Attenuation of Iodine 125 Radiation With Vitreous Substitutes in the Treatment of Uveal Melanoma

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Objective: To demonstrate attenuation of radiation from iodine 125 (I^125) to intraocular structures using liquid vitreous substitutes.

Methods: Four candidate vitreous substitutes were tested for attenuation using empirical measurement and theoretical calculation. In vitro and ex vivo cadaveric dosimetry measurements were obtained with lithium fluoride thermoluminescent dosimeters to demonstrate the attenuation effect of vitreous substitution during I^125 simulated plaque brachytherapy. Theoretical dosimetry calculations were based on Monte Carlo simulation.

Results: In a cylindrical phantom at a 17-mm depth, liquid vitreous substitutes as compared with saline showed significant reduction of radiation penetration (48% for 1000-centistoke [cSt] silicone oil [polydimethyl-n-siloxane], 47% for 5000-cSt silicone oil [polydimethyl-n-siloxane], 40% for heavy oil [perfluorohexylpolydimethyl-n-siloxane], and 35% for perfluorocarbon liquid [perfluoro-n-octane]). Human cadaveric ex vivo measurements demonstrated a 1000-cSt silicone oil to saline dose ratio of 35%, 52%, 55%, and 48% at arc lengths of 7.6, 10.6, 22.3, and 28.6 mm from the plaque edge, respectively, along the surface of the globe. Monte Carlo simulation of a human globe projected attenuation as high as 57% using 1000-cSt silicone oil.

Conclusions: Intraocular vitreous substitutes including silicone oil, heavy oil, and perfluorocarbon liquid attenuate the radiation dose from I^125. Cadaveric ex vivo measurements and Monte Carlo simulation both demonstrate radiation attenuation using 1000-cSt silicone oil at distances corresponding to vital ocular structures.

Clinical Relevance: Attenuation of radiation with silicone oil endotamponade in the treatment of uveal melanoma may significantly reduce radiation-induced injury to vital ocular structures.

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mhor to the affected structures, and systemic conditions such as diabetes mellitus.\textsuperscript{7,10,11} No treatment for radiation maculopathy or papillopathy has been proven to be effective in a randomized clinical trial.

The target dose to the tumor apex in the COMS was 85 Gy (to convert to rad, multiply by 100).\textsuperscript{12,13} Current plaque design methods are based on the parameters of tumor base diameter and tumor height. Collateral injury to the optic nerve and macula has been retrospectively observed to occur at threshold doses of approximately 35 Gy and 21 Gy to each structure, respectively.\textsuperscript{14,15} The maximum tolerance dose to the optic nerve for blindness is 50 Gy based on the Radiation Therapy Oncology Group recommendation of 1.8 Gy per fraction, 5 fractions per week.\textsuperscript{16} Using the COMS protocol, plaque design is not altered even if collateral injury is anticipated to occur.

Radiation injury to vital structures may be shielded with the use of materials such as lead that have a higher effective atomic number and density than tissue. However, solid metals are not amenable to use within the eye.

Based on these considerations, we present a new method to reduce radiation penetration through the eye from plaque brachytherapy. This study demonstrates the ability of 4 liquids commonly used in vitreoretinal surgery to attenuate gamma radiation from \textsuperscript{125}I. In the future, placement of one of these liquids in the eye at the time of plaque brachytherapy may significantly reduce collateral injury to adjacent structures in vivo (Figure 1).

**METHODS**

Four candidate vitreous substitutes were tested for attenuation effect using both empirical measurement and theoretic calculation methods. The measurements were conducted using individually calibrated high-sensitivity lithium fluoride thermoluminescent dosimeters (TLDs) (TLD-100H; Thermo Fisher Scientific, Inc, Waltham, Massachusetts). Dosimetry calculations based on a Monte Carlo code were also performed to verify the measured attenuation effect. In vitro and ex vivo dosimetry was studied to simulate the attenuation effect of vitreous substitution during \textsuperscript{125}I plaque brachytherapy for the treatment of uveal melanoma.

**RADIATION ATTENUATION EFFECT OF 4 CANDIDATE VITREOUS SUBSTITUTES**

The radiation attenuation effect was assessed for 4 substances commonly used in vitreoretinal surgical procedures. They are the following: (1) 1000-centistoke (cSt) silicone oil (SILIKON 1000 silicone oil; Alcon Laboratories, Inc, Fort Worth, Texas); (2) 5000-cSt silicone oil (ADATO SIL-OL 5000; Bausch & Lomb, Inc, Rochester, New York); (3) heavy oil (Densiron 68; Geuder AG, Heidelberg, Germany); and (4) perfluorocarbon liquid (perfluoro-n-octane) (Perfluoron; Alcon Laboratories, Inc). A sodium chloride saline solution was used as a control. Both 1000-cSt and 5000-cSt silicone oils are purified polymeric polydimethyl-siloxane, approved by the US Food and Drug Administration for long-term retinal endotamponade. The 2 oils differ only in polymer length and thus viscosity; 1000-cSt silicone oil is less viscous than 5000-cSt silicone oil. Densiron 68 heavy oil is a blend of polydimethyl-n-siloxane and perfluorohexylcote that is denser than water. It is not approved by the US Food and Drug Administration but is available in Europe for retinal endotamponade. Perfluoro-n-octane is a US Food and Drug Administration-approved heavy liquid used in vitreoretinal surgery.

**TLD Measurement**

High-sensitivity lithium fluoride TLDs, $3 \times 3 \times 0.5$ mm in dimension, were calibrated and assigned individual chip factors to compensate for the difference in individual chip responses. The estimated SD of the TLD readings for the dose range used in this study is 2.3%. The corrected TLD readings were further converted to radiation doses using a third-order polynomial regression formula, which has an adjusted $r^2$ greater than 0.99000994 for the dose range of interest. A thin plastic cylindrical cup, 26 mm in diameter and 20 mm in height, was filled with $9.0$ mL, or 17 mm in height, of each candidate substance. A brachytherapy \textsuperscript{125}I source (MED3631-A/M; North American Scientific Medical, Chatsworth, California) was placed above the cylinder, and 4 TLD-100H chips (Figure 2) were placed on the bottom. The whole system was put on a plastic slab to simulate radiation backscatter in a human body. The TLD chips were irradiated for approximately 25 hours for each attenuating solution. The measured doses were further corrected for source decay and collecting time difference.

**Monte Carlo Calculation**

Theoretical calculations of the attenuated radiation dose were performed using a general-purpose Monte Carlo code.
(MCNPX_26C). This standard modeling package, capable of simulating coupled photon-electron interactions with media in a 3-dimensional heterogeneous geometry system, has recently been studied by our group and found accurate in predicting dose distributions in tissue from 125I brachytherapy seeds. The calculated radial dose function in water of an 125I source from this module showed good agreement with the consensus data of the American Association of Physicists in Medicine Task Group No. 434 and the Monte Carlo calculations of Rivard.18 The discrepancy was within ±5% for radial distance less than 3.0 cm and gradually increased to ±14% at a distance of 7.0 cm.

The TLD measurement geometry described earlier was also simulated using Monte Carlo calculations to verify the measured attenuation. Monte Carlo simulation requires estimation of the effective atomic number of each vitreous substitute. The 1000-cSt silicone oil is a polydimethyl-n-siloxane (C3H8O)n polymer with a repeating middle chain. The 5000-cSt silicone oil has a similar composition except for a slightly higher viscosity due to the longer average chain length. The exact average chain length for each substance is protected by trade secret. However, a comparison using the Monte Carlo model of polydimethyl-n-siloxane effective atomic numbers of 1 and 10 repeating middle chains found minimal difference in calculated attenuation effect. The Monte Carlo calculation was not performed for Densiron 68 heavy oil as the proportional mixture of polydimethyl-n-siloxane and perfluorohexyl-octane is protected by trade secret. However, a comparison using the Monte Carlo model of polydimethyl-n-siloxane effective atomic numbers of 1 and 10 repeating middle chains found minimal difference in calculated attenuation effect. The Monte Carlo calculation was not performed for Densiron 68 heavy oil as the proportional mixture of polydimethyl-n-siloxane and perfluorohexyl-octane is protected by trade secret. However, a comparison using the Monte Carlo model of polydimethyl-n-siloxane effective atomic numbers of 1 and 10 repeating middle chains found minimal difference in calculated attenuation effect.

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The measured and calculated penetration factors of the 4 candidate substances compared with those of saline are listed in Table 2. The most robust attenuation effect was from 1000-cSt silicone oil (48%), followed by 5000-cSt silicone oil (47%), heavy oil (40%), and perfluorocarbon liquid (35%). The attenuation results of Monte Carlo calculations ranged from 42% to 52% and were within 6% to 11% agreement of measured results (Table 2 and Figure 4).

Ex vivo testing demonstrated attenuation of radiation to structures opposite the plaque (Table 1). With a plaque placed 7.6 mm temporal to the optic nerve, mean attenuation was 35% at the proximal optic nerve, 52% at the distal optic nerve, 55% at the equator, and 48% at the ora serrata.

Monte Carlo Modeling

A 15-seed eye plaque, 16 mm in diameter, was simulated using a Monte Carlo model to account for the intrinsic seed properties, the physical seed geometry, and the gold plaque. The calculation was based on a spherically symmetric globe with an equatorial diameter equal to 24 mm and filled with water or replacement silicone oil. The sclera was modeled as a 1-mm-thick, separate spherical layer surrounding the globe. The dose ratios at the same vital structures were estimated as earlier.

RESULTS

The measured and calculated penetration factors of the 4 candidate substances compared with those of saline are listed in Table 2. The most robust attenuation effect was from 1000-cSt silicone oil (48%), followed by 5000-cSt silicone oil (47%), heavy oil (40%), and perfluorocarbon liquid (35%). The attenuation results of Monte Carlo calculations ranged from 42% to 52% and were within 6% to 11% agreement of measured results (Table 2 and Figure 4).

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Measurements at the macula (4.2 mm from the plaque edge) were highly variable, and some dose ratios were higher than 1.000. The TLD localization was accurate to the nearest millimeter. However, measurements near the plaque margin are increasingly susceptible to dose variation because of inaccuracies in localization. The overall experimental error can be assessed by including the following uncertainties: (1) the SD of TLD readings is 2.5%; (2) plaque and TLD localization inaccuracy of up to 1 mm may result in measurement errors as high as 9.2% at the macula, 6.9% at the proximal optic nerve, 3.0% at the distal optic nerve, 1.6% at the equator, and 0.5% at the ora serrata; and (3) a slight tilt of the plaque may cause a significant change in the doses delivered to the points near the plaque edge such as the macula and proximal optical nerve.
Monte Carlo simulation of the human globe projected a dose reduction of 25% at the macula, 35% at the proximal optic nerve, 57% at the equator, and 58% at the ora serrata (Table 3).

Table 1. Human Ex Vivo Measurements Comparing Radiation Attenuation of 1000-centistoke Silicone Oil vs Vitreous at Selected Points on the Surface of the Globe

<table>
<thead>
<tr>
<th>Point Location</th>
<th>1000-cSt Silicone Oil vs Human Vitreous, Measured Dose Ratio</th>
<th>Dose Ratio, Mean (SD)</th>
<th>Attenuation, Mean, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>A Macula</td>
<td>1.393&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.75</td>
<td>25</td>
</tr>
<tr>
<td>B Proximal optic nerve</td>
<td>1.306&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.65</td>
<td>35</td>
</tr>
<tr>
<td>C Distal optic nerve</td>
<td>Not measured</td>
<td>0.50</td>
<td>52</td>
</tr>
<tr>
<td>D Equator</td>
<td>0.548</td>
<td>0.435</td>
<td>57</td>
</tr>
<tr>
<td>E Ora serrata</td>
<td>0.584</td>
<td>0.425</td>
<td>58</td>
</tr>
</tbody>
</table>

Abbreviations: cSt, centistoke; NA, not applicable.
<sup>a</sup>Ratios of doses were measured using high-sensitivity thermoluminescent dosimeters with and without 1000-cSt silicone oil substitution.
<sup>b</sup>The elemental composition and mass density are protected by trade secret; thus, the effective atomic number could not be calculated.

Table 2. In Vitro Comparison of Radiation Attenuation by Vitreous Substitutes Relative to Saline

<table>
<thead>
<tr>
<th>Solution</th>
<th>TLD Measurement</th>
<th>SD</th>
<th>MC Calculation</th>
<th>MC Calculation vs TLD, % Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline</td>
<td>1.000</td>
<td>2.18</td>
<td>1.000</td>
<td>NA</td>
</tr>
<tr>
<td>1000-cSt silicone oil</td>
<td>0.518</td>
<td>1.97</td>
<td>0.484</td>
<td>−6.6</td>
</tr>
<tr>
<td>Heavy oil</td>
<td>0.601</td>
<td>2.78</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>5000-cSt silicone oil</td>
<td>0.527</td>
<td>0.88</td>
<td>0.484</td>
<td>−8.2</td>
</tr>
<tr>
<td>Perfluorocarbon liquid</td>
<td>0.653</td>
<td>1.29</td>
<td>0.581</td>
<td>−11.0</td>
</tr>
</tbody>
</table>

Abbreviations: cSt, centistoke; MC, Monte Carlo; NA, not applicable; TLD, thermoluminescent dosimeter.
<sup>a</sup>Normalized penetration factor of vitreous substitutes, 17 mm in height, from iodine 125 radiation.
<sup>b</sup>The elemental composition and mass density are protected by trade secret; theoretical penetration could not be calculated.

Table 3. Monte Carlo Modeling of Radiation Attenuation Comparing Radiation Attenuation of 1000-centistoke Silicone Oil vs Saline at Selected Points on the Surface of the Globe

<table>
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<tr>
<th>Point Location</th>
<th>1000-cSt Silicone Oil vs Saline, Calculated Dose Ratio</th>
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Abbreviations: cSt, centistoke; NA, not applicable; NC, not calculated.
<sup>a</sup>Ratios of doses were calculated at various ocular structures on a simulated globe using a Monte Carlo code with and without 1000-cSt silicone oil substitution.

Monte Carlo simulation of the human globe projected a dose reduction of 25% at the macula, 35% at the proximal optic nerve, 57% at the equator, and 58% at the ora serrata (Table 3).

The COMS supported the use of globe-conserving 125I brachytherapy<sup>12</sup>; however, nearly half of patients lose ambulatory vision (visual acuity ≤20/200) within 3 years.<sup>3</sup> An effective means of shielding the macula and optic nerve from collateral injury has been heretofore unproven. In this article, we have demonstrated the ability of silicone oil to significantly reduce radiation penetration. Substitution of vitreous with silicone oil at the time of plaque brachytherapy may allow for complete treatment of the tumor with reduced collateral injury and improved visual outcomes.

Radiation blockade is routinely performed by radiation oncologists in other parts of the body. Radio-opaque materials (usually metal) are constructed to focus the shape of the radiation field. Unfortunately, it is extremely difficult to fixate a solid metal within the eye. Liquid metals such as mercury would be limited by toxicity.

Figure 4. In vitro measurement and Monte Carlo calculation of penetration of iodine 125 (125I) gamma radiation through a 17-mm depth of vitreous substitutes. cSt indicates centistoke; PFCL, perfluorocarbon liquid (perfluoro-n-octane). The effective atomic number of heavy oil is protected by trade secret; theoretical penetration could not be calculated.
In 1990, Finger et al. injected liquid iodinated contrast dyes, including iohexol and iophendylate, into rabbit eyes to block radiation. Marked attenuation of radiation occurred; however, the solubility of the dyes resulted in rapid clearance from the globe. Dye toxic effects, including intraocular inflammation and retinal degeneration, limited clinical applicability of these agents.

The most notable technique in current use for the prevention of collateral injury from plaque brachytherapy is the collimated plaque developed by Astrahan et al. The standard COMS gold plaque provides excellent posterior and lateral shielding in the orbit, but there is no shielding anterior to the scleral plane. By recessing the radioactive seeds into slots within the collimated plaque, side scatter is sharply reduced. This design may be particularly helpful for reducing optic nerve and macular damage in the treatment of tumors adjacent to vital structures; however, the design does not reduce the dose to structures directly across from the plaque.

In this study, we performed detailed theoretical calculations and in vitro and ex vivo measurements to confirm the radiation attenuation effect of 1000-cSt silicone oil, 5000-cSt silicone oil, heavy oil, and perfluorocarbon liquid. The 1000-cSt silicone oil is a commercially available product that has the most robust attenuation effect. It has been shown to be nontoxic, nonpyrogenic, nonmutagenic, nonirritating, and readily removable, which make it an attractive tool for long-term endotamponade in vitreoretinal surgery. These attributes make silicone oil attractive as a radiation-blocking substance.

LIMITATIONS

Clinical application of this technique requires consideration of the effect of silicone oil on the tumor as well as tolerability of the procedure. Silicone oil endotamponade should not alter the radiation dose delivered to the tumor as the oil will not be present between the tumor and the radioactive plaque. A backscatter effect from the silicone oil, which might result in increased dose to the tumor, was calculated to be negligible using Monte Carlo modeling.

In the first 2 globes tested in this study, the relative radiation dose was greater than 1,000 for TLD chips near the plaque. In globe 1, chips placed 4.2 and 7.6 mm from the plaque margin resulted in relative radiation dose ratios greater than 1,000, and in globe 2, only the chip 4.2 mm from the plaque margin showed a dose ratio greater than 1,000. These findings are inconsistent with the measurements in globe 3 as well as Monte Carlo calculations. Possible causes of these findings include the effect of a notched plaque (globe 1), imprecision in TLD localization, and possible plaque edge tilt. The first globe used a notched plaque. While the notch was placed 180° from the TLDs, it is possible that some radiation was unshielded. For this reason, the notched plaque was not used for subsequent tests. Dose variability may proportionally increase with proximity to the plaque margin due to difficulty in placing and stabilizing a 3-mm square chip. Progressively meticulous attention was paid to plaque localization with each successive test. Finally, plaque tilt may significantly affect delivery of the radiation dose, resulting in reduction of the dose to the tumor apex (approximately 10%-20% for each millimeter of tilt) as well as an increase of the dose to structures lateral to the tilted edge.

CLINICAL APPLICATION

The target dose to the tumor apex in the COMS was 85 Gy. The optic nerve has a tolerance dose for blindness of 50 Gy when irradiated with a regular high-dose-rate teletherapy scheme (1.8 Gy per fraction, 5 fractions per week). Based on the linear quadratic model, the tolerance dose for blindness is equivalent to a dose of approximately 60 Gy with a continuous low-dose-rate irradiation for 168 hours (7 days). However, retrospective studies have demonstrated clinical evidence of optic neuropathy and maculopathy with threshold doses of 35 Gy and 21 Gy to each structure, respectively.

The potential benefit of radiation shielding may be calculated from a cohort of patients with choroidal melanoma. In a prospective study of 42 patients treated with 125I plaque brachytherapy, the median total radiation doses were 36.2 Gy (range, 6.56-240.5 Gy) to the fovea and 42.8 Gy (range, 6.47-145.5 Gy) to the optic nerve. Post hoc analysis of this cohort reveals that a 25% reduction of radiation to the macula would result in 21% fewer patients subjected to the 21-Gy threshold dose, while a 50% reduction in the macular dose would result in 42% fewer patients subjected to the threshold dose. A similar calculation at the optic nerve indicates that a 25% reduction in radiation to the optic nerve would result in 24% fewer patients sustaining the threshold dose of 35 Gy or higher, and a reduction by 50% would reduce this number of susceptible patients by 52%.

CONCLUSIONS

We have described a novel finding that silicone oil and other vitreous substitutes attenuate gamma radiation from an 125I source. Our empirical data and theoretical calculations both demonstrate that silicone oil attenuates radiation in the human eye by as much as 55% compared with saline.

In the future, this technique may be applied by performing vitrectomy and silicone oil endotamponade at the time of plaque treatment of uveal melanoma. The melanoma will still be directly irradiated using the established protocol, but radiation to other healthy ocular structures may be shielded. Vitrectomy with silicone oil endotamponade is a common and established surgical technique used in the treatment of retinal detachment, diabetic retinopathy, and macular hole. Safety and tolerability of short-term silicone oil endotamponade is well established.

Future in vivo studies are required to confirm the safety and efficacy of simultaneous plaque placement, vitrectomy, and silicone oil endotamponade followed by plaque and oil removal. Attenuation of injury to vital ocular structures is calculated to reduce clinical radiation-induced complications by approximately 50%. This new technique may improve our ability to preserve vision in patients treated with plaque brachytherapy for choroidal melanoma.
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Correspondence: Tara A. McCannel, MD, PhD, Department of Ophthalmology, Jules Stein Eye Institute, University of California, Los Angeles, 100 Stein Plaza, Los Angeles, CA 90095 (tmccannel@sei.ucla.edu).

Author Contributions: Dr Oliver had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Additional Contributions: Bradley R. Straatsma, MD, JD, provided insightful comments on the manuscript.

REFERENCES