Genipin-Crosslinked Donor Sclera for Posterior Scleral Contraction/Reinforcement to Fight Progressive Myopia

Anquan Xue,1 Linyan Zheng,1 Guilin Tan,2 Shaoqun Wu,2 Yue Wu,2 Lingyun Cheng,2,3 and Jia Qu1
1Eye Hospital and School of Ophthalmology and Optometry, Wenzhou Medical College, Zhejiang, China
2Institute of Ocular Pharmacology, School of Ophthalmology and Optometry, Wenzhou Medical University, Zhejiang, China
3Jacob’s Retina Center at Shiley Eye Institute, Department of Ophthalmology, University of California San Diego, San Diego, California, United States

Correspondence: Lingyun Cheng, Institute of Ocular Pharmacology, School of Ophthalmology and Optometry, Wenzhou Medical University, 270 Xueyuan Road, Wenzhou, Zhejiang 325027, China; l1cheng@ucsd.edu.
Jia Qu, School of Ophthalmology and Optometry, Wenzhou Medical University, 270 Xueyuan Road, Wenzhou, Zhejiang 325027, China; jqu@wzmc.edu.cn.
Submitted: December 21, 2017
Accepted: June 13, 2018

PURPOSE. Myopia has become a global public health problem, particularly in East Asia where myopic retinopathy has become one of the leading causes of blindness and visual impairment in the elderly population. The purpose of this study was to evaluate the efficacy of posterior scleral contraction/reinforcement (PSCR) surgery on controlling the progressive elongation of axial length of highly myopic eyes in young patients.

METHODS. This is a prospective self-controlled interventional case series. Forty young patients (<18-years old) with progressive high myopia received PSCR with a genipin-crosslinked donor scleral strip for one eye and the fellow eye served as concurrent control without surgery. The main outcome measurement was the change of axial length over 2 to 3 years of follow-up.

RESULTS. Immediately after the surgery, axial length was shortened and subsequently increased by 0.32 mm over the follow-up period. In contrast, axial length of the fellow eyes increased by 0.82 mm over the same period (P < 0.001, paired t-test). PSCR delayed axial elongation in eyes with or without staphyloma. No significant change of visual acuity, cornea refractive power, or retina thickness was noted between the surgery and fellow eyes. None of the patients lost visual acuity compared with the baseline. The procedure was well tolerated with only temporary corneal refractive axis shifts that recovered by the 6-month postsurgical visit.

CONCLUSIONS. PSCR with genipin-crosslinked sclera is safe and effective to restrain eye globe elongation in young patients within a 2- to 3-year follow-up period.

Keywords: human sclera, genipin-crosslinking, highly myopic eyes, scleral contraction and reinforcement, progressive myopia

Myopia has become a global public health problem, particularly in East Asia where myopic retinopathy has become one of the leading causes of blindness and visual impairment in the elderly population.1,2 Most high-myopia complications are related to increased globe axial length and stretching of the sclera, choroid, and retina. It is an unmet need to find effective treatments that slow axial elongation and myopia progression. Thus far, several treatment attempts have been investigated, including various types of spectacle and contact lenses, orthokeratology, and pharmaceutical agents, such as atropine eye drops.3-6 Most of these therapies have variations and modifications of PSR,15,16 we reported a modified PSR surgery and its early results of 30 young patients with progressive high myopia.17 The study had a self-controlled design in which the patients had only one eye subjected to PSR while the contralateral eye served as an internal control. That study demonstrated statistically significant surgical effect on the progression of axial myopia although the effect was small at the 18-month follow-up. In that study, donor sclera was preserved in ethanol before use and the small surgical effect could be due to weak donor sclera. In addition, the previous surgical technique did not include tightening of the donor scleral strip to support the posterior pole of the globe and the study results indicate less surgical benefit for eyes with staphyloma.17 With the recent advancement of crosslink technology in the bioscience field, crosslinking treatments have been applied to living corneas to enhance their mechanical strength for keratoconus management, and crosslinked heart valves are used to replace diseased aortic and pulmonary heart valves in humans.19 Crosslinking can enhance the tensile strength of tissue20 and we believe that crosslinked donor sclera will also have a higher resistance to biological enzyme degradation. With better tensile strength and resistance to degradation, the donor sclera can better restrain the myopic eye globe to prevent further elongation of the axial length. There are several commonly used crosslinking agents, such as glutaraldehyde.20 Recently, genipin has emerged as a safer choice.21,22 Genipin-crosslinking has been used for enhancing the strength of...
articular cartilage, human patella tendons, and posterior scleral reinforcement with excellent biocompatibility. Genipin is definitely a superior crosslinking agent due to its stability, biocompatibility, and general safety.

In the current study, we used genipin-crosslinked human donor sclera to contract and reinforce the posterior sclera of highly myopic eyes in young patients. In contrast to PSR surgery, the posterior sclera contraction/reinforcement (PSCR) procedureshortens eye globe axial length by tightly pulling the donor sclera for better support of staphyloma. In addition, crosslinking of the donor tissue provides better reinforcement of the posterior sclera to prevent long-term elongation of the eye globe. Because the efficacy of PSCR is still under investigation, we examined the eye with longer axial length of each patient had PSCR surgery while the contralateral eye was left untouched as control.

**MATERIALS AND METHODS**

**Human Donor Sclera Crosslinking**

Human donor sclera was obtained from a local eye bank after the cornea had been removed for transplantation. The donor sclera was cleaned under a surgical microscope by removing episcleral tissue followed by the evisceration of the globe's contents. The clean sclera was soaked in a solution of 0.1% genipin (Wako, Japan) and 37.5% ethanol at 25°C for 5 weeks. Then the sclera was sterilized in a 3% povidone iodine solution for 12 to approximately 24 hours, and rinsed with 75% ethanol. Bacteriologic and pyrogen tests were conducted to confirm that the donor tissue was sterile and free of toxins. The sterile crosslinked sclera was kept in an airtight container of 75% ethanol until use.

**Tensile Strength Testing of the Donor Sclera**

Biomechanical properties of ethanol-preserved donor sclera (non-crosslinked) and genipin crosslinked donor sclera were examined by a stretch–stress test26 using 3 x 12-mm pieces. The test was repeated six times for each donor tissue condition. The sclera pieces were cut from an already ethanol-treated or genipin-crosslinked sclera, from posterior to anterior, centered at the equator. Ethanol-treated sclera came from a 76-year-old donor and genipin-crosslinked sclera from a donor who was 67-years old. The scleral pieces were vertically fixed along the long axis using the tensile testing fixtures of the INSTRON system (System ID: 3343B11879; Norwood, MA, USA). The samples were pulled vertically with a uniaxial stretching 50-N force sensor to a 20% length extension at a speed of 1 mm/min. The elastic modulus of the sclera strip was calculated using the output data in the linear phase (tensile load between 0.01–0.03 MPa) of load-displacement stress-strain curves by the Bluehill 3 software (INSTRON).

**Accelerated Enzymatic Degradation Study**

Protease XIV (Streptomyces griseus Sigma Prod. No. P5147; Sigma-Aldrich, St. Louis, MO, USA) was dissolved in PBS to 1U/mL with 1% penicillin-streptomycin. Five-millimeter diameter discs of genipin-crosslinked and non-crosslinked (ethanol preserved) donor sclera were punched from the remaining sclera near the equatorial region after the spindle-shaped donor sclera strip was taken out for PSCR surgical use. Each disc came from one donor sclera. Four discs were studied in enzymatic solution and three in PBS for each group. Once the discs were placed into the prepared enzymatic solution or PBS, they were incubated at 37°C for 24 hours. At the end of each 24-hour cycle, the incubation solution was carefully removed before drying the tissue under 37°C and weighing. Fresh enzymatic solution or PBS was then added for a new cycle.

**Clinical Investigation**

From November 2011 to August 2014, 40 young patients (≤18-years old) with high myopia participated in this prospective study and had posterior scleral contraction/reinforcement surgery on one eye while the contralateral eye was left untouched. The entry criteria were as follows: (1) patients showed spherical equivalent progression rates of roughly −1.00 diopter (D)/y or more; (2) patients had a global axial length of ≥24.5 mm if patients were younger than 8-years old or ≥24.5 mm for patients between 8- and 18-years old. The age of 8 years was used as a delineator because the eye size and growth rate are different between the ages of 1 to 8 years and 8 to 20 years.

Prior to the study, all patients received a full ophthalmic examination. Those who had glaucoma, cataract, strabismus, nystagmus, acute, and chronic inflammatory diseases of the eye and lacrimal ducts, or retinal detachment were excluded from the study. Informed consent was obtained after a full discussion of the possible complications and the desired positive outcomes. This study adhered to the tenets of the Declaration of Helsinki and was approved by the Ethics Committee of the Eye Hospital, Wenzhou Medical University. Patients and parents agreed to receive the surgery on one of their eyes and consented to at least 2 years of follow-up after surgery. In addition, parents and patients were informed that PSCR surgery can control myopic progression to some extent, and that we expect a better surgical effect than the previous published study due to the genipin-crosslinking technique. It was also explained that 2 years of follow-up evaluation is needed to scientifically determine the effect of the surgery. If the surgery is successful in controlling axial expansion, the fellow eye surgery will be recommended. The surgery was performed on the eye with longer axial length or with higher refractive power. If both eyes had similar axial lengths or refractive powers, the patient and the parent made the decision of a surgery eye. Before surgery, both eyes underwent a baseline examination measuring refractive errors (presented as the spherical equivalent), best-corrected visual acuities (BCVAs; converted to LogMAR for statistical analysis), IOPs, corneal refractive powers (presented as K1, K2), axial lengths by IOLMASTER (Carl Zeiss Meditec AG, Jena, Germany), and a fully dilated fundus examination. The patients stayed in the hospital for 1 week after the surgery and were instructed to come back for follow-up visits at 2 weeks, 6 months, 12 months, and 24 months. At each visit, the examinations performed at the baseline visit were again conducted.

Upon the surgery, the cross-linked donor sclera was sized according to the estimation that the length of the spindle-shaped donor sclera strip is approximately 1.5 times the axial length of the receiver eye globe; the strip width at the middle is approximately 0.4 times the axial length of the receiver eye globe while the width of the donor scleral strip at the two ends are 3 to 5 mm.28 The detailed PSCR procedure and illustrations for this type of surgery was described in the previous publication.17,28 Briefly, under general anesthesia a 210° conjunctival peritomy was performed along the inferior temporal limbus followed by the exposing and isolation of the inferior and lateral rectus muscles. Traction sutures were placed around the two ocular muscles to pull the anterior side of the globe toward the superior nasal side. With the help of the traction sutures and a muscle hook, the scleral strip was sequentially inserted under the inferior oblique, lateral rectus, and inferior rectus muscles. During this process, protecting the orbital septum and vortex veins is very important. The two ends of the strip were sutured to the anterior sclera of the receiver globe, 3 to 4 mm behind the insertion of the inferior. #
and superior rectus muscles, using 5-0 nylon sutures. Care was taken to ensure that the reinforcement strip was flat and stretched tightly to support the posterior pole. After surgery, levofloxacin eye drops (Santen Pharmaceutical Co., Ltd, Osaka, Japan), pranoprofen eye drops (Senju Pharmaceutical Co., Ltd, Osaka, Japan), and sodium hyaluronate eye drops (Santen Pharmaceutical Co., Ltd) were instilled four times per day for 2 weeks.

### Statistical Analysis

For continuous data such as eye axial length, IOP, amount of axis change, and spherical equivalent, the results were expressed as mean and SD. The comparison between the surgical and fellow eye was performed using either a t-test or paired t-test. For multiple means comparison across different exam time points, Dunnett’s method was used. For the BCVA and retinal thickness data, a multiple regression was used for group or time-points comparison while adjusting for age and sex. For in vitro degradation of the sclera, regression analysis was performed using weight loss as a dependable variable, the groups as independent variable, and degradation time as covariable. \( P < 0.05 \) was considered statistically significant. JMP statistical software was used for all the analysis (JMP, Version 13; SAS Institute, Inc., Cary, NC, USA).

### RESULTS

#### Biomechanical Properties

A total of 12 scleral strips were tested. Six were crosslinked, while the other six were left as controls (non-crosslinked). The stress–strain curves (Fig. 1) demonstrate some variation; however, the curves from crosslinked scleral strips are more left-shifted compared with the curves from the non-crosslinked ones. The calculated elastic modulus of crosslinked sclera was 33.1 \( \pm \) 18 N/mm\(^2\) versus 16.4 \( \pm \) 6.4 N/mm\(^2\), increased by 102\% (\( P < 0.0001 \), t-test).

#### Ex Vivo Degradation

The degradation of the two preparations of sclera in PBS did not show a significant difference during a preliminary study of 4 weeks. Subsequently, an accelerated enzymatic solution degradation was initiated. Figure 2 demonstrates the degradation profiles of the two sclera preparations over a 6-week study. The regression analysis reveals a 0.6\% daily weight loss for

![Stress-strain curves of the tested scleral strips. The straight parts of the lines (blue) from crosslinked material are steeper and more left-shifted than the counterparts from the non-crosslinked material (red lines), indicating a larger elastic modulus of the crosslinked scleral strips. The elastic modulus was calculated from the linear phase of load-displacement stress-strain curves. The linear phase of one curve is highlighted by using cross markers instead of blue dots.](image)

![Ex vivo degradation curves of the scleral discs. The accelerated enzymatic (ENZM) degradation demonstrated more weight loss of the non-crosslinked than crosslinked sclera discs. The thicker lines are the degradation profiles in PBS and the thinner lines are the profiles in enzymatic degradation.](image)
crosslinked sclera versus a 0.85% daily weight loss for non-crosslinked sclera ($P < 0.0001$). The crosslinked sclera was 30% more resistant to the accelerated enzymatic degradation as compared with the non-crosslinked.

**Clinical Data**

**Baseline Characteristics.** Of 40 patients studied, 29 were males and 11 females with a mean age of 10-years old (3- to 17-years old). The preoperative patient data are included in Table 1. The baseline axial length and spherical equivalent for the surgery eyes were significantly larger than that of the contralateral eyes (difference $= 0.7$ mm, $P = 0.01$; and difference $=-2.0$ D, $P = 0.003$ (t-test, Table 1).

**Follow-Up Data.** Twenty-three patients completed the 2-year follow-up and 15 patients had longer than 2 years of follow-up (1067 ± 78 days, close to 3 years). Of 40 participating patients, 26 had 2 years of follow-up or longer. Three patients had PSCR surgery on their fellow eyes at the 2-year visit before the data were analyzed.

**Surgical Effect.**

**Ocular Reaction to the Surgery.** Conjunctival edema was the main observation within the first week after surgery and resolved around 2 to 3 weeks. There were 6 patients with 5 mm Hg or higher IOP than the fellow eye within the first week after surgery but all below 25 mm Hg. The average IOP for the surgery group was 17.4 ± 3.8 and 15.9 ± 2.8 for the fellow eyes. The difference was statistically significant ($P = 0.008$, paired t-test); however, effect size was less than 2 mm Hg. IOP returned to normal without medication before discharge from the hospital (1 week in hospital). IOP at the first follow-up visit was not different compared to the baseline IOP of the same eye (baseline IOP 15.3 ± 3.1 versus first visit IOP 14.7 ± 3.9 mm Hg, $P = 0.54$ paired t-test). Ten patients reported mild visual distortion, which lasted for 1 to 3 months before resolving. BCVA of the surgery eyes was 0.18 preoperative and 0.12 postoperative at the 2-year follow-up. Similarly, BCVA of the fellow eye changed from 0.14 presurgical to 0.11 postsurgical, no significant difference between the surgery group and the fellow eye group during the follow-ups was noted by comparing of BCVA logMAR mean values. No patients lost visual acuity compared with the baseline visual acuity.

**Axial Length Change.** Immediately after surgery, the axial length of the surgery eyes dropped acutely and took 2 years to approach the presurgical level (Fig. 3, red line). In contrast, the axial length of the fellow eyes steadily increased over the same period (Fig. 3, blue line). On average, the axial length of the fellow eyes increased by 0.82 mm (from 26.86–27.68 mm), while the surgery eyes increased by only 0.32 mm (from 27.54–27.86 mm). The axial length changes from the baseline were significantly greater for the contralateral eyes ($P < 0.0001$, t-test). Figure 3 explicitly demonstrates the net axial changes between the last follow-up and the baseline for each group. The blue lines indicate the contralateral eyes and the red lines indicate the surgery eyes. The blue dotted line from E to F is more than three times longer than the red dotted line from B to C in Figure 3.

Surgical effect size was also investigated among the presence or absence of staphyloma as shown in Figure 4. With PSCR, the cases with staphyloma benefited from the surgery equally as the cases without staphyloma (difference $= 0.86$ mm, $P = 0.002$). Using these 26 cases to calculate the surgical effect size per year yielded 0.22 mm less axial elongation per year than the control eyes (Table 2).

### Table 1. Pre- and Post-surgical Eye Perimeters

<table>
<thead>
<tr>
<th>Perimeters</th>
<th>Bl, n = 40</th>
<th>3 wk, n = 37</th>
<th>6 mo, n = 30</th>
<th>1 y, n = 33</th>
<th>1.5 y, n = 20</th>
<th>2 y, n = 21</th>
<th>&gt;2 y, n = 15</th>
</tr>
</thead>
<tbody>
<tr>
<td>SE, D</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCVA, logMAR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>0.20 ± 0.23</td>
<td>0.24 ± 0.24</td>
<td>0.21 ± 0.22</td>
<td>0.17 ± 0.24</td>
<td>0.17 ± 0.23</td>
<td>0.13 ± 0.23</td>
<td>0.05 ± 0.08</td>
</tr>
<tr>
<td>Fellow</td>
<td>0.15 ± 0.21</td>
<td>0.17 ± 0.24</td>
<td>0.17 ± 0.25</td>
<td>0.13 ± 0.26</td>
<td>0.13 ± 0.26</td>
<td>0.12 ± 0.24</td>
<td>0.03 ± 0.06</td>
</tr>
<tr>
<td>AL, mm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>27.60 ± 1.18</td>
<td>26.87 ± 1.13</td>
<td>27.45 ± 1.17</td>
<td>27.62 ± 1.11</td>
<td>27.50 ± 0.92</td>
<td>27.65 ± 0.96</td>
<td>27.77 ± 1.16</td>
</tr>
<tr>
<td>Fellow</td>
<td>26.90 ± 1.21</td>
<td>26.84 ± 1.15</td>
<td>27.09 ± 1.22</td>
<td>27.35 ± 1.05</td>
<td>27.18 ± 1.05</td>
<td>27.35 ± 1.00</td>
<td>27.49 ± 1.25</td>
</tr>
<tr>
<td>K1, D</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>42.34 ± 1.36</td>
<td>42.18 ± 2.67</td>
<td>42.24 ± 1.48</td>
<td>42.32 ± 1.32</td>
<td>42.48 ± 1.31</td>
<td>42.28 ± 1.23</td>
<td>42.53 ± 1.36</td>
</tr>
<tr>
<td>Fellow</td>
<td>42.16 ± 1.31</td>
<td>42.23 ± 1.36</td>
<td>42.02 ± 1.40</td>
<td>42.14 ± 1.19</td>
<td>42.27 ± 1.28</td>
<td>42.07 ± 1.16</td>
<td>42.27 ± 1.34</td>
</tr>
<tr>
<td>K2, D</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>44.21 ± 1.80</td>
<td>44.26 ± 1.73</td>
<td>43.88 ± 1.78</td>
<td>44.30 ± 1.64</td>
<td>44.02 ± 1.58</td>
<td>43.95 ± 1.48</td>
<td>44.05 ± 1.73</td>
</tr>
<tr>
<td>Fellow</td>
<td>44.19 ± 1.83</td>
<td>44.27 ± 1.77</td>
<td>43.93 ± 1.70</td>
<td>44.32 ± 1.55</td>
<td>44.19 ± 1.59</td>
<td>44.12 ± 1.55</td>
<td>44.27 ± 1.85</td>
</tr>
<tr>
<td>IOP, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fellow</td>
<td>15.41 ± 2.65</td>
<td>14.35 ± 3.89</td>
<td>16.56 ± 3.58</td>
<td>14.65 ± 3.96</td>
<td>17.22 ± 3.88</td>
<td>14.86 ± 3.58</td>
<td>14.85 ± 3.08</td>
</tr>
</tbody>
</table>

Bl, base line; SE, spherical equivalent; AL, axial length; K1, flat keratometry; K2, steep keratometry. Values are presented as mean ± SD.
Retinal Optical Coherence Tomography (OCT). At the 2-year follow-up visit, 15 patients received retinal OCT. The thicknesses of the fovea and foveal rim were not significantly different between the surgery eyes and the fellow eyes (Fig. 7). The foveal and foveal rim thicknesses were 168.57 ± 22.8 and 259 ± 19.2 μm for the surgical eyes versus 170.57 ± 23.6 and 264.5 ± 23.5 μm for the fellow eyes (P = 0.11 and P = 0.60, paired t-test).

DISCUSSION

High myopia occurring early in life often leads to chorioretinal atrophy at the macula later in life, namely in one’s fifties or sixties. High myopia occurring early in life often leads to chorioretinal atrophy at the macula later in life, namely in one’s fifties or sixties.29,30 In such eyes, the axial length of the eye globe changes rapidly during childhood and adolescence. In the adult years of life, the axial length continues to increase incrementally by scleral stretching and thinning. It has been documented that increasing degrees of myopia leads to a higher prevalence of myopic retinopathy.31 The control of axial myopia progression is a hopeful avenue to minimize myopic macular degeneration.

Currently, there is no widely accepted pharmacologic or surgical treatment to prevent the progression of global elongation in myopic eyes. PSR is one surgical approach to control global elongation; however, its efficacy has been questioned and no controlled studies have proven its usefulness until recently.10,12,32,33 Previously, we reported a fellow eye–controlled PSR study with 2.5 years of follow-up.17 That study demonstrated that the surgical procedure was well tolerated and a mild surgical effect, retarding axial elongation by 0.24 mm, was observed during the follow-up. Although the surgical effect was statistically significant; the effect size was small. We hypothesize that donor sclera degradation and loss of tensile strength may be a key factor in diminishing surgical effect. In addition, the previous study revealed that cases with staphyloma benefited significantly less from PSR. In the current study, we took a posterior scleral contraction and reinforcement approach. During the procedure, the scleral strip was tightly pulled to support the posterior scleral ectasia. All surgeries were performed by the same surgeon who judged the force needed to tighten the scleral strips. At present, there is no standard method to quantitate the tightness. In addition to modifying the surgical technique, we crosslinked the donor sclera using genipin to enhance the strength of the donor scleral strip. Genipin is an effective natural crosslinking agent with a very low level of cytotoxicity compared with...
conventional synthetic crosslinking agents. Tissues fixed with genipin have a blueish color for easy identification during the surgical procedure and maintain a high level of stability and resistance to enzymatic degradation. Compared with glutaraldehyde crosslinked material, genipin carries less risk of calcification in bio-tissues. In addition, genipin has 1/100,000th of the toxicity compared with glutaraldehyde. Current stress-strain testing revealed that the genipin-crosslinked scleral strip has twice the tensile strength of the non-crosslinked (ethanol preserved) scleral strip. It is known that crosslinking can increase tensile strength of the sclera. Wollensak and Spoerl demonstrated that in human sclera, Young’s modulus increased from 5.95 to 14.63 MPa after crosslinking by riboflavin-UVA or to 30.88 MPa after crosslinking by glutaraldehyde. Although the scleral strips tested in this study came from only two donor eyes due to the difficulty to obtain human tissue, the observed difference of tensile strength between the genipin-crosslinked and ethanol-preserved eye (102% difference) is unlikely from donor-specific differences because the donors were of similar age. More importantly, the crosslinked scleral strip was 30% more resistant to accelerated enzymatic degradation than the non-crosslinked the scleral strip. Enzymatic degradation causes weakening of the donor sclera when implanted on the patient’s eye globe. Resistance to degradation results a stronger donor scleral strip, allowing it to slow the elongation of the axial length.

The current study used a self-controlled study design in which only one eye of each patient received the posterior scleral procedure and the fellow eye served as a control. This design is of advantage to remove confounding factors, such as age, ethnicity, reading habits, or environmental effects. This approach allows us to calculate the surgical effect size by the net difference in axial change from the respective baseline of surgical and control eyes.

For mild to moderate myopia, orthokeratology or bifocal lenses have been used to prevent the progression of myopia. Cho et al. reported a longitudinal orthokeratology study showing the prevention of axial elongation by 0.25 mm in mildly myopic children over 2 years of wearing the contact lenses.

**Figure 5.** Corneal refractive power at the K1 and K2 axes at each exam time point from presurgical (baseline) to the last follow-up time point. The error bars are the standard error of mean.
lens. Similarly, bifocal spectacles have been reported to prevent progression of mild or moderate myopia. These studies showed an overall adjusted 3-year treatment effect of 0.29 D, which is statistically significant ($P = 0.004$) but not clinically meaningful. A recent meta-analysis highlighted the effect size from various interventions using single vision lenses as a reference (Table 2). However, these studies recruited patients with only moderate myopia and the atropine eye drops used yielded more favorable efficacy (0.21 mm less axial elongation per year). The patients in the current study all had high myopia and the median spherical equivalence was twice as much as the patients treated by either atropine eye drops or orthokeratology (Table 2).

In high myopia and rapidly progressing myopia, experimental myopia studies have demonstrated that the underlying pathophysiology is scleral ectasia. Management of scleral ectasia is the key to slow down myopia progression. The current study demonstrated that surgical intervention significantly retarded axial length elongation. Within the same follow-up period (2.9 years), the axial length of the fellow eyes increased from the baseline by 0.82 mm, while the surgery eyes increased by only 0.32 mm. While cases with staphyloma gained minimal surgical benefit from PSR in the previous study, PSCR is of equal benefit to eyes with or without staphyloma. It should be noted that the more myopic eye with faster progression was selected for surgery in the current study. Immediately after surgery, axial length was shortened by 0.68 ± 0.43 mm, which reflects the mechanical force of the contraction/reinforcement procedure. The axial length made a gradual recovery within 6 months before shifting into a stable, slowly advancing phase. It is interesting that such a forceful procedure did not cause significant changes to the cornea curvature as shown in Figure 5. The corneal refractive power axis was shifted $6^\circ$ to $7^\circ$ by the surgical procedure but returned to baseline by the 6-month follow-up visit as shown in Figure 6. In general, the surgical procedure was well tolerated and attested by good visual acuity and comparable retinal thickness on OCT between the surgical and fellow eyes. Some patients had transient increases in IOP during the first postoperative week, which we think was due to acute eye volume reduction caused by the shortening of the axial length during the posterior scleral contraction/reinforcement surgery. The IOP returned to normal by self-regulation of aqueous production. Similarly, the short-term postoperative visual distortion was due to retinal wrinkling caused by the shortening of the axial length. More frequent OCT follow-up after PSCR would shed more light on the dynamic changes of retina/choroidal thickness and intraretinal/choroidal structures over time.

### Table 2. Effect Size of Retarding Myopia Progression by Various Interventions

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Patient Age, y</th>
<th>Refractive SE prior to Intervention</th>
<th>Effect Size/y, From the Intervention (Mean [CI])</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSCR</td>
<td>$\leq 17$</td>
<td>Median, $-11.1$ D</td>
<td>$-0.22 [-0.26$ to $-0.17]^+$</td>
<td>Current study</td>
</tr>
<tr>
<td>Atr H</td>
<td>8–11</td>
<td>Median, $&lt;-5.0$ D</td>
<td>$-0.21 [-0.28$ to $-0.16]^+$</td>
<td>44, 52</td>
</tr>
<tr>
<td>Atr M</td>
<td>8–11</td>
<td>Median, $&lt;-5.0$ D</td>
<td>$-0.21 [-0.32$ to $-0.12]^+$</td>
<td>44, 52</td>
</tr>
<tr>
<td>Atr L</td>
<td>8–11</td>
<td>Median, $&lt;-5.0$ D</td>
<td>$-0.15 [-0.25$ to $-0.05]^+$</td>
<td>44, 52</td>
</tr>
<tr>
<td>Orthokeratology</td>
<td>8–12</td>
<td>Median, $&lt;-5.0$ D</td>
<td>$-0.15 [-0.22$ to $-0.08]^+$</td>
<td>44, 53</td>
</tr>
<tr>
<td>PASLs</td>
<td>9–12</td>
<td>Median, $&lt;-4.0$ D</td>
<td>$-0.04 [-0.09$ to $-0.01]^+$</td>
<td>44, 54</td>
</tr>
<tr>
<td>SVSLs</td>
<td>$&lt; 18$</td>
<td>Median, $&lt;-5.0$ D</td>
<td>As placebo control</td>
<td>44</td>
</tr>
</tbody>
</table>

Atr H = high-dose atropine (1% or 0.5%); Atr M = moderate-dose atropine (0.1%); Atr L = low-dose atropine (0.01%); PASLs, progressive addition spectacle lenses; SVSLs, single vision spectacle lenses; CI, confidence interval. PSCR, posterior sclera contraction/reinforcement; SE, spherical equivalent.

$^+$ Effect size calculated from the nonsurgical fellow control eyes.

$^\dagger$ Effect size calculated from the concurrent patients using SVSLs.
The PSR procedure has been used to manage retinoschisis in adult patients with favorable results. A similar surgery, posterior buckling, has also been used to control myopic progression in adult patients and has been shown to effectively control axial length expansion during 4 to 5 years of follow-up. The current study was conducted on young patients with a mean age of 10.05 ± 4.23 years. Eyes in this period of life grow much faster than in adulthood and are therefore difficult to control. However, it carries more benefit if a successful intervention is implicated during this period because myopia has not yet caused permanent retinal damage. Myopic maculopathy usually develops during one’s 50th to 60th year of life. In the study by Ward et al., all the adult high myopia patients had some degree of myopic macular degeneration. There are very few studies like the current study in the literature. A modified Snyder-Thompson posterior scleral reinforcement surgery was investigated in highly myopic Chinese children, but that study was retrospective and not self controlled, with homologous dura mater as the enforcement material. Nonetheless, the study reported statistically significant reduction in myopia progression with improved visual acuity in the surgery eye group. Compared with our own previous study that had a similar study design but without genipin-crosslinking of the donor sclera, the current study demonstrated 60% less myopic progression in the surgery eyes while the previous study had only 20% less progression. Improvement in surgical technique by tightly pulling the reinforcing scleral strip, as well as better durability of the genipin-crosslinked sclera, may have contributed to the observed larger surgical effect size on the suppression of axial elongation compared with regular sclera as the reinforcing material. In addition, reduced degradation of the crosslinked donor sclera and the tighter tension created during the PSCR procedure may also be responsible for the improved effect, especially for the cases with staphyloma. We acknowledge that the study sample size in the current report was relatively small. It is difficult to get patients to comply with the follow-up in any clinical study. We managed to achieve 65% patient adherence to follow-up exams up to 2 years or longer. In addition, we analyzed the data over different time points to show a complete picture of how myopia progression is altered by the surgery. A larger study sample size with longer follow-up data should shed more light on the safety and efficacy of this PSCR procedure to combat high myopia and the associated retinopathy later in life. In addition, the surgery was performed on the more myopic eye in each case at the patient’s/parent’s request. This could introduce bias because the rate of growth of each eye can depend on the initial axial length. A randomized clinical trial will provide unbiased data.
Acknowledgments

The authors thank Kristyn Huffman for proofreading of the final manuscript.

Supported by grants from the National Natural Science Foundation of China (Grant No. NSFC31271022; Beijing, China) and Wenzhou Major Scientific and Technological Special Project (Grant ZS2017015; Wenzhou, China). This study was also partially supported by National Science and Technology Major Project “2014ZX09303301” (Beijing, China).

Disclosure: A. Xue, None; L. Zheng, None; G. Tan, None; S. Wu, None; Y. Wu, None; L. Cheng, None; J. Qu, None.

References


