

Answering the Call: A Prospective Look at the Role of Timolol Eye Drops in the Treatment of Acute Migraine Attacks

by Sean Gratton, MD & Matthew Cossack, MD

We believe our work advances the notion that timolol eye drops are a safe, effective, and already widely available abortive treatment in select migraineurs.

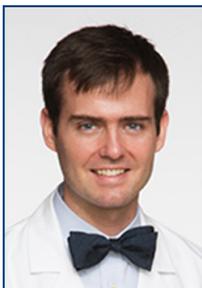
The July/August 2014 issue of *Missouri Medicine* featured several articles about the use of beta blocker eye drops to treat migraine attacks.^{1,2} These articles included a call for prospective studies to further investigate the effectiveness of these well-tolerated, affordable drugs in migraine. Answering the call put forth by John C. Hagan, III, MD and others, we performed a clinical trial, which was recently published in *JAMA Neurology* entitled “*Timolol eyedrops in the treatment of acute migraine attacks.*”³ Our research helps to support the anecdotal experiences of Doctor Hagan, Carl V. Migliazzo, MD and others published in *Missouri Medicine*, and advances the argument that timolol eye drops are beneficial to some migraine sufferers.

We completed a randomized, placebo-controlled, single-blinded crossover study, which allowed for

participants to serve as their own controls. Each subject was randomized to begin either with timolol maleate 0.5% or artificial tears drops. Subjects were seen monthly for four months, and each individual crossed over to the second drop at the two month halfway point after a three day washout period. The subjects were instructed to instill one drop into both eyes at the onset of migraine headache and thirty minutes later if needed. Subjects were asked to complete a headache evaluation sheet for each migraine attack suffered during the study period. The headache evaluation sheet tracked a number of different variables including migraine attack severity over time on a scale of zero to three. At the conclusion of the study prior to unmasking, subjects were asked to rate the effectiveness of each drop on a scale of one to four as well as which drop they preferred overall.

A total of 198 migraine attacks were studied among ten subjects. The subject-rated overall effectiveness of timolol was 2.4 compared to 1.4 with placebo. Four subjects found timolol highly effective compared to placebo while one subject found the opposite. 78% of migraines had a severity of none or mild at two hours on timolol compared to 57% with placebo. Several participants responded extremely well to the timolol, though we were unable to identify any factors that would predict responsiveness. Notably, one patient found such benefit from the artificial tear arm that she wished to replace her migraine medications with the artificial tear drops. There is a relatively high number of placebo responders in migraine patients.

Several factors were taken into consideration when determining how to best carry out this study. Patient safety was the number one priority, and for that reason



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we felt it was important not to deviate significantly from the established dosing of timolol maleate (one drop into the affected eye once a day in the morning).⁴ To deviate substantially from the recommended dosing could, at least theoretically, put patients at higher risk of adverse events than would be expected after years of timolol maleate use for glaucoma. Additionally, doing so would have been a significant hurdle during our Institutional Review Board review, and may have required an Investigational New Drug Application (IND) to the Food and Drug Administration, which would have added substantially to the administrative and financial cost of the study.⁵ It is possible that these decisions influenced the study results. For example, one might ask whether the effect of timolol would be more robust with a more aggressive dosing regimen (e.g. two drops into both eyes then repeated after ten minutes as a standard protocol). But for the reasons stated above we felt that a more aggressive dosing regimen was not appropriate.

When constructing the overall structure of the study, we used prior migraine abortive medication studies as a model. Specifically, we looked at triptan medications that do not utilize simple oral administration such as sumatriptan nasal spray and rizatriptan rapidly disintegrating tablet.^{6,7} These studies were helpful in determining how best to instruct patients to use the timolol eye drops and in determining the best, well-validated, and widely recognized outcome measures for migraine attack assessment.

We note three significant limiting factors in our study: (1) lack of investigator blinding, (2) an imperfect placebo—as artificial tears tend to cause less of a burning sensation than timolol, and (3) a small sample size. The small sample size resulted from the unfunded nature of the study and difficulty recruiting without patient reimbursement. Despite these limitations, this pilot study allowed us to quantify the effect size to allow for power calculations. A future crossover study will require 86 patients to power a study with $\alpha \leq 0.05$ and $\beta \leq 0.2$.

Timolol eye drops provide an ideal and rapid route of delivery which avoids first pass metabolism and also achieves maximum plasma concentration within 15 minutes of administration.^{2,8} This pharmacokinetic advantage may not be ideal for chronic problems like glaucoma but is well-suited for the abortive treatment of migraines.⁹ A reviewer from *JAMA Neurology* was

initially concerned that the dose of timolol could alter systemic beta adrenergic receptor regulation. Timolol 0.5% is 5mg/ml and a maximum of 200 μ l or 0.2 ml are absorbed with two bilateral sets of 50 μ l drops. That comes to a total of 1mg of timolol, in contrast to the dose for oral timolol, which is 10-30mg daily. We therefore do not believe the 0.4 to 1 mg of timolol given on a prior day influenced later migraines. Furthermore, the half-life of timolol ophthalmic is 4 hours. Thus 6 half-lives pass from day to day. We do not anticipate the small dose of 0.4 to 1 mg given inconsistently as an abortive treatment would have clinical significant effects on beta blocker receptor regulation.

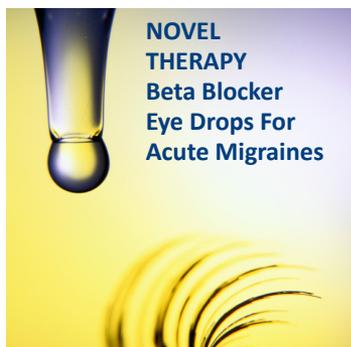
Consistent with the relatively small systemic dose, there were no adverse systemic symptoms including hypotension or bradycardia reported in our study. One patient suffered a branch retinal artery occlusion while on placebo, which was thought to be unrelated to the study.

We are pleased to have published this work, and owe a debt of gratitude to Doctors Hagan and Migliazzo, and *Missouri Medicine*. We believe that, together, our work advances the notion that timolol eye drops are a safe, effective, and already widely available abortive treatment in select migraineurs.

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Topical Beta Blockers for the Treatment of Acute Migraines in 2019

by Carl V. Migliazzo, MD & John C. Hagan III, MD

The use of beta blocker solutions for treatment of acute migraine has waited over 38 years for a large placebo-controlled study. We are making the same request of industry and academia today.

Migraine is the most prevalent neurological disease in the world. Migraine affects approximately 30 million Americans and is the leading medical cause of missed work and high among reasons listed for absent school days. The individual and national economic burden of migraine is enormous and patient suffering and disability incalculable. The advances in migraine therapy for this debilitating disease have been improving notably with triptans and the recently approved novel class of calcitonin gene related peptide (CGRP) inhibitors. The triptans may have serious side effects and must be used cautiously. CGRP inhibitors are expensive and may not be affordable to a large number of patients. Most migraineurs have some degree of dissatisfaction with their current therapy and would welcome new medications that are more effective, faster acting, safer, less expensive, and work synergistically with

existing therapy. Beta blocker eye drops offer unique potential benefits when repurposed for migraines.

We reported in *Missouri Medicine* in 2014,¹ a case report series of seven patients that had successfully used topical beta-blocker eye drops over multi-year intervals for relief of their acute migraines. These eye drops were often taken with their preferred oral analgesic. At the time, this was the largest case report series in the world's literature. We also referenced five smaller reports dating to 1980 of beta blocker eye drops used to successfully treat migraine.^{2,3,4,5,6} Two additional studies effectively treating migraines with beta blocker eye drops have been identified.^{7,8} We, as well as all the authors of previously published papers, have recommended large, placebo-controlled studies. In the 38 years since this clarion call was made no such study has been performed.

Sean Gratton, MD, Mathew Cossack MD and others of the departments of ophthalmology and neurology at the University of Missouri-Kansas School of Medicine (UMKC) have recently reported⁹ the world's first small, placebo-controlled, cross-over study of beta blocker eye drops for acute migraine. We commend them highly for their important work.

The UMKC study provided some useful data. (See page 506). Their study suffered from a lack of enrollment (only 10 patients out of a planned 26) which may have masked a true treatment effect. Seventy-eight percent of migraines had a severity of none or mild at two hours on timolol compared to 57% with placebo. The subject-rated overall effectiveness of timolol was 2.4 out of a maximum of 4 compared to 1.4 with placebo. Notably 4 of 10



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- **Migraine is a disabling, inherited neurological disease**
- **Migraine is the leading cause of disability among neurological disorders**
- **Migraine is ranked 7th highest cause of disability globally by the World Health Organization**

patients found beta blockers very effective while only 1 of placebo patients did. We consider these trends to be very encouraging.

What factors could have changed the significance of this study? Obviously, a larger enrollment would increase the power of the study. The authors have helpfully calculated that a future crossover study would require 86 patients to achieve significance at the .05% level. With only 10 patients, the UMKC study was not able to prove statistical significance. The difficulty of recruiting suitable patients indicates obtaining 86-100 appropriate subjects may require a cooperative multi-center testing protocol. The subjects would ideally have mild/moderate acute migraines without concurrent systemic or topical beta blocker therapy.

Another variable that we consider critical is the timing of the eye drop dosing. It is vital to instill the drops, one in each eye, at the first sign of an aura or migraine, and a second set within 10-15 minutes if patients do not experience major or complete relief. The UMKC protocol called for a second set no earlier than thirty minutes after the first set. After thirty minutes a migraine is usually well established and more difficult to control. The UMKC study decision to delay a second set of drops may have been necessary to secure approval from an Institutional Review Board. We have many anecdotal reports of success using beta blocker eye drops for acute migraine. We always suggest a second set of drops no later than 15 minutes after the first drops if still symptomatic. Patients report this as an important part of therapy.

Our clinical experience argues that obtaining rapid blood levels of the beta blocker is the primary factor in treatment success. It accounts for why oral beta blockers have been shown to be ineffective for acute migraines.^{10,11} The oral route takes too long to obtain therapeutic blood levels and never catch up with the migraine pain/inflammatory cascade/cortical spreading depression. Often, patients will spontaneously comment that they didn't get their drops in soon enough after the onset of symptoms and their migraine progressed. Or, they missed their eyes with the drops and waited too long before instilling a second set. Instilling eye drops in pain, with or without a visual scotoma, can indeed be challenging, especially in patients who have not used eye drops routinely. The success of systemic beta blockers for migraine prophylaxis is explained by daily oral beta blockers achieving a constant therapeutic blood level. Instilling a second set of drops in 10-15 minutes would, we believe, have improved the UMKC final results.

Is there any increased risk from instilling more than one set of timolol eye drops within 10-15 minutes? We would argue there is not, assuming the usual and well-known contraindications of beta blocker usage are applied to patient selection. Timolol 0.5% solution contains 5.0 mg of timolol per ml. There are typically 20 eye drops in one ml of solution. One drop contains 0.25 mg of timolol (5 mg/20 drops). After a second set of drops into both eyes (4 drops total), even assuming all of the medication was absorbed systemically and none spilled onto the lids, or absorbed into the eye, a total of one milligram was dosed into the systemic circulation. A typical intravenous injection of

timolol for an acute cardiac event is in the range of one to four mg, well above the amount applied topically to the eye with two sets (4 drops total) of instillations. If an intravenous injection of these therapeutic doses of timolol is safe and approved for other indications, we believe that there little or no added risk from drops that contain a lower total dosage. Our clinical experience bears this out. We have not had any patient/physicians who have reported suffering an adverse event from a second set of drops instilled 10-15 minutes after the first set. We encourage rapid blinking after instillation to aspirate the beta blocker solution into the lacrimal duct for ultimate systemic absorption by the nasal-pharyngeal mucosa. With normal eyes, eyelids and patent nasal-lacrimal ducts, one drop of timolol 0.5% solution achieves 80% beta 1 and 2 receptor blockage in 10 minutes.¹² A second set should fully achieve almost complete beta receptor blockade. Note for migraine therapy the timolol solution must be used not the gel-forming version.

Eye drops are difficult for most people to instill and impossible for some. We feel eye drop instillation is not the most effective way to achieve rapid blood levels for migraine treatment. Sub-lingual or intra-nasal beta blocker administration is easier for virtually everyone and provides better, more predictable systemic absorption.¹³ These dosing regimens are not FDA approved for timolol ophthalmic solution and would require new approval processes and possibly different chemical formulations. The FDA has issued guidelines to try and expedite new therapy for acute migraine¹⁴ and the NIH has called for development of novel migraine therapy^{15, 16} and is offering multiyear funding.

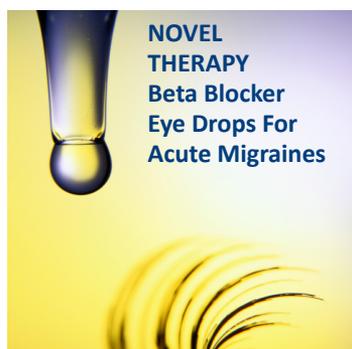
Given the cost of developing a new drug from the test-tube through FDA approval and marketing is estimated to be eight hundred million to one billion dollars, the cost of repurposing beta blockers by novel delivery for acute migraine would seem attractive to the pharmaceutical industry both because of the much lower costs of development and the greatly truncated testing and approval process. We hope the UMKC study will encourage industry

to pursue this pathway. Alternatively, a consortium of research neurology departments might submit a NIH/Department of Defense grant request for a large placebo-controlled study.

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Beta Blocker Eye Drops Have Dramatically Helped My Severe Migraines

by Carolyn Csongradi, MS

I've had migraine with auras since I was 20, which is now more than 50 years ago. I rarely have a headache without some form of aura – visual blurring, vertigo, facial numbness, language problems and confusion. The auras typically are the worst part of the migraine experience. I have a strong family history of migraine including hemiplegia – father, aunt, uncle, grandfather and includes both of my children – one of whom died in her teens during a seizure following a severe migraine episode.

Weather changes – usually cloudy, rainy days followed by bright sunshine are significant migraine triggers as are my failures to follow sensible sleep, exercise, and eating schedules. Over the past 30 years, I have tried a plethora of drugs, many of which have unacceptable side effects: atenolol, propranolol, nortriptyline, amitriptyline, indomethacin, valdecoxib, celecoxib, topiramate, prednisone, eletriptan HBF(sublingual). I have not used Botox or the newest injectables.

With advancing age and now mild persistent asthma, I no longer have access to Imitrex-type drugs or oral beta blockers, which do give me bronchospasm. This leaves me fewer options to deal not only with prophylactic migraine treatment but the frequent 'break through' headaches. Whoever said that one outgrows migraines forgot to ask me!

Currently, I take 75 mg of topiramate twice a day. As part of my allergic asthma treatment I also require daily Spiriva Respimat (2,5 mcg total) and

inhaled corticosteroids. About 6 months ago while researching the internet, I discovered an article by doctors Migliazzo and Hagan suggesting the off-label use of timolol eye drops for the treatment of migraine. Voile!

Although not recommended for those who have bronchial asthma, my ophthalmologist agreed to let me try up to 2 drops in each eye of 0.25% Timolol eye drops for acute headaches. Since that time, I have successfully aborted many headaches using one or two drops of timolol 0.25% eye drops in only one eye at the first sign of discomfort without side effects. I put the drop(s) in the eye on the side where the aura or headache is occurring, keeping my eye open and blinking rapidly. The migraine symptoms resolve in less than 30 minutes. My life continues uninterrupted, including riding my horse Jules. (see photo) What a gift!

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