Trabeculectomy with augmented adjunctive mitomycin-C and bevacizumab for persistent silicone oil induced glaucoma

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ABSTRACT

Purpose: Was to provide a solution to the problem of persistent silicone oil induced glaucoma (SOIG), which represents a common type of intractable glaucoma that usually adds to the hazards of complicated vitreoretinal surgeries. The trial aimed to evaluate the efficacy and safety of an augmented adjunctive approach of various lines combined with surgical glaucoma treatment. Patients and Methods: Twenty-four eyes of 24 patients presented with SOIG were included in this interventional case series clinical trial. All eyes underwent trabeculectomy with intraoperative mitomycin-C (MMC) application plus bevacizumab injection (1.25 mg) together with early postoperative topical MMC drops (0.03 mg/ml). The main outcome results included the cumulative probability of surgical success, intraocular pressure (IOP) values, number of anti-glaucoma drugs needed, corrected distance visual acuity, any reported complication or additional intervention. Results: This combined approach achieved a cumulative probability of success of 0.765 at the end of the 24 months study period and was in a range of 0.883 at 2 weeks and 0.647 at 6 months. Complete success was achieved in a range of 82.4% at 2 weeks and 35.3% at 18 and 24 months. There were always highly statistically significant decreases in the mean IOP values and numbers of the given IOP-lowering drugs at all postoperative time points (P was always <0.001). All complications were controlled with no major drawbacks. No significant adverse effects were caused by this combined approach. Conclusion: The combined approach could present an efficient, safe, familiar, and applicable treatment strategy for the treatment of persistent SOIG. It can provide a favorable long-term outcome representing a simple solution to the problem of persistent SOIG, which represents a challenging type of refractory glaucoma.

Keywords: Combined adjunctive trabeculectomy, topical mitomycin-C, silicone oil induced glaucoma, subconjunctival bevacizumab

Introduction

Silicone oil (SO) has been used as a vitreous substitute for long-term...
intraocular tamponade in retinal surgery since the 1960s. The oil is usually left for a period of 2–6 months depending on the type of SO, retinal detachment (RD) and surgeon’s choice. In some cases of complex RDs that oil may be left for a longer period.\textsuperscript{1,2}

The incidence of SO-induced glaucoma (SOIG) from the SO study report was 8%.\textsuperscript{3} The incidence varies widely among studies, ranging from 2.2% in 6 months to 56% in 8 months, with recent studies demonstrating a lower prevalence.\textsuperscript{4} Hence therefore, the longer that the oil is present in the eye, the more likely it is to cause secondary glaucoma. Preexisting glaucoma/angle pathology, diabetes, steroid induced response, trauma, aphakia,\textsuperscript{5} SO oil in the anterior chamber (AC), emulsified SO, heavy tamponade agents and rubeosis have been shown to be associated with a significant intraocular pressure (IOP) rise postoperatively.\textsuperscript{6} Myopia and anatomical failure were negative risk factors.

There are several proposed mechanisms of persistent SOIG including infiltration of the trabecular meshwork by silicone bubbles, chronic inflammation and synechial angle closure, trabeculitis (macrophage oil induced endocytosis), rubeosis iridis, migration of emulsified and nonemulsified SO into the AC, and/or idiopathic open angle glaucoma.\textsuperscript{5} In addition to a glaucomatous pressure dependent optic neuropathy SO may also infiltrate the optic nerve, resulting in a granulomatous retrolaminar reaction.\textsuperscript{7}

Treatment of SOIG depends largely on the clinical presentation and the mechanism of IOP elevation. Management may include topical medications alone or in conjunction with surgical and/or laser interventions. Early SO removal may result in IOP control; however, this must be weighed against the risk of recurrent RD.\textsuperscript{6} A persistent IOP rise necessitates glaucoma filtration surgery. However, SOIG can cause refractory glaucoma and present a surgical challenge\textsuperscript{8,9} because the standard filtration surgery may be technically difficult, associated with a poor prognosis and increased the risk of complications.

\textbf{Purpose}
To provide a feasible solution to the problem of persistent SOIG, by evaluating the efficacy and safety of a combined approach. This approach combined three lines of treatment realizing the additional beneficial effects of trabeculectomy with intraoperative mitomycin-C (MMC) application plus bevacizumab injection together with early postoperative topical MMC.

\textbf{Design}
Interventional case series clinical trial. The postoperative evaluation and follow-up period was 24 months.

\textbf{Setting}
Ophthalmology Department of Benha University Hospital, Benha, Egypt.

\textbf{Patients and Methods}
This trial included 26 eyes of 26 patients diagnosed with persistent SOIG. The definition of SOIG was any eye that had SO tamponade presented with IOP of \(\geq 24\) mmHg and/or IOP elevation by \(\geq 10\) mmHg than the preoperative value that sustained for \(\geq 6\) weeks.\textsuperscript{10} Persistent SOIG was defined as sustained IOP of \(\geq 21\) mmHg after SO removal. The indication for filtration surgery was uncontrolled IOP by SO removal and maximum tolerable anti-glaucoma therapy. Trabeculectomy was carried out at least 8 weeks after the SO removal surgery.

Two patients were excluded from the study because they missed postoperative follow-up visits. The mean age of the 24 included patients was 53.53 \(\pm\) 14.04 years. Informed consents were obtained from all patients after thorough explanation of the treatment approach and surgical procedures with their possible side effects and potential complications, with approval of the Research Ethics Committee at Benha faculty of Medicine, Benha University.

\textbf{Exclusion criteria}
Neovascular glaucoma, previous glaucoma surgery, patients with complicated retinal surgeries or with recurrent RD after SO removal, patients who missed \(\geq 2\) subsequent postoperative visits or did not complete the 24 months follow-up period, and patients who were not willing to give consent.

Baseline data included:
- Baseline IOP was recorded as the highest IOP after SO removal, without the use of any anti-glaucoma drugs
- Ocular hypotensive medications-their class, number, duration, and evidence of chronic inflammation were reported
- Corrected distance visual acuity in decimal notation, using standard Snellen charts.

Complete ocular examination; anterior segment slit-lamp examination, gonioscopy using Goldman contact lens, fundus examination (optic nerve head, vertical cup-disc ratio, and nerve fiber layer if possible) and history of systemic diseases (diabetes, hypertension, collagen diseases, hepatitis, etc.). At baseline: Systemic hypertension, mean HbA1c levels, HB%, lipid profile as well as prothrombin time and concentration were controlled as indicated.

\textbf{Surgical approach}
All procedures were performed under local peribulbar anesthesia by the same surgeon (Saeed AM).
Subconjunctival saline injection was first done at the site of the proposed flap to facilitate dissection of the adherent conjunctiva. Trabeculectomy was done through a fornix based conjunctival flap at the selected site of the loose, healthy conjunctiva. Half-thickness scleral flap (3.5 mm × 3.5 mm) was created and dissected into the clear cornea. A cellulose microsponge soaked in 0.3 mg/ml MMC solution (Mitomycin-C Kyowa®, Kyowa Hakko Kogyo, Tokyo, Japan) was applied to the under surface of the scleral flap for 3 min. Then, the entire area was lightly and copiously washed with irrigating saline. Standard trabeculectomy of equal size (two bites aside) was created by Kelly punch, peripheral iridectomy was made by scissors; the scleral flap was closed with two 10/0 nylon sutures. The conjunctiva was tightly closed with 8/0 Vicryl sutures (Vicryl® polyglactin 910; Ethicon Inc., Johnson and Johnson, Somerville, NJ, USA). At the end of the procedure, intracameral, and subconjunctival bevacizumab (1.25 mg of Avastin®, Roche) was injected. Any intraoperative complication was reported.

Postoperatively, MMC 0.03 mg/ml drops were prepared using artificial tears as the vehicle and were applied 3 times a day for 1–2 weeks according to the bleb appearance. To reduce systemic absorption of MMC, patients were instructed to occlude their puncti by digital compression for 5 min. Prednisolone acetate 1% and gatifloxacin 0.3% (Optipred® and Tymer®, Jamjoom Pharma, Jeddah, Saudi Arabia) eye drops were administered 5 times daily for 3 weeks. Cyclopentolate 1.0% (Cicloplejico® eye drop; Alcon CUSI, S.A. El Masnou-Barcelona, Spain) was administered 3 times daily for 2 weeks. Anti-glaucoma eye drops were tailored according to IOP values for every patient at each study visit aiming at keeping IOP ≤21 mmHg with the least tolerable drugs.

The postoperative study visits were at 2 days, 1, 2 weeks, 1, 3, 6, 12, 18, and 24 months with documentation of IOP, number of IOP-lowering drugs, best corrected visual acuity (BCVA), gonioscopy, fundus examination, complications, and additional maneuvers required to maintain filtration or to handle complications, as well as any additional surgical intervention. Efficacy, in terms of postoperative IOP reduction, was expressed as suggested by the Guidelines on Design and Reporting of Glaucoma Surgical Trials. Additional visits and investigations were done when required.

Statistical analysis
The collected data were tabulated and analyzed using SPSS version 16 software IBM. Survival curves were used to assess and compare the probability of success among the studied group. Categorical data were presented as number and percentage. While continuous variables were expressed as mean and standard deviation, with ANOVA and paired t-test and Spearman’s correlation coefficient (r) as tests of significance. The accepted level of significance in this work was stated at 0.05 (P < 0.05 was considered significant and P < 0.001 was considered highly significant).

Results
The outcome data for all patients were summarized and represented according to the guidelines’ definitions of success. Survival curve [Figure 1] demonstrates the cumulative probability of surgical success and the survival Table 1 shows the numbers in the study group analyzed at each postoperative follow-up time point of 2 weeks, 1, 3, 6, 12, 18, and 24 months. Scatter plots illustrate the proportions of study subjects who meet the criteria for success at 1, 6, 12, 18, and 24 months postoperatively [Figures 2-6]. The mean and SD values of the IOP all over the study period were represented in Table 2 and Figure 7. The mean and SD of baseline and postoperative numbers of IOP-lowering drugs all over the study period were shown in Table 3 and Figure 8. The correlation between the duration of SO tamponade and the mean values of baseline IOP, BCVA, and terminal BCVA at 24 months were demonstrated in Table 4. The intraoperative, early and late postoperative complications reported were demonstrated in Table 5.

Survival table demonstrates the cumulative probability of success and shows the numbers analyzed at each follow-up point at 1, 6, 12, 18, and 24 months [Table 1].

Scatter plots illustrate the proportions of study subjects who meet the criteria for success at 1, 6, 12, 18, and 24 months postoperatively [Figures 2-6].

There was a highly statistically significant decrease in the mean IOP when comparing the baseline value to the postoperative values at all postoperative time points (P was always <0.001) [Table 2].
There was a highly statistically significant decrease in the mean number of IOP-lowering drugs when comparing the baseline value to the postoperative values at all postoperative time points ($P$ was always <0.001).

**Table 1: Survival table demonstrates the cumulative probability of success and shows the numbers analyzed at each follow-up point at 1, 6, 12, 18 and 24 months**

<table>
<thead>
<tr>
<th>Surgical outcome at 1-month</th>
<th>Complete success (%)</th>
<th>Qualified success (%)</th>
<th>Failure (%)</th>
<th>Complete failure (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical outcome at 6 months</td>
<td>15 (62.5)</td>
<td>5 (20.8)</td>
<td>4 (16.6)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Surgical outcome at 12 months</td>
<td>16 (66.6)</td>
<td>8 (33.3)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Surgical outcome at 18 months</td>
<td>13 (54.2)</td>
<td>11 (45.8)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Surgical outcome at 24 months</td>
<td>11 (45.8)</td>
<td>10 (41.6)</td>
<td>2 (8.4)</td>
<td>2 (8.4)</td>
</tr>
</tbody>
</table>

**Figure 2**: Scatter plots illustrating the proportions of study subjects who meet the criteria for success at 1-month

**Figure 3**: Scatter plots illustrating the proportions of study subjects who meet the criteria for success at 6 months

**Figure 4**: Scatter plots illustrating the proportions of study subjects who meet the criteria for success at 12 months

**Figure 5**: Scatter plots illustrating the proportions of study subjects who meet the criteria for success at 18 months

**Figure 6**: Scatter plots illustrating the proportions of study subjects who meet the criteria for success at 24 months

**Figure 7**: A linear representation of the mean intraocular pressure values all over the study period
The mean BCVA showed a statistically significant decrease when comparing the baseline value (0.18 ± 0.12) to the 24 months' value (0.13 ± 0.11).

There was a negative correlation between the duration of SO tamponade and the mean baseline IOP and BCVA as well as the mean 24 months IOP and BCVA. The correlation was only statistically significant between the mean duration of SO tamponade and the mean baseline BCVA values.

Transient hypotony was reported in four eyes as an early postoperative complication; however, it persisted and resulted in surgical failure only in two cases reported at 2 weeks and 1-month. The two eyes achieved complete success thereafter by a simple tight bandage, topical steroid withdrawal, and conjunctival resuturing in one of them without further complications.

No significant complications were reported following MMC topical drops application (signs of allergic reactions (marked pruritus, periocular erythema, and redness), blebitis, punctual stenosis, or epiphora).

Additional interventions were reported as follows: Suturing conjunctival wound leak, suturelysis, and prophylactic intracameral and intravitreal antibiotic injection (in a case of blebitis) (one eye for each intervention).

Discussion

Glaucoma is ranked second to cataract as a late complication of SO injection. SOIG is refractory to treatment and presents a surgical challenge because the underlying mechanism may often be multifactorial in nature. SO removal preceded trabeculectomy to prevent blockage of the ostium by SO bubbles and failure of the surgery. However, SO removal alone did not result in successful IOP control because of probable complete synechial angle closure, trabecular meshwork (TM) sclerosis and collapse
due to prolonged contact with the emulsified SO bubbles, edema in the TM as a result of postoperative inflammation, and small SO droplets obstructing the TM[12] that has been confirmed pathologically as well.[13,14] Budenz et al. retrospectively reviewed the outcomes of surgical intervention for secondary glaucoma in 43 eyes that had pars plana vitrectomy (PPV) with SO injection.[15] The authors found that patients who underwent SO removal alone to control IOP were more likely to have persistent IOP elevation, and possibly required reoperation for glaucoma, while patients who underwent concurrent SO removal and glaucoma surgery were more likely to develop hypotony. Jonas et al. found that 93.4% (185 out of 198) patients with SOIG had normalization of IOP after SO removal[16] that was in contrary to Flaxel et al. and Moisseiev et al. who reported that elevated IOP persisted in all eyes (62 eyes) after SO removal[17] and 10 out of 11 eyes after removal of emulsified oil[13] respectively. Thus, in this work glaucoma surgery was carried out at least 8 weeks after the SO removal surgery.

Conventional glaucoma filtration has a limited role in the management of SOIG after PPV + SO injection, so adjuvant like MMC is used to prevent fibrosis and failure of trabeculectomy.[18] This study has a certain advantage as adding the effect of bevacizumab to that of MMC on the wound healing process in dealing cases of persistent SOIG.

Anti-vascular endothelial growth factor (VEGF) strongly influenced scar tissue formation during wound healing by reducing the amount of cytokines (e.g., fibroblast growth factor, VEGF) released from the vessels to the site of injury by blocking angiogenesis. Bevacizumab may also indirectly render the scleral flap less adherent to its original site during the immediate postoperative period, through its direct action of fibroblast modulation.[18] In addition, the wound modulator properties of anti-VEGF have revealed a dose-dependent inhibition of fibroblast proliferation exploring their use at the time of trabeculectomy, but with watertight conjunctival closure to overcome the problem of delayed wound healing.[19]

It has been demonstrated that MMC penetrates subconjunctival tissues after application over an intact conjunctiva.[20] Mietz and Kriegstein[21] applied topical MMC over the filtering bleb postoperatively and reported reduced IOP without increasing complications. Early postoperative application of MMC drops entails safe and convenient aid for successful functioning bleb.

In the current trial, MMC drops was applied in low dose (0.03 mg/ml, 3 times daily) and for short duration (1-2 weeks), thus avoided the complications of allergic reactions and punctual stenosis reported by Khong and Muecke.[22]

The combined approach applied in the current study achieved a cumulative probability of success of 0.765 at the end of the 24 months study period and was in a range of 0.883 at 2 weeks and 0.647 at 6 months. Complete success was achieved in a range of 82.4% at 2 weeks and 35.3% at 18 and 24 months. The used approach could also achieve a highly statistically significant decrease in the mean IOP when comparing the baseline value to the postoperative values at all postoperative time points (P was always <0.001). This should be considered in relation to the mean numbers of the given IOP-lowering drugs, where there was also a highly statistically significant decrease in the mean number of IOP-lowering drugs when comparing the baseline value to the postoperative values at all postoperative time points (P was always <0.001).

No similar studies using this combined approach for the treatment of persistent SOIG have been found in the literature. This combined adjunctive approach achieved higher success when compared to other studies reporting on SOIG. Budenz et al.[15] reported that success was achieved in 56% and 48% of eyes at 24 and 36 months respectively. Their surgical treatment consisted of SO removal alone in 74% patients; glaucoma surgery (trabeculectomy with or without antifibrotic agents, glaucoma drainage implant surgery and/or modified Schocket procedure) was performed with SO removal in 19% of patients.

The success rate achieved by the combined approach applied in the current work also exceeds that reported by other different lines of treatment used in SOIG. Wong et al. reported that topical and systemic anti-glaucoma medications controlled IOP in 30% of eyes. SO removal alone did not allow any of the eyes to achieve normal IOP. However, with combined SO removal and medical therapy, only 25% achieved normal IOPs. Control of IOP was achieved in 71.4% eyes that underwent surgical intervention (35.7% of that underwent trabeculectomy with MMC post-SO removal). Trans-scleral cyclophotocoagulation has shown successful IOP control in 74-82% of patients after 1-year although the visual function was poor in their patients.[23,24]

Trans-scleral cyclophotocoagulation (TSDCP) was used as an adjunctive therapy to the external filtering surgery for treatment of patients with medically uncontrolled glaucoma persisting after intravitreal SO removal.[25] Malhotra et al.[26] reported an overall IOP control of 82% with all lines of anti-glaucoma therapy, SO removal, trabeculectomy with MMC, AC shunts, and cyclodestructive procedures which are comparable to the end result of this work (76.5%) and moreover both are certainly better than Honavar et al.[21]
The results of this trial were comparable to other studies that had used TSDCP to treat SOIG with successful IOP control reported in 66–82% of patients at 1-year.[24-28]

In agreement with Pakravan et al.[29] who used MMC topical drops application for management of bleb failure, the patients of the current study similarly did not report any significant complication. This is because MMC was used in low concentration, for a short duration, and in conjunction with topical steroid therapy. Glaucoma drainage implants offer a good surgical option in cases of refractory glaucoma associated with SO.[28] But there is a possibility of SO escape via the glaucoma drainage tube.[30] Al-Jazzaf et al. found a cumulative probability of success of 76% at 1-year with the inferotemporal placement of Ahmed’s valve to reduce the chance of SO flow into the tube.[31] Although Ahmed’s valve provides a comparable cumulative success to our used approach, it had many drawbacks and disadvantages as; difficult positioning of the plate due to the presence of scleral buckle and tightly adherent conjunctiva, limitation of free full range ocular movement, tube obstruction by SO bubbles, tube-cornea touch, tube exposure, increased liability for hypotony, shallow AC, postoperative endophthalmitis especially with inferotemporal positioning of the device, increased requirements for penetrating keratoplasty and subsequent cataract extraction.[32]

The results of the current study showed that the duration of SO tamponade had an adverse impact on IOP and BCVA both before the surgery (baseline) as well as the end of the study period (at 24 months), that was only statistically significant with the mean baseline BCVA values. This was also supported by Han et al.[33] who suggested early removal of SO as it had been noted to have reduced the risk of secondary glaucoma. This could be due to SO emulsification, prolonged contact between SO bubbles and trabecular tissue resulting in impaired aqueous outflow, epi-retinal membrane proliferations under SO, SO-induced keratopathy and neuropathy.

All intraoperative, early and late postoperative complications were mild and all could be managed safely without adding more risk or significant long-term impact to the patients.

The developed hypotony may be due to the trabeculectomy procedure itself [as in a case of over filtration that improved by tight bandage and steroid withdrawal, and another one of a buttonhole that improved by conjunctival suturing]. MMC application may also play a role in hypotony development as an early complication. AC inflammation was attributed to the underlying pathology (diabetic changes and repeated intraocular surgery). Corneal edema was reported in expected cases of previous prolonged SO duration with preoperative keratopathy and higher IOP values. The high thin cystic blebs with dellen formation were known to be due to MMC application with a possible consequence of blebitis that reported in one case. Mild blebitis could be managed with aggressive topical broad-spectrum antibiotics, and passed safely without further complications. Bevacizumab had also a role in ischemic bleb formation especially in the early postoperative period. The additional interventions passed safely with no further complications.

**Conclusion**

The augmented adjunctive approach combined various lines of treatment realizing the additional beneficial effects of trabeculectomy with intraoperative MMC application plus bevacizumab injection together with early postoperative topical MMC drops. This approach could present an efficient, relatively safe, familiar and applicable treatment strategy for the problem of persistent SOIG. It could provide a favorable long-term outcome representing a simple solution to the problem of persistent SOIG, which represents a challenging type of refractory glaucoma.

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**Conflicts of interest**

There are no conflicts of interest.

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