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Tamponade in surgery for retinal detachment associated with proliferative vitreoretinopathy (Review)

Schwartz SG, Flynn Jr HW, Wang X, Kuriyan AE, Abariga SA, Lee WH

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[Intervention Review]

Tamponade in surgery for retinal detachment associated with proliferative vitreoretinopathy

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ABSTRACT

Background

Retinal detachment (RD) with proliferative vitreoretinopathy (PVR) often requires surgery to restore normal anatomy and to stabilize or improve vision. PVR usually occurs in association with recurrent RD (that is, after initial retinal re-attachment surgery), but occasionally may be associated with primary RD. Either way, for both circumstances a tamponade agent (gas or silicone oil) is needed during surgery to reduce the rate of postoperative recurrent RD.

Objectives

The objective of this review was to assess the relative safety and effectiveness of various tamponade agents used with surgery for RD complicated by PVR.

Search methods

We searched CENTRAL (which contains the Cochrane Eyes and Vision Trials Register) (the Cochrane Library 2019, Issue 1), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE (January 1946 to January 2019), Embase (January 1980 to January 2019), Latin American and Caribbean Literature on Health Sciences (LILACS) (January 1982 to January 2019), the *meta*Register of Controlled Trials (*m*RCT) (www.controlled-trials.com), ClinicalTrials.gov (www.clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en). We did not use any date or language restrictions in the electronic searches for trials. We last searched the electronic databases on 2 January 2019.

Selection criteria

We included randomized controlled trials (RCTs) on participants undergoing surgery for RD associated with PVR that compared various tamponade agents.

Data collection and analysis

Two review authors screened the search results independently. We used the standard methodological procedures expected by Cochrane.

Main results

We identified four RCTs (601 participants) that provided data for the primary and secondary outcomes. Three RCTs provided data on visual acuity, two reported on macular attachment, one on retinal reattachment and another two on adverse events such as RD, worsening visual acuity and intraocular pressure.

Study Characteristics

Participants' characteristics varied across studies and across intervention groups, with an age range between 21 to 89 years, and were predominantly men. The Silicone Study was conducted in the USA and consisted of two RCTs: (silicone oil versus sulfur hexafluoride (SF_6) gas tamponades; 151 participants) and (silicone oil versus perfluropropane (C_3F_8) gas tamponades; 271 participants). The third RCT compared heavy silicone oil (a mixture of perfluorohexyloctane (F_6H_8) and silicone oil) with standard silicone oil (either 1000 centistokes or 5000 centistokes; 94 participants). The fourth RCT compared 1000 centistokes with 5000 centistokes silicone oil in 85 participants. We assessed most RCTs at low or unclear risk of bias for most 'Risk of bias' domains.

Findings

Although SF_6 gas was reported to be associated with worse anatomic and visual outcomes than was silicone oil at one year (quantitative data not reported), at two years, silicone oil compared to SF_6 gas showed no evidence of a difference in visual acuity (33% versus 51%; risk ratio (RR) 1.57; 95% confidence interval (CI) 0.93 to 2.66; 1 RCT, 87 participants; low-certainty evidence). At one year, another RCT comparing silicone oil and C_3F_8 gas found no evidence of a difference in visual acuity between the two groups (41% versus 39%; RR 0.97; 95% CI 0.73 to 1.31; 1 RCT, 264 participants; low-certainty evidence). In a third RCT, participants treated with standard silicone oil compared to those receiving heavy silicone oil also showed no evidence of a difference in the change in visual acuity at one year, measured on logMAR scale (mean difference -0.03 logMAR; 95% CI -0.35 to 0.29; 1 RCT; 93 participants; low-certainty evidence). The fourth RCT with 5000-centistoke and 1000-centistoke comparisons did not report data on visual acuity.

For macular attachment, participants treated with silicone oil may probably experience more favorable outcomes than did participants who received SF_6 at both one year (quantitative data not reported) and two years (58% versus 79%; RR 1.37; 95% CI 1.01 to 1.86; 1 RCT; 87 participants; low-certainty evidence). In another RCT, silicone oil compared to C_3F_8 at one year found no evidence of difference in macular attachment (RR 1.00; 95% CI 0.86 to 1.15; 1 RCT, 264 participants; low-certainty evidence). One RCT that compared 5000 centistokes to 1000 centistoke reported that retinal reattachment was successful in 67 participants (78.8%) with first surgery and 79 participants (92.9%) with the second surgery, and no evidence of between-group difference (1 RCT; 85 participants; low-certainty evidence). The fourth RCT that compared standard silicone oil with heavy silicone oil did not report on macular attachment.

Adverse events

In one RCT (86 participants), those receiving standard 1000 centistoke silicone oil compared with those of the 5000 centistoke silicone oil showed no evidence of a difference in intraocular pressure elevation at 18 months (24% versus 22%; RR 0.90; 95% CI 0.41 to 1.94; low-certainty evidence), visually significant cataract (49% versus 64%; RR 1.30; 95% CI 0.89 to 1.89; low-certainty evidence), and incidence of retina detachment after the removal of silicone oil (RR 0.36 95% CI 0.08 to 1.67; low-certainty evidence). Another RCT that compared standard silicone oil with heavy silicone oil suggests no difference in retinal detachment at one year (25% versus 22%; RR 0.89; 95% CI 0.54 to 1.48; 1 RCT; 186 participants; low-certainty evidence). Retinal detachment was not reported in the RCTs that compared silicone oil versus SF_6 and silicone oil versus to C_3F_8.

Authors' conclusions

There do not appear to be any major differences in outcomes between C_3F_8 and silicone oil. Silicone oil may be better than SF_6 for macular attachment and other short-term outcomes. The choice of a tamponade agent should be individualized for each patient. The use of either C_3F_8 or standard silicone oil appears reasonable for most patients with RD associated with PVR. Heavy silicone oil, which is not available for routine clinical use in the USA, may not demonstrate evidence of superiority over standard silicone oil.

PLAIN LANGUAGE SUMMARY

Tamponade in surgery for retinal detachment associated with proliferative vitreoretinopathy

What is the aim of this review?

The aim of this Cochrane Review was to determine if substances called tamponade agents used to treat retinal detachment (RD) associated with proliferative vitreoretinopathy (PVR) are safe and effective. PVR refers to the growth and scarring of the retina.

Key messages

The choice of a tamponade agent should be individualized for each patient. The use of either C_3F_8 (one type of gas) or standard silicone oil appears reasonable. Heavy silicone oil, which is not available for routine clinical use in the USA, has no advantage or benefit over standard silicone oil.

What was studied in this review?
Retina is the innermost light-sensing tissue in the back of the eye (similar to the film within a camera), and its normal function depends on its attachment to the underlying layer. RD is a disorder of the eye in which the retina physically separates from the underlying layer of tissue. The macula is the centermost part of the retina and is responsible for the central, high-resolution, color vision. Patients with RD that involves the macular typically have more severe visual loss than patients without associated macular detachment. RD is generally treated with surgery, but surgery is not always successful. In some patients, surgery is initially successful but RD may recur months or years later. Most recurrent RDs, and some primary RDs, are associated with growth and scarring of the retina called proliferative vitreoretinopathy (PVR). The only proven therapy for RD with PVR is further surgery, where the membranes are removed from the surface of the retina and tamponade agents injected into the eye to hold the newly attached retina in place. The major tamponade agents that are available today are various gases and silicone oils. It is unknown whether these tamponade agents are effective and safe.

What are the main results of the review?
We found four randomized controlled trials with a total of 601 participants that compared various tamponade agents. All participants underwent surgery to treat RD associated with PVR.

There do not appear to be any major differences between C_3F_8 (one type of gas) and silicone oil in terms of sharpness of vision (visual acuity) or attachment of the retina to the macula, the oval-shaped area near the center of the retina. Silicone oil may be better than SF_6 (another type of gas) for attachment of the retina to the macula and other short-term outcomes.

How up-to-date is this review?
Cochrane researchers searched for studies that had been published up to 2 January 2019.

Summary of findings 1. Silicone oil compared to sulfur hexafluoride (SF6) for surgery for retinal detachment associated with proliferative vitreoretinopathy

Silicone oil compared to sulfur hexafluoride (SF6) for surgery for retinal detachment associated with proliferative vitreoretinopathy

Patient or population: surgery for retinal detachment associated with proliferative vitreoretinopathy
Setting: eye hospital
Intervention: silicone oil
Comparison: sulfur hexafluoride (SF6)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comment
	Risk with sulfur hexafluoride (SF6)	Risk with Silicone oil				
Visual acuity ≥ 5/200 at two years	325 per 1,000	510 per 1,000 (302 to 865)	RR 1.57 (0.93 to 2.66)	87 (1 RCT)	⊕⊕⊖⊖ LOW [1,2]	
Macular attachment at two years	575 per 1,000	788 per 1,000 (581 to 1,000)	RR 1.37 (1.01 to 1.86)	87 (1 RCT)	⊕⊕⊖⊖ LOW [1,2]	
Retina detachment at two years	See comment	-	-	-	-	This outcome was not reported.
Visual acuity worse than 20/200 (regardless of anatomic outcome) at two years	See comment	-	-	-	-	This outcome was not reported.
Intraocular pressure greater than 21 mmHg at two years	See comment	-	-	-	-	This outcome was not reported.
Visually significant cataract at two years	See comment	-	-	-	-	This outcome was not reported.
Quality of life measures at two years evaluated using validated scale as reported by study	See comment	-	-	-	-	This outcome was not reported.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[1] Downgraded one level for risk of bias
[2] Downgraded one level for imprecision (as based on 1 RCT with n = 87)

Summary of findings 2. Silicone oil compared to perfluropropane (C3F8) for surgery for retinal detachment associated with proliferative vitreoretinopathy

Silicone oil compared to perfluropropane (C3F8) for surgery for retinal detachment associated with proliferative vitreoretinopathy

Patient or population: surgery for retinal detachment associated with proliferative vitreoretinopathy
Setting: eye hospital
Intervention: silicone oil
Comparison: perfluropropane (C3F8)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comment
	Risk with perfluropropane (C3F8)	Risk with Silicone oil				
Visual acuity ≥ 5/200 at 3 years	406 per 1,000	394 per 1,000 (296 to 532)	RR 0.97 (0.73 to 1.31)	264 (1 RCT)	⊕⊕⊖⊖ LOW [1,2]	
Macular attachment at 3 years	739 per 1,000	739 per 1,000 (636 to 850)	RR 1.00 (0.86 to 1.15)	264 (1 RCT)	⊕⊕⊖⊖ LOW [1,2]	
Retina detachment at 3 years	See comment	-	-	-	-	This outcome was not reported.

Visual acuity worse than 20/200 (regardless of anatomic outcome) at two years	See comment	-	-	-	-	This outcome was not reported.
Intraocular pressure (IOP) greater than 21 mmHg	See comment	-	-	-	-	This outcome was not reported.
Visually significant cataract at 3 years	See comment	-	-	-	-	This outcome was not reported.
Quality of life measures at 3 years evaluated using validated scale as reported by study	See comment	-	-	-	-	This outcome was not reported.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[1] Downgraded one level for risk of bias
[2] Downgraded one level for imprecision

Summary of findings 3. Standard silicone oil compared to heavy silicone oil for surgery for retinal detachment associated with proliferative vitreoretinopathy

Standard silicone oil compared to heavy silicone oil for surgery for retinal detachment associated with proliferative vitreoretinopathy

Patient or population: surgery for retinal detachment associated with proliferative vitreoretinopathy
Setting: eye hospital
Intervention: Standard silicone oil
Comparison: heavy silicone oil

Outcomes	Anticipated absolute effects* (95% CI)	Relative effect (95% CI)	№ of participants	Certainty of the evidence	Comment

	Risk with heavy silicone oil	Risk with Standard silicone oil		(studies)	(GRADE)	
Change in visual acuity (logMAR) at one year	The mean change in acuity in the heavy oil group was 1.24 logMAR	MD -0.03 lower (-0.35 lower to 0.29 higher)	-	93 (1 RCT)	⊕⊕⊖⊖ LOW [1,2]	Change in visual acuity as a dichotomous outcome was not reported, instead, the investigators reported mean change in visual acuity and rates of recurrent RD.
Macular attachment at one year	See comment	-	-	-	-	This outcome was not reported.
Retinal detachment at one year	250 per 1,000	223 per 1,000 (135 to 370)	RR 0.89 (0.54 to 1.48)	186 (1 RCT)	⊕⊕⊖⊖ LOW [1,2]	
Visual acuity worse than 20/200 (regardless of anatomic outcome) at one year	See comment	-	-	-	-	Visual acuity was not reported as a dichotomous outcome.
Intraocular pressure (IOP) greater than 21 mmHg at one year	See comment	-	-	-	-	This outcome was not reported.
Visually significant cataract at one year	See comment	-	-	-	-	This outcome was not reported.
Quality of life measures at two years evaluated using validated scale as reported by study at one year	See comment	-	-	-	-	This outcome was not reported.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[1] Downgraded one level for risk of bias
[2] Downgraded one level for imprecision (as based on 1 RCT with n = 93)

Summary of findings 4. 5000-centistoke compared to 1000-centistoke for surgery for retinal detachment associated with proliferative vitreoretinopathy

5000-centistoke compared to 1000-centistoke for surgery for retinal detachment associated with proliferative vitreoretinopathy

Patient or population: surgery for retinal detachment associated with proliferative vitreoretinopathy
Setting: eye hospital
Intervention: 5000-centistoke
Comparison: 1000-centistoke

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comment
	Risk with 1000-centistoke	Risk with 5000-centistoke				
Change in visual acuity (logMAR) at 18 months	BCVA improved or remained unchanged in 77 participants (90.6%) No results were presented per intervention group, but authors reported that there was no statistically significant difference between intervention groups.			85 (1 RCT)	⊕⊕⊖⊖ LOW 1 2	
Macular attachment at 18 months	Reattachment of retina was reported as successful in 67 participants (78.8%) with first surgery, and 79 participants (92.9%) with the second surgery. Authors reported no between-group difference was observed in this outcome			85 (1 RCT)	⊕⊕⊖⊖ LOW 1 2	
Retina detachment - After removal of silicone oil at 18 months	136 per 1,000	49 per 1,000 (11 to 228)	RR 0.36 (0.08 to 1.67)	85 (1 RCT)	⊕⊕⊖⊖ LOW 1 2	
Visual acuity worse than 20/200 (regardless of anatomic outcome) at 18 months	See comment	-	-	-	-	Visual acuity was not reported as a dichotomous outcome.
Intraocular pressure (IOP) greater than 21 mmHg at 18 months	244 per 1,000	220 per 1,000 (100 to 474)	RR 0.90 (0.41 to 1.94)	86 (1 RCT)	⊕⊕⊖⊖ LOW 1 2	Elevated IOP (greater than 22 mmHg) at 18 months.

Visually significant cataract at 18 months	489 per 1,000	636 per 1,000 (435 to 924)	RR 1.30 (0.89 to 1.89)	86 (1 RCT)	⊕⊕⊝⊝ LOW [1,2]	
Quality of life measures at 18 months evaluated using validated scale as reported by study	See comment	-	-	-	-	This outcome was not reported.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

BCVA: Best corrected visual acuity; **CI:** Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[1] Downgraded one level for risk of bias
[2] Downgraded one level for imprecision (as based on 1 RCT with n = 85)

BACKGROUND

Description of the condition

Introduction

Retinal detachment (RD) remains a significant cause of vision loss. A variety of surgical techniques are available to treat RD. For primary RD, these procedures have a very high rate of successful anatomic retinal reattachment (overall above 90%) (Schwartz 2004). The Scleral Buckling versus Primary Vitrectomy in Rhegmatogenous Retinal Detachment (SPR) study, which excluded many relatively straightforward cases, reported single operation success rates between 60% to 80%, depending on the subgroup, and 73% overall (Heimann 2007). Most recurrent RDs, and some primary RDs, are associated with varying degrees of proliferative vitreoretinopathy (PVR), or the growth of fibrous membranes (similar to scar tissue) along the surface of the retina, which leads to traction on the retina (TRSTC 1983).

Epidemiology

Recurrent RD with PVR occurs in about 5% to 10% of patients (Charteris 2002). Major risk factors for recurrent RD with PVR include RD in the inferior (lower) portion of the eye (Singh 1986), severe ocular trauma (Kruger 2002), and giant retinal tears (Scott 2002). Other reported risk factors for recurrent RD with PVR include the inability to identify a retinal break, the use of pars plana vitrectomy (PPV) in the initial repair, preoperative PVR, preoperative choroidal detachment, and a relatively greater use of cryopexy (Cowley 1989). Recurrent RD with PVR may require multiple additional surgeries and is associated with poorer visual outcomes. These additional surgeries are associated with significantly increased costs (Patel 2004). Some patients with primary RD may also present with PVR; risk factors include large or giant retinal tears, longstanding RD, and other factors (Garweq 2013).

Presentation and diagnosis

PVR is usually diagnosed within the first few months after RD surgery. Symptoms include decreased vision in the affected eye. The diagnosis is made by dilated fundus examination in the doctor's office or outpatient clinic.

Description of the intervention

Vitreoretinal surgery is standard treatment for RD with PVR. Pars plana vitrectomy (PPV), removal of the epiretinal membranes; treatment of the retinal breaks; and injection of a tamponade agent are performed. In some cases, removal of the lens (either the crystalline lens or a previously placed intraocular lens) is performed. Tamponade is necessary to reduce the rate of fluid flow through open retinal tears, which would cause recurrent RD. The major tamponade agents available today are various gases and silicone oils. Currently available gases include air, sulfur hexafluoride (SF_6), hexafluroethane (C_2F_6), and perfluropropane (C_3F_8). The major advantage of gas tamponade is that the gas spontaneously dissipates, usually over several weeks. Currently available silicone oils come in 1000-centistoke and 5000-centistoke viscosities. Silicone oil is permanent and may eventually require surgical removal.

There are several investigational tamponade agents, including polydimethylsiloxane (PDMS) 1000 (Tognetto 2005), perfluorohexylethan (O62) (Hoerauf 2005), perfluoro-n-octane (PFO) (Rofail 2005), a mixture of perfluorohexyloctane (F_6H_8) in silicone oil (Stappler 2008), and a mixture of perfluorohexyloctane (F_6H_8) in PDMS 1000 (Heimann 2008; Tognetto 2008). Various tamponade agents with a specific gravity greater than that of water have shown evidence of toxicity in animal models, in rat retinal cell cultures in vitro, and in clinical reports (Eckardt 1990; Matteucci 2007; Singh 2001). These investigational agents are not available for routine clinical use in the USA.

Tamponade agents are useful in four broad categories of patients with RD.

1. Patients with primary RD, treated with PPV as a first-line procedure. These patients are usually treated with gas tamponade rather than silicone oil.
2. Patients with complex or recurrent RD associated with PVR. These patients are the focus of this review. These patients are typically treated with either gas or silicone oil.
3. Patients with RD associated with a giant retinal tear. These patients are treated with either gas or silicone oil.
4. Patients with inferior RD, treated with PPV as a first-line procedure. Some surgeons use heavy liquids, such as PFO or heavy silicone oil, as investigational agents in these patients.

How the intervention might work

Tamponade agents are believed to work by reducing or eliminating fluid vectors through open retinal breaks until the applied retinopexy (typically photocoagulation or cryopexy) creates a permanent seal. Gases such as SF_6 and C_3F_8 spontaneously dissipate, while silicone oil is permanent and may eventually require removal.

Why it is important to do this review

The various tamponade agents offer different advantages and disadvantages in terms of safety and effectiveness (Krzystolik 2000; Young 2005). It is over five years since the last version of this systematic was published (Schwartz 2014), hence an update was needed to evaluate both earlier and more recent evidence on the relative safety and effectiveness of various tamponade agents used with surgery for retinal detachment (RD) complicated by proliferative vitreoretinopathy (PVR).

OBJECTIVES

The objective of this review was to assess the relative safety and effectiveness of various tamponade agents used with surgery for retinal detachment (RD) complicated by proliferative vitreoretinopathy (PVR).

The specific comparisons depended on the RCTs we identified in the search. The secondary objectives of the review were to examine quality of life measures such as patient satisfaction and subjective visual improvement, and to summarize economic data such as direct and indirect costs of surgery and rehabilitation. We intended to compare:

1. the various gas tamponade agents with each other;
2. the two silicone oil preparations with each other;
3. the various gas agents versus the various silicone oils;

4. the established agents (gases, silicone oil) versus the investigational agents.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomized controlled trials (RCTs) only. We set no limitations on the various treatment arms compared.

Types of participants

We included RCTs in which participants underwent surgical repair of RD associated with PVR. We employed no restrictions with respect to age or cause of RD.

Types of interventions

We included RCTs that studied agents used as tamponade in the treatment of RD associated with PVR, such as air, sulfur hexafluoride (SF_6), hexafluroethane (C_2F_6), perfluropropane (C_3F_8), and silicone oil, as well as investigational agents such as heavy silicone oil (polydimethylsiloxane 1000), perfluorohexylethan (O62), and perfluoro-n-octane (PFO).

Types of outcome measures

Primary outcomes

The primary outcome for this review was visual acuity at one year. We analyzed outcomes at additional times of follow-up as reported in the included RCTs. We intended to compare visual acuity as a dichotomous outcome (the proportion of participants who lost three or more lines of logMAR visual acuity; participants who lost one or two lines of logMAR visual acuity were considered stabilized), and also as a continuous outcome (mean logMAR scores). We considered other dichotomous and continuous visual acuity outcomes at other time points as reported in the included RCTs.

Secondary outcomes

The secondary outcome for this review was macular attachment at one year. This was chosen because in some patients with PVR complete retinal re-attachment is not possible, but macular attachment yields generally better visual results than does persistent macular detachment. We also presented secondary outcomes measured at other time points as reported in the included RCTs.

Adverse effects (severe and minor)

Severe

1. Retina detached at one year
2. Visual acuity worse than 20/200 (regardless of anatomic outcome)

Minor

1. Intraocular pressure (IOP) greater than 21 mmHg
2. Visually significant cataract

Quality of life measures

We intended to examine patient satisfaction, subjective visual improvement, and other quality of life measures evaluated using a validated scale.

Economic data

We intended to summarize direct and indirect costs of surgery and rehabilitation and any other economic data in the included studies.

Follow-up

We restricted studies to those with at least one year of follow-up. We believe that shorter follow-up periods are less clinically relevant.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (which contains the Cochrane Eyes and Vision Trials Register) 2019, Issue 1, part of *t*he Cochrane Library (www.thecochranelibrary.com) (searched 2 January 2019), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE (January 1946 to January 2019June 2013), Embase (January 1980 to January 2019), Latin American and Caribbean Health Sciences Literature Database (LILACS) (January 1982 to January 2019), the *meta*Register of Controlled Trials (*m*RCT) (www.controlled-trials.com), ClinicalTrials.gov (www.clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en). We did not use any date or language restrictions in the electronic searches for trials. We last searched the electronic databases on 2 January 2019.

See: Appendices for details of search strategies for CENTRAL (Appendix 1), MEDLINE (Appendix 2), Embase (Appendix 3), LILACS (Appendix 4), *m*RCT (Appendix 5), ClinicalTrials.gov (Appendix 6) and the ICTRP (Appendix 7).

Searching other resources

We searched the reference lists of the studies included in the review for other potential inclusions. We did not search conference proceedings for the purpose of this review. Although we initially did not intend to contact individuals or organizations specifically for this review, because we did not believe that doing so would add significantly to the data obtainable through published trials, we contacted the investigators of included studies for clarification of methods and other data reported in published manuscripts.

Data collection and analysis

Selection of studies

At least two review authors, working independently, reviewed the titles and abstracts resulting from the searches. Two review authors reviewed the full-text manuscripts of all possibly or definitely relevant studies to determine eligibility for inclusion. We resolved any discrepancies through discussion when screening titles and abstracts and assessing the eligibility for full-text reports. We did not mask RCT details in this process. For any unclear information, we contacted the study investigators for further clarification. We recorded the studies that we excluded during full-text assessment, and described the reasons for exclusion in the 'Characteristics of excluded studies' table.

Data extraction and management

Extraction of study characteristics

We extracted the following information for each RCT.

Methods: method of allocation, masking (blinding), exclusions after randomization, losses to follow-up and compliance, unusual study design.
Participants: country where participants enrolled, number randomized, age, sex, inclusion and exclusion criteria.
Interventions: test intervention, comparison intervention (control), duration of intervention.
Outcomes: visual acuity, macular attachment, complication rates, adverse effects, quality of life, and economic outcomes.
Notes: additional details (such as funding sources).

Data extraction and entry

Two review authors, working independently, extracted data using a paper data extraction form developed and piloted by Cochrane Eyes and Vision. We resolved discrepancies by discussion. One review author entered the data into RevMan 5.3 (RevMan 2014), and a second review author verified the data entry. The main outcome measures were visual acuity, macular attachment, and various complication rates. This included dichotomous data (such as retinal detachment, proportion of participants who lost three or more lines of logMAR visual acuity), as well as continuous data (such as mean logMAR visual acuity).

Assessment of risk of bias in included studies

We reviewed the risk of bias of included studies as outlined in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). At least two review authors assessed the risk of bias for each included study according to the following criteria.

1. Selection bias (randomized sequence generation and allocation concealment).
2. Performance bias (masking of participants and researchers).
3. Attrition bias (incomplete outcome data adequately addressed).
4. Detection bias (masking of outcome assessors).
5. Reporting bias (free of selective outcome reporting).

We judged each area of potential bias as low risk of bias, high risk of bias, or unclear risk of bias. We considered methods such as central randomization and use of sequential opaque envelopes as evidence of adequate allocation concealment. We evaluated any exclusions after randomization, losses to follow-up and differential reasons for losses to follow-up in the treatment groups. Any discrepancies were resolved through discussion.

We recognized that masking of participants and surgeons (performance bias) and masking of persons assessing retinal detachment (detection bias) may not be possible in studies comparing gas to silicone oil. However, studies that had successfully masked outcome data (such as studies in which visual acuity was measured by an examiner masked to the tamponade agent) were emphasized.

Measures of treatment effect

We reported unpooled risk ratios (RRs) with 95% confidence intervals (CIs) for the dichotomous outcomes of visual acuity and macular attachment for Silicone Study 1992a and Silicone Study 1992b; RR with 95% CI for recurrent RDs and mean difference (MD) with 95% CI for visual acuity for HSO Study, and RR with 95% CI for RDs (after first and second surgery, and after the removal of silicone oil), as well as elevated IOP for Zafar 2016. If other continuous outcomes are included in future updates of the review, we will calculate MDs or standardized mean differences (SMDs) depending on the types of measurement scales used.

We initially intended to compare 'all gases' (that is, SF_6, C_2F_6, and C_3F_8) versus silicone oil, but the included studies did not compare tamponade agents in this manner. Specifically, the Silicone Study conducted two RCTs, one comparing silicone oil (1000 centistokes) with SF_6, and one comparing silicone oil (1000 centistokes) with C_3F_8, another study compared standard silicone oil (either 1000 centistokes or 5000 centistokes) with heavy silicone oil (a mixture F_6H_8 and silicone oil), and the fourth compared different viscosities of silicone oil (1000 centistokes or 5000 centistokes). Accordingly, this review used the same comparisons.

Unit of analysis issues

The unit of analysis for outcomes was eyes of individuals. All four RCTs included only one eye per participant. For future updates of the review, if a RCT randomized one eye to one tamponade group and the other eye of the same person to the other group, we will only include such a design when it appropriately considered intra-person correlation in their analyses. We will refer to the guidelines in Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011).

Dealing with missing data

We contacted the primary authors of the included studies to provide 12-month visual acuity and macula status outcome data when not reported in the published papers. We did not impute data for this review, but we will consider imputation for future updates of the review and discuss the assumptions made during imputation.

Assessment of heterogeneity

We intended to assess for statistical heterogeneity using the Chi^2 test and the I^2 statistic, but since no pooled estimates were included, these assessments of heterogeneity were not applicable. If data synthesis is considered at the time of an update to this review, we will follow the following guidelines. We will consider an I^2 value greater than 50% to indicate substantial statistical heterogeneity. In such a situation we will not report a pooled estimate. We also will not report a pooled estimate when clinical or methodological heterogeneity (from details listed in the Characteristics of included studies table) is detected. Instead, we will report a narrative or tabulated summary of the included studies. We will use a random-effects model to incorporate the heterogeneity if the I^2 value is less than 50%, unless there are fewer than three studies. If we detect no statistical heterogeneity (I^2 value of 0), or there are fewer than three studies, we will use a fixed-effect model.

Assessment of reporting biases

We assessed selective outcome reporting by comparing outcomes listed in the protocol of the RCTs and the outcomes analyzed in the final published report. For future updates of the review, when the protocol of an included study is not available, we will compare

the outcomes pre-specified in the methods section and outcomes analyzed in the results section, and will follow the guidelines in Chapter 10 of the *Cochrane Handbook for Systematic Review of Interventions* (Sterne 2011). We plan to examine funnel plots from each meta-analysis to assess reporting bias when at least 10 studies are included.

Data synthesis

No pooled estimates of included studies are reported. If pooled estimates are considered for future updates of the review, we will follow the guidelines in Chapter 9 of the *Cochrane Handbook for Systematic Review of Interventions* (Deeks 2011).

Subgroup analysis and investigation of heterogeneity

We will consider subgroup analyses, as appropriate, in future updates of this review, and will consult the guidelines for investigating heterogeneity in Chapter 9 of the *Cochrane Handbook for Systematic Review of Interventions* (Deeks 2011). One possible strategy is to divide participants by surgical history, such as participants with chronic RD with PVR and no previous surgery, participants with recurrent RD following scleral buckling only, and participants with recurrent RD following PPV and previous intravitreal tamponade (gas or oil). Another possible strategy is to divide participants with certain high-risk clinical features, such as participants with giant retinal tear, participants with open-globe trauma, and participants under 18 years of age.

Sensitivity analysis

We planned to examine the impact of the exclusion of unpublished and industry-funded studies in sensitivity analyses, but these exclusions were not applicable to the current systematic review.

'Summary of findings' tables

We presented a 'Summary of findings' table for each comparison of interest when data were available, including strengths and limitations of evidence for primary, secondary, and adverse outcomes. Two review authors independently graded the overall certainty of the evidence for each outcome using the GRADE classification (www.gradeworkinggroup.org). We assessed the certainty of evidence for each outcome as 'high,' 'moderate,' 'low,' or 'very low' according to the following criteria as described in Chapters 11 and 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2011a; Schünemann 2011b).

The following comparisons were included: 1) silicone oil (1000 centistokes) versus sulfur hexafluoride (SF_6); 2) silicone oil (1000 centistokes) versus perfluropropane (C_3F_8); 3) Standard silicone oil (either 1000 centistokes or 5000 centistokes) with heavy silicone oil (a mixture F_6H_8 and silicone oil); 4) 5000 centistokes versus 1000 centistokes. For each comparison, the following outcomes at follow-up time point ≥1 year as defined by each study post-treatment are included in the 'Summary of findings' tables.

1. Visual acuity ≥ 5/200
2. Macular attachment
3. Retina detached
4. Visual acuity worse than 20/200 (regardless of anatomic outcome) at two years
5. Intraocular pressure (IOP) greater than 21 mmHg
6. Visually significant cataract
7. Quality of life measures at two years evaluated using validated scale as reported by study

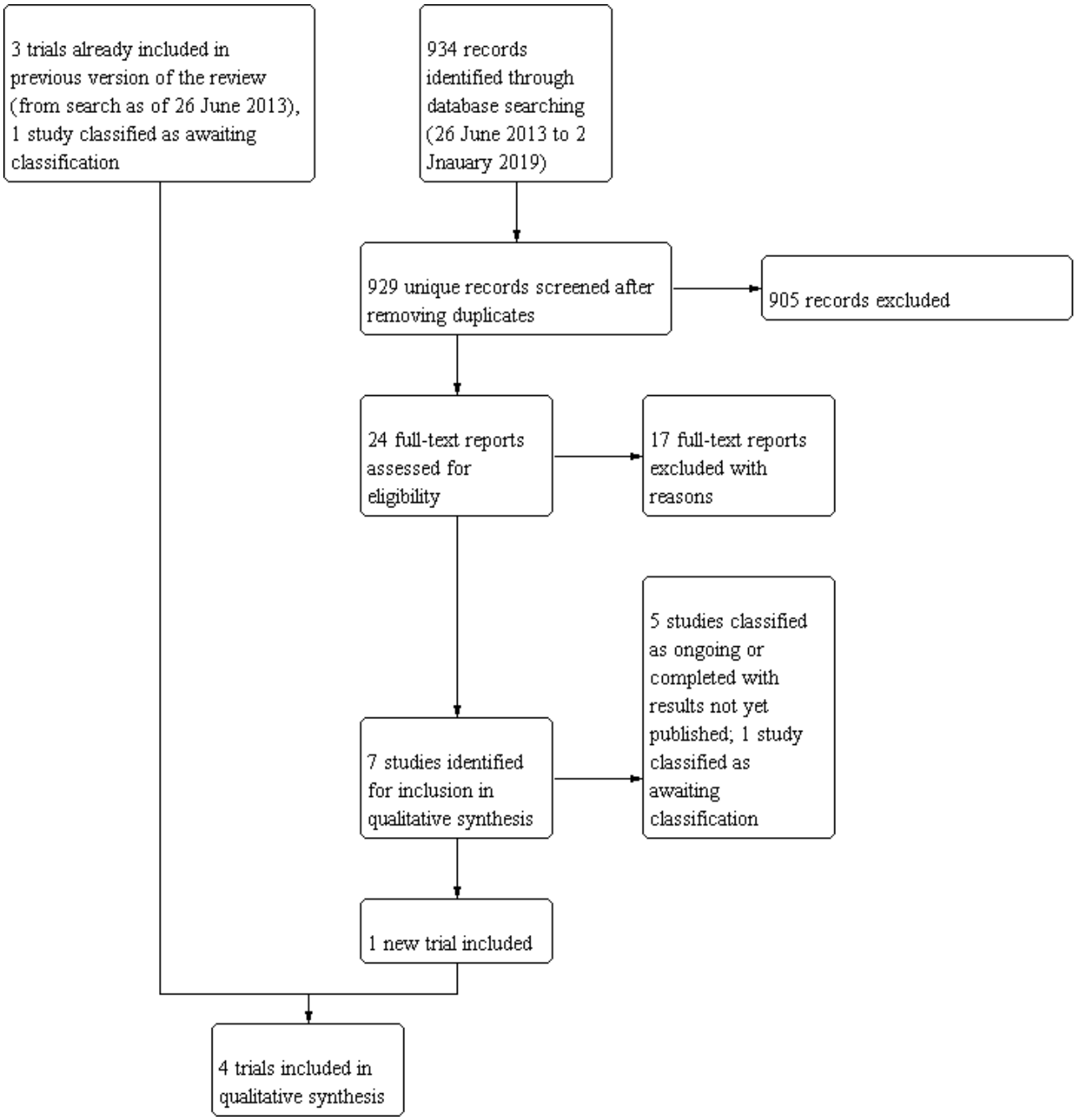
RESULTS

Description of studies

Results of the search

Detailed results of the previous search were published in the 2014 version of this review (Schwartz 2014). Briefly, three RCTs were included in total and one record was classified as awaiting classification after screening 108 records from updated search on 26 June 2013. In January 2019, an updated electronic literature search yielded 934 additional records. After duplicate removal, 929 titles and abstracts were screened by two review authors independently, of which 24 relevant full-text reports were identified. Of these, 17 full-text reports were excluded with reasons. Five studies were classified as ongoing, one was classified as awaiting classification and one new RCT (Zafar 2016) added in this update (Figure 1).

Figure 1. Study flow diagram.



Overall, we included four RCTs, excluded 37 studies (37 records), classified two studies (two records) as awaiting classification and five assessed as ongoing or completed with results not yet published.

Included studies

We identified four RCTs that met our inclusion criteria. Two RCTs (from the Silicone Study) were conducted in the USA. Enrollment for the first RCT comparing silicone oil to SF_6 gas occurred from September 1985 to September 1987 (Silicone Study 1992a). For the second part of the study period, SF_6 gas was replaced with the longer-lasting C_3F_8 gas. Enrollment for the second RCT comparing silicone oil to C_3F_8 occurred between September 1987 to October 1990 (Silicone Study 1992b). Participants aged 18 years or older and with retinal detachment (RD) associated with proliferative vitreoretinopathy (PVR) were offered randomization. One eye per patient was randomized and grouped as eyes that had not undergone prior vitrectomy (Group 1) or eyes that had undergone vitrectomy but without silicone oil injection (Group 2). The first RCT included 113 eyes in Group 1 and 38 eyes in Group 2; the second RCT included 132 eyes in Group 1 and 139 eyes in Group 2. The exclusion criteria were uncontrolled concomitant eye disease, a history of blunt trauma within three months of entry into the study, a history of penetrating trauma, a giant retinal tear of 90 ° or greater,

proliferative diabetic retinopathy, and any medical condition that could preclude participation in a three-year study.

The Heavy Silicone Oil Study (HSO Study), compared vitrectomy with heavy silicone oil (a mixture of perfluorohexyloctane (F_6H_8) and silicone oil) versus standard silicone oil (either 1000 centistokes or 5000 centistokes, per the surgeon's preference) and was performed between December 2003 and February 2008. The HSO Study was a multi-center study conducted in Germany, Austria, Sweden, the UK, China, Poland, Portugal, the Netherlands, Italy, Hungary, and the USA. Ninety-four participants with RD associated with inferior and posterior PVR or inferior RD with inferior giant retinal tear were randomized into the two intervention groups, with 46 participants in the heavy silicone oil group and 48 in the standard silicone oil group. The exclusion criteria included: RD associated with superior anterior PVR; superior giant retinal tear; retinotomies; holes or tears between 10 and 2 o'clock; diabetic retinopathy requiring treatment; glaucoma resulting in visual field defects requiring treatment; no written informed consent; age below 18 years; participation in another clinical trial; or pregnancy.

The newly included study (Zafar 2016) compared 1000-centistoke silicone oil versus 5000-centistoke silicone oil among 85 patients with superior rhegmatogenous retinal detachments associated with PVR grades B and C, which involves not more than 3 clock hours. It was conducted from January 2007 to June 2013 in Pakistan. Patients with history of any intra-ocular surgery, pre-existing glaucoma, inflammatory eye condition, traumatic RD, intra-ocular foreign bodies, aphakia and with any pre-existing retinopathy, with eyes in which the retina could not be re-attached at the time of surgery, were excluded. Patients with less than 18 months of follow-up or had incomplete records were excluded from the analysis.

The Silicone Study was funded by the National Eye Institute, National Institutes of Heath, USA, and the HSO Study was funded by the German Research Foundation (Deutsche Forschungsgemeinschaft). Zafar 2016 did not report sources of funding. None of the study investigators reported declaration of interests.

Excluded studies

We excluded 37 records altogether and listed them in the 'Characteristics of excluded studies' table with reasons for exclusion. Twenty-four of the 37 records were not RCTs, five of them were conducted in a population that is not of interest to this review, four did not use an intervention of interest, three had a follow-up duration less than one year and the remaining study was a conference abstract classified in previous review as awaiting classification, and a full report never got published.

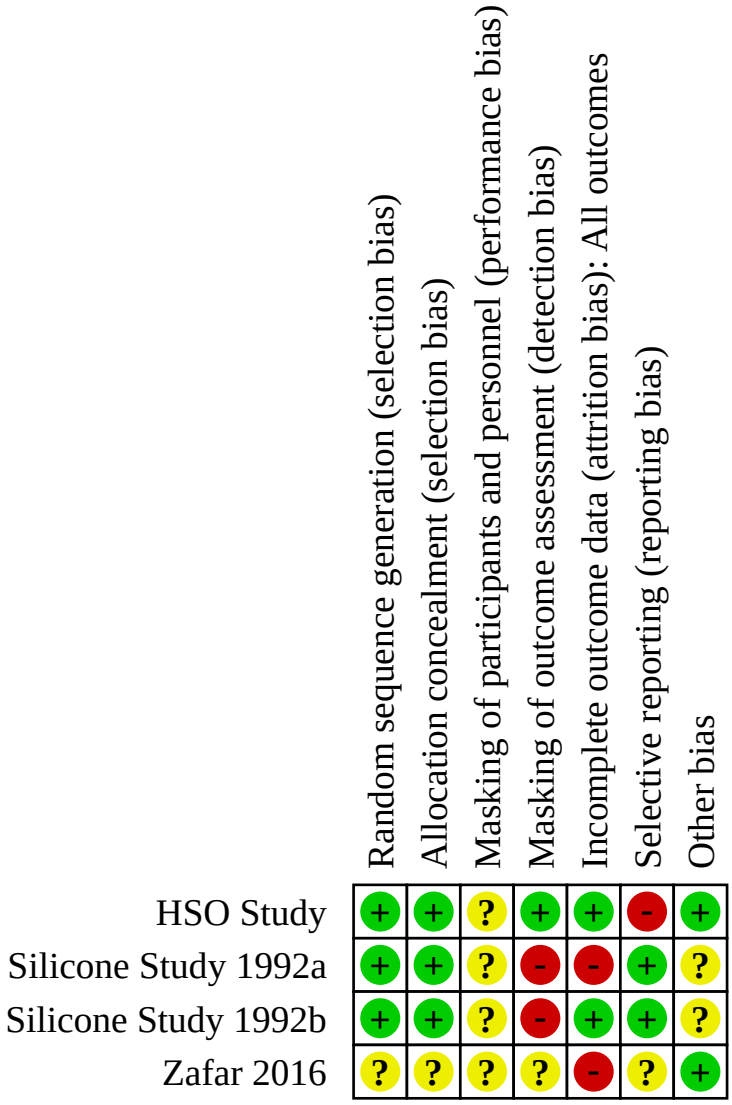
Ongoing studies and studies awaiting classification

We classified two studies as awaiting classification owing to insufficient information to determine eligibility. One was an American Academy of Ophthalmology (AAO) abstract (Oncel 2006) with no published full text, and the other study did not provide enough information to permit judgement for eligibility (Trepsat 1987). They are listed in the 'Characteristics of studies awaiting classification' table. We identified five studies that were either ongoing studies (NCT02988583) or completed more than six years ago with results not yet published (see Characteristics of ongoing studies).

Risk of bias in included studies

Four RCTs met the inclusion criteria for this review (HSO Study; Silicone Study 1992a; Silicone Study 1992b; Zafar 2016). Since the two RCTs of the Silicone Study were part of the same study protocol, they followed the same design, methods, and analyses (Azen 1991 in Silicone Study 1992a). Both the Silicone Study and HSO Study were of good methodological quality and at low risk of bias (Figure 2) except that whether the participants were masked was not reported explicitly in any of these RCTs, and the Silicone Study did not mask all outcome assessors. Zafar 2016 did not provide sufficient information to judge risk of bias in most domains.

Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Allocation

For the Silicone Study, the randomization scheme was administered centrally through the Data Coordinating Center and employed stratification and blocking to ensure equal treatment assignments within each clinical center. Treatment allocation was adequately concealed with sequential opaque envelopes delivered to each study site and opened at the time of tamponade injection. For the HSO Study, randomization was generated using permuted blocks of varying sizes, stratified by surgeon. Treatment allocation was adequately concealed with sealed envelopes opened after study enrollment. Method of random sequence generation and allocation concealment was not reported in Zafar 2016.

Masking (performance bias and detection bias)

None of the RCTs reported masking of participants or surgeons. The study outcome assessors and surgeons were not masked for the two RCTs of the Silicone Study, but were masked in the HSO Study. Masking was not reported in one study (Zafar 2016).

Incomplete outcome data

For the Silicone Study, the last observation carried forward method was used for missing data. Data were imputed for participants who missed intermediate examinations, but attended prior and subsequent examinations, only when findings were deemed consistent. In the event that a retinal detachment recurred during

the study period and required surgery, participants were analyzed using the original random treatment allocation. Randomized participants from a study centre that ceased follow-up during the study period were excluded from the analysis (12 out of 151 participants from Silicone Study 1992a and six out of 271 participants from Silicone Study 1992b). However, the first RCT (Silicone Study 1992a) also excluded 38 participants who had previous vitrectomy from the final analyses, therefore, almost a third of participants in this study did not contribute to any outcome data (51 participants out of 151), so we assessed the risk of bias as high.

For the HSO Study, participants who did not satisfy the major inclusion criteria but were already randomized (performed preoperatively) were all included in the full analysis set; three participants in the heavy silicone oil group and five participants in the standard silicone group fulfilled intraoperative exclusion criteria. One participant was excluded from analysis due to a lack of pre- and post-surgical assessment and data (only randomization sheet present).

For Zafar 2016, 11 participants (11.5%) participants who were lost to follow-up less than 18 months after surgery, or had incomplete records were not included in the final analysis. We judged high risk of bias for this domain.

Selective reporting

Both the RCTs from the Silicone Study (Silicone Study 1992a; Silicone Study 1992b) appeared to be free of selective reporting since the primary and secondary outcomes were published a priori in their respective methods paper (Azen 1991 in Silicone Study 1992a). However, in the methods paper for the HSO Study (Joussen 2007 in HSO Study), it pre-specified to measure quality of life outcomes, but no data were reported. Therefore, we assessed the reporting bias as low for the Silicone Study and high for the HSO Study. No protocol or registration was identified for Zafar 2016, therefore we assessed the reporting bias as unclear.

Other potential sources of bias

Fourteen baseline characteristics were compared between treatment arms in the Silicone Study (age, sex, study eye, prior scleral buckle, other ocular surgery, mean duration of RD, Retina Society classification, visual acuity, refractive status, intraocular pressure (IOP), corneal status, aqueous flare, aqueous cell, and neovascularization). The Silicone Study investigators reported one statistically significant difference in baseline characteristics between the eyes of participants assigned to receive SF_6 gas and those assigned to receive silicone oil (Silicone Study 1992a).The estimated duration of RD was greater in Group 2 eyes (eyes of participants with prior vitrectomy but without silicone oil injection) randomized to SF_6 compared to Group 2 eyes randomized to silicone oil. This information was not sufficient to determine whether other potential source of bias exist.We identified no other potential bias for the remaining two studies (HSO Study; Zafar 2016).

Effects of interventions

See: **Summary of findings 1** Silicone oil compared to sulfur hexafluoride (SF6) for surgery for retinal detachment associated with proliferative vitreoretinopathy; **Summary of findings 2** Silicone oil compared to perfluropropane (C3F8) for surgery for retinal detachment associated with proliferative vitreoretinopathy; **Summary of findings 3** Standard silicone oil compared to heavy silicone oil for surgery for retinal detachment associated with proliferative vitreoretinopathy; **Summary of findings 4** 5000-centistoke compared to 1000-centistoke for surgery for retinal detachment associated with proliferative vitreoretinopathy

Silicone oil versus gas tamponades

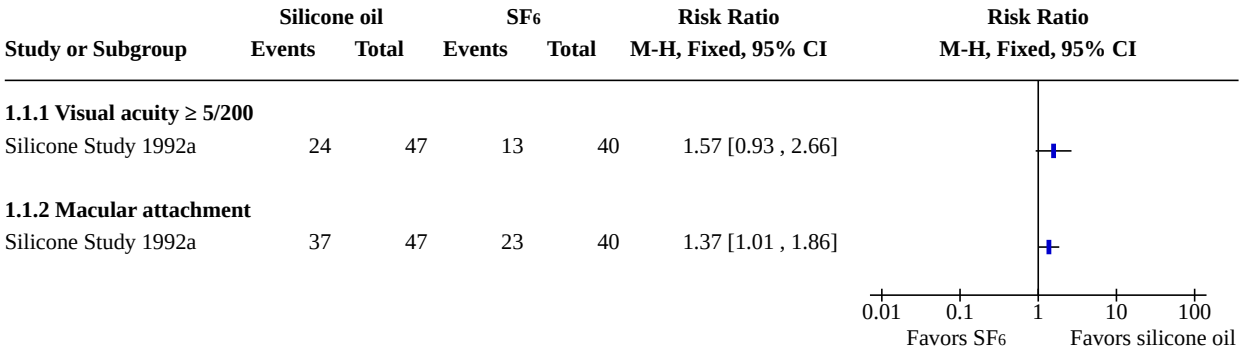
The Silicone Study conducted two RCTs, one comparing silicone oil (1000 centistokes) with SF_6 and one comparing silicone oil (1000 centistokes) with C_3F_8. Below we have described results for each outcome we pre-specified in the methods section of this review. For the first RCT comparing silicone oil (1000 centistokes) with SF_6, the study investigators performed statistical analyses only on non-vitrectomized eyes (group 1) because the sample size of eyes that had already undergone vitrectomy (group 2) was small (38 participants).

Visual acuity

We intended to compare visual acuity as a dichotomous outcome (the proportion of participants who lost three or more lines of logMAR visual acuity; participants who lost one or two lines of logMAR visual acuity were considered stabilized), and also as a continuous outcome (mean logMAR scores); however, no studies reported the proportion of participants who lost three or more lines of visual acuity, instead, participants achieving 5/200 or better visual acuity were reported for both groups. The cut-off point of 5/200 was chosen because 5/200 is considered 'ambulatory vision' (enough vision not to bump into large objects while walking) and is used in some clinical trials with severe diseases and generally bad outcomes. The Silicone Study recorded visual acuity using the Diabetic Retinopathy Vitrectomy Study protocol and charts.

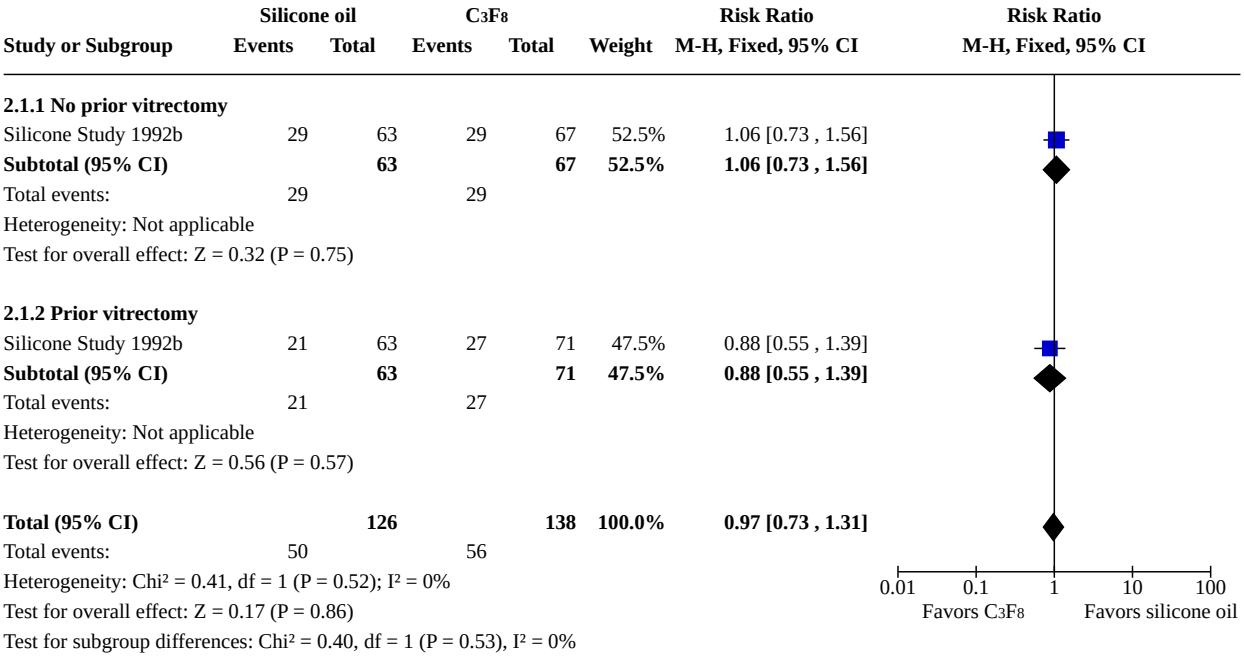
Two RCTs including 352 eyes of 352 participants contributed to this outcome at 24 months (87 eyes in Silicone Study 1992a), or at the last follow-up evaluation (264 eyes in Silicone Study 1992b). When silicone oil was compared with SF_6, the study investigators reported that eyes that had not undergone prior vitrectomy (Group 1) and were randomized to receive silicone oil more often achieved a visual acuity of 5/200 or better at one year ($P < 0.05$; data on visual acuity not reported), but there was no evidence of a difference between the groups at two years (1 RCT; 87 participants; risk ratio (RR) 1.57; 95% confidence interval (CI) 0.93 to 2.66) (Figure 3). The certainty of evidence was low, there were wide confidence intervals. We downgraded for risk of bias and imprecision.

Figure 3. Forest plot of comparison: 1 Silicone oil versus SF_6, outcome: 1.1 Visual acuity ≥ 5/200 and macular attachment at 24 months.



When silicone oil (1000 centistokes) was compared with C_3F_8, there were no evidence of a differences between the groups with respect to visual acuity of 5/200 or better at a minimum of one year, 264 participants, (RR 0.97; 95% CI 0.73 to 1.31) (Figure 4). The certainty of evidence was low, downgrading for risk of bias and imprecision.

Figure 4. Forest plot of comparison: 2 Silicone oil versus perfluropropane (C_3F_8), outcome: 2.1 Visual acuity ≥ 5/200 at last follow-up examination.



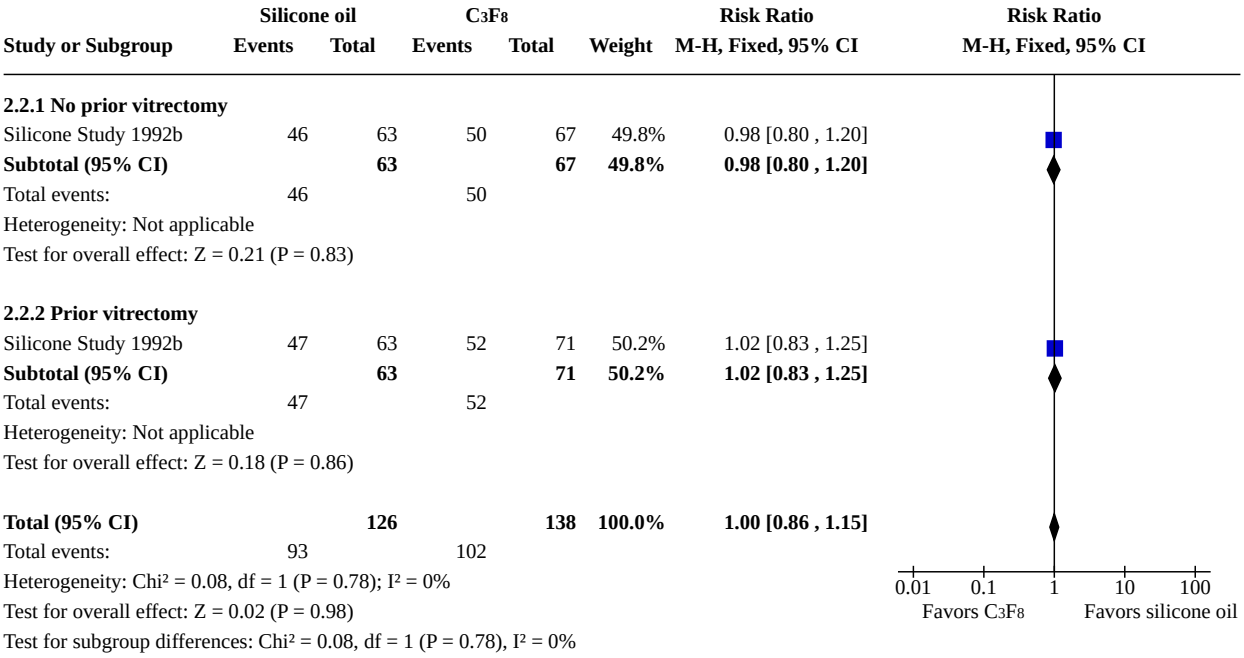
Macular attachment

Two RCTs including 352 eyes of 352 participants contributed to this outcome at 24 months (87 eyes in Silicone Study 1992a) or at last follow-up evaluation (264 eyes in Silicone Study 1992b). When silicone oil was compared with SF_6, the study investigators reported that eyes that had not undergone prior vitrectomy (Group 1) and were randomized to receive silicone oil were 37% more likely to achieve macular attachment at both one year ($P < 0.05$; data on macular attachment not reported). At two years, participants receiving silicone oil compared with SF_6, may experience slight improvement in macular attachment, (1 RCT; 87 participants; RR 1.37; 95% CI 1.01 to 1.86) (Figure 3). The certainty of evidence was low, sample size was small. We downgraded for risk of bias and imprecision.

When silicone oil (1000 centistokes) was compared with C_3F_8, there was no evidence of a differences between the groups with respect to macular attachment at a minimum of one year follow-up (1 RCT; 264 participants; RR 1.00; 95% CI 0.86 to 1.15) (Figure 5). However, the proportions of eyes with postoperative macular attachment were higher in eyes randomized to C_3F_8 versus silicone oil at each time point, and this difference favored the C_3F_8 group at 36 months (83% versus 60%; P = 0.045; standard deviation or 95% CI not

provided). The certainty of evidence was low, downgrading for risk of bias and imprecision.

Figure 5. Forest plot of comparison: 2 Silicone oil versus perfluoropropane (C_3F_8), outcome: 2.2 Macular attachment at last follow-up examination.



Adverse effects (severe, minor)

Two RCTs comprising 366 eyes of 366 participants contributed to the adverse event outcomes.

Severe (retina detached at one year and visual acuity worse than 20/200)

Retina detachment and visual acuity worse than 20/200 were not reported in the two RCTs.

Minor (intraocular pressure (IOP) greater than 21 mmHg and visually significant cataract)

Intraocular pressure greater than 21 mmHg was not reported in the RCTs, however, IOP greater than or equal to 30 mmHg was reported in one eye treated with SF_6 gas and no eyes treated with silicone oil in the first RCT, and two eyes treated with C_3F_8 gas and one eye with the silicone oil for the second RCT (RR 1.04; 95% CI 0.10 to 11.40) (Silicone Study 1992b) during the follow-up for three years. The certainty of evidence was low, there were wide confidence intervals. We downgraded for risk of bias and imprecision.

Visually significant cataract

SF_6, C_3F_8, and silicone oil can worsen cataracts. However, it was unlikely that cataract progression played a major role in the visual outcomes because most eyes were pseudophakic or aphakic at one year. In the silicone oil versus SF_6 study, about 40% of the eyes were phakic at baseline, and the lens was subsequently removed in 69% of the eyes in the silicone oil group and 90% in the SF_6 group for the non-vitrectomized eyes (RR 0.76; 95% CI 0.53 to 1.09) (Silicone Study 1992a). In the silicone oil versus C_3F_8 study, 48% of eyes were phakic at baseline, and the lens was subsequently removed in 91% of these eyes in the silicone oil group and 86% in the C_3F_8 gas group for the non-vitrectomized eyes (RR 1.06; 95% CI 0.88 to 1.26), and in 93% of the eyes in the silicone oil group and 100% in the C_3F_8 group (1 RCT; 87 participants; RR 0.71; 95% CI 0.53 to 0.95) (Silicone Study 1992b). The certainty of evidence was low. We downgraded for risk of bias and imprecision.

Quality of life measures

The Silicone Study did not specifically address quality of life measurements.

Economic data

The Silicone Study did not specifically address economic analysis, but a subsequent economic model including data from the Silicone Study reported that surgery for retinal detachment (RD) associated with proliferative vitreoretinopathy (PVR) was cost-effective. In eyes that had not undergone previous pars plana vitrectomy (PPV), silicone oil (USD per quality-adjusted life year (QALY) gained of USD 40,252) was slightly more cost-effective than C_3F_8 (USD per QALY gained of USD 46,926). In eyes that had undergone previous PPV, C_3F_8 (USD per QALY gained of USD 46,162) was more cost-effective than silicone oil (USD per QALY gained of USD 62,383) (Brown 2002).

Standard silicone oil versus heavy silicone oil

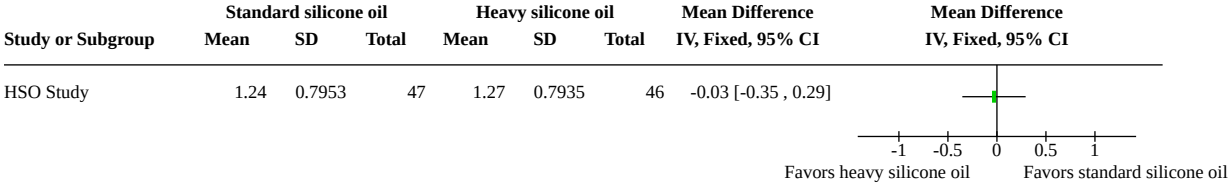
The HSO Study conducted one RCT, comparing standard silicone oil (either 1000 centistokes or 5000 centistokes, per the surgeon's preference) and heavy silicone oil (a mixture of

perfluorohexyloctane (F_6H_8) and silicone oil) in participants with inferior RD associated with PVR.

Visual acuity

We intended to compare visual acuity as a dichotomous outcome (the proportion of participants who lost three or more lines of logMAR visual acuity; participants who lost one or two lines of logMAR visual acuity were considered stabilized), and also as a continuous outcome (mean logMAR scores); however, change in visual acuity as a dichotomous outcome was not reported, instead the investigators reported mean change in visual acuity and rates of recurrent RD. A total of 93 eyes of 93 participants contributed to this outcome at one year. The adjusted mean logMAR visual acuity was 1.24 (standard error (SE) 0.116) in the standard silicone oil group and 1.27 (SE 0.117) in the heavy silicone oil group. Non-inferiority of heavy silicone oil compared to standard silicone oil could not be demonstrated with respect to change in visual acuity at 12 months (mean difference (MD) -0.03; 95% CI -0.35 to 0.29) (Figure 6).The certainty of evidence was low, downgrading for risk of bias and imprecision.

Figure 6. Forest plot of comparison: 3 Standard silicone oil versus heavy silicone oil, outcome: 3.1 Change in visual acuity at one year.



Macular attachment

Macular attachment was not reported in the HSO Study.

Adverse effects (severe, minor)

The (HSO Study) had 94 eyes of 94 participants that contributed to adverse events at one year.

Severe (retina detached at one year and visual acuity worse than 20/200)

Retina detachment

Retinal detachments were reported both before and after the removal of silicone oil (RCT; 93 participants), and no evidence of a difference was found between the two tamponade agents with respect to rates of recurrent RD at one year (before removal: RR 0.75; 95% CI 0.41 to 1.36; after removal: RR 1.30; 95% CI 0.49 to 3.47). The certainty of evidence was low, we downgraded for risk of bias and imprecision (Analysis 3.2).

Visual acuity worse than 20/200

As described above, visual acuity was not reported as a dichotomous outcome.

Minor (intraocular pressure (IOP) greater than 21 mmHg and visually significant cataract)

Minor adverse events including IOP greater than 21 mmHg and cataract were not reported in the HSO Study. Instead, the HSO Study reported that of the 94 participants, four died, 26 had recurrent retinal detachment, 22 developed glaucoma, four developed cataract, and two had capsular fibrosis. However, numbers for each silicone oil group were not specified.

Quality of life measures and economic data

The HSO Study did not specifically address quality of life measurements or economic data.

1000-centistoke silicone oil versus 5000-centistoke silicone oil

The Zafar 2016 study compared standard 1000-centistoke silicone oil versus 5000-centistoke silicone oil in participants with superior rhegmatogenous retinal detachments associated with PVR grades B and C (involving 1 to 3 clock hours). Forty-four and 41 participants were randomized into 1000 centistokes and 5000 centistokes, respectively. Eighty five eyes of 85 participants were included in the analysis.

Visual acuity

Best corrected visual acuity had improved or remained unchanged in 77 participants (90.6%) at the end of follow-up period of 18 months. No results were presented per intervention group, but authors reported that there was no evidence of a difference between intervention groups. The certainty of evidence was low, downgrading for risk of bias and imprecision.

Macular attachment

Reattachment of retina was successful in 67 participants (78.8%) with first surgery, and 79 participants (92.9%) with the second surgery. Investigators reported no between-group difference was observed for this outcome.

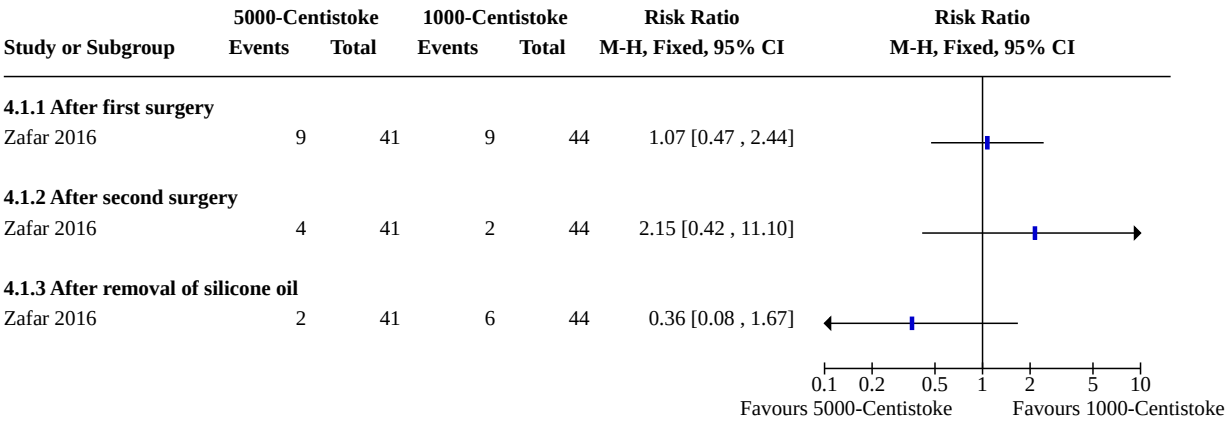
Adverse effects (severe, minor)

Severe (retina detached and visual acuity worse than 20/200)

Retina detachment

Retinal detachments were reported after first surgery, second surgery, and after the removal of silicone oil. There was no evidence of a difference in rates of recurrent RD between the two tamponade agents (after first surgery: RR 1.07; 95%CI 0.47 to 2.44; after second surgery: RR 2.15; 95%CI 0.42 to 11.10; after the removal of silicone oil: RR 0.36 95%CI 0.08 to 1.67) (Figure 7). The certainty of evidence was low for all the estimates, as estimates were imprecise. We downgraded for risk of bias and imprecision.

Figure 7. Forest plot of comparison: 4 5000-centistoke vs 1000-centistoke, outcome: 4.1 Retina detachment.



Visual acuity worse than 20/200

Visual acuity was not reported as a dichotomous outcome.

Minor (intraocular pressure (IOP) greater than 21 mmHg and visually significant cataract)

Elevated IOP was defined greater than 22 mmHg in this study. No evidence of between-group difference was observed in elevated IOP (1 RCT; 77 participants; RR 0.90; 95%CI 0.41 to 1.94) (Figure 8) and visually significant cataract (RR 1.30; 95%CI 0.89 to 1.89) (Figure 9). The certainty of evidence for both outcomes was low. we downgraded each outcome for risk of bias and imprecision.

Figure 8. Forest plot of comparison: 4 5000-Centistoke vs 1000-Centistoke, outcome: 4.2 Elevated intraocular pressure (IOP)(greater than 22 mmHg).

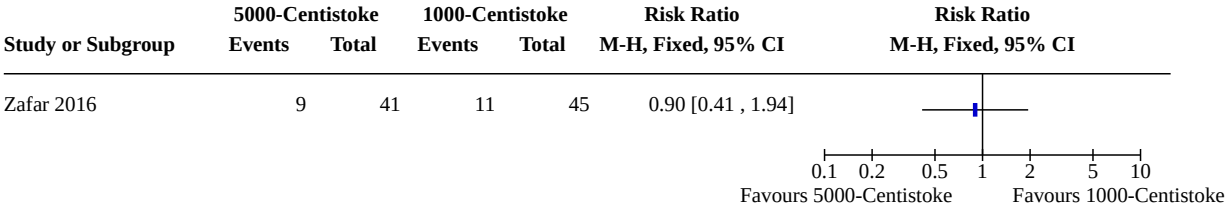
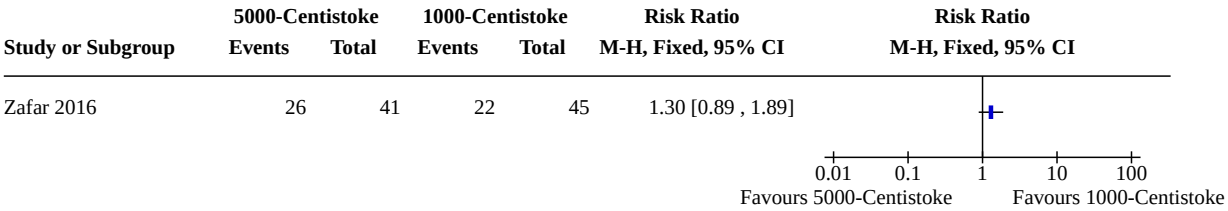


Figure 9. Forest plot of comparison: 4 5000-centistoke vs 1000-centistoke, outcome: 4.3 Visually significant cataract.



Quality of life measures and economic data

Quality of life measurements or economic data were not examined in Zafar 2016.

DISCUSSION

Summary of main results

The Silicone Study comprised two well-designed prospective, multicenter, RCTs of participants with retinal detachment (RD) associated with proliferative vitreoretinopathy (PVR). The first RCT, comparing silicone oil to SF_6, was conducted between 1985 and 1987. The second RCT, comparing silicone oil to C_3F_8, was

conducted between 1987 and 1990. Pars plana vitrectomy (PPV) and infusion of either silicone oil or C_3F_8 gas appeared to show comparable results for final visual acuities of 5/200 or better at one year and macular attachments at one year. SF_6 gas was associated with worse anatomic and visual outcomes than silicone oil, although some of these differences diminished after two years.

The HSO Study was a well-designed prospective, multicenter, RCT of participants with RD associated with PVR. The RCT compared standard silicone oil (either 1000 centistokes or 5000 centistokes, per the surgeon's preference) with heavy silicone oil (a mixture of perfluorohexyloctane (F_6H_8) and silicone oil), which is not approved by the US Food and Drug Administration (FDA) and is not available outside a clinical trial. Despite the many theoretical benefits of a heavier-than-water tamponade agent in treating participants with inferior vitreoretinal pathology, no important advantages were reported in this study.

The Zafar 2016 study conducted between 2007 and 2013 among participants with RD associated with PVR compared 1000-centistoke silicone oil with 5000-centistoke silicone oil. Investigators found no evidence of a difference between the two groups for retinal reattachment or visual acuity. Adverse events such as RD and elevated intraocular pressure (IOP) did not differ between both groups,suggesting no clear benefit between 1000 centistokes and 5000 centistokes silicone oil.

Overall completeness and applicability of evidence

In the intervening two decades since the Silicone Study began, there have been many advances in vitrectomy instrumentation, intraoperative viewing systems, and surgical techniques. The silicone oil used in the Silicone Study was not approved by the US FDA and differed in many respects from the higher quality, more purified oils used today.

In addition, although SF_6 and C_3F_8 are still used today, many surgeons now prefer 5000-centistoke silicone oil to the 1000-centistoke oil used in the Silicone Study, although Scott 2005 observed no evidence of a difference in macula-off retinal redetachment rates (P = 0.72); retinal redetachment rates (P = 0.68); and visual acuity 5/200 or better, in a review of records of participants who underwent retinal detachment repair with 1000-centistoke silicone oil versus 5000-centistoke silicone oil.

Perfluoro-n-octane (PFO) became available in 1988 as an intraoperative tool to achieve retinal re-attachment. PFO was not available for any of the participants enrolled in the first RCT of the Silicone Study (oil versus SF_6), which completed enrollment in 1987. PFO was available for some, but not all, participants enrolled in the second RCT (oil versus C_3F_8). In addition, the investigational use of PFO and other heavy liquids as intermediate-term tamponade agents was not described until more recently.

The Silicone Study also excluded participants with a history of penetrating trauma, giant retinal tears greater than 90°, and proliferative diabetic retinopathy. Similarly, the HSO Study excluded participants with active diabetic retinopathy, visually significant glaucoma, pregnancy, and participants under 18 years of age. The (Zafar 2016) study excluded participants with pre-existing glaucoma, inflammatory eye condition, traumatic RD, intra-ocular foreign bodies, aphakia and with any pre-existing retinopathy. For these reasons, the results reported in these RCTs may not be applicable to many participants undergoing contemporary surgical procedures or those with pre-existing ocular conditions.

Quality of the evidence

The overall quality of the evidence was moderate. Three of four RCTs employed proper methodology for random sequence generation and allocation concealment. None of the RCTs clearly stated whether the study participants were masked, so we assessed performance bias as unclear for all four RCTs. The HSO Study performed masking of outcome assessors while the Silicone Study (Silicone Study 1992a; Silicone Study 1992b) did not, so we assessed two RCTs from the Silicone Study as at high risk of detection bias, the RCT from HSO Study as at low risk, and the Zafar 2016 RCT as unclear risk of bias as masking of outcome assessors was not reported. Two out of the four RCTs had less than 10% of participants lost to follow-up (low risk of attrition bias for Silicone Study 1992b from the Silicone Study, and the HSO Study). The Silicone Study 1992a had almost a third of participants lost to follow-up (50/151 were excluded from analyses), so we assessed it as at high risk of attrition bias. We assessed the Silicone Study as at low risk of reporting bias and the HSO Study at high risk because it pre-specified measurement of a quality of life outcome but no data were reported. We assessed the (Zafar 2016) study at high overall risk of bias, as most 'Risk of bias' domains were either judged at unclear or high.

Potential biases in the review process

Although conducting a highly sensitive search for studies, we identified only three RCTs relevant to this review topic. These RCTs compared different tamponade agents, used different statistical methods, and reported outcomes at different time points. Due to the heterogeneity among the RCTs, comparing the treatment effects in meta-analysis was not possible. Rather, we presented the results of the individual studies, which carry their own potential biases as discussed in other sections of this review. If adequately designed RCTs are published in the future with standardized outcomes, then additional data could improve the overall evidence in this review.

Agreements and disagreements with other studies or reviews

This is an update of a review initially published in 2009 (Schwartz 2009). This update is broadly consistent with the prior version; the HSO Study, which was published since the last version, has been added. To our knowledge, no other reviews on this specific topic have been published during this timeframe.

Authors' conclusions

AUTHORS' CONCLUSIONS

Implications for practice

Based on results from the Silicone Study, participants with retinal detachment (RD) associated with proliferative vitreoretinopathy (PVR) had good results with pars plana vitrectomy (PPV) with either C_3F_8 gas or silicone oil tamponades. There is a suggestion that C_3F_8 may have certain advantages with respect to long-term anatomic outcomes in some participants, although the visual results appear similar between the tamponade agents. The choice

of tamponade agent is usually made on an individual, patient-by-patient basis. Factors to be considered include the configuration of the detachment, the location of the retinal breaks, the lens status, the visual status of the fellow eye, the patient's ability to comply with postoperative positioning requirements, the patient's need to travel by air in the early postoperative period, and individual physician and patient preferences.

As tamponade agents, C_3F_8 and silicone oil appear to have visual and anatomic advantages over SF_6, especially within the first year after surgery, but SF_6 may be a reasonable choice in certain clinical situations.

Based on the results from the Zafar 2016 study, the 1000-centistoke silicone oil compared with 5000-centistoke silicone oils or the heavy silicone oil mixture used in the HSO Study (a mixture of perfluorohexyloctane (F_6H_8) and silicone oil) does not offer any additional benefits relative to standard silicone oil (either 1000 centistokes or 5000 centistokes, per the surgeon's preference) in participants with complex or recurrent RD associated with PVR.

Implications for research

The Silicone Study delineated various relative advantages and disadvantages of 1000-centistoke silicone oil, SF_6, and C_3F_8 as tamponade agents. The study that evaluated 1000-centistokesilicone oil versus of 5000-centistoke silicone oil, had high overall risk of bias and found no difference between the two groups for most of the outcomes assessed, thus a prospective clinical trial evaluated these comparisons appears warranted. Future research may develop alternative tamponade agents, particularly with a density greater than water, which would reduce the postoperative positioning requirements for many patients. Properties of an ideal tamponade agent include optical clarity, lack of toxicity, no effect on the eye's refractive state, no effect on intraocular pressure (IOP) or cataract formation, inhibition of cellular migration, and inhibition of gliosis or glial proliferation.

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This review update was managed by CEV@US and was signed off for publication by Tianjing Li and Richard Wormald.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

HSO Study

Study characteristics	
Methods	Study design: prospective, multicenter, randomized controlled trial Number randomized (total and per group): 94 participants total, 46 in the heavy silicone oil group and 48 in the standard silicone oil group Number analyzed (total and per group): 93 participants total, 46 in the heavy silicone oil group and 47 in the standard silicone oil group Exclusions and loss to follow-up: “One control patient having no data except the randomization sheet was excluded from the analysis” Study follow-up: 12 months

HSO Study *(Continued)*

	Sample size calculation: power of 80%
Participants	Country: Germany, Austria, Sweden, the UK, China, Poland, Portugal, the Netherlands, Italy, Hungary, USA Age (mean ± SD): Heavy silicone oil group: 65.54 years ± 12.20 Standard silicone oil group: 61.87 years ± 15.69 Gender: M:F = 19:28 for the standard silicone oil group and 35:11 for the heavy silicone oil group Inclusion criteria: “Inferior and posterior PVR grade C-A6, P12 according to Machemer at 10 over 6 to 2 hrs (PVR only as rhegmatogenous retinal detachment or a complication of trauma) or inferior retinal detachment with giant retinal tear in the inferior hemisphere (10 over 6 to 2 hrs)” Exclusion criteria: "-Superior anterior PVR grade C A6 between 2, 12 and 10 o’clock -Superior giant retinal tear retinal detachment between 2, 12 and 10 o’clock -Retinotomy/holes/tears above 2 and 10 o’clock -Diabetic retinopathy requiring treatment -Glaucoma resulting in visual field defects requiring treatment -No written informed consent -Age below 18 years -Participation at another trial -Pregnancy"
Interventions	Intervention 1: heavy silicone oil (a mixture of perfluorohexyloctane (F_6H_8) in silicone oil) as a tamponade agent: endotamponade with heavy silicone oil Intervention 2: standard silicone oil as a tamponade agent: endotamponade with silicone oil of 1000 cSt or 5000 cSt viscosity according to the surgeon’s preference The surgical procedure for both groups included: "encircling band according to the surgeon’s preference, PPV via conventional three-port approach, removal of the flap of the retinal tear, if present, usage of perfuordecalin fluid (PFCL) to unfold the retina, retinopexy by cryopexy or laser coagulation, and relaxing retinotomies, if necessary. PFCL standard silicone exchange or PFCL-air-silicone exchange according to the individual surgeon’s preferences."
Outcomes	Primary outcome(s): Anatomical success – complete retinal reattachment at 12 months Visual acuity – mean change from baseline to 12 months (logMAR) Secondary outcome(s): “combined the evaluation of the complete retinal attachment before endotamponade removal, a quality of life analysis, and the evaluation of the number of retina-affecting reoperations within 1 year of follow-up.”

HSO Study *(Continued)*

	Time points measurements were taken: "participants were examined postoperatively within the one week of surgery, preremoval, 2 months after removal surgery, and one year after initial surgery" "Attachment of the retina is assessed blindly by the endpoint committee, who compare the preoperative fundus documentation with that taken 12 months after initial surgery. Fundus photos are taken according to the nine field regimen introduced by Irvine et al. (1988) and Azen et al. (1998); fundus drawings are in accordance with Meyer-Schwickerath & Wessing (1975). Visual acuity is the main subjective criterion for assessing the function of an eye, reflecting the patient's point of view that the improvement of VA is the most important parameter of a successful operation. The endpoint is defined as a change of VA 12 months after initial surgery compared with the preoperative measurement using letter- by-letter scoring on ETDRS charts." Unit of analysis: individual – only one eye per participant was included in the study. When both eyes of a participant were eligible, the surgeon determined the study eye Other issues with outcome assessment: none Adverse events; not reported
Notes	Study dates: December 2003 to February 2008 Funding source(s): Deutsche Forschungsgemeinschaft (DFG Ki 743/2-1 and DFG Hi 541/1-1) (Germany Research Foundation) Declaration of interests: not reported Publication language: English Trial registration number: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The randomization list was generated using permuted blocks of varying sizes, stratified by surgeon. No further stratification will take place."
Allocation concealment (selection bias)	Low risk	"After verification of the eligibility criteria (including informed consent), randomization (opening of the prepared sealed envelopes) took place."
Masking of participants and personnel (performance bias)	Unclear risk	No information provided with respect to masking of participants or study investigators
Masking of outcome assessment (detection bias)	Low risk	"The primary end-point '12 month attachment' as well as the secondary endpoints 'attachment (before removal)' and number of re-operations will be assessed by masked examiners within the end-point committee meetings based on photo documentation or surrogates. Anonymous documentation, which does not allow identification of the applied treatment, will be presented at the end-point committee meetings by the documentation centre. In this sense, the evaluation of these endpoint criteria can be considered as single-blind."
Incomplete outcome data (attrition bias) All outcomes	Low risk	"None of the randomized patients was excluded by the end-point committee. As patients who did not satisfy the major inclusion criteria were in all cases already randomized (performed preoperatively), all of them are therefore part of the full analysis set. One patient ('8701001') was excluded due to a lack of pre- and postsurgical assessment and data (only randomization sheet present).

HSO Study *(Continued)*

		Three patients in the HSO group and five patients in the standard silicone group fulfilled intraoperative exclusion criteria." "Concerning the evaluation of the anatomical success, in 20 cases the 12-month visit was substituted by the delayed 12-month visit. In cases where a 12-month visit was not available, the anatomical success was assessed as treatment failures. This is applied to 18 cases in the HSO group and 16 in the standard group." "For the analysis of VA, in cases of no valid 12-month visit, the last available observation was used (last observation carried forward) for 18 patients in the HSO group and 15 patients in the standard group."
Selective reporting (reporting bias)	High risk	The sample size of the study changed from what was specified in the protocol because of the low recruitment rate, although the study investigators recalculated the sample size and it still had 80% power for detection the difference. Also, the quality of life data were pre-specified in the methods section, but not reported in the results
Other bias	Low risk	No issues identified

Silicone Study 1992a

Study characteristics	
Methods	Study design: unmasked, multicenter randomized controlled trial Number randomized (total and per group): 151 participants in total, number per group was not reported Eyes of participants were stratified as follows (only one eye per participant randomized): Eyes that had not undergone prior vitrectomy (Group 1): 113 in total, 47 in the standard silicone oil group and 46 in the heavy silicone oil group Eyes that had undergone vitrectomy but without silicone oil injection (Group 2): 38 in total, number per group was not reported Number analyzed (total and per group): Statistical analyses were performed only on group 1 data because the sample size of group 2 was small: total: 101 participants; 49 in the SF_6 gas group and 52 in the silicone oil group Exclusions and loss to follow-up: 12 participants in group 1 were excluded, all participants in group 2 were excluded Study follow-up: 36 months Sample size calculation: no
Participants	Country: USA Age (mean ± SD): mean ± SD not reported, median age was 62.1 years (range 25 to 84) for the SF_6 gas group and 66.2 years (range 24 to 84) for the silicone oil group Gender: M:F=16:33 for the SF_6 gas group and 17:35 for the silicone oil group Inclusion criteria: participants with proliferative vitreoretinopathy with a classification of at least C-3 grade, at least age 18, visual acuity better than light perception, and sufficient contracture so intraocular dissection was required

Silicone Study 1992a *(Continued)*

	Exclusion criteria: participants with uncontrolled concomitant eye disease, occurrence of blunt trauma to the eye within 3 months of randomization, history of penetrating trauma to the eye, presence of a giant tear ≥ 90°, presence of proliferative diabetic retinopathy, and the existence of any condition that would prevent 3-year follow-up
Interventions	Intervention 1: sulfur hexafluoride gas (SF_6): 49 eyes (Group 1), 15 eyes (Group 2) Intervention 2: silicone oil: 52 eyes (Group 1), 23 eyes (Group 2)
Outcomes	The study did not separate primary or secondary outcomes. All outcomes included: visual acuity, retinal reattachment, refraction; development or change in ocular complications affecting the cornea, iris, or lens; and measurements of intraocular pressure at 10 days, and 1, 3, 6, 12, 18, 24, and 36 months following randomization Secondary outcome(s): N/A Time points measurements were taken: 1, 3, 6, 12, 18, 24, and 36 months
Notes	Study dates: 1 September 1985 to 30 June 1991 Funding source(s): trial sponsored by the National Eye Institute. Silicone oil provided by the Dow Corning Corporation Declaration of interests: not reported Publication language: English Trial registration number: NCT00000140

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization scheme generated by the Data Coordinating Center; stratification and blocking methods employed to ensure equal treatment assignments within each clinical center
Allocation concealment (selection bias)	Low risk	Investigators used sealed opaque envelopes supplied in limited numbers by the Data Coordinating Center
Masking of participants and personnel (performance bias)	Unclear risk	No information provided with respect to masking of participants or study investigators
Masking of outcome assessment (detection bias)	High risk	"A surgeon cannot be masked to the treatment during the operative procedure. During follow-up examinations, silicone fluid produces a characteristic appearance in the eye unlike that of a long-acting gas, making it impossible to mask study technicians."
Incomplete outcome data (attrition bias) All outcomes	High risk	Last observation carried forward method used for missing data, but data inferred only if "consistent" findings for prior and subsequent examinations. Randomized participants from a center that ceased recruitment (n = 12) and randomized participants with a history of prior vitrectomy (n = 38) were excluded from the analysis
Selective reporting (reporting bias)	Low risk	This study appeared to be free of selective reporting. Outcomes were reported in a prior manuscript describing trial design and participant baseline characteristics

Silicone Study 1992a *(Continued)*

Other bias	Unclear risk	The baseline estimated duration of retinal detachment was greater in Group 2 eyes (eyes of participants with prior vitrectomy but without silicone oil injection) randomized to SF_6 compared to Group 2 eyes randomized to silicone oil

Silicone Study 1992b

Study characteristics	
Methods	Study design: unmasked, multicenter randomized controlled trial Number randomized (total and per group): 271 participants in total, number per group was not reported Eyes of participants were stratified as follows (only one eye per participant randomized): Eyes that had not undergone prior vitrectomy (Group 1): 132 in total, number per group not reported Eyes that had undergone vitrectomy but without silicone oil injection (Group 2): 139 in total, number per group not reported Number analyzed (total and per group): 265 participants in total, 138 in the C3F8 gas group and 127 in the silicone oil group Eyes that had not undergone prior vitrectomy (Group 1): 131 in total, 67 in the C_3F_8 gas group and 64 in the silicone oil group Eyes that had undergone vitrectomy but without silicone oil injection (Group 2): 134 in total, 71 in the C_3F_8 gas group and 63 in the silicone oil group Exclusions and loss to follow-up: 6 participants were excluded Study follow-up: 36 months Sample size calculation: no
Participants	Country: USA Age (mean ± SD): mean ± SD was not reported, median age for the groups were listed below: Group 1: 66.2 years (range 20-86) for the C_3F_8 gas group and 66.0 years (range 21-89) for the silicone oil group Group 2: 63.3 years (range 22-88) for the C_3F_8 gas group and 61.6 years (range 27-84) for the silicone oil group Gender: Group 1: M:F=47:20 for the C_3F_8 gas group and 43:21 for the silicone oil group Group 2: M:F=48:23 for the C_3F_8 gas group and 49:14 for the silicone oil group Inclusion criteria: participants with proliferative vitreoretinopathy with a classification of at least C-3 grade, at least age 18, visual acuity better than light perception, and sufficient contracture so intraocular dissection was required Exclusion criteria: participants with uncontrolled concomitant eye disease, occurrence of blunt trauma to the eye within 3 months of randomization, history of penetrating trauma to the eye, presence of a giant tear ≥ 90°, presence of proliferative diabetic retinopathy, and the existence of any condition that would prevent 3-year follow-up

Silicone Study 1992b *(Continued)*

Interventions	Intervention 1: Perfluropropane gas (C_3F_8): 67 eyes (Group 1), 71 eyes (Group 2) Intervention 2: Silicone oil: 64 eyes (Group 1), 63 eyes (Group 2)
Outcomes	Primary outcome(s): Visual acuity, retinal reattachment, refraction; development or change in ocular complications affecting the cornea, iris, or lens; and measurements of intraocular pressure at 10 days, and 1, 3, 6, 12, 18, 24, and 36 months following randomization Secondary outcome(s): N/A Time points measurements were taken: 1, 3, 6, 2, 18, 24, and 36 months. Number of eyes included in the last follow-up analysis: 67 of 67 eyes (Group 1) and 71 or 71 eyes (Group 2) randomized to C_3F_8; 63 of 64 eyes (Group 1) and 63 of 63 eyes (Group 2) randomized to silicone oil. One participant randomized to silicone oil in Group 1 died after the baseline visit
Notes	Study dates: September 1, 1987 to 30 June 1991; "one center terminated follow-up in 1988 and patient data were excluded (n = 1 from Group 1; n = 5 from Group 2)" Twelve-month visual acuity and macula status outcomes were displayed in graphs; investigators contacted for 12-month outcomes Funding source(s): trial sponsored by the National Eye Institute. Silicone oil provided by the Dow Corning Corporation Declaration of interests: not reported Publication language: English Trial registration number: NCT00000140

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization scheme generated by the Data Coordinating Center; stratification and blocking methods employed to ensure equal treatment assignments within each clinical center
Allocation concealment (selection bias)	Low risk	Investigators used sealed envelopes supplied in limited numbers by the Data Coordinating Center
Masking of participants and personnel (performance bias)	Unclear risk	No information provided with respect to masking of participants or study investigators
Masking of outcome assessment (detection bias)	High risk	"A surgeon cannot be masked to the treatment during the operative procedure. During follow-up examinations, silicone fluid produces a characteristic appearance in the eye unlike that of a long-acting gas, making it impossible to mask study technicians."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Last observation carried forward method used for missing data, but data imputed only if "consistent" findings for prior and subsequent examinations.

Silicone Study 1992b *(Continued)*

		Randomized participants (n = 6) from center that ceased recruitment were excluded from the analysis
Selective reporting (reporting bias)	Low risk	This study appeared to be free of selective reporting. Outcomes were reported in a prior manuscript describing trial design and participant baseline characteristics
Other bias	Unclear risk	No differences in baseline characteristics

Zafar 2016

Study characteristics	
Methods	Study design: single-center randomized controlled trial Number randomized (total and per group): 96 participants total; number per group was not reported Number analyzed (total and per group): 85 eyes of 85 participants total, 44 in 1000-centistoke group and 41 in 5000-centistoke group Exclusions and loss to follow-up: 11 (participants with less than 18 months of follow-up or with incomplete records were excluded) Study follow-up: 18 months; 22.8 ± 3.2 (mean follow-up ± SD) Sample size calculation: not reported
Participants	Country: Pakistan Age (mean ± SD): 5000-centistoke group: 45.98 years ± 15.6 1000-centistoke: 44.43 years ± 16.8 Overall: 45.2 years ± 16.2 Gender: M:F = 24:17 for 5000-centistoke group and 28:16 for 1000-centistoke group Inclusion criteria: "Participants, aged 21 - 70 years, with rhegmatogenous RD in the superior quadrants, associated with PVR grades B and C were enrolled for this study. In case of PVR-C, only those patients who had the focal sub-type, involving 1 - 3 clock hours, were included". Exclusion criteria: patients with history of any intra-ocular surgery, pre-existing glaucoma, inflammatory eye condition, traumatic RD, intra-ocular foreign bodies, aphakia and with any pre-existing retinopathy. Also excluded were eyes in which the retina could not be re attached at the time of surgery, all patients who had a follow-up of less than 18 months or had incomplete records were excluded from the analysis.
Interventions	Intervention1: 5000-centistoke: The operative procedures consisted of pars plana vitrectomy, intravitreal triamcinolone acetonide suspension to identify any proliferative membrane, relief of epiretinal traction, retinal reattachment by PFCL and simultaneous internal drainage of subretinal fluid, cryopexy or endolaser photocoagulation and fluid-oil exchange. The vitreous cavity was filled with silicone oil (5000-centistoke) to the iris plane. Relaxing retinectomy was done in some cases, if needed. Intervention 2: 1000-centistoke: The operative procedures consisted of pars plana vitrectomy, intravitreal triamcinolone acetonide suspension to identify any proliferative membrane, relief of epiretinal traction, retinal reattachment by PFCL and simultaneous internal drainage of subretinal fluid, cryopexy

Zafar 2016 *(Continued)*

	or endolaser photocoagulation and fluid-oil exchange. The vitreous cavity was filled with silicone oil (1000-centistoke) to the iris plane. Relaxing retinectomy was done in some cases, if needed.
Outcomes	The study did not separate primary or secondary outcomes. All outcomes included: visual acuity, best-corrected visual acuity, intraocular pressure and postoperative complication Secondary outcome(s): N/A Time points measurements were taken: 1st and 3rd postoperative day, the end of first week, weekly for the first month, monthly for the next five months, 12, 18, and 24 months Adverse events; Silicone oil emulsification 32 eyes (37.6%) higher in the 1000-centistoke compared to the 5000-centistoke group (P = 0.004). Affected patients later underwent surgery for oil removal. Corneal decompensation, uncontrolled intra-ocular hypertension and high anisometropia due to the presence of silicone oil in the eye also necessitated silicone oil removal.
Notes	Study dates: from January 2007 to June 2013 (enrolment stopped after June 2011) Funding source(s): not reported Declaration of interests: not reported Publication language: English Trial registration number: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation was not reported; "they were randomly assigned to either the 1000 or 5000 centistokes silicone oil group and only one eye was enrolled in each patient."
Allocation concealment (selection bias)	Unclear risk	No information provided with respect to allocation concealment
Masking of participants and personnel (performance bias)	Unclear risk	No information provided with respect to masking
Masking of outcome assessment (detection bias)	Unclear risk	No information provided with respect to masking
Incomplete outcome data (attrition bias) All outcomes	High risk	11/96 (11.5%) who were randomized were not included in the final analysis; "all patients who had a follow-up of less than 18 months or had incomplete records were excluded from the analysis"
Selective reporting (reporting bias)	Unclear risk	No protocol or registration described; not sufficient information to assess the reporting bias
Other bias	Low risk	Study appears to be free from other sources of bias

cSt: centistokes
ETDRS: Early Treatment Diabetic Retinopathy Study
HSO: heavy silicone oil
PFCL: perfluorocarbon liquid
PPV: pars plana vitrectomy
PVR: proliferative vitreoretinopathy
RD: retinal detachment

SD: standard deviation
VA: visual acuity

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abellan 1986	Not a randomized trial
Avci 2001	Not a randomized trial
Brazitikos 2005	RCT that excluded patients with PVR stage C or greater, and not all patients received a tamponade agent
Chang 1988	Not a randomized trial
Gao 1993	Not a randomized trial
Hammer 1997	RCT that had compared sulfur hexafluoride gas and silicone oil fro PVR patients, however, study reported only 180 days of follow-up
Hutchins 2003	Not a randomized trial
ISRCTN53986599 2017	Not a randomized trial
ISRCTN95808249 2017	Not intervention of interest
Jurišić 2018	Not a randomized trial
Kralinger 2010	RCT that had compared silicone oil and acetyl-salicylic acid suspension for PVR patients, however, study reported a follow-up period of six months
Krasnik 1998	Not a randomized trial
Latecka-Krajewska 1998	Not a randomized trial
Laval 2015	Not population of interest
Lean 1989	Not a randomized trial
Li 1995	Not a randomized trial
Lomeo 1997	Not a randomized trial
Lu 2002	Not a randomized trial
Malbran 1987	Not a randomized trial
Mathis 1984	Not a randomized trial
NCT00120445	Not population of interest
NCT00485199	Not intervention of interest
NCT02675543	Not an intervention of interest
NCT03433547	Not intervention of interest

Study	Reason for exclusion
Neetens 1985	Not a randomized trial
Oncel 2005	Conference abstract, the study was never published
Pastor 1998	Not a randomized trial (retrospective study)
Pertile 1999	Not a randomized trial, did not include patients with RD and PVR (macular hole study)
Peyman 1987	RCT, but average follow-up 8.4 months
RushEye 2020	Not a population of interest
Soheilian 2006	Not a randomized trial, (retrospective study)
Stefer 1991	Not a randomized trial (case series)
Tufail 1997	Not a randomized trial, did not compare tamponade agents
van Effenterre 1987	Not a randomized trial (case series)
Vidne 2018	Not a randomized trial
Xu 2016	Not a randomized trial
Zheng 2018	Not population of interest

PVR: proliferative vitreoretinopathy
RD: retinal detachment
RCT: randomized controlled trial

Characteristics of studies awaiting classification *[ordered by study ID]*

Oncel 2006

Methods	Randomized controlled trial
Participants	**Inclusion:** 45 participants with complicated retinal detachments **Exclusion:** not reported
Interventions	**Intervention:** Heavy silicone oil (viscosity of 1400 cSt, density = 1.06 g/cm^3) **Comparison intervention:** Standard silicone oil
Outcomes	**Primary:** Retinal re-attachment (time of follow-up unknown) **Secondary:** not reported **Maximum follow-up:** not reported
Notes	**Start date:** not reported **Estimated end date:** not reported Conference abstract from the American Academy of Ophthalmology Meeting (2006). This trial does not appear to have ever been published. [No full publication found]

Trepsat 1987

Methods	Not reported
Participants	Not reported
Interventions	Not reported
Outcomes	Not reported
Notes	

cm: centimeter
cSt: centistokes
g: grams

Characteristics of ongoing studies *[ordered by study ID]*

NCT00403702

Study name	Comparison of two high-density silicone oils in complicated rhegmatogenous retinal detachment. Recruitment status: unknown, last updated 30 June 2009
Methods	Randomized controlled trial
Participants	**Inclusion:** participants aged ≥ 18 years with complicated persistent retinal detachment due secondary to proliferative vitreoretinopathy **Exclusion:** diabetes, uveitis, glaucoma
Interventions	**Intervention:** oxane HD (oil-RMN3-mixture) **Comparison intervention:** densiron (F6H8)
Outcomes	**Primary outcomes:** visual acuity, anatomical results **Secondary outcomes:** complication: hypotony, vitreous hemorrhage, inflammatory reaction, cataract, chronic hypotony, IOP elevated intraocular pressure, pseudohypopyon, fibrin, emulsification droplets in the anterior chamber **Maximum follow-up:** not reported
Starting date	August 2006 **Estimated completion date:** August 2007
Contact information	clinicaltrials.gov/ct2/show/NCT00403702
Notes	Recruitment status unknown (last updated: June 30, 2009)

NCT01255293

Study name	A prospective, randomized study comparing 1000 centistoke and 5000 centistoke silicone oil tamponade for repair of proliferative vitreoretinopathy retinal detachments and diabetic tractional retinal detachments

NCT01255293 *(Continued)*

Methods	Randomized controlled trial
Participants	**Inclusion:** child or adult participants with rhegmatogenous retinal detachment or tractional retinal detachment due to grade C or worse proliferative vitreoretinopathy or proliferative diabetic retinopathy **Exclusion: i**nability to re-attach the retina at the time of surgery, prior trabeculectomy or tube shunt surgery, corneal opacity which limits visualization of the trabecular meshwork.
Interventions	**Intervention:** 1000 centistoke silicone oil **Comparison intervention:** 5000 centistoke silicone oil
Outcomes	**Primary outcome:** retinal redetachment rate **Secondary outcomes:** best-corrected visual acuity at 6 and 12 months Silicone oil emulsification rate every month: Gonioscopy examination will be used at monthly postoperative visits to assess silicone oil emulsification in each patient. **Maximum follow-up:** 12 months
Starting date	November 2010 **Estimated completion date:** October 2012
Contact information	clinicaltrials.gov/ct2/show/NCT01255293
Notes	(Completed October 2012, but no results last updated 14 June 2013.)

NCT01959568

Study name	Double endotamponade with perfluorodecalin and silicone oil in retinal detachment surgery: randomized clinical trial of safety
Methods	Randomized controlled trial
Participants	**Inclusion:** participants aged ≥ 18 years with firstly diagnosed with firstly diagnosed rhegmatogenous total retinal detachment with retinal breaks located both in upper and lower retina, or with proliferative vitreoretinopathy which was impossible to remove completely during surgery **Exclusion:** severe concomitant eye pathologies (glaucoma, diabetic retinopathy, macular hole, traumas); or eye length more than 27mm.
Interventions	**Intervention:** double tamponade **Comparison intervention:** silicone oil tamponade
Outcomes	**Primary outcome:** Retinal reattachment rate in 1 month after tamponade removal **Secondary outcome:** Percentage of patients with best corrected visual acuity >/= 20.200 in 1 month after tamponade removal **Maximum follow-up:**

NCT01959568 *(Continued)*

Starting date	March 2010 **Estimated completion date:** June 2018
Contact information	clinicaltrials.gov/ct2/show/NCT01959568
Notes	(Recruiting status unknown, last updated on 28 May 2014)

NCT02988583

Study name	Emulsification of different viscosity silicone oil after complicated retinal detachment surgery: a randomized double-masked clinical trial
Methods	Randomized controlled trial
Participants	**Inclusion:** participants aged ≥ 18 years with diagnosis of complicated retinal detachment who underwent pars plana vitrectomy with intravitreal silicone oil tamponade, sign informed consent form tamponade **Exclusion:** inflammatory eye diseases i.e. uveitis, corneal scar, history of scleral buckling procedure, history of using surfactant drugs, glaucoma
Interventions	**Intervention:** Pars plans vitrectomy using low viscosity silicone oil **Comparison intervention:** Pars plans vitrectomy using high viscosity silicone oil
Outcomes	**Primary outcome:** emulsification rate at 12 months, defined as proportion of participants developing silicone oil emulsification in each arm/group **Secondary outcomes:** Retina reattachment rate at 12 months, defined as proportion of participants having retinal reattachment after surgery in each arm/group; visual improvement 12 months, defined as proportion of patients having visual improvement after surgery in each arm/group **Maximum follow-up:** 12 months
Starting date	October 2016 **Estimated completion date:** August 2019
Contact information	clinicaltrials.gov/ct2/show/NCT02988583
Notes	(Trial completed in August 2019, last updated 14 August 2019.)

NTR185 2005

Study name	Heavy Silicone Oil (HSO) versus standard silicone oil as long term vitreous tamponade
Methods	Randomized controlled trial (Completed, no longer recruiting, last updated: 14 July 2014.)
Participants	**Inclusion:** Participants with: 1. Ablatio retinae with proliferative vitreoretinopathy (PVR) 2. Giant tear below 10 - 12 hours **Exclusion:** participants with: defects above 10 - 12 hours, proliferative diabetic retinopathy, trauma, uveitis, glaucoma, monoculus

NTR185 2005 *(Continued)*

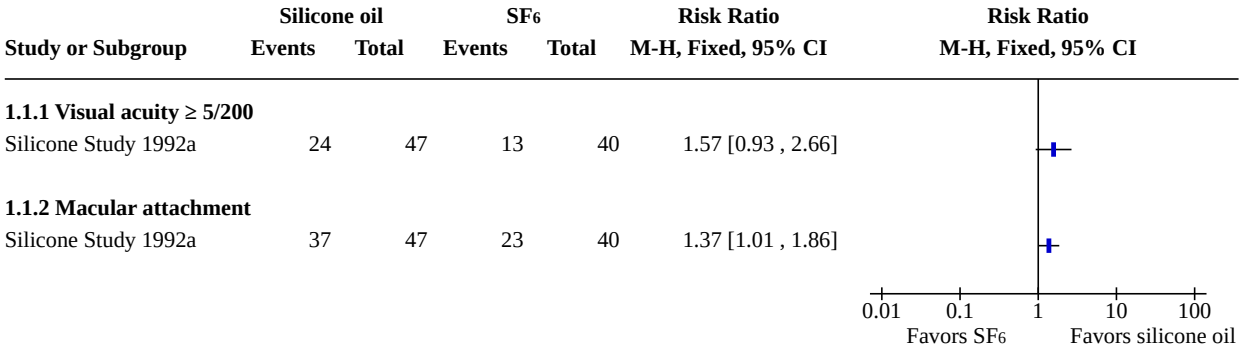
Interventions	**Intervention:** Heavy silicone oil **Comparison intervention:** Standard silicone oil
Outcomes	**Primary outcome: c**omplete retinal reattachment and Early Treatment Diabetic Retinopathy Study (ETDRS) vision after 12 months **Secondary outcome:** number of resurgeries within 12 months **Maximum follow-up:** 12 months
Starting date	May 2005 **Estimated completion date:** May 2007
Contact information	www.isrctn.com/ISRCTN47399029
Notes	No longer recruiting since December 20, 2005

DATA AND ANALYSES

Comparison 1. Silicone oil versus sulfur hexafluoride (SF_6)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Visual acuity ≥ 5/200 and macular attachment at two years	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1.1 Visual acuity ≥ 5/200	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1.2 Macular attachment	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1: Silicone oil versus sulfur hexafluoride (SF_6), Outcome 1: Visual acuity ≥ 5/200 and macular attachment at two years

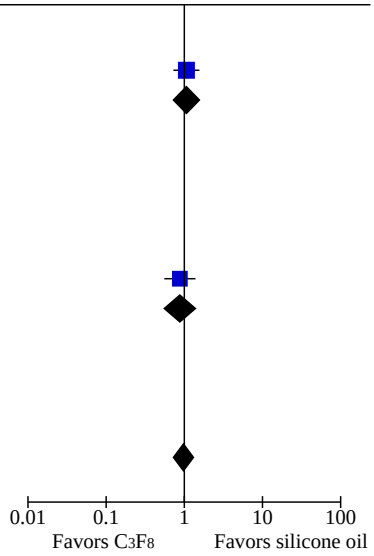


Comparison 2. Silicone oil versus perfluropropane (C_3F_8)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Visual acuity ≥ 5/200 at last follow-up examination	1	264	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.73, 1.31]
2.1.1 No prior vitrectomy	1	130	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.73, 1.56]
2.1.2 Prior vitrectomy	1	134	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.55, 1.39]
2.2 Macular attachment at last follow-up examination	1	264	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.86, 1.15]
2.2.1 No prior vitrectomy	1	130	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.80, 1.20]
2.2.2 Prior vitrectomy	1	134	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.83, 1.25]

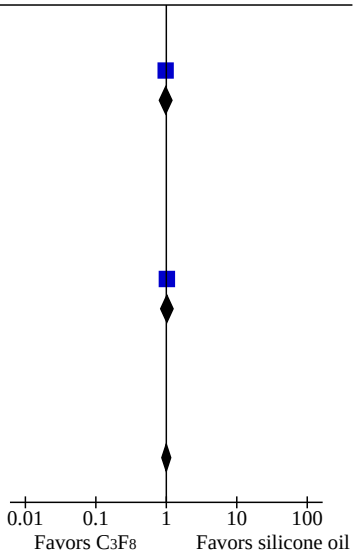
Analysis 2.1. Comparison 2: Silicone oil versus perfluropropane (C_3F_8), Outcome 1: Visual acuity ≥ 5/200 at last follow-up examination

Study or Subgroup	Silicone oil Events	Total	C_3F_8 Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.1.1 No prior vitrectomy						
Silicone Study 1992b	29	63	29	67	52.5%	1.06 [0.73 , 1.56]
Subtotal (95% CI)		**63**		**67**	**52.5%**	**1.06 [0.73 , 1.56]**
Total events:	29		29			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.32 (P = 0.75)						
2.1.2 Prior vitrectomy						
Silicone Study 1992b	21	63	27	71	47.5%	0.88 [0.55 , 1.39]
Subtotal (95% CI)		**63**		**71**	**47.5%**	**0.88 [0.55 , 1.39]**
Total events:	21		27			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.56 (P = 0.57)						
Total (95% CI)		**126**		**138**	**100.0%**	**0.97 [0.73 , 1.31]**
Total events:	50		56			
Heterogeneity: Chi² = 0.41, df = 1 (P = 0.52); I² = 0%						
Test for overall effect: Z = 0.17 (P = 0.86)						
Test for subgroup differences: Chi² = 0.40, df = 1 (P = 0.53), I² = 0%						



Analysis 2.2. Comparison 2: Silicone oil versus perfluropropane (C_3F_8), Outcome 2: Macular attachment at last follow-up examination

Study or Subgroup	Silicone oil Events	Silicone oil Total	C_3F_8 Events	C_3F_8 Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.2.1 No prior vitrectomy						
Silicone Study 1992b	46	63	50	67	49.8%	0.98 [0.80 , 1.20]
Subtotal (95% CI)		**63**		**67**	**49.8%**	**0.98 [0.80 , 1.20]**
Total events:	46		50			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.21 (P = 0.83)						
2.2.2 Prior vitrectomy						
Silicone Study 1992b	47	63	52	71	50.2%	1.02 [0.83 , 1.25]
Subtotal (95% CI)		**63**		**71**	**50.2%**	**1.02 [0.83 , 1.25]**
Total events:	47		52			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.18 (P = 0.86)						
Total (95% CI)		**126**		**138**	**100.0%**	**1.00 [0.86 , 1.15]**
Total events:	93		102			
Heterogeneity: Chi² = 0.08, df = 1 (P = 0.78); I² = 0%						
Test for overall effect: Z = 0.02 (P = 0.98)						
Test for subgroup differences: Chi² = 0.08, df = 1 (P = 0.78), I² = 0%						

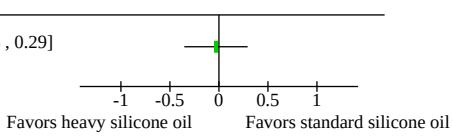


Comparison 3. Standard silicone oil versus heavy silicone oil

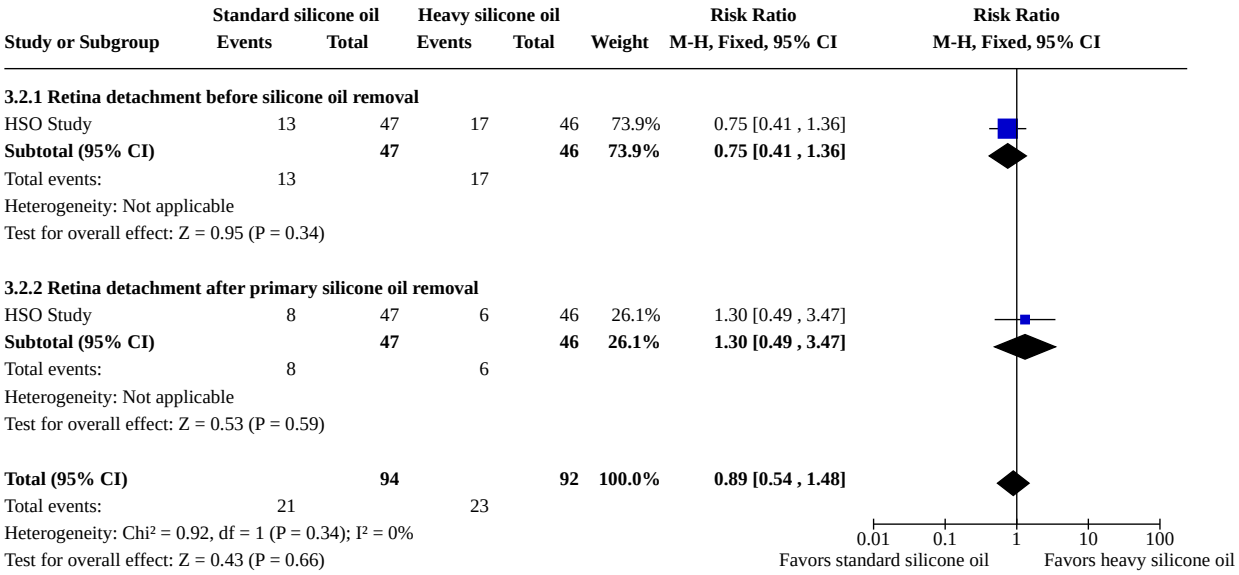
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Change in visual acuity at one year	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.2 Retina detachment	1	186	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.54, 1.48]
3.2.1 Retina detachment before silicone oil removal	1	93	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.41, 1.36]
3.2.2 Retina detachment after primary silicone oil removal	1	93	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [0.49, 3.47]

Analysis 3.1. Comparison 3: Standard silicone oil versus heavy silicone oil, Outcome 1: Change in visual acuity at one year

Study or Subgroup	Standard silicone oil Mean	SD	Total	Heavy silicone oil Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
HSO Study	1.24	0.7953	47	1.27	0.7935	46	-0.03 [-0.35 , 0.29]



Analysis 3.2. Comparison 3: Standard silicone oil versus heavy silicone oil, Outcome 2: Retina detachment

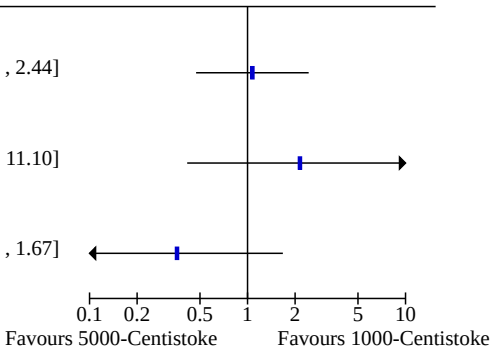


Comparison 4. 5000-Centistoke vs 1000-Centistoke

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Retina detachment	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1.1 After first surgery	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1.2 After second surgery	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1.3 After removal of silicone oil	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.2 Elevated intraocular pressure (IOP)(greater than 22 mmHg)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.3 Visually significant cataract	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

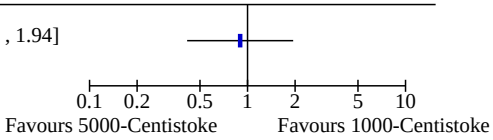
Analysis 4.1. Comparison 4: 5000-Centistoke vs 1000-Centistoke, Outcome 1: Retina detachment

Study or Subgroup	5000-Centistoke Events	5000-Centistoke Total	1000-Centistoke Events	1000-Centistoke Total	Risk Ratio M-H, Fixed, 95% CI
4.1.1 After first surgery					
Zafar 2016	9	41	9	44	1.07 [0.47 , 2.44]
4.1.2 After second surgery					
Zafar 2016	4	41	2	44	2.15 [0.42 , 11.10]
4.1.3 After removal of silicone oil					
Zafar 2016	2	41	6	44	0.36 [0.08 , 1.67]



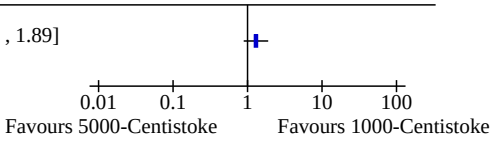
Analysis 4.2. Comparison 4: 5000-Centistoke vs 1000-Centistoke, Outcome 2: Elevated intraocular pressure (IOP)(greater than 22 mmHg)

Study or Subgroup	5000-Centistoke Events	5000-Centistoke Total	1000-Centistoke Events	1000-Centistoke Total	Risk Ratio M-H, Fixed, 95% CI
Zafar 2016	9	41	11	45	0.90 [0.41 , 1.94]



Analysis 4.3. Comparison 4: 5000-Centistoke vs 1000-Centistoke, Outcome 3: Visually significant cataract

Study or Subgroup	5000-Centistoke Events	5000-Centistoke Total	1000-Centistoke Events	1000-Centistoke Total	Risk Ratio M-H, Fixed, 95% CI
Zafar 2016	26	41	22	45	1.30 [0.89 , 1.89]



APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor Retinal Detachment
#2 MeSH descriptor Retinal Perforations
#3 MeSH descriptor Vitreous Detachment
#4 retina* near/2 break*
#5 retina* near/2 tear*
#6 retina* near/2 detach*
#7 retina* near/2 perforat*
#8 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7)
#9 MeSH descriptor Silicone Oils
#10 silicone oil*
#11 tamponade*
#12 MeSH descriptor Sulfur Hexafluoride

#13 sulfur hexafluoride*
#14 hexafluoroethane*
#15 MeSH descriptor Fluorocarbons
#16 MeSH descriptor Dimethylpolysiloxanes
#17 perfluoropropane*
#18 polydimethylsiloxane*
#19 perfluorohexylethan*
#20 perfluoro-n-octane
#21 (#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20)
#22 (#8 AND #21)

Appendix 2. MEDLINE (OvidSP) search strategy

1. randomized controlled trial.pt.
2. (randomized or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. exp animals/
10. exp humans/
11. 9 not (9 and 10)
12. 8 not 11
13. exp retinal detachment/
14. exp retinal perforation/
15. exp vitreous detachment/
16. (retina$ adj2 break$).tw.
17. (retina$ adj2 tear$).tw.
18. (retina$ adj2 detach$).tw.
19. (retina$ adj2 perforat$).tw.
20. or/13-19
21. exp silicone oils/
22. silicone oil$.tw.
23. tamponade$.tw.
24. exp sulfur hexafluoride/
25. sulfur hexafluoride$.tw.
26. hexafluoroethane$.tw.
27. exp fluorocarbons/
28. exp dimethylpolysiloxanes/
29. perfluoropropane$.tw.
30. polydimethylsiloxane$.tw.
31. perfluorohexylethan$.tw.
32. perfluoro-n-octane.tw.
33. or/21-32
34. 20 and 33
35. 12 and 34

The search filter for trials at the beginning of the MEDLINE strategy is from the published paper by Glanville et al (Glanville 2006).

Appendix 3. Embase (OvidSP) search strategy

1. exp randomized controlled trial/
2. exp randomization/
3. exp double blind procedure/
4. exp single blind procedure/
5. random$.tw.
6. or/1-5
7. (animal or animal experiment).sh.
8. human.sh.
9. 7 and 8
10. 7 not 9

11. 6 not 10
12. exp clinical trial/
13. (clin$ adj3 trial$).tw.
14. ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).tw.
15. exp placebo/
16. placebo$.tw.
17. random$.tw.
18. exp experimental design/
19. exp crossover procedure/
20. exp control group/
21. exp latin square design/
22. or/12-21
23. 22 not 10
24. 23 not 11
25. exp comparative study/
26. exp evaluation/
27. exp prospective study/
28. (control$ or prospectiv$ or volunteer$).tw.
29. or/25-28
30. 29 not 10
31. 30 not (11 or 23)
32. 11 or 24 or 31
33. retina detachment/
34. retina tear/
35. vitreous body detachment/
36. (retina$ adj2 break$).tw.
37. (retina$ adj2 tear$).tw.
38. (retina$ adj2 detach$).tw.
39. (retina$ adj2 perforat$).tw.
40. or/33-39
41. silicone oil/
42. silicone oil$.tw.
43. tamponade$.tw.
44. sulfur hexafluoride/
45. sulfur hexafluoride$.tw.
46. hexafluoroethane$.tw.
47. fluorocarbon/
48. dimeticone/
49. perfluoropropane$.tw.
50. polydimethylsiloxane$.tw.
51. perfluorohexylethan$.tw.
52. perfluoro-n-octane.tw.
53. or/41-52
54. 40 and 53
55. 32 and 54

Appendix 4. LILACS search strategy

retina$ and detach$ or perforat$ or break$ or tear and silicone or sulfur hexafluoride$ or hexafluoroethane$ or fluorocarbon$ or dimethylpolysiloxane$ or perfluoropropane$ or polydimethylsiloxane$ or perfluorohexylethan$

Appendix 5. *meta*Register of Controlled Trials search strategy

(tamponade or oil) and retina

Appendix 6. ClinicalTrials.gov search strategy

(Tamponade OR Silicone Oil) AND Retina

Appendix 7. ICTRP search strategy

Retinal detachment = condition AND (Tamponade OR Silicone Oil) = intervention

WHAT'S NEW

Date	Event	Description
2 January 2019	New citation required but conclusions have not changed	Issue 5 2020: One new study (Zafar 2016) included
2 January 2019	New search has been performed	Issue 5 2020: Searches updated

HISTORY

Protocol first published: Issue 3, 2006
Review first published: Issue 4, 2009

Date	Event	Description
3 February 2014	New citation required but conclusions have not changed	Issue 2, 2014: One new study (HSO Study) included
3 February 2014	New search has been performed	Issue 2, 2014: Electronic searches were updated
16 June 2010	Amended	External source of support added.
29 July 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

For the original review

Conceiving the review: SGS
Designing the review: SGS
Coordinating the review: SGS
Undertaking manual searches: SGS, ES
Screening search results: SGS, ES
Organizing retrieval of papers: SGS, ES
Screening retrieved papers against inclusion criteria: SGS, ES
Appraising quality of papers: SGS, ES
Abstracting data from papers: SGS, ES, AE
Writing to authors of papers for additional information: SGS
Obtaining and screening data on unpublished studies: SGS
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Analysis of data: SGS, HWF, ES, AE
Interpretation of data: SGS, HWF
Writing the review: SGS, WHL, HWF, ES, AE
Securing funding for the review: SGS
Guarantor for the review: SGS

For the previous update of the review

Screening search results: SGS, XW
Organizing retrieval of papers: SGS, XW
Screening retrieved papers against inclusion criteria: SGS, XW
Appraising quality of papers: SGS, XW
Abstracting data from papers: SGS, XW

Writing to authors of papers for additional information: SGS
Obtaining and screening data on unpublished studies: SGS
Data management for the review: SGS, XW
Entering data into RevMan: SGS, XW
Analysis of data: SGS, HWF, XW
Interpretation of data: SGS, HWF
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For the current update of the review

Screening search results: SGS, SAA
Organizing retrieval of papers: SGS, SAA
Screening retrieved papers against inclusion criteria: SGS, SAA
Appraising quality of papers: SGS, SAA
Abstracting data from papers: SGS, SAA
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DECLARATIONS OF INTEREST

Stephen G Schwartz, MD, MBA has served on advisory boards for Welch Allyn.
Harry W Flynn, Jr, MD is a co-author on several of the studies that were eligible for inclusion in this review. Dr Flynn has no disclosures.
Xue Wang, MBBS, MPH, has no known declarations of interest.
Ajay E. Kuriyan, MD, MS receives grant funding from Second Sight, Inc. and Genentech and serves/served on the advisory board for the following entities: Alimera Sciences, Allergan, Bausch Health, Genentech, and Regeneron.
Samuel A. Abariga, MD, MPH, MS, has no known declarations of interest.
Wen-Hsiang Lee, MD, has no known declarations of interest.

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  The views expressed in this publication are those of the authors and not necessarily those of the NIHR, NHS, or the Department of Health.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We included 'Summary of findings' tables that examined seven outcomes for each comparison.

INDEX TERMS

Medical Subject Headings (MeSH)

Fluorocarbons [*administration & dosage]; Intraocular Pressure; Macula Lutea; Randomized Controlled Trials as Topic; Retinal Detachment [etiology] [prevention & control] [*therapy]; Secondary Prevention; Silicone Oils [*administration & dosage]; Sulfur Hexafluoride [*administration & dosage]; Visual Acuity; Vitreoretinopathy, Proliferative [*complications]

MeSH check words

Adult; Aged; Aged, 80 and over; Female; Humans; Male; Middle Aged; Young Adult