



# Clinical Feasibility and Safety of Scleral Collagen Cross-Linking by Riboflavin and Ultraviolet A in Pathological Myopia Blindness: A Pilot Study

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## ABSTRACT

**Introduction:** To investigate the feasibility and safety of scleral ultraviolet A (UVA) cross-linking (scleral CXL) on pathologically blindness.

**Methods:** This was a prospective, observational clinical study. Five patients with monocular blindness due to pathological myopic maculopathy were enrolled. Eyes with best corrected visual acuity (BCVA) under 0.05 were defined as experimental eyes. The fellow eyes were defined as control eyes. Patients first underwent posterior scleral reinforcement (PSR) surgery in the

control eye. Thereafter, scleral CXL surgery was performed in the experimental eye on the same day. Visual acuity, BCVA, slit lamp biomicroscopic examination, intraocular pressure measurement, corneal specula microscopies, axis length measurement, funduscopy with pupil dilation, color fundus photography, full-field flash electroretinography, optical coherence tomography, and color Doppler flow imaging were performed at baseline, 1 week, 1 month, 3 months, 6 months, and 12 months after surgery.

**Results:** No signs of inflammation were observed after operation and throughout the follow-up period. Retinoschisis was improved, while choroidal neovascularization fibrosis and retinal and choroidal atrophy were unchanged after scleral CXL. There were no statistically significant differences in the ophthalmic artery, central retinal artery, and posterior ciliary artery parameters of color Doppler flow imaging or in retinal thickness, within experimental and control eyes, at baseline, 1 week, 1 month, 3 months, or 12 months ( $P > 0.05$ ).

**Conclusions:** This pilot study verified the feasibility and safety of scleral CXL on human blindness. The UVA-CXL on the sclera of human eyes seems to have the same effect as PSR in preventing progressive pathological myopia in the future.

**Trial Registration:** Chinese Clinical Trial Registry (ChiCTR2100042422).

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**Keywords:** Clinic; Cross-linking; Pathological myopia; Safety; Sclera

### Key Summary Points

Pathological myopia is among the major causes of visual impairment worldwide.

Scleral cross-linking (CXL) can increase scleral biomechanics and control the progression of myopia.

Scleral CXL was applied at the clinic in order to evaluate the feasibility and safety of this procedure.

Scleral CXL has the same effect as posterior scleral reinforcement in preventing progressive pathological myopia.

Scleral CXL may be a potential method to control the progression of myopia at clinic.

## INTRODUCTION

Pathological myopia is among the major causes of visual impairment worldwide [1, 2]. There are currently about 163 million people with high myopia in the world, and this number is expected to increase to about 943 million by 2050 [3]. With the deepening of myopia, which involves excessive elongation of the eye axis, the eye develops various pathological changes, including posterior scleral staphyloma, myopic macular disease, and optic neuropathy. High myopia is a major cause of legal blindness worldwide, and particularly in Asian countries [4].

Pathological myopia-related fundus complications refer to a range of chorioretinal lesions that develop secondary to myopia. Patchy atrophy, macular atrophy, and choroidal neovascularization (CNV) cause irreversible and usually bilateral visual impairment in working-age individuals [5, 6]. Currently, there are no

effective treatments for advanced retinal choroidal atrophy in myopic macular disease. Thus, early prevention of the development of myopia, before excessive axial elongation occurs, is crucial.

Posterior scleral reinforcement (PSR) surgery is currently the operation most commonly performed to control myopia progression [7]. A scleral graft is placed over the macular area by insertion of the inferior oblique muscle, and the two ends of the graft are sutured to the superior and inferior nasal quadrants, wrapping the posterior pole. A recent study revealed that PSR may maintain the microcirculation of eyes with posterior staphyloma and thereby stabilize the best-corrected visual acuity [8, 9].

Riboflavin/UVA scleral cross-linking (CXL) is another potential treatment for progressive pathologic myopia. It was initially demonstrated by Wollensak and Spoerl [10]. Many studies have confirmed the efficacy of this treatment in strengthening scleral tissue by creating cross-links in the collagen of the sclera [11–13]. Our research group has also done a lot of work on scleral CXL. Proposed the saturation time point of riboflavin infiltration of the sclera, and formulated a riboflavin infiltration plan [14]. Since posterior pole scleral CXL is not convenient to operate in clinical practice and may damage the optic nerve, we investigated the differences in biomechanical changes of posterior and equatorial scleral CXL, and found that equatorial scleral CXL can have the same effect of preventing axial growth [11]. We further verified the long-term safety and efficacy of the scleral CXL in the eyes of rhesus monkeys [15, 16]. The results confirmed that the scleral CXL is safe and effective, which laid the foundation for the application of clinically preventing myopia axial growth.

Therefore, in this pilot study, we applied scleral CXL to individuals with clinical pathological blindness in one eye, in order to evaluate the feasibility and safety of this procedure, in comparison with PSR surgery performed in the fellow eye, with a view to applying the scleral CXL procedure for clinical prevention and control of myopia.

## METHODS

### Subjects

This was a prospective, observational clinical study involving five patients with pathological myopia, from June 2020 to June 2021, at the Department of Ophthalmology of Beijing Tongren Hospital. All patients were blind as a result of pathological myopic maculopathy in a single eye. We excluded patients with glaucoma, corneal opacities, uveitis, retinal vascular disease, retinal detachment, and non-myopia-related maculopathy, as well as those with a history of intraocular surgery other than cataract surgery. The eyes with best-corrected visual acuity (BCVA) under 0.05 were defined as experimental eyes, while the fellow eyes were defined as control eyes. This study was approved by the Institutional Ethics Committee of Beijing Tongren Hospital (ChiCTR2100042422), Capital Medical University, and was conducted in accordance with the tenets of the Declaration of Helsinki. All participants provided signed informed consent for their participation.

### Clinical Examination

Patients were followed up at 1 week, 1 month, 3 months, 6 months, and 12 months after surgery. Preoperative and postoperative examinations included UCVA, BCVA, slit lamp biomicroscopy, intraocular pressure (IOP) and axis length measurement using the IOL Master (Carl Zeiss Inc., Jena, Germany), dilated-pupil funduscopy, color fundus photography (Hybrid Digital Mydriatic Retinal Camera CX-1, Canon Inc., Tokyo, Japan and Optos 200TX, Optos plc; Dunfermline, Scotland), and full-field flash electroretinography (f-ERG; RETIport® system; Roland, Wiesbaden, Germany). Manifest refraction was performed by two qualified optometrists. The decimal VA was converted into logMAR values for statistical analysis.

### Measurement of Color Doppler Flow

Color Doppler flow imaging (CDFI) was obtained using the commercial MyLab90 device

(Esaote, Genova, Italy). The peak systolic velocity, end-diastolic velocity, and resistivity index parameters of the ophthalmic artery (OA), central retinal artery (CRA), and posterior ciliary artery (PCA) were measured in all eyes by a single experienced radiologist. Patients were placed in the supine position with their eyes closed and were asked not to move their eyes to avoid creating artifacts. A probe with a sufficient quantity of gel was placed on the upper eyelid, avoiding the use of excessive pressure.

### Measurement of Retinal Thickness

Both eyes of each patient were scanned using the Swept-Source optical coherence tomography (OCT) device (Ver 9.0.0281, Carl Zeiss Meditec, Inc.). The automatic eye tracking technology maintains fixation on the retina. Macular and retinal thickness measurements of the nine Early Treatment Diabetic Retinopathy Study (ETDRS) subfields from a 6-mm<sup>2</sup> area were analyzed. The nine macular sectoral subfields were the 1-mm central, four intermediate zones, and four outer zones (superior, temporal, inferior, and nasal). The numerical values recorded for each of the nine zones were used in the analysis of retinal thickness.

### Surgery

Under general anesthesia, the patient first underwent PSR surgery in the control eye, followed by scleral CXL surgery in the experimental eye. Each eye was re-sterilized as for an independent operation. All PSR surgery was performed by YQ and all scleral CXL surgery was performed by FJZ.

### PSR Surgery

Under general anesthesia, a 210° peritomy of the conjunctiva was performed along the inferior-temporal axis of the limbus, and the inferior and lateral rectus muscles were isolated and exposed. The two muscles were maneuvered by traction sutures while the eyeball was pulled toward the superior nasal side. After the inferior oblique muscle was isolated, a homologous

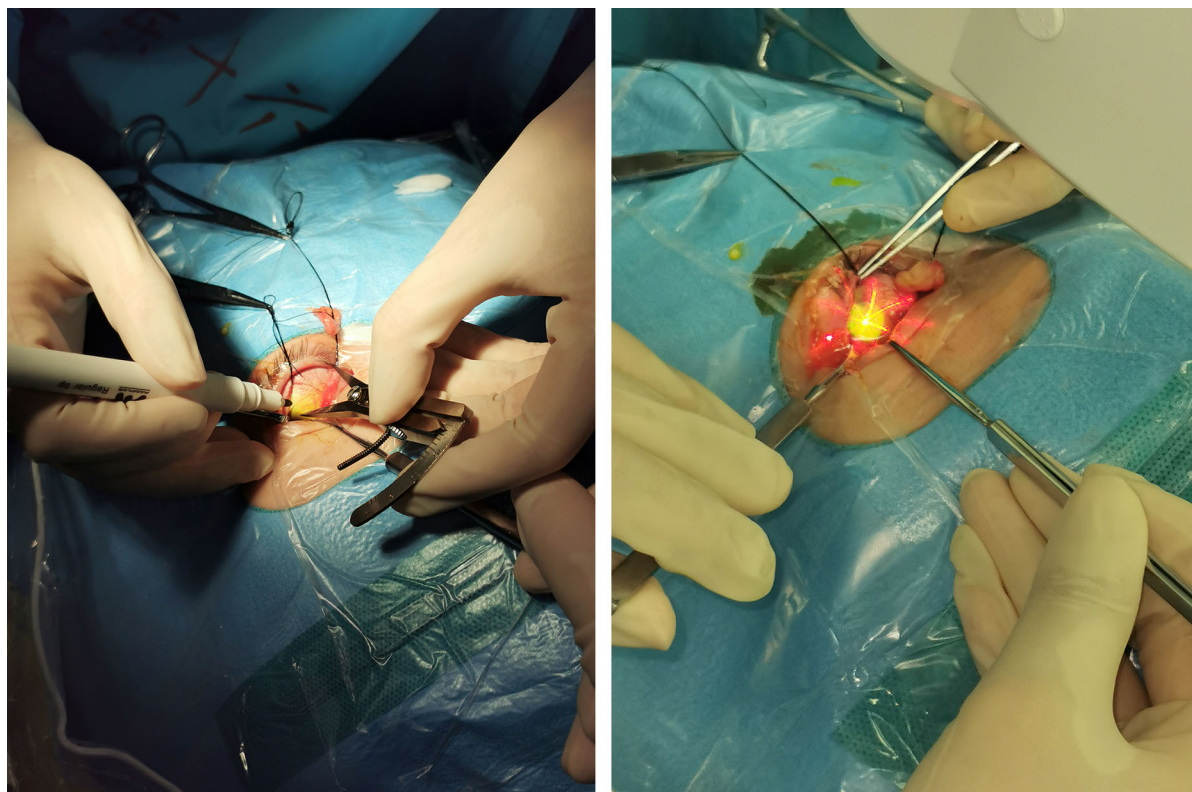
human scleral strip with a width of 6–10 mm was sequentially inserted underneath the lateral rectus, inferior oblique, and inferior rectus muscles. The superior end of the strip was fixed at the nasal side of the scleral insertion of the superior rectus muscle, while the inferior end of the strip was anchored at the nasal side of the scleral insertion of the inferior rectus muscle. The scleral strip was stretched into a U-shape to wrap around the posterior pole and the scleral staphyloma corresponding to the macular area and was flattened with the help of strabismus hooks. The relative position between the scleral strip and optic nerve was checked with a strabismus hook. The distance was kept at approximately 1 mm to ensure that the strip covered the foveal region without compressing the optic nerve. The whole operation took about 40 min.

### Scleral CXL

Under general anesthesia, a 180° peritomy of the conjunctiva was performed along the

inferior–temporal axis of the limbus, and the inferior and lateral rectus muscles were isolated and maneuvered by traction sutures to rotate the eyeball to expose the irradiation zones. The irradiation zone was 10 mm in diameter at the inferior temporal equatorial sclera, which was from 2 mm before the equator to 8 mm behind the equator. Photosensitizer solution containing 0.1% riboflavin (0.1% riboflavin, 20% Dextran 500, Peschke D, PESCHKE Trade, Hünenberg, Switzerland) was dropped once every minute onto the irradiation zone 30 min before and during the 30-min irradiation period.

UVA irradiation (365 nm) was applied perpendicular to the sclera of the CXL eyes by means of a UVA device (UV-X 1000, Avedro, Waltham, America) with a surface irradiance of 3.0 mW/cm<sup>2</sup> for a period of 30 min (total dose of UVA, 5.4 J/cm<sup>2</sup>) (Fig. 1). The whole operation took about 1 h.



**Fig. 1** Scleral CXL procedure

After surgery, the preset sutures were removed, and the conjunctiva was sutured with absorbable surgical sutures. A 0.3% gatifloxacin eye gel and tobramycin dexamethasone were applied to all eyes four times a day for 1 week to avoid infection.

### Statistical Analysis

SPSS version 18.0 (SPSS, Chicago, IL, USA) was used for all statistical analyses. Measurements are presented as mean  $\pm$  standard deviation. Two-way repeated measures analysis of variance (ANOVA) was used to assess the differences among the eyes at baseline and the scheduled follow-up time points and differences between experimental eyes and control eyes.  $P < 0.05$  was considered statistically significant.

## RESULTS

Five patients with 10 eyes diagnosed with pathological myopia were recruited. Patient 2 had renal failure, so follow-up was not completed after 3 months. As a result of the impact of COVID-19, the other four patients all missed

the 6-month postoperative follow-up but completed 12 months follow-up.

Table 1 shows the baseline characteristics of patients' eyes. The mean SE was  $-22.13 \pm 5.57$  D and the mean AL was  $33.04 \pm 3.59$  mm in the experimental eyes, while the mean SE was  $-18.25 \pm 7.64$  D and the mean AL was  $31.91 \pm 4.29$  mm in the control eyes. Figure 2 shows the state of the fundus in these eyes. In experimental eyes, OCT showed retinoschisis in two eyes, CNV fibrosis in one eye, and retinal atrophy in two eyes. In control eyes, OCT showed retinoschisis in two eyes, CNV fibrosis in one eye, retinal atrophy in one eye, while one eye appeared relatively normal (Fig. 2). Figure 3 shows the baseline retinal thickness of both experimental eyes and control eyes.

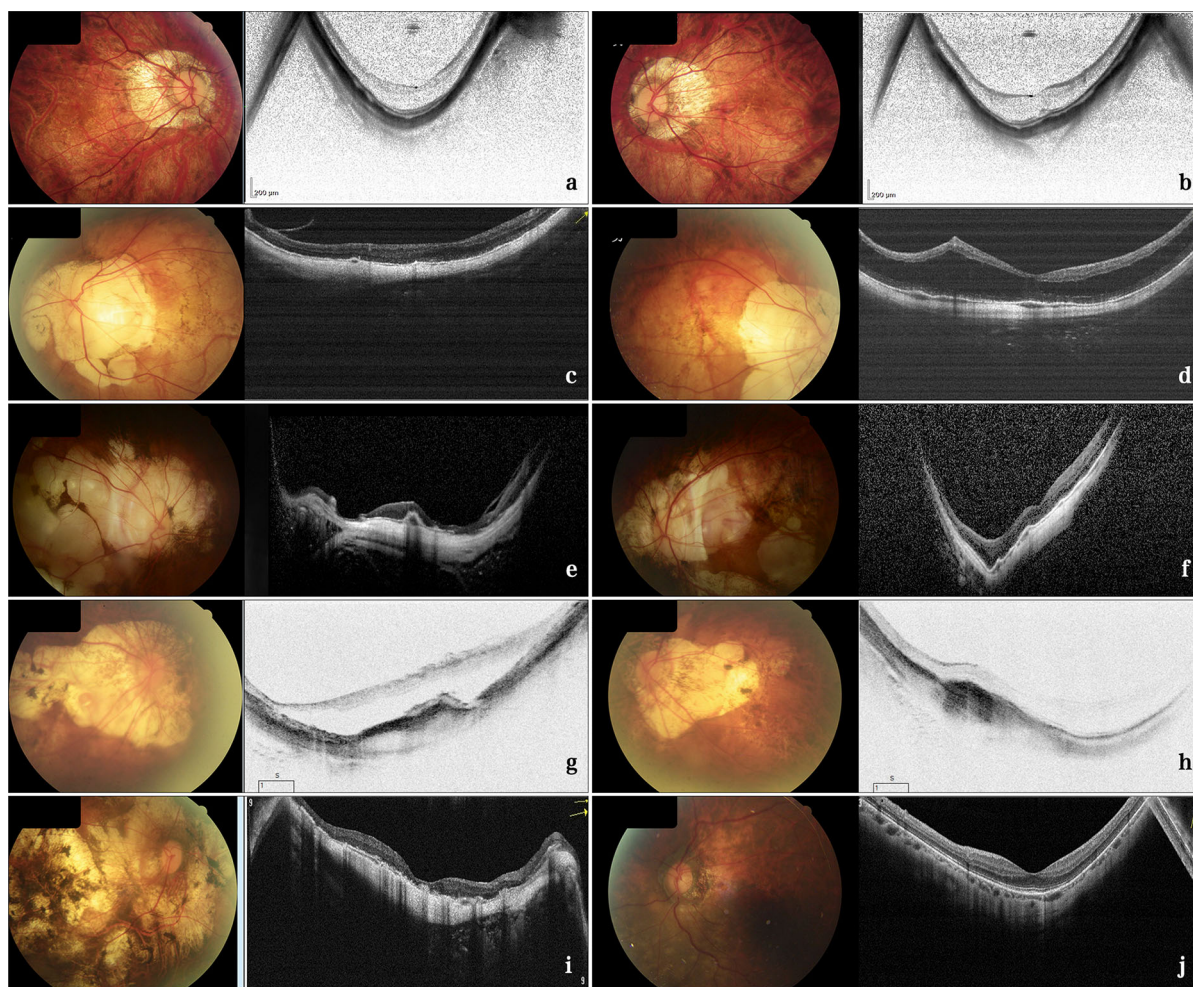
No signs of inflammation were observed after surgery or throughout the follow-up period. After surgery, none of the patients had any symptoms such as redness or eye pain. Conjunctival sutures were removed under a slit lamp at 1 week after surgery. The conjunctiva was well aligned, no conjunctival granulomas were formed, and no complications, such as scleral dissolution, occurred.

**Table 1** General patient characteristics

Patient no.	Age (years)	Sex	Eye	BCVA	SE (D)	AL (mm)	Cells (/mm <sup>2</sup> )
1	30	Male	E	0.05	- 29.00	37.75	3012.9
			C	0.1	- 29.00	37.74	2863.1
2	65	Male	E	LP	- 20.50	32.08	2390.5
			C	0.2	- 14.50	30.55	2317.5
3 <sup>a</sup>	71	Female	E	0.03	+ 0.50	35.63	1374.1
			C	0.3	- 1.50	34.81	2408.6
4	80	Female	E	FC	- 15.50	29.01	2325.8
			C	0.2	- 15.50	29.32	2582.5
5	55	Female	E	FC	- 22.00	30.72	3579.4
			C	0.8	- 12.50	27.15	3558.3

*E* experimental eye, *C* control eye, *BCVA* best corrected visual acuity, *SE* spherical equivalent, *AL* axial length, *Cells* corneal endothelial cells, *LP* light perception, *FC* finger counting

<sup>a</sup>Received phaco + intraocular lens 5 years previously



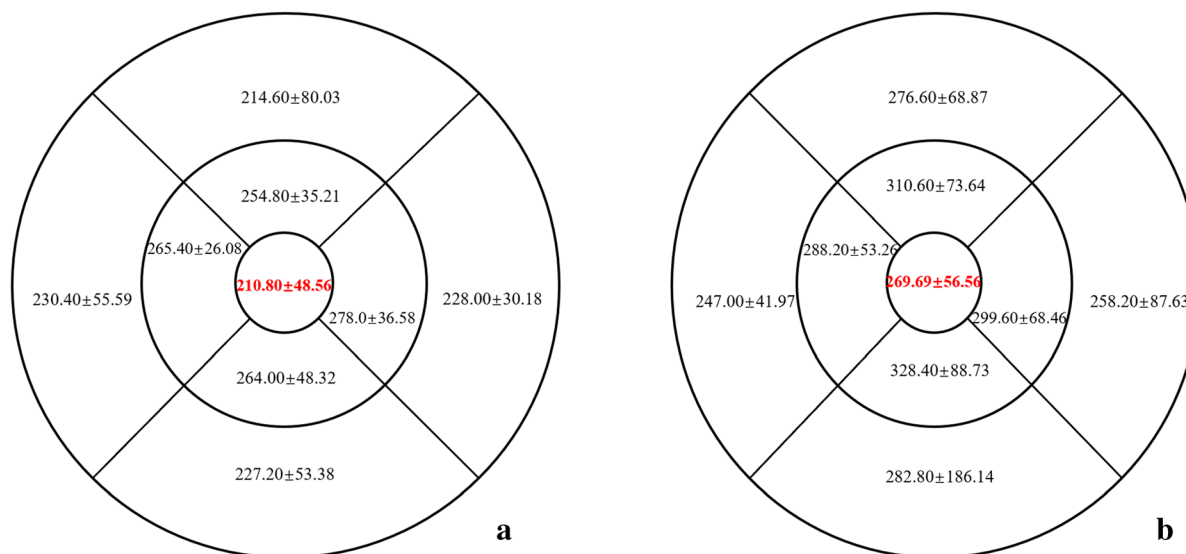
**Fig. 2** Fundus situation at baseline. **a** Experimental and **b** control eye of patient 1; **c** experimental and **d** control eye of patient 2; **e** experimental and **f** control eye of

patient 3; **g** experimental and **h** control eye of patient 4; **i** experimental and **j** control eye of patient 5

Table 2 shows the spherical equivalent and axial length (AL) at different pre- and postoperative periods in experimental eyes and control eyes. The differences within groups were not significant ( $P > 0.05$ ). It is noteworthy that the fluctuations of patients 1's SE was relatively large ( $-29.00$  D/ $-29.00$  D at baseline, and  $-40.00$  D/ $-40.00$  D,  $-33.00$  D/ $-30.00$  D,  $-40.00$  D/ $-40.00$  D, and  $-38.00$  D/ $-37.00$  D in the experimental eye/control eye at 1 week, 1 month, 3 months, and 12 months, respectively). The other four patients' SE values were relatively stable. At the last follow-up, the axial length of both experimental and control eyes was slightly prolonged in three patients, while

the axial length of other two patients was shortened (Table 2). The corneal endothelial counts of baseline were  $2536.54 \pm 826.35$  and  $2746.00 \pm 499.43$  in experimental eye and control eye, respectively; those at last follow-up were  $2409.65 \pm 915.91$  and  $2697.80 \pm 32.95$ , respectively. The difference is not statistically significant. Intraocular pressure was in the normal range at all postoperative time points.

The stability and reliability of the f-ERG data were poor because three patients could not tolerate the corneal electrode and had poor fixation. The f-ERG examination was explicitly refused by these patients at postoperative follow-up time.



**Fig. 3** Baseline retinal thickness of both experimental eyes and control eyes

The fundus conditions at the last follow-up are shown in Fig. 4. After the pupils were dilated, the fundus was checked carefully, and no retinal necrosis or pigment disorder was found in the experimental eyes at the irradiation zones. OCT examination showed complete retinoschisis resolution in both of patient 1's eyes, partial resolution in both of patient 4's eyes (with a little fold in the control eye), and a slight change in patient 2's control eye. OCT also showed that myopic CNV fibrosis was unchanged in both patient 3's eyes and patient 4's control eyes. Retinal and choroidal atrophy of both of patient 5's eyes remained unchanged. Thus, taken together, retinoschisis was improved, while CNV fibrosis and retinal and choroidal atrophy were unchanged after both surgeries.

The OA, CRA, and PCA parameters of CDFI are shown in Fig. 5. There were no statistically significant differences between or within experimental and control eyes at baseline, or at 1 week, 1 month, 3 months, or 12 months post-procedure.

The differences of central retinal thickness between experimental and control eyes at baseline were significant, while there were no statistically significant differences between or within experimental and control eyes at baseline, or at 1-week, 1-month, 3-months, or

12-months postoperatively in other area. (Fig. 6).

## DISCUSSION

Pathological myopia has been reported as the primary cause of blindness or low vision in 12–27% of the world's population, and is particularly prevalent in Asia [2, 17]. The excessive axial elongation and associated local ectasia of the posterior sclera eventually lead to characteristic retinal and choroidal lesions [18]. Thus, there is an urgent need for a method to slow down the progression of myopia and to avoid complications.

Previous studies have shown that scleral CXL techniques can strengthen scleral biomechanical rigidity [15] and control myopia progression [19]. We previously verified the long-term safety of scleral CXL in rhesus monkeys' eyes, both in terms of ocular biological parameters in vivo and histopathological parameters in vitro. There are still some differences between human eyes and rhesus monkey eyes. Before applying this method to clinically prevent and control myopia progression on a large scale, we still need to explore the feasibility and safety of scleral CXL in human eyes. Posterior scleral reinforcement (PSR) is the most widely used

**Table 2** Axial length and SE at different time points before and after surgery in experimental and control eyes

Patient no.	Eye	Baseline		1 week		1 month		3 months		12 months	
		AL (mm)	SE (D)	AL (mm)	SE (D)	AL (mm)	SE (D)	AL (mm)	SE (D)	AL (mm)	SE (D)
1	E	37.75	– 29.00	37.72	– 40.00	37.99	– 33.00	37.95	– 40.00	38.03	– 38.00
	C	37.74	– 29.00	37.72	– 40.00	37.83	– 30.00	37.87	– 40.00	37.96	– 37.00
2	E	32.08	– 20.50	32.01	– 32.00	32.10	– 32.00	32.14	– 32.00	–	–
	C	30.55	– 14.50	30.65	– 19.50	30.53	– 18.50	30.60	– 18.00	–	–
3	E	35.63	+ 0.50	35.61	– 3.25	34.79	– 3.25	35.88	– 2.50	36.03	– 2.25
	C	34.81	– 1.50	34.68	– 2.25	34.76	– 2.25	34.99	– 2.25	35.06	– 2.25
4	E	29.01	– 15.50	28.88	– 13.50	28.96	– 14.50	28.83	– 13.50	28.87	– 13.75
	C	29.32	– 15.50	29.33	– 17.25	29.28	– 17.75	29.34	– 17.75	29.44	– 17.75
5	E	30.72	– 21.50	30.35	– 26.25	30.55	– 28.75	30.55	– 27.50	30.20	– 23.50
	C	27.15	– 12.00	27.11	– 12.75	27.09	– 13.25	27.10	– 12.75	27.19	– 12.75

*E* experimental eye, *C* control eye, *AL* axial length, *SE* spherical equivalent

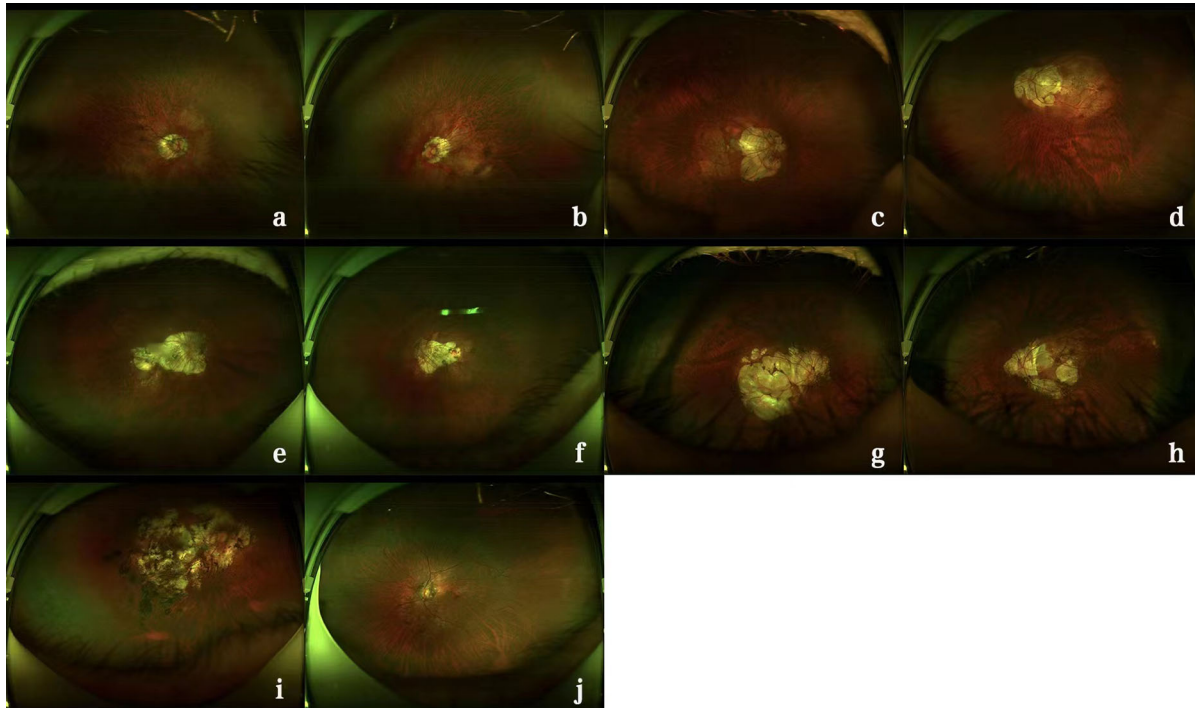
method to control the progress of high myopia. Compared with PSR, scleral CXL forms additional covalent bonds between stromal collagen molecules, which not only solved the problem of insufficient reinforcement material but also reduced the complications associated with foreign implants. Therefore, we considered it important to investigate the feasibility and safety of scleral CXL in pathologically blind eyes, and compare with PSR to see whether it has the same effect, in view of applying this procedure clinically for prevention and control of myopia instead of PSR.

In the present study, we used scleral CXL in pathologically blind human eyes, which has not been reported previously. The surgical plan was improved compared to that in the original

animal study. A method to effectively expose the equatorial posterior sclera without severing the muscle was explored and realized. This guaranteed the effectiveness of the operation. Thus we here succeeded in transfer of the technique of scleral CXL from animal experimental eyes to clinical human eyes. No signs of inflammation were observed after either type of surgery, or throughout the follow-up period. At the last follow-up, patients' feelings and satisfaction with both surgery types were surveyed, and all patients reported experiencing greater comfort in the experimental eye.

No signs of inflammation were found after surgery or throughout the follow-up period. In the analysis of ocular biometry, the refractive status, AL, and central retinal thickness were





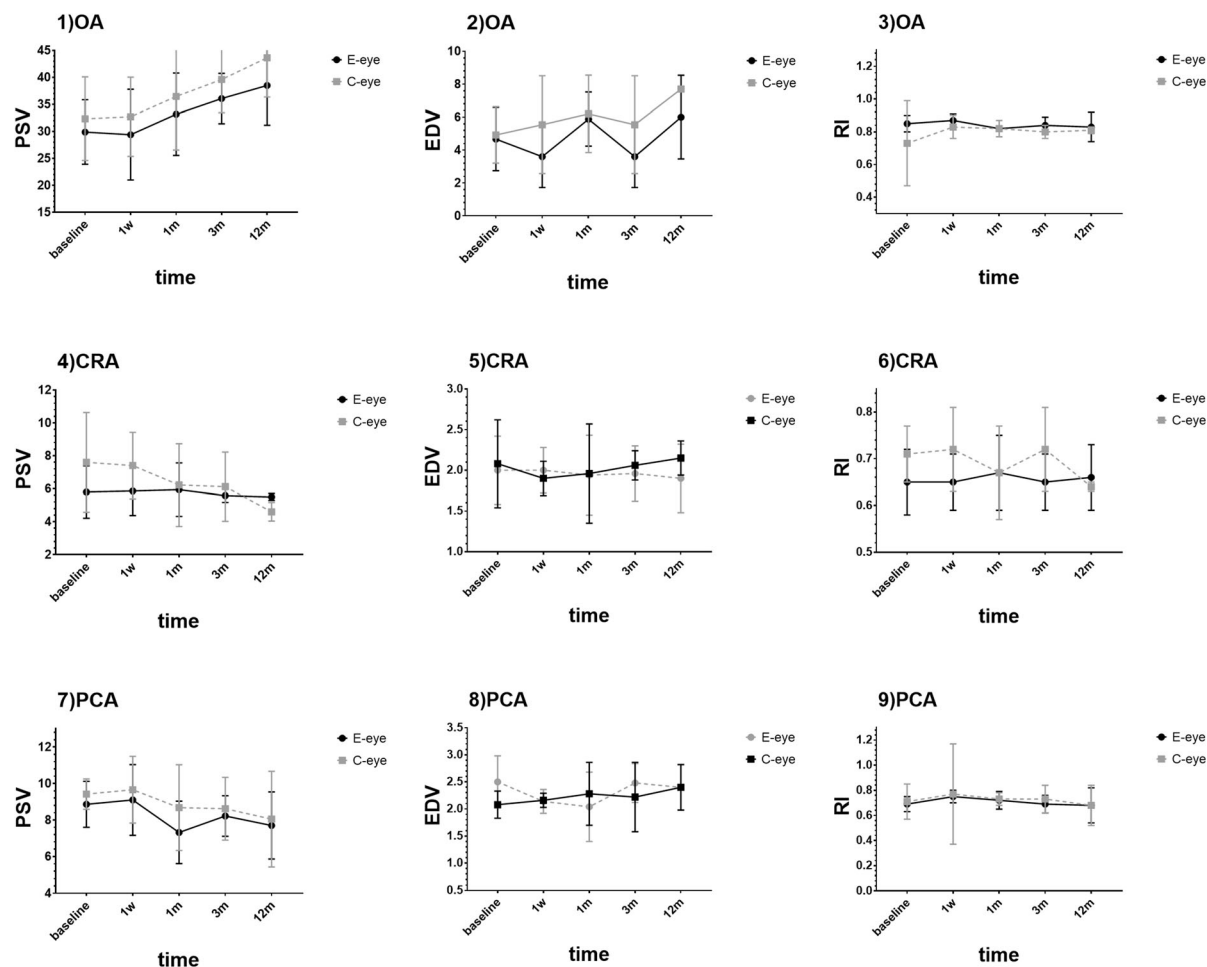
**Fig. 4** Color fundus photography (optos) at last follow-up. **a** Experimental and **b** control eye of patient 1; **c** control and **d** experimental eye of patient 2;

**e** experimental and **f** control eye of patient 3; **g** experimental and **h** control eye of patient 4; **i** experimental and **j** control eye of patient 5

significantly worse in the experimental eyes at baseline, while the differences at any of the time points within experimental eyes and control eyes were not significant. There were no significant differences in corneal endothelial counts between and within experimental eyes and control eyes at any of the follow-up time points. The results were consistent with our previous experiments [16, 20, 21], illustrating that scleral CXL did not affect basic ocular biological parameters of pathologically blind eyes. Retinoschisis was improved, while CNV fibrosis and retinal and choroidal atrophy were unchanged after scleral CXL.

At the last follow-up, the axial length of both experimental and control eyes was slightly prolonged in three patients, while the axial length of other two patients was shortened. Although the effectiveness of scleral CXL in controlling the axial length is not yet clear, it can be speculated from these five patients that its maintenance effect on axial length may be equivalent to that of PSR.

Previous studies [22, 23] showed that the central retinal thickness of high myopia was about 273.62  $\mu\text{m}$ , while the central retinal thickness of experimental eyes in our research was significantly thinner at about 210.80  $\mu\text{m}$ . In this case, the retina is more likely to progress and become thinner or thicker as a result of CNV, edema, and hemorrhage. Qiao et al. [24] found that the retinal thickness of the parafovea sector decreased significantly after PSR, which they attributed to relaxation of anterior directed forces from the internal limiting membrane or adherent vitreous cortex. In this research, we found that retinoschisis was improved, and CNV fibrosis and retinal and choroidal atrophy were unchanged 12 months postoperatively after both surgeries. And the differences within experimental and control eyes at baseline, or at 1 week, 1 month, 3 months, or 12 months postoperatively were not statistically significant. We believe that both surgical methods can prevent further

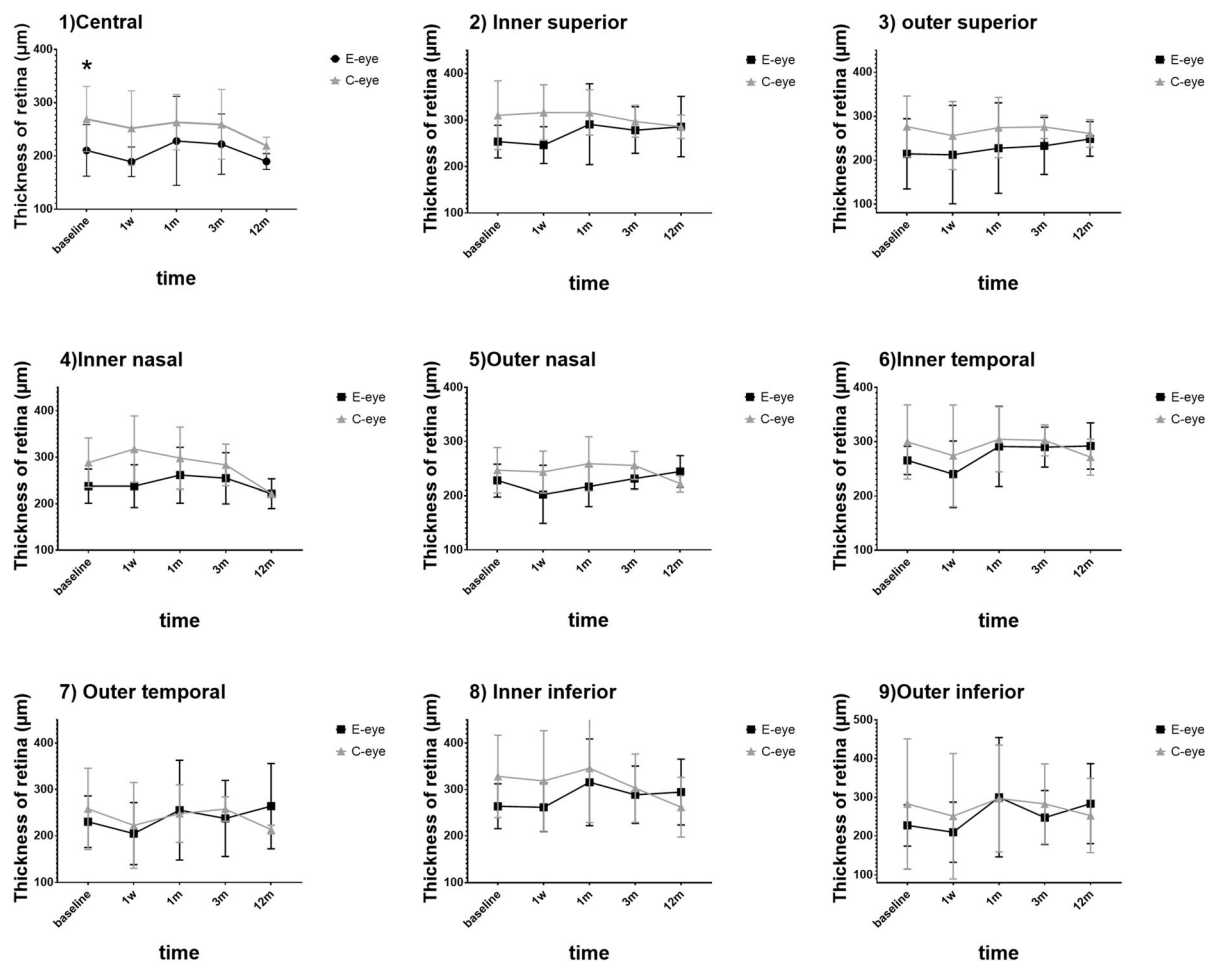


**Fig. 5** Preoperative and postoperative measurements of PSV, EDV, RI in OA, CRA, and PCA. CRA, central retinal artery; EDV, end diastolic velocity; PCA, posterior ciliary artery; OA, ophthalmic artery; RI, resistive index

deterioration of fundus lesions to a certain extent.

The vessel density of the superficial capillary plexus and choroidal thickness monitored by OCT angiography (OCTA) were initially assessed. As a result of the markedly long AL and lack of fixation of the blinded experimental eye, it was difficult to capture accurate data. Therefore, the OCTA test was abandoned. CDFI is another noninvasive and quantitative method for monitoring vascular hemodynamics [25, 26]. In the present study, retinoschisis and CNV occurred at different degrees in the fundus of each of the five patients. Previous studies found that PSR can improve CNV and macular splitting in pathological myopia cases [27, 28]. It can increase postoperative choroidal blood flow and improve the macular ischemic and hypoxic

environment through retrobulbar stimulation and generation of new, nourishing blood vessels. However, some studies reported that only early blood flow (6 months) was improved after posterior scleral reinforcement, while no significant long-term difference was found by color Doppler ultrasonography [29]. Ozen and Aslan [25] evaluated late monocular blindness through color Doppler ultrasonography and showed that vascular hemodynamics were not affected. In the present study, we evaluated the retrobulbar flow parameters of the scleral CXL eyes and compared them with those of the PSR eyes. We found no statistically significant differences in these parameters between or within experimental and control eyes at baseline, or at 1 week, 1 month, 3 months, and 12 months postoperatively. However, there was a non-



**Fig. 6** Preoperative and postoperative measurements of retinal thickness

statistically significant but notable slightly improving trend of blood flow at the posterior pole after CXL, while the blood flow after PSR showed a downward trend at 12 months (Fig. 5). This result was consistent with previous studies [9, 29], reflecting that PSR can only improve short-term blood flow and had no long-term effect. Although the difference between experimental and control eyes was not statistically significant, we can speculate that scleral CXL has the same effect as PSR, both improving or maintaining blood flow in the posterior pole to a certain extent.

Potential limitations of this study should be mentioned. First, the results of retinal function were not provided. On the one hand, retinal function of pathologically blind eyes itself was abnormal, when the sample size was only five cases, the difference was hardly statistically

significant. On the other hand, the patients were generally older and explicitly refused the f-ERG test because of uncomfortable testing procedures. Hence, further research on a larger sample of pathologically eyes is required. Second, the retinal and choroid parameters measured in this study were limited to the posterior pole of the eyeball, because no OCT device currently provides software for measurement in the equatorial region. However, this study aimed to explore the feasibility and safety of equatorial cross-linking during clinical practice on the basis of previous studies.

## CONCLUSION

This pilot in vivo study verified the feasibility and safety of scleral CXL in human blind eyes.

No obvious infection occurred and retinoschisis was partly improved after the operation. So, this equatorial posterior sclera CXL seems to have the same effect as PSR and may be a potential method for preventing progression of pathological myopia in the future.

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**Author Contributions.** Conceptualization: the design of the study, conducting the study, review and approval of the manuscript: Fengju Zhang. Data collection, data management, data analysis, interpretation of the data, preparation: Yu Li. Perform PSR surgery: Yue Qi. Assisted operation: Mingshen Sun and Yu Li. Provided the instrument used in the experiment and made contribution the design of work: Changbin Zhai, Wenbin Wei. All authors read and approved the final manuscript.

**Disclosures.** Yu Li, Yue Qi, Mingshen Sun, Changbin Zhai, Wenbin Wei, and Fengju Zhang confirm that they have no conflicts of interest to disclose.

**Compliance with Ethics Guidelines.** This research followed the tenets of the Declaration of Helsinki. And approved by the Institutional Ethics Committee of Beijing Tongren Hospital (ChiCTR2100042422), Capital Medical University. All participants provided signed informed consent for their participation.

**Data Availability.** The data sets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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