



Intravitreal Silicone Oil with a Silicone-free versus a Siliconized Syringe

Intravitreal injections (IVIs) pose associated risks that become substantial given their widespread application. Risks such as intraocular pressure (IOP) elevation,¹ noninfectious endophthalmitis,² and floaters³ may result from the presence of intravitreal silicone oil (SiO).

The prevalence of SiO is high even in asymptomatic patients, with >75% of individuals receiving IVIs with siliconized syringes presenting some intravitreal SiO.^{3,4} Although most cases tend to be asymptomatic or exhibit spontaneous improvement in complaints,² vitrectomy for SiO removal is not uncommon,³ and filtering surgeries might be needed to manage sustained IOP elevations.¹

The primary source of SiO contamination in IVIs is most likely the syringe. Silicone oil is routinely used in the lubrication of various syringes and can detach from the inner lining when interacting with medication, air bubbles, and agitation.^{5,6} Siliconized needles can also be a source of SiO contamination in SiO-free syringes.⁷

Considering the large scale in which IVIs are performed globally and the relevance of SiO-related adverse events, we developed a study to compare the release of SiO in patients undergoing IVI with siliconized or SiO-free syringes.

This double-masked, randomized, single-center, parallel clinical trial included IVI-naïve diabetic subjects, who were subjected to 6 monthly bevacizumab IVIs. The protocol was approved by the Institutional Review Board of Federal University of Sergipe and registered at <https://ensaiosclinicos.gov.br/rg/RBR-10tn82jt>. This study followed all tenets of the Declaration of Helsinki.

Eligibility criteria included age >18 years, diabetic retinopathy with indication for intravitreal bevacizumab, transparent ocular media, and best-corrected visual acuity between 20/25 and 20/400. Exclusion criteria were prior IVIs, advanced glaucoma, other macular degenerations, retinal dystrophies, uveitis, prior vitreoretinal surgery, contraindication to antiangiogenics, intraocular surgery within last 3 months, pregnancy, breastfeeding, and severe cardiovascular diseases.

Participants were randomly assigned to 2 groups using a proprietary algorithm: Zero Residual Silicone Oil-free 0.2 ml (ZR-SF) (SJJ Solutions) and Becton-Dickinson Ultra-Fine (BD-UF) Insulin 0.3 ml syringe (Becton-Dickinson). Both syringes were attached to siliconized needles.

Participants and examiners were masked to treatment allocation, and doctors who performed the IVIs did not examine the participants. Subjects received 6 monthly injections and were evaluated on the slit lamp before the first injection, at day 3, and 4 weeks after each injection. Each evaluation included anterior segment biomicroscopy, tonometry, and fundus examination. Participants were queried about pain, discomfort, or any symptoms experienced. Best-corrected visual acuity was assessed at the first and last visits.

Bevacizumab (1.25 mg/0.05 mL) was drawn under aseptic conditions by a single trained professional using a siliconized filter

needle to draw from the vial. Intravitreal injections were performed by trained ophthalmologists (V.S.C. and F.M.M.) under topical anesthesia, in the temporal superior quadrant, 3.5 to 4 mm from the limbus.

Primary outcome was the presence of SiO at any time point. Secondary outcomes were maximum quantity of SiO, Frankfurt Floater and World Health Organization Five Well-Being Index scores at baseline and at 6 months, IOP, best-corrected visual acuity, and presence of anterior chamber cells, pain, and hyperemia throughout the study. Oval and transparent droplets were presumed to be SiO, and were graded according to [Table S1](#) (available at www.ophtalmologyretina.org).

Statistical analysis was performed using Python 3.9 and JASP version 0.18.3.0 (<https://jasp-stats.org>). Descriptive statistics are presented. According to data type and distribution, analysis of covariance, repeated measures analysis of variance, Student *t* tests, Wilcoxon signed-rank tests, and chi-square tests were performed.

A total of 55 eyes from 47 participants completed the protocol, from which 25 (53%) were female, with mean age of 60.7 ± 8.13 years. Grouping yielded 26 eyes in BD-UF and 29 in ZR-SF group. In BD-UF group, 14 (54%) eyes were from females and 10 eyes (38%) were right eyes. In ZR-SF group 18 (62%) eyes were from females, and 16 (55%) were right eyes. [Table S2](#) (available at www.ophtalmologyretina.org) presents complimentary descriptive statistics.

Presumed SiO (pSiO) was detected in 43 (78%) eyes, with 25 (96%) in BD-UF group against 18 (62%) in ZR-SF group ($P = 0.016$). [Figure S1](#) (available at www.ophtalmologyretina.org) illustrates the difference in maximum pSiO levels. The maximum overall grading was 1+ or lower in only 8 (31%) eyes in BD-UF group, against 25 (86%) in ZR-SF ($P < 0.001$).

A significant difference in pSiO grading was observed between evaluations ($P < 0.001$), with a difference between injection 1 and injections 5 ($P = 0.003$) and 6 ($P = 0.001$), and injection 2 against injections 5 ($P = 0.042$) and 6 ($P = 0.023$). When comparing syringes over time, this trend is only observed in the BD-UF group, which can be clearly visualized in [Figure 2](#). A significant difference ($P = 0.027$) was observed between syringes.

No significant differences were observed when comparing any of the secondary outcomes.

Our findings demonstrate that the amount of intravitreal pSiO is higher in individuals receiving injections with the siliconized syringe compared with the SiO-free one. Although this was expected,⁶ pSiO was detected in many subjects in the SiO-free syringe group, albeit in a much smaller quantity. The most likely explanation for this finding is the use of siliconized needles either for filtering or injection.⁷

Another important finding of this study was the characterization of pSiO accumulation with repeated IVIs. This hypothesis had been suggested previously,⁴ but lacked empirical confirmation.

Our study did not find statistically significant differences in IOP and sterile inflammatory events, possibly because of the relatively small number of injections and small sample size.^{1,2} We also did not observe significant differences in quality-of-life questionnaires and floaters, which might be attributed to the relatively low educational level of this study's subjects.

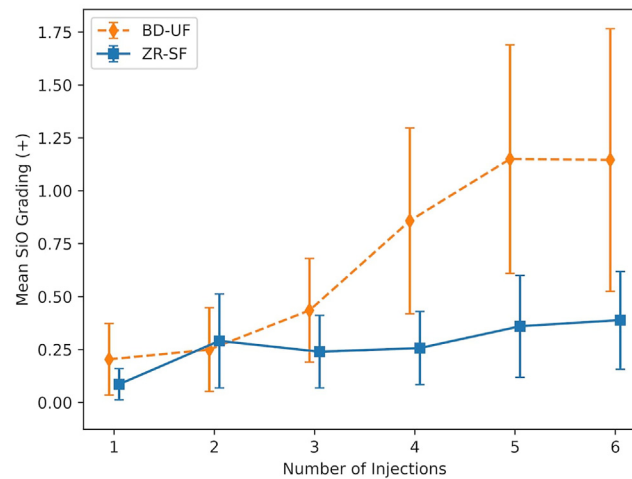


Figure 2. Mean SiO grading per injection. Line graph depicting mean SiO gradings for each group. A clear difference is observable between groups starting from the fourth injection, and a positive correlation between number of injections and grading of intravitreal SiO was observed mainly in participants of the BD-UF group, indicating a cumulative pattern of SiO deposition after multiple intravitreal injections with a siliconized syringe. BD-UF = Becton-Dickinson Ultra-Fine; SiO = silicone oil; ZR-SF = Zero Residual Silicone Oil-free.

The limitations of this study include the use of siliconized needles, a short follow-up period, a subjective method for quantifying pSiO that was incapable of measuring subvisible particles and analyzing the composition of these, and restricted sample size. Although sufficient for the main objective, this sample size might have provided insufficient statistical power for secondary outcomes.

In conclusion, individuals receiving monthly IVI of bevacizumab with a SiO-free syringe demonstrated significantly lower quantity of presumed intravitreal SiO droplets. No significant difference was observed in symptoms, IOP, and postinjection inflammation. Therefore, the authors recommend using SiO-free syringes for IVIs to mitigate SiO-related complications.

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Footnotes and Disclosures:

Disclosures:

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No animal subjects were used in this study.

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Abbreviations and Acronyms:

BD-UF = Becton-Dickinson Ultra-Fine; **IOP** = intraocular pressure; **IVI** = intravitreal injection; **pSiO** = presumed silicone oil; **SiO** = silicone oil; **ZR-SF** = Zero Residual Silicone Oil-free.

Keywords:

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References

1. Eadie BD, Etminan M, Carleton BC, et al. Association of repeated intravitreal bevacizumab injections with risk for glaucoma surgery. *JAMA Ophthalmol*. 2017;135:363–368.
2. Melo GB, Figueira ACM, Batista FAH, et al. Inflammatory reaction after aflibercept intravitreal injections associated with silicone oil droplets released from syringes: a case-control study. *Ophthalmic Surg Lasers Imaging Retina*. 2019;50:288–294.
3. Thompson JT. Prospective study of silicone oil microdroplets in eyes receiving intravitreal anti-vascular endothelial growth factor therapy in 3 different syringes. *Ophthalmol Retina*. 2021;5:234–240.

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4. Melo GB, Dias Junior CS, Morais FB, et al. Prevalence of silicone oil droplets in eyes treated with intravitreal injection. *Int J Retina Vitreous*. 2019;5:34.
5. Melo GB, Dias Junior CS, Carvalho MR, et al. Release of silicone oil droplets from syringes. *Int J Retina Vitreous*. 2019;5:1.
6. da Cruz NFS, Polizelli MU, Muralha FP, et al. Ocular inflammation after agitation of siliconized and silicone oil-free syringes: a randomized, double-blind, controlled clinical trial. *Int J Retina Vitreous*. 2022;8:41.
7. Melo GB, da Cruz NFS, do Monte Agra LL, et al. Silicone oil-free syringes, siliconized syringes and needles: quantitative assessment of silicone oil release with drugs used for intravitreal injection. *Acta Ophthalmol*. 2021;99:e1366–e1374.