CASE REPORT

Long-Term Use of Topical Carbonic Anhydrase Inhibitor Combined with an Initiation of the Two Different Eyedrops for Persistent Macular Hole Following Vitrectomy Combined with Internal Limiting Membrane Peeling: A Case Report

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The authors present a long-term course of a woman in her late 50s with persistent full-thickness macular hole (FTMH) after vitrectomy combined with internal limiting membrane peeling subsequently achieved MH closure after receiving topical therapy. Specifically, successful MH closure was observed at eight weeks following an initiation of topical nepafenac, prednisolone acetate, and carbonic anhydrase inhibitor (CAI). Thereafter, the patient was maintained on topical CAI only and achieved 20/32 vision OS with nearly complete restoration of ellipsoidal layers at 18 months postoperative. To conclude, topical therapy may be considered as a non-invasive approach for persistent, cystic, small-apertured MH after vitrectomy procedures. Continuous uses of topical CAI may be of value for sustaining the long-term results.

Keywords: Macular hole; Internal limiting membrane; Cystoid macular edema; Topical carbonic anhydrase inhibitor; Topical NSAID

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Chronic large full-thickness macular hole (FTMH) could potentially remain open following vitrectomy. Secondary procedures involving manipulations of tissue grafts have been proposed to promote glial cells proliferation and photoreceptor migration[1]. Meanwhile, non-surgical management using eyedrops has been implemented to facilitate the closure of secondary small-diameter FTMH by reinforcing cystic resolution combined with fluid resorption[2].

Here, the authors reported a patient with a closure of post-vitrectomy persistent macular hole (MH) following administration of topical therapy. Interestingly, this is the first report with a long-term sequence of the continuing use of topical carbonic anhydrase inhibitor (CAI).

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Case Report

A 57-year-old woman presented with decreased vision in the left eye (OS) with the baseline best-corrected visual acuity (BCVA) of 20/200 OS. The optical coherence tomography (OCT) revealed stage-4 FTMH OS with a minimum MH diameter of 961 μm (Figure 1A). She had been taking topical bimatoprost/timolol once daily in both eyes (OU) and topical 1% brinzolamide/0.2% brimonidine twice daily OU for primary open-angle glaucoma for several years. She was scheduled for vitrectomy combined with cataract surgery, an internal limiting membrane (ILM) flap, and 14% perfluoropropane gas tamponade in February 2020.

Intraoperatively, the inversion technique was unsuccessful because the ILM flap was inadvertently stripped off from the fovea. One month postoperative, the MH appeared persistent with the smaller minimum diameter of 141 μm (BCVA 20/200) (Figure 1B). After thoroughly discussing all treatment options, the patient decided to opt for topical eyedrops, including 0.1% nepafenac and 1% prednisolone acetate three times daily. Topical bimatoprost/timolol was discontinued to avoid macular edema associated with prostaglandin eyedrops. Topical brinzolamide/brimonidine was switched to topical dorzolamide/timolol (Cosopt; Merck & Co, Inc., NJ) twice daily OS. MH became closed with intraretinal

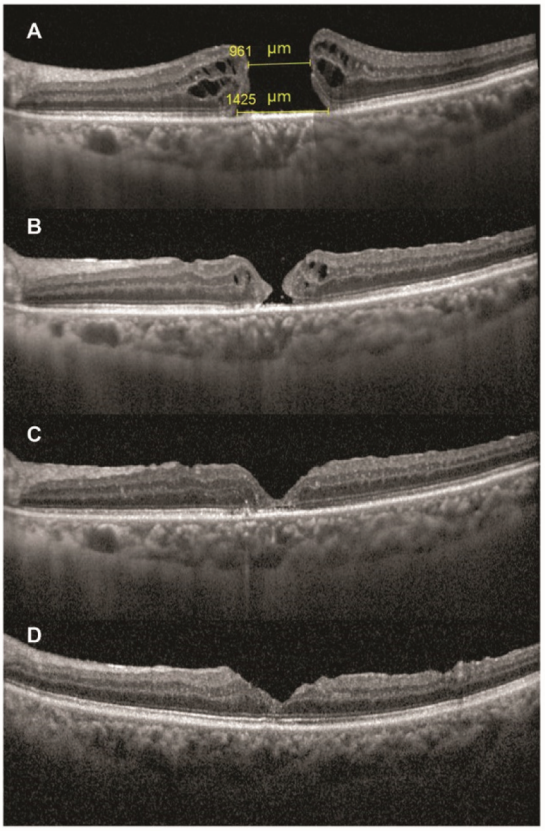

Figure 1. Preoperative optical coherence tomography image showed large macular hole (MH) without attached posterior hyaloid or significantly tractional membranes (A). Persistent MH at 1-month post-vitrectomy (B) subsequently accomplished closure coinciding with cystic resolution after receiving topical therapy (C). The outer retinal layers were reestablished, 18-month postoperative (D).

cysts resolution eight weeks after the initiation of the eyedrop regimen (BCVA 20/160) (Figure 1C). The steroid eyedrop was immediately withdrawn, whereas topical nepafenac was maintained until five months post-vitrectomy.

Eighteen months postoperative, the OCT demonstrated the restoration of ellipsoidal layers without epiretinal proliferation (BCVA 20/32) (Figure 1D), or recurrence of epiretinal membrane (Figure 2A). The absence of macular ILM was confirmed by arcuate patterns of dissociated optic nerve fiber layers (Figure 2B, C). At the final follow-up visit, which was 31 months postoperative, OU showed a mild form of punctate epithelial erosions, and the MH remained closed with 20/32 vision (Figure 2D). The patient reported good adherence to glaucoma medications as previous dosage throughout the follow-up. Informed consent for publication was obtained from the patient.

Discussion

The presented patient with persistent macular holes could achieve satisfactory long-term outcomes by using topical therapy alone. Regarding rationale behind the eyedrop regimen, a combination of topical non-steroidal anti-inflammatory drugs (NSAIDs) and steroids was evidenced to be efficient for resolving pseudophakic cystoid macular edema (CME)[3]. Topical CAI promotes retinal fluid absorption across the retinal pigment epithelium (RPE) into the choroid by acidifying subretinal space and increasing chloride ion transposition[4]. What distinguishes this patient from the previous case series is a long-term topical dorzolamide use, which was a part of her glaucoma treatment. Such topical maintenance therapy could be associated with the absence of both MH reopening and foveal reparative processes such as, a lamellar hole formation with epiretinal proliferation, throughout the postoperative period. Correspondingly, the previous study demonstrated a trend towards better prevention of MH reopening with maintenance topical therapy[5]. Although there is no definite agreement on the time of treatment discontinuation, the authors propose that re-bridging of the subfoveal external limiting membrane (Figure 1D) should represent an early sign of foveal structure integrity and the optimal cut-off for stopping the treatment[6].

Since the combined phacovitrectomy may have contributed to postoperative CME, ones may argue that such failed-to-close MH could have been avoided if the patient underwent cataract surgery as a staged procedure. However, a recent meta-analysis showed that the combined surgery demonstrated a significant reduction in rates of MH non-closure or reopening (relative risk of 0.18) compared to those receiving sequentially performed operations[7].

Previous study observed that chronic CME resolutions coincided with secondary MH closures that occurred after using topical therapy for treating their original causes[2]. Among the reported cases, an absence of vitreomacular traction was identified as the common feature in eyes achieving favorable outcomes. This concept has led to the idea of pharmacologic treatment aiming at intraretinal fluid alleviation and thereafter should promote the apposition of small primary FTMH with cystic hydration. Consistently, large cystic areas relative to base MH diameter of greater than 32% were significant OCT biomarker for high postoperative

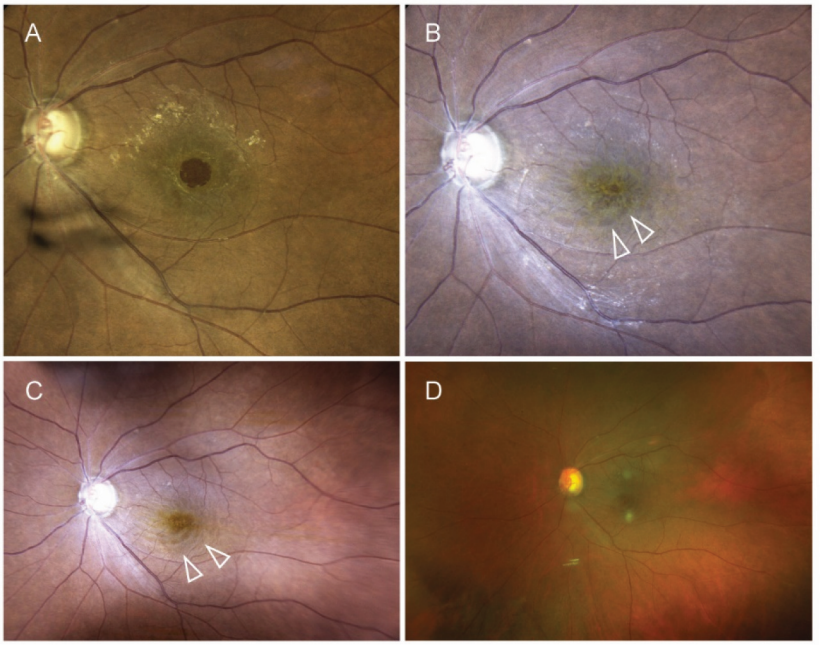

Figure 2. A sequence of color fundus photography corresponding to Figure 1. Preoperative color fundus photography showed a large macular hole (MH) surrounded by epiretinal membrane (A). One month postoperative, the MH persisted with the smaller diameter (B) and subsequently closed with an absence of internal limiting membrane causing the arcuate patterns of dissociated optic nerve fiber layers (arrows) (C) after receiving topical therapy for eight weeks. 31 months postoperative, MH remained closed with 20/32 vision (D).

MH closure rate[8]. Referring to our patient, although the cystic components in our patient may not appear prominent, the minimal diameter of 141 μm was larger than mean values of the previously reported patients who achieved closure by topical eyedrops, which was 80 to 86 μm[2,5].

Previous research has shown that MH can spontaneously close, either with or without surgical intervention. Hence, it is noteworthy that MH closure in the present patient may have closed spontaneously, even without the use of topical eyedrops. An interventional comparative study or matched case-control study is required to establish a definitive effect of their temporal association. Theoretically, spontaneous MH closure in non-surgical cases is primarily based on a bridging mechanism of the ILM, which furthers facilitates the coalescence of the Müller cells and astrocytes[9]. Regarding the present patient, although an absence of the ILM confirmed by dissociated retinal nerve fiber layers (Figure 2B, C) may partly enable the hole closure by the reduced horizontal traction, the likelihood of spontaneous MH closure was relatively low given the absence of lamellar hole-associated epiretinal proliferation (Figure 1C, D) that typically expands in more prominent configuration, Therefore, MH closure could be a result of collapsed intraretinal fluid after receiving the eyedrops.

Treatment options for failed-to-close FTMH following ILM removal include fluid-gas exchange, extended ILM peeling, macular hydro-dissection, or MH patch using a tissue graft[1,10]. Compared to other modalities, a combination of topical eyedrops is a less-invasive approach that can be considered an alternative option for persistent small cystic MH during the early postoperative period, where persuading patients to undergo secondary interventions might not be straightforwardly accepted. Of all the eyedrops in "cocktail" therapy, topical CAI appears to be safe and well tolerated, with less side effects over a long-term period.

In summary, pharmacologic treatment may achieve closure of post-vitrectomy FTMH possessing cystoid hydration and non-existent residual traction. A long-term usage of topical CAI was well tolerated and may be essential for reaching satisfactory outcomes in this patient.

What is already known on this topic?

Persistency of chronic macular hole after vitrectomy frequently required complex surgical interventions to achieve the hole closure.

What does this study add?

Topical therapy can be considered an alternative, non-invasive approach for persistent, small-apertured, cystic macular holes after standard vitrectomy. Continuous treatment with topical CAIs may be essential to prevent reopening and accomplish satisfactory long-term outcomes.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. The patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that her name and initial will not be published and that efforts will be made to conceal identity. Any potentially identifiable patient information was removed from the present report. The Institutional Review Board of the Faculty of Medicine Vajira Hospital has exempted the following study in compliance with the international guidelines for human research protection as Declaration of Helsinki, The Belmont Report, CIOMS Guideline, International Conference on Harmonization in Good Clinical Practice (ICH-GCP) and 45CFR 46.101(b).

Conflicts of interest

No financial disclosures or conflicting relationship exists for any authors. Topical eyedrops have not been approved by the Food and Drug Administration (FDA) for macular hole treatment.

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