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REVIEW ARTICLE

Vision loss associated with silicone oil endotamponade in vitreoretinal surgery – a review

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Abstract

Purpose To clarify the definition, prevalence and classification of different types of unexplained vision loss associated with silicone oil (SO) endotamponades (SO in situ (SOIS) or after removal of SO (ROSO)) in vitreoretinal surgery and identifying the most specific clinical findings and suggesting possible causes.

Methods Review of the literature regarding randomized clinical trials (RCTs), retrospective case–control, cohort studies and case series evaluating the risk of using SO, published in English between 1994 and 2023, conducting a computer-based search of the following databases: PubMed, Web of Science, Scopus and Embase. The search was supplemented using the Medline option 'Related Articles' and consulting review articles on the topic.

Results Findings from reported clinical examinations in SOIS and ROSO are analyzed and finally different theories regarding the underlying pathophysiology are described. From the clinical point of view, findings have been found in OCT, OCTA, microperimetry and electrophysiological studies. Other clearly identifiable causes of vision loss related to the use of SO are listed and commented as differential diagnosis. Finally, the different physiopathological theories of the two types of causes of unexplained vision have been analyzed.

Conclusion Unexpected vision loss under or after SO tamponade (SOIS and ROSO) is a significant concern which is probably underestimated because it is not a clearly defined and known entity. The most frequently described changes were in the ganglion cell complex but this unexpected vision loss remains a serious and unexplained concern for vitreoretinal surgeons and should be identified by clinicians, addressed by manufacturers and reported to Health Authorities as a serious incident according to the new regulation.

Keywords Vitreoretinal surgery · Endotamponade · Silicone oil · Vision loss · SOIS · ROSO

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Key messages

What is known:

- Unexpected central visual loss under silicone oil tamponade or after its removal is a rare and not well known entity.

What is new:

- We present a recent literature review to elucidate their pathomechanism.
- Multimodal imaging is a helpful tool for understanding. The most commonly described damage is to the ganglion cell complex.
- In order to improve the understanding of this still unclear phenomenon, more attention should be paid in registry studies.

Introduction

Silicone oil (SO) became widely used in vitreoretinal surgery for repairing giant retinal tears, proliferative vitreoretinopathy (PVR), tractional retinal detachments, trauma, and viral retinitis, among other uses [1]. In addition, due to their good results, SO tamponades have recently become more popular in elective cases, such as persistent macular holes, especially when amniotic membranes are used as a scaffold [2]. The fact that patient and physician's expectations for visual outcomes even in complicated vitreoretinal cases have increased, has also put a focus on SO tamponades themselves as a possible cause of vision loss, as some reports regarding vision loss associated with SO without a clear cause have been published in the recent past [3–6]. After Pastor et al. have reported significant vision loss and catastrophic individual histories associated with the use of a medical device, the vitreoretinal community has been made aware of the importance of tamponades and their possible toxic effects [7–10].

Prolonged contact of SO with ocular structures in vitrectomized eyes can be associated with several well-reported complications such as cataract, glaucoma, keratopathy, emulsification and migration in the anterior chamber [11]. These complications are partly related to the duration of exposure of ocular tissues to SO and some of them may be reversible after its removal. However, the pathogenesis of "unexplained" silicone oil-related visual loss is less clear. In particular, functional changes in the neurosensory retina induced by SO toxicity are difficult to distinguish from damage caused either by the underlying retinal pathology leading to vitrectomy or by surgical manipulation [12].

From the clinical point of view there are two different situations: vision loss under SO tamponade that is with SO in situ (SOIS) and vision loss after the removal of silicone oil (ROSO). Different authors began to publish cases or small series of cases in the early 2000s [3]. Visual loss was also shown to occur with an incidence of 10% 1–5 months with SOIS [13]. The Pan American Collaborative Retina Study (PACORES) has reported the rate of unexplained visual loss in patients undergoing surgery between 2000–2012. This was a retrospective data analysis at eleven centers from across Latin America and Spain. In this series 13% (42/324) suffered a significant visual loss following ROSO. Twenty-three (7.1%) lost vision secondary to known causes but in the remaining 19 (5.9%) eyes, the loss of vision had no explanation. Factors associated with the phenomenon included higher intraocular pressure with SOIS and also longer duration of tamponade [6]. Furthermore, other groups have subsequently reported visual loss 1 day to 1 month after ROSO, with an incidence ranging from 1 to 33% [4, 6]. However, there is still no clear definition of the clinical pictures that define both entities, and the pathophysiological mechanisms are not well understood.

This review of the literature intends to analyze the pathophysiology explanations for both visual loss pictures, with SOIS and after ROSO, describing the functional and anatomical findings.

Review of the literature

Definition

Although there is no accepted definition, we consider according to some reports a vision loss decrease higher than 2 Snellen lines [14] (Table 1), once other subtle causes of macular involvement in eyes with SO have been ruled out, such as intraretinal microcystic changes, subtle epiretinal membranes, presence of microbubbles of SO in the prefoveolar space and others [15].

Visual loss with SO in situ(SOIS)

Probably one of the first reports of this variety of "unexplained" vision loss was the series published by Herbert et al. and these authors found no specific data and

Table 1 Case reports and studies to unexpected vision loss under or after silicone oil

	Reference	Number of patients with unexpected vision loss (of ≥ 2 lines)	Silicone oil in centistokes	Time to unexpected vision loss
SOIS	Herbert et al. 2005 [5]	5 cases (Mac on; 4/5 GRT)	1300 + 5700	mean 2.7 months
SOIS	Christensen et al. 2012 [18]	8/162 (Mac on)	5500	mean 145 days
SOIS	Tode et al. 2016 [17]	3/15 (Mac on)	5000	-
ROSO	Newsom et al. 2004 [3]	7 cases (Mac on 6/7; GRT 5/7)	1000	-
ROSO	Cazabon et al. 2005 [4]	3 cases (Mac on; 1/3 GRT)	5700	~ 1 week
ROSO	Toso et al. 2014 [53]	1 case	1000	immediatly
ROSO	Moya et al. 2015 [19]	14/421—> 10/14 (Mac on; GRT)	1300	mean 141 days
ROSO	Roca et al. 2017 [6]	19/ 324 (5.9%)	1000 + 5000	-
ROSO	Moussa et al. 2023 [82]	5/43 (11.6%; 1000) 3/18 (16.7%; 5000)	1000 + 5000	-
SOIS + ROSO	Shalchi et al. 2015 [15]	4 cases (Mac on; 3/4 GRT)—> 3/4 SOIS; 1/4 ROSO	1000	SOIS: 2 weeks-4 months ROSO: immediatly
SOIS + ROSO	Scheerlinck et al. 2016 [13]	11/37 (29.7%)—> 8/11 SOIS; 3/11 ROSO	2000	SOIS: mean 18 weeks
SOIS + ROSO	Ghoraba et al. 2017 [14]	12/554 (2.2%)—> 7/12 SOIS; 5/12 ROSO (Mac on)	5000	SOIS: mean 267 days ROSO: within 1 month
SOIS + ROSO	Ma et al. 2020 [31]	7 cases—> 4/7 SOIS; 3/7 ROSO	5000	SOIS: 1–1.5 months ROSO: immediatly
SOIS + ROSO	Pichi et al. 2020 [33]	3 cases—> 2/3 SOIS; 1/3 ROSO	5000	SOIS: 1–2 months ROSO: 1 week 1
SOIS + ROSO	Barth et al. 2023 [84]	SOIS: 9/22 (Mac on) ROSO: 2/22 (Mac on) -> 9/11 GRT	5700	SOIS: mean 139 days ROSO: 2 weeks

GRT, giant retinal tear; *ROSO*, removal of silicone oil; *SOIS*, silicone oil in situ

recommended an early extraction of SO [5]. The pathogenesis of SO-related visual loss is still unclear [4–6, 13, 16] and the number of cases may be underestimated because clinicians probably don't take this picture into account when they examine patients.

Neither the clinical features are well defined. Shalchi et al. reported sudden permanent visual loss with SO in situ in 3 patients within 2 weeks to 4 months [15]. Tode et al. also reported permanent central vision loss with SO tamponade within 3 months in 8 patients undergoing vitrectomy for rhegmatogenous macular detachment [17]. Half of these patients experienced visual loss within the first 6 weeks [17]. Other studies also showed visual loss with an incidence of 10% under SO in situ after 1–5 months [5, 16]. Scheerlink et al. even showed an incidence of SO-related unexplained visual loss (> 2 Snellen lines) of 30%, with duration of tamponade as the only risk factor [13]. These patients had a small scotoma within the central 2° on microperimetry [13]. However, it is still not fully understood why such visual loss occurs during silicone oil tamponade.

Visual loss after SO removal (ROSO)

A different issue is to look for an explanation for the sudden vision losses that occur after the extraction of SO (the so-called ROSO). Christensen and la Cour described vision loss in three eyes immediately after ROSO, while Moya et al. reported a higher incidence of visual loss a few weeks after silicone in 10 patients who underwent vitrectomy with oil tamponade with SO for fovea-sparing giant tears retinal detachment [18, 19]. Some possible hypotheses are those based on the characterization of the intraocular changes induced by SO analyzing different compounds found in the peri-silicone liquid, once SO has been removed. Some of them refer to excess potassium or imbalances in growth factors and cytokines. However, the key question is how to explain its relative low incidence.

Anatomical and functional changes

Patients that are symptomatic describe a painless vision loss that can occur suddenly after or prolonged over time under the tamponade and after SO removal. The most important findings are on the ultrastructural level seen in SD-OCT (spectral domain-optical coherence tomography) scans. Most authors describe a thinning in the perifoveal region especially located in the retinal ganglion cell layer region [18] and in the inner retina [15]. In some patients a central scotoma is reported, even under tamponade [15, 20].

Central scotoma

Unexplained SO-related vision loss may present as a central scotoma on visual field testing [3, 5, 15]. However, Scheerlink et al. concluded that the distinct pattern of severely reduced central sensitivity (small scotoma within the central 2°) on microperimetry in patients with SO-related visual loss is different from the microperimetric pattern seen in retinal detachment (RD) with preoperative macular involvement, having similar visual acuity but where SO is not used. Therefore, microperimetry may be of great value in the diagnostic workup of cases with a combination of both macular detachment and SO-related visual loss [13]. In another study, they included 40 patients having different situations: macula-on/-off RD and gas, macula-on/-off RD and SO[20]. They concluded that foveal sensitivity was decreased in eyes after SO tamponade compared to gas tamponade [18].

Herbert et al. reported an unexplained central scotoma beginning during SO tamponade in a case series of five patients undergoing vitrectomy for macula-on RD (4 with giant retinal tear). The mean duration of oil in the eye was 2.7 months when the scotoma was noted and remained after ROSO. After ROSO, no abnormalities were found on fluorescein angiography and OCT. However, pattern electroretinography suggested macular dysfunction in four patients [5].

As an anecdotic finding Nicholson and Bakri showed one case where severe visual loss due to a central scotoma, was probably caused by prefoveal silicone oil emulsification demonstrated by OCT. In those cases visual loss could be reversible after prompt removal of SO [21].

Optical coherence tomography

There is no doubt that the application of optical coherence tomography (OCT) has made it possible to identify many of the structural alterations present in these patients of unexpected vision loss.

The central visual loss is accompanied by a visual field defect corresponding to a thinning of the combined ganglion cell layer and inner plexiform layer (IPL) within the inner parafoveal ring [22]. As the inner parafoveal ring contains the largest number of ganglion cells and they have the shortest axons, they could be more susceptible to toxicity.

One explanation is mechanical compression by the SO causing ischaemia of the superficial capillary plexus and apoptosis, resulting in damage to ganglion cell bodies and dendrites. An associated significant thinning of the inner retinal layers of the ganglion cell complex (retinal nerve fibre layer (RNFL), ganglion cell layer, inner plexiform layer) compared to untreated fellow eyes has been shown in several studies [23–30]. SD-OCT of seven eyes with SO-related unexpected visual loss showed thinning of the ganglion cell layer compared to the healthy fellow eye [31]. Consistent with this finding, OCTA (optical coherence tomography angiography) also showed reduced vessel density in the superficial capillary plexus. The inner plexiform layer was also thinned, although RNFL thickness was preserved [31]. Such a significant reduction in the ganglion cell layer and inner plexiform layer compared to the fellow eye was also shown in another case series of vision loss under SO tamponade, in which all other retinal layers were reported to be anatomically normal [17]. These observations of ganglion cell layer thinning have been seen in patients with and without macular involvement [23–25, 32]. The effect of inner macular thinning has also been demonstrated with gas tamponade, although visual acuity remains lower with SO [18].

However, it could be argued that, especially in retinal detachment, the effect of macula-off detachment on photoreceptors is more likely to result in visual loss than SO toxicity with subsequent ganglion cell apoptosis [33]. However, Raczyńska et al. did not observe statistical differences between macula-on and macula-off groups with respect to the ganglion cell complex [32].

Effects of SO tamponade in reduction in RNFL thickness should be taken cautiously because SO made OCT measurements non reliable [26, 34]. RNFL thinning appears to be strongly associated with visual outcomes in SO patients with retinal detachment [26]. In support of this, patients with unexplained visual loss after silicone oil tamponade have been shown to have foveal RNFL loss, whereas patients without visual loss have preserved RNFL [15, 17].

An association between RNFL changes on OCT and visual outcomes was demonstrated in 50% of a cohort who presented with sudden central vision loss within the first postoperative month [27]. The most metabolically active area on the temporal side and along the macular bundle appears to be most susceptible to microenvironmental changes induced by SO tamponade [27].

However, other studies showed an increase of RNFL thickness [28, 30]. For example, Zoric Geber et al. showed higher RNFL thickness at all follow-ups up to 6 months in the SO filled eye after vitrectomy for retinal detachment, although different axial lengths and optical media may have influenced the result [28]. It was also shown that peripapillary RNFL thickness was significantly higher than in the fellow eye, after SO removal [30, 35].

OCT has demonstrated several structural changes [36] related to unexplained visual loss that need further investigation, such as microcystic macular changes in the inner nuclear layer of affected eyes [15]. Moreover, there are many studies in the literature that do not find specific alterations by OCT in these patients [13].

And once again the problem is how to interpret the low prevalence of these and other findings, which may or may not be related to SO since there are no experimental studies on animal models equivalent to humans that demonstrate a clear cause-effect relationship.

Intraretinal silicone oil droplets

A possible explanation for RNFL thickening could be the presence of emulsified silicone oil vacuoles within the retinal layers of vitrectomised eyes, which may lead to chronic inflammatory cellular infiltration with macrophages and giant cells [37]. Such emulsified silicone oil vacuoles could be interpreted as small hyperreflective globules, intraretinally, subretinally and underneath epiretinal membranes by SD-OCT as early as 4 weeks after SO administration [38, 39]. They were mostly found in eyes with visual loss under SO [17]. Histological studies in animal models and enucleated eyes have confirmed that these hyperreflective cups in the retina are silicone oil-filled vacuoles [40]. SO particles can be visualized at the level of the optic nerve head and photoreceptors using adaptive optics [41].

Even subsequent retrolaminar silicone oil migration to the optic chiasm has been reported in a patient with glaucoma and SO injection after retinal detachment, resulting in bilateral visual loss [42]. Histopathological analysis of enucleated eyes with SO showed that 19% of retrolaminar optic nerves had variable numbers of SO vacuoles [43].

But the problem arises of relating these findings to so-called unexplained vision loss. In any case, we believe that these are findings that should be sought in this type of patients.

Optical coherence tomography angiography (OCTA)

Another explanation of SO-related severe visual loss could be shown in optical coherence tomography angiography (OCTA) to be associated with superficial retinal microvasculature damage and ganglion cell apoptosis [31].

Ma et al. investigated macular perfusion changes and ganglion cell complex loss in 7 patients with unexplained visual loss after vitrectomy and SO using optical coherence tomography angiography (OCTA). They found a significant reduction in superficial capillary plexus vessel density in the affected eyes compared to controls. The focal loss volume and global loss volume were significantly higher in affected eyes, but there was no difference in the thickness of the ganglion cell complex. They concluded that SO induced severe visual loss is associated with damage to the superficial retinal microvasculature and ganglion cell apoptosis [31].

Jiang et al. investigated peripapillary changes after vitrectomy and SO tamponade for retinal detachment in 22 eyes showing a decrease in radial peripapillary capillary vessel density secondary to loss of retinal nerve fibre layer thickness, which recovered in the early postoperative period but was still below normal levels [44].

Another recent study by Christou et al. on macular microcirculation after retinal detachment and macular involvement showed an enlargement of the foveal avascular zone and a decrease in vessel density and perfusion density of the superficial capillary plexus in 14 patients 1 month after SO tamponade and attributed this to ischaemic changes in the macular area after retinal detachment repair with SO tamponade. They also concluded that flow density in the macular capillary plexus may be an indicator of visual outcome [45].

Lee et al. showed that the foveal avascular zone in the deep capillary plexus was larger and the vessel density in the deep capillary plexus was lower in eyes with SO than in the fellow eyes. Also, they showed that the duration of SO tamponade was significantly correlated with the increase in foveal avascular zone and decrease in vessel density in the deep capillary plexus. Therefore, they concluded that these changes may reflect vascular insufficiency in eyes with SO tamponade and may provide a possible explanation for the pathogenesis of retinal thinning and unexplained visual loss [46].

Electrophysiology

Some animal studies have shown a loss of horizontal and bipolar cell synaptic processes in areas of the retina in contact with SO [47], possibly leading to macular changes on electroretinograms (ERG).

Doslak stated the ERG declined rapidly in SO-filled eyes, 15% of normal, and even with the most extreme variations of the other parameters, there was still a reduction (60%) of the ERG [48]. Furthermore, Christou et al. who reported that the amplitudes of the a- and b-waves were significantly higher after SO removal than those before ROSO, which means the photoreceptors should have recovered after the SO was removed [49].

Cazabon et al. reported on three patients who underwent vitrectomy for retinal detachment and showed macular damage on multifocal electroretinograms, especially in the outer retinal layers [4].

Al-Nashar et al. could further show in 34 eyes with complex primary rhegmatogenous macular detachment under SO that a- and b-waves of ERG were greatly reduced, but amplitudes of the ERGs increased after removal of the SO, with no differences between 3 and 6 months of removal [50].

Even after an average of 21 months of SO removal, Azarmina et al. found significantly increased ERG a- and b-wave amplitudes in 28 patients under scotopic and photopic conditions shortly after SO removal. These changes in ERG a- and b-wave amplitudes were attributed to the insulating effect of SO [51].

Ozaki et al. compared eleven eyes with complex vitreoretinopathy and SO with normal fellow eyes. They confirmed that a- and b-wave amplitudes of the affected eyes

were significantly smaller than those of the fellow eyes during SO tamponade. The ratio of affected/normal fellow eye b-waves increased significantly after ROSO and can be used to predict the amplitude after ROSO which would serve according to the authors as an element of functional prognosis [52].

All these studies included complex retinal detachment with macular involvement. But specific measurements in patients with unexpected VA loss are very limited. There are only 7 cases, showing severe macular dysfunction [3]. However, electrophysiology could be helpful to determine the location and possible nature of various dysfunctions along the visual pathway.

Visual evoked potential

Toso et al. described a case of unexplained sudden visual loss after ROSO (1000 ct) following successful repair of rhegmatogenous macula-off detachment with normal OCT, fluorescein angiography and electrophysiology (electro-ocular retinography, pattern and multifocal electroretinograms). Only the visual evoked potentials (VEP) showed a reduced amplitude, probably due to optic nerve damage [53].

Scheerlink et al. used VEP in three patients with reduced retinal sensitivity at 3.5° and 5.5° on microperimetry. The P100 latencies in the affected eyes were increased compared to the unaffected eyes, but within normal limits. The amplitudes for the checkerboard stimuli were reduced in the affected eyes, but also for the large stimuli in the unaffected eyes of two patients. They concluded that it was not possible to distinguish between macular or optic nerve damage [13].

Pathophysiological explanations

Direct mechanism

The presence of silicone oil in the vitreous cavity can exert mechanical stress on the retinal tissue. This mechanical stress can disrupt normal retinal architecture, compromise blood flow, and cause physical damage to the retinal cells [54–56].

The discussion of a direct toxic effect of SO has been widely debated, especially since toxic substances have also been described in removed oil [57]. It has also been shown that SO droplets can penetrate the retina [38, 39, 41]. This can directly damage the ganglion cell complex or cause inflammatory processes leading to cell death [38].

We would hypothesize that probably most of the negative effects are associated with impurities or with the lipophilic nature of SO. During the production of SOs some manufacturers use a one-step purification process resulting in a higher fraction of siloxane chains of low molecular weight) also volatile compounds and UV-active substances that by consensus have been called impurities [58].

Low molecular weight components (LMWCs) form the building blocks of longer chain molecules within SO but are difficult to remove during the final stages of the purification process. LMWCs are small molecules with the ability to diffuse into cells and can therefore be potentially cytotoxic to retinal cells due to their proinflammatory nature [59]. Recent in vitro analysis of the levels of cytotoxicity of LMWCs on a variety of retinal cell lineages confirmed that cyclical LMWCs within SO are more cytotoxic than linear LMWCs [60].

As cyclical LMWCs are more commonly found within commercially available SO than linear LMWCs, they are one element that both retinal surgeons and manufacturers should be aware of as a potential source of toxicity. However, LMWCs are part of the normal composition of SO and only those with a lower molecular weight are considered toxic [60, 61].

The other option that can be added to the previous one is the proven ability of SO to dissolve lipids. In 2007 it was demonstrated that SO is capable of extracting lipophilic compounds from inside the eye, and although some of them may be of plasma origin, other lipophilic compounds are clearly of cellular origin [9, 10]. These findings have been corroborated by other authors [57, 62, 63]. Hammer et al. did not actually detect the presence of lipophilic substances but assumed their presence and speculated that they may be one of the causes of emulsification [64].

Therefore, it seems plausible to speculate that the permanence of SO, in some eyes, produces toxicity on the cells of the ciliary body and internal layers of the retina, mainly acting over the cell membranes that can explain the loss of vision. This effect should be in relation to the time of endotamponade and would be the final cause of the thinning in the layers of the retina that is observed by imaging of many of these patients [27, 65]. It has also been speculated that the effect of phototoxicity would be related to the loss of macular pigments, lutein and zeaxanthin, being both lipophilic substances [66].

Indirect mechanism

Cytokines

It is also reasonable to hypothesize that an accumulation of proinflammatory cytokines in the fluid between the SO and the macula may be an indirect cause of vision loss [57, 67–69]. Asaria et al. in 2004 analyzed proteins and growth factors in the retro-oil fluid. They found a rise in fibrinogenic (bFGF) and inflammatory (IL-6) growth factors and proteins which contribute to the process of retro-oil perisilicone

proliferation and subsequent fibrocellular membrane formation and PVR [67].

Recently, through a proteomic study of the vitreous fluid, high values of Cadherin 2, transferrin, and altered cell adhesion and lysosome function molecules that may partially contribute to SO-related vision loss have been found [70]. In particular, authors consider that transferrin may be a potential visual outcome biomarker and may provide a research direction to explore the potential mechanism of retinal toxicity of SO [70]. And it is interesting that they involve for the first time a genetic-based response in these cases of vision loss.

It seems beyond doubt that the presence of SO produces an increase in pro-inflammatory cytokines and that this inflammation is greater if the so-called heavy silicones are used [71]. Intraocular complications secondary to inflammation are well known by ophthalmologists, but perhaps we are not so familiarized with the effects of neuroinflammation on the retina. Chronic inflammations accelerate neurodegenerative processes that include retinal structures [72]. Even more, chronic microglial activation is implicated in the mechanisms of neurotoxicity [73] and it has been demonstrated that emulsified silicone oil changes the activity level of retinal microglia [74].

However, Shimizu et al. found no significant correlation between retinal thickness change and cytokine levels, but sub-silicone oil fluid in eyes with SO contains higher concentrations of cytokines and lower concentrations of iron and can be biologically distinguished from anterior chamber fluid and vitreous fluid [75]. However, sub-silicone oil fluid and vitreous fluid samples were not taken from the same eyes. Similarly, no specific association with visual loss under SO tamponade was found [75].

Phototoxicity

Another indirect mechanism could be the phototoxicity of light on the ganglion cells [76], whose axons are rich in mitochondria and therefore particularly susceptible to light damage [77].

The macular pigment normally protects retinal cells from light damage, but silicone oil can dissolve the macular pigment and expose the cells to high light intensities. Herbert et al. speculated that phototoxicity may have a role, because SO transmits light more in the blue spectrum than aqueous [5]. Furthermore, SO would be able to solve fat soluble macular pigments, lutein and zeaxanthin, that are thought to protect the macula from photo-oxidative damage. They measured the macular pigment optical density using a modified confocal scanning laser ophthalmoscope and two wavelength autofluorescence techniques 3 weeks after SO removal. The results showed a substantially reduced macular pigment optical density in the eye that had SO compared to the fellow one. In addition, as a highly transparent vitreous substitute, SO increases the light exposure of retinal ganglion cells [76, 77]. Under normal conditions, mitochondria are able to remove reactive oxygen intermediates generated by oxidative stress resulting from light exposure of retinal ganglion cells [76]. Such light phototoxicity may occur during SO tamponade [78] or at the time of SO removal [76]. However, this phototoxicity hypothesis does not explain the characteristics of this visual loss and the problem of why this complication is not more common.

ROSO

In 2005 Cazabon et al. published three cases of unexplained vision loss after ROSO. In the discussion the authors tried to explain the phenomenon with the theory of an intraretinal excess of K^+ (called K^+ sink) [4]. It is well known that Müller cells buffer the extracellular potassium ion concentration by siphoning excess K^+ ions into the vitreous fluid (vitreous sink). When vitreous is replaced by SO, buffering of intraretinal increases of K^+ ions is achieved by a different route through aqueous fluid between the oil and the retina. When SO is removed there is a sudden dramatic physiochemical alteration in the aqueous milieu resulting in impaired buffering of K^+ ions. Thus, an increase of K^+ ions is produced in the retina, inducing excitotoxicity and eventually neuronal cell damage [4].

This theory has been refuted by other authors. Scheerlinck et al. analyzed several ions in the retro-oil fluid of 16 patients including two patients with SO-related visual loss. The authors did not find elevated K^+ levels making the 'potassium accumulation' hypothesis unlikely [13]. More recently Shimizu et al. analyzed 57 samples of sub-silicone oil fluid measuring major inflammatory cytokine levels and electrolytes and comparing them with those found in vitreous and anterior chamber fluid. Retinal thickness changes during SO endotamponade were not correlated with the presence of any inflammatory cytokines. Levels of ferrous iron, but not of potassium, showed a significant decrease in sub-silicone oil fluid compared with vitreous. So, the K^+ sink theory does not seem to be confirmed [75].

As a mere hypothesis, we think that the effect of acute hypotension that occurs when eliminating SO is not ruled out. The so-called decompression retinopathy, associated with cystoid macular edema has been related to other types of surgeries, including glaucoma [79] but it may have some role in unexplained vision loss after SO removal. In this sense another option is that an alteration in blood perfusion to the retina at the time of SO removal may be a contributing factor [4]. It would probably be interesting to analyze with OCTA some cases of retinopathy due to decompression and evaluate its effect on foveal vascularization.

Another hypothesis would be that SO causes chronic inflammation and therefore dysregulation, which over time

is compensated between pro- and anti-inflammatory factors, which are usually neuroprotective. Extracting SO eliminates the mechanical barrier and breaks the balance. But this is pure speculation.

However, there are some other interesting facts. Cazabon et al. suggested that another possible cause for visual loss could be the harmful effects of soluble growth factors and free radicals. SO would act as a physical barrier to these substances and removing it could allow more widespread dispersion and possibly damage by accumulation at the macula [4].

It is well known that photoreceptors constitutively express IL-27 receptor and respond to IL-27 signaling by producing anti-inflammatory molecules; and IL-10 is a suppressor of cytokine signaling 1 (SOCS1) through signal transducer and activator of transcription 1 (STAT1) -dependent mechanisms [80]. In an experimental model of retinal detachment [81] it has been demonstrated that interleukin IL-6 prevents photoreceptor cell death during periods of retinal separation from the retinal pigment epithelium. There is some recent work looking at different cytokines in the sub-silicone space [68] although it is concentrated in a better understanding of PVR. We have recently analyzed IL6, IL8, IL10, TGFb1, TGFb2 and TGFb3 concentration in the supernatant fluid by multiplex bead immunoassay Luminex 100 and the preliminary conclusion is that there are a combination of pro-inflammatory and anti-inflammatory cytokines and that this balance could be disrupted by eliminating SO [8].

However, the question is why it is not more common, which would be expected if the causes were simply changes in the environment. The low prevalence suggests some individual susceptibility [9]. Interestingly, Moussa et al. could not find an association between ROSO and Densiron in a multivariate analysis [82].

Conclusion

While the exact mechanisms of unexpected vision loss with SOIS or after ROSO remain unclear, individual factors might also play an important role in the pathogenesis. There are a large number of national datasets around the world collecting data on retinal diseases [83]. However, very few, if any, have been designed to look for visual loss following ROSO, and retrospective data analysis to establish a rate of visual loss or any risk factors is often difficult due to a lack of specific detail relating to conditions that could mimic this phenomenon. The attention of the vitreoretinal community should be focused on this topic and we are more and more aware of this important phenomenon.

Even though the prevalence of unexpected vision loss under SIOS and ROSO is low, patients should be informed about this possible complication. Silicone oil should be used with caution and for as short a time as possible, especially for patients with macula on situation and giant retinal tears [84]. Removal within the first 3 months with a stable retinal situation can be aimed for. A controlled intraocular pressure situation and SD-OCT control with regard to ganglion cell complex changes and emulsification are recommended as parameters for monitoring and earlier extraction.

It is important that we should as clinicians try to generate the safest environment for our patients. While no vitreoretinal surgeon is expected to be an expert in chemistry, we should all be aware of the fact that the purity of the SOs that we use could play an important role and is one thing that we should have controlled. Cases should be noted as a first step and included into the registries and communicated to the serious incident recording systems in different countries, at least those of the European Union. Manufacturers must also incorporate this information into the instructions for use of SO. Thus, we might be able to learn more about the subtle nature of pathophysiology and maybe find a way in the future to improve the situation for the patients.

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Declarations

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