SCIENTIFIC REPORT

Is silicone oil optic neuropathy caused by high intraocular pressure alone? A semi-biological model

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Background: Silicone oil endotamponade is used for the repair of complicated retinal detachments. Cataract, glaucoma and corneal endothelial dysfunction are the most frequent complications of silicone oil tamponade. Clinical and histopathological studies have revealed that silicone oil can penetrate into the optic nerve and into the brain. The mechanism by which silicone oil moves from intraocular into the optic nerve is still under debate. To investigate the effect of intraocular pressure only, a post-mortem experimental histological study was performed to determine whether silicone oil penetration from the globe into the optic nerve after vitrectomy and silicone oil instillation is a purely pressure-related phenomenon. Although a post-mortem study excludes physiological processes, it serves as a model for the study of pure physical forces onto biological structures.

Methods: The study was carried out on 20 human eyes with their optic nerves attached. All specimens had been harvested from patients without known eye disease. The vitreous body was removed with a syringe and the globe was filled with silicone oil. A lipophil fluorescence marker (Bodipy) was added in 8 eyes. The mean intraocular pressure after silicone oil filling measured 40 mm Hg and the globes stayed under pressure for up to 16 weeks. The eyes and optic nerves were stained with H&E and examined with light, phase-contrast and fluorescence microscopy.

Results: None of the 20 specimens examined showed silicone oil in the retrolaminar portion of the optic nerve.

Conclusions: Migration of silicone oil into the optic nerve was not demonstrated in this human post-mortem study. Therefore other factors, such as pre-existing glaucomatous damage to the disc region and/or active transport mechanisms must be involved in the development of silicone oil-associated optic neuropathy.

Silicone oil tamponade has been shown to be beneficial for the repair of difficult retinal detachments.¹ A number of complications of this procedure have been reported, including cataracts, endothelial dysfunction and glaucoma. Histological studies have revealed penetration of silicone oil into the cornea, the ciliary body, the retina, and the optic nerve, and magnetic resonance imaging has even revealed migration of silicone oil into the ventricles of the brain.^{2–7} Elevated intraocular pressure is thought to be the driving force in the pathophysiology of silicone oil optic neuropathy, although some authors have proposed that silicone oil can be actively transported in macrophages.⁸ The mechanism by which silicone oil migrates into the optic nerve is still incompletely understood.

MATERIAL AND METHODS

Twenty globes, with their optic nerves attached, were removed from 10 human cadavers (6 men, 4 women) no later than

8 hours after death following qualified consent. The mean age at death was 72.4 years. There was no known history of ophthalmic disease or previous ophthalmic operation in any of the patients. Access to the optic nerve and the globe was obtained through the orbital roof. The orbital portion of the optic nerve and the globe were carefully dissected from the surrounding tissues and the optic nerve was ligated slightly at the distal end with a 4–0 silk suture. The vitreous body (average 3.5 ml) was aspirated via the pars plana with an 18-gauge needle (Hypodermic by B/Braun, 18G 1.5). In order to remove the prepapillary posterior hyaloid, the tip of the needle was directed towards the optic disc. Silicone oil (Adato Silol 5000) was injected via the pars plana. In order to facilitate the detection of silicone oil, a lipophilic fluorescence marker (Bodipy) in a dilution of 1:1000 was added to the silicone oil in eight eyes. The time from silicone injection to histological preparation was 9–16 weeks in the eyes without Bodipy and 7–14 days (to prevent diffusion of the marker into ocular tissue) in the eyes with Bodipy. The target intraocular pressure was measured with a Perkins tonometer. In two eyes, a pressure of 10 mm Hg was produced, in six eyes a pressure of 30 mm Hg, in two eyes 40 mm Hg and in 10 eyes more than 50 mm Hg. In order to keep the pressure steady until the time of preparation, the inserted needle was occluded with a combi stopper (B/Braun). All globes were fixated in a 4% formaline solution. Vitrectomy, silicone oil instillation and formaline fixation was used in four eyes of pigs that were used as controls for intraocular pressure development under the used model. None of these eyes showed loss of intraocular pressure after an observation time of 50 days.

Histological methods

The fixated globes were dissected equatorially. An axial dissection was then performed through the lamina cribrosa and the optic nerve. For routine histology the sections were dehydrated and embedded via toluol in paraffin blocks and cut into sections 10 µm thick and stained with H&E. For demonstration of fluorescence-stained silicone oil, the samples were shock frozen in nitrogen and processed with a Kryostat into 20 µm serial sections for examination with a confocal laser microscope (Leica, SP1). All paraffin sections were examined with a light microscope (Axioskop, Zeiss, Germany) and quantitatively evaluated. Photographs were taken with the Progress 3021 mF camera microscope system (Jenoptik Laseroptik Systeme, Germany) and processed with Photoshop 7.0 (Adobe Systems Inc., California, USA). Sections from all portions of the optic nerve were also examined using phase-contrast microscopy.

RESULTS

The retina, the lamina cribrosa and the prelaminar and retrolaminar portion of the optic nerve were examined by microscope. The retina was detached from the pigment epithelium in all sections examined. Most of the retinas

Figure 1 A. Fluorescence microscopy of retinal layer. Note autofluorescence of pigment epithelium (arrow), helpful for positive controls in Bodipy stained specimens. B. Fluorescence microscopy of optic disc (asterisk) and retrolaminar portion of optic nerve. Note autofluorescence of oligodendrocytes.

examined showed an intact anatomy. A few specimens showed intraretinal fluorescence-stained silicone oil inclusions. In all of these specimens, however, the retina had been disrupted during the histological preparation. No silicone oil inclusions were detected in intact retinas. The excavations of the optic discs were not systematically examined. In those sections that were examined, no pathological excavations were found.

Autofluorescence of the pigment epithelium and autofluorescence of the nuclei of the oligodendrocytes were demonstrated by fluorescence microscopy (fig 1). No silicone oil (with and without fluorescence marker) and no silicone oil associated vacuoles could be detected in any of the optic nerves examined (fig 2)

DISCUSSION

The present study used light and fluorescence microscopy to examine 20 optic nerves for the presence of silicone oil after post-mortem vitrectomy and silicone oil instillation. No silicone oil or silicone oil-associated vacuoles could be found in any of the specimens examined.

Silicone oil for endotamponade after vitrectomy for complicated retinal detachments was introduced by Cibis *et al.*¹ in 1962. Experimental studies on animals by Armaly⁹ suggested a good tolerance to silicone oil. The biological tolerance for oil, however, has been questioned and studied by various other authors in eyes that were enucleated because of painful glaucoma. Late complications resulting from silicone oil inclusion have been reported, including cataract, glaucoma, retinal changes and endothelial keratopathy.^{10–17}

Previously reported histological studies on enucleated eyes have revealed silicone oil vacuoles in the iris, the corneal endothelium, Descemet's membrane, the anterior capsule of

the lens, the trabecular meshwork, the ciliary body, the choroid and the optic nerve.^{10–17} In addition, silicone oil vacuoles in the optic nerve were reported by Shields and Eagle,¹⁸ who described pseudo-Schnabel's cavernous degeneration in an optic nerve of an eye that had previously been treated with silicone oil tamponade for the repair of retinal detachment. The earliest appearance of silicone oil in the optic nerve was reported in eyes with elevated intraocular pressure 1 month after oil instillation.^{10, 16}

While some authors consider an elevated intraocular pressure to be the main factor for the shift of silicone oil from the vitreous cavity into the optic nerve, others postulate an active transport mechanism.⁸ A study based on histological examinations found no correlation between the number of vacuoles in the optic nerves and the intraocular pressure measured prior to enucleation.¹⁰ In another study including 74 eyes, 24% showed empty vacuoles in the optic nerves of the enucleated eyes. Silicone oil vacuoles replaced up to 40% of the cross-sectional area behind the lamina. Budde *et al.*¹⁶ propose an active transport mechanism for silicone oil, similar to that of mucopolysaccharides. CD 68-positive macrophages were identified with immunohistochemistry by Budde *et al.*¹⁶ and by Papp *et al.*⁸ at the border of optically empty vacuoles in the optic nerve. According to their understanding, silicone oil-filled macrophages could reach the brain via the subarachnoid space of the optic nerve.

The fact that silicone oil was found in the chiasmal and retrochiasmal region of the brain (ventricles) is indeed suggestive for an active transport mechanism as it is difficult to imagine how simple hydraulic pressure from the globe could shift silicone oil over such a long distance.^{3–5, 19, 20}

Considering the long distance from the vitreous cavity to the chiasm and the ventricles, an active transport mechanism seems more likely than simple hydraulic pressure.

The results of the present study strongly support the hypothesis that an active transport mechanism is involved in the development of silicone oil optic neuropathy. As no silicone oil or silicone oil-associated vacuoles could be demonstrated in any of the 20 eyes that we examined in this post-mortem study, pressure alone seems unlikely to be the main pathophysiological mechanism. As pressure is in direct relation to volume (pressure decreases instantly as soon as volume decreases), it seems unlikely that pressure alone could transport the oil behind the lamina cribrosa into the optic nerve. None of the control eyes used for observation of pressure constancy demonstrated loss of initial pressure after an observation time of 50 days.

We are aware that a post-mortem study is only able to make conclusions within certain limits. One of them is the lack of any physiological and biological activity. The same weakness,

Figure 2 A. H&E stained optic nerve head demonstrating an intact anatomical structure of the disc as well as of the retrolaminar portion of the optic nerve. Optic disc vessels (arrow). B. Optic nerve head demonstrating a layer of silicone oil with Bodipy (asterisk), light microscopy. Note, no invasion of silicone oil into intact tissue. C. Fluorescence microscopy. Bodipy stained silicone oil layer adherent to the retina (asterisk). D. Phase-contrast microscopy demonstrating intact disc and normal retrolaminar optic nerve. Bodipy stained silicone oil layer (asterisk).

however, has its strength by rendering a model in which only purely physical forces are at work. Looking at this purely physical model, we were not able to demonstrate silicone oil or associated cues in the optic nerves examined and we suggest therefore that physics alone is not enough to cause silicone oil optic neuropathy. An active mechanism of transport must therefore be assumed for silicone oil migration into the optic nerve.

Silicone oil optic neuropathy may be more frequent than diagnosed. It is therefore advisable to perform imaging studies in patients with otherwise unexplained visual field loss after successful vitrectomy.

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