OUTCOMES OF SULFUR HEXAFLUORIDE (SF₆) VERSUS PERFLUOROPROPANE (C₃F₈) GAS TAMPONADE FOR MACULAR HOLE SURGERY

SUNG SOO KIM, MD, PhD,* WILLIAM E. SMIDDY, MD,† WILLIAM J. FEUER, MS,† WEI SHI, MS†

Purpose: To compare outcomes of macular hole surgery using sulfur hexafluoride (SF₆) gas versus perfluoropropane (C₃F₈) gas for idiopathic macular hole repair.

Design: Retrospective, interventional, comparative cohort study.

Methods: Institutional clinical practice. A consecutive group of patients undergoing macular hole surgery with SF₆ group (38 eyes of 38 patients) and a nonconsecutive, contemporaneous, comparison group with C₃F₈ was used (41 eyes of 39 patients). Vitrectomy for macular hole surgery using either of two different gases for internal tamponade. Best corrected logarithm of minimal angle resolution visual acuity, anatomic closure, reoperations, development of cataract, and complications such as retinal detachment.

Result: The macular hole closure rate was similar in both groups [34/38 (90%) with SF₆ gas versus 37/41 (91%) with C₃F₈ gas, P = 0.91]. At 6 months after macular hole surgery, best-corrected visual acuity was improved compared with baseline visual acuity by a mean of 0.32 logarithm of minimal angle resolution in the SF₆ group (P = 0.045) and 0.52 logarithm of minimal angle resolution in the C₃F₈ group (P < 0.001). Development of vision-impairing cataract in phakic eyes was not different, but the myopic shift was greater in the C₃F₈ group (P = 0.016).

Conclusion: Macular hole surgery using SF₆ gas yields similar results as with C₃F₈ gas and may be a good option.


Macular hole surgery (MHS) typically involves internal gas tamponade and face down positioning. A range of gas types and mixtures and various positioning regimens have been reported generally with good success. There is a paucity of data comparing one positioning regimen or one type of gas to another. A higher success rate for MHS with longer lasting mixtures compared with a shorter lasting mixtures of perfluoropropane (C₃F₈) was reported,¹ but the shorter duration gas, sulfur hexafluoride (SF₆) was described in the initial report of MHS² and in the more highly successful follow-up report.³ Currently, SF₆ is used by approximately one third of surgeons.⁴ Long lasting gas (such as C₃F₈) may offer more extensive tamponade, but impairs vision longer, which may delay or compromise a patient’s return to daily activities such as work and driving and prohibits air travel as long as 8 weeks. Subsets of some large MHS series have yielded data on both SF₆ and C₃F₈ use, but have not been systematically compared. The effect of duration or rigor of prone positioning has also not been

From the *Department of Ophthalmology, Yongdong Severance Hospital, Yonsei University College of Medicine, Seoul, South Korea; and †Department of Ophthalmology, Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, Miami, Florida.

Supported by Research to Prevent Blindness and NEI Core Center Grant P30 EY014801.

Reprint requests: William E. Smiddy, MD, 900 NW 17th Street, Miami, FL 33136; e-mail: wsmiddy@med.miami.edu

1408
definitely studied and was not evaluated in the current study.

The purpose of this study was to evaluate outcomes of MHS using 20% SF₆ gas tamponade compared with 16% C₃F₈ gas tamponade.

**Methods**

The study protocol was approved by the Human Subjects Research Office of the University of Miami Miller School of Medicine. Surgeries were performed from May 2002 through February 2007 by one surgeon (W.E.S.). Commonly, 20% SF₆ tamponade was offered to patients who required air travel within 2 weeks and, in some cases, to one-eyed patients to hasten visual rehabilitation (the SF₆ group). Trauma-induced and high myopia-associated cases were excluded. A comparative cohort study design was used by comparing the consecutive SF₆ group with a cohort of patients who received MHS using C₃F₈ during the same week as matched (for technique), comparative controls. Occasionally, more than one C₃F₈ case was operated in the same week as an SF₆ case, accounting for the difference in size of case and control cohorts. Many other patients in the author’s practice underwent MHS using C₃F₈, but only the matched group was tabulated for comparison.

Preoperative data obtained for each patient included age, gender, stage, and duration of symptoms of macular hole. The lens status was assessed preoperatively and at the follow-up visits. The best-corrected visual acuity (BCVA) and manifest refractive error (measured using a phoropter) were measured preoperatively and postoperatively. Snellen visual acuity was converted to the negative logarithm of minimal angle resolution (logMAR) for statistical analysis and comparison.

The surgical technique involved a standard 3-port, 20-gauge pars plana vitrectomy with induction of posterior vitreous detachment (PVD) using a silicone tip suction cannula in cases of Stage 2 or 3 macular holes. A barbed MVR blade, vitreoretinal pick, and fine forceps were used to peel the internal limiting membrane (ILM) in all cases; staining of ILM with indocyanine green (ICG) was performed only for selected cases in which visibility was compromised. When used, five drops of 0.25% ICG was instilled for 5 seconds after doing a nearly complete fluid-air exchange; then, the ICG was aspirated and fluid replaced the air for the peeling step. After peeling and examining the peripheral retina, a complete fluid gas exchange was performed and 20% SF₆ or 16% C₃F₈ gas was flushed through the eye. All patients were asked to maintain maximal face down positioning for 1 week postoperatively. Practical and reliable quantitative measures of degree and duration of positioning do not exist; thus, “maximal” was a 24 hour/day target that may have varied in extent. Examinations were planned at 1 week, 1 month, 3 months, and 1 year postoperatively and at other times as clinically indicated.

Postoperatively, the macula was examined using biomicroscopy; optical coherence tomography (Stratus OCT™, Carl Zeiss Meditec, Inc., Dublin, CA) testing was used in selected cases, because in most cases optical coherence tomography was not necessary to make the diagnosis and information obtained would not have altered management. The time at which a macular hole closure was determined and absorption of gas bubble occurred were noted for each group. Cataract progression after MHS and perioperative complications were identified. The amount of refractive change and development of vision-impairing cataract (defined as either having had or having been recommended for cataract surgery after MHS) were also evaluated.

The main outcome measures were anatomical success rate and visual improvement. Visual improvement was defined as reduction of at least 0.3 logMAR unit from the preoperative to final postoperative follow-up examination, which approximates a three Snellen line acuity improvement.

Preoperative and postoperative characteristics of each group were tabulated and compared. Means of continuous variables were compared with student’s two-sided t-test. Proportions were compared with the chi-square test; the exact permutation chi-square test was used when sample sizes were small. Ordinal variables, including months followed, were described with medians and ranges and compared with Mann–Whitney test. To evaluate the effect of each gas on the crystalline lens, time interval to the decision for cataract extraction after MHS was measured and analyzed with Kaplan–Meier survival curve. Cox proportional hazards regression was used to measure the relative risk of cataract progression by type of gas. Preoperative and postoperative refractive changes (spherical equivalent) were tabulated and compared with t-test.

**Results**

There were 38 cases (SF₆ group) and 41 controls (C₃F₈ group). The groups were similar with regard to age, preoperative BCVA, and duration of MH symptoms (Table 1). The mean ages (68.6 years versus 66.5 years) and the duration from initial onset of MH
symptoms to the surgery (median of 3 months in both group) were similar. Although there was no difference in prevalence of PVD between the two groups (P = 0.82, chi-square test), the C₃F₈ group had more Stage 3 holes and fewer Stage 2 holes than the SF₆ group (P = 0.002, Fisher exact test).

There was a 21:17 (55%) male predominance in the SF₆ group, in contrast to a 30:11 (73%) predominance of females in the C₃F₈ group (P = 0.009, chi-square test). The preoperative BCVA distribution was similar (0.86 versus 0.99, P = 0.17, two-sample t-test), as was the distribution of eyes with MH symptom duration longer than 6 months for each group (26% for SF₆ versus 15% for C₃F₈, P = 0.002, chi-square test).

The C₃F₈ group had a longer postoperative follow-up period (median 5.5 months) compared with the SF₆ group (median 1.8 months) (P < 0.001, Mann–Whitney test), probably because SF₆ patients were more commonly from out of town, and, accordingly, were less likely to return for a long-term follow-up examination.

The anatomical success rates in the SF₆ and the C₃F₈ groups were similar for all subgroups (P = 1.00, logistic regression): overall (90% versus 91%), Stage 2 (94% versus 100%), Stage 3 (100% versus 90%), and Stage 4 (77% versus 87%). The duration of macular hole symptoms, stage, presence of PVD, and use of ICG dye staining for ILM peeling did not significantly affect the relation of anatomical success rate to type of gas used (Table 2), and the difference in success rates between gases remained nonsignificant after adjusting for these factors (P = 0.84, logistic regression). Only absence of PVD was significantly related to anatomical success (P = 0.048, logistic regression) which, of course, is a surrogate for the Stage 4 classification. The difference between rates of successful surgeries in the two groups was not significant (P = 1.00); the beta error of these data cannot exclude a possibility difference smaller than 14% in favor of C₃F₈ or 13% in favor of SF₆.

As expected, the gas bubble was absorbed sooner in the SF₆ group (median 14 days) than in the C₃F₈ group (median 45 days, P < 0.001, Mann–Whitney test), which allowed earlier assessment of MH closure in the SF₆ group (13 days versus 34 days).

Postoperative BCVA logMAR was similar for both groups at all postoperative time periods (Table 3), and
visual acuity improved in both groups after surgery except at 1 month after surgery in C₃F₈ group because of the presence of the gas bubble. LogMAR improved from 0.99 (20/200 Snellen) to 0.45 (20/60 Snellen) for the C₃F₈ group and from logMAR 0.86 (20/150) to logMAR 0.37 (20/50 Snellen) for the SF₆ group at 1 year. There were no significant differences between the groups in logMAR acuities or logMAR acuity improvements at any time point among the 32% of cases which were pseudophakic preoperatively (all \( P > 0.30 \)). The distributions of eyes which showed halving of resolved visual angle were similar between both groups (Figure 1), including only pseudophakic cases, 14 (34%) of C₃F₈ and 11 (28%) of SF₆.

To evaluate predictive factors for visual outcomes, the following variables were included in logistic regression models for preoperative or postoperative risk factors for BCVA at 3 and 6 months: gas type used, gender, preoperative BCVA, PVD, stage of macular hole, use of ICG, intraoperative complications, duration of MH symptoms, and preoperative lens status. For both 3- and 6-month time points worse preoperative acuity was highly significantly associated with postoperative improvement (\( P < 0.001 \)). At 3 months, use of ICG was associated with a lower odds of improvement (\( P = 0.023 \)) and at 6 months shorter duration of symptoms was associated with improved acuity (\( P = 0.003 \)). No ophthalmoscopic signs of ICG toxicity were noted, though, and ICG was only used in cases with poorer visibility by virtue of intraocular lens or crystalline lens opacities or poor contrast because of lack of retinal pigment epithelium pigmentation. No other variables were statistically significantly related to visual improvement.

Retinal breaks were detected or suspected in 4 (5%) eyes in the current study and treated with external...
cryotherapy intraoperatively. Self-limited postoperative vitreous hemorrhage occurred in 2 (5%) C₃F₈ eyes. One (2%) C₃F₈ eye received later surgery for subsequent retinal detachment, and 1 (3%) SF₆ eye developed neovascular glaucoma attributed to diabetic retinopathy. Three eyes (4%) underwent repeat MHS: two (both Stage 3) C₃F₈ eyes at 9.5 and 80 months and one (Stage 4) SF₆ eye at 3 weeks after the original surgery.

The preoperative lens status distributions were similar in both groups (Table 4). The cumulative proportion of preoperatively phakic eyes undergoing cataract surgery at 6 months were 48% and 66% for the C₃F₈ and SF₆ groups, respectively (P = 0.096, log-rank test) (Figure 2). Analysis with Cox proportional hazards regression, adjusting for age and the presence of a cataract at the time of MHS, showed a risk of undergoing cataract surgery 2.0 times higher (95% confidence interval 1.00 to 3.88) for the SF₆ group compared to the C₃F₈ group.

Table 4. Lens and Refraction Change by MHS

<table>
<thead>
<tr>
<th>Lens status before surgery</th>
<th>SF₆ (n = 38)</th>
<th>C₃F₈ (n = 41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pseudophakic (%)</td>
<td>11 (29)</td>
<td>14 (34)</td>
</tr>
<tr>
<td>phakic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clear lens (%)</td>
<td>8 (21)</td>
<td>9 (22)</td>
</tr>
<tr>
<td>Early cataract (%)</td>
<td>19 (50)</td>
<td>18 (44)</td>
</tr>
<tr>
<td>Spherical equivalent in phakic eyes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before MHS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean diopters (range), phakic</td>
<td>−0.17 (−6.13 to 3.25)</td>
<td>0.47 (−3.25 to 3.5)</td>
</tr>
<tr>
<td>Mean diopters (range), pseudophakic</td>
<td>−0.55 (−2.63 to 1.5)</td>
<td>0.17 (−1.13 to 1.88)</td>
</tr>
<tr>
<td>C₃F₈ vs. SF₆, P = 0.063†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phakic vs. pseudophakic, P = 0.38†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-MHS myopic shift after absorption of gas‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (diopters), phakic</td>
<td>−0.82</td>
<td>−1.42</td>
</tr>
<tr>
<td>Mean (diopters), pseudophakic</td>
<td>0.02</td>
<td>−0.58</td>
</tr>
<tr>
<td>C₃F₈ vs. SF₆, P = 0.016§</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phakic vs. pseudophakic, P = 0.002§</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Chi-square test.
†Two-way analysis of variance.
‡Means adjusted for preoperative refraction.
§Two-way analysis of covariance.
MHS, macular hole surgery.
confidence interval: 0.9–4.5) for SF₆ gas than C₃F₈ gas among phakic eyes, although this was not statistically significant (P = 0.072, with risk ratio 2.1, 95% confidence interval: 0.94–4.7). Preoperatively, there was a borderline significant difference between spherical equivalent refractions of each group (P = 0.063), but the extent of postoperative myopic shift was significantly larger in patients treated with C₃F₈ gas than SF₆ gas in both phakic and pseudophakic eyes. The myopic shift was larger in phakic eyes and in those eyes that were less myopic preoperatively (Table 4).

Discussion

Kelly and Wendel used SF₆ gas for internal tamponade in their seminal study on MHS, reporting an anatomical success rate of 73%.² Their results were better in a follow-up study, also using SF₆, and others have also reported high anatomical success rates (over 90%) with shorter acting gas such as SF₆ or even room air.⁶⁻⁷ Although a majority of vitreoretinal surgeons use C₃F₈, approximately 1/3 report using SF₆, presumably with excellent results. Others have variously combined shorter duration of gas with little or no face-down positioning.⁸⁻¹⁵ Spaide has demonstrated that in selected cases with very early macular hole formation, release of the vitreous without any gas tamponade is sufficient to induce macular hole closure. These reports notwithstanding, a majority of clinical reports (which report anatomical success rates over 90%) have espoused C₃F₈ usage, most commonly in conjunction with face-down positioning for 1 to 2 weeks.¹⁹,²⁰ The duration or extent of the positioning regimen was not evaluated in the current study.

Gas tamponade is hypothesized to enhance macular hole closure after removal of tangential force via its flotation force at the macula, its surface tension which excludes vitreous fluid from the subretinal space, and by its role as a template to direct reparative inner retinal cell migration.²¹,²² ILM peeling is widely considered to facilitate macular hole closure,¹⁰,²³,²⁴ perhaps by removing an element of traction or by stimulating gliosis.²²

In the current study, no statistically significant difference between 20% SF₆ gas and 16% C₃F₈ gas was observed in inducing macular hole closure regardless of stage or duration of symptoms, although the power of the test (beta error) was such that this study cannot exclude a difference as large as 14%. The comparative cohort study design was chosen to minimize differences in surgical technique or management practice in recent years. Both groups included relatively large

Fig. 2. Kaplan–Meier curve of the cumulative proportion of preoperatively phakic eyes undergoing cataract surgery at the time points after macular hole surgery (MHS).
numbers of Stage 4 and reoperated macular holes (34% versus 37%) compared with other reported series (which typically included approximately 20% Stage 4 macular holes)\textsuperscript{3–10,20}; this may have accounted for slightly lower overall success rates compared with series reporting success well over 90%. One report which included SF\textsubscript{6} and C\textsubscript{3}F\textsubscript{8} cases found a 93.5% anatomical success with SF\textsubscript{6} compared with 96.7% in C\textsubscript{3}F\textsubscript{8} gas tamponade,\textsuperscript{5} but autologous platelet concentrate use may have confounded differences. Brooks\textsuperscript{20} had a small subset of SF\textsubscript{6} eyes and found a tendency for poorer results with SF\textsubscript{6} compared with C\textsubscript{3}F\textsubscript{8}.

Advantages of SF\textsubscript{6} include earlier confirmation of closure compared with the C\textsubscript{3}F\textsubscript{8} group and sooner return to air travel and other daily activities because of more rapid visual recovery commensurate with gas resorption. Closure of macular holes within 3 days after ILM peeling has been reported with confirmation by optical coherence tomography imaging.\textsuperscript{25}

Another strategy proposed to allow sooner air travel, visual rehabilitation, or less stringent prone positioning was using silicone oil as a tamponade agent.\textsuperscript{26} However, the visual success rates have been widely reported as being lower with silicone oil\textsuperscript{27–29} which, now, is generally used only in selected cases.

Limitations of the current study include its retrospective design (i.e., the lack of randomization), the limited postsurgical follow-up, and the longer follow-up in patients receiving the C\textsubscript{3}F\textsubscript{8} gas. Despite these constraints, this study design could rule out a large difference (\(\geq 15\%\)) in the anatomical success rates with the two gases.

Numerous previous studies have documented the association of vitrectomy and progressive nuclear sclerosis and some suggest this may be further increased by the use of intraocular gas.\textsuperscript{30,31} One study suggested that face-down positioning prevents cataract formation in phakic patients.\textsuperscript{10} The logical inference follows that the longer a gas bubble is in contact with the lens (as with C\textsubscript{3}F\textsubscript{8}) the more likely cataract formation would occur, but cataract progression was not prevented by shorter a gas bubble in the current study; in fact, it was higher for SF\textsubscript{6} (Figure 1). Although it seems that cataract extraction was also indicated sooner for SF\textsubscript{6}, this might have reflected a selection bias in the SF\textsubscript{6} cohort whose examination time points were limited by their more commonly out of country status. This highlights the possibility (that is common to many similarly desired retrospective case series) that cataract extraction is not an ideal surrogate for cataract formation. In phakic eyes, the larger myopic shift after absorption of gas bubble in the C\textsubscript{3}F\textsubscript{8} group compared with the SF\textsubscript{6} group most likely reflects early nuclear sclerosis especially because the C\textsubscript{3}F\textsubscript{8} group was evaluated approximately 1 month later than the SF\textsubscript{6} group to have allowed gas bubble resorption. Alternatively, it may be due to the longer or residual mechanical displacement effect of the lens by the gas bubble.

This study suggests that MHS with SF\textsubscript{6} gas tamponade combined with ILM peeling and face-down positioning offers a suitable alternative for many (if not most) patients with macular holes, especially if sooner air travel or more rapid visual rehabilitation is imperative.

References

17. Spaide RF. Closure of an outer lamellar macular hole by