

Review Article

Sulfur Hexafluoride (SF₆) versus Perfluoropropane (C₃F₈) in the Intraoperative Management of Macular Holes: A Systematic Review and Meta-Analysis

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Purpose. A systematic literature search was conducted to identify and review studies comparing SF₆ to C₃F₈ as a tamponade agent in the intraoperative management of macular holes. **Methods.** Publications up to October 2018 that focused on macular hole surgery in terms of primary closure, complications, and clinical outcomes were included. Forest plots were created using a weighted summary of proportion meta-analysis. Analysis was performed separately for SF₆ and C₃F₈. A random effects model was used, and corresponding I² heterogeneity estimates were calculated. **Results.** Nine pertinent publications studying a total of 4,715 patients were identified in 2000 to 2017, including two randomized studies ($n = 206$), two prospective studies ($n = 170$), and five retrospective or registry-based studies. Similar rates of closure between SF₆ and C₃F₈ were reported in eight out of nine studies, regardless of subgroup analyses. All studies reporting visual outcomes showed similar results when comparing SF₆ to C₃F₈ at one to six months of follow-up. Neither agent was clearly associated with increased risk of ocular hypertension, cataract formation, or other adverse events. Meta-analytic pooling of the closure rates in the SF₆ group resulted in 91.73% (95% confidence interval: 88.40 to 94.55, I²: 38.03%), and for C₃F₈, the closure rate was 88.36% (95% confidence interval: 85.88 to 90.63, I²: 0.0%). **Conclusions.** Both SF₆ and C₃F₈ appear to have achieved similar visual outcomes and primary closure rates and neither was associated with an increased risk of adverse events. Considering the more rapid visual recovery with SF₆, there appears to be no evidence to support C₃F₈ as the tamponade agent of choice for macular hole surgery.

1. Introduction

Macular hole surgery was first described by Kelly and Wendel in 1991 [1]. Although their 5-step technique has remained largely unchanged, debate still exists concerning several key aspects of the procedure [2]. These include whether to peel the internal limiting membrane (ILM), the use and type of dye, and the duration of face-down positioning following surgery [3, 4].

Another heatedly debated aspect is the choice of tamponading agent [3, 5, 6]. The most commonly used compounds are sulfur hexafluoride (SF₆) and perfluoropropane (C₃F₈). However, hexafluoroethane (C₂F₆), room air, and silicone oil are also employed [7]. Although the procedure was initially described with use of SF₆, subsequent clinical

trials used C₃F₈ further adding to the debate [1, 8–10]. To the authors' best knowledge, no systematic review or meta-analysis has yet been published, comparing the two agents.

The aim of this study was to systematically review the literature for studies that compared SF₆ to C₃F₈ as a tamponade agent in the intraoperative management of macular hole surgery, perform a pooled meta-analysis of the data, and discuss any differences found with respect to clinical outcomes and adverse effects.

2. Materials and Methods

2.1. Literature Search. A systematic literature search was conducted using MEDLINE, Scopus, Google Scholar, and The Cochrane Library, reviewing all available published

clinical studies up to October 2018. The following keywords were used, in various combinations: macular hole, MH, sulfurhexafluoride, sulfur hexafluoride, SF₆, perfluoropropane, C₃F₈, gas, short-acting, long-acting, tamponade, bubble, pneumatic, and retinopexy. A bibliographic search of relevant studies identified additional publications. A flow diagram of the screening and inclusion process is illustrated in Figure 1.

2.2. Eligibility Criteria. Full publications in English that directly compare SF₆ and C₃F₈ in the intraoperative management of macular hole surgery, in terms of primary closure, complication rates, and clinical outcomes were included (not abstracts or letters to the editor). Studies performed on animal or cadaver eyes, as well as case reports and nonempirical opinion articles, were excluded.

2.3. Screening and Synthesis. The review process was conducted under the guidance of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) criteria to support reporting [11]. Two reviewers (IH and MM) independently implemented the search strategy for relevant publications. Selected publications were then approved by the senior investigator who also devised the search strategy (YB).

2.4. Statistical Analyses. To better illustrate the main anatomical outcome of primary closure, forest plots were created using a weighted summary of proportion meta-analysis. Analysis was performed separately for SF₆ and C₃F₈. A random effects model was used (as implemented by DerSimonian and Laird, 1986 [12]), and corresponding *I*² heterogeneity estimates were generated. Data were tabulated and analyzed using SPSS for Windows version 22.0 software by IBM Inc. (Armonk, NY, USA). Graphs were created using MedCalc software version 16 (Mariakerke, Belgium).

3. Results

Data comparing the use of SF₆ and C₃F₈ for macular hole surgery were extracted from nine studies published during 2000 to 2017 (Table 1), studying a total of 4,715 patients. Two of the studies were randomized by design and included a total of 206 patients. Two studies prospectively enrolled patients without randomization (170 patients), and the remaining five were retrospective or registry based. Figure 1 illustrates the flow of the inclusion process.

3.1. Intraoperative Management. Several differences existed between the studies with respect to the surgical technique. The first relates to ILM removal as a routine part of the operation.

ILM peeling was routinely performed in six of the nine studies. In two studies (Essex et al. [4] and Tognetto et al. [7]), a majority of patients (97.7% and 67.7%, respectively) underwent ILM peeling while the remainder did not. The authors elected not to routinely perform ILM peeling of

prospectively enrolled patients in only one study (Mulhern et al.) [16].

Tognetto et al. expanded their investigation, comparing the outcomes of patients who underwent ILM peeling with those who had not [7]. They analyzed the retrospective data of 1,627 patients from different countries, who had been operated on for idiopathic macular hole. They found that ILM peeling improved hole closure only for longstanding macular holes or those in advanced stages [7].

A second aspect in which studies differed was the choice of gas concentration. The SF₆ concentration was 20% in four of the nine studies. Mulhern et al. used 23%, Kumar et al. used 25%, and Briand et al. used between 20 and 25% SF₆. The C₃F₈ concentrations similarly varied, ranging from 13% used by Modi et al. to 18% by Kumar et al. However, most used concentrations ranged between 14% and 16% C₃F₈ (Table 1).

3.2. Postoperative Management. Face-down positioning varied between studies. Most studies recommended two to seven days of prone positioning; however, some (e.g., Mulhern et al.) requested patients who received SF₆ maintain a prone head position for up to 4 weeks [16].

A registry-based analysis by Essex et al. sheds further light on this topic [4]. They analyzed the outcome of 2,367 patients from Australia and New Zealand who underwent primary idiopathic macular hole surgery. Approximately 26% of these patients were not advised to remain in prone position postoperatively, and among those who were advised, most were instructed to remain prone between three and seven days. Essex et al. further compared the outcomes between patients who were not advised a postoperative face-down position to those who were and found that no prone positioning was noninferior for holes of less than 400 μm in diameter, while for larger holes noninferiority could not be concluded [4].

3.3. Primary Anatomical Closure. Most studies used anatomical closure as the primary outcome; their results are summarized in Table 1. Closure rates ranged from 85% to 100%, with most in the 90% to 95% range.

A comparison of SF₆ and C₃F₈ showed similar rates of closure in eight of the nine studies, including the two randomized controlled studies by Casini et al. [3, 5]. One study by Essex et al. using a more stringent noninferiority analysis with a relatively narrow noninferiority margin (5%) also demonstrated noninferiority of SF₆ compared to C₃F₈ [4]. Only one study by Tognetto et al. reported a higher success rate with SF₆ (93.6% versus 87.2%); however, the authors provide no statistical foundation for this claim [7].

Several studies further analyzed subgroups in an attempt to detect a subset of patients, which might benefit from one agent over the other. Modi et al. examined different hole sizes, stages, and durations; Casini et al. also examined different stages; and Kim et al. compared the agents independently for different stages, durations of symptoms, presence of posterior vitreous detachment, and whether indocyanine green dye was used for ILM peeling [3, 6, 15].

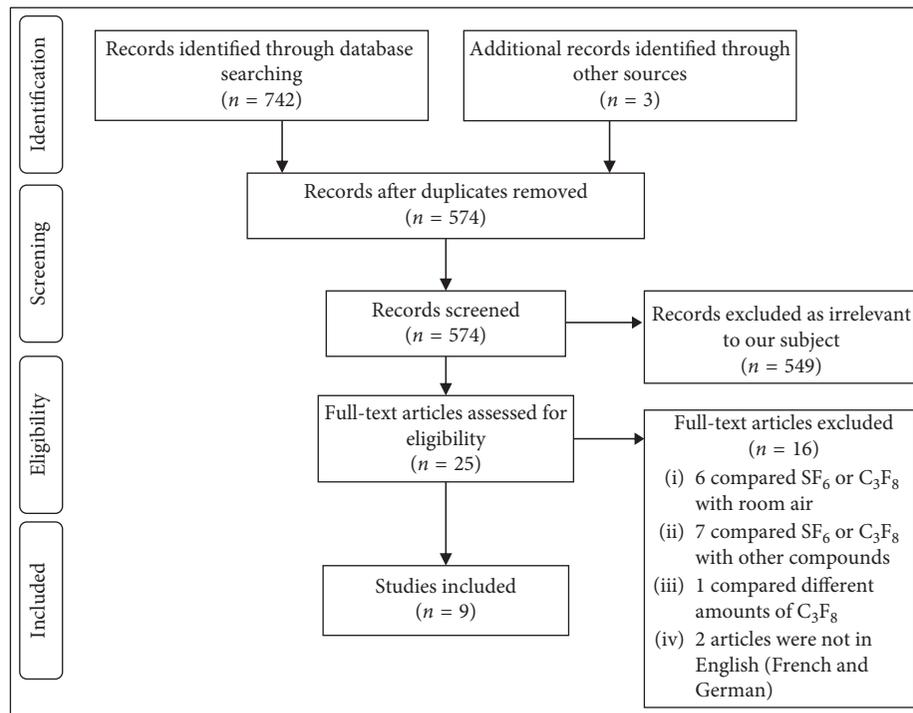


FIGURE 1: Flow diagram of the inclusion process. Flow diagram of the search and inclusion process based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [11].

They all found SF₆ to produce results similar to C₃F₈ regardless of the subgroup analyzed (Table 1).

3.4. Visual Acuity. Six studies reported visual acuity outcomes following surgery [3, 5, 6, 14–16]. All showed similar results when comparing SF₆ to C₃F₈ at one to six months of follow-up (Table 1). Improvement following SF₆ gas ranged from 2.7 to 5.9 Early Treatment Diabetic Retinopathy Study (ETDRS) lines, while following use of C₃F₈ ranged between 2.7 and 6.9 ETDRS lines. Five of the six studies report comparative statistics on visual improvement between groups, and all find no significant differences (Table 1). The randomized trial by Casini et al. as well as the prospective cohort study by Xirou et al. showed that visual acuity was initially better in the group treated with SF₆ but was eventually found to be similar [3, 14].

3.5. Complications. Most studies reported on short-term and long-term complication rates in each group. The randomized controlled trial by Briand et al. showed similar results in terms of cataract development and extraction, a similar time interval between surgery and cataract extraction ($p = 0.184$) and similar rates of retinal tears (4% vs. 7%), retinal detachment (4% vs. 0%), and ocular hypertension (21% vs. 19%, all $p = 1.0$) [5]. The retrospective report by Modi et al. on 177 patients revealed a decreased incidence of cataract and ocular hypertension (1.99 vs. 4.02 mmHg) in the group treated with SF₆, as well as a nonsignificantly lower incidence of glaucoma (9.0% vs 6.1%) [6]. Xirou et al., in a prospective study on 46 patients, revealed similar elevations

of intraocular pressure [14]. Kim et al. reported similar rates of cataract development; however, myopic shift rates were greater in the C₃F₈ group (SF₆: -0.82 diopters vs. C₃F₈: -1.42 diopters for phakic patients, $p = 0.016$). Finally, in the prospective trial by Mulhern et al., similar rates of posterior subcapsular cataract were seen (55% after C₃F₈ vs. 37% after SF₆; $p = 0.20$) and mean intraocular pressure spike maximum was nonsignificantly higher in the SF₆ group (32.5 mmHg vs. 23.7 mmHg; $p = 0.131$) [16].

3.6. Pooled Analysis of Primary Closure. Forest plots of proportion of patients who achieved anatomical closure with each compound are presented in Figures 2 and 3. Meta-analytic pooling of the closure rates in the SF₆ group resulted in 91.73% (95% confidence interval: 88.40 to 94.55, I^2 : 38.03%, p value for heterogeneity = 0.126). For the patients who received C₃F₈, the pooled anatomical closure rate was 88.36% (95% confidence interval: 85.88 to 90.63, I^2 : 0.0%, p value for heterogeneity = 0.864).

4. Discussion

In this study, a systematic review and meta-analysis of studies comparing SF₆ and C₃F₈ gas tamponades for macular hole surgery was performed. Macular hole closure rates were found to be similar regardless of whether SF₆ or C₃F₈ was used and were typically in the 90–95% range. Visual acuity outcomes were also similar but tended to improve faster with SF₆. Rates of complications (including cataract formation, ocular hypertension, and retinal tears) varied among studies and appeared to be inconsistently related to either agent.

TABLE 1: Publications reporting on clinical outcomes of macular hole repair using either SF₆ or C₃F₈ gas tamponade.

Study [Ref]	Year	Design	Number of patients	Postoperative face-down positioning duration	Gas concentration	ILM peeling	Anatomical closure	Results: primary closure	Results: visual improvement*	Results: complications
Modi et al. [6]	2017	Retrospective comparative study	SF ₆ : 67 C ₃ F ₈ : 111 Total: 177	SF ₆ : 45 minutes of every hour (duration NR) C ₃ F ₈ : 45 minutes of every hour (duration NR)	20% SF ₆ 13% C ₃ F ₈	All cases	SF ₆ : 86.4% C ₃ F ₈ : 86.5%	Similar ($p = 0.982$), irrespective of hole size, stage, or duration	SF ₆ : 2.7 lines (0.900 ± 0.383 to 0.629 ± 0.375 logMAR) at 3–6 months C ₃ F ₈ : 4.2 lines (1.03 ± 0.39 to 0.61 ± 0.40 logMAR) at 3–6 months No significant difference ($p = 0.066$)	SF ₆ exhibited a decreased incidence of cataract and ocular hypertension (1.99 vs. 4.02 mmHg) as well as a nonsignificantly lower incidence of glaucoma (9.0% vs. 6.1%) Patients treated with SF ₆ experienced greater improvement of visual acuity at 1 week ($p < 0.01$) but not at 1 month
Casini et al. [3]	2016	Randomized controlled trial	SF ₆ : 70 C ₃ F ₈ : 77 Total: 147	SF ₆ : 2 days C ₃ F ₈ : 2 days	20% SF ₆ 14% C ₃ F ₈	All cases	SF ₆ : 90% C ₃ F ₈ : 91%	Similar, independent of stage	SF ₆ : 5.9 lines (0.894 to 0.301 logMAR) at 1 month C ₃ F ₈ : 6.9 lines (0.965 to 0.272 logMAR) at 1 month	
Essex et al. [4]	2016	Registry-based study	SF ₆ : 1,653 C ₃ F ₈ : 702 Total: 2,456	SF ₆ : 0–14 days C ₃ F ₈ : 0–14 days	NR	97.7% of cases	Mean of both 95.0% (individually NR)	SF ₆ noninferior, regardless of macular hole size	NR	NR
Briand et al. [5]	2015	Randomized controlled trial	SF ₆ : 31 C ₃ F ₈ : 28 Total: 59	SF ₆ : 7 days C ₃ F ₈ : 14 days	20–25% SF ₆ 15% C ₃ F ₈	All cases	SF ₆ : 93.3% C ₃ F ₈ : 92.9%	Similar ($p = 0.943$)	SF ₆ : 3.5 lines at 12 months C ₃ F ₈ : 3.4 lines at 12 months No significant difference ($p = 0.787$)	Similar in terms of cataract development and extraction and adverse events
Kumar et al. [13]	2014	Prospective cohort study	SF ₆ : 20 C ₃ F ₈ : 42 Total: 62	SF ₆ : 18 hours daily for 3 days C ₃ F ₈ : 18 hours daily for 3 days	25% SF ₆ 18% C ₃ F ₈	All cases	SF ₆ : 85% C ₃ F ₈ : 90.5%	Similar ($p = 0.67$)	NR	NR
Xirou et al. [14]	2012	Prospective cohort study	SF ₆ : 23 C ₃ F ₈ : 23 Total: 46	SF ₆ : 2 days C ₃ F ₈ : 2 days	20% SF ₆ 14% C ₃ F ₈	All cases	SF ₆ : 100% C ₃ F ₈ : 96%	Similar	SF ₆ : 3.8 lines (0.67 ± 0.20 to 0.29 ± 0.12 logMAR) at 6 months C ₃ F ₈ : 2.8 lines (0.90 ± 0.10 to 0.62 ± 0.23 logMAR) at 6 months No significant difference ($p = 0.06$)	Patients treated with SF ₆ experienced greater improvement of visual acuity initially but was similar in the following 6 months. Similar elevations of intraocular pressure

TABLE 1: Continued.

Study [Ref]	Year	Design	Number of patients	Postoperative face-down positioning duration	Gas concentration	ILM peeling	Anatomical closure	Results: primary closure	Results: visual improvement*	Results: complications
Kim et al. [15]	2008	Retrospective comparative study	SF ₆ : 38 C ₃ F ₈ : 41 Total: 79	SF ₆ : 7 days C ₃ F ₈ : 7 days	20% SF ₆ 16% C ₃ F ₈	All cases	SF ₆ : 90% C ₃ F ₈ : 91%	Similar ($p = 0.91$), regardless of stage, duration of symptoms, presence of PVD, and use of ICG dye for ILM peeling	SF ₆ : 4.9 lines (0.86 ± 0.41 to 0.37 ± 0.43 logMAR) at 12 months C ₃ F ₈ : 5.4 lines (0.99 ± 0.43 to 0.45 ± 0.35 logMAR) at 12 months No significant difference ($p > 0.30$)	Cataract development was similar. Myopic shift was greater in the C ₃ F ₈ group ($p = 0.016$)
Tognetto et al. [7]	2006	Retrospective cohort study	SF ₆ : 1,004 C ₃ F ₈ : 337 Total: 1,627	SF ₆ : NR C ₃ F ₈ : NR	NR	67.7% of cases	SF ₆ : 93.6% C ₃ F ₈ : 87.2%	Higher success rates with SF ₆	NR	NR
Mulhern et al. [16]	2000	Prospective comparative study	SF ₆ : 31 C ₃ F ₈ : 31 Total: 62	SF ₆ : 14–30 days C ₃ F ₈ : 6 days	23% SF ₆ 16% C ₃ F ₈	Not routinely performed	SF ₆ : 96.7% C ₃ F ₈ : 93.5%	Similar ($p = 1.0$)	SF ₆ : 2.8 lines (0.86 ± 0.18 to 0.575 ± 0.31 logMAR) at 3 months C ₃ F ₈ : 2.7 lines (0.88 ± 0.21 to 0.61 ± 0.37 logMAR) at 3 months No significant difference ($p = 0.719$)	Incidence of posterior subcapsular cataract was similar. Mean IOP spike maximum was nonsignificantly higher in the SF ₆ group

NR, not reported; C₃F₈ perfluoropropane; SF₆, sulfur hexafluoride; ILM, internal limiting membrane; PVD, posterior vitreous detachment; ICG, indocyanine green; IOP, intraocular pressure. *Expressed in Early Treatment Diabetic Retinopathy Study (ETDRS) chart lines.

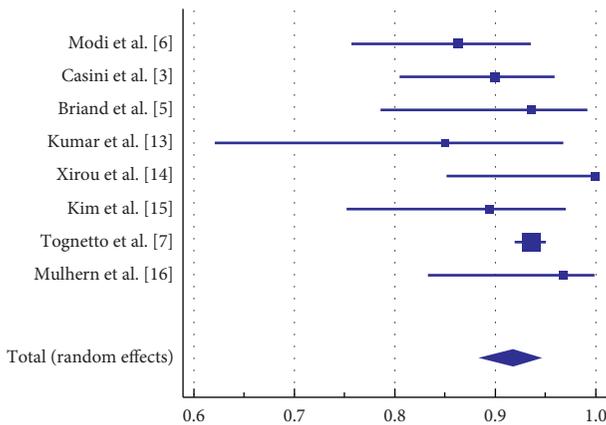


FIGURE 2: Forest plot of the proportion of patients who achieved anatomical closure following the use of SF₆ gas. Meta-analytic pooling of the proportion of patients who achieved anatomical closure following surgery in the SF₆ group. Pooled estimate was 91.73% (95% confidence interval: 88.40% to 94.55%, I^2 : 38.03%, p value for heterogeneity = 0.126). Size of the squares is proportional to the number of cases in the study. Error bars represent 95% confidence intervals. The diamond shape represents the pooled estimate.

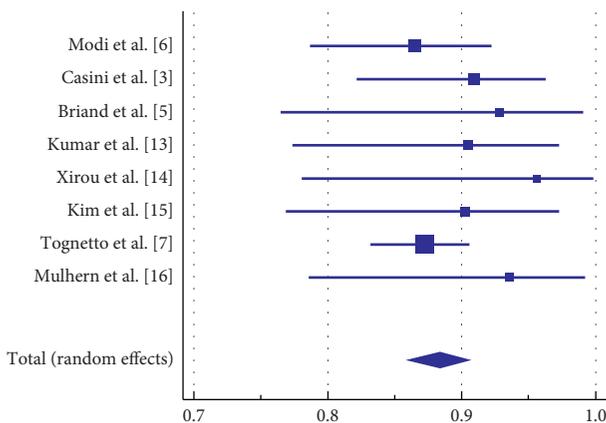


FIGURE 3: Forest plot of the proportion of patients who achieved anatomical closure following the use of C₃F₈ gas. Meta-analytic pooling of the proportion of patients who achieved anatomical closure following surgery with C₃F₈: pooled estimate was 88.36% (95% confidence interval: 85.88% to 90.63%, I^2 : 0.0%, p value for heterogeneity = 0.864); size of the squares is proportional to the number of cases in the study. Error bars represent 95% confidence intervals. The diamond shape represents the pooled estimate.

Following macular hole repair, contact of the gas bubble with the retina causes the extrusion of subretinal fluid and maintains anatomical position, as well as possibly providing a scaffold for cellular proliferation [14]. It therefore seems reasonable that a larger, longer-acting, bubble would provide further benefit. However, some evidence suggests that hole closure occurs very early in the postoperative period, perhaps as early as the first 24 hours [17]. A recent study by Masuyama et al. showed that repair of the macular hole typically occurs between 4 and 7 days postoperatively and is presumed to be facilitated by ganglion and Muller cells [18].

Long-lasting gasses (such as C₃F₈) may offer more extensive tamponade; however, they also impair vision longer. It is possible that such longer-acting agents are not required, considering the short timescales in which macular hole repair occurs. The outcomes of this review appear to support this notion, as use of SF₆ produced similar clinical outcomes to C₃F₈ in terms of both primary closure and visual outcomes.

This study has several limitations. It included non-randomized trials in the analysis. However, given the small number of randomized studies performing a direct comparison of SF₆ and C₃F₈ for macular hole surgery, we elected to include relevant retrospective and registry-based studies, in order to increase the power of the meta-analysis. Given the findings of this study, the need for more prospective randomized studies evaluating this comparison may be questionable. In addition, several differences between the studies concerning the surgical technique may have introduced biases to the analyses. However, we discussed and compared variations in surgical technique found across these studies.

5. Conclusions

To the authors' best knowledge, this is the first systematic review and meta-analysis comparing SF₆ and C₃F₈ as a tamponading agent for macular hole surgery. We found that SF₆ and C₃F₈ resulted in both similar visual outcomes as well as similar primary closure rates. Neither agent was clearly associated with increased risk of ocular hypertension, cataract formation, or other adverse events. Visual recovery with SF₆ tended to occur earlier. It is probable that shorter-acting tamponade agents such as SF₆ may be sufficient for macular hole surgery; we found no evidence to support C₃F₈ as the tamponade gas of choice.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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