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Silicone oil in vitreoretinal surgery: indications, complications, new developments and alternative long-term tamponade agents.

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Abstract

Silicone oil (SO) has been used as a long-term tamponade agent in the treatment of complicated vitreoretinal diseases for about half a century, during which time many advances in surgical techniques and technologies have been made. This review summarises the chemical and physical properties of SO, its indications and complications, including particularly emulsification. The mechanisms and risk factors of emulsification are discussed, as well as novel strategies for its effective removal. Finally, the review focuses on new improved formulations of SO, including research into slow release pharmacological agents within SO and provides an overview of alternatives to SO for the purpose of long-term tamponade that are being developed.

I. Introduction

Silicone oil (SO) was first introduced by Cibis as an intravitreal implant in the treatment of retinal detachment (RD). Scott, Heimann, and many others reported on the use of SO in a variety of complex scenarios in Europe as early as in 1962.(Cibis et al. 1962; Scott 1975; Heimann et al. 1984) Following an evaluation in a collaborative study in 1994, SO was approved by the Food and Drug Administration as an endotamponade in the USA.(Giordano & Refojo 1998) Despite advances in vitreoretinal techniques, SO with its important properties of intraocular inertness, transparency, and permanence until removed, making it irreplaceable in treating complicated vitreoretinal diseases. It will continue to be indispensable in certain cases

for the foreseeable future. The broad indications and effectiveness for use of SO have been recognised by vitreoretinal surgeons, particularly in the treatment of complex retinal detachments. On the other hand, after anatomical success, it is generally recommended that SO should be removed, as long-term SO in the vitreous cavity can lead to a variety of complications. Although the majority of these can be controlled through drugs or further surgeries, there are also problems with refractory secondary-glaucoma and silicone oil related visual loss (SORVL) which are more problematic and in which the underlying mechanism still needs further investigation. Emulsification of SO in particular has been recognised as being a common cause of many SO-related complications.(Federman & Schubert 1988) To reduce emulsification rates and also ease the practical surgical difficulties of injection and removal through narrow gauge vitrectomy systems, new formulations of SO have been developed, although the clinical outcomes and their relative resistance against emulsification are still controversial. (Caramoy et al. 2010; Caramoy et al. 2011; Maier et al. 2011; Stalmans et al. 2015) Similarly, the use of SO as a mechanism for the slow release of pharmacological agents has been proposed.(Cauldbeck et al. 2016; Cauldbeck et al. 2018) Recently, other novel vitreous substitutes have been developed including the foldable capsular vitreous body, hydrogel-based intravitreal tamponades and medium-chain triglycerides.(Lin et al. 2012; Soler et al. 2017; Wang et al. 2018) In this review we aim to provide an overview of SO and other new developments in long term tamponade technology.

Methods

We carried out a literature review of the role and development of silicone oil in ophthalmic applications over a period of 20 years. The published literature articles were searched using PubMed with the following keywords: silicone oil, properties of silicone oil, emulsification, tamponade, risk factors, vitreoretinal surgery, retinal detachment, removal of silicone oil, and vitreous substitute. The references selected were mostly large sample retrospective clinical studies, relatively authoritative review articles and laboratory science articles. Special attention was given to studies focusing on prevalence and incidence of SO emulsification in vitrectomy surgery.

II. Properties of silicone oil, its indications, complications and emulsification

Properties of silicone oil

SO was developed as an intraocular tamponade principally because of its physical properties of transparency, chemical inertness, high surface tension and high interfacial tension with water. To achieve effective retinal reattachment, a tamponade agent must be able to prevent fluid migration to subretinal space. Due to high interfacial tension between SO and water (44 dynes cm⁻¹), (Giordano & Refojo 1998) SO is effective in preventing aqueous migration through retinal breaks into the subretinal space, effectively closing the break and maintaining retinal attachment to allow peri-break adhesion forms if retinopexy has been applied. (Giordano & Refojo

1998)

Standard SOs for ophthalmic use are synthetic polymers composed of polydimethylsiloxanes (PDMS) with different sizes of chains.(Giordano & Refojo 1998) Its chemical structure is shown in Figure 1. The shear viscosity of SO is dependent on the molecular chain length (molecular weight). SO with longer molecular length possesses higher shear viscosity which reduces the movement of the SO bubble within the vitreous cavity. When SO is placed in the posterior segment, it limits fluid flow within the vitreous cavity, and therefore also preventing the hydraulic based migration of aqueous humour through retinal breaks into the subretinal space. The range of viscosities of SO currently used clinically lies between 1000 and 5700 mPa.s.(Caramoy et al. 2010) In general, SO with higher viscosity has a lower tendency to emulsify.(Giordano & Refojo 1998) However it is still debateable whether 5000 mPa.s SO presents definite advantages over 1000 mPa.s SO in terms of better intraocular stability and lower emulsification rate, which is discussed later.(Scott et al. 2005; Zafar et al. 2016; Ratanapakorn et al. 2020) The molecular weights of the most commonly used SOs in ophthalmic surgeries, namely 1000 mPa.s and 5000 mPa.s, are 37 and 65 kDa respectively. (Chan et al. 2011) However, PDMS chains with molecular weight ≤ 1 kDa (LMW-SO) that can be synthesised inadvertently during the manufacturing process, have been suggested to lead to ocular inflammation and toxicity.(Brunner et al. 2011) These small molecule PDMS can also promote emulsification, and were found to be present in a number of commercially available SOs in the market perhaps explaining some of the adverse reactions.

(Mendichi et al. 2019; Dresch 2020)

The density is also an important property to be considered when selecting different ophthalmic tamponade agents in retinal detachment surgery. The density of standard SO is around 0.97 g/cm^3 , which is lower than water, meaning it is buoyant in water. It is therefore used as a retinal tamponade to treat most advantageously for the superior retinal breaks. If the retinal detachment is located inferiorly, patients are typically advised to maintain a prone position until retinal adhesion is established from retinopexy so to facilitate retinal reattachment.(Giordano & Refojo 1998) It should be noted that, although buoyancy is important in terms of the resting position of the bubble, the effect of any buoyant forces are thought to be negligible for break closure;(Wong et al. 2005) Instead, the break is closed due to the high interfacial tension of the bubble across the break and prevent the migration of fluid to the subretinal space.

Heavy silicone oil (HSO)

To tackle the inefficiency of inferior retina tamponade, a heavier than water formulation of SO termed 'heavy silicone oil' has been developed and used clinically.(Petersen et al. 1986; Peyman et al. 1987; Gremillion et al. 1990) The first attempts to produce HSO, were formulated by substituting some of the methylated groups of conventional SO to fluorinated groups, with a resultant higher specific gravity than conventional SO. However, such fluorinated SO could only be used as short-term tamponade due to severe complications, namely early emulsification and

inflammation.(Heimann et al. 2008), By blending SO with materials with densities greater than water, new formulations of HSO have become available and have shown promising results in in-vivo animal tests and initial clinical trials.(Rizzo et al. 2005; Wong et al. 2005; Rizzo et al. 2006; Rizzo et al. 2007; Williams et al. 2013) Furthermore, these HSOs are already in use in some European countries.(Heimann et al. 2008; Russo et al. 2018; Caporossi et al. 2019) The substances vary in their SO and heavy components, resulting in products with different specific gravities and viscosities.(Heimann et al. 2008; Jousen & Wong 2008) The compositions and the physical properties of these HSOs are summarised in Table 1.

Current uses, indications and complications

The indications for SO are relative and vary significantly depending on surgeon and patient preference, with well-known differences between countries. The most frequent indication for use of SO is rhegmatogenous retinal detachment (RRD) with established proliferative vitreoretinopathy (PVR), and RRD with a high risk of developing PVR such as giant tears; signs of uveitis; or preoperative choroidal detachment.(Giordano & Refojo 1998; Batman & Cekiç 1999) SO is also used to treat RRD where it is impossible or not desirable to do effective retinopexy (e.g. macular hole RRD), (Giordano & Refojo 1998; Stalmans et al. 2015) and RRD with extensive posterior breaks or situations where new breaks are very likely to occur including cytomegalovirus (CMV). Other common indications include PDR unable to undergo primary laser retinopexy due to chronic retinal detachment, schisis or oedema, (Brouman et al. 1989; Giordano & Refojo 1998), exudative retinal detachment

caused by intraocular tumor,(Wei et al. 2014) and hypotony associated with chronic uveitis or anterior PVR. (Barr et al. 1993; Kapur et al. 2010) Idiopathic large macular holes, although less common, is also be treated by SO tamponade. (Ivanovska-Adjievska et al. 2012) SO could also be considered as a better choice as a short-term tamponade for patients with difficulty of maintaining a prescribed head position or the need of air or high altitude travel. (Giordano & Refojo 1998)

SO has been shown to be as effective as inert gases in terms of anatomical success in cases of RRD.(Feng et al. 2017) However, the risk of postoperative chronic hypotony was found to be significantly lower using SO when compared with inert gases in severe PVR (grade $\geq$ C3). Considering that diffuse anterior contraction of retina remained an independent risk factor of chronic hypotony, SO tamponade shows some advantages in the treatment of anterior PVR with hypotony.(The Silicone 1992; Barr et al. 1993)

However, a variety of complications particularly relating to longer term tamponade have been reported with variable incidences. These include cataract formation (~70% depending on follow up), glaucoma due to a variety of causes, chiefly emulsification (up to 13%), keratopathy, again due to emulsification with chronic endothelial contact (up to 10%),(Federman & Schubert 1988) and, controversially, a reduction in choroidal thickness, which may be related to the long term intraocular pressure effects.(Caramoy et al. 2014; Odrobina et al. 2017; Issa et al. 2020) Migration of SO, both intraocular (between the anterior chamber and vitreous chamber in phakic eyes or subretinal migration) and extraocular (through

sclerostomies or perforation sites) have also been reported.(Yu & Apte 2005; Grzybowski et al. 2014) There have also been sporadic reports of abnormal SO adherence to the retina called “sticky SO” noted at the time of removal, which is most likely related to remnants of perfluorocarbon liquids, and perfluorooctane in particular.(Veckeneer et al. 2008)

Silicone oil-related visual loss (SORVL) has also provoked concerns in the use of SO. SORVL can be defined as profound visual loss (>2 Snellen lines) during SO tamponade or, more typically at the time of SO removal without any apparent explanation.(Scheerlinck et al. 2016) Although the aetiology and prevalence of SORVL is still unclear, it has been most frequently reported in cases with giant retinal tear and macular sparing RRD where the reported incidence has been up to 50%.(Moya et al. 2015) The hypothesised aetiology of SORVL included a limited vitreous cavity potassium sink, increased concentration of fibrogenic growth factors in the retro-oil fluid,(Asaria et al. 2004) phototoxic damage due to ultraviolet light, reduced lipid soluble factors including lutein, zeaxanthin and vitreous humour ascorbate.(Williams et al. 2008) The duration of SO tamponade may also be a risk factor of SORVL and early oil removal is increasingly advocated in appropriate cases with cases being rare with short term tamponade of 8 weeks or less.(Scheerlinck et al. 2016) The clinical features of SORVL vary including a reduction in inner retinal thickness,(Christensen & la Cour 2012) central scotoma, visual field defect,(Williams et al. 2008) and abnormal electrophysiological response.(Cazabon et al. 2005) Further studies are needed to evaluate the risk and understand the

mechanism of SORVL.

Conventional SO is less effective in treating inferior retinal breaks due to its buoyancy in water and, therefore, reduced ability to prevent aqueous flow through the inferior breaks in the upright position. Therefore, the primary indication for the use of HSO is for the treatment of inferior retinal break detachments, especially those complicated by PVR.(Wolf et al. 2003; Jousseaume & Wong 2008; Stappler et al. 2009) Evidence has also shown that the aqueous separation volume between HSO and retina is reduced compared to conventional SO.(Abdelkader et al. 2011) This means that HSO is more efficient in tamponading the inferior retina than conventional SO. However, no significant advantage has been shown in terms of anatomical success by using HSO when compared with conventional SO in different studies.(Wickham et al. 2010; Jousseaume et al. 2011; Kocak & Koc 2013) Therefore, the additional utility of HSO in treating inferior retinal detachment is still controversial.(Mancino et al. 2013) In addition, HSO has shown higher complication rates including raised IOP in the early postoperative period and more severe inflammatory reaction in some studies.(Wong et al. 2009; Semeraro et al. 2019) This is possibly due to displacement of debris (e.g. photoreceptor and RPE remnants) into the anterior chamber by sequestration and possibly the separation of the high density liquid additives that contribute to the increase in specific gravity of the HSO.(Chan et al. 2014)

Correlation of the timing of SO removal and retinal redetachment

Considerable experience has shown that the duration of oil tamponade does not affect

final anatomical success.(Falkner et al. 2001; Teke et al. 2014; Rhatigan et al. 2018)

However, a slightly higher retinal redetachment rate was reported with the tamponade duration less than 3 months, probably relating to PVR.(Casswell & Gregor 1987)

PVR has a median onset of 2 months following surgery and typically SO is left in place until this period has elapsed before removal. (Giordano & Refojo 1998)

Bearing in mind the comments above regarding SORVL and the duration of tamponade, the recommended removal time of SO between surgeons and individual cases varies widely depending on the retinal condition being treated, the stability of the retina and whether retinal attachment has been achieved, or is likelihood to remain following oil removal. Surgeons should evaluate individually the optimal time of SO removal on a case by case basis.(Rhatigan et al. 2018) No causal relationship has been found between the redetachment rate with preoperative visual acuity, the viscosity of SO and techniques of SO removal.(Rhatigan et al. 2018)

Emulsification – a major cause of SO-related complications

SO emulsification is regarded as one of the most important causes of SO-related complications. Emulsified SO droplets have been seen in both the anterior and posterior segments, and have even been detected in the optic chiasm and brain.(Federman & Schubert 1988; Grzybowski et al. 2014) Emulsification has been thought to be related to the occurrence of keratopathy, late-onset glaucoma, and optic neuropathy. The potential mechanisms vary including contact between emulsified droplets with corneal endothelial cells, inflammation in the trabecular meshwork and

direct SO infiltration of angle structures.(Miller et al. 2014) Therefore, research targeted at the mechanism and risk factors for emulsification, and novel removal strategy are important.

The onset of emulsification of SO *in vivo* has been reported as ranging from 5 to 24 months with a mean of 13.2 ± 4.8 months, although various clinical factors discussed later can shorten this time significantly.(Toklu et al. 2012) The mechanism of emulsification of SO is still not completely understood. The widely accepted hypothesis is that small SO droplets are separated from the main SO bubble due to shear forces induced by saccadic eye movements.(Chan et al. 2011) The shear stress is generated at the SO/aqueous interface due to the relative motions between the oil, the aqueous film, and the eye wall during the saccades. This induced stress leads to the breakup of SO molecules from the main SO bubble and forms droplets, as illustrated in Figure 2a. The dispersed droplets are then stabilised by blood constituents and migrate to different parts of the eye following aqueous circulation (Figure 2b). The relative motions between SO and the eye wall arise because liquids in the eye do not follow the eye movements completely. The viscosity of the liquid dictates the magnitude of the relative motion between the liquid and the eye. A liquid with a higher viscosity has a greater ability in momentum diffusion. Therefore, the higher the viscosity of the liquid, the greater extent of the liquid to follow the eye movement.(Chan et al. 2011) In addition, the induced shear stress is directly proportional to the velocity of the relative motions. In other words, the more significant the relative motion, the higher the relative velocity, and therefore the

higher the shear stress acting on the SO/aqueous interface that triggers the emulsification. As viscous SO tend to have lesser relative motion against the eye movement, the induced shear stress acting on the SO/aqueous interface should be lower than that to the case with less viscous SO. This explains why, theoretically, the increase in viscosity of SO reduces the extent of emulsification.

A recent hypothesis suggested that emulsification of SO can also be triggered by the elongation and break-up of SO filaments following adherence between SO and ocular tissue,(Lu et al. 2019) and has been further supported by a recent study.(Wang et al. 2020) The tensile stress was generated when SO adheres onto the retina surface followed by the eye movement. This force induced the extension and break-up of SO filaments, therefore leading to the generation of SO droplets. It should be noted that this scenario should occur rarely as SO seldom adheres to the retinal surface in-situ unless there has been the adjunctive use of perfluorocarbon liquids.(Veckeneer et al. 2008; Romano et al. 2012)

The risk of emulsification is increased by a variety of factors. The physical properties of SO that may affect emulsification rates include its shear viscosity and interfacial tension.(Giordano & Refojo 1998) SO with a high shear viscosity should be more resistant to emulsification.(Zafar et al. 2016) However, such an effect seems not to increase significantly beyond a viscosity of approximately 5000 mPa.s. (Heidenkummer et al. 1991) A reduction in interfacial tension between SO and intraocular fluid promotes emulsification.(Giordano & Refojo 1998) Various impurities in SO have been reported to promote emulsification including short chain

SOs,(Nakamura et al. 1990) catalyst remnants,(Russo et al. 2018) and different molecular side groups in SO. (Heidenkummer et al. 1991) Emulsification of SO is also related to factors other than its material properties. Shear stress associated with eye movement is suggested to be the primary cause of emulsification,(Chan et al. 2014) which partly explains the higher emulsification rates seen in active children. In addition, other risk factors to promote emulsification have also been proposed. The presence of biomolecules which are amphiphilic,(Lu et al. 2019) including plasma lipoproteins, apolipoproteins and red blood cells, can reduce interfacial tension, and facilitate emulsification and at the same time, stabilise the emulsified droplets after formation. This problem is also thought to be greater in children and uveitis. Heat energy from surgical handpieces and laser,(Francis et al. 2007) intraoperative use of perfluorocarbon liquids and semi-fluorinated alkanes,(Russo et al. 2018) and fluctuations of temperature during surgery,(Romano et al. 2017) have also been suggested as risk factors of emulsification. Conversely, the change in eye geometry induced by scleral buckling, and a more complete SO fill may lead to a lower emulsification rate.(de Silva et al. 2005)

Qualification and quantification of SO emulsification in situ

Although significant efforts have been made to minimise emulsification, its onset seems inevitable in some patients and can be difficult to detect by routine clinical examinations. SO emulsification in-vivo can be qualitatively assessed by clinical observation with slit-lamp microscopy, SD-OCT and MRI. Emulsified SO droplets have been observed in the anterior chamber, vitreous cavity, retina and optic

nerve.(Yu & Apte 2005; Potts et al. 2018) To quantitatively assess SO emulsification, aqueous samples of washout after SO removal have been analysed by a variety of techniques including Coulter counting and laser light scattering to measure both the size and number of the emulsified SO droplets.(Chan et al. 2015; Chan et al. 2017) Interestingly, using these devices, the majority of droplets have been found to be below 2 μm in size, which is too small to be observed clinically via gonioscopy or slit-lamp biomicroscopy. Recent clinical studies also obtained similar findings. (Yu et al. 2020; Yu et al. 2020) This information may account for some otherwise clinically unexplained complications related to SO, namely secondary glaucoma without observable emulsification, and provide future research directions.

New approaches of removal of emulsified droplets

Some problems caused by emulsification cannot be alleviated simply by conventional removal of SO.(Romano et al. 2010) This raises the need to develop novel strategies that more effectively remove emulsified SO droplets, including the non-visible ones. Various authors have advocated triple-fluid/air exchange to maximise emulsification removal.(Berrod et al. 1994; Bopp & Kellner 2019) However, emulsified droplets can typically still be detected in the anterior chamber and within the retina, even in the optic nerve after removal by this technique.(Grzybowski et al. 2014) Indeed, a recent study has shown that the technique of fluid-air exchange is not effective at removal of emulsified droplets, and may even reduce their removal as the oil spreads and adheres to the retina under air.(Shiihara et al. 2017) To tackle this problem, perfluorobutylpentane (F4H5) has been suggested as an intraoperative agent to

remove residual SO in the vitreous cavity due to its excellent miscibility with SO.(Stalmans et al. 2015) However, as F4H5 has a much higher density and is immiscible with water, F4H5 cannot directly contact with most of the leftover emulsified droplets suspended within the aqueous phase reducing its effectiveness at dissolving and removing SO droplets. To solve this, a rinsing agent that may be able to remove the emulsified SO droplets more effectively has been proposed. Using a mixture of a volatile liquid (e.g. LMW-SO or perfluorobutylpentane (F4H5)) and a hydrophobic surfactant, SO droplets can be encapsulated via a double emulsification mechanism and then aspirated. The use of this liquid agent can significantly reduce the amount of left-over SO droplets compared with saline solution rinsing in-vitro, and has been shown to be compatible with different retinal cell lines in-vitro, suggestive of its biocompatibility, although more experience in its in-vivo use is needed.(Chan et al. 2015; Chan et al. 2018)

III. Recent development and innovation of SO

New SO with reduced viscosity and emulsification

New formulations of SO have been developed in attempt to reduce emulsification, and to ease the surgical challenges of insertion and removal of viscous oil with the increasing use of narrower gauge vitrectomy systems. Adding a small amount of high-molecular-weight (HMW, 423 kDa) SO into conventional SO increases its shear thinning properties.(Williams et al. 2010) Shear thinning means that the viscosity of

SO decreases when it is subjected to a shear force, a force that acts parallel to the direction of the movement of SO, the situation when oil is injected through a narrow lumen cannula. (Figure 3a) This allows the use of SO with a high resting viscosity with narrow gauge vitrectomy systems. This innovation has also been suggested to result in a more emulsification-resistant oil in-vitro. The authors attributed this improvement to the increase in extensional viscosity, a fluidic property that resists the breakup of oil during its elongation from shear stresses during eye movements (Figure 3b).(Caramoy et al. 2010; Caramoy et al. 2011; Caramoy et al. 2015) However, the clinical outcomes using this new formulation of SO are still controversial. Some reports have showed a satisfactory anatomical result and a lower rate of emulsification compared with conventional SO.(Stalmans et al. 2015; Hussain et al. 2017) However, early emulsification in as short as two days to two weeks postoperatively has also been reported in other studies.(Maier et al. 2011; Ni et al. 2019) The same concept has also been applied to produce new formulations of HSO, which are more resistant against emulsification but without compromising the ease of injection. (Caramoy et al. 2010; Caramoy et al. 2011; Caramoy et al. 2015)

Silicone oil as a drug delivery system

To enhance the functionality of SO tamponades, the potential to deliver drugs via or alongside SO has also been explored. Recent studies have reported that various drug delivery devices can be used safely and with some success in SO-filled eyes.(Banerjee et al. 2017; Iglicki et al. 2019) However, as the amount of aqueous in the vitreous chamber is much lower in a SO-filled eye than a normal eye, meaning that the

concentration of water-soluble drug formulation in this aqueous phase could be higher, and lead to retinal toxicity. This can be balanced by reducing the dose, although this can result in rapid clearance, as has been observed with antibiotics and aqueous triamcinolone acetonide solution.(Hegazy et al. 1999; Fernandes-Cunha et al. 2014) Clinical studies with low-dose triamcinolone acetonide,(Ahmadieh et al. 2008; Chen et al. 2011; Banerjee et al. 2016) and a recent, large, randomised control trial using a slow release dexamethasone implant in SO-filled eyes have not demonstrated a statistically-significant reduction in PVR, although incidence of PVR was not the primary outcome.(Banerjee et al. 2017)

SO has clear potential as a sustained-release drug reservoir due to its long-term residence in the eye. Drugs with higher lipophilicity can dissolve more readily in SO. It should be noted, however, that SO is not a lipid oil, and so the saturation concentrations of relatively lipophilic drugs such as triamcinolone acetonide and dexamethasone in SO are often relatively low (Pastor et al. 2008). In general, two strategies have been employed to exploit SO as a device to extend drug release: injection of standard drug solution into SO at the point of infusion, and dissolving drugs into the SO prior to infusion. Triamcinolone acetonide is a drug that has been used most widely in combination with SO, being typically injected into the oil bubble after insertion.(Spitzer et al. 2009) The drug forms a suspension with the oil acting as a reservoir, and the drug forms crystal at the oil/aqueous interface relatively quickly (minutes-hours, depending on concentration and observable in the oil for months). (Spitzer et al. 2009; Da et al. 2016) When drugs are combined with SO prior to

infusion, more consideration must be given to the formulation. The time taken to dissolve drugs fully into SO is in the order of days to weeks, and achieving homogenous dissolution in higher viscosity oil (e.g. 5000 mPa.s) special equipment. It can also be technically challenging to quantify drug loading and solubility.(Cauldbeck et al. 2018) A series of studies using acetylsalicylic acid reported relatively high drug loading in 5000 mPa.s SO (1.67 mg/mL), although filtration to remove undissolved drug was not performed. (Kralinger et al. 2001) In a subsequent clinical trial, the acetylsalicylic acid-SO solution was filtered to remove undissolved drug crystals and resulting in significantly lower drug loading of 0.2 mg/mL (Kralinger et al. 2010)). *In vitro*, a burst release was observed, with concentration reduced after three days and the drug metabolite, salicylate, was undetectable after thirty days. In rabbit studies, drug was detected in ocular tissues up to 5 days post-implantation without observation of any toxicity. (Kralinger et al. 2001; Kralinger et al. 2001) In clinical studies, these drug-loaded oils were demonstrated to be safe, but no clinical benefit was observed, possibly due to the low amount of drug loaded into the oil.(Kralinger et al. 2010) To the best of our knowledge, no other clinical studies using drugs dissolved in SO have been reported. Both the all-trans and 13-cis isoforms of retinoic acid, dissolved in 5000 mPa.s SO and 180 mPa.s silicone-fluorosilicone copolymer oils, have been studied in rabbit models of fibroblast-induced PVR.(Araiz et al. 1993; Nakagawa et al. 1995; Veloso Jr et al. 1997) Those studies showed that, at a drug loading concentration of 9 µg/mL (lower than the saturation concentration), reduction in PVR was reported, but the drug was mostly released from the SO by seven days. These

studies highlight the potential of SO for drug delivery, and the difficulties of trying to obtain drug release over the four to six-week period that may be relevant in the pharmacological treatments of PVR.(Guidetti et al. 2008) PDMS-based additives may provide a means to increase drug loading and extend release into this clinically-relevant period. One such additive uses chain-end modification of PDMS to bind all-trans retinoic acid. (Cauldbeck et al. 2018) These additives with drugs bonded, can be blended into unmodified SO to increase the load of drug in oil and, in *in vitro* studies, have extended the period over which the drug was released to over seven weeks. Drug release profile was independent of the initial loading concentration, allowing a means to avoid release of cytotoxic doses of drug at early time point. An alternative family of additives was developed based on PDMS-based statistical graft copolymers which allows hydrogen bonding with the acid functional drugs.(Cauldbeck et al. 2016) Again, in contrast to unmodified SO, all-trans retinoic acid was released over more than seven weeks from the SO into an aqueous *in vitro* environment. Extended release of ibuprofen was also reported, although the release period was only increased from three days, to just over one week. These studies demonstrate the potential of PDMS-based additives to offer routes to modify and extend the drug release behaviour of silicone oil tamponades. Care must be taken, however, to balance the possible benefits of drug release with potential of additives to have negative impacts on other important properties of the SO, such as emulsification resistance.(Lu et al. 2019)

IV. Novel alternatives to SO in vitreoretinal surgery

Related to the well documented problems of SO, especially emulsification, its role in vitreoretinal surgery has been challenged by the recent development of the foldable capsular vitreous body, the breakthrough of hydrogel materials for vitreous cavity tamponade, and the medium-chain triglycerides that is undergoing the clinical trial.

Foldable Capsular Vitreous Body

To avoid the problems of oil emulsification with long term tamponade, the foldable capsular vitreous body (FCVB) has been developed. It consists of a thin capsule made up of a silicone rubber elastomer with a silicone tube-valve system secured under the conjunctiva (Figure 4).(Lin et al. 2012) Through early in-vitro and animal trials, FCVB has been demonstrated to have promising mechanical, optical, and biocompatible properties. (Gao et al. 2008; Liu et al. 2010) Over the last decade, it has been used as a new intravitreal tamponade in the treatment of severe cases of RRD with very poor vision that could not be reattached completely with SO. Balanced salt solution (BSS) or more preferred SO can be injected to inflate the capsule to support the shape of the vitreous cavity and by appositional closure of the retinal breaks.(Gao et al. 2008; Lin et al. 2011; Lin et al. 2012; Zhang et al. 2019) Through long-term postoperative follow-up, the results showed that FCVB can effectively tamponade the retina with a slight elevation of IOP and visual acuity.(Lin et al. 2012) Although FCVB has shown no adverse effects clinically, its use is still limited to a small number of cases. Its use in eyes with better vision and the long-term safety and

efficacy needs to be investigated with clinical trials. Therefore, at the current stage, it cannot be fully substituting the role of SO as intraocular tamponade in vitreoretinal surgery. Although it will avoid complications related to emulsification and migration of SO into the anterior chamber, it will not compensate for the deficit in aqueous production and hypotony which is often the problem in eyes with severe PVR related retinal detachments currently requiring long term oil tamponade. It will however, like SO, reduce uveoscleral outflow in areas of retinectomy, maximising intraocular pressure in these situations. Its exact role in sighted eyes, however, remains uncertain.

Hydrogel-based intravitreal tamponade

Hydrogel biomaterials have been broadly used in a variety of regenerative medicine applications.(Spang & Christman 2018) Due to its excellent hydrophilicity, hydrogels could theoretically completely occupy the volume of the vitreous cavity and prevent fluid movement through the retinal defect,(Annaka et al. 2011) ameliorating the requirement to position and offer improved biocompatibility. It could also potentially avoid the complication of cataract formation due to the use of SO after vitrectomy. Different types of natural materials have been proposed including collagen, hyaluronic acid, chitosan and other natural polymers.(Kleinberg et al. 2011) Synthetic polymers like Poly(1-vinyl-2-pyrrolidone), Polyacrylamide, Poly(vinyl alcohol), Poly(vinyl alcohol methacrylate) have also been tested.(Baino 2011) Biocompatible natural polymers have been reported to be limited by their low mechanical strength and rapid and variable degradation rates. Conversely, synthetic polymers have been reported showing poorer biocompatibility, inflammation and

long-term toxicity but with more tuneable chemical properties.(Kleinberg et al. 2011)

Moreover, the problem of biofouling, a major hurdle of these hydrogel-based materials to be developed as a long-term tamponade, has not been properly solved. (Su et al. 2015; Januschowski et al. 2018) Biofouling refers to the nonspecific adsorption of proteins to the surface of the implanted biomaterials which can elicit immune reaction and fibrosis.(Bixler & Bhushan 2012) Recently, the concept of a double network hydrogel has been a breakthrough in the field of hydrogel research. This concept has allowed the fabrication of hydrogels with improved and new properties, including a self-healing ability, higher tolerance to shear stress, anti-biofouling capability, rapid network recoverability, higher viscosity and improved biocompatibility.(Wang et al. 2018) Fascinatingly, one of the hydrogels has been shown the potential to reform a vitreous-like structure after degradation, with the presence of vitreous proteins and structure in vivo after 6 months.(Liu et al. 2019) As well as a potential vitreous substitute, hydrogels have also been considered as ophthalmic drug delivery systems to deliver anti-VEGF agents including ranibizumab, dexamethasone, bevacizumab and aflibercept (Yu et al. 2015; Anwary et al. 2018) —

However, as the research is only in the stage of preclinical animal model testing, there is still a considerable long way to go through clinical trials and regulatory approval, before hydrogels can be shown to be safe and effective to be used as vitreous substitute and/or sustained drug delivery systems in routine ophthalmic practice.

Medium-chain Triglycerides (MCTs)

MCTs are a class of triglycerides with the main component of caprylic and capric fatty acids and a small percentage of caproic and lauric fatty acids. (Traul et al. 2000) They are highly biocompatible and now widely used as nutritional therapies in the treatment of diseases associated with dysfunction of lipid absorption.(Ruppin & Middleton 1980) Recently, their application in ophthalmology has also been explored. In the form of an oil-in-water emulsion, MCTs have the potential to be used as drug carriers for sustained release of dexamethasone palmitate in vitreous cavity.(Daull et al. 2013) Furthermore, with physical properties similar to conventional SO, MCTs present great potential to be alternatives of SO as an intraocular tamponade agents in animal studies with no obvious retinal toxicity.(Auriol et al. 2013; Soler et al. 2017)

V. Conclusion

The unique physical properties and long-term safety record of SO has meant that it has retained its essential role as a long-term tamponade agent in complex vitreoretinal situation. However, emulsification which is the major cause of SO-related complications, is still seemingly inevitable in some cases and cannot be ignored. Studies of the mechanism and risk factors of emulsification and novel strategies to improve the completeness of SO removal are helping to reduce the frequency of complications. Meanwhile, purification of SO is required and the effect of LWM components and impurities on SO related visual loss and toxicity still need further study and regulation.(Steel et al. 2020) New formulations of SO and HSO have been developed and shown promising results in terms of safety and efficacy. However,

prospective randomised clinical trials with large sample size are required to further justify their importance and efficacy in ophthalmic applications. Although SO is being challenged by other new materials as potential vitreous substitutes, it will still be irreplaceable in vitreoretinal surgery in the near future.

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Figure Legends

Figure 1 Chemical structure of standard silicone oil, polydimethylsiloxane (PDMS), with n as the repeating unit.

Figure 2 The process of emulsification of silicone oil in the eye. (a) Relative motion between silicone oil and the aqueous film induces shear stress to create oil droplets. The length of the arrows indicates the magnitude of the velocity. (b) The oil droplets are stabilised by surface-active biomolecules, like blood constituents, proteins and glycolipids, which can be found in the aqueous fluid in the eye.

Figure 3 (a) The shear stress acting on SO during injection into the eye. High-molecular-weight SO chains tend to disentangle to form straighter chains under high shear stress. This reduces the resultant shear viscosity of SO which eases the injection. (b) The increase in the extensional viscosity of SO resists the breakup under tensile force to form droplets.

Figure 4 The FCVB and the procedure of implantation. (a) The FCVB consists of two parts, the capsule and a valve. (b) Before implantation, airtightness of the capsule is confirmed. (c) The FCVB, after deflation, is folded ready for implantation. (d) high transparency is observed in vitro. Reproduced with permission. Copyright©2010 International Centre for Artificial Organs and Transplantation and Wiley Periodicals, Inc. (e) Procedures of the implantation of FCVB. Pars plana vitrectomy was firstly performed, then the folded FCVB was inserted to the vitreous cavity through a scleral cut. After that, SO or PBS was injected through the valve to inflate the FCVB. The valve was then sutured under the conjunctiva. Reproduced with permission. Copyright © 2015 Association for Research in Vision and Ophthalmology.

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