• Basic Research •

# Refractive status and histological changes after posterior scleral reinforcement in guinea pig

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## Abstract

● **AIM:** To investigate the refractive and the histological changes in guinea pig eyes after posterior scleral reinforcement with scleral allografts.

● **METHODS:** Four-week-old guinea pigs were implanted with scleral allografts, and the changes of refraction, corneal curvature and axis length were monitored for 51d. The effects of methylprednisolone (MPS) on refraction parameters were also evaluated. And the microstructure and ultra-microstructure of eyes were observed on the 9d and 51d after operation. Repeated-measures analysis of variance and one-way analysis of variance were used.

● **RESULTS:** The refraction outcome of the implanted eye decreased after operation, and the refraction change of the 3 mm scleral allografts group was significantly different with control group ($P$=0.005) and the sham surgical group ($P$=0.004). After the application of MPS solution, the reduction of refraction outcome was statistically suppressed ($P$=0.008). The inflammatory encapsulation appeared 9d after surgery. On 51d after operation, the loose implanted materials were absorbed, while the adherent implanted materials with MPS group were still tightly attached to the recipient's eyeball.

● **CONCLUSION:** After implantation of scleral allografts, the refraction of guinea pig eyes fluctuated from a decrease to an increase. The outcome of the scleral allografts is affected by implantation methods and the inflammatory response. Stability of the material can be improved by MPS.

● **KEYWORDS:** posterior scleral reinforcement; methylprednisolone; inflammation; myopia; guinea pig
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## INTRODUCTION

Posterior scleral reinforcement (PSR) can strengthen the biomechanics of sclera, becoming an active treatment to prevent the expansion of the sclera. This invasive procedure has been applied for treating pathological myopia with staphyloma[1] and myopic fundus lesions[2-3] acting as a buckle. The effect of PSR has been widely reported to be clear and effective. It can inhibit the growth of the axial length (AL) and even shorten the AL[4-5]. On the other hand, since the AL of the eye is controlled, the postoperative refraction tends to be stable. As the key part effecting operation outcome, the selection of patch grafts is worthy of attention. Surgical effectiveness, stability, and safety are important criteria for selecting appropriate graft materials. Various types of patch grafts have been developed, each with their own set of disadvantages[6-8]. Allogeneic materials are widely used due to the easy availability of the materials and the genetic similarities[9].

However, it has been previously reported in the literature that the stability of PSR surgeries is not always stable. Whitmore *et al*[10] reported that loose implantation may lead graft material to be involved in the pathological process of the recipient eye. In the long-term observation, the recipient sclera was likely to be affected by the inflammatory response during the absorption of the donor material[11]. According to our surgical experience, there were also cases where the graft material was

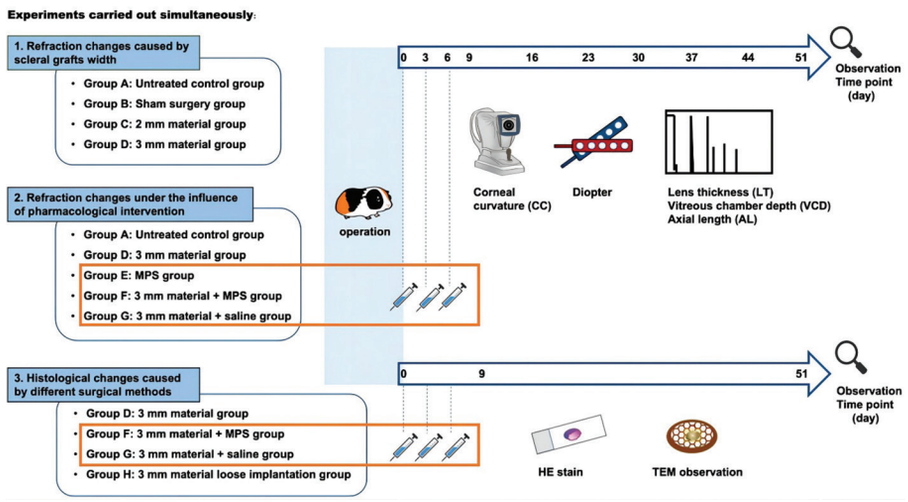


**Figure 1 Experimental design and animal grouping.**

unstable and absorbed. Previous studies have focused more on the refractive outcomes of PSR, but there was few research on tissue response, especially studying effects of surgical methods and pharmacological interventions.

Guinea pigs have choroid and retinal pigment epithelium in their eyes and are docile to apply refractive measurement awake[12]. Besides, the intensive allergic reaction to allogeneic tissues is easy to cause in guinea pig, so that cumulative histological changes can be observed in a short period[13]. In this experiment, we studied the refractive status and histological changes after PSR with scleral allografts on different surgical methods and pharmacological interventions.

## MATERIALS AND METHODS

**Ethical Approval** This study was approved by the Ethics Committee of Wenzhou Medical University and followed the ARVO principles for the treatment of animals on ophthalmology and vision research. Healthy 4-week-old British guinea pigs of 140 to 170 g were obtained with a diopter (D) of +1 to +7 D, and anisometropia of both eyes ≤1.5 D. Guinea pigs were fed in a 12/12h light-dark cycle (L=13 lx; D=0 lx) and provided with sufficient food and water.

**Experiment 1: the Refraction Changes Caused by Scleral Grafts Width** The guinea pigs were divided into 4 groups: untreated control group (group A), sham surgery group (group B), 2 mm material group (group C) and 3 mm material group (group D), *n*=10. In group B, the conjunctival sac was opened, and the extraocular muscles were separated, but no material was implanted. Groups C and D were implanted with 2 mm and 3 mm materials, respectively.

**Experiment 2: the Refraction Changes Under The Influence of Pharmacological Intervention** Methylprednisolone (MPS) was selected to explore the influence of glucocorticoids (GCs) on refractive status and histology. The 40 guinea pigs were divided into 4 groups: untreated control group (group A), 3 mm material group (group D), MPS group (group E), 3 mm material+MPS group (group F) and 3 mm material+saline group (group G). On the 0, 3, and 6d after operation, 0.1 mL MPS sodium succinate (containing 4 mg MPS) was retrobulbar injected for group E and F, and saline was injected for group G. Group E was just applied with MPS injection but no graft implantation.

**Experiment 3: Histological Changes Caused by Different Surgical Methods** The right eyes of 32 guinea pigs were implanted with 3 mm scleral grafts and were divided into 4 groups according to different implantation methods, 8 guinea pigs in each group: 3 mm material group (group D), 3 mm material+MPS group (group F) and 3 mm material+saline group (group G) and 3 mm material loose implantation group (group H). The transplanted materials in groups D, F, and G were all tightly implanted to the recipient sclera. The samples were collected on the 9d and 51d after the operation, respectively, and observed under light microscope (3 animals) and electron microscope (1 animal; Figure 1).

**Scleral Allografts Preparation** The conjunctiva and musculature of guinea pig eyes were removed under microscope. The eyeball excluding the anterior segment was preserved in 95% ethanol for half an hour dehydration. After that, the sclera tissue was cut to a predetermined width with a sharp blade. Then the materials were immersed in 75% ethanol, and the retinal and choroidal tissues were both removed. The 95% ethanol (4°C) was used to preserve the materials and sterile saline was prepared for hydration 5min before use.

**Surgical Procedure** The 0.4 to 0.6 mL of mixed anesthetic (xylazine hydrochloride: ketamine=5:1) was used for sub-peritoneal anesthesia. Proparacaine hydrochloride eye drops (Alcon, Belgium) were applied for topical anesthesia in conjunctival sac followed with the periocular area disinfection. After the conjunctiva sac was opened from limbus, the medial, superior, and inferior rectus muscles were suspended and separated. The scleral allografts were implanted under

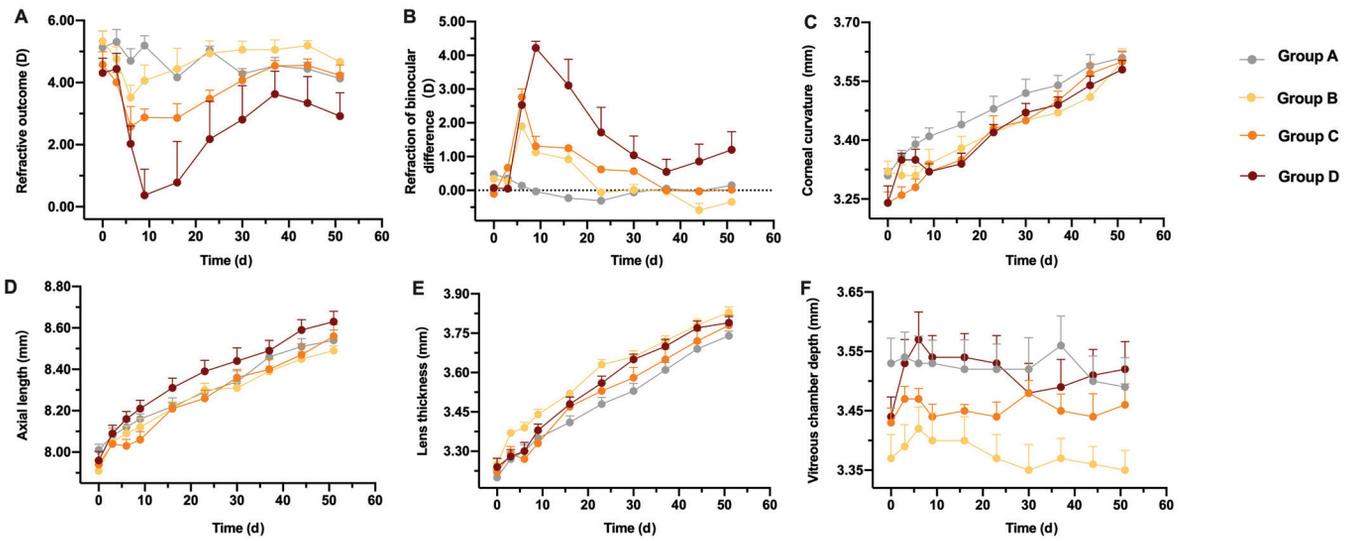


**Figure 2 Refractive status changes after implantation of scleral allografts in guinea pig in 51d** A: The refraction changes; B: The difference of binocular eyes refraction, the right eye of the group A was taken as control; C: The changes of cornea curvature; D: Axial length; E: Lens thickness; F: Vitreous chamber depth postoperatively. Group A: Untreated control group; Group B: Sham surgery group; Group C: 2 mm material group; Group D: 3 mm material group. Statistics were represented by mean±SEM. *n*=10.

the medial rectus from lower nasal to upper temporal and was trimmed flat according to the needs of the group[14]. The implanted length was ensured as 15 to 18 mm, and then the conjunctival tissue was re-covered. At the end of the operation, 0.3% levofloxacin eye solution (Santan, Japan) was applied for twice.

**Refractive Parameters Measurement** Refractive measurement was detected with cycloplegia preoperatively and on 3, 6, 9, 16, 23, 30, 37, 44, and 51d after operation by an optometrist who was blinded to the animal's identity. Refraction in the vertical meridian was measured using an eccentric infrared retinoscopy 3 times for each eye. Corneal curvature (CC) of two mutually vertical meridian were measured with a keratometry (Topcon, OM-4, Japan). Length of the eye axial components, including lens thickness (LT), vitreous chamber depth (VCD), and AL were measured by an A-scan ultrasonography (Cinescan A/B, France). Each eye was measured 10 times and the average was taken as the final value[15].

**Microstructural and Ultra-microstructural Observations** Immediately after the guinea pigs were sacrificed, the eyeballs were fixed with 4% paraformaldehyde for 24h. After dehydration with graded alcohol, samples were immersed in xylene and sliced into 5 μm thickness. Slices were observed under a light microscope (Olympus, Japan) after hematoxylin-eosin staining. As for ultra-microstructural observations, the eyeball including the grafts was fixed with paraformaldehyde for 24h and 1% osmic acid for 1h and dehydrated with graded ethanol. Samples embedded in epoxy resin were made into ultrathin sections (80 nm) for double stain using lead and uranium. Images were observed under a transmission electron microscope (TEM; H-7500, HITACHI, Japan).

**Statistical Analysis** Repeated measures analysis of variance was used to compare the results of guinea pig diopters at multiple time points. One-way analysis of variance was used to compare the results of postoperative changes in parameters between multiple groups at the same time point.

## RESULTS

**Refraction Changes** Compared with group A ($P$=0.005) and B ($P$=0.004), group D had statistically significant differences in refraction, which decreased first and then increased. Taken the right eye as control, group D was also significantly different in binocular refractive difference (△D) compared with group A ($P$=0.003) and group B ($P$=0.014). Between-group factors had an impact on the refraction ($F$=4.302, $P$=0.012), △D ($F$=3.917, $P$=0.018), and VCD ($F$=3.571, $P$=0.025), but had no effect on changes in CC ($F$=1.184, $P$=0.154), AL ($F$=1.687, $P$=0.191), and LT ($F$=2.023, $P$=0.141). In group D, there was a short-term fluctuation in CC on the 3d and 6d after operation, which was speculated to be caused by the operation. The 9d after the operation, the conjunctival incision healed, and the CC returned to the original trend (Figure 2).

**Methylprednisolone Effects on Refraction** The 9d after operation, the refraction change in group F was significantly smaller than that of group D ($P$=0.008) and group G ($P$=0.013; Figure 3A). The AL change of group A was significantly smaller than group D ($P$=0.016) and group G ($P$=0.032). And the AL change of group E was also significantly smaller than group D ($P$=0.002) and group G ($P$=0.004). However, there were no significant differences between groups A, E, and F ($P$>0.05; Figure 3C). The VCD value change of group D was significantly different from group A ($P$=0.010) and group E ($P$=0.003; Figure 3D). The variation of CC ($F$=0.172,

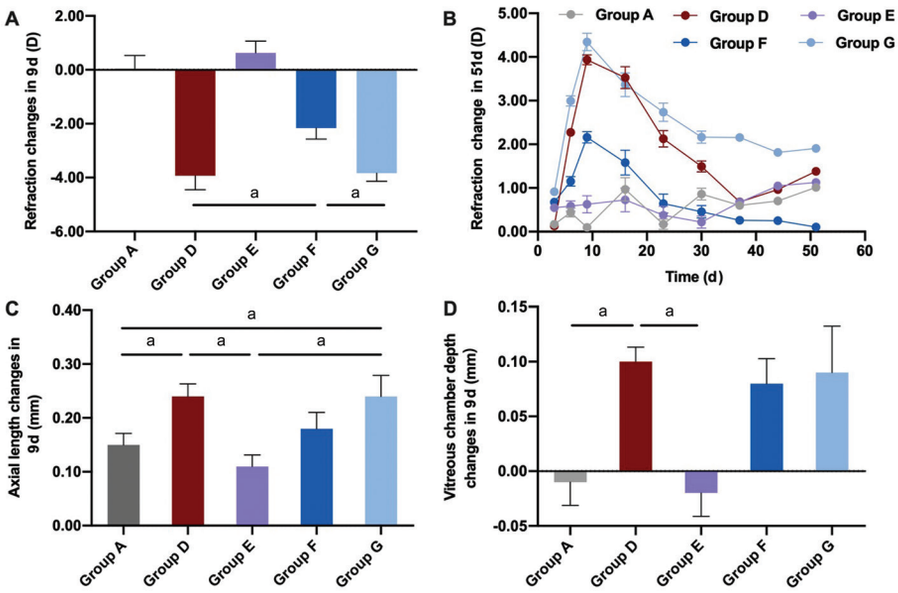


**Figure 3 Effect of the MPS on refractive status of guinea pig eyes after operation** A: The changes of refraction; B: The refraction changes postoperative in 51d; C: Axial length; D: Vitreous chamber depth with MPS or saline injection 9d after operation. The curves were presented as the difference between postoperative refraction and the baseline refraction value on the 0d. Group A: Untreated control group; Group D: 3 mm material group; Group E: MPS group; Group F: 3 mm material+MPS group; Group G: 3 mm material+saline group. Statistics were represented by mean±SEM. $n$=10, $^aP$<0.05. MPS: Methylprednisolone.

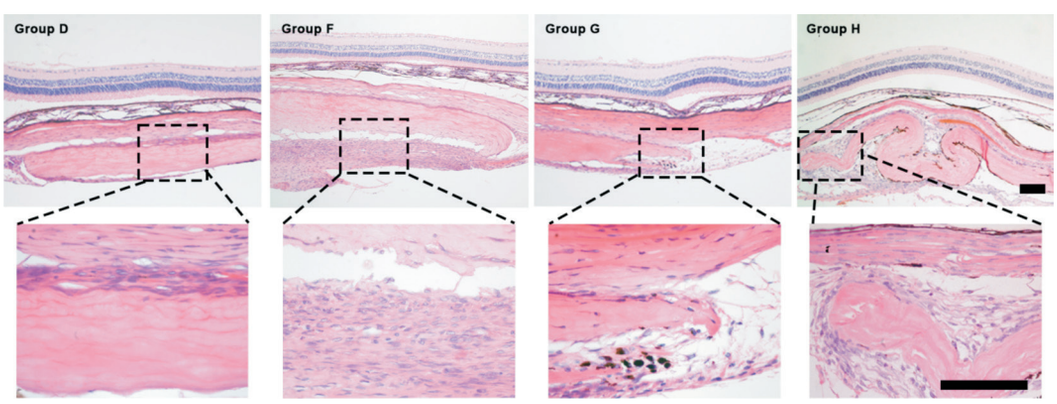


**Figure 4 Scleral graft of group D, F, G, and H 9d after operation (100× and 400×)** Group D: 3 mm material group; Group F: 3 mm material+MPS group; Group G: 3 mm material+saline group; Group H: 3 mm material loose implantation group. Scale bar=100 μm. MPS: Methylprednisolone.

$P$=0.681) and LT ($F$=0.077, $P$=0.783) had no significant difference among groups.

**Microstructural Observation** The materials all adhered to the recipient's sclera tightly except group H 9d after operation (Figure 4). Obvious edema and the absorption tendency were observed where there were no GCs application, especially in group H. While no obvious graft edema and densest fibrous encapsulation appeared in group F after the injection of MPS. The encapsulation was thickest in group F (for about 10 layers) and thinner in other groups (contained 3-5 layers). The surrounding inflammatory encapsulations consisted of cellulose layers and cells, including fibroblasts, neutrophils, and phagocytes (some phagocytes contain pigment granules). In the recipient eye, there are large and deeply stained nuclei cells in sclera, especially in group H.

At the end of the experiment, the scleral allografts of group H were almost completely absorbed, while the scleral allografts of group F were the thickest, for nearly twice as the normal sclera (Figure 5). Fibroblasts scattered among the scleral graft collagen fibers, which were closely connected to the normal scleral tissue with a homogeneous trend (group F). The other two groups of scleral allografts (group D and group G) also presented the absorption tendency. The morphology of cells in the scleral graft varied among groups. There were more macrophages and even Langerhans giant cells in group H. In group F, the fibroblasts were parallel arranged with a higher density, and there were some phagocytic cells containing pigment granules at the edge of encapsulation.

**Ultra-microstructural Observation** The collagen of the implanted material swelled, and the periodic transverse stripes of the collagens turned indistinct 9d after the operation (Figure 6A, 6B). And fibroblasts phagocytizing pigment granules can

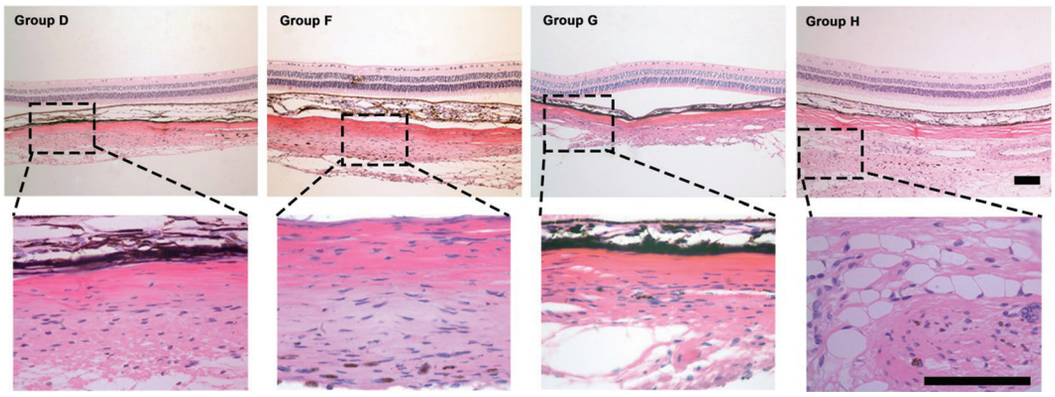


**Figure 5 Scleral graft of group D, F, G, and H 51d after operation (100× and 400×)** Group D: 3 mm material group; Group F: 3 mm material+MPS group; Group G: 3 mm material+saline group; Group H: 3 mm material loose implantation group. Scale bar=100 μm. MPS: Methylprednisolone.

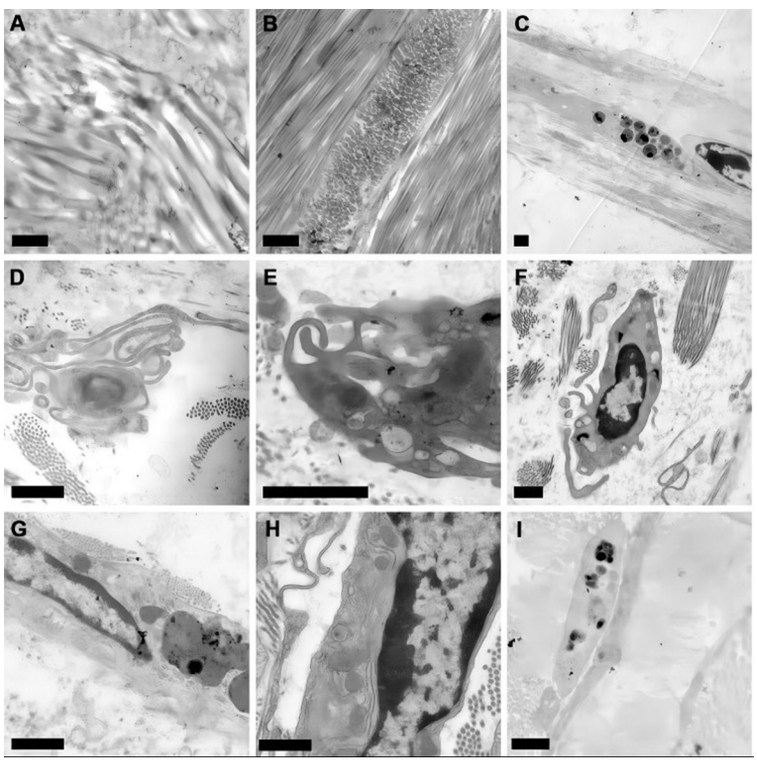


**Figure 6 Ultrastructural observation after implantation of scleral allografts** A, B: The swelling collagen of scleral graft (A) and recipient's sclera (B) 9d postoperatively (20 000×); C: The fibroblast with pigment granules and lysosomes in the encapsulation (8000×); D: The new collagen and macrophages with pseudopodia (30 000×); E: The macrophages with lysosomes (60 000×); F: The fibroblast with lysosomes in it (15 000×); G: The lysosomes near the fibroblast (30 000×); H: The fibroblast with plentiful endoplasmic reticulum and Golgi body (30 000×); I: The fibroblast with pigment granules of the graft sclera 51d postoperatively (20 000×). Scale bar=1 μm.

be seen around the scleral allograft (Figure 6C). The 51d after the operation, phagocytes and fibroblasts could be seen in the scleral allografts. Macrophage cell contained lysosomes phagocytizing the denatured collagen fibers can also be observed (Figure 6D, 6E). Some new collagen fibers gradually appeared around the fibroblasts. There were pigment granules and lysosomes (Figure 6F, 6G) even rough endoplasmic reticulum (Figure 6H) existed in fibroblasts cell. There was large number of fibroblasts with phagocytosed pigment particles appeared in the undigested scleral graft (Figure 6I). The TEM results in the early and late postoperative periods both confirmed that the edema, dissolution, phagocytosis, and regeneration of collagen were seen among different groups.

## DISCUSSION

From this study, we found that the outcome of PSR is the consequence of a variety of factors, including surgical techniques and pharmaceutical treatments. After implantation of scleral allografts, the refraction of the implanted eye showed fluctuation. Implantation methods and the inflammation control have obvious effects on scleral allografts absorption.

There have been many studies reported the relationship between the scleral inflammation and myopia. Gross *et*

*al*[16] reported a case of reversible myopia in a patient with necrotizing scleritis after strabismus surgery. Zeiter[17] reported a case of reversible myopia caused by scleritis, which was treated only with nonsteroidal antiinflammatory drugs (NSAIDs) to control the inflammation. Cytokines in tears can serve as biomarkers of progressive high myopia and autoimmune inflammation[18-19]. Therefore, we hypothesized that the postoperative inflammatory response was related to myopia. Our experiments found that the wider strips led to a stronger inflammatory response, and the MPS suppressed this response, reducing the development of myopia. Chronic inflammation may play a crucial pathogenic role in tree shrew form deprivation myopia[20]. Allergic inflammation has been reported to promote the development of myopia[21]. Patients suffered with inflammatory disease have a higher incidence of myopia, and higher expression levels of inflammatory factors such as c-Fos, NF-κB, IL-6, and TNF-α[22]. Previous studies also suggested that the suppression of inflammation may lead to the inhibition of myopia development[23]. Prunella vulgaris (PV)[24] and resveratrol[25] were confirmed to reduce inflammation and inhibit the development of myopia. As for the refractive status, different refraction trend was observed in implanted eye of this experiment, which first decreased and then increased.

The refractive change after the operation was due to the inflammatory reaction. When there is no significant difference in CC, AL becomes the main factor affecting refraction, which is negatively related to refraction[26]. The postoperative inflammatory reaction induced the scleral graft to swell and stimulated the eyeball to obtain an elongated axial. And finally, the refractive status changed exactly during the window of inflammation. Besides, the myopic refractive status was released after the application of MPS, which indicated that inhibited inflammation had less effect on refractive change. The time window, GCs intervention, and histological observation revealed that refractive changes were due to an inflammatory reaction. A short-term drift of emmetropia[4,27] has been reported in the early stage of PSR operated in human. This difference may be attributed to the fact that, unlike the human species, guinea pigs reacted sensitively to allografts transplantation with strong inflammatory response, which induced the scleral remodeling and the development of myopia.

From the results of histological observations, we found changes including encapsulation formation, hyperplasia, and absorption. Adherent implantation and MPS intervention were conducive to the formation of a tight encapsulation, which was the basis for the stable existence of the scleral graft. Scholars believe that the encapsulation layer can prevent the release of foreign antigens and stabilize the material structure[28]. Curtin[29] found that the autologous fascia tissue that did not adhere closely to the rabbit sclera failed to form a complete encapsulation, resulting in the destruction and vascularization of the collagen lamellae at the periphery of the implanted allogeneic scleral tissue. We discovered that fibroblasts grow into and homogenize with the recipient sclera in scleral graft. Previous studies have also reported the inflammatory responses and granulation tissue deposition followed by collagen fibrosis after synthetic materials applied in PSR[30-31]. Accumulation of fibroblasts and the formation of new collagen fibers can be stimulated by effectively managed postoperative inflammatory response, which increased the mechanical strength of recipient sclera. We also found that scleral grafts loosely implanted without inflammation control were eventually absorbed and lost expected surgery effect. In our previous clinical postoperative follow-up, scleral allografts loosely implanted may be eventually degraded and absorbed, which reduced the material tensile strength and eventually affected the efficacy of PSR. In the implanted eyes without MPS application, the scleral allografts turned to be edematous and absorbed. Many monocytes and macrophages in response to inflammatory factors and chemotaxis were observed to surround the scleral allografts and recipient's sclera after surgery. The accumulated lysosomal vesicles released by monocytes and macrophages can phagocytose a lot of denatured collagen tissue and release protease, affecting the structural stability of the recipient sclera, causing the scleral fibers to be dissolved and absorbed.

As for the inflammation between the graft and recipient, factors related to inflammation and vascularization may play an important part. Previous study on rabbit scleral reconstruction revealed that transforming growth factor β receptor 1 (TGF-β1) decreased but bone morphogenetic protein 2 (BMP2) increased during the 56d observation. collagen type 1 (COL1) and fibroblast growth factor (FGF) decreased on the 7d and increased on the 56d, while the matrix metalloproteinase 2 (MMP2) showed an opposite trend[32]. Besides, mechanical stimulation changed scleral fibroblast viscoelastic of different regions. The scleral fibroblasts in the fusion region had great biomechanical properties to resist mechanical force[33]. The scleral fibroblasts of recipient became softer, and those of fusion region became stiffer. The scleral fibroblast viscoelastic of different regions became more identical to promote the fusion of the sclera and enhance the biomechanical properties of sclera.

In summary, the possible mechanism of the decrease in refractive power of guinea pig eyes after allogeneic scleral strip implantation was that, the implantation of allogeneic strips induced chemotaxis and phagocytosis of monocytes and macrophages, and the released lysosomal enzymes affected the stability of scleral collagen in the recipient eye, leading to AL and refraction changes. While the application of MPS helped to stabilize the refractive outcome and inhibit

AL growth. Therefore, attention should be paid to the effects of surgical material implantation methods and the intensity of inflammatory response in PSR surgery. First, during the operation, the tissue material must be flatly attached to the scleral surface, so that a uniform scleral reinforcement layer can be formed, which was conducive to the stable existence of the graft material. Second, the degree of induced inflammatory response should be controlled within a reasonable range. On the one hand, the inflammatory response was needed to promote the accumulation of fibroblasts and formation of new collagen. On the other hand, the phagocytosis and decomposition of mononuclear macrophages need to be inhibited to reduce the degradation of the donor sclera, making the surgery process move towards the thickness strengthening and biomechanical characteristics improving of the sclera.

There are also some limitations in this study. Transplant reaction sensitivity in guinea pig eyes is different from human eyes, therefore there may be some differences in post-operative inflammatory response in humans. Besides, the postoperative intraocular pressure should be monitored to evaluate the safety of the operation. And further molecular biology research on the inflammatory factor expression levels and extracellular matrix components changes after operation also need to be studied.

In conclusion, after the implantation of the scleral allografts, the refraction status of the guinea pig eyes may fluctuate, and this process can be partially inhibited by GCs. The adherent implantation method and inflammatory control contributed to the outcome of the scleral allografts, promoting the formation of collagen fibers and encapsulation and avoid the decomposition.

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**Conflicts of Interest: Huang YY,** None; **Zhou LY,** None; **Chen GF,** None; **Peng D,** None; **Pan MZ,** None; **Zhou JB,** None; **Qu J,** None.

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