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doi: 10.12788/jfp.0427

Migraine relief in 20 minutes using eyedrops?

One randomized crossover trial demonstrated the effectiveness of this simple, affordable treatment for patients with acute migraine pain.

PRACTICE CHANGER

Consider timolol maleate 0.5% eyedrops as a quick and effective abortive therapy for migraine.¹

STRENGTH OF RECOMMENDATION

B: Based on a single randomized controlled trial.¹

Kurian A, Reghunadhan I, Thilak P, et al. Short-term efficacy and safety of topical β -blockers (timolol maleate ophthalmic solution, 0.5%) in acute migraine: a randomized crossover trial. *JAMA Ophthalmol*. 2020;138:1160-1166.

ILLUSTRATIVE CASE

A 35-year-old woman with no significant past medical history presents for follow-up of migraine. At the previous visit, she was prescribed sumatriptan for abortive therapy. However, she has been having significant adverse effect intolerance from the oral formulation, and the nasal formulation is cost prohibitive. What can you recommend as an alternative abortive therapy for this patient's migraine?

Migraine is among the most common causes of disability worldwide, affecting more than 10% of the global population.² The prevalence of migraine is between 2.6% and 21.7% across multiple countries.³ On a scale of 0% to 100%, disability caused by migraine is 43.3%, comparable to the first 2 days after an acute myocardial infarction (42.2%) and severe dementia (43.8%).⁴

Abortive therapy for acute migraine includes nonsteroidal anti-inflammatory drugs (NSAIDs), triptans, ergots, and antiemetics. However, these options are predominantly administered by mouth; non-oral formulations tend to be cost prohibitive and difficult to obtain.

Nausea and vomiting, common components of migraine (that are included in *International Classification of Headache Disorders, 3rd edition* [ICHD-3] criteria for migraine⁵) present obstacles to effective oral administration if experienced by the patient. In addition, for migraine refractory to first-line treatments, abortive options—including the recently approved calcitonin gene-related peptide (CGRP) receptor antagonists ubrogepant and rimegepant—are also cost prohibitive, potentially costing more than \$1000 for 10 tablets (100 mg), depending on insurance coverage.⁶

Two oral beta-blockers, propranolol and timolol, are approved by the US Food and Drug Administration for migraine prophylaxis. Unfortunately, oral beta-blockers are ineffective for abortive treatment.⁷ Ophthalmic timolol is typically used in the treatment of glaucoma, but there have been case reports describing its benefits in acute migraine treatment.^{8,9} In addition, ophthalmic timolol is far cheaper than medications such as ubrogepant.¹⁰ A 2014 case series of 7 patients discussed ophthalmic beta-blockers as an effective and possibly cheaper option for acute migraine treatment.⁸ A randomized,

crossover, placebo-controlled pilot study of 198 migraine attacks in 10 participants using timolol eyedrops for abortive therapy found timolol was not significantly more effective than placebo.⁹ However, it was an underpowered pilot study, with a lack of masking and an imperfect placebo. The trial discussed here was a controlled, prospective study investigating topical beta-blockers for acute migraine treatment.

STUDY SUMMARY

Crossover study achieved primary endpoint in pain reduction

This randomized, single-center, double-masked, crossover trial compared timolol maleate ophthalmic solution 0.5% with placebo among 43 patients ages 12 or older presenting with a diagnosis of migraine based on ICHD-3 (beta) criteria. Patients were eligible if they had not taken any antimigraine medications for at least 1 month prior to the study and were excluded if they had taken systemic beta-blockers at baseline, or had asthma, bradyarrhythmias, or cardiac dysfunction.

Patients were randomized 1:1 to treatment with timolol maleate 0.5% eyedrops or placebo. At the earliest onset of migraine, patients used 1 drop of timolol maleate 0.5% or placebo in each eye; if they experienced no relief after 10 minutes, they used a second drop or matching placebo. Patients were instructed to score their headache pain on a 10-point scale prior to using the eyedrops and then again 20 minutes after treatment. If a patient had migraine with aura, they were asked to use the eyedrops at the onset of the aura but measure their score at headache onset. If no headaches developed within 20 minutes of the aura, the episode was not included for analysis. All patients were permitted to use their standard oral rescue medication if no relief occurred after 20 minutes of pain onset.

The groups were observed for 3 months and then followed for a 1-month washout period, during which they received no study medications. The groups were then crossed over to the other treatment and were observed for another 3 months. The primary

outcome was a reduction in pain score by 4 or more points, or to 0 on a 10-point pain scale, 20 minutes after treatment. The secondary outcome was nonuse of oral rescue medication.

Forty-three patients were included in a modified intention-to-treat analysis. The primary outcome was achieved in 233 of 284 (82%) timolol-treated migraines, compared to 38 of 271 (14%) placebo-treated migraines (percentage difference = 68 percentage points; 95% CI, 62-74 percentage points; $P < .001$). The mean pain score at the onset of migraine attacks was 6.01 for those treated with timolol and 5.93 for those treated with placebo. Patients treated with timolol had a reduction in pain of 5.98 points, compared with 0.93 points after using placebo (difference = 5.05; 95% CI, 4.19-5.91). No attacks included in the data required oral rescue medications, and there were no systemic adverse effects from the timolol eyedrops.

WHAT'S NEW

Evidence of benefit as abortive therapy for acute migraine

This randomized controlled trial (RCT) showed evidence to support timolol maleate ophthalmic solution 0.5% vs placebo for treatment of acute migraine by significantly reducing pain when taken at the onset of an acute migraine attack.

CAVEATS

Single-center trial, measuring limited response time

The generalizability of this RCT is limited because it was a single-center trial with a study population from a single region in India. It is unknown whether pain relief, adverse effects, or adherence would differ for the global population. Additionally, only migraines with headache were included in the analysis, limiting non-headache migraine subgroup-directed treatment. Also, this trial evaluated only the response to treatment at 20 minutes, and it is unknown if pain response continued for several hours. Headaches that began more than 20 minutes after the onset of aura were not evaluated.



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CHALLENGES TO IMPLEMENTATION**Timolol's systemic adverse effects require caution**

Systemic beta-blocker effects (eg, bradycardia, hypotension, drowsiness, and bronchospasm) from topical timolol have been reported. Caution should be used when prescribing timolol for patients with current cardiovascular and pulmonary conditions. **JFP**

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