

Nasally Delivered 0.5% Timolol Beta Blocker Successfully Treats Acute Migraines in a Referral Headache Clinic: A Case Series

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Ten of 16 patients (62.5%) with refractory acute migraines responded favorably to novel, nasal delivery of 0.5% timolol, and successfully continue its use. Larger, placebo-controlled, multi-center studies should be done expeditiously.



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Abstract

This is the first reported case series of nasally delivered beta blocker (timolol 0.5%) for the treatment of acute migraine.

In a retrospective chart review, 16 patients were found who had received intranasal timolol for sub-optimally treated acute migraines. Of these, 10 (62.5%) reported to their provider that the medication was helpful. Encouragingly, the treatment was beneficial even for patients previously refractory to other medications. Intranasal timolol was well tolerated, with only one patient reporting mild nasal congestion and no other side effects reported. These findings suggest the need for a prospective pilot study followed by a larger double-blind randomized placebo-controlled trial to determine the overall efficacy and safety of nasally delivered beta blockers for acute migraine treatment.

Introduction

Oral beta blockers, taken daily, have been proven useful in migraine prevention; propranolol

and timolol are FDA approved for this indication.¹ Episodic oral beta blocker treatment of acute migraine has not been successful. It is hypothesized that the difference in responsiveness is the prolonged time to achieve therapeutic beta blocker blood levels by oral administration at first onset of acute migraine.²

In 2014, Migliazzo and Hagan³ reported the first case series of successful treatment of acute migraine using topical 0.5% timolol eye drops. Findings were validated in subsequent placebo-controlled studies.^{4,5} A single study purported to show that topical timolol eye drops were not effective for acute migraine treatment.⁶ This study was later challenged as having flaws in trial design and implementation.⁷

Therapeutic application of timolol eye drops for acute migraine requires a dexterous patient with functional eyelids and patent lacrimal duct drainage onto normal nasal mucosa. Additionally, the patient must first be examined by an ophthalmologist and found to have no ocular contraindication.³

Nasal spray delivery of beta blockers has been postulated to be easier, more effective and more suitable for migraine patients than topical drops to the eye.⁸

This retrospective chart review outlines the clinical experience with the use of nasally delivered 0.5% timolol solution in 16 patients. A single representative case report is presented.

Case Report

A 39-year-old female initially presented to the author's (SCK) headache clinic after a fall causing head injury that substantially worsened her baseline migraines. She presented with status migrainosus which was successfully treated with occipital and trigeminal branch nerve blocks and changes to her preventive medication regimen. She was a poor responder to triptan medication and was overusing over-the-counter (OTC) analgesic medications. Due to poor insurance coverage and excessive patient co-pay, she had difficulty getting access to newer CGRP blocking medications.

Timolol 0.5% nasal spray was prescribed for acute migraine treatment. She reported this to be quite helpful in aborting migraine attacks that broke through her preventive medications. Over time, she has used nasal timolol spray for multiple migraines with recurring success. She continues to use timolol nasal spray as a first line acute treatment option. She has reported no side effects. The preventive medication adjustments, along with this novel acute treatment option, led to cessation of her overuse of OTC analgesics. She reports a notable improvement in her personal and professional life.



Figure 1. Sample nasal timolol 0.5% prescription (figure used with permission from Tyler Chamberlain, PharmD).

Methods

The referral headache neurology practice of one of the authors (SCK) has previously worked with a compounding pharmacy to be able to prescribe nasal timolol to patients not satisfied with their current acute treatment regimen. The compounding pharmacy, O'Brien Pharmacy, produces a solution of 0.5% timolol combined with Mucolox™ to enhance nasal absorption which is given in a nasal aerosol delivery device (Figure 1). Each metered 0.1 ml spray delivers 0.5 mgs timolol to the nasal mucosa. When prescribed, patients are advised to use one spray in each nostril as quickly as possible at the onset of an acute migraine. If necessary, they are told they can use a second set of nasal sprays 15 minutes later. No more than four sprays are allowed

within a 24-hour period. Because this treatment is novel and they report dissatisfaction with their previous abortive options, patients have been asked to use timolol solely as their rescue medication. Also because of the novelty of treatment, patients have been routinely

asked in their follow-up clinical visits whether they felt the treatment was effective and whether they had any side effects. Patients are not offered timolol nasal spray if they are already on a beta blocker or if they had contraindications to the medication.

The charts of all patients who received nasal timolol from May 2022 to August 2023 were reviewed. Based on their headache history, the first author (SCK) assigned patients an “intractability score” (Figure 2) to delineate how refractory their migraine headaches were to previous treatments. This score ranged from one to five with five being the most refractory migraines.

Figure 2. Migraine Intractability Score

1. Episode migraine, prescription treatment naive.
2. Episodic migraine, not on preventive therapy, tried and failed one triptan for acute treatment .
3. Episodic or chronic migraine, on first or second preventive medication, tried and failed two triptans for acute treatment.
4. Chronic migraine, failed 2 or more preventive medications and multiple acute medications (triptans, CGRP antagonists, NSAIDs).
5. Chronic refractory migraine, poorly responsive to most preventive and acute medications.

Table 1. Abbreviations: CM-chronic migraine; EM-episodic migraine; w/-with; w/o-without; F-female; M-male

Positive response to timolol			No response to timolol		
Sex, age	Diagnosis	Intractability Score	Sex, age	Diagnosis	Intractability Score
F, 39	CM w/o aura	4	F, 38	CM w/o aura	3
M, 53	CM w/aura	5	M, 66	CM w/o aura	5
F, 51	CM w/o aura	3	M, 67	CM w/o aura	3
M, 45	EM w/ aura	2	F, 42	CM w/aura	4
F, 65	CM w/o aura	5	F, 43	CM w/aura	5
F, 39	CM w/aura	4	F, 54	CM w/o aura	3
F, 26	CM w/o aura	3			
F, 42	CM w/o aura	4			
F, 32	CM w/o aura	4			
M, 54	CM w/ aura	5			

The score factored in the number of migraine days per month (episodic – less than 15 headache days per month or chronic – greater than 15 headache days per month) and medication response history (acute and preventative therapies).

Results

Thirty acute migraine prescriptions for nasal spray timolol 0.5% were generated from May 2022 to August 2023. Of these, 16 patients ultimately filled the prescription. Reasons for not filling the prescription included: lack of insurance coverage for compounded prescriptions, lack of familiarity with compounding pharmacies, or intolerance of nasal spray medications. Out of pocket-cost was an uncommon reason for not filling. Notably, the pharmacy price for a single, 15 ml compounded 0.5% timolol nasal spray is \$77.45 and \$112.03 for 30 ml (January 2024).

Of the 16 patients that filled and tried the prescription, 10 reported a favorable response (62.5%) and added the new therapy as an ongoing supplementary acute migraine treatment option. Six patients (37.5%) reported they did not perceive any favorable response (Table 1). Only one patient reported side effects of the medication, and this was mild nasal congestion. Notably, this patient also reported a positive response and chose to continue the medication. In the patients who responded favorably,

the intractability score ranged from 2 to 5 with an average of 3.4. The score in those who did not respond ranged from 3 to 5 with an average of 3.8.

Discussion

Oral beta blockers are an established preventative therapy for migraine, but these require daily dosing to achieve and maintain therapeutic blood levels. Previous studies examining oral beta blockade as an acute treatment for migraine were unsuccessful,⁹ likely because the extensive first pass metabolism prevented rapid achievement of the therapeutic level. Beta blockers, in solution form,

applied to normal nasal mucosa achieve blood levels comparable to intravenous injection.¹⁰ The previously reported effectiveness of timolol applied topically to the eye for abortive migraine treatment has been proposed to be due to drainage of the beta blocker through the lacrimal system onto the nasal mucosa.³

In this small retrospective series, 10/16 (62.5%) of patients reported improvement in migraine after trying timolol 0.5% by nasal spray at the onset of their migraine. It is not clear how many times each patient tried the medication or how much improvement was achieved, but these 10 patients did choose to continue with the medication long term. Encouragingly, this series included patients that were previously refractory to other treatments. The nasal application of timolol was well tolerated, and negated contraindications for topical eye medication, such as eyelid ectropion or lacrimal system dysfunction. While this series demonstrates the promise of another option for abortive migraine treatment, additional larger randomized placebo-controlled trials are required.

Conclusion

Despite the growing number of treatment options, there continue to be migraine patients with no response to the current available medications. As science continues to explore new drug targets through translational research, it is also reasonable to



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revisit older generation medications while exploring novel delivery systems. In the period since the 2014 Migliazzo-Hagan case series,³ there has been growing interest in the therapeutic promise of rapidly absorbed beta blockers.^{11,12,13,14,15,16,17,18,19} This study adds to the growing body of literature supporting topical timolol as an option for acute migraine treatment.

Note

The compounded, prescription only, nasal timolol spray is available from O'Brien's Pharmacy, 913-322-0001, 800-627-4360, 913-322-0002 (fax), mail@obrienrx.com; website: <https://obrienrx.com/>

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