Silicone Oil as an Intra-Ocular Tamponade in Vitrectomy: Morphological and Clinical Studies to Evaluate its Biological Effects

Ph.D. Thesis

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INTRODUCTION

In vitreoretinal surgery silicone oil has been employed for over four decades as an intraocular tamponade in the treatment of cases of complicated retinal detachment.

The eye's tolerance for this material has been examined in numerous morphological studies, both for animal and human eyes. It is well known that the silicone-oil filled eye has a higher risk of developing problems with cataract, glaucoma, or keratopathy. Also, on the basis of a number of studies it may be inferred that it is possible for the oil to infiltrate various proximate tissues of the eye. Vacuoles characteristic of silicone oil have been found to occur in the stroma of the cornea and iris, the trabecular meshwork, the ciliary body, and in the retina. The first studies reporting hypothesised oil-infiltration into the optic nerve were published in the 1980s. Earlier studies had only been able to infer such infiltration, since examination using optical microscopy could not determine the origin of the observed empty vacuoles.

One side-effect of the usage of silicone oil which occurs with especially high frequency is the development of cataract; this can occur even in cases where the oil is removed only a short time after its intra-ocular implantation. The exact mechanism of cataract development in such cases is not known, but we may hypothesise that the problem arises from the direct contact of the oil with the bag of the lens; either from possible inherent toxicity of the oil, or because of changes to the metabolic processes of the lens-bag consequent on its modified environment. If such lens-cloudiness is severe enough to impair vision, there is the possibility of cataract extraction from the oil-filled eye. If possible, it will then be expedient to remove the silicone oil and the cataract in a combined operation performed in a single session.

OBJECTIVES

1. Aims of the investigation of extra-ocular migration of silicone oil

According to the results of certain histological investigations, silicone oil used as an intra-ocular tamponade may under some circumstances infiltrate the optic nerve, even the remote section of the nerve behind the lamina cribrosa. In the light of these observations some authors have raised the possibility that the silicone oil might even migrate to the brain. The first set of investigations was intended to clarify the validity of this hypothesis.

The investigations sought to answer the following questions:

- Can extraocular migration of the silicone oil be demonstrated?
- By what mechanism can silicone oil migrate to the central nervous system?

Another objective of the study was to investigate the possible role of macrophages in the tissue-migration of silicone oil; this mechanism has been hypothesised in a number of published studies.

2. Aims of the investigation into the effects of migration of silicone oil into the optic nerve on the basis of an animal study

Our own previous studies as well as published information in the literature give rise to the hypothesis that silicone oil employed as an intra-ocular tamponade can migrate to extra-ocular tissues of the central nervous system. The animal-study part of the investigation sought to answer the following question:

- Is it possible to demonstrate the migration of silicone oil to the more remote sections of the optic nerve?

Besides the immediate objective of investigating the long-term (after 1 year) effects on optic-nerve morphology of the use of high-viscosity (5000 cSt) silicone oil as an intra-ocular tamponade in vitrectomy, it was of further interest to establish the precise number of nerve-fibres in the optic nerve of the rabbit, an animal which is frequently used as an

experimental model for ophthalmic studies. We also wished to investigate the numbers of the various non-neuronal components of the optic nerve (astrocytes, oligodendrocytes, oligodendrocyte precursor cells, microglia, fibroblasts) at this follow-up period.

3. Aims of the investigation of a group of patients subject to a combined operation for transpupillary cataract-extraction/ silicone oil removal

Cataract development following pars plana vitrectomy with use of silicone oil generally occurs in the phakic eye within two years of the intervention. In many cases the planned time for removal of the oil and that for cataract extraction fall close to one another, and therefore it would appear to be advantageous to combine these two operations. In the Ophthalmic Clinic of the Friedrich Alexander University in Erlangen, Germany, we studied a group of patients who had undergone a new surgical procedure to do this, in which transpupillary cataract extraction is combined with silicone-oil removal. We wished to investigate the intra- and post-operative experiences with this procedure, and particularly the incidence of complications.

METHODS EMPLOYED, AND EXAMINATIONS PERFORMED

1. Methods employed to examine the extra-ocular migration of silicone oil

Case report. A 75-year-old female patient, a sufferer from type II diabetes for 15 years, was operated on for proliferative diabetic retinopathy in the right eye. Combined vitrectomy was performed, with silicone oil tamponade. Two months after the operation, the silicone oil was removed because of the development of secondary glaucoma. One year later the eye had become non-functional and painful, and enucleation was performed.

Histological method. The enucleated globe was fixed in 4% formalin, dehydrated in ethanol, and embedded in paraffin wax. Microtome sections of thickness 5 µm were examined by optical microscopy after haematoxylin-eosin (HE) and PAS staining.

X-ray analysis (EDX). Samples of the embedded tissue were examined for microelement content using energy-dispersive X-ray spectroscopy (EDX). The measurements were performed with a Zeiss DSM 940 scanning electron microscope (Opton, Germany) in conjunction with a LINK AN 10/55S X-ray detector and element analyser (Link Analytical Ltd., UK).

Immunohistochemistry. Macrophages were revealed using CD 68 antibody marker (DAKO, Glostrup, Denmark), in 1:100 dilution.

2. Methods employed in animal studies on the effects of silicone oil migration into the optic nerve

The experiments were performed on four adult rabbits. The animals were pigmented (non-albino), and of body-weight 2.0–2.5 kg. Standard 20 G pars plana vitrectomy was performed on the right eye of each animal. After removal of the vitreous gel the globe was filled with silicone oil (5000 cSt viscosity; Adatomed GmbH, Dornach, Germany), and the scleral incisions stitched using 7/0 Vycril filament. The un-operated left eyes served as controls. Subsequently one of the animals died, from unknown causes, and

consequently the further examinations were performed using the remaining three.

After a period of one year following the operation the animals were anaesthetised with sodium pentobarbital and then killed using a transcardial perfusion of 4% paraformaldehyde in phosphate buffer solution (PB; 0.1M, pH 7.4). The brain of each animal, together with the ocular globes and the respective 15 mm-long optic nerves, was separated from the bony tissues.

Short (3 mm long) samples of the optic nerve on both the left and right sides were excised at the following positions: (a) immediately behind the eyeball; (b) at a location 6 mm from the eyeball; (c) immediately prior to the optic chiasm. The tissue samples were dehydrated in ethanol and embedded in paraffin wax. From the mid-point of each sample, a 3 µm-thick coronal section was cut using a microtome. The sections were stained using haematoxylin-eosin, and examined by optical microscopy to locate any vacuoles suggestive of the presence of silicone oil.

From the stained sections a series of digital photographs was prepared using an Olympus BX51 research microscope (magnification of objective: 40x) in conjunction with an Olympus DP50 high-resolution digital microscope camera. The images were optimised for brightness and contrast using the Corel Photo-Paint 12 software (Corel Corporation, Ottawa, Canada), and then analysed by computer to count the numbers of non-neuronal elements (astrocytes, oligodendrocytes, oligodendrocyte precursor cells, microglia, fibroblasts).

In order to determine the overall cross-sectional area of the nerve bundle, low-magnification images were also prepared (magnification of objective: 4x) which showed the complete nerve cross-section. These images also contained a calibrated “scalebar”. Print-outs of the low-magnification images were used to enable precise measurement of the nerve cross-sectional area.

Samples were also obtained from other tissues of the eyes. The eye-globes were dehydrated in ethanol and embedded in paraffin wax. Then 5 µm thick slices were cut at various different planes, and the samples stained using haematoxylin-eosin.

For the purpose of counting the numbers of nerve-fibres, another set of tissue-samples was excised from the optic nerves, this time a segment of the nerve originally extending

from 9 to 12 mm from the globe. The tissue-blocks were post-fixed for 1 hour in 1% osmium tetroxide, dehydrated in ethanol, and embedded in epoxy-resin (Durcupan, ACM Fluka, Sigma-Aldrich Chemie GmbH, Germany). Slices of thickness 0.75 µm were prepared with an ultramicrotome. The samples were photographed using an Olympus BX51 research microscope (immersion objective, magnification 60x, n.a. 1.40) in conjunction with an Olympus DP50 high-resolution digital microscope camera. The images were optimised for brightness and contrast using the Corel Photo-Paint 12 software (Corel Corporation, Ottawa, Canada), and then printed-out using an hp color LaserJet 1500L printer (Hewlett Packard Company, Paolo Alto, CA, USA). It was possible to count all the myelinated nerve-fibres shown on the printed-out images; and this was done for the samples both from the control side and the operated side. The nerve cross-sectional area was measured, as well as the numbers of non-neuronal elements. Mean and variance values were calculated, and significance comparisons made using the unpaired Student t-test. The level for statistical significance was set at $p < 0.05$.

3. Study of new surgical technique: cataract extraction with combined transpupillary silicone oil removal

Patients examined in the research. We performed a retrospective study on a group of patients who between 1996 and 1998 had undergone a new surgical procedure, cataract extraction with combined transpupillary silicone oil removal, in the Ophthalmic Clinic of the Friedrich Alexander University in Erlangen, Germany. The group comprised 43 patients (22 females, 21 males). Pars plana vitrectomy had been performed in the following circumstances: cerclage (n = 20); removal of epiretinal membrane (n = 27); use of perfluorodecalin (n = 25); laser coagulation (n = 11); cryocoagulation (n = 23); and retinal relaxation by retinotomy (n = 9). In 32 cases the indication for silicone-oil implantation was proliferative retinopathy following a retinal-buckling operation; in 9 cases the removal of a long-established rhegmatogenic retina or large retinal tears; one case of macular foramen in a high-myopic eye; and one case of a penetrating injury to the eye-globe. According to the reports of the preoperative examinations prior to the cataract-extraction/ oil-removal intervention, in all cases the retina was intact and did not show any alterations (e.g. epiretinal membrane) requiring further vitreoretinal surgery. If such alterations had been present, the surgeon would have performed a pars plana intervention.

The ages of this group of patients ranged between 21 and 79 years (mean 56.1 ± 14.3 years). The refractive error prior to the oil-implantation had been in the range from -22.0 D to +6.0 D (mean -3.2 D ± 7.1 D).

For the combined operation, in 23 cases retrobulbar anaesthesia (4 ml injection of 2% Mepivacain) was used; while in the other 20 cases, where retrobulbar injection was impractical due to high myopia, or at the patient's expressed wish, intratracheal narcosis was employed.

Surgical technique. In the combined operation, lens-removal using phacoemulsification was first performed via a sclero-corneal tunnel, then with tweezers a 3-4 mm diameter capsulorhexis was performed on the posterior capsule. Via the tunnel-incision a 20G cannula attached to an extraction-pump/ rinsing apparatus was used to extract the silicone oil and replace it with balanced saline solution (BSS). The saline solution flowed through the rear capsulotomy to the rearmost part of the vitreous chamber. Care was taken to avoid contact with the fundus, including its periphery. The lens-capsule was re-filled with viscoelastic material. In most of the eyes an artificial lens of PMMA material was implanted in the posterior chamber, either in the lens-capsule or in the ciliary sulcus. The tunnel-wound was stitched using 10/0 nylon filament, and finally the anterior chamber was filled with saline solution via the paracentesis opening.

RESULTS AND CONCLUSIONS

1. Results concerning extra-ocular migration of silicone oil

Histology. In the visual-microscopy examination of the samples, we noted empty "bubbles" characteristic of silicone oil in the samples obtained from the following tissues: the anterior chamber; the trabecular meshwork; the optic nerve; the subarachnoidal space; and the central retinal artery.

X-ray analysis (EDX). In the tissues showing signs suggestive of the presence of silicone oil, EDX analysis revealed high peaks corresponding to the element silicon in samples from the same tissues, namely: the anterior chamber; the trabecular meshwork; the optic nerve; the subarachnoidal space; and the central retinal artery. In control samples, taken from areas of the eye where optical microscopy did not reveal any abnormal characteristics, no such silicon peak was found. This was also the case for control-samples obtained from a different eye-globe, not exposed to silicone oil, which had been enucleated on account of intra-ocular choroidal melanoma. The investigations thus demonstrated a new route for silicone-oil migration, which may permit it to reach the central nervous system.

Immunohistochemistry. Using CD 68 antibody marker to detect the presence of macrophages, it was possible to show their presence in the optic nerve, as well as in the central retinal artery. In EDX analysis, the macrophages too showed a high silicon content. Thus it was also demonstrated that macrophages play a role in the transport of silicone oil.

2. Results of animal experiments on the effects of silicone oil migration into the optic nerve

In the histological examinations, in comparing the samples obtained from the retinas of the control eyes with those from the operated eyes, it was found that in the latter the nerve-fibre layer showed thinning. There were also the vacuoles indicative of the direct

tissue-infiltration of silicone oil; and in the vicinity of these vacuoles, the density of ganglion-cells was reduced.

In the examination of the haematoxylin-eosin stained cross-sectional samples of the optic nerve, in no case were vacuoles suggestive of the presence of silicone oil found, not even in that part of the nerve where it emerged from the globe.

In the optic nerve from the control (non-operated) eyes the number of nerve-fibres was 418 313 ± 29 703. In the case of the eyes exposed to silicone oil, the number of nerve-fibres was drastically reduced, to 45 620 ± 23 905 ($p < 0.0001$).

On the control side, the cross-sectional area for the different parts of the optic nerve was 0.568 ± 0.065 mm^2 (for the sample taken from 2 mm behind the eye-globe); 0.853 ± 0.159 mm^2 (for the sample from the nerve mid-section); and 1.363 ± 0.065 mm^2 (for the sample from the position 2 mm prior to the optic chiasm). In comparison, the sectional areas for the corresponding nerve-samples on the operated side were significantly reduced: 0.228 ± 0.061 mm^2 ($p < 0.01$); 0.355 ± 0.107 mm^2 ($p < 0.001$), and 0.699 ± 0.249 mm^2 ($p < 0.05$).

The numbers of non-neuronal elements (astrocytes, oligodendrocytes, oligodendrocyte precursor cells, microglia, fibroblasts) counted in the nerve cross-section were as follows, for the different parts of the nerve. For the sample from immediately behind the eye-globe, 2080 ± 170 (control side) and 2132 ± 224 (operated side); from the nerve mid-section, 1846 ± 309 and 1978 ± 205 respectively. For these two positions there was no significant difference between the numbers for the control side and operated side ($p > 0.05$). However for the section just prior to the optic chiasm the number was significantly larger on the operated side: 3040 ± 433 (control) vs. 3888 ± 403 (operated side; $p < 0.01$).

Thus on the basis of this animal study it appears probable that for eyes subjected to vitrectomy and filled for an extended period with high-viscosity silicone oil, the number of myelinated nerve-fibres in the optic nerve will be drastically reduced. This would explain the sometimes substantial loss of visual function experienced in some cases where the vitrectomy was in fact successful from the anatomical aspect. In contrast to this dramatic reduction in the number of myelinated nerve-fibres, the numbers of non-

neuronal elements was not reduced (in fact, was even significantly increased, for the part of the nerve just prior to the optic chiasm). It may be hypothesised that this circumstance results from some kind of long-term compensation mechanism.

3. Results of the study on the surgical technique of cataract extraction with combined transpupillary silicone oil removal

In all the patients it was possible to remove substantially all of the silicone oil (judged by the criterion that no oil-drops greater than 0.5 mm diameter remained within the bulbus). In 42 of the 43 patients an intra-ocular lens (IOL) was implanted: in 10 cases in the ciliary sulcus, and in 32 cases in the lens capsule. The remaining case was a female patient who (pre-operatively) had extreme myopia (AL = 31.9 mm); here the postoperative ametropia was only -2.0 D, with no IOL fitted. Concerning complications, in one case re-operation was necessary due to luxation of the IOL into the vitreous chamber. Minor bleeding within the vitreous chamber occurred in rare cases, but this ceased within 3 days. In 11 patients, re-detachment of the retina occurred, at a time between 5-91 days postoperatively; the cause was re-proliferation of the epiretinal membrane, or peripheral retinal detachment. No significant difference was found between the cases in which re-detachment occurred and those where it did not, in terms of the duration for which the oil had previously been present (mean duration 12.7 ± 10.8 months vs. 8.8 ± 5.5 months; $p = 0.15$, Mann-Whitney test). In the 11 re-detachment cases another vitreo-retinal intervention was necessary; and in ten of these patients the visual outcome ranged between light-perception and a visual acuity (VA) of 0.3 (median 0.08). For the remaining such eye the outcome VA was 1.0. The mean follow-up time was 9.8 ± 7.8 months. For the other 32 eyes, the postoperative acuity was strongly dependent on that existing in the initial state.

Certain conditions damaging to visual function and sometimes connected with cataract operation (previously undetected cystoid maculopathy, decompensation of the corneal endothelium or epithelium) were not reported. Since the technique included the performance of posterior capsulorhexis, there was no possibility of the development of secondary cataract. For the 24 eyes where the follow-up time was at least 3 months

(mean 9.4 ± 5.8 months), the visual outcome was between hand-movement and a VA of 0.8 (median 0.2). For 14 of these 24 patients, the visual perception improved by at least 2 lines on the Snellen chart.

In this third part of the investigation, a new surgical technique, transpupillary removal of silicone oil combined with cataract extraction, was assessed. Intra- and postoperative experiences, and the results achieved, were studied in a substantial number of patients with an extended follow-up period. It was concluded that the technique represents a valid alternative to the traditionally-used transscleral method.

NEW RESULTS OBTAINED, AND THEIR CLINICAL SIGNIFICANCE

1. With the aid of EDX analysis it was possible to demonstrate the presence of a particular chemical element (silicon) in the optic nerve, in the central retinal artery, and in the subarachnoidal space. (This element is a constituent component of silicone oil, but is not normally present at all in biological tissues.) This points to a possible route by which silicone oil could migrate to the central nervous system.

2. With the aid of EDX analysis it was possible to demonstrate the presence of the element silicon (a constituent component of silicone oil) in macrophages.

3. In the course of the investigations it was possible to accurately determine the number of myelinated nerve-fibres in the optic nerve of the pigmented rabbit, an animal which is frequently employed for ophthalmic studies. The number of nerve-fibres found was 418 313 ± 29 703).

4. In the course of the animal investigation the previous observation was confirmed, that for eyes subjected to vitrectomy and filled with silicone oil for an extended period, the number of myelinated nerve-fibres in the optic nerve may be drastically reduced. This may well explain the sometimes appreciable loss of visual function experienced in cases where the operation was anatomically successful.

5. In the course of the animal investigation it was established that for eyes filled with silicone oil for a substantial period, although there is a drastic reduction of the number of myelinated nerve-fibres, the number of non-neuronal elements (e.g. astrocytes, oligodendrocytes, oligodendrocyte precursor cells, microglia) in the optic nerve is not reduced. Indeed, in the section of the nerve just prior to the optic chiasm their number was significantly increased in comparison to the control sample; on this basis it is possible to hypothesise the operation of some type of long-term compensatory reaction.

6. A new surgical procedure, combined transpupillary removal of silicone oil and cataract extraction, was investigated on the basis of the long-term follow-up of a substantial patient-population. Intra- and postoperative experiences were studied, and it was concluded that the technique represents a valid alternative to the traditionally-used transscleral method.

LIST OF PUBLICATIONS

1. Published papers on the research topic

Papers published in international scientific journals

1. **Papp A,** Tóth J, Kerényi T, Jäckel M, Süveges I. (2004) Silicone oil in the subarachnoidal space - a possible route to the brain? **Pathol Res Pract,** 200: 247-252. **IF: 0.681**

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