Surgery for Idiopathic Full-Thickness Macular Hole

Two-Year Results of a Randomized Clinical Trial Comparing Natural History, Vitrectomy, and Vitrectomy Plus Autologous Serum: Moorfields Macular Hole Study Group Report No. 1

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Objectives: To determine the benefits of idiopathic full-thickness macular hole (FTMH) surgery compared with observation and to evaluate the use of autologous serum as an intraoperative adjunct.

Methods: A randomized clinical trial was performed to evaluate the anatomic and visual benefits of FTMH surgery for lesions of 9 months or less symptom duration and visual acuity of 20/60 or less. We compared surgery with natural history and determined whether use of intraoperative adjunctive autologous serum improves the surgical outcome. Eyes were randomized to (1) observation, (2) vitrectomy, or (3) vitrectomy plus serum and were followed for 24 months to assess anatomic status and visual function.

Results: In total, 185 eyes of 174 patients were enrolled. In the observation group, spontaneous closure of the FTMH occurred in 7 (11.5%) of 61 patients, with little or no change in overall acuity levels in 24 months. In contrast, the surgical groups had an overall closure rate of 80.6% (100/124) at 24 months, with 45% of eyes achieving Snellen acuity of 20/40 or greater. Surgical eyes had better median near acuity than observation eyes by 6 lines (N5 vs N14). Use of autologous serum did not seem to affect anatomic or visual results. At 24 months, 72 (58.1%) of 124 surgical eyes had undergone cataract extraction.

Conclusions: Surgery for FTMH is safe and effective and is associated with significant visual improvement compared with the natural history. Autologous serum application does not enhance the results of surgery.


Numerous studies have described the benefits of surgical treatment for idiopathic full-thickness macular hole (FTMH). The rationale for performing a vitrectomy and gas tamponade is 2-fold. First, vitrectomy allows the removal of direct vitreous traction from the fovea and, second, postoperative gas tamponade results in flattening and reapposition of the hole edges, which facilitates glial repair after surgery. In this way, after successful anatomic closure of the hole, normal or near normal foveal architecture could be reestablished, with an improvement in vision.

Although the natural history of FTMH has been assumed to carry a poor anatomic and visual prognosis, a variety of studies have described arrest, spontaneous closure of holes, or both. The incidence of improvement in acuity in untreated holes has been estimated to be 3.4% to 10.0%. Studies describing surgical treatment for FTMH have been mostly uncontrolled; they have estimated that the proportion of patients experiencing improvement in visual acuity of 2 or more Snellen lines after surgery for stage 2, 3, or 4 holes is approximately 40% to 83%. Other studies have reported improved anatomic and visual results with the use of intraoperative adjuncts such as transforming growth factor β2, autologous serum, autologous platelets, and thrombin and fibrin mixtures, with 50% to 100% of eyes achieving an improvement of at least 2 Snellen lines. These adjuncts are thought to improve anatomic and visual results by promoting glial repair of the hole after surgery.

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From the Vitreoretinal Service, Moorfields Eye Hospital, London, England. A complete list of the members of the Moorfields Macular Hole Study Group appears on page 234. The authors have no relevant financial interest in this article.

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peripheral field defects, retinal tears (3%), retinal detachments (RDs) (1.8%-14.0%), retinal pigment epithelium damage or phototoxicity (1%-3%), and glaucoma. The incidence of adverse effects highlights the importance of randomized clinical trials (RCTs) that include observational controls and incorporate strict criteria for ensuring that particular medical centers involved use only surgeons who have a high level of surgical experience.

The Vitrectomy for Macular Hole Study Group (VMHSG) conducted an RCT, including an observational arm. The study demonstrated only a modest benefit in the group undergoing surgery for stage 2, 3, and 4 lesions compared with the observation group. In addition, an unusually high incidence of vision-threatening complications was reported. A variety of issues regarding methodologic design make these data difficult to interpret. The study protocol precluded cataract surgery in the surgical cases at any stage of the trial. Thus, as nucleosclerosis is common after surgery, much of the visual benefit in the treatment cohort would have been masked.

Now, although the treatment of choice for idiopathic FTMH is surgery, it is generally agreed that further RCT data are required to evaluate the exact benefit of surgery compared with the natural history of the condition. This article describes a masked-observer, RCT evaluating (1) the benefit of surgery compared with observation and (2) the benefit of autologous serum application as an intraoperative adjunct compared with surgery alone for recent-onset idiopathic FTMH. The study was carried out at a single center, Moorfields Eye Hospital, with an experienced consultant surgeon (Z.G.) performing all of the operations. Enrollment was conducted between November 1, 1993, and October 31, 1997. This study adheres to the CONSORT (Consolidated Standards of Reporting Trials) statement.

### METHODS

#### SUMMARY

- Prospectively defined hypotheses tested: (1) surgery for idiopathic FTMH results in a better outcome than observation and (2) vitrectomy plus use of autologous serum results in a better outcome than vitrectomy alone
- Single-center, RCT with masked observers
- Patients with recent-onset (≤9 months) idiopathic FTMH were randomized to 3 arms for intervention: observation, vitrectomy, and vitrectomy plus autologous serum
- Prospectively defined primary outcome measures: anatomic closure of the hole and best-corrected visual acuity
- Outcomes were assessed at 3, 6, 12, 18, and 24 months, with statistical analysis 3, 12, and 24 months after enrollment
- A single, independent, experienced consultant surgeon (Z.G.) performed all treatments and was not involved in randomization or assessment of outcomes
- Assessors of anatomic and visual outcomes (E.E. and A.M.) were masked to the allocation status of individual patients
- Statistical analysis was performed by an independent statistician (J.G.).

### STUDY PROTOCOL

#### Study Population, Patient Eligibility Screening, and Study Enrollment

The study population included all patients with idiopathic FTMH who sought care at Moorfields Eye Hospital; they were considered for inclusion according to the criteria given in Table 1. Patients were examined to confirm the diagnosis of FTMH and to determine the staging according to the Gass classification. Eligible patients were counseled, and those willing to participate in the RCT were contacted within a few days for an “entry” assessment to record the following baseline characteristics: date of study entry; patient age and sex; affected side; nuclear opacity and intraocular pressure; symptom duration; Log Minimum Angle of Resolution (LogMAR), Snellen, and near visual acuities; hole stage (Gass classification); horizontal and vertical hole diameters; and intraretinal cystoid change.

#### Interventions: Surgical Techniques

Intervention consisted of vitrectomy alone or vitrectomy plus autologous serum application. Patients randomized to a surgical arm underwent surgery within 2 weeks of allocation by an experienced consultant surgeon (Z.G.) at Moorfields Eye Hospital. After a 3-port pars plana vitrectomy, posterior vitreous cortex separation was effected using direct aspiration over the posterior pole with the vitreous cutter. The vitrectomy was then completed, and epiretinal membrane peeling was performed using a disposable pick. No attempt was made to remove the internal limiting membrane. A careful examination of the retinal periphery was then made, and any breaks were treated by retinopexy at that stage. This was followed by a fluid-air exchange and “drying” for 10 minutes, with the sclerotomy sites closed with plugs. Any fluid accumulated at the posterior pole was then removed using a 34-gauge extrusion cannula. The procedure was then completed with a gas exchange using 16% perfluoropropane. Eyes in the vitrectomy plus serum group underwent the same procedure, with application of autologous serum after the 10 minutes of air drying, before the air-gas exchange. The serum was prepared using 10 mL of venous blood drawn from the patient’s antecubital vein, under sterile conditions, and was spun at 3000 rpm for 10 minutes. Approximately 0.25 mL of the supernatant was then applied over the macula through a blunt-ended cannula after the air-drying phase and left for an additional 10 minutes. The surplus was then removed via a back-flush cannula.

Patients were instructed to posture face down immediately for 2 weeks. Assessment was carried out 1 day, 2 weeks, 6 weeks, and 3 months after primary surgery, with additional visits as indicated. In eyes in which the FTMH remained open

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**Table 1. Inclusion and Exclusion Criteria for Entry Into the Study**

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
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<tr>
<td>Symptom duration ≤9 mo</td>
<td>Symptom duration &gt;9 mo</td>
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<tr>
<td>Visual acuity ≤20/60</td>
<td>Previous ocular surgery or other ocular disease</td>
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<tr>
<td>Positive Watzke-Allen test result</td>
<td>Amblyopia</td>
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<tr>
<td>Full-thickness macular hole stage 2, 3, or 4</td>
<td>Significant cataract greater than grade 1 nucleosclerosis</td>
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<tr>
<td>Informed consent</td>
<td>Systemic disease affecting retinal function, eg, diabetes mellitus</td>
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national 29 eyes were required, resulting in a total of 185 eyes. (N=156) was required. Assuming a loss of up to 20% of pa-

The following stopping rules were prospectively defined at the study onset:

**Target Sample Size Projection**

A standard power calculation was used to determine sample sizes. A priori assumptions, from previously published data, were as follows:

- Observation would result in a 5% improvement
- A treatment effect of 50% was expected in the combined vitrectomy groups compared with the observation group, based on the data of Kelly and Wendel and colleagues.\(^3\)\(^4\) (the best available in 1993)
  - A treatment effect of 40% was expected in the vitrectomy plus serum group compared with the vitrectomy group.

To detect these effects at a significance of \(P=0.05\) and a power of 0.9, it was calculated that a sample size of 52 eyes per arm (N=156) was required. Assuming a loss of up to 20% of patients owing to default and death during the study, an additional 29 eyes were required, resulting in a total of 185 eyes.

**Stopping Rules**

The following stopping rules were prospectively defined at the study onset:

- All participants were to be followed for a minimum of 24 months after baseline (enrollment) and were discharged from the study at that point if stable and not requiring further intervention
- When all participants had reached the minimum 24 months of follow-up, the code would be broken and statistical analysis would be performed
- An interim analysis would be performed only in the event of a strong clinical suggestion that either treatment or observation resulted in substantial morbidity compared with the other groups; in such an event, the study would be terminated on ethical grounds if the interim analysis confirmed these suggestions.

**Outcome Measures**

The 2 outcome measurements, defined prospectively, were anatomic closure of the hole and visual acuity. The hole was defined as closed only if it had disappeared completely after surgery on clinical examination, in the presence of a negative Watzke-Allen test result, with confirmation of closure by fluorescein angiography. Otherwise, the hole was classified as open. Visual function was assessed using full refraction under standard lighting conditions in 3 ways: Snellen, LogMAR, and near acuities.

The LogMAR acuity was measured using the logarithmic letter chart used in the Early Treatment Diabetic Retinopathy Study.\(^7\)\(^0\)-\(^7\)\(^2\) This method has a variety of advantages over the standard Snellen chart, which, although useful for measuring the general level of visual acuity, is difficult to use in measuring changes in acuity.\(^7\)\(^0\)-\(^7\)\(^2\)

The testing conditions, using full refraction, were the same for LogMAR and Snellen acuities. Near vision was assessed using a standard near-acuity reading chart, with full refraction, held 30 cm from the patient's eye under the same conditions as the LogMAR and Snellen acuities. This is a nonlogarithmic scale in which N5 (these letters project the minimum angle of resolution at 30 cm for the normal eye) is the smallest print and N48 is the largest. Reading speed was not measured.

Also recorded were adverse effects of treatment. Intraoperative events recorded were lens touch, macula or retina touch, retinal pigment epithelium touch during drying of the FTMH, iatrogenic horseshoe tear, and additional retinopexy for pre-existing lattice degeneration. Postoperative events recorded were RD or horseshoe tear, a second surgery after unsuccessful primary FTMH surgery, and progression of ncleosclerosis.

One observer (E.E.), using the funduscopic, photographic, and fluorescein angiography, assessed the hole status. As far as funduscopic assessment was concerned, it was not possible to postoperatively mask between surgery and observation, as examination alone would reveal whether a vitrectomy had been performed. However, the assessor was masked as far as vitrectomy vs vitrectomy plus serum, as it was not possible to distinguish between them on clinical grounds.

Photographic and fundus fluorescein angiographic assessments were performed by examining digitalized images, which were coded separately so that the assessor was masked to the identity of the patient. Only if the funduscopic, photographic, and fundus fluorescein angiographic criteria were all met could a hole be classified as closed. In the event of a discrepancy, a second masked assessor was used. The assessor of visual acuity (A.M.) was masked to the allocation status.

**Masking**

Hole Status and Visual Acuity Assessors

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**Surgeon, Data Analyst, Patients, and Allocation Sequence Control**

The surgeon (Z.J.G.) was not masked to the allocation status. The data analyst was an independent statistician (J.G.) who was not masked to the allocation status. Patients were not masked in any way. The allocation sequence code was held solely by an independent study coordinator (M.D.) throughout the study. Only when all patients had reached 24 months' follow-up or in the event that an interim analysis was required would the code be broken for analysis by the study statistician.

**Data Analysis**

Exploration of Baseline Characteristics

Data comparisons for all baseline variables were made statistically among the 3 groups and between the combined surgical group...
and the observation group to confirm that randomization had been successful. The χ² test was used to test for associations between categorical variables and randomization groups. A 1-way analysis of variance was used to test the hypothesis that all means were equal among randomization groups for continuous variables. In addition, baseline variables in completers were compared among the randomization groups at each time (3, 12, and 24 months) to identify any biases. To exclude biases attributable to missing data, comparisons of baseline variables among completers, defaulters, and those with missing data entries were made at 3, 12, and 24 months within and among randomization groups.

Analysis of Outcome Measures

Exploration of Outcome Measures: Repeated-Measures Model. The analysis focused on 2 strategies: (1) comparing the combined surgical group (vitrectomy and vitrectomy plus serum) with the observation group to determine the effect of surgery per se on anatomic hole closure and visual outcome and (2) comparing all 3 randomization groups separately to determine whether use of serum improves the results of surgery.

A repeated-measures model was used for each eye at 3, 12, and 24 months. The effects of treatment per se on FTMH closure and vision were analyzed using the observation group as the control and the combined surgical group as treatment. A repeated-measures model was used for each eye at 3, 12, and 24 months using correlated binary response data. The model tested 3 possible treatment effects: (1) treatment as a fixed effect (ie, treatment vs nontreatment is primarily responsible for the observed outcome), (2) time in months as a fixed linear effect (ie, the postbaseline period is responsible for the outcome effect rather than treatment itself), and (3) interaction between treatment and time (treatment × month) (ie, whether the effect of treatment on the outcome changes with the postbaseline period elapsed).

An eye was treated as a random effect, and the correlation between outcome measurements for each eye was modeled using a simple power law.

Multiple Regression Analysis for Exploring Prognostic Factors for Outcome. This approach was used to identify any baseline, intraoperative, or postoperative factors that were prognostic for a favorable outcome after surgery. All eyes were analyzed using an intention-to-treat approach. For categorical outcomes, analysis was performed using the χ² test, and for quantitative outcomes, by comparison of means. All significance testing was 2-sided. Continuous variables that were strongly skewed were transformed to a logarithmic scale for purposes of analysis.

RESULTS

FLOW THROUGH THE STUDY

The flow of eyes through the study is summarized in Table 2. Of 368 eligible eyes, 185 (174 patients) were randomized between November 1, 1993, and October 31, 1997: 61 to observation, 59 to vitrectomy, and 65 to vitrectomy plus serum. Similar numbers of defaulters occurred in all 3 groups at all assessment times. Three patients died during the study, 1 in the observation group (between the 12- and 24-month visits) and 2 in the vitrectomy plus serum group (between 3 and 12 months and 1 between 12 and 24 months). The other defaults were accounted for by missed visits rather than by missing data. At baseline, 3 eyes had missing data for visual acuity (Snellen, LogMAR, and near). These data represent a high capture rate overall. One study entry violation occurred in an eye that had symptoms of 10 months’ duration.

Eleven patients had both eyes randomized. Seven of these patients initially had unilateral holes and subsequently developed an FTMH in the fellow eye, which was then randomized. The other 4 patients had bilateral FTMHs when first seen and had both eyes randomized on the same date. Of these 11 patients, 5 had an observation/vitrectomy plus serum pairing, 2 an observation/vitrectomy pairing, 2 a vitrectomy/vitrectomy pairing, 1 a vitrectomy plus serum/vitrectomy plus serum pairing, and 1 a vitrectomy/vitrectomy plus serum pairing.

BASELINE ANALYSIS

The baseline characteristics recorded for patients and eyes at entry are summarized in Table 3 and Table 4. No significant differences in baseline characteristics were apparent among the randomization groups. There was a greater proportion of men in the observation group (26.2%) compared with the vitrectomy (20.3%) and vitrectomy plus serum (13.8%) groups, but this difference did not reach statistical significance (P = .10). The vitrectomy group had a greater proportion of stage 3 holes (57.6%) than stage 2 holes (30.5%) vs the vitrectomy plus serum group (41.5% and 49.2%, respectively). Observation eyes had similar proportions of stage 3 (45.9%) and stage 2 (39.3%) lesions. These differences did not reach statistical significance (P = .07). Similar analyses were conducted for completers at 3, 12, and 24 months to explore whether missing data affected baseline comparability, and no differences were evident.

TREATMENT EFFECTS: ANATOMIC CLOSURE AND HOLE SIZE

The anatomic results in the randomization groups at 3, 12, and 24 months are given in Table 5. In the observation group, most FTMHs remained open, although 7 (11.5%) of 61 closed spontaneously during the study: 6 within 3 months and 1 between 3 and 12 months. None of the 7 FTMHs subsequently reopened on follow-up.

In the vitrectomy group, the FTMH closure rate was 78.0% (46/59) at 3, 12, and 24 months. In the vitrectomy,
tomy plus serum group, the closure rate was 87.7% (57/65) at 3 months, 86.2% (56/65) at 12 months, and 83.1% (54/65) at 24 months. Overall, in the combined surgical groups, the closure rate was 83.1% (103/124) at 3 months, 82.3% (102/124) at 12 months, and 80.6% (100/124) at 24 months. In 2 eyes, 1 in the vitrectomy group and 1 in the vitrectomy plus serum group, the hole reopened after initially successful surgery, at 20 months and 14 months, respectively. Both holes were closed after a second operation. Thus, the overall reopening rate after initial closure with surgery was 2.0% (2/100) at 24 months.

In the repeated-measures model analysis, the only significant factor for hole closure was treatment effect ($\chi^2=279.1; P<.001$), confirming that the outcome effect, that is, anatomical closure, depends only on whether surgery was performed. Time in months did not seem to affect hole closure ($\chi^2=0.38; P=.83$), confirming that the post-baseline period per se did not affect anatomic outcome. A strong correlation between hole status for each eye between different times (correlation between 3 and 12 months was 0.938, between 3 and 24 months was 0.938, and between 12 and 24 months was 0.962) showed that individual eyes rarely have a change in anatomical hole status between different postbaseline times. No significant interaction was apparent between treatment effect and time (treatment x month) ($\chi^2=0.26; P=.99$), confirming that the effect of surgery did not change with time after baseline.

The analyses were repeated to examine the difference between vitrectomy and vitrectomy plus serum application, using vitrectomy as control and vitrectomy plus serum as treatment. No significant differences were found. Similar repeated-measures model analyses were carried out to evaluate the effects of treatment per se on FTMH diameter. The analysis included all eyes in each group so that in the 2 surgical groups, both successfully and unsuccessfully treated eyes were included.

Table 6 summarizes horizontal and vertical hole diameters in the 3 randomization groups at baseline and 3, 12, and 24 months. In the observation group, the mean (SD) horizontal diameter increased predominantly during the first 12 months, from 386.05 (154.27) µm at baseline to 433.19 (195.42) µm at 3 months and 482.76 (213.37) µm at 12 months, with minimal enlargement thereafter to 494.49 µm at 24 months.
(227.69) µm at 24 months. This represents an overall increase of 25% during the first 12 months and 29% in 24 months. A similar increase was evident in vertical diameter.

There was strong evidence that horizontal and vertical diameters were positively skewed, so a logarithmic scale was used for the analysis. Treatment was associated with a significant reduction in horizontal (F2,67=2.55; P=.008) and vertical (F2,67=4.50; P=.02) diameters compared with observation. In addition, there was also a significant increase in horizontal (F1,110=7.23; P=.008) and vertical (F1,130=10.02; P=.002) diameters in all 3 groups between 3 and 24 months. This reflected the overall increase in hole size in the observation group with time and the increase in diameter in failed surgical eyes in the vitrectomy and vitrectomy plus serum groups. There was no apparent association between treatment and time (treatment × month) for horizontal or vertical diameter in any group. The analysis was also performed to compare the vitrectomy plus serum group with the vitrectomy group as a control, and no significant differences were found.

TREATMENT EFFECTS: VISUAL ACUITY

The LogMAR, Snellen, and near visual acuities showed similar trends over time between 3 and 24 months (Table 7). For each response, eyes in the treatment groups had consistently better visual outcomes than those in the observation group. Snellen and near visual acuity were transformed to a logarithmic scale for the purpose of statistical analysis. In the analysis, repeated measures for each response at 3, 12, and 24 months were analyzed using statistical software (PROC MIXED in SAS; SAS Institute Inc, Cary, NC). The model included treatment as a fixed effect, time (months) as a linear fixed effect, and the correlation between measurements for each eye was modeled using a simple power law. In the initial analysis, treatment per se was compared with observation as the control. In the observation group, there was a mild decrease in LogMAR and Snellen acuities between 3 and 24 months, whereas the vitrectomy and vitrectomy plus serum groups showed an increase in LogMAR and Snellen acuities in the same period. Near vision decreased in observation eyes but remained stable in surgical eyes between 3 and 24 months.

Compared with baseline, observation eyes retained mean LogMAR around 0.7 (Snellen equivalent, 20/100), with median Snellen acuity dropping 1 line, from 20/120 at baseline to 20/200 at 24 months, and median near acuity dropping from N10 to N14 during the 24 months. In contrast, surgical eyes (vitrectomy and vitrectomy plus serum) improved in mean LogMAR acuity by 0.26 (equivalent to 2 Snellen lines), in median Snellen acuity from 20/120 to 20/60, and in median near acuity even more dramatically from N10 to N5 between baseline and 24 months.

In the combined surgical group (vitrectomy and vitrectomy plus serum), the number of eyes with Snellen acuity of 20/40 or better (the legal requirement for driving in the United Kingdom) increased from 0 of 124 at baseline to 41 (33%) of 124 at 3 months, 42 (34%) of 124 at 12 months, and 55 (44%) of 124 at 24 months.

This is in marked contrast to the observation group, in which the number of eyes with Snellen acuity of 20/40 or better increased from 0 of 61 at baseline to 3 (5%) of 61 at 3 months, 6 (10%) of 61 at 12 months, and 4 (7%) of 61 at 24 months. In surgical eyes, LogMAR and Snellen visual acuities improved bimodally between baseline and 3 months and between 12 and 24 months, with little change between 3 and 12 months, whereas practically all near visual acuity improvement occurred between baseline and 3 months.

At 24 months, surgical eyes bettered observation eyes by a mean of 0.26 LogMAR (0.42 vs 0.68), by a median of 3 Snellen lines (20/60 vs 20/200), and by a median of 5 near lines (Table 7). The beneficial effects of surgery were more dramatic for near visual acuity. There were no significant differences in visual responses between the vitrectomy and vitrectomy plus serum groups.

In the repeated-measures model analysis, all visual responses showed a significant surgical effect, with surgical eyes showing a better visual outcome than observation eyes. There was a significant correlation between visual improvement in the surgical eyes compared with the observation eyes with time and a significant interaction between treatment and time (Table 8). The analysis was repeated to compare vitrectomy plus serum eyes with vitrectomy eyes, and no differences were evident for any measure of visual acuity.

TREATMENT EFFECTS: ADVERSE EVENTS

The incidence of intraoperative and postoperative adverse events observed during the trial is summarized in Table 9 and Table 10. There were no differences between the vitrectomy and vitrectomy plus serum groups. Intraoperative u-tears, caused iatrogenically during posterior vitreous cortex peeling or at the entry sites, occurred in 4 (3.2%) of 124 surgical eyes and required intraoperative retinopexy. In another 6 eyes, preoperative...
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were successfully treated with an RD operation involv-
ing superior u-tears around the entry sites. Of the 7 RDs, 3
were associated with the FTMH itself. The 2 late RDs were associated with new
due to inferior u-tears, 1 to a superonasal u-tear, and 1 to
postoperative period. This complication was an unex-
pected finding initially (it had not been reported in the
literature at the time, to our knowledge), and after the
first patient to report this complication had been evalu-
ated, all surgical eyes underwent preoperative and post-

Of the 2 eyes developed late RD: 2 months after uncomplicated
phakoemulsification cataract surgery (12 months after
initial FTMH surgery) in 1 eye and 16 months after ini-
tial surgery in the other eye. Of the 5 early RDs, 3 were
due to inferior u-tears, 1 to a superonasal u-tear, and 1 to
the FTMH itself. The 2 late RDs were associated with new
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literature at the time, to our knowledge), and after the
first patient to report this complication had been evalu-
ated, all surgical eyes underwent preoperative and post-
operative (at 3 months) field analysis with Goldmann perimetry. Perimetric analysis revealed that another 15 (12.1%) of 124 eyes had minor, asymptomatic, peripheral, wedge-shaped defects involving less than 10° of field.

A second operation, after initially unsuccessful FTMH surgery, was performed in 18 (14.5%) of 124 surgical eyes, with equal numbers in the 2 surgical groups, and resulted in closure in 14 eyes (78%). Of the other 4 eyes in which a second operation was unsuccessful, 3 patients declined further surgery and 1 had a third operation that was unsuccessful.

The most common complication in the postoperative period was the development of nucleosclerosis, which occurred with a similar incidence in the vitrectomy and vitrectomy plus serum groups (Table 10). Nucleosclerosis was detected clinically as early as 3 months after FTMH surgery, with the mean overall grading increasing from 0.919 at baseline to 1.396 at 3 months, 2.180 at 12 months, and 2.400 at 18 months. By 24 months there was a small decline to 2.348 compared with 18 months.

The cumulative cataract surgery rate increased from 1.6% at baseline to 2.348 compared with 18 months. By 24 months there was a small decline to 2.348 compared with 18 months.

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### Table 9. Intraoperative and Postoperative Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Vitrectomy Group (n = 59)</th>
<th>Vitrectomy Plus Serum Group (n = 65)</th>
<th>Total (N = 124)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinal pigment</td>
<td>0</td>
<td>4 (6.2)</td>
<td>4 (3.2)</td>
</tr>
<tr>
<td>Retinal pigment epithelium touch</td>
<td>1 (1.7)</td>
<td>3 (4.6)</td>
<td>4 (3.2)</td>
</tr>
<tr>
<td>U-tear</td>
<td>1 (1.7)</td>
<td>3 (4.6)</td>
<td>4 (3.2)</td>
</tr>
<tr>
<td>Cataract surgery</td>
<td>0</td>
<td>1 (1.5)</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Nucleosclerosis</td>
<td>0</td>
<td>3 (4.6)</td>
<td>3 (4.6)</td>
</tr>
<tr>
<td>Nucleosclerosis grading, mean (SD)</td>
<td>0.932 (0.365)</td>
<td>0.908 (0.458)</td>
<td>0.919 (0.415)</td>
</tr>
<tr>
<td>Cataract surgery, No. (%)</td>
<td>0</td>
<td>1 (1.5)</td>
<td>1 (1.5)</td>
</tr>
</tbody>
</table>

### Table 10. Progression of Nuclear Cataract and Cataract Surgery

<table>
<thead>
<tr>
<th>Variable</th>
<th>Vitrectomy Group (n = 59)</th>
<th>Vitrectomy Plus Serum Group (n = 65)</th>
<th>Total (N = 124)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing, No. (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nucleosclerosis grading, mean (SD)</td>
<td>0.919 (0.365)</td>
<td>0.908 (0.458)</td>
<td>0.919 (0.415)</td>
</tr>
<tr>
<td>Cataract surgery, No. (%)</td>
<td>0</td>
<td>1 (1.5)</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td>3 mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing, No. (%)</td>
<td>2 (3.4)</td>
<td>1 (1.5)</td>
<td>3 (4.6)</td>
</tr>
<tr>
<td>Nucleosclerosis grading, mean (SD)</td>
<td>1.456 (1.402)</td>
<td>1.344 (0.623)</td>
<td>1.396 (1.060)</td>
</tr>
<tr>
<td>Cataract surgery, No. (%)</td>
<td>0</td>
<td>1 (1.5)</td>
<td>1 (1.5)</td>
</tr>
</tbody>
</table>

### PROGNOSTIC FACTORS FOR ANATOMIC AND VISUAL OUTCOME

Multiple regression analysis showed that general baseline factors (age, sex, and side) had no effect on anatomic and visual outcomes at 3, 12, and 24 months for the surgery and observation groups. However, FTMH stage and diameter (horizontal and vertical) were inversely correlated to anatomic and visual outcomes (an advanced stage and larger diameter had a worse outcome) but were dependent. Cystoid change had no effect on outcome.

Better Snellen and LogMAR acuities at baseline were associated with better anatomic and visual outcomes but depended on hole stage and size. Baseline near acuity did not affect either outcome. Symptom duration also did not seem to affect either outcome. Thus, it seems that the major prognostic baseline factor for anatomic and visual outcomes after surgery and observation is hole stage. Factors such as FTMH diameter and baseline visual acuity are surrogate factors for FTMH stage in this analysis.

A similar analysis showed that intraoperative complications (Table 9) did not affect either outcome. Of the 7 eyes with RD, 4 retained good visual acuity (LogMAR, 0.1-0.5; Snellen, 20/30-20/60; and near, N5-N12). These were eyes in which reattachment was achieved with 1 operation. The other 3 had macular involvement and significant proliferative vitreoretinopathy requiring extensive surgery with silicone oil, and they retained only poor LogMAR (0.7-1.0) and Snellen (20/200 to counting fingers) acuities. Retinal detachment did not affect closure, with all 7 eyes retaining closed holes. The lack of statistical correlation between the occurrence of an RD and a poor visual outcome is related to the small number of eyes with this complication.
Eyes in which FTMH closure was achieved after a second operation had slightly worse LogMAR and Snellen acuities, but similar near acuities, than eyes in which closure had been achieved after the first operation. The presence of a postoperative field defect, whether symptomatic or asymptomatic, did not seem to affect either outcome. Eyes that had undergone cataract surgery had similar anatomic outcomes as those that did not, indicating that cataract extraction does not cause substantial reopening of the hole. Similarly, these eyes had LogMAR, Snellen, and near acuities comparable to those that had not undergone cataract surgery. Thus, the most important complication of treatment that resulted in a poor visual outcome was RD with macular involvement and proliferative vitreoretinopathy.

**SUBGROUP ANALYSIS**

Further analysis, using the strategy described in the “Data Analysis” subsection, was performed on the study cohort with eyes divided into 2 subgroups: Gass stage 2 lesions and Gass stage 3 and 4 lesions.

For stage 2 lesions, 5 (21%) of 24 eyes had spontaneous closure in the observation group, whereas 47 (96%) of 49 treated lesions were closed at 24 months’ follow-up, representing a significant treatment effect (χ² = 146.6; P < .001) (Table 11). There was no treatment effect related to time or an effect for treatment × month. In treated eyes, similar closure rates were evident for the vitrectomy group (18 [100%] of 18 eyes) and the vitrectomy plus serum group (29 [94%] of 31 eyes).

For stage 3 and 4 lesions, 2 (6%) of 36 eyes had spontaneous closure in the observation group (both eyes were stage 3 at baseline) at 24 months compared with 53 (77%) of 69 treated eyes, again representing a significant treatment effect (χ² = 53.8; P < .001), with no effect related to time or an effect for treatment × month (Table 12). Closure rates were again similar for vitrectomy eyes (28 [74%] of 38 eyes) and vitrectomy plus serum eyes (25 [81%] of 31 eyes).

For stage 2 lesions, treated eyes had a mean LogMAR acuity 2.5 lines (P = .03) and a mean Snellen acuity 2.0 lines (P = .03) greater than observation eyes at 24 months, with no significant difference between vitrectomy and vitrectomy plus serum eyes. For stage 3 and 4 lesions, treated eyes had a mean LogMAR acuity 3.0 lines (P = .02) and a mean Snellen acuity 2.0 lines (P = .004) greater than observation eyes at 24-month follow-up, with no significant difference between vitrectomy and vitrectomy plus serum eyes.

The RCT described herein evaluated the benefit of surgery for FTMH compared with the natural history and determined whether use of intraoperative autologous serum improves the outcome of surgery. The results show conclusively that surgery is associated with a better anatomic closure rate (81% vs 11%) and a better visual outcome compared with observation, and use of autologous serum does not seem to improve the outcome of surgery. The data also corroborated findings from previous studies showing that the outcome for stage 2 lesions is more favorable than that for stage 3 and 4 lesions.

To date, the only randomized trial comparing surgery with observation for FTMH is that described by the VMHSG, which did not show any significant benefit of surgery.10,11,13,60,65 Furthermore, this study had a relatively high rate of sight-threatening complications after surgery. As far as the role of autologous serum is concerned, although an uncontrolled retrospective analysis conducted by the VMHSG showed that use of autologous serum was used it had little or no significant effect on outcome,10,11,13,60,65 its role has never been subjected to RCT evaluation.

Our study had a masked-observer design rather than a double-masked design because sham surgery to the observation group would not have been possible or desirable ethically. A variety of design characteristics, which strengthened the study, deserve emphasis. First, the study was conducted in a single tertiary referral center, with all initial FTMH operations and subsequent operations being performed by an independent, experienced sur-
the first 12 months. This is somewhat lower than the rate of hole reopening after successful surgery. In our study, only 2 (1.6%) of 124 lesions reopened after successful surgery, both occurring late (at 14 and 24 months). There were no cases of reopened holes during the first 12 months. This is somewhat lower than the rate of 4% to 5% in other series that included eyes with longer follow-up. In addition, it may have been that in other series, some holes classified after surgery as closed were in fact open, thus increasing the initial success rates.

In the observation group, spontaneous closure was associated with the development of a posterior vitreous detachment in all 7 eyes. Most occurred in stage 2 lesions (5 in stage 2 and 2 in stage 3), suggesting that spontaneous closure occurs in lesions in which a posterior vitreous detachment (with relief of vitreous traction) occurs early in the natural history, while the defect is small and amenable to glial repair. Hole diameter analysis confirmed that although the FTMH remains open in 88.3% of observation eyes, only a modest increase in size occurs after baseline, in accordance with previous studies, of approximately 25% during the first 12 months and 29% in 24 months.

In the surgical groups, mean horizontal and vertical diameters decreased by 70% to 75% overall after surgery. The mean residual diameter in the combined surgical cohort is attributable to eyes with persistent FTMH after unsuccessful surgery. The lack of significant differences between the vitrectomy and vitrectomy plus serum groups confirms that serum has little effect on the anatomic outcome after surgery.

The clear difference in anatomic outcome between observation and surgical eyes was also translated into a significant difference in visual function. Whereas the observation group had relatively stable mean LogMAR (decrease of 0.02) and median Snellen (decrease of 1 line) acuities and a 2-line decline in median near acuity in 24 months, surgical eyes demonstrated a substantial improvement. The latter showed a biphasic improvement in LogMAR (0.26, equivalent to 2 Snellen lines) and Snellen (2 lines) acuities. The first phase occurred immediately after FTMH surgery, during the first 3 months, owing to the effect of FTMH closure after surgery resulting in immediate improvement because of realignment and functional recovery of foveal photoreceptors. The period between 3 and 12 months was characterized by relatively stable vision in the surgical group owing to further visual acuity improvement, associated with gradual and slow recovery of photoreceptor function at the macula being masked by nuclear cataract progression. The second phase of visual recovery, between 12 and 24 months, owing to “unmasking” by phacoemulsifications, 72% of which were carried out during this period, accounted for 50% of the overall improvement in surgical eyes, confirming the importance of cataract surgery in the postoperative period. This also accounts for the poor visual improvement in surgical eyes compared with observation eyes reported by the VMHSG, where surgical eyes were precluded from cataract extraction after macular hole surgery.

The marked functional benefit of surgery was also confirmed by the number of eyes achieving Snellen acuity of 20/40 (the legal minimum requirement for driving in the United Kingdom) or better, with 45% of surgical eyes but only 7% of observation eyes achieving this level.

Near visual acuity was improved even more dramatically than distance acuity after surgery, with surgical eyes achieving a median of N5 at 24 months and observation eyes achieving a median of N14, a median difference of 6 lines. Near acuity showed only a uniphasic pattern of improvement in the surgical groups, with essentially all improvement occurring immediately after FTMH surgery. Nuclear cataract and eventual extraction had little impact on near acuity, which is not unexpected, as nucleosclerosis is known to have a more pronounced effect on distance acuity.

Advanced FTMH stage was the most significant predictor of adverse anatomic and visual outcomes for observation and surgery at 24 months. Although a large FTMH diameter was also predictive of an adverse outcome, regression analysis suggested it to be not independent of hole stage, or a surrogate marker. Better baseline LogMAR and Snellen acuities were associated with a better outcome for observation and surgery, probably reflecting more preserved foveal photoreceptor populations at baseline. These findings broadly confirm previ-
ous data from controlled and uncontrolled natural history13,39-46,78-80 and surgery13-38 studies.

The lack of effect of symptom duration on outcome can be accounted for in 2 ways. First, the study only included recent-onset lesions (≤9 months’ duration), and in such lesions, duration of 0 to 9 months may not be an important factor compared with duration in lesions of more than 1 year, in which we have shown in a previous study81 that this variable is associated with a worse outcome. Second, symptom duration, in recent-onset lesions, is a relatively inaccurate and subjective preoperative variable, particularly as most are unilateral, with patients perhaps remaining asymptomatic until the lesion is discovered incidentally.

In general, the incidence of intraoperative and postoperative sight-threatening complications was considerably lower than that reported in the VMHSG10,31,33,60,63 The RD rate of 5.6% was considerably lower than the 14% reported by the VMHSG10,31,33,60,63 but higher than the rates in other uncontrolled data. Most (5 of 7) RDs occurred during the first 6 weeks after FTMH surgery. In 3 eyes, detachment was related to inferior breaks, which could have been missed during surgery. Alternatively, they may have arisen in the early postoperative period as a result of superior vectoral tractional forces, at the inferior vitreous bases, generated by surface tension at the inferior surface of the bubble as it contracts over time. Although inferior breaks and RDs have been observed with a higher frequency after surgery with long-acting gas tamponade, such as macular hole surgery, the underlying pathogenesis remains unclear. The surgical technique used in our study included a thorough examination of the retinal periphery using scleral indentation before the fluid-gas exchange. This is an important step in ensuring that iatrogenic tears are treated.

The other adverse effect observed in our study was postoperative visual field defects. At the onset of the study, this had not been observed by our group, or indeed by any other group, and had not been reported in the literature, to our knowledge. After the first patients reported field defects, which were confirmed by field analysis, Goldmann perimetry was performed before surgery (baseline) and at 3 months in all surgical eyes. In due course, it became evident that visual field defects were relatively rare and did not constitute sufficient reason to terminate the study. Overall, only 4 (3.2%) of 124 surgical eyes developed symptomatic field defects, although another 15 (12.1%) of 124 developed very minor, peripheral wedge defects that were asymptomatic. These findings led to a separate study49 to evaluate the mechanisms responsible for the defects. These data and a variety of other studies49-58 suggest that the most likely cause is mechanical damage to inner retinal nerve fibers caused by either vitreopapillary traction during posterior vitreous cortex separation or the effects of air drying during surgery.

In summary, this article described a masked-observer RCT to evaluate the benefit of FTMH surgery compared with the natural history and determined whether application of intraoperative adjunctive autologous serum improves the results of surgery. The data showed successful randomization, with a high capture rate during follow-up. There was significant anatomic and visual improvement in surgical eyes compared with observation eyes. Treatment was associated with a low incidence of sight-threatening complications, confirming that FTMH surgery is a safe and effective procedure that should be considered and offered where appropriate. Use of autologous serum did not seem to have a significant impact on the results, and its role in FTMH surgery remains unproved.

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Moorfields Macular Hole Study Group


