Surgical Management of Macular Holes

A Report by the American Academy of Ophthalmology

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Objective: The document describes macular hole surgery and examines the available evidence to address questions about the efficacy of the procedure for different stages of macular hole, complications during and after surgery, and modifications to the technique.

Methods: A literature search conducted for the years 1968 to 2000 retrieved over 400 citations that matched the search criteria. This information was reviewed by panel members and a methodologist, and it was evaluated for the quality of the evidence presented.

Results: There are three multicenter, controlled, randomized trials that constitute Level I evidence and compare the value of surgery versus observation for macular hole. There are three multicenter, controlled, randomized trials studying the use of adjuvant therapy in macular hole repair. Postoperative vision of 20/40 or better has been reported in 22% to 49% of patients in randomized trials. The risks of surgical complications include retinal detachment (3%), endophthalmitis (<1%), cataract (>75%), and late reopening the hole (2% to 10%).

Conclusions: The evidence does not support surgery for patients with stage 1 holes. Level I evidence supports surgery for stage 2 holes to prevent progression to later stages of the disease and further visual loss. Level I evidence shows that surgery improves the vision in a majority of patients with stage 3 and stage 4 holes. There is no strong evidence that adjuvant therapy used at the time of surgery results in improved surgical outcomes. Patient inconvenience, patient preference, and quality of life issues have not been studied. *Ophthalmology 2001;108:1328–1335 © 2001 by the American Academy of Ophthalmology.*

Introduction

The American Academy of Ophthalmology (AAO) prepares Ophthalmic Technology Assessments (OTA) to evaluate new and existing procedures, drugs, and diagnostic and screening tests. The goal of an OTA is to review the peer-reviewed and published scientific literature, to distill what is well established about the technology, and to help define and refine the important questions to be answered by future investigations. Assessments are submitted to the Academy's Board of Trustees for consideration as official Academy statements after appropriate review by all contributors, including legal counsel.

Background

Macular hole is a condition in which an anatomic opening or dehiscence develops in the fovea. The precise pathogenesis of macular hole formation remains controversial, but it probably involves tangential and/or anteroposterior vitreofoveal traction. Macular hole formation typically evolves over a period of weeks to months through a series of stages that were first described by Gass.[1,2] Impending macular hole (stage 1A) is characterized by flattening of the umbo (loss of the foveal depression) and a central yellow spot in the macula. In stage 1B there is a yellow ring with loss of the foveal depression. Initially it was suggested that stages 1A and 1B macular holes represented progressive foveolar serous retinal detachments without vitreofoveolar separation. Recent ocular coherence tomography (OCT) data suggest that perifoveal posterior hyaloid separation with persistent adherence of the posterior hyaloid to the foveal center is the first event in macular hole formation.[3–6] This results in an intraretinal split that progresses into intraretinal cystic changes corresponding to the clinical features of stage 1 macular hole. Stage 2 is characterized clinically by a small retinal defect (hole) inside the yellow ring. Ocular coherence tomography demonstrates stage 2 to be a complete, full-thickness retinal defect. In stage 3 macular holes, a larger (≥400 micron) hole is apparent with a rim of elevated retina and complete separation of the posterior hyaloid from the macula. An operculum on the posterior hyaloid may or may not be clinically apparent, but is usually seen on OCT.

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Table 1. Randomized Controlled Trials (Level I Evidence) on Vitrectomy for Early Stages of Macular Hole

Study	Treatment Group	Number Enrolled	Follow-up Time (mos.)	Compliance to Follow-up	Progress to Stage 3 or 4	>20/40	<20/80	Mean ETDRS Score	Mean ETDRS Vision	Surgical Outcome Measured
DeBustros[9] Stage 1	Surgery	27	average 17	60/62 (97%) overall	10 (37%)	11%	33%			Progression to stage 3 or 4 determined by stereo photos
	Observation	35			14 (40%) p = 0.81	14% p = 0.014	20%			
Kim[10] Stage 2	Surgery	17	12	15/17 (88%)	3/15 (20%)			0.49	20/62	Progression to stage 3 or 4 determined by stereo photos
	Observation	25		21/25 (84%)	15/21 (71%) p = 0.006			0.60 p = 0.17	20/80	

ETDRS = Early Treatment of Diabetic Retinopathy Study

Stage 4 macular hole is present when the posterior hyaloid separates from the optic disc.

Patients with stage 1 and stage 2 macular holes typically have vision between 20/25 and 20/80. Vision in stage 3 and stage 4 macular hole eyes is usually 20/100 to 20/400. The vision in stage 3 and stage 4 eyes rarely improves spontaneously. Kelly and Wendell discovered the use of vitrectomy techniques to close macular holes in 1991.[7] Surgery for macular holes consists of a core vitrectomy, removal of the posterior cortical hyaloid and obvious epiretinal membranes, and a filling of the vitreous cavity with a long-lasting gas or silicone oil. Some surgeons also advocate removal of the internal limiting membrane and/or injection of an adjuvant on the hole at the time of surgery. The patient then usually maintains a face-down position for 7 to 14 days.

Questions for Assessment

The purpose of this assessment was to address the following questions:

- Does surgery reverse visual loss from macular hole?
- At what stage of the disease do patients derive the most benefit from surgery?
- What modifications to surgery should be used?
- What kind of tamponade should be used in macular hole surgery?

Description of Evidence

The literature search was conducted for the years 1968 to 2000 in MEDLINE and the Cochrane library using the MeSH term "retinal perforations" and the truncated text word "hole." Results were limited to articles in English or German, and the search retrieved over 400 citations. This information was reviewed by panel members and a methodologist, who assigned a rating to each study as follows. Level I is assigned to properly conducted, well-designed randomized clinical trials; Level II is assigned to well-designed controlled trials without randomization or well-designed cohort and case-control analytic studies; and Level III is assigned to case series. Members of the Ophthalmic Technology Assessment Committee and other AAO committees reviewed drafts of this document prior to formal approval by the Board of Trustees.

There are three multicenter, controlled, randomized trials that constitute Level I evidence and compare the value of surgery versus observation for macular hole[8–10] (tables 1 and 2). De Bustros reported results in patients with stage 1 macular holes.[9] This study had very good compliance to protocol and follow-up, but the strict eligibility criteria enrolled a small number of participants, limiting the power of this study to detecting only large treatment effects (30%). Kim et al for the Vitrectomy for Treatment of Macular Hole Study Group enrolled patients with stage 2 macular holes. They reported good compliance to protocol and follow-up, although there was an unequal allocation to study arms that resulted in fewer eyes than estimated receiving surgery.[10] The study of Freeman et al for the Vitrectomy for Treatment of Macular Hole Study Group analyzed patients with stage 3 and stage 4 holes and had very good compliance to protocol and follow-up, although the 6 months' follow-up reported was relatively short.[8] The outcome measures of these three studies included multiple measures of visual dimensions but did not include measures of quality of life. There are three multicenter, controlled, randomized trials studying the use of adjuvant therapy in macular hole repair (Table 2).[11–13] Smiddy et al reported surgical success of 86% of participants at 6 months.[11] The study reported by Thompson et al had a short follow-up of 3 months; the lack of difference in visual acuity noted in the results may be due to low power.[12] Paques et al reported results of 91% of participants at 6 months in a study with very good compliance to protocol and follow-up.[13] These three studies supply Level I evidence for the outcomes reported.

Case series (Level III evidence) have been included for reporting bilateral visual function,[14] patient satisfaction,[15] complications, and additional surgical results.[14,16–35] Two prospective natural history studies give Level II evidence about full-thickness macular hole (FTMH) occurrence in the

Table 2. Randomized Controlled Trials (Level I Evidence) for Surgery for Stage 3 or 4 Macular Holes

Study	Treatment Group	Number Enrolled	Follow-up Time (mos.)	Follow-up Compliance	Surgical Success	>20/40	>20/60	Mean Visual Acuity	Mean ETDRS Score/Vision	Surgical Success Definition
Freeman[8]	Original operation	64	6	94%	36/52 (69%)				0.76 logMAR 20/115	Closure of the hole determined by stereo photos
	Observe	65		89%	2/56 (4%) (p = 0.001)				0.92 logMAR 20/166 (p = 0.05)*	
Smiddy[11]	Original operation	44	3	100%	16/30 (53%)					Flattening of edges determined clinically
	Bovine $TGF\beta_2$	44			53/58 (91%) (p = 0.001)					
Thompson[12]	Original operation	65	3	63/65 (97%)	35/57 (61%)	7/57 (12.3%)	24/57 (42%)	20/80		Edges no longer visible; determined clinically
	Recombinant $TGF\beta_2$	65		57/65 (87%)	49/63 (78%) (p = 0.08)	14/63 (22%) (p = 0.49)	30/63 (48%) (p = 0.80)	20/80+2 (p = 0.22)		
Paques[13]	Original operation	53	6	91% at 6 mos. overall	46/57 (81%)				56	Reapposition of the edges of the hole determined clinically
	APC	57			50/53 (94%) (p = 0.04)				60 (p = 0.25)	

*Adjusted for hole duration and maximum hole diameter

$TGF\beta_2$ = transforming growth factor β_2; APC = autologous platelet concentrate

fellow eye.[36,37] Most papers retrieved and reviewed were retrospective case series for which bias may influence reported surgical outcomes. Analyses are primarily descriptive and outcomes reported are generally limited to complication rates, anatomical closure rates, and distance visual acuity.

In all studies retrieved, the definition of surgical success varied; some studies considered flattening of the edges of the hole to be a surgical success while others required closure of the edges of the hole. Most studies did not standardize follow-up time or adjust for time differences in the analysis of functional outcomes. When visual acuity and hole closure are assessed at varying intervals, it is difficult to attribute these results to the surgery, because patients were assessed at different stages of recovery or disease progression. Many studies did not control for prognostic factors such as duration of symptoms, size, and presence of an epiretinal membrane.[8,16,38–40] Further, some series included operations on stage 2 holes, which may have a better prognosis.

Description of Results

Does Surgery Reverse Visual Loss from Macular Hole?

Freeman et al for the Vitrectomy for Treatment of Macular Hole Study Group (Table 2) compared the value of surgery versus observation for stage 3 or 4 macular hole.[8] In the surgery group, 36 of the 52 (69%) stage 3 or 4 holes were closed compared with only 2 of 56 (4%) eyes in the observation group ($P < 0.001$). Statistically the surgically treated eyes had significantly better visual acuity at 6 months, as reflected by better ETDRS chart visual acuity (20/115 vs. 20/166, $P < 0.004$) and Bailey-Lovie word reading test scores (20/155 vs. 20/166, $P < 0.01$). No significant differences were found between the two groups for word reading speed scores. After adjusting for baseline visual acuity and hole duration and size, the benefit of surgery persisted for word reading ($P = 0.02$) and marginally for ETDRS visual acuity ($P = 0.05$). A final visual acuity of 20/26 or better was achieved in 11 eyes in the surgery group as opposed to 2 eyes in the observation group. A clear benefit in closure rate and final visual acuity was shown, even though the mean hole duration was 18.8 months in the surgery group and 28.6 in the observation group (Level I evidence). The benefits of surgery for stage 3 or stage 4 macular hole were demonstrated.

The outcomes of surgery for full-thickness macular holes in uncontrolled studies are presented in Table 3. The more favorable anatomic and visual outcomes noted in these series may be attributed to including patients with macular holes of shorter duration than those of patients included in the randomized trials. In addition, the results may reflect advances in surgical technique and experience.

Patients report a benefit from macular hole surgery, even

Table 3. Outcomes of Surgery in Uncontrolled Studies

Study (year)	Modifications to Surgery	Anatomic Success	Minimum Standard of Success	Minimum Follow-up (mos.)	>20/40	>20/50	>20/60	Lines of Improved Vision
Brooks[34] (2001)	ILM peeling	116/116 (100%)	Closure	6	82/116 (71%)			4.9
Kang[35] (2000)	ILM peeling	51/56 (91%)	Complete disappearance of hole edges	3	27/56 (48%)			54% gained 2 or more
Margherio[33] (2000)	Preretinal tissue/ILM peeling	51/59 (85%)	Closure	6		38/59 (64.4%)		
	No peeling	44/48 (92%)				41/48 (84.5%)		
Mester[29] (2000)	ILM peeling	44/46 (96%)	Flattening of the edges with no subretinal fluid	3				85% gained 2 or more
Park[16] (1999)	ILM peeling	53/58 (91%)	Closure	6		31/58 (53%)		
Olsen[25] (1998)	Fibrinogen only	32/45 (71%)	Flattening of the edges	6				2.8
	Fibrinogen and ILM peeling	23/24 (96%)	Flattening of the edges	6				2.3
Pearce[15] (1998)	APC	25/30 (83%)	Flat with no subretinal fluid	3	8/30 (27%)			
Minihan[18] (1997)	APC	48/50 (96%)	Subretinal fluid surrounding the hole resolved	12	21/50 (42%)		31/50 (62%)	
Gaudric[31] (1997)	APC	72/77 (93%)	Flattening of the edges	Not given		72% (52/72)		
Tornambe[24] (1997)	Face-up positioning	26/33 (79%)	Flattening of the edges	12		16/33 (48%)		
Smiddy[32] (1997)	ILM peeling	39/43 (91%)	Flattening of edges	3	14/33 (33%)			65% gained 3 or more
Polk[14] (1996)	$TGFB_2$	61/71 (86%)	Flattening of the edges	3				82% gained 2
Lansing[30] (1993)	$TGFB_2$	22/23 (96%)	Flattening of the cuff of subretinal fluid	12	11/23 (48%)		19/23 (85%)	

ILM = internal limiting membrane; RPE = retinal pigment epithelium; APC = autologous platelet concentrate; $TGFB_2$ = transforming growth factor β_2

though they must undergo surgery, maintain an uncomfortable position for a week or more, and are likely to need cataract surgery (Level III evidence). Polk and associates closed 61 of 71 (86%) macular holes with one operation.[14] Six patients had a reoperation resulting in the closure of an additional two macular holes. Of the 71 eyes, 35 (49%) had a final vision of 20/40 or better. In patients with 20/40 or better in the fellow eye, the operated eye became the better eye in 9/48 (19%), and the average visual impairment according to the American Medical Association guidelines for disability decreased from 17% to 9%. In patients with 20/50 or worse in the fellow eye, the operated eye became the better eye in 70% of cases, bilateral visual function improved by one level in 39%, and the average visual impairment according to the American Medical Association guidelines for disability decreased from 52% to 35%.[14]

In 25 of the 30 eyes (83%) that Pearce et al evaluated, the macular hole was closed.[15] Half of the patients had two more lines of improvement and 27% had visual acuity of 20/40 or better. In terms of patient satisfaction, 53% said that they could read a newspaper better, 70% could see faces better, and 57% could read bus numbers better (Level III evidence).[15] In addition to the cost of the surgery and the difficulty of maintaining a face-down position postoperatively, there are ocular complications. Acute complications include retinal tears in about 3% of operations[13,14,16–20] and occasional cases of endophthalmitis.[8,20,21] Long-term complications include nuclear sclerotic cataract in the vast majority of patients[14,22,23] and retinal detachment in 1% to 3%.[13,16,18–21,24,25] In addition, the repaired macular hole may reopen in 2% to 10% of cases.[20,21,26–28] Finally, in assessing the value of macular hole surgery, it is important to consider that a patient who has a FTMH in one eye has about a 15% risk of developing a FTMH in the fellow eye (Level II evidence).[36,37]

At What Stage of the Disease Do Patients Derive the Most Benefit from Surgery?

De Bustros (Table 1) reported the only randomized, prospective trial of patients with stage 1 macular hole (Level I evidence).[9] All patients had a stage 3 or 4 macular hole in their fellow eye. The patients were randomized to vitrectomy or observation and 97% were followed for an average of 17 months. In the observation group 14 of 35 eyes (40%) progressed to stage 3 or 4 macular hole, while in the vitrectomy group 10 of 27 eyes (37%) progressed (P = 0.81). Postoperatively, 33% of the surgery group had a visual acuity of 20/80 or worse compared with 20% of the observation group. The trial was terminated prematurely due to low recruitment, but surgery does not appear to be warranted for stage 1 macular holes.

Kim and colleagues (Table 1) reported the only randomized, prospective trial of patients with stage 2 macular hole (Level I evidence).[10] All patients had a full-thickness macular hole in their fellow eye. The patients were randomized to vitrectomy or observation, and approximately 90% were followed for 12 months. In the observation group 15 of 21 (71%) eyes progressed to full thickness stage 3 or 4 macular hole. Their mean baseline ETDRS visual acuity was 20/69, deteriorating to 20/80 at 12 months. In the surgery group, only 3 of 15 (20%) of the eyes progressed to FTMH. The ETDRS visual acuity was stable, 20/60 at baseline and 20/62 at 12 months. Thus, although the observation group had a statistically significant, higher rate of progression to hole formation ($p = 0.006$), there was no statistically significant difference in the final visual acuity ($p = 0.17$) between the two groups. However, using the Bailey-Lovie word-reading test, the surgery group had a visual acuity of 20/78, compared with 20/135 in the observation group ($P = 0.006$). Although the study was a randomized clinical trial, it enrolled only a small number of patients and therefore may not have sufficient statistical power to detect a visual acuity difference between the surgery and observation groups. Since progression from stage 2 macular hole to stage 3 or 4 macular hole is usually associated with visual loss, this study supports surgery for stage 2 macular holes (Level I evidence).

What Modifications to Surgery Should be Used?

Transforming growth factor β_2 (TGFβ_2) was investigated with the hope that it would induce glial cells to close the hole.[11,30,41] Successful flattening of the edges of the hole of 91% to 96% of cases stimulated the search for adjuvants. They include autologous serum,[38,42–45] an absorbable partially cross-linked gelatin (collagen) plug, thrombin-activated fibrinogen,[25] thrombin,[47] plasmin,[43] and autologous platelet concentrate (APC).[15,17,31] Another modification to Kelly and Wendel's initially reported operative techniques is peeling of the internal limiting membrane (ILM).[16,25,29,32–34,49] Of these modifications to the original operation, well-designed controlled trials or cohort or case-control analytic studies have been reported only for TGFβ_2 and APC.

Smiddy and colleagues' multicentered prospective, randomized trial (Table 2) compared 44 eyes treated with bovine TGFβ_2 with 44 eyes given placebo (Level I evidence).[11] The 3-month results were reported for 100% of the patients. In the placebo group, the edges of the hole were flattened in 53% of the eyes compared with 91% of the TGFβ_2 group ($p < 0.001$). The visual results of this study were not reported.[11]

Thompson and associates' multicentered, prospective, randomized trial (Table 2) compared 65 eyes treated with recombinant TGFβ_2 with 65 eyes given placebo (Level I evidence).[12] The 3-month results were reported for 97% of the TGFβ_2 and 87% of the placebo group. In the placebo group the edges of the hole were flattened in 61% of the eyes compared with 78% of the recombinant TGFβ_2 group. The difference was not statistically significant ($p = 0.08$). There was also no statistically significant difference in visual acuity results between the two groups. A final visual acuity of 20/40 or better was achieved in 12% of the placebo group versus 22% of the TGFβ_2 group ($p = 0.49$). The mean visual acuity of the placebo group was 20/80 versus 20/80+2 in the TGFβ_2 group ($p = 0.22$).

Autologous platelet concentrate has been used as an adjuvant because platelets' alpha granules contain growth factors (TGFβ_2 and platelet-derived growth factor), known to promote the wound-healing process. The study reported by Paques et al (Table 2) was multicentered, prospective, randomized, and double masked (Level I evidence).[13] It compared 53 eyes treated with APC with 57 eyes given placebo. The 6-month results were reported for 91% of the 110 patients. The authors did not break the follow-up data into the surgery and placebo groups, but they considered the hole closed in the placebo patients lost to follow-up. The hole was closed in 81% of the placebo group versus 94% of the APC group ($p = 0.04$). The mean ETDRS visual acuity score was similar in the placebo group and the APC group (56 vs 60, $p = 0.25$). The inclusion of information about the proportion of patients with greater than 20/40 visual acuity might have provided some additional insight.

Margherio and colleagues[33] reported results from a retrospective comparative study on a series of consecutive patients who underwent surgery for idiopathic macular holes of less than one year's duration with two different techniques. Cohort 1 ($n = 59$) received surgery with preretinal/ILM peeling. Cohort 2 ($n = 48$) received surgery in which no attempt was made to remove preretinal tissue. There was no statistical difference between the two cohorts in the proportion of eyes that had successful hole closure and no statistical difference when comparing for postoperative visual improvements.

In contrast, a report by Brooks[34] concluded that ILM peeling improved visual and anatomic success. This study was a retrospective comparison of 211 patients with idiopathic macular hole who were analyzed as follows. One group received macular hole surgery without ILM peeling ($n = 44$ eyes), a second group received ILM peeling ($n = 116$ eyes), and a third group of patients whose macular hole was of more than 6 months' duration received surgery with ILM peeling ($n = 65$ eyes). In patients with hole duration of less than 6 months, 100% of those who received ILM peeling were anatomic successes versus 82% (36/44) of eyes without ILM peeling. Forty-five percent (20/44) of eyes without ILM peeling achieved 20/40 or better visual acuity versus 71% (82/116) of those with ILM peeling. These findings were statistically significant.

In summary, no Level I or Level II evidence suggests that these modifications to surgery improve the success rate.

What Kind of Tamponade Should be Used in Macular Hole Surgery?

A retrospective case series reported by Thompson and associates[50] found that the closure rate with 16% perfluoropropane (C_3F_8) was statistically significantly better than with lesser concentrations of C_3F_8. There were no significant differences in visual acuity among the three treatment groups.

A study without a control group of silicone oil tamponade without face-down positioning suggests that this technique may be an alternative for those patients who must travel or cannot maintain face-down positioning. However, they must undergo a second operation to remove the silicone oil.[51] In a comparative trial, Pertile and Claes compared silicone oil tamponade (n = 35 eyes) with SF_6 tamponade (n = 19 eyes) in patients with stage 3 or 4 holes. They found that 74% of patients in the silicone oil group had a postoperative best-corrected visual acuity of 20/50 or better compared with 47% of patients treated with gas tamponade.[52]

Conclusions

Macular hole surgery results in a flattening of macular hole edges in over 80% of patients. The evidence does not support surgery for patients with stage 1 holes. Level I evidence supports surgery for stage 2 holes to prevent progression to later stages of the disease and further visual loss. For patients with stage 3 and stage 4 holes, surgery improves the vision in a majority of patients based on Level I evidence. Postoperative vision of 20/40 or better has been reported in 22% to 49% of patients in randomized trials. The risks of surgical complications include retinal detachment (3%), endophthalmitis (<1%), cataract (>75%), and late reopening of the hole (2% to 10%). There is no strong evidence that adjuvant therapy used at the time of surgery results in improved surgical outcomes. Patient inconvenience, patient preference, and quality of life issues have not been studied.

Future Research

Additional questions about macular hole surgery that need to be addressed are as follows.

- Does ILM peeling offer surgical and functional benefit?
- Does decreasing or eliminating face-down position time affect surgical outcomes?
- What is the best treatment for recurrent macular holes?
- What is the risk of opening a closed hole after cataract extraction?
- How does cataract extraction affect long-term visual outcome?
- How does macular hole surgery impact patients' quality of life?

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Category	Abbrev	Specific Financial Interests
Product	P	Financial interest in equipment, process, or product presented.
	Pc	Such interest in potentially *competing* equipment, process, or product.
Investor	I	Financial interest in a company or companies supplying the equipment, process, or product presented.
	Ic	Such interest in a potentially *competing* company.
Consultant	C____	Compensation received within the past three years for consulting services regarding the equipment, process, or product presented.
	Cc____	Such compensation received for consulting services regarding potentially *competing* equipment, process, or product.
		Examples of compensation received include:
	C1 or Cc1	1. Retainer
	C2 or Cc2	2. Contract payments for research performed
	C3 or Cc3	3. Ad hoc consulting fees
	C4 or Cc4	4. Substantial non-monetary perquisites
	C5 or Cc5	5. Contribution to research or research funds
	C6 or Cc6	6. Contribution to travel funds
	C7 or Cc7	7. Reimbursement of travel expenses for presentation at meetings or courses
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