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Original Article

Biocompatibility and retinal support of a foldable capsular vitreous body injected with saline or silicone oil implanted in rabbit eyes

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Abstract

Introduction: The aim of this study was to evaluate over a 180-day period the biocompatibility and retinal support of a foldable capsular vitreous body injected with either saline or silicone oil implanted in rabbit eyes.

Methods: A standard three-port pars plana vitrectomy was performed, and foldable capsular vitreous bodies were implanted into the vitreous cavity of rabbit eyes ($n = 18$). Silicone oil tamponade was used as the control group ($n = 5$). Of the foldable capsular vitreous body-implanted eyes, either saline ($n = 9$) or silicone oil ($n = 9$) was injected into the foldable capsular vitreous body to support the retina. The treated eyes were examined using a slit lamp with a non-contact slit-lamp lens, a tonopen, a non-contact specular microscope and a B-scan ultrasound during the 180-day implantation period. A histological examination was performed at 90 and 180 days.

Results: During the 180-day implantation period, no significant corneal keratopathy or intraocular inflammation was noted, and the intraocular pressure (IOP) and corneal endothelial numbers remained steady among the three groups. B-scan ultrasonography showed a smoothly increased echogenicity in front of the retina in group of foldable capsular vitreous bodies injected with saline. Gross examination showed that the foldable capsular vitreous bodies injected with saline or silicone oil smoothly supported the retina. The saline or silicone oil inside the foldable capsular vitreous body was homogeneous, transparent and filled the foldable capsular vitreous body. Histological examination showed no obvious abnormality of the cornea, ciliary body or retina in the foldable capsular vitreous body-implanted eyes.

Conclusions: These results suggest that foldable capsular vitreous bodies injected with either saline or silicone oil showed good biocompatibility and retinal support in rabbit eyes over a 180-day implantation time.

Key words: biocompatibility, complication, foldable capsular vitreous body, silicone oil, vitreous substitute.

Introduction

Proliferative vitreoretinopathy (PVR) is a consequence of rhegmatogenous retinal detachment, giant retinal tears and penetrating ocular trauma. PVR usually requires complex vitreoretinal surgery to prevent these diseases from progressing. Therefore, the introduction of an optimal vitreous substitute in the course of a vitrectomy is essential.

Although various vitreous substitutes are available, there have been issues with these agents, including potential complications. Intraocular gases

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had a risk of elevating intraocular pressure (IOP) and fast intraocular absorption.[1] Conventional silicone oil was widely applied clinically as an intraocular tamponade for retinal detachment, but despite the retinal attachment rate being up to 80%, it had to be removed earlier because of many complications, including silicone oil emulsification, secondary glaucoma and keratopathy.[2–9] Heavy silicone oil had been introduced to treat inferior retinal detachment because of its heavy gravity but unfortunately, it had the weaknesses of significant intraocular inflammatory reactions and caused more severe complications than conventional silicone oil.[10–13] Natural polymers, semi-synthetic polymers and synthetic polymers (poly[1-vinyl-2-pyrrolidinone], and polyvinyl alcohol) seemed to be more biocompatible with ocular tissues according to available investigations, but they biodegraded quickly and the residual monomer-polymers displayed potential cytotoxicity.[14–17] The long-term biocompatibility of these materials needed to be investigated, and to this day there is still a lack of suitable materials to replace the vitreous body.[18–20]

We previously invented a new product to replace the natural vitreous by a foldable capsular vitreous body (FCVB) investigated extensively in a rabbit model and implanted into 11 human eyes in the treatment of severe retinal detachment, with a 3-month follow-up.[21–23] The current study explored whether FCVB injected with either saline or silicone oil in the rabbit model had long-term biocompatibility or significant complications, and evaluated its role of retinal support over a 180-day implantation time.

Methods

Animal preparation and surgical procedure

Twenty-three New Zealand albino rabbits weighing 2.0 to 3.0 kg were used for the *in vivo* study involving pars plana vitrectomy and the implantation of the vitreous substitutes relevant to the study. All procedures were in accordance with the Association for Research in Vision and Ophthalmology Statement for the Use of Animals in Ophthalmic and Vision Research.

Prior to the surgery, the FCVBs were washed three times with double-distilled water (ddH_2O) and were sterilized by heating in ddH_2O at 100°C for 30 min. The rabbits underwent general anesthesia with an intramuscular injection of ketamine hydrochloride (30 mg/kg) and chlorpromazine hydrochloride (15 mg/kg), and their pupils were dilated with tropicamide (Mydrin P; Santen, Osaka, Japan). Under an operating microscope (OPMI VISU 200 plus, Carl Zeiss, Jena, Germany), a standard three-port PPV was performed on the right eye of each rabbit using the Geuder vitrectomy system. The FCVBs were implanted into the vitreous cavity of the rabbit eyes ($n = 18$). Silicone oil tamponade (Acri.Sil-ol 5000; Acri.Tec, GmbH, Berlin, Germany) was used as the control group ($n = 5$). In the FCVB-implanted eyes, either saline ($n = 9$) or silicone oil ($n = 9$) was injected into the FCVB capsule to support the retina. The FCVB was folded into three petals and implanted into the vitreous cavity by lengthening the original sclera's incision at 12 o'clock by 3 mm without a fluid–air exchange. Then either 1.1 mL of saline or 1.1 mL of silicone oil was injected into the FCVB via a needle inserted into the drainage valve, and the valve was subsequently fixed under the conjunctiva. The scleral incisions were closed with 8–0-coated Vicryl sutures. The left eye did not undergo surgery and served as the contralateral control.

The surgery ended with a subconjunctival injection of gentamycin and dexamethasone, and then a compound tobramycin and atropine (1%) ointment was put under the eyelid of the surgically altered eye.

Follow-up clinical observations

After surgery, a slit-lamp microscope (YZ-5F; Topcon Co., Tokyo, Japan) with a non-contact slit-lamp lens (78D Double Aspheric, Volk Co., Mentor, OH, USA) was used to examine and record conjunctival congestion, corneal oedema, anterior chamber exudation, anterior chamber depth (ACD), lens opacity and fundus conditions at 1, 3, 7, 14, 28, 56, 90 and 180 days.

A tonopen (Tono-pen avia, Reichert Co., Oak Harbor, OH, USA) was used to examine the IOP preoperatively and postoperatively at 1, 3, 7, 14, 28, 56, 90 and 180 days.

A non-contact specular microscope (SP-3000P, Topcon Co.) was used to assess the modality and density of corneal endothelial cells at 180 days. To do so, the rabbit's head was fixed on the front of the device and both eyes were examined. Endothelial images were captured three times in the automatic mode from the central cornea. Images with good contrast were selected and transferred to the ImageNet system, and at least 50 contiguous cells were analysed.

Postoperatively, a B-scan ultrasound (CineScan A/B, Quantel Medical, Clermont-Ferrand, France) was performed at 7, 14, 28, 56, 90 and 180 days to determine the position and relationship between the FCVB and the retina.

Gross appearance and histological examination

The rabbits were euthanatized by an overdose of intramuscular injection of ketamine and chlorprom-

azine (1:1) at 90 days ($n = 5$, FCVB injected with saline; $n = 5$, FCVB injected with silicone oil; $n = 1$, silicone oil tamponade alone) and at 180 days ($n = 4$, FCVB injected with saline; $n = 4$, FCVB injected with silicone oil; $n = 4$, silicone oil tamponade alone). After enucleation, all ocular samples were dissected with an examination of the gross appearance of the ocular structure and the FCVB under an operating microscope. Both the experimental and control ocular samples were then immediately fixed in a 4% neutral paraformaldehyde solution and were processed for routine paraffin embedding. Ten consecutive 6-mm-thick sections of each sample were made and stained with hematoxylin–eosin. A light microscope was used to evaluate the ocular histopathological changes on the cornea, ciliary body and retina. The contralateral ocular samples were also examined as controls.

Statistical analysis

All results were analysed using a statistical package (SPSS 13.0, SPSS, Cary, NC, USA). Data was reported as mean ± standard deviation or median ± interquartile range if results were an asymmetry distribution. A paired samples *t*-test, a Wilcoxon matched-pairs signed-ranks test, was used to compare the treated and contralateral eyes of the same animal. A one-way ANOVA, a Kruskal–Wallis test with a multiple comparison test (least significant difference [LSD]-*t*-test), was used for comparisons involving more than two groups of animals. Statistical significance was considered at a *P*-value of ≤ 0.05 in a two-tailed test.

Results

Clinical findings

Slit lamp

Slit-lamp examinations revealed that the anterior segment inflammation of all eyes abated on the seventh day after FCVB implantation. Although a few FCVB-implanted eyes had severe inflammation in the anterior chamber (fibrinous exudation and hyphema) after surgery, they recovered within seven days postoperatively with intensive anti-inflammatory treatments. Among the three groups, there was no other obvious inflammatory reaction or other disease (keratopathy or shallow anterior chamber) except cataracts, which emerged in the anterior segment of the eyes over 180 days (Fig. 1a).

The two experimental groups showed varying degrees of lens opacity. In the FCVB injected with saline group, there was 50% (4/8, except lensectomy: $n = 1$) and 75% (3/4) complete lens opacity (absence

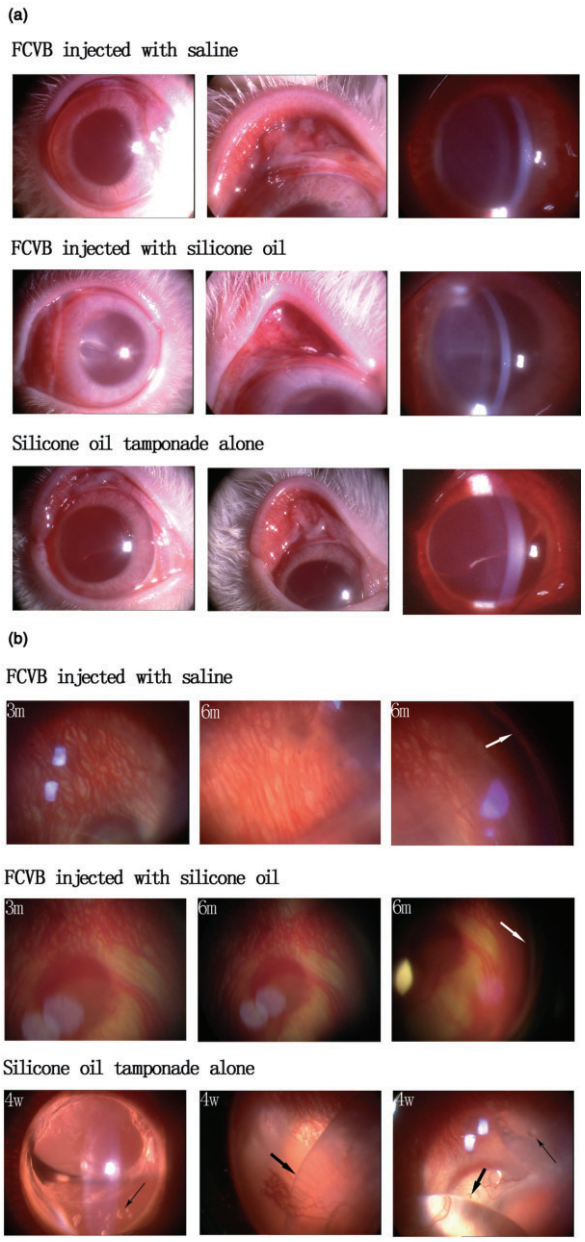

Figure 1. Photograph of 180-day examinations using slit-lamp with a non-contact slit-lamp lens. (a) Anterior ocular segment. Anterior segment inflammations abated within 7 days after surgery among the three groups. No obvious inflammation reaction or other disease emerged in the anterior segments of the eyes for 180 days among the three groups, except cataracts. (b) Posterior ocular segment (inverted image). The experimental groups had no abnormal events for six months. The fundus was clear and the capsular wall (white thick arrow) of the FCVB fit perfectly with the retina in all quadrants. However, the silicone oil tamponade group had silicone oil vesicles on the posterior surface of the lens (black thin arrow) and in the vitreous cavity (black thin arrow). There was an oil–fluid interface (black thick arrow) in the vitreous cavity, and silicone oil gradually dissolved into the intraocular fluid in the shape of a membrane (white thin arrow) in the vitreous cavity. FCVB, foldable capsular vitreous body.

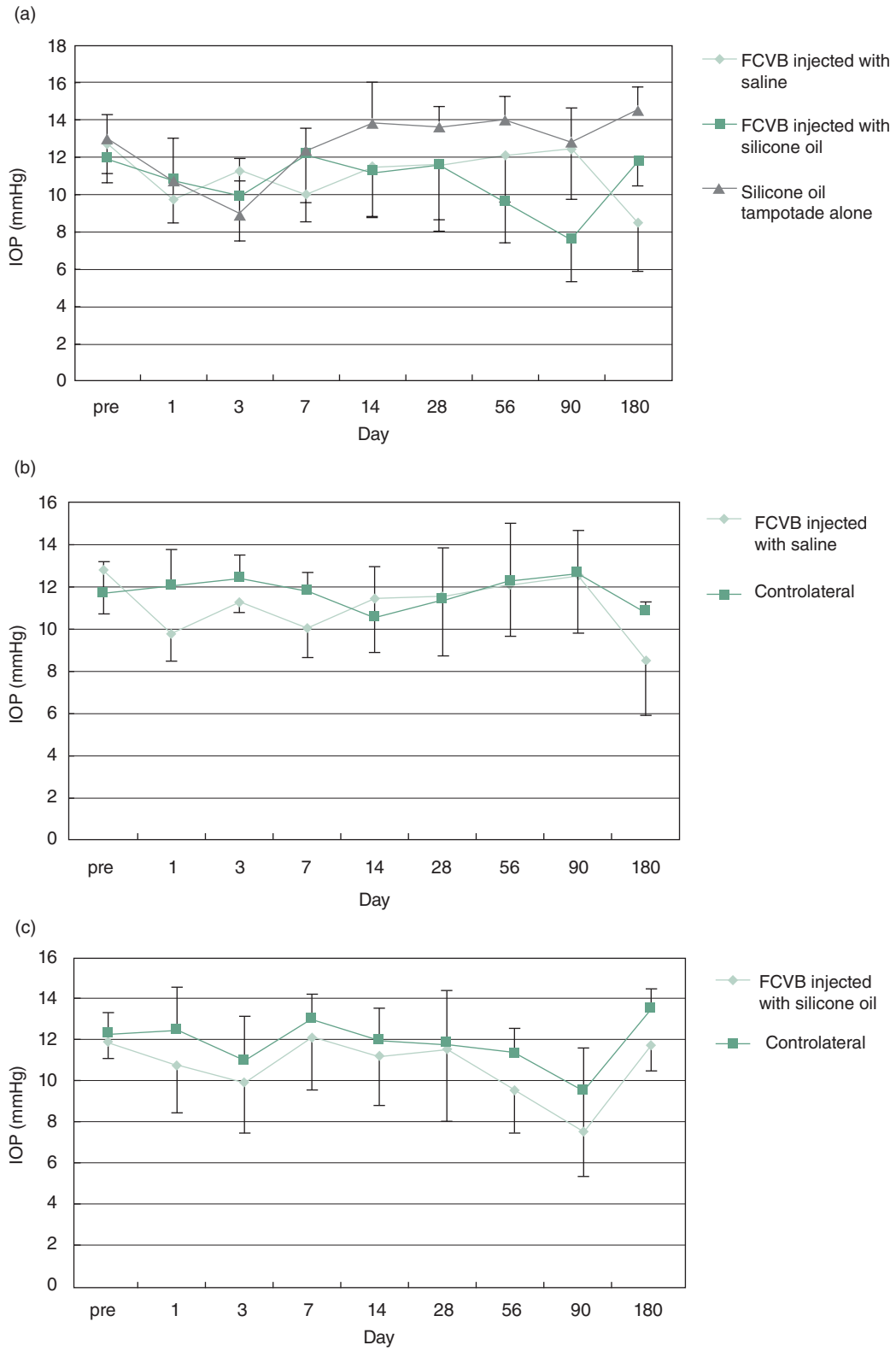

Figure 2. Fluctuation of intraocular pressure during *in vivo* study over 180 days. (a) There was no statistically significant difference in intraocular pressure (IOP) preoperatively or at 1, 3, 7, 14 and 28 days, but it was significant at 56, 90 and 180 days postoperatively among the three groups (one-way ANOVA: $P = 0.216$, $P = 0.655$, $P = 0.378$, $P = 0.188$, $P = 0.162$, $P = 0.398$, $P = 0.004$, $P = 0.001$ and $P = 0.004$, respectively). The IOP fluctuation curves were gradual in variation at each point among the three groups. (b, c) IOP was not statistically significantly different between treated (right) and control (left) eyes at each point in either the foldable capsular vitreous body (FCVB) injected with saline group (b) or the FCVB injected with silicone oil group (c).

of fundus reflection) at 90 and 180 days, respectively. In the FCVB injected with silicone oil group, there was 83% (5/6, except lensectomy: $n = 3$) and 100% (2/2, except lensectomy: $n = 2$) complete lens opacity in 90 and 180 days, respectively. The silicone oil tamponade alone group showed 40% (2/5) lens opacity at 90 days.

Non-contact slit-lamp lens

Examinations using a slit-lamp with a non-contact slit-lamp lens revealed no abnormal events such as silicone oil emulsification, retinal hyperaemia or optic atrophy in the experimental groups for 180 days. The fundus was clear and the capsular wall of the FCVB fit perfectly with the retina in all quadrants. However, many silicone oil vesicles were found on the posterior surface of the lens in all eyes ($n = 5$) of the silicone tamponade group on the first day after surgery, and the number of silicone oil vesicles increased and existed in the vitreous cavity during subsequent observations. In addition, they all had an oil–fluid interface and were filled with a two-thirds volume of silicone oil in the vitreous cavity (3/3) on the first day. The silicone oil gradually dissolved into the intraocular fluid in the shape of the membrane around the oil–fluid interface in all eyes (3/3), except lens opacity in two eyes, resulting in a decreasing silicone oil tamponade in the vitreous cavity in the control group. The oil–fluid interface even exceeded the inferior border of the optic disc in one eye, as shown in Figure 1b.

Other ophthalmological findings

IOP

No statistically significant differences were found among the three groups in the IOP preoperatively or at 1, 3, 7, 14 and 28 days, but they were found at 56, 90 and 180 days postoperatively (one-way ANOVA: $P = 0.216$, $P = 0.655$, $P = 0.378$, $P = 0.188$, $P = 0.162$, $P = 0.398$, $P = 0.004$, $P = 0.001$ and $P = 0.004$, respectively). However, these differences were in the normal range at each time point (Fig. 2a). The IOP fluctuation curves were relatively gentle in variations at each point in all groups. A downward trend was evident at one and 3 days postoperatively among the three groups because of a possible leakage of aqueous humor at the incision for the FCVB implantation before it healed during the first 3 days. Although the FCVB injected with silicone oil group trended downward at 90 days, it returned to a normal level at 180 days. In addition, there was no statistically significant difference between the treated and contralateral control eyes at each point in either the FCVB injected with saline group or the FCVB injected with silicone oil group over the 180 days (P value is not shown, Fig. 2b, c).

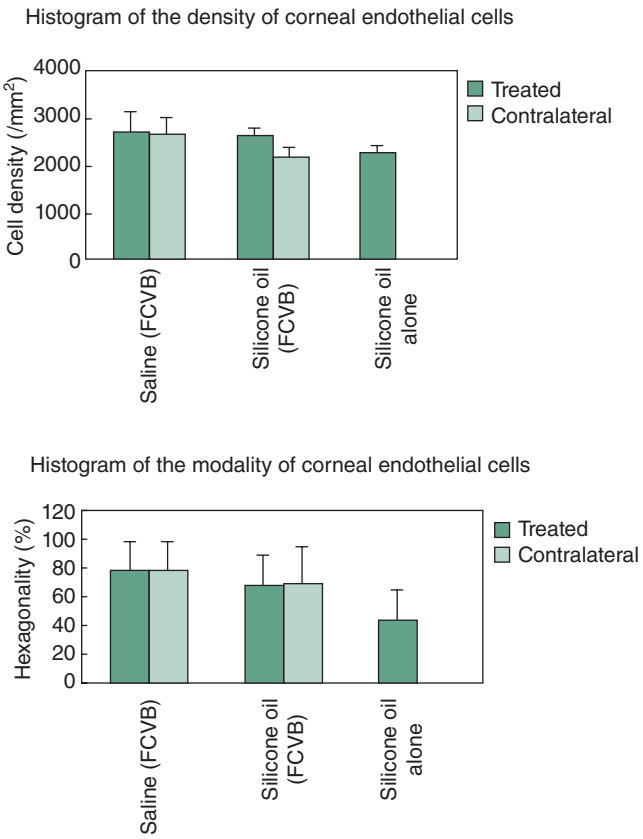

Figure 3. Non-contact specular microscopy of corneal endothelial cell at 90 and 180 days. The density of corneal endothelial cells showed no evidence of differences between the foldable capsular vitreous body (FCVB) injected with saline and silicone oil groups, and it was even higher than the silicone oil tamponade alone control group. There was no statistically significant difference between the treated and contralateral control eyes in the FCVB injected with saline group (paired samples t-test: $P = 0.880$). There was a statistically significant difference in the density of corneal endothelial cells between the treated and contralateral eyes in the FCVB injected with silicone oil group (paired samples t-test: $P = 0.033$). The different modalities (hexagonality) of corneal endothelial cells were not statistically significant among the three groups.

Non-contact specular microscopy

As shown in Figure 3, the density of the corneal endothelial cells was not different between the FCVB injected with saline and the FCVB injected with silicone oil groups, but it was higher than that of the silicone oil tamponade alone control group (LSD-t test: FCVB injected with saline compared with FCVB injected with silicone oil: $P = 1.000$; FCVB injected with saline compared with silicone oil tamponade alone; $P = 0.016$; FCVB injected with silicone oil compared with silicone oil tamponade

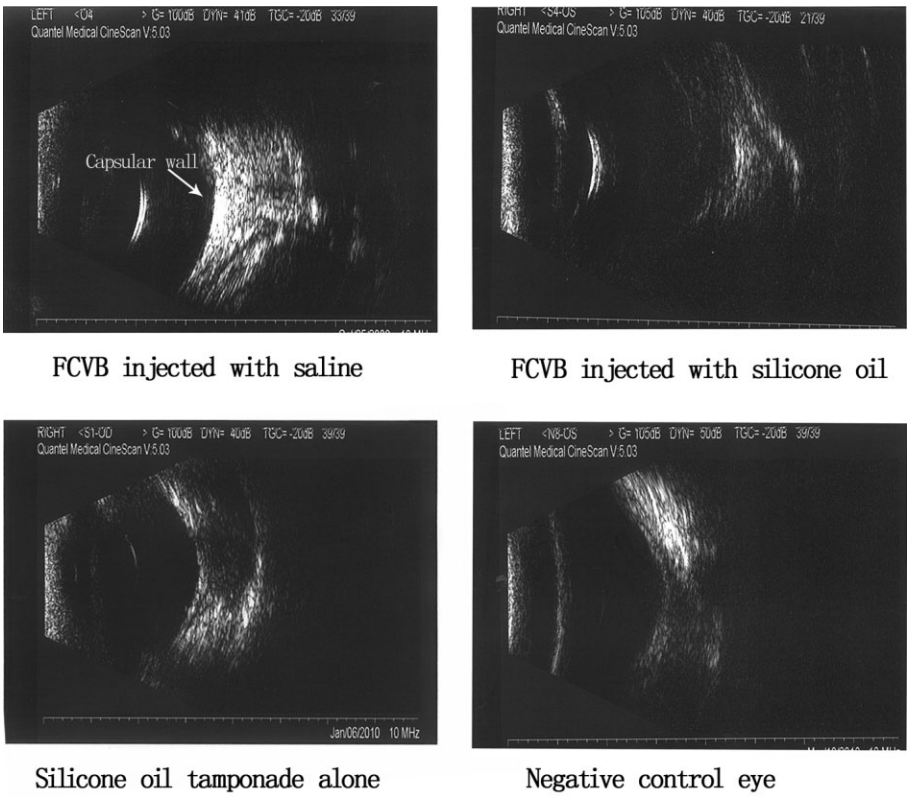

Figure 4. B-scan ultrasonography. B-scan ultrasonography found mild opacity echoes in the vitreous cavity and a smooth curve epiretinal echo enhancement in the rabbit eyes with foldable capsular vitreous bodies (FCVBs) injected with saline. Interference information was evident in the silicone oil in the eyes of the FCVB injected with silicone oil group. Mild opacity echoes in the vitreous cavity were noted in the silicone oil tamponade group.

alone, $P = 0.016$). There was no statistically significant difference between the treated and contralateral control eyes in FCVBs injected with saline (paired samples *t*-test: $P = 0.880$). There was a statistically significant difference in the density of corneal endothelial cells between the treated and contralateral eyes in the FCVB injected with silicone oil group (paired samples *t*-test: $P = 0.033$). The modality (hexagonality) of the corneal endothelial cells was not statistically significant among the three groups (Fig. 3).

B-scan ultrasonography

This scan found some mild opacity echoes in the vitreous cavity and a smoothly increased epiretinal echogenicity in all FCVB injected with saline rabbit eyes ($n = 9$), which appeared to be the posterior wall of the FCVB. But there was interference of the silicone oil in the FCVB injected with silicone oil eyes during the 180 days. However, the silicone oil tamponade eyes seemed to present some mild vitreous opacity echoes ($n = 4$), even with the silicone oil interference information, as shown in Figure 4.

Histological findings

Gross examination of the ocular specimens showed that the capsular wall of the FCVB could fit perfectly with the retina in the vitreous cavity, and the wall of the FCVB remained transparent in FCVBs injected with either saline or silicone oil. The appearance of saline or silicone oil inside the FCVB was homogeneous, transparent and filled the capsular bag of the FCVB.

In the histological examination, the layers of cornea epithelial cells and the epithelial cells of the ciliary body were intact, without a loss of normal ocular tissue and with full thickness of the retina. There was no evidence of pathological changes in any ocular tissues or structural abnormalities such as deformations, degeneration or inflammation in either of the two experimental groups. However, the silicone oil tamponade alone group showed many vacuoles in and disorganization of the ciliary body (Fig. 5).

Discussion

This study demonstrated that the strategy of FCVB injected with either saline or silicone oil in rabbit eyes had good biocompatibility and retinal support during a 180-day observation time. Most importantly, the FCVB injected with silicone oil had fewer complications, including silicone oil migration and emulsification, both clinically and histologically.

Our previous study had tested the mechanical, optical and biocompatible properties of FCVB as a suitable vitreous substitute.[24] Moreover, in the rabbit PVR model, we found that the FCVB with a balanced

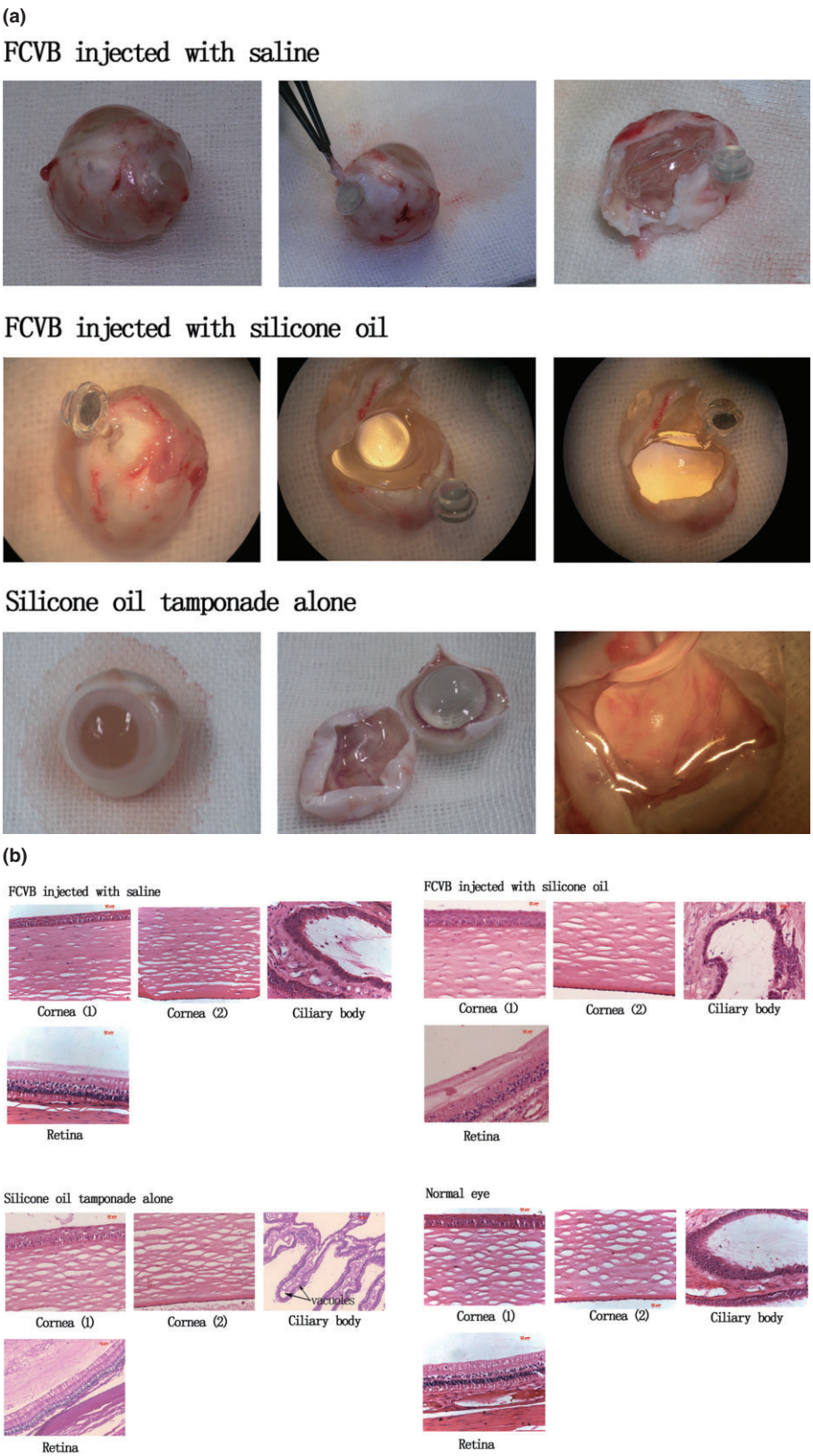

Figure 5. Gross appearance and light micrography of ocular specimens at 180 days. (a) Gross appearance of ocular specimens. The capsular wall of the foldable capsular vitreous body (FCVB) fit perfectly into the retina in the vitreous cavity and was transparent in both FCVBs injected with saline and FCVBs injected with silicone oil. The appearance of both saline and silicone oil was homogeneous, transparent and filled the capsular bag of the FCVB. (b) Light micrography of ocular specimens. There was no loss of normal ocular tissue, and the full layers of cornea, ciliary body and retina maintained their integrity. No evidence was seen of pathological changes or structural abnormality in any ocular tissues of the two experimental groups. However, the silicone oil tamponade alone group showed many vacuoles in and disorganization of the ciliary body.

salt solution (BSS) very closely mimicked the morphology and restored physiological functions such as support, refraction and cellular barriers during a 3-month observation period, without silicone oil complications.[22] In addition, FCVBs injected with BSS changed refraction less than silicone oil or heavy silicone oil tamponade.[25] We recently conducted an exploratory study of 11 patients implanted with

FCVBs with BSS in the treatment of severe retinal detachment at Zhongshan Ophthalmic Center and found that it had good flexibility, safety and efficacy during a 3-month observation period.[23]

In this study, FCVBs injected with either saline or silicone oil served as suitable vitreous substitutes and were kept in the rabbits' eyes during the 180 days of observation. Silicone oil, an organic polymer of high molecular weight, stayed in the FCVB and avoided migrating into the neighboring intraocular structure, thereby decreasing silicone oil-induced complications. It has been reported that the mechanism of silicone oil emulsification depends not only on purity and viscosity, but also on disturbance of the surroundings,[26–29] and as a vitreous substitute FCVB could serve as an isolator to avoid silicone oil emulsification by reducing the influence of surrounding events.

However, the silicone oil emulsification phenomenon has been found in clinical examinations in the silicone oil tamponade alone group (Fig. 1b). Although there was no typical sign of silicone oil migrating into the anterior chamber, the histological examination found that many vacuoles in the ciliary body might be silicone oil droplets. Therefore, an obvious silicone oil migration had occurred at the cellular level in the silicone oil tamponade alone group. Possible explanations for the lack of visible silicone oil droplets migrating into the anterior chamber in our control group are that rabbit eyes have a large spherical lens and the zonular fibers could partly prevent relatively large silicone oil droplets from entering into the anterior chamber; our study was based on a small sample ($n = 5$, silicone tamponade alone); and no lensectomy was performed in the control group. In addition, Versura *et al.* reported that it was observed by light microscopy and scanning electron microscopy that silicone oil droplets penetrated into the ocular tissues at the anterior segment level in all eyes as early as four weeks in rabbit eye intravitreal injected with silicone oils (1000 or 3000 cSt).[30]

FCVBs might play a better retinal support role in the long term compared with silicone oil tamponade alone. The supporting power of the FCVB exerted on the retina was a force of curve compliance and displayed an all-round supporting property, which made the FCVB a complete retinal attachment, as shown in the B-scan ultrasonography (a prominently smoothly curved echo enhancement) and clinical examinations (all quadrants of capsular wall of FCVB fitting to retina) during 180 days of observations. In addition, FCVBs injected with silicone oil could play a better retinal support role by avoiding silicone oil migration into the anterior chamber and silicone oil emulsification, as well as maintaining the original volume and interfacial tension of silicone oil, whereas the supporting force of FCVBs injected with saline could be affected by the leakage of a little saline into the vitreous cavity through the 300-nm mini-apertures in the capsule.[31]

The normal fluctuation of IOP in both FCVB groups was contradictory to the hypotony found in our exploratory clinical trial. An explanation could be that the patients participating in the exploratory clinical trial had severe conditions before FCVB implantation, especially ciliary body disfunction.[23] In addition, the absence of conflict between FCVB and the ciliary body in human eyes in a UBM examination in the clinical trial and the absence of damage to the ciliary body in histological examinations in this animal study confirm that the FCVB does not affect the function of the ciliary body and maintains a normal IOP.[23]

The explantation surgery of the FCVB was performed easily; however, we did not perform FCVB explantation surgery at 180 days in this study. All samples were enucleated for gross appearance and histological examination. In human FCVB explantation surgery, FCVBs were easily removed through a 2-mm sclera incision as follows:[23] dissection of 10–2 o'clock conjunctiva to fully explore the FCVB valve, aspiration of the fluid (BSS or silicone oil) inside the FCVB via the FCVB valve, then lengthening of the sclera incision by 2 mm to remove the FCVB the from vitreous cavity.

This study provided a practical basis for our ongoing multicentre clinical trial in China, which might provide a new therapeutic tool in the field of vitreoretinal surgery. In addition, the study proved that FCVBs could serve as a common carrier system and provide a foundation for injecting other materials into the FCVB.

We realize that we lacked transmission electron microscopy to further evaluate the biocompatibility in subcellular structures. In addition, we were not able to get the ERG signal to evaluate retina function in the FCVB-implanted eyes because of the insulation of the FCVB material. The high incidence of cataracts was unresolved in the rabbit eyes, whether they were caused by the material of the FCVB or the lens structure of their eyes. As such, the influence of FCVB on the human lens should be further evaluated, as 10 of 11 eyes were aphakia and only one eye was phakia in our exploratory clinical trial.[23] These FCVB materials should be modified to enhance biocompatibility.

In conclusion, FCVBs injected with either saline or silicone oil showed good biocompatibility and retinal support in rabbit eyes over a 180-day implantation time. In addition, FCVBs injected with silicone oil can reduce complications associated with silicone oil, such as migration into anterior chambers and emulsification.

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