Facedown Positioning Following Surgery for Large Full-Thickness Macular Hole
A Multicenter Randomized Clinical Trial

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IMPORTANCE The value of facedown positioning following surgery for large full-thickness macular holes is unknown.

OBJECTIVE To determine whether advice to position facedown postoperatively improves the outcome for large macular holes.

DESIGN, SETTING, AND PARTICIPANTS This randomized, parallel group superiority trial with 1:1 randomization stratified by site with 3 months' follow-up was conducted at 9 sites across the United Kingdom and included participants with an idiopathic full-thickness macular hole of at least 400 μm minimum linear diameter and a duration of fewer than 12 months. All participants had vitrectomy surgery with peeling of the internal limiting membrane and injection of perfluoropropane (14%) gas, with or without simultaneous surgery for cataract.

INTERVENTIONS Following surgery, participants were randomly advised to position either facedown or face forward for 8 hours daily for 5 days.

MAIN OUTCOMES AND MEASURES The primary outcome was closure of the macular hole determined 3 months following surgery by masked optical coherence tomography evaluation. Secondary outcome measures at 3 months were visual acuity, participant-reported experience of positioning, and quality of life measured by the National Eye Institute Visual Function Questionnaire 25.

RESULTS A total of 185 participants (45 men [24.3%]; 156 white [84.3%]; 9 black [4.9%]; 10 Asian [5.4%]; median age, 69 years [interquartile range, 64-73 years]) were randomized. Macular hole closure was observed in 90 (85.6%) who were advised to position face forward and 88 (95.5%) advised to position facedown (adjusted odds ratio, 3.15; 95% CI, 0.87-11.41; \( P = .08 \)). The mean (SD) improvement in best-corrected visual acuity at 3 months was 0.34 (0.69) logMAR (equivalent to 1 Snellen line) in the face-forward group and 0.57 (0.42) logMAR (equivalent to 3 Snellen lines) in the facedown group (adjusted mean difference, 0.22 [95% CI, 0.05-0.38]; equivalent to 2 Snellen lines); 95% CI, 0.05-0.38; \( P = .01 \)). The median National Eye Institute Visual Function Questionnaire 25 score was 89 (interquartile range, 76-94) in the facedown group and 87 (interquartile range, 73-93) in the face-forward group (mean [SD] change on a logistic scale, 0.08 [0.26] face forward and 0.11 [0.25] facedown; adjusted mean [SD] difference on a logistic scale, 0.02; 95% CI, −0.03 to 0.07; \( P = .41 \)).

CONCLUSIONS AND RELEVANCE The results do not prove that facedown positioning following surgery is more likely to close large macular holes compared with facing forward but do support the possibility that visual acuity outcomes may be superior.

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Key Points

**Question** Is the closure of large macular holes improved by advising facedown positioning postsurgery?

**Findings** In this randomized clinical trial of 185 participants, macular hole closure in those advised to position facing down was not superior to macular hole closure in those facing forward.

**Meaning** The results do not prove that facedown positioning following surgery is more likely to close large macular holes.

Methods

**Consent and Ethics**

The research adhered to the tenets of the Declaration of Helsinki. The trial was approved by the national ethics committee and registered with ISRCTN (12410596) and the UK Clinical Research Network Portfolio (17966). Participants gave their fully informed written consent before enrollment.

**Design**

The detailed methods are described in the published protocol (Supplement 1). We performed a multicenter interventional parallel group superiority comparative randomized clinical trial comparing facedown positioning with face-forward positioning, with 1:1 randomization stratified by site. Consolidated Standards of Reporting Trials guidelines were followed.

**Participants**

We included participants with an idiopathic full-thickness macular hole of at least 400-μm minimum linear diameter and a duration of fewer than 12 months who elected to have surgery for macular hole with or without simultaneous surgery for cataract. All participants had vitrectomy surgery with peeling of the inner limiting membrane and injection of perfluoropropane (C3F8), 14%, gas, with or without simultaneous surgery for cataract. No additional intervention (such as inner limiting membrane flap) was performed. If postoperative positioning was advised to support a retinal tear identified during surgery, participants were excluded before randomization.

**Intervention**

Following surgery, participants were randomly advised to position either facedown or face forward for at least 8 consecutive or nonconsecutive hours daily for 5 days. All participants were advised to avoid a faceup position for 5 days. Positioning was explained with the help of written instructions and diagrams.

**Outcomes**

The primary outcome was anatomical closure of the macular hole at 3 months following surgery determined by spectral-domain optical coherence tomography (OCT) evaluation. Two independent retinal specialists, masked to treatment allocation, graded independently the outcome in each instance as closed, open and flat (without a cuff of subretinal fluid), open and elevated (with a cuff of subretinal fluid). The categories open and flat and open and elevated were combined into a single category of open for analysis.

The secondary outcome measures at 3 months were best-corrected visual acuity (BCVA) measured using a Snellen chart at a standard distance of 6 m, participant-reported experience of positioning on a scale from 0 (very difficult) to 10 (very easy), and participant-reported health and quality of life evaluated using the National Eye Institute Visual Function Questionnaire 25 (NEI VFQ-25) from 0 (worst health and quality of life) to 100 (best health and quality of life). We also investigated the participants’ own judgments of their individual outcomes by asking each the question “Given what you now know, would you still have elected to have the operation?”

**Randomization and Masking**

Participants were randomly advised, in a 1:1 ratio, to position either face forward or facedown. The randomization was stratified by site using random permuted blocks of size 4 or 6 in equal proportions. The randomization was performed using a secure bespoke online randomization service implemented by...

Full-thickness macular holes are conventionally managed by surgical removal of the vitreous gel to relieve any persistent traction acting at the macula and intraocular injection of a gas bubble to provide a temporary scaffold that promotes hole closure. Following the surgical procedure, a period of facedown positioning may be advised to improve the outcome by maintaining consistent close contact of the gas bubble with the macula at the posterior pole. However, facedown positioning can be arduous, uncomfortable, and disabling; it is of unproven benefit and presents a risk of harm. A systematic review in 2011 found that, for macular holes smaller than 400 μm in minimum linear diameter, the estimated association of facedown positioning with hole closure was not statistically significant. For macular holes larger than 400 μm minimum linear diameter, the evidence from randomized clinical trials suggested that postoperative positioning may improve the rate of hole closure. However, the evidence was insufficient to draw firm conclusions with which to guide practice because it was based on fewer heterogeneous studies, with the use of several different tamponade gases within a single study, and lacking patient-reported outcomes. A subsequent large retrospective nonrandomized noninferiority study did not exclude the possibility of benefit. The aim of this study was to determine whether advice to position facedown postoperatively improves the outcome of surgery for large (≥400 μm) full-thickness macular holes.

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the Pragmatic Clinical Trials Unit. Randomization was performed following surgery to ensure the masking of the surgeon to the treatment allocated. The independent retina specialists responsible for grading OCT scans were also masked to the treatment allocation. The participants themselves and the clinical teams managing their care were unmasked.

Statistical Considerations and Sample Size
The sample size calculation and statistical analysis plan are described in Supplement 2. Clinical consensus was that face-down positioning would be recommended if this was to improve the rate of success by 15%. This was the smallest clinically relevant treatment difference that we sought to detect. Previous findings indicated that surgery for large macular holes (≥400-μm diameter) without advice to position face-down results in anatomical hole closure in 80%. To detect a 15% difference in outcomes with 85% power and 95% confidence, we sought to include 86 participants in each of the 2 treatment groups. With an anticipated 10% loss to follow-up, we aimed to recruit 96 participants to each group. Dichotomous outcomes were analyzed by mixed logistic regression and continuous outcomes by mixed linear regression. Analyses were adjusted for the fixed effects of macular hole size and phakic lens status at baseline and a random effect of site. The fitted logistic regression model for the primary outcome, which estimates the treatment effect as an odds ratio, was also used to calculate absolute risk differences for particular covariate values. A logistic transformation (log(x/(1-x))) was applied to NEI VFQ-25 scores to give them a less skewed distribution. Further details of analyses are given in the published analysis plan. P values were 2-tailed with no correction for multiple analyses with statistical significance at .05. Analyses were conducted with Stata, version 14.2 (StataCorp).

Results
Baseline Characteristics
A total of 206 participants were enrolled in the study (Figure). Of these, 22 withdrew before randomization because they no longer met the inclusion criteria or no longer wished to participate. A total of 185 participants were randomized (Table 1); of these, 1 participant (0.5%) withdrew before treatment allocation and 3 from each group (3.2%) were excluded following randomization because they were found to be ineligible owing to a macular hole dimension of less than 400-μm minimum linear diameter. No participant was lost to follow-up. The group advised to position face-down included more black participants and fewer Asian participants and had a slightly smaller median macular hole diameter. The baseline characteristics of the 2 groups otherwise appeared similar.

Outcomes
Primary Outcome
The grading of macular hole status on OCT scans at 3 months was consistent between the 2 masked graders in every instance. In 1 instance, in the absence of an OCT scan, the outcome (open hole) was determined by unmasked clinical examination. Successful macular hole closure was observed in 77 (85.6%) of those advised to position face forward and in 84 participants (95.5%) advised to position face-down (adjusted odds ratio, 3.15; 95% CI, 0.87-11.41; P = .08). Hole size (but not lens status) was strongly associated with risk, and consequently when the odds ratio is translated to an absolute risk difference scale, this risk difference is dependent on macular hole size (but not on lens status) (Table 2). At the median macular hole size (488.5 μm; interquartile range [IQR], 450-578), the odds ratio of 3.15 corresponded to an absolute risk difference of 4.1% (95% CI, −0.8% to 9.1%), or a number needed to treat of 24.

Table 1. Baseline Characteristics

| Characteristic                                      | Positioning, No. (%) | Face-forward (n = 90) | Facedown (n = 88) |
|-----------------------------------------------------|----------------------|-----------------------|-------------------|
| Race/ethnicity                                      |                      |                       |                   |
| White                                               | 78 (86.7)            | 78 (88.6)             |
| Black                                               | 2 (2.2)              | 7 (8.0)               |
| Asian                                               | 8 (8.9)              | 2 (2.3)               |
| Mixed                                               | 0 (0.0)              | 1 (1.1)               |
| Other                                               | 2 (2.2)              | 0 (0.0)               |
| Laterality, left side                               | 47 (52.2)            | 49 (55.7)             |
| Duration of symptoms, median (IQR), mo             | 5 (3-7)              | 5 (4-7)               |
| BCVA, median (IQR)                                  | 20/200 (20/80-200/200) | 20/200 (20/80-200/200) |
| Lens status, phakic                                 | 78 (86.7)            | 72 (81.6)             |
| Cataract surgery performed                          | 44 (48.9)            | 45 (51.1)             |
| Macular hole diameter on OCT, median (IQR)          | 517 (460-588)        | 480 (446-557)         |
| Quality of life VFQ-25, mean (SD)                   | 77.1 (17.4)          | 76.4 (17.9)           |
| Vitrefoveal detachment present                      | 32 (35.6)            | 33 (37.5)             |

Abbreviations: BCVA, best-corrected visual acuity; IQR, interquartile range; OCT, optical coherence tomography; VFQ-25, Visual Function Questionnaire 25.
Secondary Outcomes
The mean (SD) logMAR-converted BCVA at 3 months was 0.87 (0.57) (Snellen equivalent, 20/160 OU) in the face-forward group and 0.68 (0.39) (Snellen equivalent, 20/100 OU) in the face-down group (adjusted mean difference, 0.16; 95% CI, 0.02–0.30; \( P = .02 \)) (Table 3). The mean (SD) improvement in BCVA at 3 months was 0.34 (0.69) logMAR (equivalent to 1 Snellen line) in the face-forward group and 0.57 (0.42) logMAR (equivalent to 3 Snellen lines) in the facedown group. The adjusted mean difference in mean improvement in logMAR acuity was 0.22 (equivalent to 2 Snellen lines) (95% CI, 0.05–0.38; \( P = .01 \)). In a post hoc analysis of visual acuities, we found that deterioration by 0.3 logMAR (15 Early Treatment Diabetic Retinopathy Study letters) or more affected 90 participants (12%) positioning face forward but only 88 (1%) of those positioning face-down (\( P = .01 \)) (Table 3). The proportion of participants reporting at 3 months that, given their experience, they would still have elected to have the operation was 90.5% in the face-forward group and 90.4% in the facedown group (adjusted odds ratio, 1.01; 95% CI, 0.36–2.88; \( P = .98 \)). The median NEI VFQ-25 score was 87 (IQR, 73–93) in the face-forward group and 89 (IQR, 76–94) in the facedown group (adjusted mean difference on a logistic scale, 0.02; 95% CI, −0.03 to 0.07; \( P = .41 \)). There were no related unexpected serious adverse events.

Discussion
Surgical approaches for macular hole repair share key common techniques but also include variations that can confound the interpretation of outcomes unless appropriately controlled. Our trial was designed to determine the effect of positioning as it is commonly advised by many UK retina surgeons considering their preferred practice as determined by a survey of members of the British and Eire Association of Vitreoretinal Surgeons and their judgment of clinical equipoise. In this way, we could ensure efficient recruitment to the trial and generate results that were directly relevant to common practice. Our findings are applicable specifically to surgery for macular holes at least 400-μm minimum linear diameter with...
the use of perfluoropropane, 14%, gas and positioning face-
down 8 hours daily for 5 days; the findings are not directly rel-
etive to the use of alternative tamponade agents or position-
regimens. We elected to compare facedown positioning not with free positioning but with seated face-forward position-
ing so as to mitigate a perceived risk of harm from physical over-
activity; the relative immobility of the seated position may re-
sult in a stress associated with intraocular fluid currents other-
ised by physical activity in gas-filled eyes.13 We chose hole closure as the primary outcome on the advice of
the prospect of further intervention that might be necessary
to close a macular hole that was persistently open despite sur-
gery. In this randomized clinical trial of 158 participants, macu-
lar hole closure in those advised to position facing down was
not shown to be superior to macular hole closure in those facing forward. However, secondary visual acuity outcomes
appeared to be superior in the facedown group.

Limitations
The study has several limitations. Participants were not pro-
vided with specific advice regarding positioning while sleep-
ing because our lay advisory group judged that compliance
while sleeping would be unfeasible for many people; a pos-
sible confounding effect cannot be excluded despite the ran-
domized trial design. We chose not to estimate the adherence
of participants with the advice to position postoperatively
because such measurement is of unknown reliability and could
influence behavior artificially. Instead we sought to deter-
mine pragmatically the effect of the advice to position as de-
scribed. Given that trial participants reported difficulty with
facedown positioning, the compliance of those advised to po-
sition facedown may have been poorer than those advised to
position face forward. However, in clinical practice, the
effect on compliance is likely to be in a similar direction.
Because the trial was powered statistically to detect a differ-
ence in success rate of 15%, an effect size of less than 15% is
not excluded. We chose to describe the effect in terms of the
odds ratio, which may overestimate the risk compared with the
risk ratio. The apparent change in risk difference with hole size
is a consequence of the mathematical conversion from a log
odds scale to a risk difference scale (an expression of our find-
ings about the treatment effect from the logistic regression)
and is not considered evidence of an interaction. We are not
able to determine definitively whether the benefit to visual acu-
ity is a consequence of hole closure owing to the limited size
of the trial and its design. Because the visual acuity of the
participants’ contralateral nonoperated eyes was not col-
clected, we are not able to interpret the differences between
groups for the NEI VFQ-25 data regarding the better seeing
eye, which can substantially influence this measure in reti-
nal disease.14 The study was designed to determine the
effect of positioning in primary surgery for macular holes
and does not enable the evaluation of outcomes following
further surgery for the few macular holes persistently open
despite primary surgery.

Conclusions
On the evidence of the findings, people with macular holes of
a diameter of 400 μm or greater can be informed that surgery
using the technique described and positioning face forward of-
ers an estimated 86% likelihood of hole closure. The find-
ings do not provide definitive evidence that the advice to po-
sition facedown improves the outcome for macular hole closure
or visual acuity. The findings of prespecified and post hoc
analyses suggest a modest benefit to visual acuity at 3 months,
which was one of several secondary outcomes. In the ab-
ence of definitive evidence of an effect on hole closure, a
possible benefit to visual acuity is unexplained, although face-
down positioning might protect phakic eyes against gas-
induced cataract. For people with macular holes of a diam-
er of 400 μm or greater, the results of this trial provide
evidence to predict the likely outcome of surgery and guide
their choice of positioning postoperatively.
The high success rate for macular hole (MH) surgery is a great source of satisfaction for patients and vitreoretinal surgeons. The discovery of not lasering the macular hole when treating an associated retinal detachment established a therapy that previously did not exist. Subsequent studies and experience by many others have identified prognostic subsets that have better or poorer outcomes, such that anatomic success exceeds 90% in most cases, with satisfyingly moderate visual improvement in at least 75%.

It was only natural for the experience reported by Kelly and Wendel to establish intraocular gas tamponade with face-down positioning as critical therapeutic elements, by extension of treatment for rhegmatogenous retinal detachments. Unequivocally, face-down positioning is the most difficult aspect for the patient. Hence, the dogma of sustained, long-term, compulsive face-down positioning has been questioned and examined from many perspectives. High success rates have been demonstrated with shorter-acting gas (even room air) and shorter face-down duration (as little as a day), albeit for small MHs. Indeed, in selected cases, with relief of vitreomacular traction without tamponade, success has been reported surgically as well as pharmacologically. These studies have called into question the role of internal tamponade in creating MH closure. Indeed, early postoperative optical coherence tomography studies have demonstrated morphologic MH closure in most eyes on the first postoperative day.

The size (independently or as a covariate with other factors) of the MH seems to be the most important factor determining postoperative success. In recent years, the emergence and growing adoption of the internal limiting membrane flap technique for such eyes has been reported. First described for very large MHs, its use seems to be extending to medium-sized MHs.

In this issue of JAMA Ophthalmology, Pasu et al present the largest series, to our knowledge, in which a multicenter randomization to face-down positioning vs a more limited, liberal, head-forward approach has been tested for larger MHs. In their study, the authors did not find significantly different anatomic success rates between the groups, but they did find statistically significantly better mean visual acuity in the facedown positioning group (20/80 vs 20/120). Of course, the visual acuity results are paramount to the patient and should probably be considered the most important outcome metric.

The authors’ study design did not include a noninferiority evaluation. In a superiority study (such as this one), the lack of a statistically significant outcome should not lead to a conclusion that the groups’ anatomic results are the same. The ubiquity of this incorrect conclusion in the medical literature can be problematic when interpreting results of randomized controlled trials.

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