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Comparative assessment of intraocular inflammation following standard or heavy silicone oil tamponade: a prospective study

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ABSTRACT.

Purpose: **To evaluate the inflammation associated with the use of standard silicone oil (polydimethylsiloxane; PDMS) and heavy silicone oil (HSO) Densiron-68™ in patients undergoing vitrectomy for retinal detachment.**

Materials and Methods: **A prospective study was performed involving 35 patients scheduled to undergo vitrectomy for retinal detachment. Patients received PDMS or Densiron-68™ HSO according to superior or inferior retinal localization of the tears, respectively. For assessing the inflammation, prostaglandin E2 (PGE_2) and interleukin-1α (IL-1α) levels were evaluated in the aqueous.**

Results: **Thirty-five eyes of 35 patients completed the study: 20 eyes received HSO, and 15 eyes received PDMS. The mean aqueous PGE_2 level was significantly higher in HSO patients than in PDMS patients (869.16 ± 242.83 pg/ml versus 369.38 ± 209.7 pg/ml, respectively; $p < 0.0001$). The mean aqueous IL-1α level was also significantly higher in HSO patients than in PDMS patients (81.40 ± 36.9 pg/ml versus 40.8 ± 32.5 pg/ml, respectively; $p = 0.002$). In HSO, a moderate positive correlation between the endotamponade duration and both PGE_2 ($r = 0.44$; $p = 0.05$) and IL-1α ($r = 0.48$; $p = 0.033$) levels was observed. In PDMS, a strong positive correlation between the endotamponade duration and both PGE_2 ($r = 0.89$; $p < 0.0001$) and IL-1α ($r = 0.68$; $p = 0.006$) levels was observed.**

Conclusion: **Although both HSO and PDMS yielded favourable success rates in the surgical treatment of complicated retinal detachments, HSO triggered a more severe inflammatory reaction, in a time-dependent manner.**

Key words: heavy silicone oil – inflammation – retinal detachment – standard silicone oil – vitrectomy

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Introduction

Introduced in 1962, silicone oil has been the most commonly used vitreous substitute in vitreoretinal surgery over the past 50 years, and to date, it remains the only widely accepted long-term vitreous substitute (Cibis et al. 1962). The use of a vitreous substitute that is heavier than water has been recently suggested for use as an intraocular tamponade in surgical cases of complicated retinal detachment of the inferior quadrants (Azen et al. 1998). To date, three groups of heavy tamponades have been introduced into surgical practice: fluorinated silicone oil or fluorosilicone, perfluorocarbon liquids and semifluorinated alkanes, such as perfluorohexyloctane (F_6H_8) (Morescalchi et al. 2014). Densiron-68™ is a commonly used solution comprising F_6H_8 and 5000c silicone oil, with a specific gravity of 1.06 and a viscosity of 1387 mPas.

According to the evidence reported in the literature, the heavy tamponades are more prone to cause intraocular inflammation compared with standard silicone oil, especially if they remain in the eye for several months (Morescalchi et al. 2014). Side-effects of heavy silicone oil (HSO) are associated with the chemical and physical properties of the tamponading compound and are similar to those associated with conventional silicone oil (Semeraro et al. 2014). Four main mechanisms are reported in the genesis of the inflammatory reaction to standard and HSO: direct toxicity and immunogenicity, toxicity due to impurities or instability of the agent, oil emulsification and mechanical injury due to gravity

(Mackiewicz et al. 2007). However, the inflammation associated with HSO appears to be due to a delayed type IV hypersensitivity reaction and varies greatly because the duration of application significantly affects the level of inflammation in the eye (Morescalchi et al. 2014).

For the safe and effective use of retinal tamponades, an awareness of their physical, chemical and inflammatory properties is a prerequisite; vitreoretinal surgeons select the most suitable tamponade on the basis of this knowledge. In this study, we prospectively evaluated the inflammation associated with both 1000 cSt silicone oil (100% polydimethylsiloxane; PDMS) and 1200 cSt HSO (Densiron-68™) in patients undergoing vitrectomy for retinal detachment. To the best of our knowledge, this is the first study designed to compare the inflammatory complications associated with Densiron-68™ and standard silicone oil.

Materials and Methods

This study was conducted at the University Eye Clinic of 'Spedali Civili di Brescia' in accordance with the ethical principles of the Declaration of Helsinki. The Ethics Committee of Spedali Civili di Brescia (Italy) approved the study protocol (registered with clinicaltrials.gov, identifier NCT02361645). All study participants provided written informed consent.

This was a prospective study including 35 eyes of 35 patients consecutively enrolled from September 2015 to March 2016; the patients were scheduled to undergo 23-gauge, three-port pars plana vitrectomy for retinal detachment, and all patients completed the study. Inclusion criteria were age ≥18 years and retinal detachment with multiple or giant breaks, such as it requires the tamponade with silicone oil. The exclusion criteria were diabetes mellitus, previous vitrectomy in the study eye, previous buckle surgery, previous intravitreal injection, concurrent retinovascular or other ocular inflammatory disease, history of ocular trauma and concomitant intake of any topical or systemic NSAID or corticosteroid therapy.

Patient demographics and baseline characteristics are listed in Tables 1 and 2. Fifteen eyes received 1000 cSt PDMS silicone oil (100% PDMS; density 970 kg/m^3; Alchimia Srl, Ponte San Nicolò, PD, Italy), and 20 eyes received HSO Densiron-68™ (mixture of 69.5% ultrapure PDMS and 30.5% perfluorohexyloctane; viscosity of 1200 cSt and density of 1040 kg/m^3; Fluoron GmbH, Ulm, Germany) according to superior or inferior retinal localization of the tears, respectively (Table 2).

All phakic patients were operated with phacoemulsification of the crystalline lens plus intraocular lens (IOL) implant at the time of vitrectomy to allow a careful cleaning of the vitreous base. Vitrectomy surgery was performed using a 23-gauge transconjunctival system, and no triamcinolone was used during any step of the surgery.

After the removal of the posterior hyaloids, the vitreous base was thoroughly removed. All visible proliferative vitreoretinopathy (PVR) membranes were dissected, and relaxing retinotomies were performed, in two eyes, in the inferior retina of PDMS group. The retinal periphery was inspected for retinal breaks that were marked with endodiathermy, after that the retina was reattached using perfluorocarbon liquid and air. Three rows of endolaser treatment were applied behind the posterior vitreous base in all patients (200 spots, 200–250 mW according to retinal pigmentation). Finally, after a complete perfluorocarbon liquid-to-air exchange, the eye was filled with PDMS or Densiron-68™ according to tear localization. All patients in both groups were prescribed topical dexamethasone (six times per day) and homatropine (two times per day).

Both PDMS and HSO were removed using a 23-gauge instrument. Patients with PDMS were positioned in prone position for 2 hr before the surgery, while patients with HSO were maintained in supine for the same amount of time. At the beginning of the surgery, 0.5–1.0 ml of undiluted aqueous was removed before opening the infusion. Samples were immediately frozen and stored at −40 °C until analysis.

Measurements of prostaglandin E2 and interleukin-1α levels

Vitreous samples were defrosted and subjected to semiquantitative determination of prostaglandin E2 (PGE_2) levels. Analyses were performed using Dynex Technologies DSX™ (v. 6.03; Chantilly, VA, USA) according to the manufacturer's instructions. Briefly, the analysis was based on the competition between PGE_2 and PGE_2-acetylcholinesterase conjugate (AChE; PGE_2 tracer) for a limited amount of PGE_2 monoclonal antibody. As the concentration of the PGE_2 tracer was constant while the concentration of PGE_2 samples varied, the amount of PGE_2 tracer, which was able to bind to the PGE_2 monoclonal antibody, was inversely proportional to the concentration of PGE_2 in the well.

The interleukin-1α (IL-1α) assay was based on a double-antibody 'sandwich' technique. Each well of the microtiter plate supplied with the kit was coated with a monoclonal antibody specific for IL-1α. This antibody can bind to any IL-1α introduced into the well. An AChE that binds selectively to a different epitope on IL-1α was also added to the well, forming a 'sandwich' by binding on opposite sides of the IL-1α molecule. The concentration of the analyte was then determined by measuring the enzymatic activity of the AChE by adding Ellman's reagent to each well.

Table 1. Patient demographics and baseline characteristics.

	HSO (N = 20)	PDMS (N = 15)
Age: mean (SD), years	62.3 (16.7)	58.9 (12.8)
Sex: n (%)		
Men	15 (75)	11 (73)
Women	5 (25)	4 (27)
Lens status (%)		
Phakic	10 (50)	6 (40)
Pseudophakic	10 (50)	9 (60)
Preoperative visual acuity: mean (SD), decimal	0.15 (0.12)	0.14 (0.09)

HSO = heavy silicone oil, PDMS = polydimethylsiloxane, SD = standard deviation.

Statistical analysis

Descriptive statistics were used to present demographic and ocular baseline characteristics. An independent-samples t-test was performed to determine whether there were differences in PGE_2 and IL-1α levels between the PDMS

Table 2. Anatomical and clinical characteristics at baseline.

	HSO (N = 20)	PDMS (N = 15)	p value
Phakic/pseudophakic	13/7	9/6	1
No. of breaks	1.65 ± 0.67	1.73 ± 0.70	0.725
Location of breaks (clock hours)	4–8	9–3	–
Macula status on/off	11/9	7/8	0.738
Duration of detachment (days)	4.15 ± 1.7	4.2 ± 1.9	0.94
PVR			
A	6	5	–
B	3	2	–
C (1–4)	11	8	–

HSO = heavy silicone oil, PDMS = polydimethylsiloxane, PVR = proliferative vitreoretinopathy.

Table 3. Anatomical and functional outcomes at the time of oil removal.

	HSO (N = 20)	PDMS (N = 15)
Retinal reattachment: n (%)	18 (90)	12 (80)
Visual acuity: mean (SD), decimal	0.26 (0.15)	0.28 (0.1)
IOP: mean (SD), mmHg	22.1 (5.1)	19.5 (6)
Requiring IOP treatment: n (%)	20 (100)	9 (60)
Microemulsion of silicone in AC: n (%)	20 (100)	10 (67)
Posterior synechiae: n (%)	15 (75)	7 (47)
Endotamponade period: mean (SD), weeks	12.8 (4.8)	12.3 (6.2)

AC = anterior chamber, HSO = heavy silicone oil, IOP = intraocular pressure, PDMS = polydimethylsiloxane, SD = standard deviation.

and HSO groups. The sample size of 35 patients provided a power of 0.81, for demonstrating an effect size of 0.87 between the two groups, at a significance level of 0.05. A Pearson's product–moment correlation was run to assess the relationship between both PGE_2 and IL-1α levels and the duration of the ocular endotamponades. All statistical analyses were performed using SPSS software v. 20 (IBM Corp, Armonk, NY, USA). $p < 0.05$ was considered statistically significant.

Results

Heavy silicone oil (HSO) and PDMS patients underwent the removal of the intraocular tamponade agent after a mean (±standard deviation) period of 12.8 ± 1.1 and 12.3 ± 0.6 weeks, respectively ($p = 0.17$). In the HSO group, at the time of oil removal, anatomical success was achieved in 18 eyes (90%), while recurrence of retinal detachment was present in two eyes (10%; Table 3). These two eyes required further surgery. In the PDMS group, anatomical success was achieved in 12 eyes (80%). Three eyes (20%) required further surgical procedures. The best-corrected visual acuity (BCVA) significantly improved from 0.15 ± 0.12 (decimal scale) to 0.26 ± 0.15 in the HSO group and from 0.14 ± 0.09 to 0.28 ± 0.1 in the PDMS group ($p < 0.001$, for both groups).

An increase in intraocular pressure (IOP) >25 mmHg was noted in all HSO patients in the 3-month follow-up before oil removal. All cases were controlled with topical combination of 0.5% timolol and 2% dorzolamide. Three patients required the addition of 0.004% travoprost at bedtime, and one patient required a short course of oral acetazolamide, after experiencing a peak IOP of 35 mmHg. In the PDMS group at the 3-month follow-up, IOP was controlled in nine eyes (60%) with a topical combination of 0.5% timolol and 2% dorzolamide or 0.004% travoprost, while six eyes (40%) did not require IOP-reducing therapy.

During the surgery for oil removal, in all patients treated with HSO and in 10 patients (67%) treated with PDMS, a microemulsion of silicone oil was observed in the anterior chamber. Moreover, posterior synechiae between the iris and the IOL were observed in 15 eyes (75%) filled with HSO and in seven eyes (47%) filled with PDMS (Table 3). Posterior synechiae were present in all eyes that underwent combined surgery with phacoemulsification.

The mean aqueous PGE_2 level was 869.16 ± 242.83 pg/ml in HSO patients, which was higher than that in PDMS patients (369.38 ± 209.7 pg/ml; $p < 0.0001$). Similarly, the mean aqueous IL-1α level was higher in HSO patients (81.40 ± 36.9 pg/ml) than in PDMS patients (40.8 ± 32.5 pg/ml; $p = 0.002$).

There was a moderate positive correlation between the endotamponade duration and both PGE_2 ($r = 0.44$; $p = 0.05$) and IL-1α ($r = 0.48$; $p = 0.033$) levels in HSO patients (Fig. 1). Similarly, in PDMS patients, there was a strong positive correlation between the endotamponade duration and both PGE_2 ($r = 0.89$; $p < 0.0001$) and IL-1α levels ($r = 0.68$; $p = 0.006$; Fig. 2).

Discussion

This prospective study evaluated the inflammation associated with standard silicone oil (PDMS) and the HSO Densiron-68™ in patients undergoing vitrectomy for retinal detachment. Results show that the intraocular inflammatory reaction is greater in eyes filled with HSO compared with PDMS. This inflammation significantly correlated with the endotamponade duration in both groups; this positive correlation further supports the evidence of side-effects when silicone oil is used for a long period (Theelen et al. 2004; Stappler et al. 2011; Morescalchi et al. 2014; Schwarzer et al. 2014). To our knowledge, this is the first report on a direct comparison between the inflammatory outcomes of standard silicone oil and HSO.

The stability and immunological tolerability of PDMS make it relatively safe as a long-term internal tamponade. Histological examination of the human retina after more than 3 years of PDMS endotamponade did not show significant morphological alterations; however, intraretinal or intracellular deposits suggestive of silicone might be observed in attached retinas (Kirchhof et al. 1986).

Heavy silicone oils (HSOs) are derived from a mixture of a highly viscous PDMS (>5000 mPas) and different semifluorinated alkanes (F_6H_8, F_4H_5 and F_4H_6), or a similar substance (RMN-3, a partly fluorinated olefin),

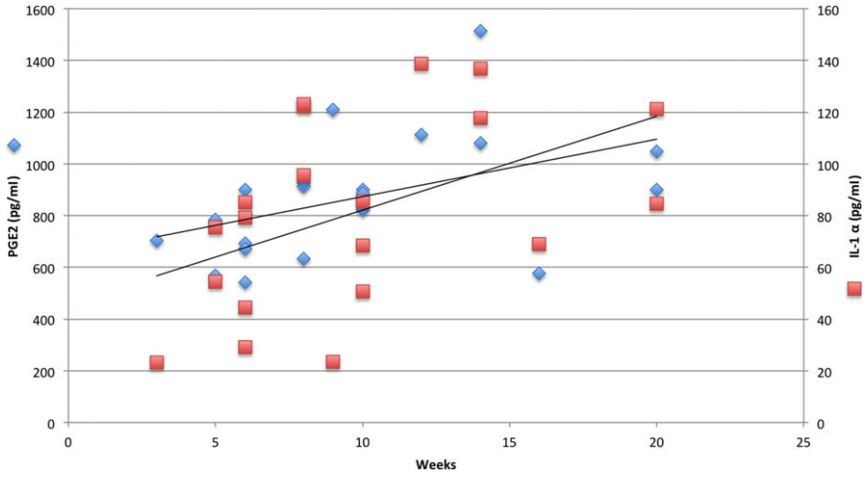

Fig. 1. Scatterplot of the moderate linear relationship between endotamponade duration and both PGE2 and IL-1α levels with heavy silicone oil. Blue rhombuses represent PGE2, and red squares represent IL-1α. Solid line represents PGE2 trendline, and dashed line represents IL-1α trendline. IL-1α = interleukin-1α; PGE2 = prostaglandin E2.

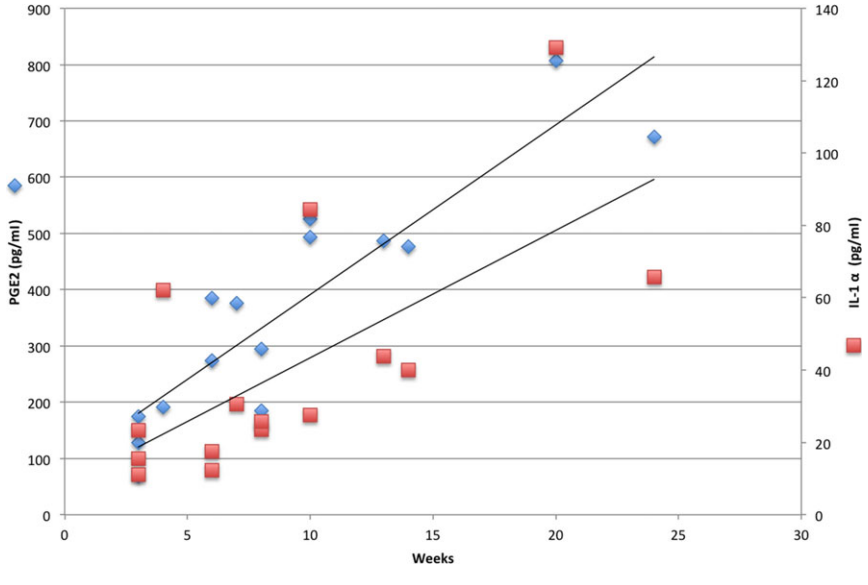

Fig. 2. Scatterplot reporting the strong linear relationship between endotamponade duration and both PGE2 and IL-1α levels with standard silicone oil. Blue rhombuses represent PGE2; red squares represent IL-1α. Solid line represents PGE2 trendline; dashed line represents IL-1α trendline. IL-1α = interleukin-1α; PGE2 = prostaglandin E2.

and these have a lower tendency to create dispersion and emulsion. However, the concentration of the two components may vary with time and temperature, and potential chemical decomposition of HSO has been reported (Banaee 2012; Morescalchi et al. 2014) where the heavier component tends to settle over time in the inferior part of the bubble, separating from PDMS. As previously reported, Densiron-68™ is a mixture of 30.5% F_6H_8 and 69.5% polymethylsiloxane and possesses a high viscosity to reduce dispersion and emulsification. Our results show that silicone oil tends to stimulate inflammation in a time-dependent manner and that HSO is more inflammatory than standard silicone oil. This could be partially explained by a mild separation of Densiron-68™ in polymethylsiloxane and F_6H_8, leading to microemulsion of the latter. Heavy silicone oil (HSO) demerger and emulsification are also stimulated by the presence of red blood cells, plasma lipoproteins, apolipoproteins, encircling bands and other substances previously used intraoperatively (PFCL, remnants of oil or vitreous) and especially by the oil/aqueous movement generated by eye movements resulting in shearing forces (Savion et al. 1996; Morescalchi et al. 2014; Semeraro et al. 2014). Microemulsion is suspected to trigger chemotaxis of inflammatory cells and phagocytosis that stimulate a foreign body-type reaction and consequent phagocytosis by macrophages.

This possibility is supported by the observation of macrophages originating in the immune response, as these are the white cells most commonly represented in the inflammatory infiltrate (Zeana et al. 1999; Vote et al. 2003). Moreover, immunoglobulin or fractions of complement have been reported to be detectable on the surface of the vitreous substitute months after silicon oil expositions (Morescalchi et al. 2014). Therefore, the inflammation associated with HSO appears to be due to a delayed type IV hypersensitivity reaction. This is consistent with the significant correlation between inflammation and duration of the endotamponade found in the present study. In turn, intraocular inflammation promotes early emulsification of the endotamponade (Kociok et al. 2005), and the consequent diffusion of molecules from the endotamponade promotes further inflammation. Therefore, emulsification is probably both the effect and the cause of the intraocular inflammation, while individual agents might be a stimulant for inflammatory reaction (Majid et al. 2008).

The rate of postoperative inflammation associated with Densiron-68™ varies greatly across different trials, depending mostly on the tamponade duration. Sandner and Engelmann (Sandner & Engelmann 2006) evaluated the intraocular adverse effects after a 3-month endotamponade with Densiron-68™ and reported a mild-to-moderate anterior chamber reaction, mainly during the first postoperative days, accompanied by flaring in the anterior chamber with possible fibrin exudation. Banaee (2012) reported a case of massive reaction in the anterior chamber, with an associated deposition of oil globules behind the cornea, and iris depigmentation, together with pigment globules both on the iris and floating in the anterior chamber. A time-dependent inflammatory reaction

is consistent with a study by Auriol et al. (2008) in which authors reported a high rate of inflammatory reactions (40.7%) associated with a long (>6 months) persistence of Densiron-68™.

It is quite difficult to differentiate between inflammation caused by the endotamponade and the inflammatory reaction associated with the underlying retinal diseases. However, the inflammation has been proved to be related to the immunogenicity of the compounds and to the surfactants that modify the interfacial tension (IT) (Savion et al. 1996). Regarding the immunogenicity, the PDMS droplets induce a macrophagic foreign body reaction associated with the phagocytosis of PDMS emulsion by retinal pigment epithelium (RPE) cells (Wong et al. 2009). This granulomatous reaction is sustained by epithelioid cells that are responsible for the cascade of inflammation (De Queiroz et al. 1992; Morescalchi et al. 2014). Regarding the surfactants, they are amphiphilic compounds extending in both oil and water with different tails. The surfactants are either biosurfactants produced by the eye itself or impurity present, as low molecular weight component or other impurities, during the manufacturing process of PDMS. The surfactants are able to reduce the IT, as cohesion force of a liquid aiming to increase the 'wall tensions', promoting the emulsion of PDMS. As previously reported, HSO is a mixed compound obtained by adding a semifluorurate (alkane or ether) to PDMS. The semifluorurate reduces the IT and also promotes immunogenic reaction responsible for inflammation and emulsion (Hiscott et al. 2001). This is the reason why it is recommended to remove the HSO within 3 months.

In the current study, IOP appeared to be greater in the HSO group with 100% of patients requiring topical treatment (untreated IOP >25 mmHg) versus 60% of patients in the PDMS group. This might be explained by the different tendency for emulsification of the two tamponades. Indeed, HSO is known to remain stable for 3 months, while PDMS 1000 cSt is stable for 3–6 months (Nguyen et al. 1992; Hiscott et al. 2001). This is consistent with the surgical finding of emulsion droplets in the anterior chamber and posterior synechiae between the iris and the IOL in the current study. Over time, these small droplets might induce a mild chronic reaction in which the macrophages react towards the tamponade emulsion as a foreign body. Therefore, they are able to promote iris synechiae and increase IOP. Moreover, PGE_1 and PGE_2 increase IOP by inducing vasodilatation and increasing the permeability of the blood–aqueous barrier (Semeraro et al. 2015).

It has been also reported, from a systematic review of randomized clinical trials, a trend of ocular hypertension in eye treated with HSO compared to PDMS (Romano et al. 2015). The HSO was associated with significant higher IOP in the first 2 weeks post-op period when compared with PDMS, where the difference was not significant at 1 month post-op (Wong et al. 2009). The raised IOP was difficult to treat (Costagliola et al. 2009). The reason for an increase of IOP in the early post-op may be due higher rate of retinectomy in the HSO group. Retinectomy is generally associated with increased inflammation due to the breakdown of blood–ocular barrier and bleeding at the edge of cut retina (Wong et al. 2009). On the contrary, the late postoperative increase of IOP in eye treated with HSO is mainly related to the inflammation induced by the HSO. In fact, the HSO is a solution of semifluorinated alkane and PDMS, where the F_6H_8 has low viscosity and higher propensity for dispersion (Wong et al. 2005).

Our study has a few limitations: firstly, the patients were not properly randomized, but they received PDMS or HSO according to the clinical practice (localization of the retinal tear). However, there were no differences between groups in terms of PVR or period of retinal detachment. Secondly, phacoemulsification itself can stimulate inflammation and breakdown of the blood–retinal barrier, although phacoemulsification procedures were uneventful and carried out in both groups. Thirdly, we enrolled a limited number of patients. However, despite a relatively high standard deviation in the vitreous levels of PGE_2 and IL-1α, the statistical significance between PDMS and HSO is pronounced.

In our study, both HSO and PDMS yielded favourable success rates in the surgical treatment of complicated retinal detachments. Decision regarding whether to utilize either should be made on a case-by-case basis. Overall, HSO triggered a higher inflammatory reaction, mainly due to its emulsification tendency, and the extent of the inflammation appeared to be proportional to the duration of tamponade application. In particular, our study showed that the PGE_2 and IL-1α aqueous levels were more than double in eyes with HSO compared to those in eyes with PDMS. In conclusion, as indicated by our results, the retention time of HSO should be kept short and restricted as much as possible. In patients scheduled for vitrectomy with silicone oil, IOP should be closely monitored and IOP-reducing treatment promptly commenced. Finally, appropriate anti-inflammatory therapy with steroidal or non-steroidal anti-inflammatory drugs, together with cycloplegics, should be considered for the duration of the HSO tamponade retention.

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