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Review

RISK OF SILICONE OIL AS VITREOUS TAMPONADE IN PARS PLANA VITRECTOMY

A Systematic Review and Meta-Analysis

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Purpose: The authors examined the differences between silicone oil and other vitreous tamponades or placebo in performing pars plana vitrectomy.

Methods: This review and meta-analysis was conducted in accordance with the PRISMA guidelines. Seven databases and the reference lists of the retrieved randomized controlled trial articles were searched to identify eligible studies. The primary outcomes were the rate of redetachment after endotamponade removal, the rate of reoperation, and poor visual acuity. The secondary outcomes were adverse events and quality of life related to postoperative position.

Results: Ten articles (12 trials) were included. There were no significant differences between silicone oil and other agents in most of the primary and second outcomes. Only the risk of hypotony was found to be significantly lower when filling with silicone oil, compared with other agents. No trial reported the quality of life related to postoperative position.

Conclusion: Based on the available studies, the authors conclude that there is no significant difference in the risk of poor outcomes between pars plana vitrectomy with silicone oil and that with other vitreous tamponades with different surgical histories.

RETINA 0:1–12, 2017

Artificial vitreous tamponades are used to re-establish intraocular volume, assist in separating membranes adherent to the retina, manipulate retinal detachments, and mechanically flatten detached retinas.[1] They play an increasingly important role in pars plana vitrectomy (PPV). New vitreous tamponades[2–5] have been developed, composed of gases (e.g., air and perfluorocarbon gases) and liquids (e.g., silicone oil and perfluorocarbon liquids). In particular, silicone oil has wide applications for facilitating the closure of retinal breaks and reducing subretinal leakage.

Since the introduction of silicone oil as a vitreous tamponade, there have been many advances in intraoperative viewing systems, and surgical instrumentation and techniques. Although PPV with silicone oil is often reserved for the most complicated cases, including desperate cases with poor prognoses, more and more studies and reviews have been optimistic in their evaluation of the successful aspects (e.g., retinal attachment, macular attachment, or vision improvement) of silicone oil or vitreous tamponade.[6,7] However, recently, a number of case series reported central visual loss after uncomplicated surgery with silicone tamponade in eyes which had seemingly good visual potential.[8] These discouraging cases have led clinicians to reconsider the use of silicone oil.

We examined this problem from a dialectical view. By focusing on the "negative aspects" (e.g., failure risk, adverse events, or bad quality of life postsurgery), we may uncover more evidence regarding the feasibility of this surgical strategy. In other words, we wanted to know whether silicone oil should be used, and how to use it effectively. In this systematic review, we compared silicone oil versus placebo and other

vitreous tamponades by examining some crueler outcomes: the primary objective was to determine the failure rate of surgery with different tamponades. The second objective was to determine the effects of silicone oil versus other agents (or placebo) on adverse events and quality of life related to postoperative position. Our goal is to assist surgeons in the selection of silicone oil in eye diseases through a comparison of the relative safety of silicone oil with placebo or other tamponade agents used in surgery.

Methods

Information Sources

This review and meta-analysis was conducted in accordance with the PRISMA guidelines. We retrieved randomized controlled trials (RCTs) evaluating the risk of silicone by conducting computer-based searches of the following databases: Medline, Cochrane Library (CENTRAL), EMBASE, the Web of Science databases, Scopus, CNKI (a Chinese database), and WANFANG DATA (a Chinese database) with the following search strategy (see **Table, Supplemental Digital Content 1**, http://links.lww.com/IAE/A595, which lists the search strategy of our meta-analysis).

No language restrictions were applied for the search strategy. The searches for titles and abstracts were executed electronically. Two reviewers independently retrieved the full text of the study if the title and abstract met the eligibility criteria of the study. Additional searches were performed within the reference lists of systematic reviews and eligible studies. The last search was performed in August 20, 2016. Any disagreements were resolved through discussion.

Selection Criteria

The full texts of potentially relevant articles were reviewed to identify studies that met the inclusion and exclusion criteria. The articles were considered eligible if the studies were RCTs that compared the outcomes and complications between silicone oil and placebo or other vitreous tamponade, such as air, sulfur hexafluoride (SF_6), hexafluoroethane (C_2F_6), perfluoropropane (C_3F_8), heavy silicone oil, or others. We excluded abstracts from conferences, republished data, and reviews. Any disagreements were resolved by consensus between the investigators.

Quality Assessment

Two reviewers independently rated the quality of each eligible study by assessing its methodology, and any disagreements were resolved by discussion. The risk of bias for each study was assessed on the basis of the primary outcome with the Cochrane Collaboration's tool.[9] Working independently, two authors judged each area of potential bias in the studies as low, high, or unclear risk of bias.

Data Extraction

Two authors, working independently, extracted and summarized the relevant characteristics of each eligible study using a standardized form: first author—year of publication, sample size, baseline characteristics of the study, and type of tamponades. They then extracted the outcomes. The primary outcomes were the rate of redetachment after endotamponade removal, the rate of reoperation, and poor visual acuity. The secondary outcomes were adverse events and quality of life related to postoperative position.

We elected to extract the outcome from the data of the final follow-up examination in each study. If the study used a unique measuring method or unit, we attempted to convert the findings into a conventional method or unit that was used in most of the included studies. When extracting the data, we used two strategies. The first strategy involved directly obtaining the original data from the article. The second strategy involved calculation and transformation of raw data from the article to attain the data we needed, considering that poor outcomes may not be directly obtainable because many articles report only successful results (e.g., retinal attachment, macular attachment, or vision improvement). Disagreements between

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Supported by the National Natural Science Foundation of China (81271008), Science and Technology Planning Project of Guangdong Province, China (2015B020211004).

None of the authors has any conflicting interests to disclose.

All aspects of the meta-analysis were performed under the auspices of writers. X. Feng, C. Li, Q. Zheng, X. Qian, L. Yin, Y. Wang collated data, contributed to the discussions of the results, analyzing data, and commented on drafts of the report. The project was organized by W. Shao and Y. Li, who were responsible for formulating the question, developing the protocol, receiving, and checking data. The project was managed by Q. Gao and W. Li. The report was drafted by X. Feng.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.retinajournal.com).

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reviewers regarding data extraction were resolved through discussion.

Statistical Analysis

We used RevMan 5.0 (http://tech.cochrane.org/) for statistical analysis and to derive a forest plot to show the results of individual studies and pooled analysis. The weighted odds ratio (OR) and mean difference were used to compare dichotomous and continuous variables, respectively. All results were reported with 95% CIs.

All estimates from individual studies were investigated for statistical and clinical heterogeneity. We assessed for statistical heterogeneity using the chi-square test and the I^2 statistic. Pooled analyses of control groups were performed according to the I^2 value. If the I^2 value was less than 40%, we used a random-effects model to incorporate the heterogeneity. If the I^2 value was more than 40%, which might indicate substantial statistical heterogeneity, we performed subgroup analyses. Before commencing the study, we devised some hypotheses for the possible cause of heterogeneity to examine if subgroup analyses were needed. The hypotheses were as follows: 1) a different tamponade in the control group, such as a group of gases with silicone oil, a group of silicone oil with placebo, and a group of silicone oil with heavy silicone oil; 2) previous surgical history, such as a group with previous surgical history and a group without previous surgery. The meta-analyses used a Mantel–Haenszel random-effects model for more conservative effect estimates. Publication bias was assessed through visual inspection of funnel plot asymmetry.

Results

Study Identification and Characteristics

Ten eligible articles reporting on 12 trials (two articles consisted of two trials each) met the inclusion criteria and were included in the final analysis.[10–19] Identification of eligible studies is summarized in Figure 1. The details of the search, as the search results, the number of citations, and studies with reasons for exclusions, are listed in the supplementary data (see **Table, Supplemental Digital Content 2**, http://links.lww.com/IAE/A596, which demonstrates the results of database search and **see Table, Supplemental Digital Content 3**, http://links.lww.com/IAE/A597, which demonstrates the reasons for study exclusion).

The included studies were published from 1992 to 2014. There were 905 patients (in 521 patients from seven trials, the eye was filled with silicone oil or

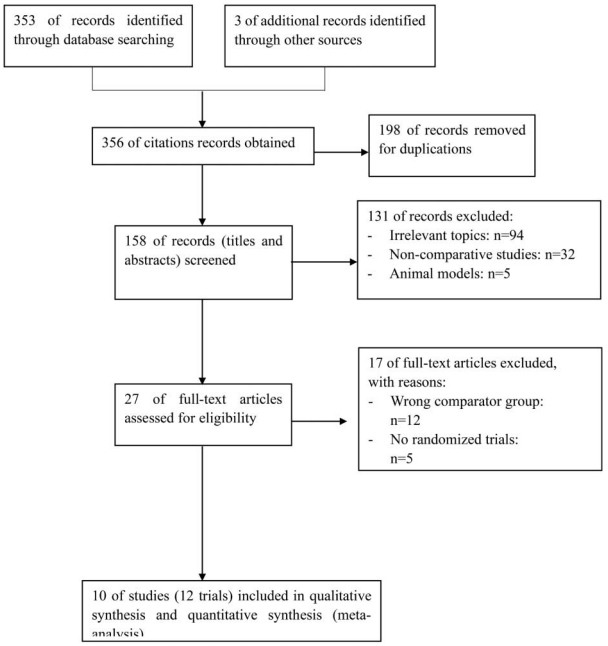

Fig. 1. Flow diagram of studies identified, included, and excluded.

gases[10–14]; in 261 patients from three trials, the eye was filled with silicone oil or placebo[15–17]; in 123 patients from two trials, the eye was filled with silicone oil or heavy silicone oil[18,19]). Although a language restriction was not placed on the search, all the included trials were reported in English. The details of the study patients and interventions are provided in Table 1.

Risk of Bias

All the included studies were of good methodological quality. Regarding selection bias, attrition bias, and other bias, all the studies had a low risk. For allocation concealment, 11 studies (Peyman et al; Hammer et al; Nagpal et al; Do et al; Avitabile et al; Azad et al; Joussen et al; The silicone oil study report 1ab, 1992; and The silicone oil study report 2ab, 1992) were rated as low risk; these studies explicitly reported the method of concealment (sealed envelopes that were opened after study enrollment). The study by Batman and Cekic was identified as unclear risk. However, for blinding (e.g., performance bias and detection bias), whether the participants or surgeons were masked was reported in six studies (Avitabile et al; Azad et al; The silicone oil study report 1ab, 1992; and The silicone oil study report 2ab, 1992). We considered that masking surgeons might not be possible in studies of operation with different tamponades. Thus, we rated the performance bias of all the six trials as high risk. Others were rated as unclear risk. Two trials (Avitabile et al and Azad et al) had masked outcome assessors. The detection bias of the two trials

Table 1. Characteristics of the RCT Studies Included in This Meta-Analysis

Study	Follow-up, Months	Case/ Control	Age, Year	F/M Case/ Control	Type of Tamponade	Other Type of Interventions
Peyman et al[10]	6–13 (*8.4)	25/25	44/45†	17/33	Silicone oil vs. gas (20% C_3F_8 or 30% C_4F_8)	1. Photocoagulation 2. Or encircling explant
Silicone study Report 1 Group 1, 1992	18	64/67	66.0/66.2†	21/43, 20/47	Silicone oil VS 20% SF_6	1. Endolaser photocoagulation 2. Or exocryocoagulation
Silicone study Report 1 Group 2, 1992	18	63/71	61.6/63.3†	14/49, 23/48	Silicone oil VS 20% SF_6	1. Endolaser photocoagulation 2. Or exocryocoagulation
Silicone Study Report 2 Group 1, 1992	18	64/67	66/66.2†	21/43, 20/47	Silicone oil VS 14% C_3F_8	1. Endolaser photocoagulation 2. Or exocryocoagulation
Silicone Study Report 2 Group 2, 1992	18	63/71	61.6/63.3	14/49, 23/48	Silicone oil VS 14% C_3F_8	1. Endolaser photocoagulation 2. Or exocryocoagulation
Hammer et al[13]	6	18/16	62.9/68.9†	—	Silicone oil VS SF_6	1. Endolaser photocoagulation 2. Or exocryocoagulation
Batman and Cekic[14]	60	25/22	43.4†	15/32	Silicone oil VS C_3F_8	1. Endolaser photocoagulation 2. Or exocryocoagulation
Azad et al[15]	112 ± 55 days	12/12	10.08 ± 3.70/66 ± 6.82	2/22	Silicone oil VS placebo (core vitrectomy alone)	—
Avitabile et al[19]	6	15/15	64/60	7/8, 6/9	Silicone oil VS heavy silicone oil (Densiron)	Endolaser photocoagulation
Joussen et al[18]	12	47/46	61.87 ± 15.69/65.54 ± 12.20	28/19, 11/35	Silicone oil (standard) VS heavy silicone oil	—
Nagpal et al[16]	6	64/65	40/42.5	49/15, 44/21	Silicone oil VS placebo (vitrectomy alone)	1. Intravitreal antibiotics (vancomycin and ceftazidime or dexamethasone) 2. Cryopexy
Do et al[17]	9	55/53	—	—	Silicone oil VS placebo (standard PPV)	1. Intravitreal antibiotics (vancomycin and ceftazidime) 2. Endolaser

*Average.
†Median age.

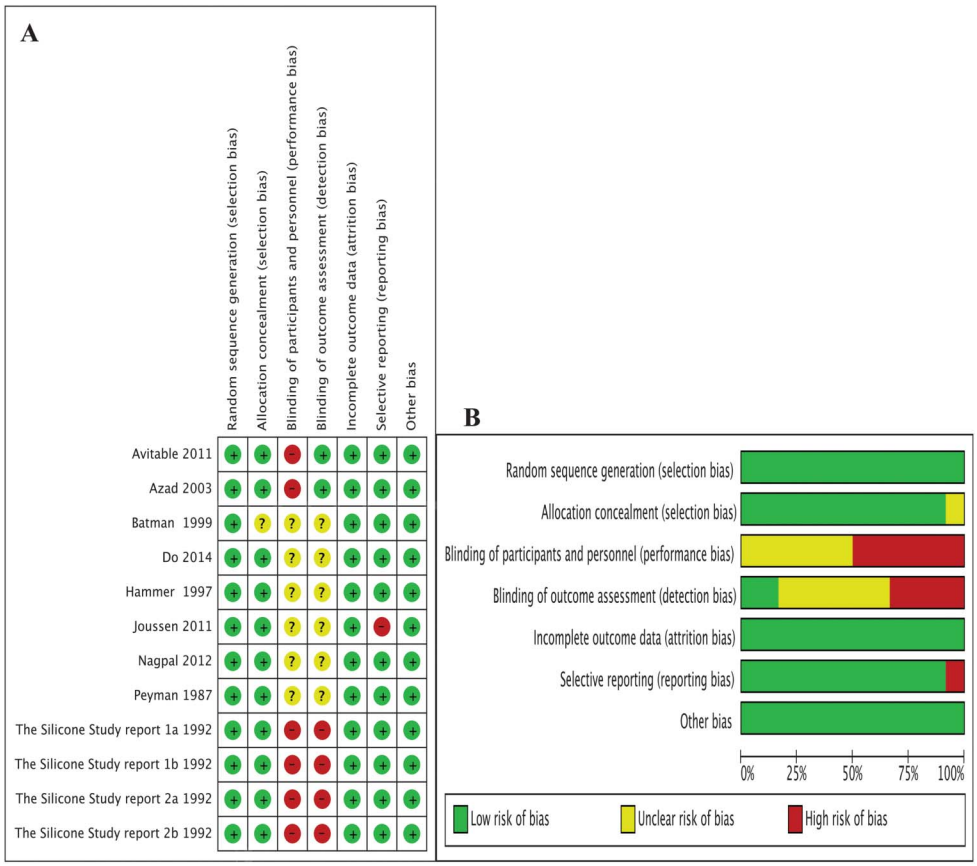

Fig. 2. Risk of bias summary and graph: review authors' judgments about each risk of bias item for each included study.

was rated as low risk. The detection bias of four studies (The silicone oil study report 1ab, 1992 and The silicone oil study report 2ab, 1992) was rated as high risk, although we considered that masking might not be possible in studies of postoperative outcome with different tamponades. The other studies were rated as unclear risk. For reporting bias, only 1 trial (Joussen et al) was rated as high risk because it did not provide explicit data, and 11 trials were rated as low risk. Details of the risk of bias assessment are provided in Figure 2.

Effects of Interventions

Primary outcome. ***The rate of redetachment after endotamponade removal.*** Among the 12 included trials, all reported the numbers of retinal redetachment after endotamponade removal and the corresponding 95% CIs. The pooled estimate (Figure 3) showed an OR of 0.67 (95% CI, 0.42–1.06). Although the rate of retinal redetachment with silicone oil (29.69%, n = 136/458) was lower than with other tamponades (or placebo) (35.79%, n = 160/447), there was no significant difference. The I^2 was 47%, indicating there was heterogeneity in the pooled studies.

We attempted to explain the heterogeneity by using subgroup analysis (see **Figure, Supplemental Digital Content 4 [A, B]**, http://links.lww.com/IAE/A607, which shows the results of the subgroup analysis regarding the rate of redetachment after endotamponade removal). It noted that the I^2 for the silicone oil group and placebo group was decreased to 0% (see **Figure, Supplemental Digital Content 4A**, http://links.lww.com/IAE/A607, which shows the effects of different tamponades in control groups). This also indicated a significant difference between them, demonstrating that PPV with silicone oil had less risk (13.74%, n = 13/131) than with placebo (35.79%, n = 42/140) (OR, 0.32; 95% CI, 0.17–0.61, I^2 = 0%). Likewise, no difference was demonstrated between the silicone oil group and gas group (OR, 0.86; 95% CI, 0.50–1.48, I^2 = 40%), or between the silicone group and heavy silicone group (OR, 1.13; 95% CI, 0.22–5.84, I^2 = 64%). In the group with previous surgical history (see **Figure, Supplemental Digital Content 4B**, http://links.lww.com/IAE/A607, which shows the effects of different surgical histories), there was no significant difference between them (OR, 0.72; 95% CI, 0.25–2.54, I^2 = 66%). However, in the group without previous surgical history, there was a significant difference

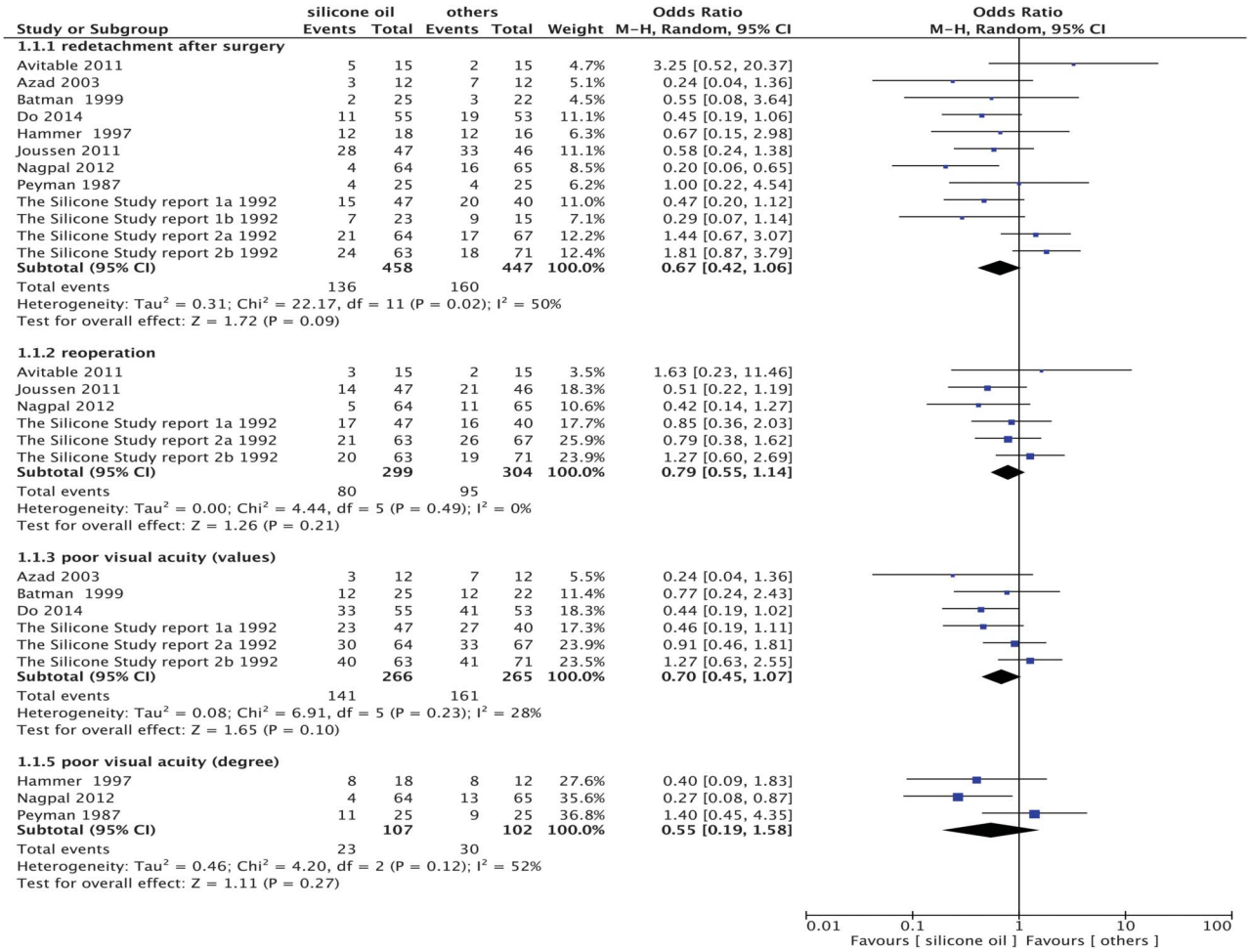

Fig. 3. Forest plot and meta-analysis in total.

between silicone oil and others (OR, 0.61; 95% CI, 0.37–1.01, I^2 = 42%), indicating that PPV with silicone oil (26.27%, n = 93/354) clearly carried lower risk than with the other tamponades (35%, n = 121/345).

The rate of reoperation. Six studies provided data regarding the rates of reoperation. The extracted data excluded routine removal of endotamponade (Figure 3). Pars plana vitrectomy with silicone oil (26.75%, n = 80/299) carried a lower risk of reoperation than others (31.25%, n = 95/304); however, the result was not significant (OR, 0.79; 95% CI, 0.55–1.14, I^2 = 0%). Moreover, there was no significant difference observed in the subgroup analyses (see **Figure, Supplemental Digital Content 5**, http://links.lww.com/IAE/A608, which shows the results of the subgroup analysis regarding the rate of reoperation).

Poor visual acuity. At the final follow-up examination, two studies reported poor visual acuity as a continuous outcome. However, raw data were not available from these two studies. Ten studies reported poor visual acuity as a dichotomous outcome. Of these, 6 studies provided data in the form of the number of patients whose visual acuity was less than 5/200, and 3 studies provided data in the form of the number of patients whose visual acuity was unchanged or declined. In these six (OR, 0.70; 95% CI, 0.45–1.07, I^2 = 28%) and three studies (OR, 0.55; 95% CI, 0.19–1.58, I^2 = 52%), there was no significant difference in patients with silicone oil and with others (Figure 3). We also used subgroup analysis (see **Figure, Supplemental Digital Content 6 [A, B]**, http://links.lww.com/IAE/A609, which shows the results of the subgroup analysis regarding outcomes of poor visual acuity). In the group without previous surgical history (see **Figure, Supplemental Digital Content 6B**, http://links.lww.com/IAE/A609, which shows the analysis of different surgical histories), the risk of poor visual acuity with silicone oil (49.75%, n = 101/203) was lower than with others (61.85%, n = 120/194), and it was a significant difference (OR, 0.60; 95% CI, 0.40–0.90, I^2 = 0%).

Secondary outcomes. Eleven studies examined the occurrence of any adverse events. Adverse events included change of intraocular pressure (IOP), emulsification of silicone oil, anterior segment complications (impact on lens, corneal abnormalities, migration of oil drops into the anterior chamber, rubeosis, and hyphema), and posterior segment complications (macular lesions, epiretinal membrane, choroidal detachment, recurrent vitreous hemorrhage, progressed proliferative, and subretinal silicone oil). We estimated the rate of complications with silicone oil and with other tamponades in total (Figure 4) and also performed subgroup analysis on the effects of different tamponades in control groups. However, there were not enough data to examine the effects of different surgical histories (see **Figure, Supplemental Digital Content 7 [A, B, C, D]**, http://links.lww.com/IAE/A610, which shows the results of the subgroup analysis regarding secondary outcomes).

Intraocular pressure with vitreous endotamponade. The change of IOP included raised IOP (greater than 21 mmHg) and hypotony (lower than 8 mmHg), while the vitreous cavity was filled with endotamponade. A total of 708 patients were enrolled in 9 RCTs that reported raised IOP after undergoing PPV surgery with silicone oil (11.97%, n = 43/359) and other vitreous tamponades (or placebo) (10.31%, n = 36/349) (Figure 4). There was no difference in the risk of raised IOP (OR, 1.24; 95% CI, 0.75–2.06, $I^2 = 0\%$). No significant difference was found in the subgroup analysis either (see **Figure, Supplemental Digital Content 7A**, http://links.lww.com/IAE/A610, which shows the results of the subgroup analysis regarding outcomes of raised IOP). Five trials reported the incidence of hypotony (Figure 4). The risk after filling with silicone oil (16.17%, n = 33/204) was lower than with other tamponades (or placebo) (29.61%, n = 61/206) after PPV surgery ($P < 0.05$, OR, 0.47; 95% CI, 0.29–0.76, $I^2 = 0\%$). In the subgroup analysis with a different control tamponade (see **Figure, Supplemental Digital Content 7B**, http://links.lww.com/IAE/A610, which shows the results of the subgroup analysis regarding outcomes of hypotony), we found that silicone oil (16.14%, n = 31/192) carries less risk than gas (29.89%, n = 58/194) ($P < 0.05$, OR, 0.46; 95% CI, 0.28–0.76, I2 = 0%).

Emulsification. Only two studies reported the emulsification of silicone oil and different controls. The pooled estimate showed a risk ratio of 3.17 (95% CI, 0.64–15.63) (Figure 4). There was no significant difference. No exact data regarding the time of emulsification were provided.

Anterior segment complications. Seven trials reported the rate of impact on the lens, including lens/IOL (intraocular lens) removal, visually significant cataract for phakic eye, and opacification of the posterior capsule for pseudophakic eyes. Nine trials reported the rate of corneal abnormalities, which included epithelial and/or stromal edema, corneal opacity, including localized opacity, and band or bullous keratopathy. Regarding these two rates, there were no significant differences between silicone oil (43.80%, n = 106/242) (25.11%, n = 108/430) and other vitreous tamponades or placebo (43.62%, n = 106/243) (27.14%, n = 114/420) (Figure 4). In the subgroup analysis, there were no significant differences (see **Figure, Supplemental Digital Content 7C, D**, http://links.lww.com/IAE/A610, which shows the results of the subgroup analysis regarding outcomes of anterior segment complications).

Posterior segment complications. Macular lesions, mainly including macular pucker, macular ischemia, cystoid macular edema, macular hemorrhage, and scars, were reported in 4 RCTs of 229 patients, yielding no differences between silicone oil (10.25%, n = 12/117) and other vitreous tamponades (or placebo) (11.60%, n = 13/112) (OR, 0.78; 95% CI, 0.16–3.78, $I^2 = 49\%$). No significant difference was observed in either the merged analysis (OR, 1.17; 95% CI, 0.40–3.37, $I^2 = 0\%$) (Figure 4) or subgroup analysis (see **Figure, Supplemental Digital Content 7E, F**, http://links.lww.com/IAE/A610, which demonstrates the results of the subgroup analysis regarding outcomes of posterior segment complications).

Quality of life related to postoperative position. No study reported data on the quality of life related to postoperative position.

Discussion

The purpose of vitreous tamponades was to reduce or eliminate fluid vectors after PPV to create a permanent seal, or to keep the media clear for postoperative examination and additional treatment. However, different agents have different advantages and disadvantages. Surgeons may need more evidence to aid in the selection of a suitable tamponade agent.

In this review, we broadly examined the differences between silicone oil and other vitreous tamponades or placebo in performing PPV. The important outcomes, such as the failure rate of surgery, adverse events, and quality of life related to postoperative position have been estimated. Only 12 studies, all of which were indexed in databases, were identified for inclusion in

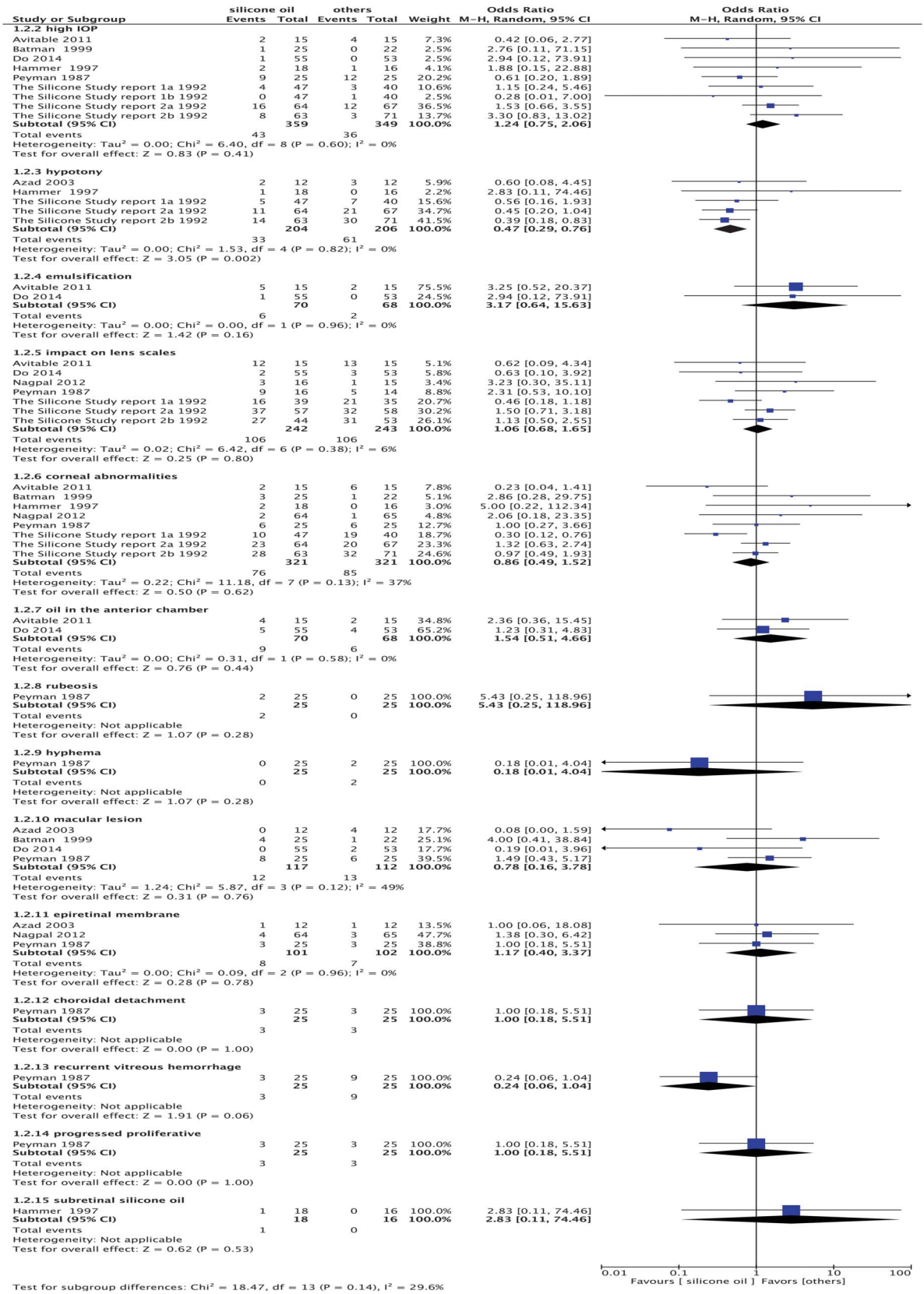

Fig. 4. The rate of complications of forest plot and meta-analysis in total.

this review. An extensive search strategy was implemented, but no studies from the gray literature were found. Although there is a likelihood that some valuable unpublished information on silicone oil was missed, we believe that the included studies adequately represent the available information regarding silicone oil and other vitreous tamponade agents. All included studies made comparisons between silicone oil and other currently available major tamponade agents, such as various gases (C_3F_8, SF_6, and C_4F_8) and heavy silicone oil.

When designing the meta-analysis, we aimed to discover whether silicone oil should be used, and how to use it effectively. For the former, we combined the different control groups to compare them with silicone oil, as our assumption was that different tamponades in the control groups may have similar effects, and studies could, therefore, be pooled together. On examination, there was a mild-to-moderate degree of heterogeneity.

We believed that a broad comparison of silicone oil and control endotamponades might be possible. We attempted to assess the differences by analyzing various subgroups, such as different previous surgical history. However, there was not enough information in some subgroups; thus, a comparison of the treatment effects in the meta-analysis was not possible.

Based on our pooled estimates of the risk of redetachment after endotamponade removal and the risk of reoperation (excluding routine removal of the endotamponade), there was no significant difference between silicone oil and others. This conclusion was supported by a recent meta-analysis by Schwartz et al.[6] Furthermore, we should note that the risk of redetachment after surgery in the silicone oil group and in the others was 29% and 35%, respectively, which means that approximately a third of patients still cannot achieve good anatomical reduction after PPV with any vitreous tamponade agent. Furthermore, close to a third of patients may need more than two operations. According to the original studies, most reoperations were either caused by rhegmatogenous retinal detachment,[11,12] persistent infection and unsettled retina,[15] or by reopening of the macular hole and redetachment.[18,19] We also were concerned with functional restoration. In the risk of poor visual acuity, both with silicone oil and with others, almost half of the patients in six trials had visual acuity less than 2/500 after surgery, and more than a fifth to one-quarter of patients in three trials had unchanged or a decline in visual acuity. The high risk of bad outcomes cannot be neglected, although these results were supported by other reports[1] that silicone oil is not always successful and has an anatomical success rate of around 70%.

By following the a priori hypothesis to explain potential heterogeneity, we used subgroup analysis that included subgroups of different vitreous tamponades in the control group, and subgroups of different previous surgical histories. In examining the heterogeneity of the studies, we detected some trends toward the reduction of the I^2 value, which suggested that different vitreous tamponade, different basic disease, and different previous surgical history did have some effect on the results.

The first subgroup analysis explored whether the heterogeneity could possibly be explained by the use of a different control tamponade. In the subgroup using silicone oil and gas, the risk with silicone oil was lower than with gas. More than one-third of patients who were treated with two vitreous tamponades suffered redetachment and needed more than one reoperation. In addition, almost half of the patients' visual acuity was unchanged or showed a decline. This outcome was markedly different from that of other reports.[20]

We supposed that the difference might be attributable to the age of the included studies. In recent years, many advances in PPV instrumentation, intraoperative viewing systems, and surgical techniques have been developed, especially the use of perfluorocarbon liquids and prophylactic 360° lasers. The common use of perfluorocarbon liquids as a tool in PPV improves the anatomical success[21] and reduces the risk of iatrogenic tears to the retina.[22] Using prophylactic 360° lasers also reduces the risk of redetachment.[23] As a result, we suggest that more RCTs comparing silicone oil and gas need to be conducted to guide surgeons' selection of vitreous tamponade.

In the subgroup of silicone oil versus heavy silicone oil, only two studies were included. Moreover, no raw data were available from the studies to perform a subgroup analysis examining poor visual acuity. Of the two original studies, one study (Avitabile et al) compared PPV with silicone oil endotamponade and Densiron endotamponade for retinal detachment with macular hole and posterior staphyloma in highly myopic eyes, and the other (Joussen et al) compared the effect of PPV with heavy silicone oil (Densiron 68) and with silicone oil for patients with proliferative vitreoretinopathy of the lower retina. Although the risk of reoperation and redetachment in the study by Avitabile was less than 25%, the sample size was small. We therefore express reservations regarding their conclusion that PPV with Densiron is a preferred surgical procedure for the repair of macular hole retinal detachment in highly myopic eyes with posterior staphyloma.[19] The risk of reoperation and of redetachment in the study by Joussen was more than

30%. This study also failed to demonstrate the superiority of a heavy tamponade.[17] Both the results and conclusion were different from those of other researchers.[24]

It is unfortunate that those studies that demonstrated functional and anatomical success rates were noncomparative or nonrandom. We are of the opinion that using heavy silicone oil as an endotamponade is still controversial. Whether it is better than standard silicone oil as a primary tamponade agent may require further investigation.

The second subgroup analysis explored whether different surgical histories could explain the heterogeneity. In the subgroup with a history of previous surgery, three studies reported the risk of redetachment, and only one study reported the risk of reoperation and poor visual acuity. The former had high heterogeneity, whereas the latter did not provide enough information. In the subgroup without a previous history of PPV, nine studies reported the risk of redetachment, and five studies reported the risk of reoperation and poor visual acuity. All the outcomes had low heterogeneity, except the risk of poor visual acuity, which was provided as degrees.

We carefully studied the specific values from the pooled estimates. In the subgroup with a history of previous surgery, all the risks of the vitreous tamponade agents were higher than in other studies, such as in the study by Quiram,[25] which showed that the risk of silicone oil was 30% and the risk of others was 82%, and Mancino,[26] whose study showed that the risk of silicone oil was just 10%. We believe that different experimental designs and the dates of publication were the main factors behind these results. Their retrospective nature and the relatively small number of subjects may have limited these studies. Furthermore, our included original studies may have been limited by the surgical techniques available at the time of publication. In the subgroup without a history of previous surgery, the risk with silicone oil was nearly 25%, and the risk with others was nearly 30%, which was the same as in the study by Sodhi et al.[27]

However, when discussing the safety of vitreous endotamponade, the risk of complications cannot be forgotten. Some complications can cause severe visual impairment, to the point of requiring further surgery to repair. In our included RCTs, only the common complications (e.g., raised IOP, hypotony, impact on lens, corneal abnormalities, migration of oil drops, rubeosis, hyphema, macular lesions, epiretinal membrane, choroidal detachment, recurrent vitreous hemorrhage, progressed proliferative, and subretinal silicone oil) were reported. We estimated the rate of complications with silicone oil and with other tamponades in total, and also performed a subgroup analysis on the effects of different tamponades in the control groups. However, there were not enough data to examine the effects of different basic diseases and the effects of different surgical histories. Among them, the risk of hypotony was significantly different between silicone oil and others. In the subgroup analysis, the risk of hypotony in the silicone oil subgroup was lower than in the gas subgroup. We speculate that this is because gas bubbles are more prone to leakage than silicone oil. This result suggests that hypotony should be more of a consideration when selecting gas as an endotamponade.

We also found that the risk of macular lesion with silicone oil was higher than with gas in the subgroup of silicone oil versus gas, but lower than with a placebo in the subgroup of silicone oil versus placebo. Unfortunately, not all the original studies analyzed the results relating to macular lesion. A study from Katira et al[28] supposed that the retinal pigment epithelium cells, which can disperse into the vitreous cavity after retinotomy, act as progenitor cells for membrane formation and retinal distortion in the macular area. Along with face-down positioning, this may concentrate these cells over the macular area, increasing macular pucker formation. We favored this view. However, it is unclear why the risk of macular lesion with silicone oil was higher than with gas. Clarifying this requires larger prospective trials.

As in other reviews, the other complications did not show significant differences between silicone oil and other endotamponades. Only two studies reported the rate of emulsification of silicone oil or heavy silicone oil, but did not provide exact data about the time of emulsification. Recent studies found that many of the complications of silicone oil are indeed secondary to emulsification, as these separated droplets of emulsified silicone oil infiltrate intraocular tissues in both the anterior and posterior segments, leading to bullous keratopathy,[29] glaucoma, inflammation, and proliferative vitreoretinopathy formation.[30] Several reports have even demonstrated that the migration of silicone oil droplets into the retina and the optic nerve could decrease patients' vision and harm their central visual field.[31] Furthermore, there have been multiple reports of droplets of emulsified silicone oil infiltrating the brain.[32,33] However, such findings are rare and affect only a small number of cases. We propose that more RCTs are needed to resolve the controversy.

One of our evaluated parameters was the quality of life related to postoperative position. After PPV surgery with silicone oil or gas, a period of face-down positioning is often advised, with the aim of improving the functional and anatomical success by maintaining

contact of the endotamponade meniscus with the macula. However, this face-down positioning is uncomfortable, and associated adverse events have been discussed. There were many trials comparing nonsupine positioning and face-down positioning through anatomical and functional results after surgery.[34] From the outset of this review, we sought information from the patients' perspective in addition to clinical data. We intended to estimate the quality of life of patients relative to the different postoperative positions required by different endotamponades. However, there was no study that reported the quality of life related to postoperative position. We therefore propose that researchers in the future consider this aspect in the future.

In general, using either silicone oil or other vitreous tamponade may pose some risk of failure and adverse events, yet we cannot let this risk limit the effort to pursue the development of new vitreous tamponades. Recently, new long-term tamponades have appeared, such as hydrogels[35] and FCVBs (foldable capsular vitreous bodies).[36,37] Hydrogels show good biocompatibility and transparency, and their main advantage is that their behavior is similar to that of the natural vitreous body.[38] For the time being, they are at an early experimental stage, and their effects in long-term toxicity require more testing.[39] FCVBs are being tested in clinical trials. Initial studies have shown that FCVB with silicone oil is effective and safe.[40] However, more research must be conducted on its functions of oxygen and metabolism transportation.[41]

Limitations

The present meta-analysis had some limitations that must be taken into account. Firstly, some studies were relatively dated, i.e., they used older-fashioned surgical methods and strategies, which might increase the risk of bias. Secondly, the endpoints were inconsistent between studies, and there were insufficient data for us to assess based on unified endpoints, which might also increase the risk of bias. Finally, no study reported the quality of life related to postoperative position, which was one of our original objectives.

Nevertheless, this meta-analysis had enough data to reach the conclusions that there was no significant difference in the risk of poor outcomes between PPV with silicone oil and other vitreous tamponades with different basic surgical histories. We designed multiple strategies to identify studies, strict criteria to include and evaluate them, and provided subgroup and sensitivity analysis to minimize the heterogeneity, with the goal of providing the most updated information.

Conclusion

Among the evidence available for comparison, there was an obvious lack of newer RCTs. Based on the available studies, we can conclude that there was no significant difference in the risk of poor outcomes between PPV with silicone oil and other vitreous tamponades with different basic surgical histories. Whether the surgery requires silicone oil and how to use it effectively should be further investigated by future RCTs.

Key words: poor outcomes, vitrectomy, silicone oil, systematic review, vitreous tamponade.

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