• Basic Research •

Effects of lens extirpation with anterior vitrectomy on vitreous three-dimensional mesh structure

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Abstract

• AIM: To investigate the changes in vitreous gel structure after lens extirpation combined with anterior vitrectomy in rabbit eyes.

• METHODS: Twenty-eight chinchilla rabbits were divided into three groups. The control group (Group I) included 16 eyes from eight rabbits who did not receive any treatment. Group II included 20 eyes from 10 rabbits that underwent lens aspiration only. Group III included 20 eyes from 10 rabbits that underwent lens aspiration combined with posterior capsulotomy and anterior vitrectomy. Eyes were harvested on the 30th and 60th day postoperatively, respectively. Changes in vitreous gel stretch length due to gravity and the rate of vitreous liquefaction were observed. The collagen content in the vitreous body was examined using the L-hydroxyproline test. Electronic microscopic images were obtained from each eyeball.

• RESULTS: On both the 30th and 60th day postoperatively, the vitreous gel length of group III was significantly shorter than group I and group II (P<0.05), while the rate of liquefaction of the vitreous body in group III was significantly higher than group I and group II (P<0.05). The collagen content in group III was also higher than that in group I and group II (P<0.05).

• CONCLUSION: Loss of vitreous gel mass is more likely to occur in the eyes of rabbits receiving anterior vitrectomy. Lensectomy combined with anterior vitrectomy may damage the stable three-dimensional mesh structure of collagen, which could aggravate vitreous gel liquefaction.

• KEYWORDS: lens extirpation; anterior vitrectomy; vitreous body; vitreous liquefaction

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INTRODUCTION

Congenital cataracts are commonly seen in pediatric patients and are usually treated with surgical extirpation. Previously, the most common primary surgery for pediatric cataracts was lensectomy without posterior capsulorhexis and anterior vitrectomy. Subsequently, the operation was modified and posterior capsulorhexis and anterior vitrectomy were combined and has since been considered the standard procedure in small children. This method reduces the risk of visual axis opacities caused by after cataract. However, among pediatric patients, whether anterior vitrectomy affects the overall structure, causes pathological changes of the vitreous body, or induces long-term complications (such as macular edema and/or retinal detachment) is largely unknown. The mechanism studies addressing these questions are also rare.

For adults, it had been reported that there is an increased risk of retinal detachment in patients who have undergone cataract surgery[1-3]. For pediatric patients, postoperative retinal detachment after cataract surgery has also been considered a complication after primary surgery[4]. Based on data from aphakic cases, the incidence of retinal detachment after pediatric cataract surgery is 1% to 3.2%[5-6]. However, whether different surgical methods for the treatment of pediatric cataracts will influence the risk of later detachment is unknown.

In this study, the rabbit eye was chosen because it shares many anatomic similarities with the human eye. The effects on the vitreous structure after undergoing simple lens extirpation or lensectomy combined with anterior vitrectomy were compared. This rabbit animal study focus on investing vitreous gel stretch length, vitreous liquefaction and vitreous collagen content following lens extraction alone and lens extraction with posterior capsulorhexis with anterior vitrectomy, compared to controls in attempt to conceptualize theoretical background on post operative vitreous structural 3D configuration that may be compared to paediatric cataract management.

SUBJECTS AND METHODS

Experimental Animals and Experimental Reagents

Experimental animals and materials Twenty-eight healthy

juvenile chinchilla rabbits with no ophthalmic diseases in the anterior or posterior segments and that weighed 1-1.5 kg were provided by the Experimental Animal Center of Tongji Medical College of Huazhong University of Science and Technology. Protease inhibitors (0.5 mg/L leupeptin, 1 mmol/L edetate disodium, 0.7 mg/L pepstatin, 0.2 mmol/L phenylmethanesulfonyl fluoride) were purchased from AMRESCO; pepsin was purchased from Sigma. Hydroxyproline test boxes were purchased from Nanjing Jiancheng Bioengineering Institute (China). The experimental animal employment license is No. SYXK (Hubei Province, China) 2004-0028.

Animal grouping The twenty-eight rabbits were divided into three groups. Group I is control, Group II is lens aspiration alone, and Groups III is lens aspiration combined with posterior capsule removal and anterior vitrectomy. Group I consists of eight rabbits (16 eyes) that did not receive any treatment. Group II consists of ten rabbits (20 eyes) that underwent lens aspiration alone (*i.e.* the posterior capsules of the lens remained intact), and Group III consists of ten rabbits (20 eyes), which lens were aspirated and posterior capsules and anterior vitreous bodies were cut.

Experimental Methods Before the operation, 0.3% norfloxacin eye drops were applied to the conjunctival sacs and compound tropicamide eye drops were applied for complete mydriasis in Groups II and III. Animals were anaesthetized using a muscular injection of ketamine hydrochloride (50 mg/kg) and chlorpromazine hydrochloride (25 mg/kg), followed by ophthalmologic surface anesthesia with 0.5% dicaine solution. For antiseptic treatment of the skin around the eyes, 1% povidone iodine was used. A 3-mm corneal tunnel incision was made, sodium hyaluronate was injected into the anterior chamber, and a continuous annular-form capsulorhexis was made. Hydrodissection was then performed using a balanced salt solution in order to separate the lens cortex from the lens capsule. The eyes in Group II were only treated with lens cortex and/or soft nuclear aspiration, with the preservation of an intact posterior capsule. In Group III, in addition to lens cortex aspiration, the posterior capsule and vitreous anterior limiting membrane were incised followed by shearing of the anterior vitreous bodies without simultaneous aspiration. Dexamethasone (TobraDex) eye drops (four times every day for 3-5d) were applied and compound tropicamide eye drops (twice a day for 5d) were used to maintain mydriasis.

One eye in group II and one in Group III were excluded from the experiment due to serious corneal opacity. One eye in group III was also excluded because of iatrogenic retinal detachment. The conjunctiva, cornea, anterior chamber, pupil, vitreous body, and retina of the remaining 37 eyes (19 in Group II and 18 in Group III) were evaluated with a slit-lamp and indirect ophthalmoscopy. Results were recorded daily for the first 3d, then once a week for the rest of the experimental period. The last recordings were performed on the 60th postoperative day.

Determination of the physical properties of the vitreous and collagen Four rabbits (eight eyes) in Group I, five rabbits (nine eyes) in Group II, and five rabbits (nine eyes) in Group III were examined on the 30th postoperative day. Four rabbits (eight eyes) in Group I, five rabbits (ten eyes) in Group II, and five rabbits (nine eyes) in Group III were observed on the 60th post-operative day. The harvested eyes were incised circumferentially approximately 2 mm posterior to the corneal limbus. The vitreous body was separated cleanly from the posterior portion. The intact vitreous was dissected carefully from the ciliary body, zonules, and lens using blunt forceps.

Determination of the vitreous extension range The natural stretch length of the vitreous body under the gravity was measured by clamping the basilar part of the vitreous body with ophthalmic microsurgical tweezers and raising it slowly.

Determination of the vitreous liquefaction rate Gel/liquid vitreous separation was performed according to the method described by Ueon[7-8]. Each vitreous sample was poured into a plastic, resin-coated fiberglass net (mesh opening approximately 1.5 mm; net size 10×16 cm) that was positioned on the top of a rectangular piece of filter paper (Fisher No.1, 10×16 cm; Fisher, Pittsburgh, PA, USA). Liquefied vitreous passed through the mesh to reach the filter paper, which absorbed the liquid immediately. The gel component of the vitreous was separated from the liquefied vitreous using the net. The gel portion remaining in the net was transferred to a pre-weighed plastic dish (8 cm in diameter). Separation was performed at 25 ℃ in 30s. The gel vitreous was weighed and the percentage of the gel vitreous was calculated as the wet weight of the separated gel vitreous divided by the wet weight of the initial vitreous. The liquefaction rate of the vitreous body was calculated according to the following formula[9]: vitreous body liquefaction rate (%) =liquefied vitreous body weight (g)/[liquefied vitreous body weight (g)+gelatinous vitreous body weight (g)] ×100%.

Extraction and determination of collagen: extraction of collagen Initially, 0.5 mL vitreous gel was centrifuged (10 000 rpm) for 30min and the supernatant was removed. The pellet was homogenized in a tissue homogenizer with 0.5 mL protease inhibitor for 30min at 0 ℃, centrifuged at super-high-speed (100 000 rpm) for 45min, and the supernatant was then removed. A 1 mol/L equivalent amount of acetic acid and pepsin (10 mg/100 mg specimens) was added to the pellet, which was stirred overnight at 4 ℃ and centrifuged (20 000 rpm) for 30min. The supernatant was collected and its pH was adjusted to 7.2 by adding 1 mol/L NaOH. It was then dialyzed overnight at 4℃ in 0.01 mol/L Na_2HPO_4 and 0.0625 mol/L Tris hydrochloric acid solution (Tris-HCL) (pH=6.8), centrifuged, and ultra filtrated. The concentration of collagen fibers in the vitreous body was determined using the hydroxyproline test boxes according to the manufacturer's instructions[10].

Ultrastructural examination On the 60th postoperative day, the eyeballs of each group were enucleated, suspended in 4℃ 2.5% glutaraldehyde solution for 10min, incised 10 mm circularly approximately 2 mm away from the corneal limbus and then fixed in 2.5% glutaraldehyde solution again for 24h. Next, each eyeball was separated into two hemispheres by cutting through all the layers along the circumference from 12 o'clock to 6 o'clock. After 30min fixation in pre-cooled 2.5% glutaraldehyde solution, a small specimen (1 cm×1 cm) on the posterior pole, close to the optic nerve head, was removed and fixed in glutaraldehyde at 4℃ refrigerator for 24h. The ultra structural changes in the vitreous retinal interface were observed using scanning electron microscopy (SEM).

Statistical Analysis All experiments were performed in triplicates. The results are presented as the mean±standard deviation. One-way-analysis of variance (ANOVA) was used to identify significant differences with subsequent post-hoc Student's *t*-test. Statistical analyses were performed using Statistical Package for Social Sciences 13.0 (SPSS Inc., USA). A *P*-value less than 0.05 were used to identify significant results in the analyses.

RESULTS

Postoperative Ocular Examination Within 60d of the operation, all corneas were transparent. On the 1st postoperative day, conjunctival congestion was clearly observed. The symptoms gradually began to resolve at approximately postoperative day 2-3 and disappeared between days 5-7. There were cellulose exudates in the anterior chamber, which was mainly located around the pupil in the early stages, which then disappeared during postoperative days 2-5 after being treated with mydriatic and steroids eye drops. Posterior synechia appeared to varying degrees (four eyes in Group II and six eyes in Group III), but the visual axis remained clear. No sign of retinal detachment was detected during observation.

Changes of Vitreous Stretch Length On the 30th postoperative day, the vitreous extension range in Group III was 2.078±0.173 cm, which was smaller than that measured in Groups I and II (P<0.05). On the 60th postoperative day, Group I had the highest vitreous extension range (2.900±0.251 cm), while Group III had the lowest (1.811±0.226 cm). All the differences were statistically significant (P<0.05) (Table 1).

Status of Vitreous Liquefaction On postoperative days 30 and 60, Group III had the highest vitreous liquefaction rates. On the postoperative day 60, Group III had greater vitreous liquefaction rates than on postoperative day 30. All the differences were statistically significant (P<0.05). The vitreous liquefaction rate in Group II was higher than Group I, but the difference was not statistically significant (P>0.05) (Table 2).

Concentration of Vitreous Collagen Fiber by Using the L-hydroxyproline Method On postoperative day 30 and 60, the concentration of vitreous hydroxyproline in Group III was higher than that in Groups I and II. In Group III, the value was higher on day 60 than on day 30. All of these differences were statistically significant (P<0.05). The concentration of hydroxyproline in Group II was higher than Group I, but the difference was not statistically significant (P>0.05) (Table 3).

Table 1 Vitreous extension range in each group mean±SD; cm

Group	Postoperative 30d	Postoperative 60d
Group I	2.813±0.224	2.900±0.251
Group II	2.711±0.220	2.560±0.158[a]
Group III	2.078±0.173[a,b]	1.811±0.226[a,b,c]

[a]Compared with Group I, P<0.01; [b]Compared with Group II, P<0.05; [c]Compared with postoperative day 30 Group III, P<0.05.

Table 2 Liquefaction rate of the vitreous body in each group mean±SD; %

Group	Postoperative 30d	Postoperative 60d
Group I	24.36±2.07	25.36±2.33
Group II	26.33±2.31	26.24±3.44
Group III	38.88±5.93[a,b]	45.37±5.54[a,b,c]

[a]Compared with Group I, P<0.01; [b]Compared with Group II, P<0.01; [c]Compared with postoperative day 30 of Group III, P<0.05.

Table 3 Concentration of vitreous hydroxyproline in each group mean±SD; μg/mL

Group	Postoperative 30d	Postoperative 60d
Group I	2.025±0.218	2.063±0.267
Group II	2.224±0.317	2.090±0.310
Group III	2.411±0.310[a,b]	2.733±0.245[a,b,c]

[a]Compared with Group I, P<0.01; [b]Compared with Group II, P<0.05; [c]Compared with postoperative day 30 of Group III, P<0.05.

Ultrastructural Changes on Vitreous Retinal Interface In Groups I and II, numerous bulges on the retinal inner limiting membrane (ILM) were observed with SEM. There were irregular tray-like or flake-like areas of remaining vitreous cortex (Figure 1). Group II had less remaining vitreous cortex than Group I, and the remaining cortex was scattered in a punctate pattern (Figure 2). Group III had little vitreous cortex and the retinal ILM was relatively smooth (Figure 3).

DISCUSSION

Congenital cataract is commonly seen in pediatric patients and is usually treated with surgical extirpation. Since the incidence of after-cataracts in pediatric patients with congenital cataract that receive extracapsular extraction is 100%, many ophthalmologists also incise the posterior capsule of the lens and cut off the anterior vitreous when performing cataract extraction[11]. This way reduces the incidence of after-cataracts, whereas, clinically it has been reported that there is a related increase in complications, such as cystoid macular edema and retinal detachment, after cataract extraction with anterior vitrectomy[5,12]. No relevant research to verify this clinical observation has been performed thus far. In this study, the effects of different surgical procedures on vitreous structure were compared in an animal model.

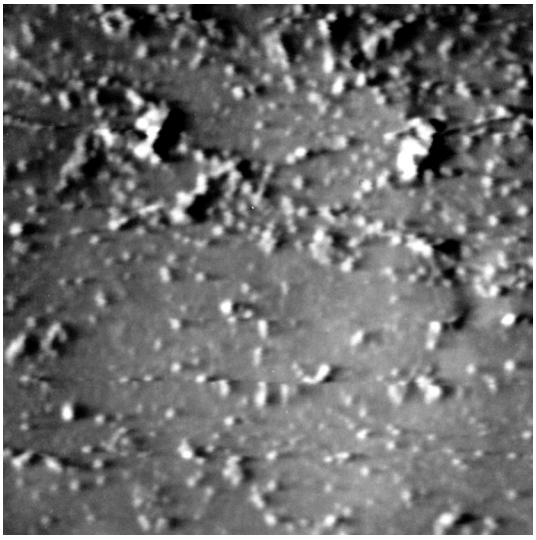

Figure 1 Large quantity of vitreous cortex shown on the inner limiting membrane surface in group I (scanning electron microscopy, ×500).

Figure 2 Vitreous cortex attached on the inner limiting membrane surface of group II but sparser than in group I (scanning electron microscopy, ×500).

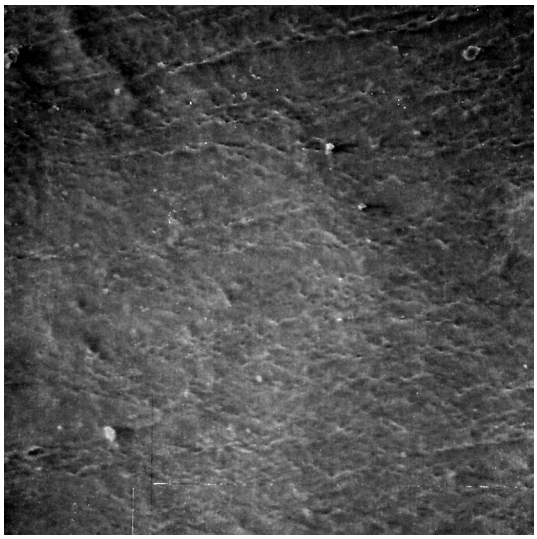

Figure 3 Smooth surface of the inner limiting membrane in group III with scattered areas of punctate vitreous cortex (scanning electron microscopy, ×200).

Effect of Anterior Vitrectomy on Vitreous Structure The vitreous consists of 98% water and 2% type II collagen fibers, and hyaluronic acid. Collagen fibers from a net stent in three dimensional structures, filled with hyaluronic acid, and large quantities of water molecules are contained to keep the collagen fibers open and prevent agglomeration. Together, they maintain the stability of the vitreous gel structure. Once the collagen starts to agglomerate, the collagen fiber stent collapses, and liquefaction occurs in the vitreous body[13-14]. As a result of aging, progressive spontaneous liquefaction of the vitreous body may take place[15]. By the age of 90, most of the vitreous body is liquefied[16-17]. The occurrence of vitreous liquefaction can be accelerated by some pathological causes such as inflammation, trauma, and bleeding[18-20]. In this study, the liquefaction rate of the simple lens aspiration group (Group II) was 26.33%, similar to the untreated control group (Group I, which was 24.36%), and did not demonstrate any obvious vitreous liquefaction. However, when combined with anterior vitrectomy (Group III), the vitreous liquefaction was much higher than Group I indicating that the anterior vitrectomy had an effect on the gel structure of the vitreous body. Due to a certain level of collagen content in the vitreous body, the collagen fiber agglomerates in the condensed vitreous body causing a relative increase in content of collagen when vitreous liquefaction occurs. Compared with Groups I and II, Group III had less vitreous gel content and significantly decreased extension range (P<0.05). However, the collagen content of the vitreous gel in Group III was increased. These results suggest that anterior vitrectomy has an effect on gel structure, as well as vitreous liquefaction and condensation.

Our results demonstrate that anterior vitrectomy causes a loss of gel mass and possible loss of elasticity. The mechanism of anterior vitrectomy accelerating vitreous liquefaction may be that anterior vitrectomy destroys the net stent supported by collagen fiber when it is removed from the vitreous body. The vitreous gel structure is altered when the water-like liquid is separated from the vitreous humor due to changes in the rheological properties of the gel component. The loss of gel mass may result from a number of reasons including syneresis, clotting, shrinkage of the three-dimensional meshwork, cracking or tearing of the meshwork, reduced gel strength, reduced elasticity, viscosity changes, and protein modifications that break down the meshwork, among others[21]. At the same time, the damage to the integrated vitreous body reduces its capacity to block the entry of intravascular macromolecules into the vitreous body. The inflammatory reaction after surgery also causes the cells to release phospholipase and arachidonic acid[22]. The latter is converted into prostaglandin (PG), which increases the permeability of blood vessels, destroys the blood-retinal barrier, among others and accelerates its liquefaction. The concentration of some serum components, such as

fibronectin (FN) and transglutaminase (TG), in the vitreous may increase because of increased vascular permeability. Studies have shown that[23-24] FN and TG contributed to the formation of cross links between vitreous collagen (and other factors possibly contributed to crosslink formation during ocular diseases), which could trigger collagen gel contraction. The formation of collagen-FN-collagen crosslinks catalyzed by TG may play a major role in the vitreous contraction observed in several vitreoretinal disorders[21,25].

Clinical Significance of the Vitreous Liquefaction after Anterior Vitrectomy Many retinal diseases are related to abnormalities of the vitreous structure. The liquefaction of the vitreous body promotes the occurrence of posterior vitreous detachment, which has been proved by our SEM observation in this study. The images showed that there were large quantities of tray-like and flake-like remaining vitreous cortex on the surface of ILM in Groups I and II, but very little vitreous cortex was left in Group III and the retinal ILM was relatively smooth. These results indicated that complete posterior vitreous detachment occurred in Group III. Once posterior vitreous detachment takes place, the mobility of the vitreous and retraction of collagen fibers in the condensed vitreous body increase. The traction on the corresponding retinal tissue at the vitreous-retinal adherence position is elevated. A retinal tear caused by such traction may lead to retinal detachment. At the same time, the traction due to proliferation of peripheral vitreous body after surgery of cataract may also promote the formation of retinal tears[26]. It has been reported that the relative risk of rhegmatogenous retinal detachment post-cataract surgery was approximately 2.3 times higher than without surgery[27]. In addition, it is interesting to compare the axial lengths of eyes that undergo retinal detachment with normal eyes, since greater axial length is associated with a higher risk of retinal detachment[28]. Previous studies of the risk of retinal detachment after pediatric cataract surgery have had short follow-up periods (3.5 to 6.8y) and were based only on aphakic eyes[5-6]. In one study, retinal detachment is estimated to occur in 3% of children within the first 20y after surgery for isolated pediatric cataracts[29]. Generally, most cases of rhegmatogenous retinal detachment occur in the elderly. Therefore, the occurrence of retinal detachment after cataract extraction with anterior vitrectomy is clearly earlier than expected.

The collagen fibers located around the lens are firmly attached to the posterior lens capsule and end at the basilar membrane of the macula. Anterior vitrectomy produces a mechanical traction on these fiber. This traction may be transferred to the macula, leading to pathological changes of the vitreous body and macula. Posterior vitreous detachment caused by vitreous liquefaction could increase the liquefied vitreous mobility and contracting of vitreous collagen fiber, which may result in the development of vitreous-macular traction syndrome or macular edema at the macula a position where the vitreous body is very tightly attached to retina[30]. In adult patients with aphakic cystoids, the incidence of macular edema was much higher than that of those people without cystoids[31]. In the follow-up studies of pediatric patients who underwent surgery with simple lens aspiration and lensectomy combined with anterior vitrectomy for congenital cataracts, Hoyt and Nickel[32] proposed that the incidence of cystoid macular edema in the eyes underwent lensectomy with anterior vitrectomy was much higher than those that did not undergo anterior vitrectomy. He did not advocate anterior vitrectomy in cataract surgery except when treating complicated infantile cataracts. These clinical reports indicate that anterior vitrectomy may increase and/or accelerate the occurrence of complications after cataract surgery, which further verifies the clinical significance of our results.

Clinical Suggestions In summary, the result of the present study has shown that lensectomy with anterior vitrectomy on baby rabbit eyes can decrease the vitreous gel content and extension range. These findings suggest that damage to the vitreous structure may cause additional severe vitreous retinal pathological changes compared with after-cataracts. This study used rabbit's eye since it shares many similarities with the human eye anatomically[33]. However, the rabbit eye is of the half-vessel type in the fundus, while the human eye is of the pan-vessel type. The rabbit retinal vessels are very superficial; the outer layer of the retina is supplied by the capillary network of the choroid, so even a slight change in avascular retinal area may be amplified[34]. Therefore, histologically, the rabbit eye cannot tolerate external insults as effectively as the human eye. The inflammatory reaction of the rabbit eye is relatively severe and the exudation membrane forms easily, leading to the acceleration of vitreous body liquefaction. Similarly, the inflammatory reaction after cataract surgery in infants is more severe and lasts longer than in adult patients, in which it is related to the high reactiveness of tissues and incomplete development of the blood-eye barrier[35]. Therefore, after surgery for congenital cataracts, it is much easier for a fibromembrane to from behind the iris and around pupils. Its extensive adherence with the iris and ciliary body could also promote the occurrence of anterior proliferative vitreoretinopathy (aPVR), which is also an important factor in causing retinal detachment after surgery for congenital cataracts. At the same time, lensectomy with anterior vitrectomy cannot completely prevent the formation of after-cataract. Worse, the incidence of retinal detachment is increased due to the proliferation of the vitreous body[36]. In this study, the comparison between the short-term follow-up of different surgical procedures showed differences in the

vitreous gel content and extensive range, despite not finding any retinal detachment during this observation period. Thus, we need large, long-term studies to examine the changes in the three-dimensional mesh structure of the vitreous after pediatric cataract surgery. Given that the rabbit eye does not provide a representative model for congenital cataracts in infants, future studies should aim to extend these investigations to infants' cataracts. In conclusion, the results of the present study provide an experimental basis for choosing the appropriate surgical method for treating congenital cataracts. Further long-term studies are suggested to determine whether lensectomy combined with anterior vitrectomy for pediatric patients increases the incidence of long-term complications.

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