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Intravitreal Injections for Macular Edema in Silicone Oil Filled Eyes

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Purpose: Macular edema is a known complication following complicated retinal detachment repair with silicone oil (SiO) tamponade. Limited previous research has not led to a consensus regarding the safety and efficacy of intra-SiO injections. Consequently, we aim to present our case series study on intra-SiO injections for postoperative macular edema.

Methods: A retrospective, single-center, case series study of eight eyes that developed macular edema postoperatively following complicated retinal detachment repair surgery with SiO tamponade, were treated with different forms of intravitreal injections such as steroids or anti-vascular endothelial growth factor (VEGF). The main outcome measures included visual acuity (VA), central subfield macular thickness (CSMT), and the type and number of injections.

Results: The mean age (±SD) of the patients was 64.75±8.9 years. The mean follow-up period (±SD) was 3.1±2.2 years. The mean (±SD) number of injections was 8.25±7.24. Mean (±SD) VA (in LogMAR) and CSMT before injections were 1.7±0.8 and 488 ±104 µm, respectively. At the last follow-up visit, the mean (±SD) VA and CSMT were 1.4±0.7 (p-value=0.45) and 396±184 µm (p-value=0.11), respectively. Overall, patients showed a partial response without a significant worsening of the macular edema and VA. No complications were reported following repetitive intravitreal injections.

Conclusion: Macular edema in silicone oil-filled eyes may be safely and effectively treated with intravitreal injections to halt its deterioration and preserve vision, especially when SiO removal is not anticipated in the foreseeable future.

Keywords: intravitreal injections, silicone oil, retinal detachment, Retina, optical coherence tomography, OCT, macular edema, cystoid macular edema, CME

Introduction

Silicone oil (SiO) is a commonly used intraocular tamponade in complicated vitreoretinal surgeries. It maintains the adhesions between the neurosensory retina and the retinal pigment epithelium (RPE), especially after complicated retinal detachments due to proliferative vitreoretinopathy (PVR), tractional detachment caused by proliferative diabetic retinopathy (PDR), viral retinitis, giant retinal tears, or trauma.[1,2]

SiO has been reported to cause retinal changes such as cystoid macular edema (CME), submacular fluid, macular epiretinal membrane (ERM) and undulated inner retinal layer.[3] The incidence of post-vitrectomy macular edema may range from 6% to 36%.[4–7] Macular edema (ME), either vitrectomy-related or SiO-induced, may involve increased growth and inflammatory factors, which have been reported in retro-SiO fluid studies, including interleukin 6 (IL-6) and LDH.[8] Other causes may be due to underlying diseases such as retinal vein occlusion (RVO) and diabetic retinopathy (DR).[9–13]

In complicated cases, when SiO removal may lead to recurrent retinal detachment, it is preferable to keep the SiO tamponade for an extended period to ensure retinal attachment and stabilization.[14,15] Unfortunately, these eyes may be more frequently prone to develop macular edema.[16] There are several potential treatment options available to address post-vitrectomy macular edema.[17–20] These treatments include topical and systemic nonsteroidal inflammatory drugs (NSAIDs), intravitreal anti-vascular endothelial growth factor (anti-VEGF) injections, and periocular, intravitreal, or

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systemic steroids. In cases of refractory macular edema after topical treatment or caused by co-existent retinal pathologies, intravitreal injections are the mainstay of treatment.[21]

The presence of SiO tamponade may affect the delivery and concentration of drugs injected into the vitreous cavity, and hence their effectiveness is questionable.[22,23] Limited research has been conducted on treating macular edema in silicone oil-filled eyes by intravitreal SiO injections. A few studies have shown that intravitreal SiO injections of anti-VEGF, steroids, or other therapeutic agents are effective for treating macular edema and preserving vision (Table 1).[22–37] Intra-SiO injections were not associated with special complications and were deemed to be safe. Nevertheless, there is still a lack of consensus regarding their efficacy, which restricts their application on clinical grounds. Consequently, we aim to share our experience in using intra-SiO injections for treating postoperative macular edema in patients after complicated retinal detachment repair surgery who were left with silicone oil tamponade.

Methods

This is a retrospective case series study from a single referral center. The study was conducted in accordance with the tenets of the Declaration of Helsinki and was approved by the institutional ethics committee of the Hadassah-Hebrew University Medical Center.

Eight eyes (eight patients), that had undergone a complicated retinal detachment surgical repair with silicone oil tamponade and had developed macular edema during follow-up visits, were included in the study. Macular edema, including intraretinal and subretinal fluid, was diagnosed based on Optical Coherence Tomography (OCT) imaging using Spectral Domain-OCT (Heidelberg Engineering, Heidelberg, Germany).[38,39]

The data collected included age, gender, previous medical and ocular history, type of intravitreal injections, number of intravitreal injections, treatment regimen, follow-up period, visual acuity (VA), central subfield macular thickness (CSMT) and features of the retinal fluid (intraretinal or subretinal fluid) based on OCT images. VA and CSMT values were obtained before the first intravitreal injection, before every subsequent injection and at the last follow-up.

All values of VA were converted to LogMAR. To provide numerical values for low visual acuities, the following conversions were made: LP (light perception) = 4 (Snellen equivalent 0.0001), HM (hand movement) = 3 (Snellen equivalent: 0.001), FC (finger counting) = 2 (Snellen equivalent: 0.01).[40]

Intravitreal injections were performed according to standard protocols using a 1 mm Luer lock syringe and 30-gauge needle that was inserted for 3–4 mm at the inferior quadrants. The injections were performed slowly to avoid mixing the drug with the silicone oil bubble. Intravitreal injections included Triamcinolone Acetonide (TA, 4mg/0.1cc), sustained-release dexamethasone intravitreal implant (Ozurdex, 0.7 mg) and anti-VEGF (Bevacizumab 1.25mg/0.05cc, Aflibercept 2mg/0.05cc).

Statistical Analysis

Data was recorded in Microsoft Excel and analyzed using GraphPad Prism 7.0. The *t*-test was used for statistical significance testing of interval scale parameters across two groups. For statistical analysis of VA in LogMAR or CSMT, the Wilcoxon signed rank test was used. The threshold for statistical significance was defined as P-value < 0.05.

Results

Eight eyes of eight patients were included in the study (5 males and 3 females). The mean age (±SD) of the patients was 64.75±8.9 years. All patients had undergone previous complicated retinal detachment surgery and were left with silicone oil tamponade. All eyes were pseudophakic except patient number 6 (Table 2). They all had similar type of SiO, 1300cs (centistokes), except patient #2 who had 5000cs SiO tamponade, and patient #7 who had Oxane® 5700cs heavy SiO (Table 2).

All eyes developed macular edema during their follow-up visits. The mean time (±SD) elapsed between retinal detachment surgery and the development of macular edema was 9±16.5 months (range 0.2–49.3 months). Intraretinal fluid (IRF) was the main component of this edema in all patients. In addition, patient #1 had submacular hemorrhage and patient #2 had subretinal fluid (SRF) (Table 2).

Table 1 Review Table

Study	Diagnosis	#Eyes	Injection Type	Main Outcome	Results	Complications
Da et al[22]	Vitrectomized ex vivo pig eye model filled with silicone oil	1	Intravitreal Triamcinolone	Investigation of the intraocular migration and distribution	TA droplet sank to the interface of silicone oil and aqueous almost immediately after injection and remained inside the silicone oil bubble for as long as 16 minutes. The in vitro results showed that, after the shrinkage of the droplet, TA gradually precipitated leaving only a lump of whitish crystalline residue inside the droplet for about 100 minutes.	After 100 min., TA quickly broke the interface and dispersed into the underlying aqueous within 15 seconds.
Baek et al[23]	Vitrectomized silicone oil filled eyes after tractional retinal detachment surgery	46	Intravitreal Bevacizumab	VA and CMT	Mean change in LogMAR visual acuity was larger in the injected group, 12 months postoperatively. It exhibited a lower mean and mean change in central macular thickness, 1 month postoperatively.	1 vitreous hemorrhage, 2 fibrovascular membrane proliferation, 2 IOP increase.
Falavarjani et al[28]	Vitrectomized silicone oil filled eyes with proliferative diabetic retinopathy and neovascular glaucoma	5	Intravitreal Bevacizumab	Neovascular glaucoma response	In all eyes, INV regressed and intraocular pressure was controlled within 7 days. Visual acuity improved in all eyes.	No
Altun et al[29]	Proliferative diabetic retinopathy with tractional diabetic macular edema under silicone oil	52	Intravitreal Dexamethasone Implant	BCVA and DME response	BCVA was statistically significantly higher in the injected group. DME treated with intravitreal Anti-VEGF was more prevalent in the non-injected group. There was no statistically significant difference in the proliferative vitreoretinopathy development rate between the groups.	No
Meshi et al[30]	Vitrectomized silicone oil filled eyes viral retinitis	2	Intravitreal Ganciclovir and Foscarnet	Viral retinitis response	Significant retinitis regression with long-term retinitis control was achieved in both patients throughout follow-up.	No
Imamura et al[31]	Macaque eyes filled with silicone oil in the vitreous cavity	8	Intravitreal vancomycin and ceftazidime	Evaluate the pharmacokinetics of intravitreal vancomycin and ceftazidime	The half-lives of vancomycin in the aqueous humor of normal, vitrectomized, and silicone oil-filled eyes were 29.4, 21.1, and 6.8 hours, respectively, and those of ceftazidime were 20.4, 5.2, and 3.1 hours, respectively.	There was no change in ECD and ERG was not declined after intravitreal injection in all groups.
Hsu CR et al[32]	Vitrectomized silicone oil filled eyes with macular edema	12	Intravitreal Dexamethasone implant	BCVA and CMT	The mean LogMAR BCVA improved at 1, 3, and 6 months, without a statistical significance. Maximal CMT resolution was observed at 1 month after intravitreal injection. The CMT value improved significantly at 1, 3, and 6 months.	No

(*Continued*)

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Table 1 (Continued).

Study	Diagnosis	#Eyes	Injection Type	Main Outcome	Results	Complications
Gao et al[33]	Vitrectomized silicone oil filled eyes with cystoid macular edema	2	Intravitreal Triamcinolone	VA and CME response	Immediately after injection, the TA appeared as a dome shaped pellet located in the silicone oil inferiorly. It then dissipated and was not visible 1 week after. Visual acuity and CME improved after 3 weeks and then got worse 1 month later. Repeated injections were successful.	No
Ahmadieh et al[34]	Vitrectomized silicone oil filled eyes with proliferative vitreoretinopathy	75	Intravitreal Triamcinolone	Visual acuity, rate of retinal attachment and recurrent PVR	Retinal reattachment was achieved in 32 eyes (84.2%) and 29 eyes (78.4%) in the adjunctive treatment and control groups, respectively, at 6 months. No statistically significant difference was observed between the 2 groups in visual acuity, rate of recurrent PVR, re-operation rate, and rise of intraocular pressure.	No
Spitzer et al[35]	Artificial vitreous space chamber filled with silicone oil.	1	Intravitreal Triamcinolone	Investigation of distribution and pharmacokinetics	Injected TA sank slowly through the silicone oil and started to sediment below the silicone oil bubble. No TA could be retrieved from the silicone oil bubble. In contrast, when a suspension of silicone oil and TA was prepared before injection, stable noncytotoxic amounts of TA could be retrieved for up to 90 days.	After mere injection, the sedimented TA crystals showed a pronounced cytotoxic effect.
Hsu J et al[36]	Vitrectomized silicone oil filled eyes with proliferative vitreoretinopathy related retinal detachment repair	20	Intravitreal Bevacizumab	VA, retinal reattachment rate or ERM formation	No significant difference in final VA, retinal reattachment rate or ERM formation was observed between injected and non-injected groups	No

Table 2 Basic Characteristics of the Patients Included in the Study

Patient	Age	Gender	Disease	Lens status	Type of Silicone Oil	Time from RD to ME (months)	Type of ME (IRF/SRF)	Follow up period (years)	Total injections	Type of injections	Additional Topical Treatment
p. 1	81	F	S/P RD, PVR, PCV	IOL	1300cs	2.5	IRF	1.6	5	B	NSAIDS
p. 2	70	F	S/P RD, PCV	IOL	5000cs	49.3	IRF + SRF	7.1	20	B	No
p. 3	57	M	S/P RD, PVR, PDR, DME	IOL	1300cs	2.2	IRF	1.7	2	1 TA, 1 Ozurdex	NSAIDS
p. 4	67	M	S/P RD, PVR, DME	IOL	1300cs	10.1	IRF	4	18	2 sub-tenon Kenalog 2 TA, 6 B, 8 A	NSAIDS & Steroids
p. 5	62	M	S/P RD, Schisis	IOL	1300cs	6	IRF	2.5	3	1 sub-tenon Kenalog 2 TA	NSAIDS & Steroids
p. 6	51	M	S/P RD, PDR, DME	Phakic	1300cs	2.5	IRF	1.8	1	TA	No
p. 7	64	M	S/P RD, PVR	IOL	5700 cs Heavy SO	7	IRF	5.2	10	TA	NSAIDS & Steroids
p. 8	66	F	S/P RD, PDR, DME	IOL	1300cs	0.2	IRF	0.8	7	B	No

Abbreviations: DME, Diabetic Macular Edema; ME, Macular edema; PCV, Polypoidal choroidal vasculopathy; PDR, Proliferative Diabetic Retinopathy; PVR, Proliferative Vitreoretinopathy; S/P, status post; RD, Retinal Detachment; RE, Right Eye; LE, Left Eye; IRF, Intraretinal Fluid; SRF, Subretinal Fluid; TA, Triamcinolone Acetonide; SO, Silicone oil; cs, centistoke; B, Bevacizumab; A, Aflibercept; F, Female; M, Male.

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The mean follow-up period (±SD) was 37.2±26.4 months (range 9.6–85.2 months). The mean number of injections throughout the study period was 8.25±7.24 (median 6, range 1–20). The mean number of injections per year was 3.15 ±2.94. The number and type of injections that each patient received are summarized in Table 2. Eyes that received anti-VEGF injections were treated by the Treat and Extend (T&E) protocol while patients who received steroid injections were treated by the Pro-Re-Nata (PRN) protocol. During the study period, patient #3 underwent SiO removal surgery 9 months after the RD repair surgery. Patient #6 underwent SiO removal surgery 6 months after the RD repair surgery, and this was combined with cataract extraction due to visually significant posterior subcapsular cataract. Five patients received topical anti-inflammatory treatment before proceeding to intravitreal injections when macular edema was suspected to have an inflammatory component (Irvine-Gass Syndrome, Table 2).

The mean (±SD) visual acuity (VA, in LogMAR) and central subfield macular thickness (CSMT) before injections were 1.7±0.8 and 488±104 μm, respectively (Table 3). At the last follow-up visit, the mean (±SD) VA (LogMAR) and CSMT were 1.4±0.7 and 396±184 μm, respectively. In a comparison between VA and CSMT before injections and at the last follow-up, there was no statistically significant difference (p-value=0.45 and 0.11, respectively), but there was a clear trend of improvement (Table 3). During the treatment period, the eyes showed, in general, a fair response without significant worsening of the macular edema and VA (Figures 1, 2 and 3). Even though patients #3 and #6 underwent silicone oil removal surgery, the macular edema persisted, and they continued treatment with anti-VEGF injections afterwards.

Two out of eight patients experienced side effects. Patient #3 experienced partial emulsification of the SiO 3 months following intravitreal Ozurdex injection and the SiO was extracted 9 months after the initial RD repair surgery. Patient #6 had progression of posterior subcapsular cataract 3 months after intravitreal TA injection. The SiO was removed in combination with cataract extraction, 6 months post the initial RD repair surgery, with improved vision during follow-up visits, postoperatively. None of the patients experienced elevated intraocular pressure, severe vision loss, retinal detachment, or endophthalmitis.

Discussion

Silicone oil (SiO) filled eyes may develop macular edema postoperatively.[41] Although macular edema may be related to underlying diseases, it may also be silicone oil-induced or vitrectomy-related, as underlying inflammation has been shown to play a role. The incidence of macular edema after vitrectomy with SiO tamponade may range between 6% to

Table 3 Clinical Outcomes

Patient	VA		CSMT		Time from 1st injection until last follow up (years)
	Before injections	Last F/U	Before injections	Last F/U	
P. 1	3	2	371	415	1.4
P. 2	2	2	373	275	3
P. 3	2	2	534	269	1.5
P. 4	2	1.3	652	775	2.1
P. 5	0.5	0.3	472	328	1.7
p. 6	2	0.8	610	331	1.5
p. 7	1	0.6	474	229	4.2
p. 8	1	2	420	553	0.7
Mean ±SD	1.7 ± 0.8	1.4 ± 0.7	488 ± 104	396 ± 184	2.1 ± 1.1
P-value	0.45		0.11		

Abbreviations: VA, Visual Acuity in LogMAR; CSMT, Central Subfield Macular Thickness (μ), F/U, Follow-up.

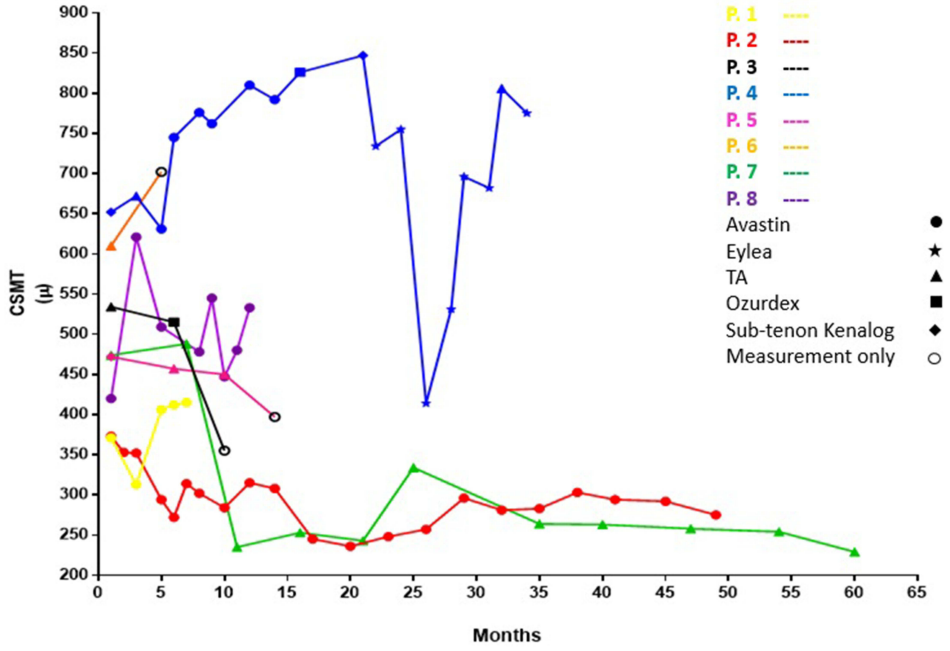

Figure 1 Central Subfield Macular Thickness (CSMT, in microns) graph for all patients (P. 1 to 8) at the day of receiving injection along the study period. On each point, the type of injection is represented by a sign as shown on the right side of the figure.

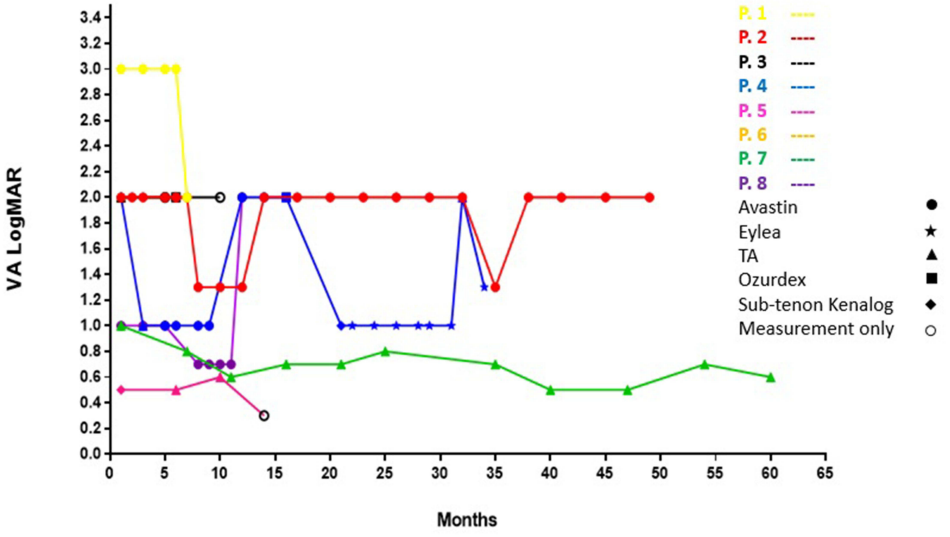

Figure 2 Visual acuity graph in LogMAR for all patients (P. 1 to 8) at the day of receiving injection along the study period. On each point, the type of injection is represented by a sign as shown on the right side of the figure.

36% as reported by multiple studies.[4] In addition, a longer duration of silicone oil tamponade may increase the risk of developing macular edema.[3,16,41–43] In our study, macular edema developed, on average, 9 months postoperatively (range 0.2–49.3 months). Yang et al reported an earlier incidence, 5.7 months after surgery.[16]

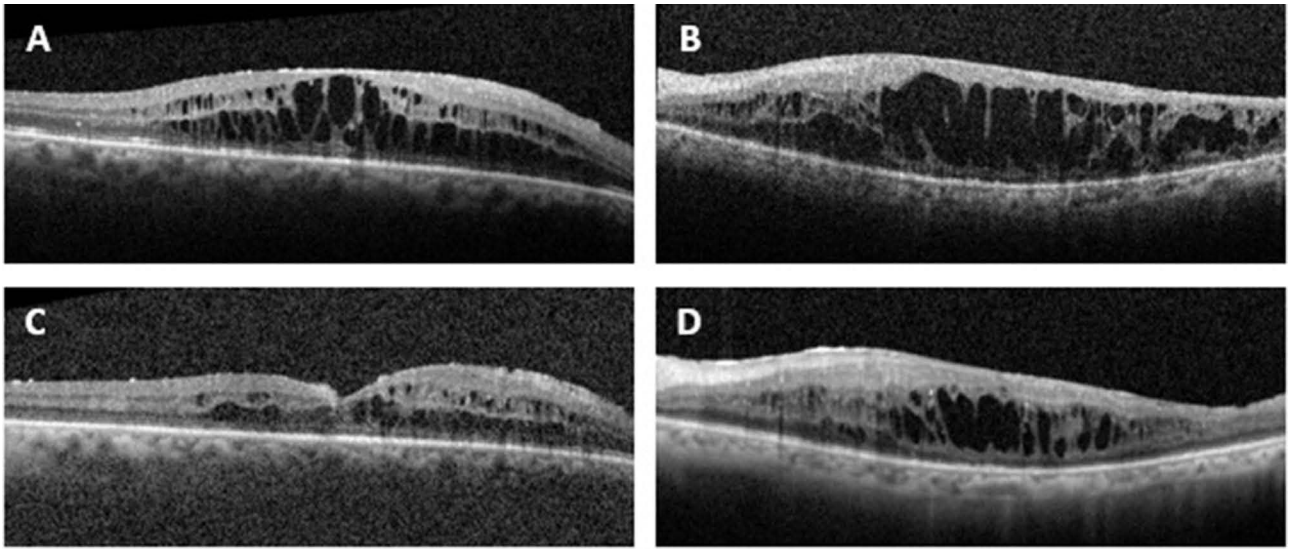

Figure 3 B-mode OCT horizontal section scans of two patients. (**A**) Patient #3 before receiving intra-silicone oil injection of Ozurdex. (**B**) Patient #4 before receiving intra-silicone oil anti-VEGF (Aflibercept) injection. (**C**) Patient #3 four months after receiving intra-silicone oil Ozurdex injection, showing improvement of the macular edema. (**D**) Patient #4 three months after receiving two intra-silicone oil anti-VEGF (Aflibercept) injections with 6 weeks interval between both injections, showing improvement of the macular edema.

The vitreous cavity has been increasingly used as a reservoir for drugs to treat intraocular diseases.[44] Any intraocular tamponade may alter the elimination rate of drugs from the vitreous cavity.[45] Therefore, the presence of SiO can affect drug pharmacokinetics and pharmacodynamics, which may interfere with the macular edema response to intravitreal injections. Previous studies reported on using intravitreal injections of anti-VEGF or steroids for treating macular edema in patients after vitrectomy and SiO tamponade.[27,28] Several studies showed promising results and good response to treatment,[23,29] however, others concluded that SiO may not be a good candidate as a drug reservoir (Table 1).[22,46,47] Unlike other studies which reported on using mainly one type of intra-SiO injection during their investigation, here we present a case series using repetitive multiple types of injections, in the same eye if needed, as well, including different Anti-VEGF agents and steroids (Table 2).

In our study, VA and CSMT did not significantly improve after intra-SiO injections, as was reported by others.[32,34,36] Nevertheless, there was a trend of improvement in both aspects (Table 3, Figures 1, 2 and 3). The insignificance may be attributed to the small number of participants and further studies with bigger samples are needed. However, leaving patients with untreated macular edema may cause irreversible deterioration of vision and intractable macular damage.[48,49] Therefore, treating these complicated cases, at least in order to preserve vision and prevent the worsening of macular edema, is valuable and worth considering.

In terms of side effects of intra-SiO injections, none of our patients experienced endophthalmitis or severe vision loss. There were no cases of elevated intraocular pressure, visual disturbances, or destabilization of the retinal attachment status. Special complications were absent as reported by other studies (Table 1). Emulsification of SiO was observed only in one patient (patient 3) three months after Ozurdex injection, and the SiO was removed shortly afterwards. However, it is unclear whether the Ozurdex injection promoted SiO emulsification, or if it is the natural course of the SiO lifetime. All patients were pseudophakic, except one patient (patient #6) who developed a visually significant posterior subcapsular cataract three months after intravitreal TA injection, and hence SiO was removed in combination with cataract extraction. Even though both patients underwent silicone oil removal surgery, the macular edema persisted, and they continued treatment with intravitreal anti-VEGF injections thereafter. Hence, the macular edema was mainly due to their underlying retinal disease and less likely vitrectomy-related or SiO-induced.

Regarding patients who received intra-SiO TA injections, TA was observed accumulating in the inferior vitreous cavity under the SiO during their follow-up visits (Figure 4). TA injection was performed using a 30-gauge needle,

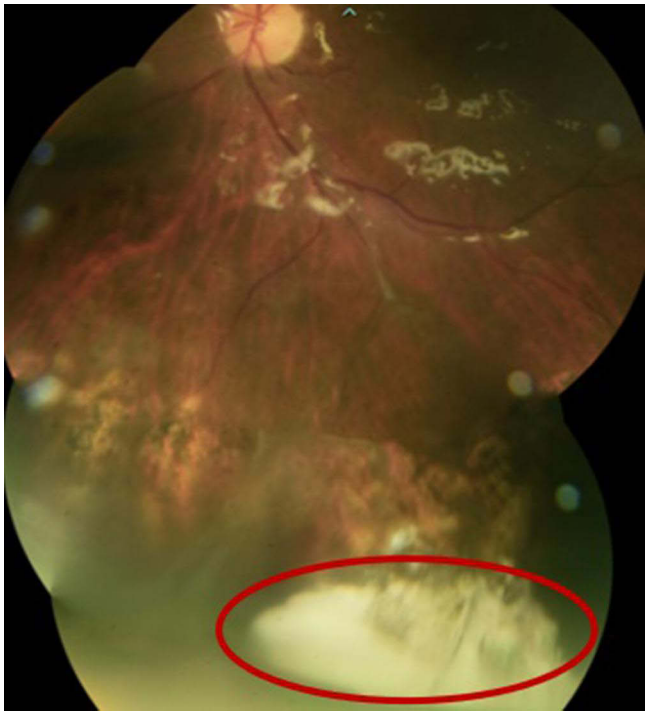

Figure 4 A Fundus picture focusing on the inferior retina of the left eye of patient 4, showing whitish material inferiorly underneath the silicone oil tamponade representing TA accumulation (the red circle).

according to a standard protocol similar to anti-VEGF injections. Then, TA was injected slowly, in order to lower the risk of TA mixture with the SiO. Spitzer et al demonstrated that when TA is injected into SiO-filled eyes, biologically active concentrations are present only below the oil bubble and no TA is retained in the bubble, possibly because silicone oil has a lower specific weight than TA preparations. Furthermore, high local concentrations of TA crystals may be present on the retinal surface because of sedimentation. This sediment may interfere with vision when it is present in the macular area.[35] Nevertheless, none of our patients complained about floaters or decrease of vision related to the presence of TA in the vitreous cavity.

Accumulation of drug substance in the inferior meniscus of the fluid underneath the SiO may be gravity-driven and was reported by Falavarjani et al while treating neovascular glaucoma (NVG), after vitrectomy and SiO endotamponade, with intravitreal anti-VEGF (Bevacizumab) injections.[23] In our study, there were no reports of anti-VEGF substance accumulation under the SiO. Interestingly, Falavarjani et al injected 2.5mg bevacizumab instead of the more commonly used dose of 1.25 mg, with good clinical response and no signs of retinal toxicity. Consequently, in patients treated with intra-SiO 1.25mg Bevacizumab injections, higher doses may be considered for persistent macular edema. However, future studies are required to further validate this issue.

Certain limitations should be considered in our study, including its retrospective nature, a small number of participants, a relatively short period of follow-up for some of the patients and a small number of injections. Best-corrected visual acuity was not available, and the measured Snellen visual acuity was converted to LogMAR. In addition, multiple patients were treated with additional anti-inflammatory topical drops and their effect on macular edema cannot be analyzed separately. Nonetheless, they were used mostly as a trial to postpone or obviate the need for intravitreal injections.

Conclusions

SiO-filled eyes may develop macular edema postoperatively that requires treatment. Based on our case series study, intra-SiO injections of anti-VEGF or steroids were safe and relatively effective. Both types were not associated with serious

complications. Consequently, macular edema in silicone oil-filled eyes may be safely and effectively treated with intravitreal injections, to halt deterioration and preserve or improve vision, especially when SiO tamponade removal is not on the horizon.

Data Sharing Statement

The datasets generated or analyzed during the current study are available from the corresponding author upon a reasonable request.

Ethics Approval and Consent to Participate

The study was conducted in accordance with the tenets of the Declaration of Helsinki and was approved by the institutional ethics committee of the Hadassah-Hebrew University Medical Center (HMO-0082-23). As this was a retrospective study, we obtained a waiver of informed consent from the institutional ethics committee of the Hadassah-Hebrew University Medical Center. There is no publication of identifiable information, such as images or case details.

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Disclosure

The authors have no relevant financial or non-financial interests to disclose.

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