FULL-THICKNESS MACULAR HOLE CLOSURE WITH TOPICAL MEDICAL THERAPY

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Purpose: To examine the efficacy and clinical characteristics of successful full-thickness macular hole closure with topical therapy.

Methods: Retrospective case series of full-thickness macular holes managed by a single retinal physician (DS) diagnosed and treated from 2017 to 22.

Results: Of 168 patients with full-thickness macular holes, 71 patients were started on steroid, carbonic anhydrase inhibitor, and nonsteroidal antiinflammatory (NSAID) drops. 49 patients (mean 67 years, 59% women) were included in the analysis, and 22 patients were excluded for poor follow-up. In total, 7/49 were secondary post-PPV holes and 42/49 were idiopathic. In addition, 18/49 eyes (36.7%) achieved closure on topical therapy, of which 13 were idiopathic. Hole size was directly correlated with odds of closure: for every 10 μm decrease in size and odds of closure increased by 1.2× (P = 0.001, CI 1.1–1.4). Average time to closure was 107.2 days (range 20–512 days) and was not correlated with hole size (P = 0.217, CI −0.478 to +1.938). The presence of VMT was found to be inversely related to successful closure (OR 6.1, P = 0.029, CI 1.2–31.3). There was no significant difference in final best-corrected visual acuity for eyes undergoing primary pars plana vitrectomy versus those trialing drops before undergoing pars plana vitrectomy (P = 0.318, CI −0.094 to +0.112).

Conclusion: In the first study to date to report the overall efficacy and clinical characteristics of successful macular hole closure with topical therapy, drops achieved an overall closure rate of 36.7%, with higher efficacy in smaller holes and those without VMT. Rates of MH narrowing and reduction in central foveal thickness acted as predictors of effectiveness of drop therapy.

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Full-thickness macular holes (FTMHs) are anatomic breaks in the neurosensory retina occurring at the fovea, resulting in progressive central vision loss and distortion. They can develop after ocular trauma or surgery, but most are idiopathic.[1] The pathophysiology of FTMHs is still under further investigation, but the combined tractional–hydration theory has been proposed, which propose that both the hydration of retinal tissue and the tractional forces from the vitreous and internal limiting membrane play important roles in macular hole formation and its subsequent repair. In fact, the theory consists of three sequential phases: an initiating anteroposterior and tangential traction phase, the progression or hydration phase, and the closure or dehydration and external limiting membrane repair phase.[2,3]

Full-thickness macular holes are traditionally managed surgically with a pars plana vitrectomy (PPV) with or without internal limiting membrane peeling and gas tamponade. Though efficacious, PPVs are costly and invasive and can be associated with postoperative complications and significant morbidity, such as the risk for intraocular infection, the need for subsequent cataract surgery, risk for retinal detachment, visual field loss, and the challenges of face-down positioning.[1,4] In recent years, several small reports have described successful closure of macular holes using topical therapy, including steroids, carbonic anhydrase inhibitors (CAIs), beta blockers, and nonsteroidal antiinflammatory drops.[5–9] These topical therapies are relatively noninvasive and may pose fewer ocular complications compared with traditional PPV. The proposed mechanism behind these drops is aimed at combatting the underlying pathophysiology of FTMHs as proposed by the combined tractional–

hydration theory – namely, through cystoid dehydration through the retinal pigment epithelium, allowing the ELM to reestablish and the hole edges to reappose.[2,3] The antiinflammatory and dehydrating effects of these drops have been found to be efficacious in treating other conditions of retinal edema, such as Irvine–Gass syndrome and retinitis pigmentosa.[10–14] Therefore, the authors postulate that similarly these medications may tilt the scale in favor of macular dehydration in FTMHs, allowing for fluid resorption and hole closure.

Despite these individual case reports and small case series exploring the use of topical drops for macular holes, no studies have reported the overall efficacy and safety profile of using medical therapy for FTMHs. Furthermore, the associated characteristics associated with successful macular hole closure to either medical or surgical treatment have remained unexplored. As a result, the authors conducted this study to examine the overall efficacy, safety, and imaging characteristics associated with the treatment of macular holes with medical and surgical modalities.

Methods

This single-site retrospective case series of FTMHs treated between 2017 and 2022 by a single surgeon (DS) was approved by the University of Chicago Institutional Review Board. The study was conducted in accordance with the provisions of the Declaration of Helsinki and was performed in compliance with the Health Insurance Portability and Accountability Act.

Inclusion criteria were patients with FTMH, confirmed by optical coherence tomography (OCT, Zeiss Cirrus HD-OCT 5000 or Heidelberg SPECTRALIS optical coherence tomography), who either (1) attempted topical medical therapy and had a minimum of two follow-up appointments or (2) who did not qualify for a trial of topical medical therapy and therefore underwent a PPV with at least two follow-up appointments. The same optical coherence tomography machine was used for each patient at each subsequent follow-up. Topical therapy consisted of the following: (1) topical steroids, comprising prednisolone acetate 1% every 6 hours or difluprednate 0.05% every 6 to 12 hours; (2) nonsteroidal antiinflammatory drugs (NSAIDs), comprising ketorolac–tromethamine 0.5% or bromfenac 0.07% every 6 to 8 hours; and (3) CAIs, comprising brinzolamide 1% or dorzolamide 2% every 8 to 12 hours. The patient's age, sex, race, visual acuity and intraocular pressure at each visit, lens status, refractive error, ocular history, ocular imaging findings (optical coherence tomography) at every visit, and treatment regimen and modalities were collected. Patients with insufficient data were excluded.

Statistical Analysis

Simple descriptive statistics were used to describe the demographic data of the sample. Logistic and linear regression models were used to evaluate factors associated with hole closure and final logMAR visual acuity, respectively. Differences were considered statistically significant at a P value of < 0.05.

Results

A total of 168 consecutive patients were diagnosed with FTMHs during the study period. Of them, 71 patients underwent a trial of combination topical therapy consisting of steroid, carbonic anhydrase inhibitor, and NSAID drops. In this subset, 49 patients (mean age 67 years, 59% women) were included in the analysis, and 22 were excluded because of poor follow-up (Figure 1 and Table 1). Baseline characteristics and hole size were balanced and comparable between those included and excluded in this series. A minority of cases (7/49, 14%) were secondary post-PPV holes, while the rest (42/49, 86%) were idiopathic. Among these 49 eyes, 18 (36.7%) achieved closure on topical therapy, 13 (72%) of which were idiopathic. The mean FTMH size of the eyes that attempted drops was 289 um ± 231 um (range 60–1079 um). All eyes had macular cystoid hydration at presentation, 20/49 eyes (41%) had epiretinal membranes (ERMs), and 15/49 eyes (31%) exhibited vitreomacular traction (VMT). Lens status, systemic diabetes mellitus, and the presence of any form of intraocular inflammation were not found to be statistically associated with closure. Patients were followed for an average of 51 weeks.

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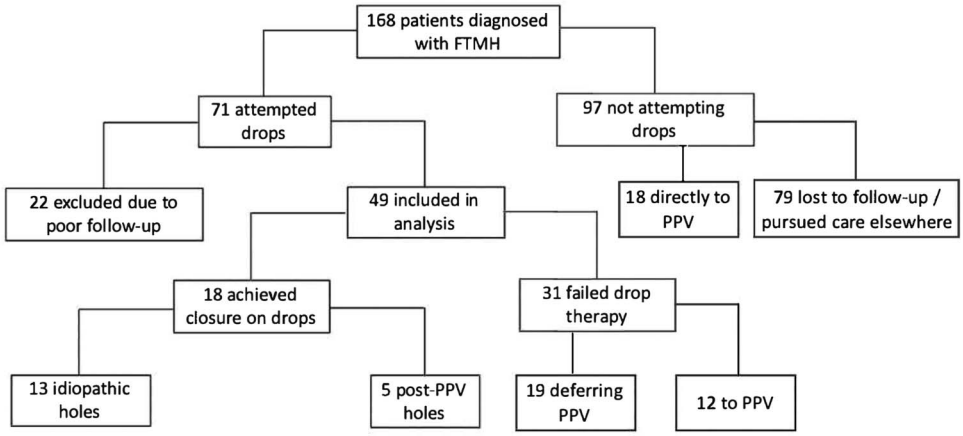

Fig. 1. Flow diagram showing inclusion and exclusion criteria used to derive final study population.

In the cases with successful closure, the mean FTMH size was 158 um ± 56 um (range 60–280 um), compared with a mean of 365 um ± 260 um (range 92–1079 um) in cases that failed drop therapy. Hole size was directly correlated with odds of closure. For every 10 μm decrease in size, odds of hole closure increased by 1.2× (P = 0.001, CI 1.1–1.4). Full-thickness macular holes <200 um had a closure rate of 72.2% and a 31× odds of closure compared with those ≥300 um (P = 0.003, CI 3.17–307). For macular holes between 200 and 300 um in size, the closure rate was found to be 27.8%; compared with holes >300 um, although they trended toward significance, they did not reach a statistically significantly greater odds of closure (OR 4.3, P = 0.211, CI 0.44–42.0). Finally, holes ≥300 um had a closure rate of 0% (Figures 2 and 3). Average time to closure with medical therapy was 107.2 days (range 20–512 days) and was not correlated with hole size (P = 0.217, CI −0.478 to +1.938).

When tracking the progression of FTMH size over time, the eyes that responded to drop therapy showed a reduction in size rapidly and dramatically. One month after initiating drop therapy, responders exhibited an average decrease in size by 47%, while nonresponders had an average decrease of 1%. After three months, responders exhibited an average decrease of 60% in hole size compared with an average of 18% in nonresponders (Figure 4). Of the 18 responders, 4 (22%) closed by 1 month, 8 (44%) closed by 2 months, 13 (72%) closed by 3 months, 16 (89%) closed by 6 months, and all closed by 1 year. In parallel, the mean central foveal thickness (CFT) decreased more dramatically in the eyes that closed successfully with drop therapy. In this study, responders had an average CFT decrease of 7% within 1 month compared with baseline, while nonresponders had an average *increase* in CFT by 5% during the first month. After three months, responders exhibited an average decrease of 9% compared with an average decrease of 2% in nonresponders (Figure 5).

The presence of VMT was found to be inversely related to successful FTMH closure on drops (OR 6.1, CI 1.2–31.3, P = 0.029). A history of vitrectomy trended toward closure on drops but did not reach statistical significance (P = 0.0841). Race, sex, the presence of ERM, lens status, the presence of diabetes mellitus, and the presence of intraocular inflammation were not found to be related to hole closure on medical therapy, although most of ERMs noted in this study were mild. Baseline visual acuity was significantly better in the group with eventual hole closure on drops (mean 20/60, logMAR 0.48 ± 0.21) as compared with those who failed drop therapy (mean 20/80, logMAR 0.60 ± 0.39) (P = 0.055) (Tables 2 and 3). Of the 18

Table 1. Clinical Characteristics of the Study Population Treated With Drops

Characteristics	Patients (n=49)
Age, mean (SD), y	67.2 (8.0)
Sex	
Female	21 (57.1%)
Male	28 (42.9%)
Race/Ethnicity	
White	37 (75.5%)
Black	9 (18.4%)
Other	3 (6.1%)
Lens status	
Phakic	30 (61.2%)
Pseudophakic	19 (38.8%)
MH thickness, mean (SD), μm	289.1 (231.2)
Associated MH characteristics	
Macular cystoid hydration	49 (100%)
Epiretinal membrane	20 (40.8%)
Vitreomacular traction	15 (30.6%)
MH etiology	
Idiopathic	42 (85.7%)
Post pars plana vitrectomy	7 (14.3%)

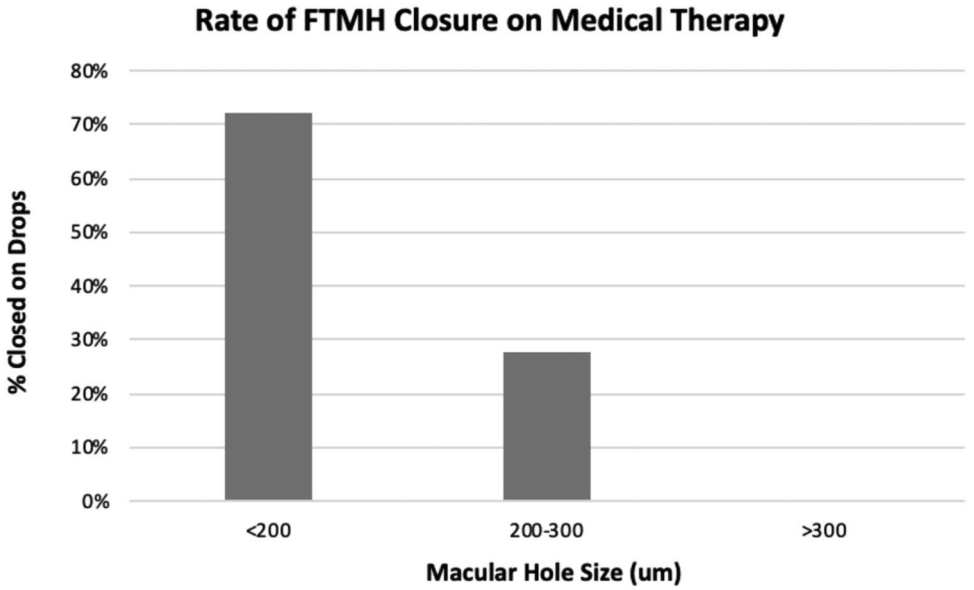

Fig. 2. Rate of FTMH closure stratified by size.

eyes that achieved FTMH closure on drops, five (28%) demonstrated a recurrence of FTMH after a mean duration of 31 weeks (range 13–56 weeks); three of the five recurrent holes closed again with drop therapy, and the remaining two were lost to follow-up. In the 49 eyes included in the analysis, nine (18%) exhibited ocular hypertension during their course of treatment with drops, of which six patients required additional medications to normalize intraocular pressure (IOP). One patient reported dizziness after initiating oral acetazolamide as a part of her IOP-lowering regimen.

In eyes with successful closure on drops, average best-corrected visual acuity (BCVA) improved from approximately 20/60 (0.477 logMAR) at initial presentation to approximately 20/30 (0.210 logMAR) after FTMH closure ($P < 0.001$). Among the FTMHs that failed to close with medical therapy, average BCVA went from approximately 20/80 (0.605 logMAR) at presentation to 20/65 (0.513 logMAR) when drops were stopped ($P > 0.05$). Finally, in patients undergoing primary PPV (N = 18) (33% stage 2 MHs, 67% stage 3–4 MHs) versus those who underwent and failed a trial of drops before subsequently undergoing a PPV (N = 12) (77% stage 2 MHs, 23% stage 3–4 MHs), there was no significant difference in final best-corrected logMAR visual acuity ($P = 0.318$, CI −0.094 to +0.112) (Table 2). The remainder of patients who failed medical therapy either pursued PPV elsewhere or were lost to follow-up.

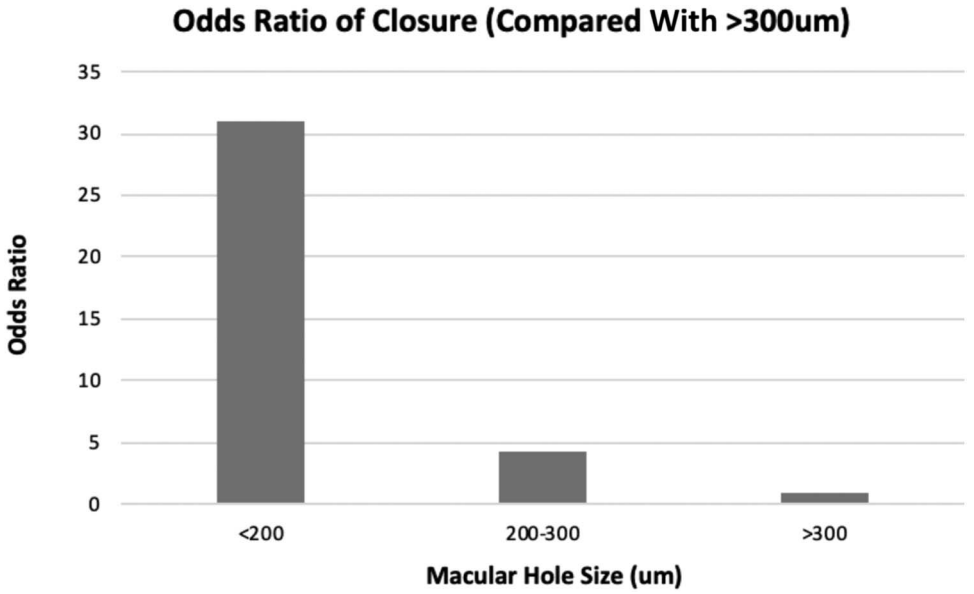

Fig. 3. Odds ratio of FTMH closure stratified by size.

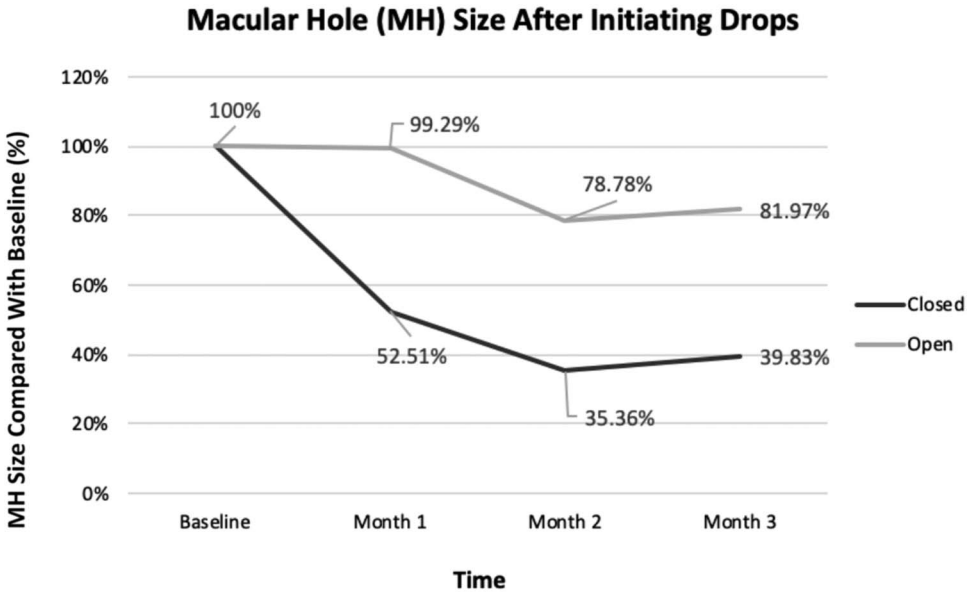

Fig. 4. Macular hole size after initiating drops as compared with baseline.

Discussion

The results of this single-center study suggest that hole size is one of the most important predictors of whether the macular hole will close on drops. Full-thickness macular holes under 200 μm in size have a substantial chance of closure with medical therapy, especially when vitreomacular traction is absent. This finding is consistent with the results from previous multicenter study from our group,[9] which described the closure of 14 cases of FTMHs on topical steroid, carbonic anhydrase inhibitor, and NSAID drops, most of which were under 200 μm in diameter. For macular holes between 200 and 300 μm in size, our findings suggest that closure with medical therapy is possible, occurring in just over a quarter of cases. It is important to note that when comparing with FTMHs over 300 μm, there was no statistically significant difference in the odds of closure on drops in this subgroup. It is possible that with a larger sample size, a more definitive odds of closure will be elucidated. In this study, no FTMHs over 300 μm in size closed on medical therapy.

Consistent with the combined tractional–hydration theory[2,3] for the pathogenesis of FTMHs, our findings suggest that the absence of vitreomacular traction heralds an increased odds of closure on medical therapy. This is not surprising, as anteroposterior traction is a key contributor to the formation of a FTMH. When this tractional force is absent, macular dehydration can occur through the dehydrating forces of the retinal pigment epithelium pump, enabling the hole edges to reappose. On the other hand, it is interesting and perhaps surprising to note that the presence of an epiretinal membrane did not affect the odds of FTMH closure with topical therapy. An epiretinal membrane, also commonly referred to as a macular pucker, is a thin layer of scar tissue over the macular that can tent up and distort the normal foveal contour. Given the intrinsic tractional quality of ERMs, it may be surprising that this study did not find its absence to be contributory to hole closure on drops. Further studies may elucidate whether the severity and extent of the ERM bear significance on hole closure, as most of ERMs in this series were mild. Finally, vitrectomized eyes trended toward having an increased odds of successful closure on drops, which remains consistent with the combined tractional–hydration theory.[2,3] Although this did not reach statistical significance, this relationship may be further elucidated in future studies.

Given that responders exhibited a much more significant reduction in macular hole size compared with nonresponders during the first 3 months after initiating drops, the results of this study can be used to prognosticate which eyes may have eventual successful closure with topical therapy. Similarly, the CFT can also be used as an adjunctive tool for predicting which eyes will respond to drops. If the MH size and CFT of an eye responds with a decrease in the first month of using drops and continues to consistently decrease over 3 months, the patient is more likely to respond as compared with the eyes that do not exhibit any decrease or show an increase in CFT after 1 month of consistent drop usage (Figure 6). Accordingly, the authors hope that these data will be useful for clinicians when deciding when to move forward with scheduling a PPV; if a patient does not respond with a dramatic decrease in hole size within 1 to 3 months,

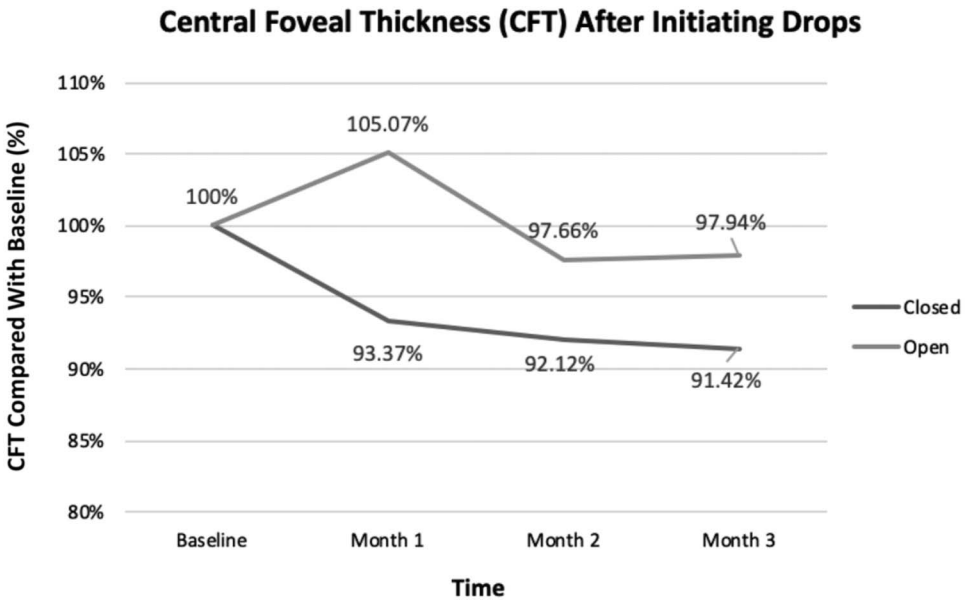

Fig. 5. CFT after initiating drops as compared with baseline.

especially in the first month, and/or does not show consistent CFT decrease over the same time frame, the authors advocate that a discussion regarding surgery should be considered with the patient regarding scheduling a tentative date for prompt PPV so as not to delay final outcomes. In this study, most patients who failed topical medical therapy and elected for subsequent PPV underwent surgery within 1 to 3 months after initiating eye drops.

Moreover, the results of this study suggest a clinically important finding – that the combination of drops used resulted in a significantly improved mean BCVA alongside hole closure ($P < 0.001$), which was not seen among the FTMHs that failed to close on drops. Therefore, the authors propose that it may reasonable, after an informed discussion with the patient, to initiate a trial of medical therapy for FTMHs under 200 μm, especially those without vitreomacular traction and possibly those occurring in vitrectomized eyes. In addition, we discovered that delaying surgical intervention with a trial of drops did not result in a poorer final best-corrected logMAR visual acuity as compared with eyes that went directly to PPV ($P = 0.318$). However, it must be noted that eyes pursuing PPVs directly had larger MHs with worse baseline BCVAs compared with those trialing and failing drops, raising the question as to whether similar final BCVA between the two groups truly signifies that delaying PPV with a trial of drops had no negative effect on final BCVA. A larger, prospective multicenter trial with equivalent comparison groups is needed to elucidate this question.

Table 2. Comparison Between the Eyes That Responded to Drops, the Eyes That Failed Group, and the Eyes That Underwent PPV Without a Trial of Drops

Treatment Strategy	Pre BCVA (LogMar)	Post BCVA (LogMar)	MH Size (μm)(std dev)	ERM	VMT	Treatment Until Closure (days)	MH Recurrence	Follow-up (days)
Drops - MH closed (n = 18)	0.477	0.210	158 (56.2)	44%	11%	112.3 (130.8)	5 (27.8%)	252.7
Drops - MH open (n = 31)	0.605*	0.513*	365 (259.8)*	39%	42%*	N/A	N/A	553.4
Subsequent PPV (n = 12)	0.566*	0.301*,†	314 (254.1)*	42%	42%*	N/A	N/A	708.3
Deferred PPV (n = 19)	0.629*	0.619*	397 (265.2)*	37%	42%*	N/A	N/A	455.5
Directly to PPV (n = 18)	0.946*	0.385*	471 (154.3)*	28%	39%*	N/A	N/A	611.8

*Indicates statistically significant intergroup differences for all other groups compared with successful MH closure on drop therapy ($P < 0.05$).

†Refers to BCVA after undergoing a trial of drops, followed by a subsequent PPV.

BCVA, best-corrected visual acuity; ERM, epiretinal membrane; HTN, hypertension; MH, macular hole; VMT, vitreomacular traction.

Table 3. Odds Ratio of Various Clinical Characteristics on Successful Closure With Drops

	Successful Closure	
Clinical Characteristic	Odds Ratio (95% CI)	*P*
Race (Black compared with White)	3.0 (0.7–13.1)	0.155
Race (other compared with White)	4.7 (0.4–57.7)	0.207
Baseline visual acuity (logMAR)	0.1 (0–1.1)	0.058
MH size (every 10 μm decrease)	1.2 (1.1–1.4)	0.001
Absence of VMT	6.1 (1.2–31.3)	0.029
Lens status (pseudophakia)	1.5 (0.4–4.8)	0.536
History of vitrectomy	4.1 (0.7–25.4)	0.084
ERM	1.3 (0.4–4.1)	0.694
Diabetes	1.4 (0.3–6.9)	0.717

ERM, epiretinal membrane; MH, macular hole; VMT, vitreomacular traction.

It is important to note that medical therapy is not completely benign and without risks. Topical steroids carry the risk of raising intraocular pressure, whereas topical NSAIDs may cause corneal irritation and, in severe cases, corneal melting. In this study, no patients developed corneal complications, although nearly one in five presented with ocular hypertension after the initiation of medical therapy, most of whom required additional IOP-lowering medications, whether in the form of topical drops or oral acetazolamide. Oral CAIs are also associated with side effects, such as stomach upset, electrolyte imbalances, and dizziness or drowsiness. Thus, the risk–benefit ratio must be weighed carefully and discussed with patients, taking into the patient's other ocular and systemic comorbidities, such as glaucoma and renal function. These risks must then be weighed against those of a PPV, including endophthalmitis, cataract, retinal detachment, hypotony, and phototoxicity, as well as the morbidity of its postoperative regimen, the constraint on patients to

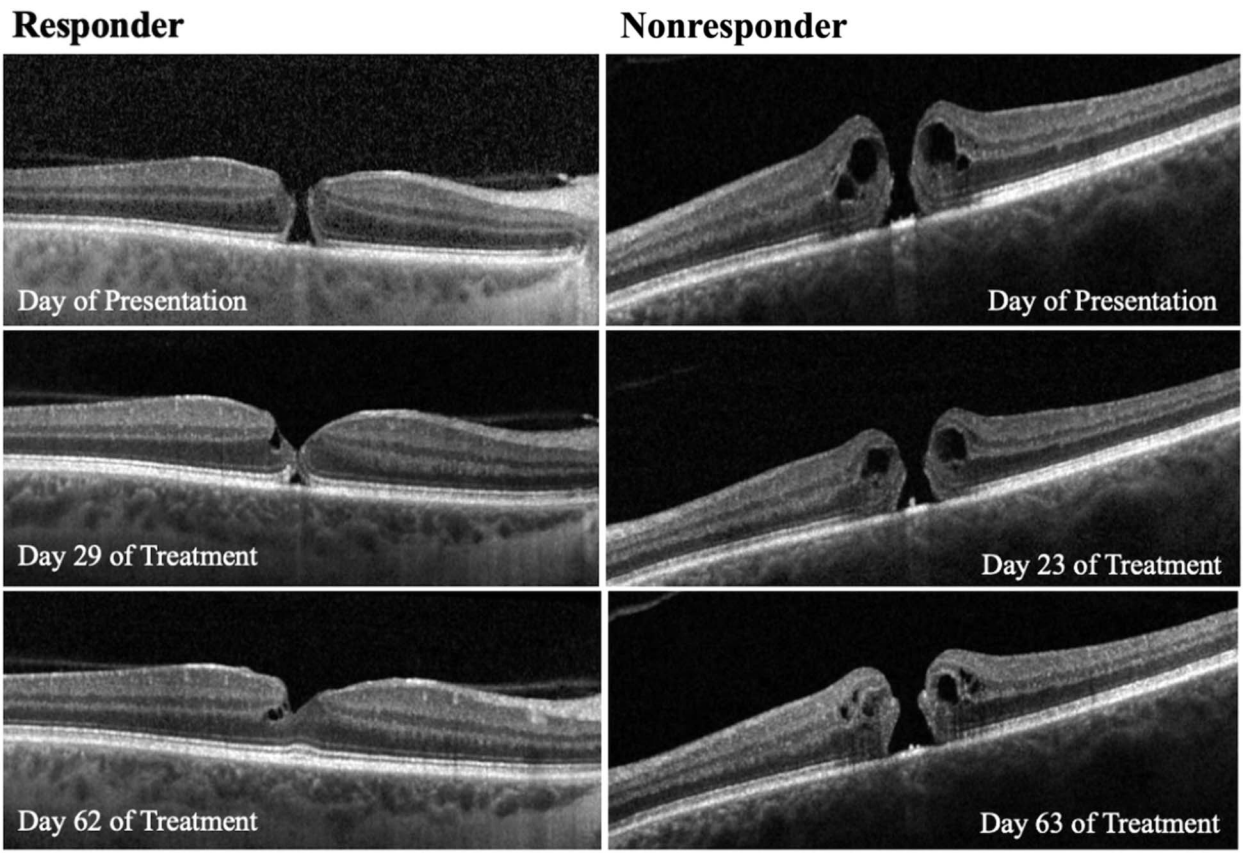

Fig. 6. Representative OCTs of responders and nonresponders.

take time off from work, and the financial burden on our health care system.[13]

Two reviews, one in 2012 by Sugiyama and the other in 2019 by Liang, reported the incidence of spontaneous macular hole closure to be between 3.7% to 6.2% and 4% to 11.5%, respectively.[14,15] The closure rate in our study among FTMHs under 200 μm in size – and even those under 300 μm in size – were much greater, suggesting that our drop regimen may facilitate FTMH closure, although prospective clinical trials are needed to elucidate whether the increased rate of closure on drops is statistically significant or merely reveals a higher rate of spontaneous closure due longer observation periods before surgery. However, the recurrence in several cases after drop cessation followed by successful closure again after reinitiation of drops may be suggestive that drops may contribute in part to hole closure.

Further research on the association between the odds of FTMH closure with prior vitrectomy, macular hole characteristics, lens status, and systemic conditions such as diabetes mellitus with a larger sample size is warranted. The authors acknowledge the limitations of this retrospective study and limited sample size and hope that a future, multicenter randomized controlled trial will further clarify the efficacy of medical therapy on FTMHs with various clinical characteristics. Furthermore, randomized prospective studies are necessary to further investigate the effect of delaying initial PPV with a trial of drop therapy on final BCVA because these two groups had different baseline characteristics in this study. Finally, it is important to note that 22 patients trialing drops were lost to follow-up. The baseline characteristics of these patients mirrored those of the 49 patients included in the study, and these patients may have pursued surgery with another retina specialist, or in some cases, the macular hole may have closed, leading to improved vision, obviating the need to return. In addition, 79 patients who did not attempt drops pursued care elsewhere or were lost to follow-up. Most of these patients traveled to our institution for consultation on whether drop therapy would be beneficial for their macular hole and, when told that their MHs were too large or advanced, returned to their local retina specialist for surgery.

In the largest study to date to report the overall efficacy and clinical characteristics of successful macular hole closure with topical therapy, drops achieved an overall closure rate of 36.7%, with higher efficacy in smaller holes and those without VMT. The combination of steroid, carbonic anhydrase inhibitor, and NSAID drops significantly improved BCVA alongside hole closure, and the rates of MH narrowing and reduction in CFT acted as predictors of effectiveness of drop therapy. In patients who are not candidates for surgical intervention, who have long preoperative waiting periods, who cannot or prefer not to tolerate the morbidity of PPV including face-down positioning, and during periods when nonurgent procedures are discouraged such as during the COVID-19 pandemic, a trial of topical therapy may be a suitable, less invasive, and cost-effective option for our patients with small FTMHs and health care system alike.

Key words: full-thickness macular hole, medications, OCT, retina, surgery.

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