

Letter to the Editor: A Randomized, Double-Blinded, Placebo-Controlled, Cross Over Study Evaluating the Efficacy and Safety of Timolol Ophthalmic Solution as an Acute Treatment of Migraine

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I am an experienced and published researcher using timolol beta-blocker ophthalmic eyedrops for the successful treatment of acute migraines.¹⁻⁵ The above referenced paper contains many errors in study design and conduct.⁶ The statistics, discussion, and conclusion are misleading.

Beta blockers are FDA approved and often effective for chronic migraine prevention by taking daily oral doses that maintain therapeutic blood levels. For acute migraine, oral beta blockers have not worked well because they take too long to achieve therapeutic blood levels.¹² There are three other ways beta blocker solutions can be used to quickly achieve therapeutic blood levels. The first is promptly and properly applied topical beta blocker eyedrops to normal eyes/eyelids/nasolacrimal ducts/nasal mucosa. Faster is sublingual beta blocker drops and the fastest is beta blocker nasal spray.¹² These last two preferred methods were not discussed in Aggarwal's paper.⁶

Ophthalmologists spend their careers listening to patients complain about the difficulties of using eye drops. Sublingual application has been studied and found effective for glaucoma control in a subgroup of drop-challenged patients.⁷ Most acute migraine patients I have treated with timolol 0.5% eye drops prefer to take them sublingual for ease of application and efficacy rather than topical to the eyes.

Absorption of beta blockers and subsequent beta receptor blockade has been studied.¹⁸ Of these three methods, nasal application has been shown to be the fastest and equivalent to intravenous beta blocker administration in a study of 80 human volunteers.⁸ Until recently, no beta blocker nasal spray was commercially available. O'Brien Pharmacy (<https://obrienrx.com/>) now prepares a compounded nasal spray of timolol with Mucolux™ delivering 0.125 mg/0.1 ml spray. The nasal spray is shaken and one spray delivered into each nostril at first onset of migraine symptoms. Patients may also take their other acute migraine medications with the beta blocker nasal spray. If migraine headache persists a second set of one spray per nostril is repeated in 10-15 minutes. A maximum of 4 sprays per 24 hours is specified. An O'Brien pharmacist contacts the patient on receiving a prescription from a licensed physician and inquires about beta blocker contra-indication and instructs on use. The cost of the medication at this writing is \$30 for a 10 ml bottle plus postage. All future research on using beta blockers for acute migraine should be done using nasal delivery. I have no financial interest in this product.

The Aggarwal study⁶ has so many other deficiencies that for reasons of space I can only list them without much discussion: patients not beta blocker naïve were included; retrospective exclusion of them taints the already scant data; the patients were not instructed to take the eye drops as quickly as possible with migraine onset; instead they had to fill out a questionnaire about the migraine; the study does not state if or when a second set of eye drops were to be instilled (ideally 10 minutes after the first if migraine persists); it is not stated whether patients were allowed to take their usual acute migraine medications which they should have been; the migraine patients were recruited from a tertiary neurological referral center with a high number of refractory migraineurs. Most important, per their own analysis, the number of patients studied does not allow any reliable statistical validity which Aggarwal nevertheless erroneously claimed. Their discussion does not include consideration of the more effective and easier to use sublingual or nasal beta blocker administration; the discussion attributes findings and conclusions to another study⁹ that are inaccurate and ignores optimistic statements of those authors about further study of beta blockers for acute migraine.¹⁰

Cossack et al.⁹ reported that 4 of their 10 studied patients found the masked beta blocker eye drop a useful addition to their acute migraine therapy versus only 1 in favor of masked placebo. They did allow a second set of eye drops but no sooner than 30 minutes because of Institutional Review Board concerns. They did discuss that if used 10-15 minutes post first insertion it might have improved their results. They did not claim statistical significance of their study but determined that "A future crossover study will require 86 patients to power a study with $\alpha \leq 0.05$ and $\beta \leq 0.2$."^{9,10} Cossack and Gratton conclude their discussion, "We believe that, together, our work advances the notion that timolol drops are a safe effective, and already widely available abortive treatment in select migraineurs."¹⁰ Neither the Cossack et al.⁹ or the Aggarwal studies were large enough for statistical significance so it is a misrepresentation for Aggarwal et al.⁶ to state "we now have two randomized-controlled trials that would not demonstrate a marked effect of the drug compared to placebo."

I hope that either the pharmaceutical industry or grant funding will soon conduct a large, adequately-powered ($N \geq 86$), placebo-controlled, cross-over study using the newly available nasal spray delivery as a novel, safe, relatively inexpensive treatment for acute migraines.

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⁹ Cossack M, Nabrinsky E, Turner H, Abraham A, Gratton S. Timolol eye-drops in the treatment of acute migraine attacks: A randomized crossover study. *JAMA Neurol* 2018; 75(8):1024-1025. PMID: 29799915.

¹⁰ Gratton S, Cossack M. Answering the call: A prospective look at the role of timolol eye drops in the treatment of acute migraine attacks. *Mo Med* 2018; 115(6):520-521. PMID: 30643343.

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