clinical trial was carried out in the Out Patient Department (OPD) & Headache Clinic, Department of Neurology, Bangabandhu Sheikh Mujib Medical University, Dhaka. A total of 120 patients around the age range of 18 to 50 years diagnosed as migraine (with aura or without aura) according to ICHD-3 criteria, were recruited as the study population. By simple random sampling procedure, using odd & even number, 60 patients were administered by Tab. Topiramate 50 mg/ day named as group-I and rest 60 patients were administered by Tab. Propranolol 80 mg /day named as group-II. Out of them in total 96 patients had completed the study due to drop out of 13 patients in group-I & 11 patients in group-II in different steps of follow up. Finally 47 patients remain in group-I and 49 patients in group-II. During trial, three follow up visits were taken for both group, 1st follow up after 4 weeks of baseline information (Before starting prophylactic medication), 2nd follow up after 4 weeks of treatment, 3rd follow up after 8 weeks of treatment. Efficacy of treatment was measured by headache frequency, duration and Severity of headache as measured by the VAS.

Results: The mean (SD) age of group-I (topiramate) and group-II (propranolol) group were found 29.72 (9.58) years and 30.96 (10.11) years respectively. Female sex was found predominant in both groups. At final follow up, there was statistically significant difference in mean (SD) value of frequency of migraine attack between topiramate and propranolol group [4.72 (2.80) vs. 3.48 (2.20); p=0.024]. Propranolol appeared statistically significant than topiramate [TPM 5.53 (2.98) vs. PRO 4.36 (1.55); p=0.047]. Regarding Severity of headache, better results also were observed in the propranolol group than topiramate ($p < 0.05$). Both drugs appeared significant in efficacy measurement ($p < 0.001$). Patient drop out was more in the topiramate group than the propranolol group (21.68 % vs. 18.34%). Furthermore, in the topiramate group, patients complained of more adverse effects than propranolol group (23.4% vs. 14.3%), which was statistically significant.

Conclusion: The present study suggests that low dose Topiramate and Propranolol are effective for migraine prophylaxis in reduction of frequency, Severity and duration of migraine headache individually and propranolol appears more effective compared to that of topiramate.

Keywords: Topiramate, Propranolol, Migraine Prophylaxis.

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INTRODUCTION

Migraine is a central nervous system disorder characterized by vascular headache associated with vasodilatation of extra-cranial vessels but may be due to disturbed neuronal activity in the hypothalamus.[1] Migraine headache ranges from moderate to very severe in intensity and lasts from 4 to 72 hours.[2] Pain from severe migraine headache can be debilitating.[3,4] Migraine headache are usually characterized by pain on one or both sides of the head. In absence of serious head injuries, stroke and tumor, the recurring

Severity of the pain indicates vascular headache rather than tension type headaches. Migraine headaches are often accompanied by photophobia, phonophobia and vomiting.[5] Migraine is an episodic primary headache disorder that is characterized by recurrent attacks of various combinations of headache and neurological, gastrointestinal and autonomic symptoms.[6] According to World Health Organization (WHO) migraine is the global burden of health related issue that study was conducted in 2000 and reported in the world Health Report 2001. Migraine included for the first time & contributing 1.4% of all years lived with disability (YLD), is the 19th cause of disability in both sexes of all ages & 12th ,accounting for 2.0% of YLD, in women (WHO, 2001). Successful management of migraine requires intensive patient's educations and through physician knowledge about available treatment options and strategies. Use of a prophylactic medication reduces headache duration, frequency, Severity and risk for rebound headache.[7] Migraine is a common condition, annually affecting 12% of the United States population, including 18% of women, 6% of men and 4% of children. Lifetime prevalence of migraine in women in the United States exceeds 25%. The prevalence of migraine has not changed since 1989, based on evidence from three large studies: American Migraine study-I, American Migraine Study-II and American Migraine Prevention and prevalence study. Migraine is generally more common in people who are in lower socioeconomic groups.[8] Migraine usually present with episodic headache that is unilateral or bilateral, pulsating in quality, moderate to severe in intensity and exacerbated by physical activity. Associated symptoms include nausea or vomiting, photophobia and phonophobia. The disorder is classified as migraine with aura and migraine without aura, according to the presence or absence, respectively of premonitory neurological symptoms. Migraine is a common and disabling primary headache disorder with worldwide prevalence of 10-12% of adult population.[9] In Bangladesh there is no data regarding the prevalence of migraine. In a study conducted in BSMMU headache clinic total 3440 patients were studied and 16.05% of them had a diagnosis of migraine.[10] In another Bangladeshi study, the tension headache (Muscle contraction headache) was the commonest type 69%, followed by migraine 26%.[10] Migraine pain results primarily from increased activity of Several agents that regulate vasodilatation and sensory function of the brain. In about 15 percent of patients, migraine attacks may be accompanied by aura (visual, sensory, or language symptoms). Other accompanying symptoms may include photophobia (excessive sensitivity to light), phonophobia (fear of loud sounds), nausea, or vomiting. Different elements need to be considered in migraine management. They include: avoidance of triggering factors, lifestyle modifications, non-pharmacological therapies and lastly medications. Pharmacological treatment is traditionally divided into acute or symptomatic treatment, preventive treatment or prophylaxis. Many migraine patients can be treated using only acute treatment 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. Prophylaxis is recommended to reduce the frequency and/or intensity of migraine headaches when patients experience more than three to five attacks per month. A variety of drugs from diverse pharmacological classes are in use for migraine prevention. Adrenergic receptor blockers (e.g. propranolol), tricyclic antidepressants (e.g. amitriptyline), anticonvulsants (e.g. topiramate and valproate), and serotonergic drugs (e.g. methysergide) are most commonly administered for this purpose, as summarized in US Headache Consortium Guidelines .More recently, topiramate was tested prospectively. Topiramate showed statistically significant efficacy in migraine prevention. Topiramate appeared to be safe and had an acceptable safety profile. Among Several treatment-emergent adverse events dose dependent weight loss is common. For these reason, slow titration of target dose of topiramate is advisable.[11]Beta-adrenergic blockers, such as propranolol, are among the most prescribed drugs for migraine prophylaxis.[12] Propranolol has been prescribed for migraine prophylaxis since 1966 when Raskin et al. discovered its effectiveness in migraine headache in their patients who were being treated for angina pectoris. There is clear evidence that propranolol is more effective than placebo in the treatment of migraine. The usual propranolol doses for migraine prevention in clinical trials have ranged from 80 to 160 mg a day.[13] In a clinical trial comparing the efficacy of propranolol with sodium valproate in migraine prophylaxis in BSMMU showed that 53.17% decline in headache frequency, 64.81% decline in headache duration &15.16% decline in headache Severity, whereas 48.98% decline in headache frequency, 62.84% decline in headache duration & 18.15% decline in headache Severity Adverse events most commonly reported with propranolol are fatigue, depression, nausea, dizziness, and insomnia. These symptoms are fairly well tolerated and are seldom the cause of premature withdrawal.[14] Antidepressants, especially tricyclic agents such as amitriptyline and nortrip-tyline, have also been a mainstay in the prophylactic therapy of migraine.[15] Amitriptyline is a mixed serotonergic and noradrenergic reuptake inhibitor with well-established efficacy in chronic pain relief and migraine prophylaxis.[15] Common adverse effects of amitriptyline include dry mouth, constipation, and sedation. They may also cause slowing of atrioventricular conduction and orthostatic hypotension.[16]

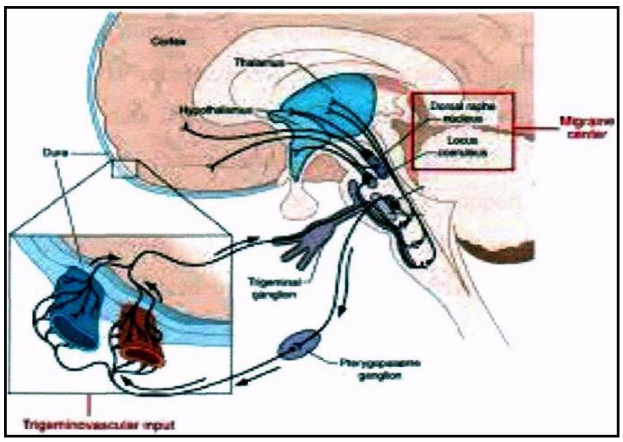

Figure 1: Brainstem pathways that modulate sensory input

The sensory symptom of migraine is probably due to dysfunction of monoaminergic sensory control systems located in the brainstem and thalamus. Activation of cells in the trigeminal nucleus results in the release of vasoactive neuropeptides, particularly calcitonin gene-related peptide (CGRP), at vascular terminations of the trigeminal nerve. Recently, antagonists of

CGRP have shown some early promise in the therapy of migraine. Centrally, the second-order trigeminal neurons cross the midline and project to ventrobasal and posterior nuclei of the thalamus for further processing. Additionally, there are projections to the periaqueductal gray and hypothalamus, from which reciprocal descending systems have established anti-nociceptive effects. Other brainstem regions likely to be involved in descending modulation of trigeminal pain include the nucleus locus coeruleus in the pons and the rostroventromedial medulla. Pharmacologic and other data point to the involvement of the neurotransmitter 5-hydroxytryptamine (5-HT; also known as serotonin) in migraine. Approximately 50 years ago, methysergide was found to antagonize certain peripheral actions of 5-HT and was introduced as the first drug capable of preventing migraine attacks. The triptans are designed to selectively stimulate subpopulations of 5-HT receptors; at least 14 different 5-HT receptors exist in humans. The triptans are potent agonists of 5-HT1B, 5-HT1D, and 5-HT1F receptors and are less potent at the 5-HT1A receptor. A growing body of data indicates that the anti-migraine efficacy of the triptans relates to their ability to stimulate 5-HT1B/1D receptors, which are located on both blood vessels and nerve terminals. Data also support a role for doparnine in the pathophysiology of certain subtypes of migraine. Most migraine symptoms can be induced by dopaminergic stimulation. Dopamine receptor antagonists are effective therapeutic agents in migraine, especially when given parenterally or concurrently with other anti-migraine agents. Migraine genes identified by studying families with familial hemiplegic migraine (FHM) reveal involvement of ion channels, suggesting that alterations in membrane excitability can predispose to migraine. Mutations involving the Cav2.1 (P/Q) type voltage-gated calcium channel *CACNA1A* gene are now known to cause FHM 1; this mutation is responsible for about 50% of FHM. Mutations in the Na-r-K+ATPase *ATP1A2* gene designated FHM 2. are responsible for about 20% of FHM, Mutations in the neuronal voltage-gated sodium channel *SCN1A* cause FHM 3. Functional neuroimaging has suggested that brainstem regions in migraine and the posterior hypothalamic gray matter region close to the human circadian pacemaker cells of the suprachiasmatic nucleus in cluster headache are good candidates for specific involvement in primary headache. Headache phase of migraine was caused by extracranial vasodilation and neurologic symptoms such as aura were produced by intracranial vasoconstriction. Regional blood flow studies have shown that in patients with migraine with aura there is a modest cortical hypoperfusion that begins in the visual cortex and spreads forwards at a rate of 2 to 3 mm/min and progress anteriorly in a wave-like fashion independent of topography of cerebral arteries. The decrease of blood flow averages 25 to 30 percent (insufficient to explain symptoms on the basis of ischaemia). The wave of hypoperfusion persists for 4 to 6 hours, does not cross the central or lateral sulcus, progressing to the frontal lobe viathe insula. Perfusion of subcortical structures is normal. Contralateral neurologic symptoms appear during temporoparietat hypoperfusion. A few patient of migraine with aura and all patients having migraine without aura, no flow abnormalities are usually seen. Thus, it is unlikely that simple vasoconstriction and vasodilatation are the fundamental pathophysiologic abnormalities in migraine.[17] Migraine aura is characterized by a slowly enlarging visual scotoma with luminous edges. It is believed to result from spreading depression, a slowly moving (2 to 3 mm/min) cortical activity. Spreading depression can be produced by variety of experimental stimuli including hypoxia, mechanical trauma and topical application of potassium. These observations suggest that neuronal abnormalities could be the cause of migraine attack. Physiologically, electrical stimulation near dorsal raphe neurons in the upper brainstem can result in migraine-like headache. There are projections from dorsal raphe that terminate on cerebral arteries alter cerebral blood flow. These are also major projections from the dorsal raphe to important visual centers. These serotonergic projections may represent the neural substrate for the circulatory and visual characteristics of migraine.[18] Pain sensitivity of migraine is primarily restricted to the meningeal blood vessels, which are densely innervated by nociceptive sensory afferent fibers of the ophthalmic division of the trigeminal nerve. It is generally recognized that the development of migraine headache depends on the activation of these afferents. In different animal models, including non-human primates, activation of the meningeal trigeminovascular afferents leads to activation of second order dorsal horn neurons in the trigeminal nucleus pars caudalis (TNC) and the two upper most divisions of the cervical spinal cord. Impulses are then carried rostrally to brain structures that are involved in the perception of pain, including Several thalamic nuclei and the ventrolateral area of the caudal periaqueductal gray region (PAG).The PAG is involved in craniovascular pain not only through ascending projections to the thalamus, but also through descending modulation (mainly inhibitory) of nociceptive afferent information. Activation of the trigeminovascular system (TGVS) also leads to release of vasoactive neuropeptides contained in their peripheral nerve endings, especially the calcitonin gene-related peptide (CGRP). In animal studies, the neuropeptides that are released by trigeminal ganglion stimulation produce vasodilation of the meningeal vessels (mainly due to CGRP), plasma extravasation and mast cell degranulation with secretion of other pro inflammatory substances in the dura (neurogenic inflammation). Evidence that activation of the TGVS occurs in humans during migraine is provided by the increased level of CGRP that is found in both the external and internal jugular venous blood during migraine attacks and its return to normal levels after treatment with sumatriptan and subsequent headache relief .The two main issues in the neurobiology of migraine headache are activation of the TGVS and pain generation after activation of the TGVS.[19] The aura resulted from a region of depressed neural activity in the visual cerebral cortex, and that the scintillations resulted from a bordering region of intense cortical excitation.[20] The neural disturbance propagated slowly across the cortex (at about 3 mm/ min). An electrophysiological correlate was reported in the rabbit cerebral cortex and termed CSD. In animals, CSD can be triggered by focal stimulation (electrical, mechanical or with high K+) of the cerebral cortex, more readily in the occipital region than other regions. It is characterized by a slowly propagating wave (2-6 mm/ min) of sustained strong neuronal depolarization that generates a transient (in the order of seconds), intense activity as it progresses into the tissue, followed by neural suppression that can last for minutes (Lauritzen, 1994), The depolarization phase is associated with an increase in regional cerebral blood flow (rCBF), whereas the phase of reduced neural activity is associated with a reduction in rCBF. The similarities between migraine visual aura

and CSD led to the hypothesis that CSD was responsible for the aura. A habituation deficit has been consistently shown for visual, auditory and somatosensory-evoked potentials. Habituation of responses to olfactory and auditory stimuli occurs more rapidly in cortical neurons than in first- or second order neurons.[21] It is therefore possible that the observed habituation deficits reflect cortical dysfunction and are consistent with cortical hyperexcitability. Lack of habituation could contribute to the enhanced susceptibility of many migraineurs to sensory stimuli. Sensory cortices are under the control of noradrenergic, cholinergic and serotonergic (5-hydroxytryp[tam]ine' or 5-HT-mediated) inputs. Noradrenergic and cholinergic from the nucleus basalis inputs enhance arousal and attention, and lead to EEG activation in the neocortex. This raises the important question of whether migraine-associated abnormalities in evoked potentials and cortical excitability are related to altered control by subcortical modulatory systems. Excessive excitation due to abnormal release of excitatory neurotransmitters is a possibility that is supported by the higher plasma concentration of glutamate in migraineurs and by the alterations in Ca2+ channel function produced by FHM mutations.[22] The extent to which some of the cortical and/or subcortical alterations are affected by repetitive CSD is also not clear, as CSD produces long-lasting changes in gene expression and might affect subcortical structures[23] Migraine aura and headache as parallel rather than sequential processes, and proposes that the primary cause of migraine headache is an episodic dysfunction in brainstem nuclei that are involved in the central control of nociception. Two findings have been considered to provide indirect support forthis idea. First, placement of electrodes in PAG region for the treatment of chronic pain can produce migraine like headaches in non-migraineurs.[24] Second, rCBF increases in Several areas of the dorsal rostra) brainstem during migraine attacks. Although the spatial resolution of the imaging techniques does not allow the distinction of most brainstem nuclei, the foci of maximum rCBF increase, as measured by PET, coincided with the dorsal raphe nucleus and locus coeruleus in patients with migraine without aura and with the red nucleus and substantia nigra in a patient with migraine with aura during a spontaneous attack. The mainstay of pharmacologic therapy is the judicious use of one or more of the many drugs that are effective in migraine. The selection of the optimal regimen for a given patient depends on a number of factors, the most important of which is the Severity of the attack. Mild migraine attacks can usually be managed by oral agent, the average efficacy rate is 50-70%. Severe migraine attacks may require parenteral therapy. In general, an adequate dose of whichever agent is chosen should be used as soon as possible after the onset of an attack. If additional medication is required within 60 min because symptoms return or have not abated, the initial dose should be increased for subsequent attacks. Migraine therapy must be individualized; a standard approach for all patients is not possible. Both the Severity and duration of a migraine attack can be reduced significantly by anti-inflammatory agents, A general consensus is that NSAIDs are most effective when taken early in the migraine attack. However, the effectiveness of anti-inflammatory agents in migraine is usually less than optimal in moderate or Severe migraine attacks. The combination of acetaminophen, aspirin, and caffeine has been approved for use by the U.S. Food and Drug Administration. Important Adverse effects of NSAIDs include dyspepsia and gastrointestinal irritation. Stimulation of 5-HT1B/1D receptors can stop an acute migraine attack. Ergotamine and dihydroergotamine are nonselective receptor agonists, while the triptans are selective 5-HT1B/1D receptor agonists. A variety of triptans (e.g., naratriptan, rizatriptan. eletriptan, sumatriptan, zolmitriptan, almotriptan, frovatriptan) are now available for the treatment of migraine. Each drug in the triptan class has similar pharmacologic properties but varies slightly in terms of clinical efficacy. Rizatriptan & eletriptan are the most efficacious of the triptans currently available in the United States. Unfortunately, triptans are not effective in migraine with aura unless given after the aura is completed & the headache initiated. They are contraindicated in individuals with history of cardiovascular & cerebrovascular disease. Oral dopamine antagonists should be considered as adjunctive therapy in migraine. Drug absorption is impaired during migraine because of reduced gastrointestinal motility. Delayed absorption occurs even in the absence of nausea and is related to the Severity of the attack and not its duration. Therefore, when oral NSAIDs and/or triptan agents fail, the addition of a dopamine antagonist such as metoclopramide, 10 mg should be considered to enhance gastric absorption. Patients with an increasing frequency of migraine attacks, or with attacks that are either unresponsive or poorly responsive to abortive treatments, are good candidates for preventive treatment. Significant Adverse effects are associated with the use of many of these agents. The mechanism of action of these drugs is unclear; it seems likely that the brain sensitivity that underlies migraine is modified. Patients are usually started on a low dose of a chosen treatment; the dose is then gradually increased, up to a reasonable maximum to achieve clinical benefit. Drugs must be taken daily. The probability of success with any one of the antimigraine drugs is 50-75%. Many patients are managed adequately with low-dose amitriptyline, propranolol, topiramate, valproate or gabapentin. If these agents fail, second line agents such as methysergide or phenelzine can be used. Once effective stabilization is achieved, the drugs is continued for 6 months & then slowly tapered to assess the continued need. These drugs may alter the natural history of migraine. Recommendations for migraine prevention have in the past focused on patients who had two or more attacks per month. These recommendations did not account for the need of the individual patient or other migraine characteristics. Recent recommendations for starting preventive therapy are. Patients should be advised to maintain a regular lifestyle, with adequate sleep, meals, exercise, and manage stress. Any identifiable trigger should be avoided. If this regimen does not adequately control their migraine attacks, prophylactic drug treatment is indicated. Adherence to the following principles will enhance the success of therapy: Propranolol is a non-selective |3-blocker.It is well absorbed after oral administration. It has extensive (first pass) metabolism & its bioavailability is low & dose dependent. It is rapidly distributed & has large volume of distribution. It is lipophilic easily cross BBB. It's half-life is 3-6 hours & mainly excreted through liver. Propranolol 40-160 mg per day is effective in reducing the frequency of migraine and in providing moderate reduction in headache intensity and/or duration. Propranolol is comparable in efficacy to flunarizine, amitriptyline, naproxen sodium, divalproex sodium, and methysergide. Other beta blockers such as metoprolol, atenolol, timolol, and nadolol are

likely to have similar benefits. Common adverse effect of Propranolol are slowing of the heart rate, lightheadedness, SOB, anorexia, depression, Tiredness, impotence etc. Contraindications to the use of beta-blockers include asthma and chronic obstructive lung disease, congestive heart failure, atrioventricular conduction defects, Raynaud's disease, peripheral vascular disease and diabetes.[25] It is a sulfamate substituted monosaccharide. It is used in partial onset seizure, primary GTCS. Prophylaxis of migraine also. Topiramate rapidly absorbed through gut (about 4 hours), peak plasma concentration 2 hour after oral administration & is about 80% bioavailable, weakly bound to plasma protein, no food effect on absorption & no active metabolite. It's half-life is 20-30 hours & mainly excreted through urine. Common adverse effect of Topiramate are blurred vision, eyeache, tingling or burning sensation, confusion, drowsiness, tiredness, dizziness, loss of appetite, agitation, weight loss Repression etc. Topiramate is started at a dose of 25 mg at bedtime. The dose is increased by 12.5-25 mg per week to reach a target of 50 mg given twice a day. Valproate at high concentrations increases GABA levels in synaptosomes, perhaps by inhibiting its degradation, by facilitating the postsynaptic responses to GABA, by increasing potassium conductance at lower concentrations and by producing membrane hyperpolarization. In patients with episodic migraine, valproate 250-750 mg/day is recommended. Sodium valproate is comparable in efficacy to propranolol, flunarizine and topiramate.[26] Other antiepileptic drugs Gabapentin, levetericetam and zonisamide are less effective than topiramate and valproate for migraine prophylaxis. Lamotrigine is not efficacious in the treatment of migraine.[26] Amitriptyline is the only antidepressant with fairly consistent support for efficacy in migraine prevention. Amitriptyline is effective in the prophylaxis of migraine at a dose of 10-75 mg per day. It is more efficacious than propranolol for patients with mixed migraine and tension-type headache .Selective serotonin reuptake inhibitors (SSRIs) have not shown significant benefits in migraine prophylaxis. Amitriptyline has been shown to increase serotonin levels in the rat brain but only in high dosage. It is possible, however, to postulate firstly that the tricyclic drug blocks the uptake of serotonin into various tissues, especially the mast cells, and thereby increases circulating levels. Other observations, however, suggest that these drugs inhibit the re-uptake from the extracellular space into the nerve ending of constrictor substances such as noradrenaline, which are released as the transmitter substance on nerve stimulation. A similar effect was shown to take place in peripheral tissues as well as in the brain. The maintenance of higher levels of such vasoconstrictor substances is another possible mode of action. Thirdly, amitriptyline may potentiate noradrenergic sympathetic vasoconstriction giving less vasodilation during the migraine attack. Adverse effects of amitriptyline include weight gain, constipation, xerostomia (dry mouth), mydriasis, blurred vision, urinary hesitancy, retention, reduced gastrointestinal motility, delirium (particularly in the elderly and in Parkinson's disease), dizziness, somnolence (drowsiness), decreased lacrimation, orthostatic hypotension, sinus tachycardia, tremor, dizziness and confusion etc. The mechanism of action of the calcium channel antagonists in migraine prophylaxis is uncertain. They prevent contraction of vascular smooth muscles and inhibition of Ca++ dependent enzymes involved in prostaglandin formation. Flunarizine in doses of 5-10 mg per day has been found to be comparable to propranolol, topiramate, and valproic acid for migraine prophylaxis.[27] Clonidine and guanafacine have been shown to be better than placebo but inferior to beta blockers at reducing headache frequency. Most commonly reported adverse events with clonidine are drowsiness and tiredness. Botulinum toxin type A (BoNT-A) is a focally acting protein that inhibits the release of acetylcholine from presynaptic nerve endings and blocks the release of pain mediators, such as substance P, glutamate, and calcitonin gene related peptide. The biologic effects of BoNT-A are reversible and last for approximately 3 to 6 months. A meta-analysis of eight randomized, double-blind, placebo-controlled trials concluded that BoNT-A was not significantly different from placebo, both from a clinical and statistical perspective. Therefore, Botulinum toxin A is not recommended for the prophylactic treatment of migraine[28] Many NSAIDs have been tried over the years for migraine prophylaxis. Naproxen (750 to 1500 mg) has been extensively investigated so far. It is especially useful in menstrual migraine. Recent interest has been focused onaspirin (75 to 150 mg) particularly in patients who need platelet inhibitors for other medical conditions.[29] Other agents such as pizotifen, buspirone, acetazolamide, montelukast and methysergide are of limited value in prophylaxis of migraine. Methysergide is associated with retroperitoneal and retropleural fibrosis after prolonged use. Feverfew (Tanacetum parthenium), butterbur extract (Petasites hybridus), magnesium, riboflavin and coenzyme Q 10 have not been proven to be conclusively effective. Lisinopril and candesartan have been shown to be effective in isolated trials and are to be preferred in patients with hypertension. Nonpharmacological interventions such as relaxation training, biofeedback and cognitive-behavioral therapy may be considered as treatment options for prevention of migraine.[30] Aerobic exercise has been tried, however its efficacy is uncertain. Hyperbaric oxygen may be an effective, but rarely practical prophylactic measure. These interventions are indicated in patients who show insufficient or no response to drugs, have contraindications or poor tolerance to drug treatment, pregnancy and significant stress. Acupuncture has been shown to be at least as effective as or possibly more effective than prophylactic drug treatment in a recent Cochrane review and has fewer side effects. Thus acupuncture should be considered a treatment option for patients willing to undergo this treatment.[31]

METHODS AND MATERIALS

It was a clinical trial study carried out to see whether Topiramate or Propranolol is more effective in migraine prophylaxis. A total 120 patients were selected, 60 in each group according to selection criteria. Study was conducted in Out Patient Department (OPD) & Headache Clinic, Department of Neurology, BSMMU, Dhaka., Bangladesh, from July 2013 to June 2015. Patient of migraine (with typical aura or without aura) according to ICHD-3 criteria, Age at entry: 18-50 years, not on any prophylactic medication, being able to fill a headache diary successfully & reliably, were included in the study. Patients having headache other than migraine, any co-morbidity: such as heart failure, hepatic or renal impairment, diabetes, bronchial asthma, malignancy, intracranial vascular aneurysm, pregnancy & breastfeeding etc. Computer based statistical analysis were carried out with appropriate techniques and systems. All data were recorded systematically in preformed data collection form

(questionnaire). Continuous data were expressed as mean and standard deviation and qualitative data were expressed as frequency distribution and percentage. Statistical analysis was performed by using window based computer software devised with Statistical Packages for Social Sciences (SPSS-21). Associations between qualitative data were analyzed by chi-square test and continuous data by Wilcoxon signed ranks test (within group) and Mann-Whitney U test (between groups) as data shows asymmetric distribution. For all statistical tests, we considered p value <0.05 as statistically significant. 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, 2013(ICHD-3).Detailed history, general examination, neurological examination including fundoscopy and relevant systemic examination were done in Neurology OPD & Headache clinic. Routine laboratory investigations (complete blood count, urine R/E, RBS) and other relevant investigations (ALT, Serum creatinine. X-ray chest P/A view, X-ray PNS O/M vie\v, ECG, CT/MRI of brain) was carried out according to need. They were taught to maintain their headache character (frequency of headache, intensity, duration of each attack, etc.) on a headache diary supplied to them & advised them to report at the headache clinic after 4 weeks. Intensity of headache was measured by Visual Analogue Scale (VAS).Visual analogue scale is a pain scoring system which includes pain score from 0 to 10. Zero indicates no distress and 10 indicates unbearable distress. VAS is graded as mild, moderate and severe in intensity. The analysis was done by comparing the number of days (duration) with headache, frequency of headache and intensity of headache according to visual analogue pain scale before starting of prophylaxis and that of 4 weeks and 8 weeks after treatment. Outcomes measured were reduction of visual analogue pain scale score, the number of days (duration) with headache, frequency of acute attacks of headache compared to the baseline with subsequent follow up, adverse effects were individually registered.

The trial evolved into 2 stages: Stage-I (4weeks): The base line period or medication (Topiramate/propranolol) free period. During this period the subjects were taught to fill their headache diary to record the baseline headache characters. Those who filled the headache diary reliably entered into the stage-2.Odd number patients are marked as group-1 & even number patients are marked as group-II by lottery. Stage- 2(8 weeks): Tab. Topiramate was given in group-I & Tab. Propranolol in group-II. The headache character was recorded by the patients themselves on headache diary. During the trial period the patients were allowed to take the rescue medication (Tab Paracetamol 500 mg, Tab. Domperidon 10 ing etc) 1-2 tab as their need. Patient of group-1 was treated by Tab Topiramate 25 mg at night for 1 week, followed by 25 mg twice daily for another 7 weeks & patient of group-II was treated by Tab. Propranolol 20 mg twice daily for 1 week, followed by 40 mg twice daily for another 7 weeks.

Ashtari et al. (2008) showed total 62 patients were randomly divided into two groups & treated by topiramate 50 mg/day and propranolol 80 mg/day respectively and they were assessed at 0,4 and 8 weeks of the study. This study demonstrated that both drugs could significantly reduce migraine headache frequency, intensity & duration, but compared with propranolol, topiramate showed better results. To ensure compliance principal investigator explained to patient about the Severity of migraine & what extent it affects his quality of life & drug was taken under direct supervision of his/her attendance & drug was supplied free of cost & blank strip was counted by the principal investigator during follow-up. To check biasness patient was informed about the aggravating & relieving factors. Among 120 patients, 96 patients had completed the study due to drop out of 13 patient in group-1 (8 patients in 1st follow-up & 5 patients in 2nd follow-up) & 11 patients in group-II (6 patients in 1st follow-up & 5 patients in 2nd follow-up) due to poor compliance, lack of transport facilities, adverse effects etc. After end of the study, dose of the drugs was titrated under direct supervision of guide/co-guide.

Aura- It may be defined as an abnormal sensation (such as bright light, zigzag lines in eyes or abnormal cutaneous sensation-paresthesia, numbness etc.) that precedes the onset of certain conditions such as migraine or epilepsy. **Insomnia-** Tt may be defined as inadequate or poor quality of sleep due to a numbers of factors such as difficulty in asleep, waking up frequently during night with difficulty returning to sleep, waking up too early in morning or unrefreshing sleep. **Journey-** It may be defined as an act of travelling from one place to another. **Low dose topiramate-** In migraine prophylaxis it is 50 mg/day, here usual dose is 25-200 mg /day. **Massage-** It may be defined as manipulation of tissues with hand or instruments for therapeutic purpose.

Mild Headache- It may be defined as headache Severity ranges from 1-3 in VAS score. **Moderate Headache-** It may be defined as headache Severity ranges from 4-6 in VAS score. **Severe Headache-** It may be defined as headache Severity ranges from 7-10 in VAS score.

Nausea- It may be defined as a feeling of sickness in the stomach characterized by an urge to vomit. **Phonophobia-** It may be defined as a fear of sounds, noise & one's own voice. **Photophobia-** It may be defined as an abnormal sensitivity to light, especially to the eyes. **Stress**- It may be defined as a state of mental or emotional strain or tension resulting from adverse circumstance.

Sensory Aura- It is an abnormal sensation such as paresthesia, tingling, numbness etc. **Visual aura-** It is an abnormal sensation such as bright light, *zigzag,* lines, tunnel vision, distortion of the shape of the objects comes on gradually develop over a period of about half an hour & fade away as migraine begin but persist throughout migraine attacks.

RESULTS

Out of 120 patients, random sampling procedure was used odd & even number. 60 patients were treated by Tab. Topiramate 50 mg/ day named as group- 1 and next 60 patients with Tab. Propranolol 80 mg /day named as group- II. Of them in total 96 patients were completed the study due to drop out of 13 patients in group- I & 11 patients in group- IT in different steps of follow up. So, at final follow up, 47 patients remain in group- I and 49 patients in group-II. During trial , three follow up visits were taken for both groups, Isl follow up after 4 weeks of baseline information (Before starting prophylactic medication), 2nd follow up after 4 weeks of treatment, 3rd follow up after 8 weeks of treatment.

Table I shows the distribution of the study population by gender. In group- I, 72.3% was female and 27.7% male. In group -II, 61.2% was female and 38.8% male. No statistically significant difference was observed between groups in terms of gender (P>0.05).

Table 1: Study population by gender

Gender	Group-I(n=47)	Group-II(n=49)	p-values*
Female	34(72.3%)*	30(61.2%)	0.284ns
Male	13(27.7%)	19(38.8%)	

ns = non-significant Group-I means Tab Topiramate group, Group-II means Tab Propranolol group*Chi square test was done to measure the level of significance' Figure within parenthesis denoted corresponding column percentage,

Table 2: Study population by age

Age(years)	Group-I(n=47)	Group-II(n=49)	Total (n=96)	p-values*
18-25	20(42.6%)*	21(42.9%)	41(42.7%)	0.475ns*
26-35	12(25.5%)	8(16.3%)	20(20.8%)	
36-45	8(17.0%)	14(28.6%)	22(22.4%)	
46-50	7(14.9%)	6(12.2%)	13(13.5%)	
Mean (SD) [yrs.]	29.72 (9.58)	30.96(10.11)		0.540ns**
Range (min-max) [yrs.]	(18-48)	(18-48)		

Group-I means Tab Topiramate group, Group-II means Tab Propranolol group, *Chi- square test was done to measure the level of significance, ** p- value was derived from Mann-Whitney U test, * Figure within parenthesis denoted corresponding column percentage.

Table 3: Occupational status of the study population

Occupation	Group-I(n=47)	Group-II(n=49)	Total *(n=96)*	p-values*
Student	21(44.7%)*	23(46.9%)	44(45.8%)	0.808ns
Service Holder	14(29.8%)	12(24.5%)	26(27.08%)	
Business	7(14.9%)	6(12.2%)	13(13.5%)	
Housewife	5(10.7%)	8(16.3%)	13(13.5%)	

Group-I means Tab Topiramate group Group-II means Tab Propranolol group,
*Figure within parenthesis denoted corresponding column percentage, *Chi-square test was done to measure the level of significance

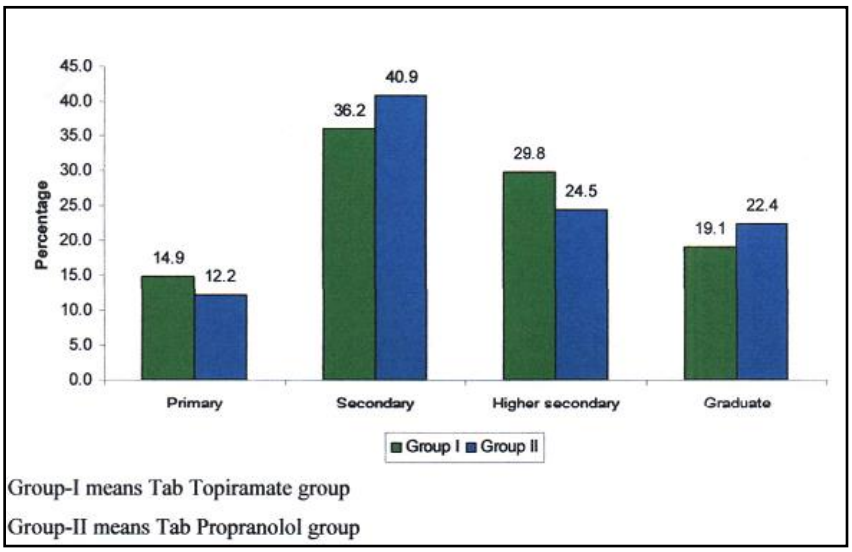

Figure 2: A bar diagram shows educational level of study population

Table IV: Associated symptoms of migraine among study population

Associated symptom	Type of Patients		Total	p-values*
	Group-I(n=47)	Group-II(n=49)	(n=96)	
Nausea	13(27.7%)*	16(32.7%)	29(30.2%)	0.594ns
Vomiting	11(23.4%)	10(20.4%)	21(21.9%)	0.723ns
Vertigo	3(6.4%)	2(4.1%)	5(5.2%)	0.612ns
Phonophobia	11(23.4%)	11(22.4%)	22(22.4%)	0.911ns
Photophobia	9(19.1%)	10(20.4%)	19(19.8%)	0.877ns

Group-I means Tab Topiramate group Group-II means Tab Propranolol group, *Figure within parenthesis denoted corresponding column percentage, ** p- value non-significant (p> 0.05), derived from chi-square test in between group-I and group-II.

Table 5: Precipitating factors of migraine among study population

Participating factors	Type of Patients		Total	p-values*
	Group-In=47)	Group-II(n=49)	(n=96)	
Stress	13(27.7%)*	14(28.6%)	27(28.1%)	0.921ns
Journey	9(19.1%)	10(20.4%)	19(19.8%)	0.877ns
Sun light	6(12.8%)	7(14.3%)	13(13.5%)	0.828ns
Insomnia	8(17.0%)	5(10.2%)	13(13.5%)	0.329ns
Fasting	5(10.6%)	4(8.2%)	9(9.4%)	0.677ns
Menstruation	4(8.5%)	5(10.2%)	9(9.4%)	0.776ns
Nil	2(4.3%)	4(8.2%)	6(6.3%)	0.429ns

Group-I means Tab Topiramate group Group-11 means Tab Propranolol group, *Figure within parenthesis denoted Corresponding column percentage, ** p -value no significant (p> 0.05), derived from chi-square test in between group-1 and group –II.

Table 6: Relieving factors of migraine among study population

Relieving factors	Type of Patients		Total	p-values*
	Group-I(n=47)	*Group-II(n=49)*	*(n=96)*	
Rest	20(42.6%)*	22(44.9%)	42(44.7%)	0.817ns
Sleep	9(19.1%)	10(20.4%)	19(19.8%)	0.877ns
Massage	6(12.8%)	4(8.2%)	10(10.7%)	0.461ns
Cold Compression	5(10.6%)	4(8.2%)	9(9.4%)	0.677ns
Nil	7(14.9%)	9(18.4%)	16(16.7%)	0.648ns

Group-I means Topiramate group Group-II means Propranolol group, ns=non-significant, *Figure within parenthesis denoted corresponding column percentage, *non-significant if p> 0.05, derived from chi-square test between group-I & group-II.

Table 7: Aura of migraine among study population

Type of Migraine	Type of Patients		Total	p-values*
	Group-I(n=47)	Group-II(n=49)	(n=96)	
With aura	7(14.9%)*	9(18.4%)	16(16.7%)	0.648ns
Without aura	40(85.1%)	40(81.6%)	80(83.3%)	

Group-I means Tab Topiramate group Group-II means Tab Propranolol group ns— non significant, *Figure within parenthesis denoted corresponding column percentage, *p- value derived from chi-square test.

Table 8: Type of aura among study population

Type of aura	Type of Patients		Total	p-values*
	Group-I(n=47)	Group-II(n=49)	(n=96)	
Visual aura	6(12.76)*	7(14.28%)	13(13.5%)	0.687ns
Sensory aura	1(2.12%)	4(4.08%)	3(3.1%)	

Group-1 means Tab Topiramate group, Group-11 means Tab Propranolol group, ns= non-significant 'Figure within parenthesis denoted corresponding column percentage, *p- value derived from chi-square test.

Table 9: Frequency of migraine attacks in group-I and group-II individually

Type of Patients	Frequency of migraine attack Mean (SD)	p-values*
Group-I (n=47)		
Baseline level	9.28(2.39)	
1st Follow up (after 4 weeks)	7.55(3.07)	0.001s
2nd Follow up (after 8 weeks)	4.72(2.80)	<0.001s
Group-II (n=49)		
Baseline level	9.29(2.46)	
1st Follow up (after 4 weeks)	6.59(3.48)	<0.001s
2nd Follow up (after 8 weeks)	3.48(2.20)	<0.001s

Group-I means Tab Topiramate group, Group-II means Tab Propranolol group, s=significant, **Wilcoxon signed ranks test was done to measure the level of significance.

Table II shows the age distribution of both groups. A total of 96 patients were included in the study. They were divided into four groups according to their age. The mean age was found 29.72 (9.58) years and range were (18-48) years in group- I and mean age were 30.96 (10.11) years and range were (18-49) years in group -II. A good number of the study patients were in 18- 25 years age group-In both groups (42.6% vs. 42.9%). This table shows no significant difference in age distribution between group-I & group-II.

Table III shows distribution of the study population by occupation. A major portion of patients were student in both group- I and group- II (44.7% vs. 46.9%) which was followed by service holder (29.8% vs. 24.5%). There was no statistical significant difference between group-I & group-II (p> 0.05).

Figure 2 shows educational level. Among all the patients, a major portion of study population was taking secondary education accounting 36.2% patients in group -I and 40.9% in group- II.

Table IV shows distribution of the patients according to associated symptoms with migraine. The most common announcing associated symptoms were nausea (27.7% vs. 32.7%) and vomiting (23.4% vs. 20.4%) in both group- I and group- II respectively.

Table V shows distribution of the patients according to precipitating factors of migraine. A major portion of patients in both group- I and group -II, proclaimed stress as precipitating factors of migraine (27.7% vs. 28.6?/o) which was followed by journey (19.1% vs. 20.4%), sunlight (12.8% vs. 14.3%) and insomnia (17.0% vs. 10.2%). There was no statistically significant difference in terms of precipitating factors of migraine between both groups.

Table VI shows distribution of the patients according to relieving factors of migraine. A major portion of patients affirmed that rest is a relieving factor which was 42.6% patients in group-I and 44.9% in group-II. The second common relieving factor of migraine was sleep in both group-I and group-II (19.1% vs. 20.4%). Other relieving factors were massage (12.8% vs. 8.2%) and cold compression (10.6% vs. 8.2%).There was no statistical significant difference between group-I & group-II considering relieving factors.

Table VII shows distribution of the patients according to type of migraine based on aura. Out of all patients, 16 (16.7%) patients had migraine with aura. Among them, 7 patients in group-I and 9 patients in group- II declared to have aura. There was no statistical significant difference between group- I and group- II considering migraine with aura (14.9% vs. 18.4%, p value> 0.05).

Table VIII shows distribution of the patients according to type of aura in migraine. Out of all patients, 16 (16.7%) patients had migraine with aura. Among them, 7 patients in group-I and 9 patients in group- II declared to have aura. A major portion of patients had visual aura (such as zigzag lines in both eyes) in group-I & group-II (12.76% vs 14.28%). followed by sensory aura (such as paresthesia in face & lips) (2.12% vs 4.08%). There was no statistical significant difference between group-1 and group- II considering type of aura.

Table IX shows distribution of the patients according to baseline, 1st& 2nd follow up frequency of migraine attack in group-I and group-II individually. The efficacy of prophylactic drug based on frequency of migraine attack was seen in both groups individually. In group-I, comparing the mean (SD) value of frequency of migraine attack at baseline level with 1st and 2nd follow up were statistically significant [Baseline 9.28 (2.39) vs. 1st FU 7.55 (3.07), p=0.001; Baseline 9.28 (2.39) vs. 2nd FU 4.72 (2.80), p=<0.001]. In group II, 1st and 2nd follow up value of frequency were statistically significant with baseline value [Baseline 9.29 (2.46) vs. 1st FU 6.59 (3.48), p=<0.001; Baseline 9.29 (2.46) Vs. 2nd FU 3.48 (2.20), p= <0.001].

Table X shows the response of prophylaxis on patients of group-I and group-II in terms of baseline, 1st& 2nd follow up of frequency of migraine attack. The mean (SD) value of frequency of migraine attack was found 9.28 (2, 39) in group-I and that of 9.29 (2.46) in group-II. P-value was non-significant considering baseline value of frequency of migraine attack. During trial in 1st follow up, Non-significant differences in level of frequency of migraine attack were observed but there was more decreasing value in patients of group-II than that of group-I [group-I 7.55 (3.07) vs. group-II 6.59 (3.48); p > 0.05]. During 2nd follow up, there was statistically significant difference was observed in frequency of migraine attack between group-I and group-II [4.72 (2.80) vs. 3.48 (2.20); p=0.024].

Table XI shows distribution of the patients according to duration of each episode of migraine (hours) in group-I and group-II individually. Efficacy of treatment based on duration of each episode of migraine (hours) was seen in both groups individually. In group-I, comparing the mean (SD) value of duration of migraine of baseline level with 1st and 2nd follow up were statistically significant [Baseline 10.85 (5.26) vs. 1st FU 8.06 (4.11) hr, p=<0.001; Baseline 10.85 (5.26) vs. 2nd FU 5.53 (2.98) hr, p=<0.001]. In group-II, 1st and 2nd follow up value of duration were statistically significant with baseline value [Baseline 10.22 (4.42) vs. 1st FU 6.97 (2.47) hr, p=<0.001; Baseline 10.22 (4.42) Vs. 2nd FU 4.36 (1.55) hr, p= <0.001].

Table XII shows the response of prophylactic drug on patients of group-I and group-II in terms of duration of each episode of migraine. The mean (SD) value of baseline duration of migraine was found in group I, 10.85 (5.26) hrs in group-1 and 10.22 (4.42) hrs in group-II, P-value was non-significant considering baseline value of duration of migraine attack.

During trial in 1st follow up, statistically non-significant differences was observed but between groups there was more decreasing value in patients of group-II than that of group-I [group-I 8.06 (4.11) vs. group-II 6.97 (2.47) hrs; p =0.344]. During 2nd follow up, statistical significant difference was observed in duration of migraine attack between group-I and group-II [5.53 (2.98) vs. 4.36 (1.55); p=0.047].

Figure 3 shows efficacy in terms of duration of each episode of migraine at baseline, 1st and 2nd follow up. It signifies that a significant decreasing trend of level of duration of migraine in group-H than group-I especially in 2nd follow up.

Table XIII shows distribution of the patients according to Severity of migraine based on categories of Visual Analogue Scale (VAS) in both groups. At baseline level, there was no statistical significant difference between group-I and group-II (Moderate: 53.2% vs. 59.2%; Severe 46.8% vs. 40.8%; p > 0.05). During clinical trial of 1st follow up, patients were distributed in all mild, moderate and severe groups but no statistical significant difference was found. In 2nd follow up, patients had better condition and distributed in mild and moderate groups. There was statistical significant difference between group-I and group-II (Mild: 61.7% vs. 81.6%; Moderate: 38.3% vs. 18.4%; p < 0.05).

Table XIV shows distribution of patients according to adverse effects. In group-1, 23.4% patients developed adverse effects and that of 14.3% in group-II. Among the adverse effects of group-I, 8.5% develop dizziness that was followed by drowsiness 6.3%. On the other hand, in group-II, 6.1% developed bradycardia, there heart rate were 50/m, 52/m &57/m and 4.1% had drowsiness and generalized weakness. There was no statistical significant difference between both groups in terms of adverse effects.

Table 10: Frequency of migraine attacks in both groups

Frequency of migraine attack	Type of Patients		p-values*
	Group-I (n=47) Mean (SD)	Group-II (n=49) Mean (SD)	
Baseline level	9.28(2.39)	9.29(2.46)	0.932ns
1st Follow up (after 4 weeks)	7.55(3.07)	6.59(3.48)	0.086ns
2nd Follow up (after 8 weeks)	4.72(2.80)	3.48(3.20)	0.024ns

Group-I means Tab Topiramate group Group-11 means Tab Propranolol group, ns=non-significant; s=significant,
*Mann-Whitney U test was done to measure the level of significance.

Table 11: Duration of each episode of migraine (hours* in sroup-1 and group-II individually

Type of Patients	Duration of each episode of migraine (Hours) Mean (SD)	p-values*
Group-I (n=47)		
Baseline level	10.85(5.26)	
1st Follow up (after 4 weeks)	8.06(4.11)	<0.001s
2nd Follow up (after 8 weeks)	5.5392.98)	<0.001s
Group-II (n=49)		
Baseline level	10.22(4.42)	
1st Follow up (after 4 weeks)	6.97(2.47)	<0.001s
2nd Follow up (after 8 weeks)	4.36(1.55)	<0.001s

Group-I means Tab Topiramate group Group-II means Tab Propranolol group, s=significant,
*Wilcoxon signed ranks test was done to measure the level of significance.

Table 12: Duration of each episode of migraine in both groups

Duration of each episode of migraine (Hours)	Type of Patients		p-values*
	Group-I (n=47) Mean(SD)	Group-II (n=49) Mean(SD)	
Baseline level	10.85(5.26)	10.22(4.42)	0.831ns
1st Follow up (after 4 weeks)	8.06(4.11)	6.97(2.47)	0.344ns
2nd Follow up (after 8 weeks)	5.53(2.98)	4.36(1.55)	0.047ns

Group-1 means Tab Topiramate group Group-II means Tab Propranolol group, ns=non-significant; significant,
*Mann-Whitney U test was done to measure the level of significance.

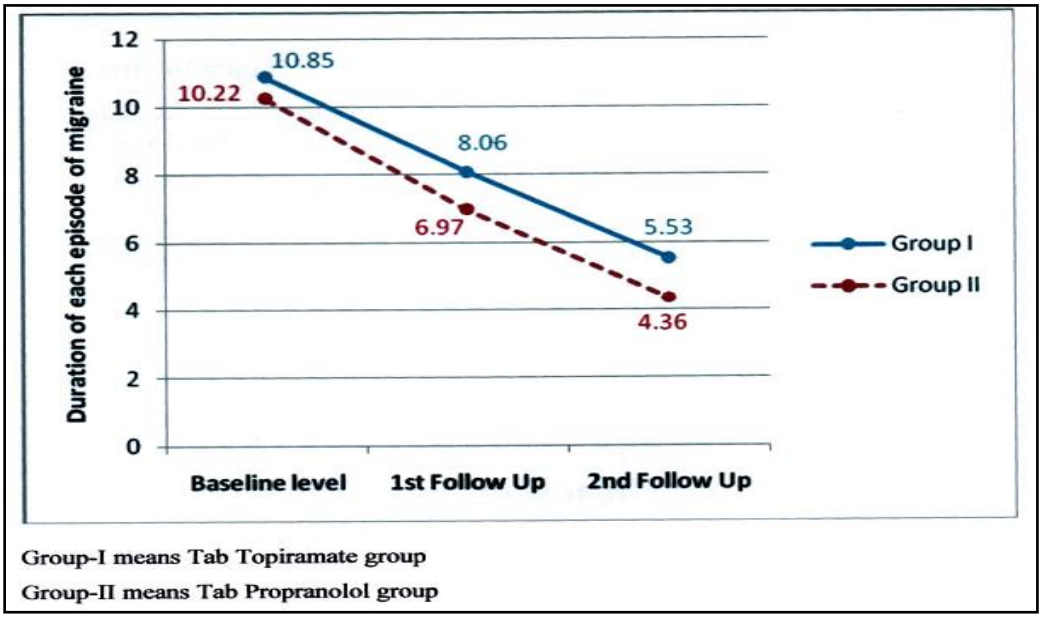

Fig 3: A line chart shows efficacy in terms of duration of each episode of migraine at baseline, 1st and 2*1follow up.

Table 13: Severity of migraine based on categories of Visual Analogue Scale (VAS) in both groups

Severity of migraine	Type of Patients		p-values*
	Group-I (n=47)	Group-II (n=49)	
Baseline level			
Moderate	25(53.2%)*	29(59.2%)	0.700ns
Severe	22(46.8%)	20(40.8%)	
1st Follow up (after 4 weeks)			
Mild	24(51.1%)	18(36.7%)	
Moderate	15(31.9%)	21(42.9%)	0.360ns
Severe	8(17.0%)	10(20.4%)	
2nd Follow up (after 8 weeks)			
Mild	29(61.7%)	40(81.6%)	0.030ns
Moderate	18(38.3%)	9(18.4%)	

Group-I means Tab Topiramate group Group-II means Tab Propranolol group ns=non-significant: s= significant,
*Chi square test was done to measure the level of significance, *Figure within parenthesis denoted corresponding column percentage.

Table 14: Adverse effects among study population

Adverse Effects	Type of Patients		p-values*
	Group-I (n=47)	Group-II (n=49)	
Yes	**11(23.4%)***	**7(14.3%)**	
Dizziness	4(8.5%)	2(4.1%)	
Drowsiness	3(6.3%	0(0.00%)	
Blurring of vision	2(4.2%)	0(0.00%)	0.405ns
Anorexia	2(4.2%)	0(0.00%)	
Bradycardia	0(0.00%)	3(6.1%)	
Generalized Weakness	0(0.00%)	2(4.1%)	
No	**36(76.6%)**	**42(85.7%)**	

Group-I means Tab Topiramate group Group-II means Tab Propranolol group, ns = non-significant,
*Chi-square test was done to measure the level of significance,*Figure within parenthesis denoted, corresponding column percentage.

DISCUSSION

Migraine is a significant detriment to daily functioning and productivity, it typically manifests as attacks of Severe, pulsating, one-sided headache and is often accompanied by nausea, phonophobia, or photophobia. Various drugs have been used for migraine prophylaxis. In the present study, efficacy and safety of topiramate and propranolol were compared. Among the many different beta-blockers, propranolol is one of the most commonly prescribed for migraine prophylaxis. It has been subjected to a number of placebo-controlled trials and is now sometimes used as a comparator drug when testing newer agents for migraine prophylaxis.[32] It is not certain exactly how beta-blockers decrease the frequency of migraine attacks, but they may affect the central catecholaminergic system and brain serotonin receptors. Recently, antiepileptic drugs including topiramate (TPM) are more commonly used in adults and adolescents for migraine prophylactic therapy. In Several randomized, double-blind, placebo-controlled, dose-ranging trials involving adult patients with episodic migraine, topiramate treatment resulted in significant benefit compared with placebo, with efficacy observed within the first month of treatment. Therefore, more randomized clinical trials and comparison of effective migraine preventive drugs are needed to detect more effective drugs and to approve their use in migraine patients. There are substantial number of publications demonstrating the efficacy of topiramate and propranolol in the treatment of migraine.[33] It is one of the former clinical trials of migraine to compare topiramate and propranolol in Bangladesh context. We compared our study findings with result of some other published articles elsewhere in the world. Analysis of age distribution showed that, the mean age was found 29.72 (9.58) years and range were (18-48) years in group-I and mean age were 30,96 (10.11) years and range were (18-49) years in group-II but no significant difference in age distribution among both groups. A good number of the study patients were 18- 25 years age group in both groups (42.6% vs. 42.9%). A study done by found mean (SD) age, 39.8 years who studied on topiramate placebo-controlled clinical trials. Also obtained mean age 40.4 ± 11,5 and 38.3 ± 12.0 years respectively. In this study, patients were younger than the patients of above mentioned studies. Out of all patients in group-I, 72.3% was female and 27.7% male. In group-II, 61.2% was female and 38.8% male. No statistically significant difference was observed between groups in terms of gender (P>0.05).[34] Also found as female groups more prone to develop migraine as 86% female measured as presence of migraine.[35] Also found more female patients of migraine 76% and 82%, respectively. These results are almost similar to our study. According to occupation, a major portion of patients were student in both group-I and group-II (44.7% vs. 46.9%) which was followed by service holder (29.8% vs. 24.5%). But there was no statistical significant difference between both groups (p> 0.05). Among all the patients, a major portion of study population had completed secondary education accounting 36.2% patients in group-I and 40.9% in group-II, Similar result was reported by another study and added that students were more prone to develop migraine.[36] The reason may be due to more chance of exposure with many provocative factors like study, watching television, tension and so

on. This finding is almost similar to the present study. According to associated symptoms of migraine, the most common announcing associated symptoms were nausea (27.7% vs. 32.7%) and vomiting (23.4% vs. 20.4%) in both group-I and group-II respectively also found similar characteristics of migraine which is consistent with the present study. At the same time, a major portion of patients in both group-I and group-IL proclaimed stress is a precipitating factors of migraine (27.7% vs. 28.6%) which was followed by journey (19.1% vs. 20.4%), sunlight exposure (12.8% vs. 14.3%) and insomnia (17.0% vs. 10.2%). But there was no statistically significant difference in terms of precipitating factors of migraine in between both groups. Another study showed that most common precipitating factors were stress/tension, fatigue and lack of sleep.[37] These findings are consistent with this study. Similar result was reported another study and mentioned that the most frequent triggers of migraine were mental exertion, exposure to the sunlight, heat and anxiety. A major portion of patients affirmed that rest is a relieving factor which was 42.6% patients in group-I and 44.9% in group-II. The second relieving factor of migraine was found as sleep in both group-I and group-II (19.1% vs. 20.4%). Other relieving factors were massage (12.8% vs. 8.2%) and cold compression (10.6% vs. 8.2%). But there were also some patients who had no relieving factors of migraine in both group-I and group-II which was 14.9% and 18.4%. Another study [38] found the relieving factors, were drug intake (79.2%), isolation (from light, sound, people, etc.) (75.4%), trying to keep still (58.5%), trying to sleep (65.2%) and inducing vomiting (11.4%). In this study relieving factors of migraine were not similar to the above mentioned study. Out of all patients, 16 (16.7%) patients had migraine with aura. Among them, 7 patients in group-I and 9 patients in group-II declared to have aura. But there was no statistical significant difference between group-I and group-II in consideration of migraine with aura (14.9% vs. 18.4%, p value >0.05). A major portion of patients had visual aura in group-I & group-II (12.76% vs 14.28%), followed by sensory aura (2.12% vs 4.08%). There was no statistical significant difference between group-1 and group- II considering type of aura. According to VAS score patients were divided into mild, moderate and severe group. At baseline level, patients were distributed into moderate and severe groups and there was no statistical significant difference between group-I and group-II (Moderate: 53.2% vs. 59.2%; Severee 46.8% vs. 40.8%; p >0.05). During clinical trial of 1st follow up, patients was distributed in all mild, moderate and severe groups but no statistical significant difference. At the end of the trial 2nd follow up, patients had better condition and distributed in mild and moderate group. There was statistical significant difference between group-I and group-II (Mild: 61.7% vs. 81.6%; Moderate: 38.3% vs. 18.4%; p < 0.05). So, this present study showed better reduction of headache intensity in propranolol group than topiramate group measured headache intensity lessened more in topiramate group than propranolol group. A study carried out found that propranolol was significantly better in reducing the intensity & duration of attack of migraine regarding adverse effects, in group-I, 23.4% patients developed adverse effects and 14.3% in group-II.[39] Among the adverse effects of group-I, 8.5% develop dizziness that was followed by drowsiness 6.3%. On the other hand, in group-II, 6.1% developed bradycardia and 4.1% had dizziness and generalized weakness. There was no statistical significant difference between both groups in terms of side effects. An adverse effect of topiramate is 16% in another study which was relatively similar with the present study. A similar adverse effect of propranolol is found in the study of Gray et al. (2004). In some studies, those were comparative trial of propranolol with other drugs showed propranolol was more effective. Such as trial comparing propranolol 160 mg and femoxetine 400 mg reported that, propranolol was superior to femoxitine when the headache index was used (p<0.05).[40,41] Even so, the trial comparing propranolol 120 mg and naproxen 1100 mg reported significantly fewer adverse events with propranolol.[42] In comparative study of propranolol with topiramate in migraine patients, there are a few studies. One of the studies suggested that low-dose topiramate and propranolol could significantly reduce migraine frequency, intensity and duration. But low-dose topiramate showed better results than propranolol. In present study, efficacy and adverse effect of topiramate and propranolol were compared and results showed that both drugs were effective in reduction of frequency, duration and Severity of headache but propranolol was more effective than topiramate. As well as, patients drop out was more in topiramate group than propranolol group (21.68 % vs. 18.34%). Furthermore, in topiramate group, patients complained of more adverse effects than propranolol group (23.4% vs. 14.3%). So, comparative studies of propranolol with topiramate showed that topiramate was more effective especially in Iran[33] but present study showed that, propranolol is more effective than topiramate in migraine prophylaxis probably due to poor metabolism of propranolol in our regional context.[43,44]

CONCLUSION

Considering statistical analyses, topiramate and propranolol both are individually safe and effective for migraine prophylaxis in reduction of frequency, Severity and duration of migraine headache. But propranolol is more effective than topiramate in respect of reducing frequency, Severity and duration of migraine.

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