Received: 1/7/2005 **Accepted: 3/15/2005**

Original Article

The preventive Role of Topical Timolol in Treatment of Migraine Headaches

M. Etemadifar MD, MR. Abedi MD*

ABSTRACT

Background: There are many various hypotheses about pathophysiology of migraine headaches. One of them is autonomic nervous system disturbance, but the exact location of the disturbance is not well known. Since most of migraine attacks are accompanied with a retro-orbital pain, we assessed the efficacy and safety of topical Timolol on blockage of β adrenergic receptors for preventing migraine headaches.

Methods: In a clinical trial study, 43 migraine patients (7 male and 36 female) were studied in two neurology clinics in Isfahan. Timolol maleate (5% eye drop) prescribed twice a day. The patients visited weekly for the first 4 weeks; then 8th and 12th week after the beginning of treatment, and the duration and frequency of attacks were evaluated. The severity of headache measured subjectively.

Results: The patients were aged 14 to 54 years, with mean age of 34.2 years and mean disease duration of 9.5 years before the study. They had 13.1 headache days per month. After treatment, the frequency of attacks reached to 3.4 attacks per month. The mean duration of each attack were 16.4 hours before treatment and 2.1 hours after treatment by using Timolol eye drop which were significantly different ($P<0.001$). The severity and duration of attacks also decreased after 12 weeks. None of them have reported adverse events after using it.

Conclusion: Timolol maleate eye drop is an effictive, well-tolerated, safe, and easy-to-use prophylactic antimigraine medication.

Key Words: Migraine headaches; Autonomic nervous system; Timolol

JRMS 2005; 10(5): 288-291

Migraine headaches are severe disabilitating headaches which have a relatively high prevalence in different parts of the world and are occured in 11.7% [1] to 23% [2] of women and 3.8% [1] to 8 % [2] of men in different countries. In Canada, it is estimated that about 27 out of 100 lost work days are due to migraine headaches at an annual cost of $500 million per year [2].

Currently, various hypotheses about pathophysiology of migraine headaches exist and include the vascular hypothesis [3], autonomic nervous system disturbances [4], and relation to special dietary items [5]. Yet, there are many unanswered questions about the pathophysiology of migraine headaches [6]. For example, "Is the change in circulation the primary cause of headaches, secondary or coincidental phenomenon?

At the present time, no final reconciliation of this conflicting data is possible; therefore, the exact mechanism (s) of migraine headaches remains incompletely explained [6]. These various hypotheses have resulted in the suggestion of numerous treatments for migraine headaches:

For example, ergot compounds [7], tricyclic antidepressant [7], divalproex [8], somatriptan family [9-11], beta-blockers [7, 12-15], botolinium toxin [16], and even surgical intervention [17] are used for the treatment and prevention of migraine headaches.

Unfortunately, none of them were completely successful and a definite prevention

*Assistant professor, Department of Neurology, Isfahan University of Medical Sciences, Isfahan, Iran
Correspondence to: Dr Masoud Etemadifar Al-Zahra Hospital, Sofeh Ave, Isfahan, Iran E-mail: Etemadifar@med.mui.ac.ir

and treatment of these headaches still remains a question. One of the main hypotheses about the genesis of migraine is autonomic nervous system disturbances[4].

β adrenergic blocking drugs are among the important drugs that have been used for the prevention of migraine headaches for several decades [7]. However, due to their nonspecific inhibition of β-adrenergic receptors, they cause various side effects [13, 18].

It is believed, nevertheless, that these systemic side effects can be prevented with more specific drugs on anatomic location of the autonomic nervous system. Moskowitz believes that the activation of small unmyelinated autonomic fibers which innervate extra cranial and intracranial vessels via trigeminal nerve causes releasing substance P and other peptides into vessel walls, increased permeability, and producing throbbing unilateral headaches [6].

On the other hand, it is known that most unilateral or frontotemporal attacks of migraine are accompanied by a severe ipsilateral retro orbital pain. The anatomical study of autonomic nervous system pathways shows some postganglionic sympathetic fibers of eye end in the dilator muscle of iris [19]. These fibers dilate the iris in sympathetic over-activity states like fear and pain.

The association of iris dilatation with nausea and vomiting during migraine attacks (which can be resulted from synchronic sympathetic over-activity in the region of celiac ganglion) may be another reason for autonomic disturbances in the patients.

Timolol is a β adrenergic receptor blocker which used for treatment of glaucoma through reducing aqueous production, decreasing intraocular pressure (IOP) and relaxing dilator muscle of iris [20], hence it might inhibit sympathetic over-activity on the level of eyes.

For the mentioned reasons, we evaluated preventive effects of sympathetic activity blockage on the frequency and severity of migraine attacks.

Subjects and Methods

This clinical trial was performed on patients with migraine headaches in two out-patients neurology clinics in Isfahan since 2001 to 2002.

The patients were simply selected in response to requests sent to other neurologists and general practitioners for referring the patients to the clinics. After explaining the method and possible complications of the prescribed drug, 51 patients who agreed to join the research were included. The patients were questioned about features of headaches including severity (by subjective criteria), frequency, duration and pattern of migraine attacks, duration of disease, clinical characteristics of pain, associated symptoms, exacerbating and relieving factors, previous treatments for headaches, and family history,.

Intraocular pressures (IOP) were measured before the study to exclude those who had abnormality in their IOP. Sterile eye drops of timolol maleate (0.5%) were prescribed twice a day (one drop in the eye at the same side of the pain).

The patients were taught how to use the drug. To prevent the washing out of the drug from eyes and its systemic effects, the patients were asked to press the inner punctums of their eyes for at list one minute after using the drug. They were also requested to discontinue all other drugs used for the treatment of migraine headaches (except the pain relieving agents for extremely severe headaches) at the 12 weeks period of the study.

They were visited on the 1st, 2nd, 3rd, 4th, 8th and the 12th weeks after beginning the drug. Eight patients were omitted due to inappropriate drug use and lack of cooperation in on-time visits. Consequently, the study was completed with 43 patients.

The data were analyzed by SPSS software.

Results

Within 43 patients, 7 (16.3%) and 36 (83.7%) patients were male and female, respectively. The mean age of them was 34.2 years with a mean disease-duration of 9.5 years.

None of the patients reported side effects after using the drug. The patients complained of frontotemporal pain (55%), temporal or unilateral (20%), bilateral (18%) and generalized headache (4%). Its quality was pulsative in 88% of patients. The most common associated symptom was nausea and vomiting. Treatment modalities -used by patients before the beginning of the study- are shown in Figure 1.

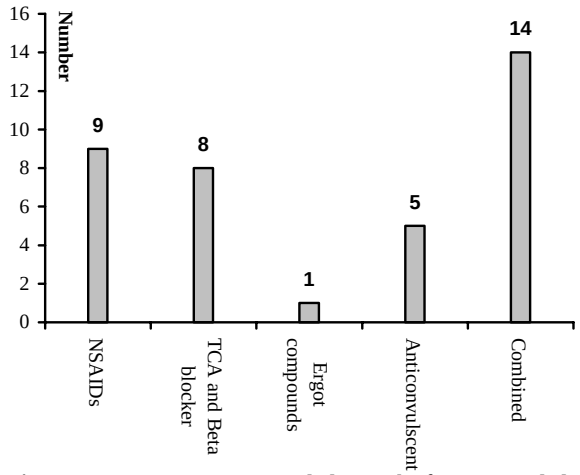

Figure 1. Treatment modalities before Timolol

The mean frequency of migraine attacks per month, the mean duration and severity of each attack (measured by subjective criteria) were decreased after using timolol eye drop significantly (p value < 0.001) (Table 1).

Table 1. Clinical characteristics of migraine attacks before and after treatment with Timolol

	Before Treatment	After Treatment
Frequency (attack per month)	13.1	3.4
Duration (hours)	16.4	2.1
Severity[1] (%)		
No headache	- (0)	10 (23.2)
Very mild	- (0)	20 (46.6)
Mild	3 (7)	5 (11.6)
Moderate	10 (23.2)	4 (9.3)
Severe	30 (69.8)	4 (9.3)

Discussion

The epidemiologic features, the mean age of patients and the age of onset of headaches were similar to other studies.

Decrease in the frequency of attacks and in the duration and severity of each attack were comparable with other drugs: In Freitag study, the frequency of attacks reached from 4.4 attacks to 3.2 attacks in month, after using Divalproex [8]. In Kozubski and Prusinski study, the frequency of attacks and duration of each attack were decreased more than 50%, after using Sodium Valproate, which was comparable to systemic β adrenergic blocker drugs [20].

In fact, Timolol eye drop cause β adrenergic receptor blockage as well as reduction in IOP[20]. Both mechanisms can be postulated for its effects on patients with migraine headaches.

One of the most important hypotheses about pathophysiology of migraine headaches is autonomic nervous system disturbances which timolol blocks β adrenergic receptors at the level of eyes, therefore its effects on the prevention of migraine headaches may be predictable.

In our study, decreasing effect of Timolol in IOP could not be an important reason of its effects in migraine patients; because, all of them had normal IOP before study. Klein et al found no relationship between open angle glaucoma and migraine [22]; however, this issue requires further investigation.

There are also many other points toward accepting the first hypothesis. One of the main pain relieving factors in migraine patients is sleep and the sympathetic system drive decreases during sleep. Moreover, in slow wave sleep, meiosis develops simultaneous decrease in sympathetic system drive. On the other hand, relaxation techniques decrease sympathetic system drive, causing a partial relief in migraine headaches [23].

Considering our results, we suggested more study with larger sample sizes, as a double blind one, with different dosage of timolol and the other ophthalmic β adrenergic blocking drugs to see whether their effects on the prevention of migraine headaches is verified. If so, Timolol or other β blockers can be used easily as a preventive method for migraine headaches.

References

1. *Martin S. Prevalence of migraine headache in Canada. CMAJ 2001; 164(10): 1481.*
2. *Migraine Headaches. Alpha Nutrition Health Education, http://www.nutramed.com/headache/index.htm.*
3. *Bednarczyk EM, Remler B, Weikart C, Nelson AD, Reed RC. Global cerebral blood flow, blood volume, and oxygen metabolism in patients with migraine headache. Neurology 1998; 50(6):1736-40.*
4. *Shechter A, Stewart WF, Silberstein SD, Lipton RB. Migraine and autonomic nervous system function: a population-based, case-control study. Neurology. 2002; 58(3):422-7.*
5. *Migraine Headaches, Mechanisms and Food Allergy. Alpha Nutrition Health Education, http://www.nutramed.com/headache/migraine_mechanisms.htm.*
6. *Headache and other Craniofacial Pains. In: Adams RD, Victor M, eds. Principles of Neurology, 5th ed. New York, NY: Mc GRaw-Hill Inc; 2000:148-170.*
7. *Simon RP, Aminoff MJ, Greenberg DA. Clinical Neurology, 4th ed. Stamford: Appleton & Lange; 1999:77-102.*
8. *Freitag FG, Collins SD, Carlson HA, et al. A randomized trial of divalproex sodium extended-release tablets in migraine prophylaxis. Neurology. 2002; 58(11):1652-9*
9. *Keam SJ, Goa KL, Figgitt DP. Spotlight on almotriptan in migraine. CNS Drugs 2002; 16(7):501-7.*
10. *Mannix LK, Adelman JU, Goldfarb SD, et al. Almotriptan versus sumatriptan in migraine treatment: direct medical costs of managing adverse chest symptoms. Am J Manag Care 2002(3 Suppl):S94-101.*
11. *Keam SJ, Goa KL, Figgitt DP. Almotriptan: a review of its use in migraine. Drugs 2002; 62(2):387-414.*
12. *Limmroth V, Michel MC. The prevention of migraine: a critical review with special emphasis on beta-adrenoceptor blockers. Br J Clin Pharmacol 2001; 52(3):237-43.*
13. *Gleiter CH, Deckert J. Adverse CNS-effects of beta-adrenoceptor blockers. Pharmacopsychiatry 1996; 29(6):201-11.*
14. *Parsekyan D. Migraine prophylaxis in adult patients. West J Med. 2000; 173(5):341-5.*
15. *Sandor PS, Afra J, Ambrosini A, Schoenen J.Prophylactic treatment of migraine with beta-blockers and riboflavin: differential effects on the intensity dependence of auditory evoked cortical potentials. Headache 2000; 40(1):30-5.*
16. *Mauskop A. The use of botulinum toxin in the treatment of headaches. Curr Pain Headache Rep. 2002; 6(4):320-3.*
17. *Guyuron B, Tucker T, Davis J. Surgical treatment of migraine headaches. Plast Reconstr Surg. 2002; 109(7):2183-9.*
18. *Brodsky M, Kamenker E, Orlov M, et al. Cardiac effect of prolonged beta blocker therapy for migraine. JAMA 1993; 270(7):880.*
19. *Williams PL, Warwick R, Dyson M, et al. Gray's Anatomy. Norwich: Churchi; Livingstone; 1989: 1190.*
20. *Hoffman BB. Adrenoreceptor Blocking Drugs. In: Katzung BG ed. Basic and Clinical Pharmacology. 5th ed Norwalk: Appleton & Lange; 1992:124-137.*
21. *Kozubski W, Prusinski A. Sodium valproate versus propranolol in the prophylactic treatment of migraine. Neurol Neurochir Pol 1995; 29(6):937-47.*
22. *Klein BE, Klein R, Meuer SM, Goetz LA. Migraine headache and its association with open-angle glaucoma: the Beaver Dam Eye Study. Invest Ophthalmol Vis Sci 1993; 34(10):3024-7.*