Original Research

Transplantation of autologous perichondrium with amniotic membrane for progressive scleral necrosis

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ARTICLE INFO

Keywords:
Scleromalacia
Necrotizing scleritis
Perichondrium transplantation

ABSTRACT

Purpose: Scleral necrosis with severe ischemia is refractory to conventional treatment because of avascular progressive necrosis. We assessed the therapeutic efficacy and safety of autologous perichondrium transplantation in patients with progressive scleral necrosis (PSN) and analyzed the clinical effects.

Methods: This study was a prospective, interventional, and noncomparative case series. Reconstructive surgery using autologous perichondrium and amniotic membrane (AM) was performed in patients with PSN who showed progressive ischemic scleral melting with impending perforation state and/or broad avascular area larger than 10 mm in diameter. The primary outcome was restoration of scleral integrity with healthy vascularized epithelium over the graft at six months after surgery. The secondary outcome was complication rate associated with autologous perichondrium graft use.

Results: Eighteen eyes of 14 patients underwent reconstructive surgery using autologous perichondrium patch and AM grafts. Observations indicated the graft provided the eyeball with successful structural integrity in 17 out of the 18 cases (94.4%) at six months after surgery. One eye showed a small scleral defect due to wound dehiscence at four month after the surgery. Additional surgery using perichondrium and AM stabilized the eye. The scleral necrosis healed completely after perichondrium and AM transplantation, even in cases with full-thickness scleral defect. The scleral integrity was maintained until the last follow-up session. There were no serious complications of endophthalmitis or graft infection.

Conclusions: Reconstructive surgery using autologous perichondrium and AM is an effective method for restoration of scleral integrity and vascularization of the episclera and conjunctiva in eyes with PSN. Therefore, autologous perichondrium can be considered as an appropriate new biologic tissue for PSN.

1. Introduction

Scleral necrosis is a form of necrotizing anterior scleritis that presents with or without typical inflammatory signs of pain or redness [1,2]. Scleral necrosis has various causes including ischemic change, infection, granulomatous or nongranulomatous inflammation, or immune-mediated reaction [1–5]. It is frequently associated with rheumatoid nodule of the sclera in patients with autoimmune disease, complications following ocular surgery, or plaque radiotherapy of uveal melanoma [1,6–10]. Nonvascularized scleral ischemia causes progressive scleral necrosis (PSN) and melting of the sclera. The integrity of the globe is maintained in most eyes. However, it can lead to perforation, infection, and enucleation of the eyeball, although this is much less frequent [8–10]. If the sclera is melted and the choroid is exposed, urgent surgical intervention is necessary to preserve the integrity of the globe because there is a high risk of secondary infection; additionally, the ocular content may become prolapsed even with even minor trauma.

Various types of graft material have been used for scleral necrosis [3,11–14]. Preserved donor sclera and amniotic membranes (AM) have been used widely as graft material with relatively acceptable results [15]. However, these acellular materials have some limitations, including intense absorption, low vascularization rate, and the risk of microbial infection [16–21]. Especially, reinforcement using

Abbreviations: AM, amniotic membranes; ANCA, antineutrophil cytoplasmic antibodies; CD, cluster of differentiation; MSCs, mesenchymal stem cells; PSN, progressive scleral necrosis

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https://doi.org/10.1016/j.jtos.2019.05.004

Received 27 December 2018; Received in revised form 10 April 2019; Accepted 16 May 2019

© 2019 Published by Elsevier Inc.

Please cite this article as: Jee Taek Kim, et al., The Ocular Surface, https://doi.org/10.1016/j.jtos.2019.05.004
conventional graft material is insufficient in the case of ocular perforation or PSN with a broad avascular zone. If PSN ensues despite conventional graft use, the current approach is only observation and lubrication [10]. Therefore, the identification of new graft materials or new operation techniques is needed.

To address this issue, we adapted the protocols for transplanting stem cell-containing perichondrium tissue on the avascular sclera and for improvement of the microenvironment of stem cell niches using amniotic membrane (AM). AM has been reported to reduce stromal melting, promote re-epithelialization, and facilitate migration of endothelial progenitor cells on the AM as a basement membrane [3,22]. The perichondrium is a dense connective tissue that surrounds the cartilage and consists of an outer fibrous layer and an inner chondrogenic layer [23]. It has been used to regenerate bone or cartilage because of the presence of pluripotent cluster of differentiation (CD) 166+ mesenchymal stem cells (MSCs) [24,25].

The purpose of the present study was to report the therapeutic efficacy and safety of reconstructive surgery using this concept and to assess the therapeutic effects of autologous perichondrium tissue.

2. Methods

2.1. Patient eligibility

This prospective, interventional, noncomparative case study was conducted between March 2011 and February 2014 after obtaining approval from the institutional review board at Chung-Ang University Hospital in Seoul, Korea. We included PSN patients with persistent and progressive scleral melting. Patients who met the following criteria were included in this study: (1) impending perforation or a perforation state of the sclera; (2) graft melting following previous surgery; (3) bacterial or fungal infection of the sclera or graft after previous surgery; (4) discomfort due to protrusion of scleral calcification with ischemic necrosis; and/or (5) broad avascular area larger than 10 mm in diameter (Fig. 1A–C). Patients with asymptomatic smaller scleral defects less than 10 mm in diameter or with shallow scleral defects that could be treated with conventional surgery using preserved sclera or AM were excluded. This study followed the tenets of the declaration of Helsinki. Informed consent was obtained from all participants with full explanation about possible advantages and adverse effects of the perichondrium transplantation.

All patients underwent a comprehensive ophthalmic examination including best-corrected visual acuity, intraocular pressure, and slit-lamp microscopy for integrity of the scleral wall or epithelialization of the scleral bed. Systemic autoimmune diseases or the presence of autoantibodies, past surgical history, microbial culture results, time lapse between primary onset and presentation, length of follow-up, and any complications were evaluated. Facilitation of epithelialization or restoration of scleral integrity was considered to be the primary outcomes at six months after reconstructive surgery.

2.2. Surgical procedure I: harvest of autologous perichondrium from the tragus

Perichondrium tissue was harvested from the patient’s ear cartilage, particularly the tragus, which has thicker perichondrium than other sites. After disinfection of the periauricular area, the tragus was infiltrated with 1% lidocaine with 1:100,000 epinephrine. A 1.5-cm incision was performed along the incisura terminalis on the inner surface of tragus with a no. 15 Bard Parker blade. Following dissection of the subcutaneous tissue, the strongly attached perichondrium over the tragal cartilage was dissected from the anterior to posterior surface with a Freer elevator (Fig. 1D). The harvested perichondrium was washed with normal saline, placed in wet gauze, and kept moist before the implantation (Fig. 1E). The surgical wound of the tragus was sutured with 5–0 nylon after controlling the bleeding.

2.3. Surgical procedure II: transplantation of the harvested perichondrium

The ocular surgical procedures were performed (Fig. 1F) by one surgeon (JCK) using the following steps: first, an AM was transplanted using eight interrupted 10-0 nylon sutures as a basement membrane after removal of the necrotic tissue of the conjunctiva and sclera. Second, the perichondrium tissue was sutured with 7–0 vicryl with the

Fig. 1. Representative case showing scleral ischemia (case 13), the surgical procedure to harvest the autologous perichondrium, and a schematic illustration of the step-by-step surgical procedure. (A) Ocular surface photograph showing avascular sclera and calcification at the center of the avascular zone (black arrow). (B) Early phase of fluorescein angiography showing severe scleral ischemia and significant nonperfusion. (C) Late phase of fluorescein angiography showing vascular leakage from episcleral vessels. (D) Surgical procedures to harvest the autologous perichondrium from the tragal cartilage. (E) Harvested perichondrium has a white color identical to that of the sclera. (F) Schematic illustration of preoperative findings and five-step layer-by-layer surgical procedure.
cartilage side down, as a sclera substitute and a stem cell source. Third, vascularized periciliar fat tissue (Tenon’s capsule) was connected to the graft to facilitate vascularization. Fourth, another AM or autologous conjunctiva or autologous oral mucosa was transplanted as an epithelial tissue to protect the grafts. Finally, the entire ocular surface was covered using a large AM with 10–0 nylon sutures for one week to protect the transplant. In the case of nearly full-thickness scleral necrosis, a double layer of perichondrium was transplanted (i.e., cases 2, 9, 10, and 18).

2.4. Perioperative management

Immunosuppressive agents and/or oral steroid (prednisolone 0.5–1.0 mg/kg/day) were used only in cases with autoimmune disease or autoantibodies for one week after the surgery and tapered gradually. The drugs were not used before the surgery, except in patients who had already been started on immunosuppressive agents prior to study enrolment. The postoperative topical eye drops included autologous serum eye drops (20–40%), 1% prednisolone acetate, 0.5% levofloxacin, and an ointment that contained 0.35% neomycin and 0.1% dexamethasone. These medications were tapered after epithelialization was complete. All patients were hospitalized for one week and then followed up every week for one month, every two months for one year, and as appropriate thereafter.

2.5. Statistical analysis

The percentage of treated eyes that met the primary and secondary outcomes was calculated.

3. Results

3.1. Patient characteristics

A total of 18 eyes from 14 patients [six women and eight men, with a mean age of 58.8 years ± 15.4 years (range: 31–75 years)] were included in this study. All participants were patients with surgically-induced scleral necrosis. Six eyes from four patients had previously undergone pterygium removal surgery, respectively. Nine eyes of seven patients and three eyes of two patients had undergone primary and recurrent pterygium removal surgery, respectively. Mean latent period between pterygium or pterygium surgery and presentation of scleral necrosis was 6.61 years ± 8.90 years (range: 1–30 years). Four patients with five eyes had rheumatoid factor (RF)-positive rheumatoid arthritis (RA), two patients with two eyes had asthma, and two patients with two eyes were anti-neutrophil cytoplasmic antibody (ANCA)-positive. Five eyes of the total of 18 eyes had histories of prior multiple reconstructive surgeries using conventional materials, which appeared melted at the time of visit in our clinic. Among the five eyes with histories of prior multiple surgery, four eyes had RF-positive RA or were ANCA-positive. Four eyes had microbial infections. The scleral integrity of two eyes was in a full-thickness perforation state, while one eye was in an impending perforation state.

Additional details including systemic disease, predisposing factors, prior reconstruction surgery, the size of scleral necrosis and scleral ischemia, and the existence of calcification are summarized in Table 1. Representative cases are presented in Fig. 2 and summarized in the Supplementary Information section.

3.2. Primary outcome

The ischemic sclera were vascularized and necrotized sclera were recovered in all cases at one month after surgery. The PSN closed successfully in 17 eyes of 18 eyes (94.4%) at six months after the surgery (Fig. 2). One eye showed a small scleral defect at four months after surgery (case 9). Complementary surgery using perichondrium stabilized the eye. Follow-up ranged from 24 to 80 months (mean: 61.2 months ± 32.1 months). The scleral integrity was maintained without recurrence up to the end of follow-up.

3.3. Secondary outcome

There were no serious complications, including cartilage formation under the graft, scleral infection, or endophthalmitis, during the follow-up period. Pseudo-tryergium and symblepharon, which is diagnosed as adhesion of the palpebral conjunctiva to the bulbar conjunctiva by overgrowth of fibrovascular tissue, occurred in two eyes in which the nasal mucosa had been used as an epithelial tissue (cases 5 and 8). These eyes recovered after removal of fibrovascular tissue and AM transplantation. Useful vision better than 0.2 (Decimal) was maintained in all patients at the end of follow-up. Detailed surgical procedures and outcomes are summarized in Table 2.

4. Discussion

This study demonstrated the feasibility of perichondrium for application in the treatment and recovery of PSN. Scleral integrity was reattained after the reconstructive surgery and maintained to the last follow-up session, which ranged from 24 months up to 80 months (mean: 61.2 months) after the procedure. It is thought that the stem cells of the perichondrium are responsible for the excellent recovery observed.

Conventional materials that have been used for scleral necrosis include the fascia lata, dura mater, periosteum, pericardium, AM, and preserved sclera [3,11–15]. These materials are acellular connective tissue except AM (cryopreserved AM has amniocytes). These acellular materials become melted in the ischemic condition and replaced by loose connective tissue after the procedure, and lost their tectonic effects [3]. Consequently, a second operation would be necessary [17]. Additionally, the preserved tissue carries the risk of bacterial, viral, or prion transmission, even though extensive screening is performed to prevent infectious diseases [18–21]. These conventional materials have shown tolerable results but might induce complications including endophthalmitis, graft necrosis, and graft dehiscence [26]. As a result, evisceration or permanent blindness has been reported with a rate of more than 20% after conventional surgery [26,27]. A critical point for successful surgery using conventional materials exists, which is associated with the size of the avascular zone or the depth of the scleral necrosis and the grade of scleral ischemia.

The past treatment history of some patients in this study also demonstrated the limitations of conventional materials such as graft melting or infection. Patient 1 (case 1) had two reconstructive surgeries before the perichondrium graft; the first applied a scleral patch graft with a conjunctival flap, while the second used a multilayer AM transplantation with nasal mucosa. Patient 2 (case 2) had also undergone reconstructive surgery twice, using pericardium and multilayer AM transplantation, respectively. Patient 4 (case 4) had undergone reconstruction with preserved sclera with AM. Patient 7 (case 8) underwent five previous surgical procedures that used AM and preserved sclera. However, these conventional acellular materials that overlaid the avascular scleral bed eventually melted. Moreover, patients 2 (case 2) and 7 (case 8) both developed a graft infection on a scleral ulcer after the previous surgery. Especially in patients with uveal prolapse, the risk of wound infection or endophthalmitis should be considered because the processed material had microbial adherence [19,21]. To date, no universally acceptable material has been identified for the treatment of patients with PSN.

Scleral ischemia is the most important finding in PSN [7,27]. Previous ocular surgery including strabismus surgery, buckling surgery, pterygium surgery with inappropriate topical antimetabolites, and irradiation therapy may result in scleral ischemia [26,27]. Scleral ischemia can also arise in patients with systemic disease including
<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Case no.</th>
<th>Gender</th>
<th>Age</th>
<th>Systemic disease &amp; autoantibody</th>
<th>Initial BCVA (Decimal)</th>
<th>Predisposing factor(s)</th>
<th>Latent period (years)</th>
<th>Previous reconstructive surgery</th>
<th>Scleral ischemia size (mm)</th>
<th>Scleral necrosis size (mm)</th>
<th>Calcification</th>
<th>Microbial infection</th>
<th>Scleral integrity</th>
<th>Corneal involvement</th>
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<td>6.0 × 13.0</td>
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<td>uveal tissue exposure</td>
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<td>F</td>
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<td>Pterygium excision</td>
<td>5 y</td>
<td>1st, allogenic pericardium Tr 2nd, multilayer AM Tr</td>
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<td>6.0 × 9.0</td>
<td>Sphingomonas paucimobilis</td>
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<td></td>
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<td>Pterygium excision</td>
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<td>F</td>
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<td>Pterygium excision</td>
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<td>Lt</td>
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<td>Impending perforation</td>
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AM, amniotic membrane; ANCA, antineutrophil cytoplasmic antibody; BCVA, best-corrected visual acuity; BLR recession, bilateral lateral rectus muscle recession (exotropia surgery); DM, diabetes mellitus; FC, finger count; HTN, hypertension; no, number; RA, rheumatoid arthritis; RF, rheumatoid factor; Tr, Transplantation; UP, uveal tissue prolapse.
Fig. 2. Surgical outcomes of autologous perichondrium transplantation for treating progressive scleral necrosis. Slit-lamp microscopic photographs of preoperative (first column) and postoperative ocular findings (second and third columns) of representative cases are presented. Brief case summaries are presented as supplementary data. For eyes with full-thickness scleral melting or significant scleral thinning (cases 2, 9, and 18), double layers of perichondrium tissue were used at a time. A lamellar corneal allograft was performed for an eye with peripheral cornea thinning over the sclera defect (cases 9) with 10–0 nylon applied to the patient’s cornea. In cases with microbial infection, broad-spectrum antibiotics or antifungal eye drops were empirically applied as initial treatment (cases 2: bacterial infection; cases 9: fungal infection). Thereafter, the regimen was changed according to the culture result and sensitivity test. Reconstructive surgery was performed after the microbial infection was controlled.

Table 2
Detailed surgical procedures, surgical outcomes and complications in patients that received autologous perichondrium grafts for progressive scleral necrosis.

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Case no.</th>
<th>Postop 6M BCVA (Decimal)</th>
<th>Perichondrium double/single layer</th>
<th>Tissue as epithelial tissue</th>
<th>Complication(s)</th>
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AM, amniotic membrane; AMT, amniotic membrane transplantation; BCVA: best-corrected visual acuity; no: number.
rheumatoid arthritis or Wegener’s granulomatosis [6]. Scleral ischemia develops predominantly in patients with underlying autoimmune disease. Patients who are positive for ANCA tend to have aggressive characteristics (cases 2 and 4) [6]. In this case series, all of the patients had a past history of ocular surface surgery, which typically includes procedures that may make the sclera more vulnerable to ischemic damage, especially in patients with rheumatic disease or ANCA positivity. Furthermore, four eyes out of the five eyes which had received prior multiple surgery had an autoimmune disease or autoantibodies. The autoimmune status of the cases might have increased the failure rate of the previous reconstructive surgery.

It is difficult for patients to recover from PSN with an acellular connective tissue graft. Revascularization and epithelialization over the scleral defect are essential for healing the scleral ischemia and ulceration; therefore, easily accessible autologous biologic tissue containing stem cells has been considered as a new candidate to substitute for traditional materials used in surgery. Finally, we identified autologous perichondrium as an option to reconstruct PSN, even in cases with full-thickness scleral defect.

Autologous perichondrium is thought to be an appropriate sclera substitute for several reasons. First, the perichondrium is a living tissue that contains MSCs within the inner layers [24,28]. Importantly, MSCs can improve angiogenesis, exhibit healing capacities, and modulate immune responses through the secretion of a number of cytokines and growth factors [25]. Numerous studies have been carried out to regenerate cartilage or bone with perichondrium containing MSCs [24,29]. We suggest that the excellent results obtained in the present study with the transplantation of perichondrium might be attributable to the existence of MSCs and secreted cytokines. Second, the perichondrium is characterized by a whitish color that is identical to the scleral color (Fig. 1E), in addition to identical fibrillar microstructures. The perichondrium has similar components to the sclera, including the presence of type I collagen. Third, the perichondrium is an autologous tissue that is easily obtained from the tragal cartilage of the ear under local anesthesia, and harvesting in this fashion is not associated with serious wound morbidity. Accordingly, tragal perichondrium/cartilage grafts have been used for tympanoplasty or rhinoplasty [30,31]. Fourth, the perichondrium has more durable and stronger tensile strength as compared with the sclera (Fig. A1). Thus, the perichondrium is an appropriate tissue to recover the structural defect of the eyeball. Finally, the perichondrium could be considered as a tissue that is evolutionarily identical to the sclera [29]. Most vertebrates develop a cartilage layer or bony layer within the sclera, although some placental mammals such as primates do not [32]. Moreover, human scleral cells retain chondrogenic potential both in vitro and in vivo [29]. Therefore, the sclera maintains characteristics that are similar to cartilage or perichondrium.

The most important surgical principles for PSN are the treatment of scleral ischemia and rapid re-epithelialization through step-by-step reconstructive procedures. The use of permanent AM graft (stromal side down) over the ischemic sclera as a basement membrane as the first step of the procedure reduces stromal melting through immunomodulatory effects and promotes implantation of the perichondrium graft [3]. The perichondrium patch graft used during the second step serves as a MSCs-containing scleral substitute with strong tensile strength. MSCs of perichondrium have pro-angiogenic potential and modulate immune responses (data not shown). In the third step, conjunctival angiogenesis and re-epithelialization or serves as epithelial tissues over the graft. It also prevents stromal melting and protects the perichondrium patch graft [3,22]. Then, the temporary AM graft (stromal side up) used in the fifth step protects the whole graft and revascularized epithelium over the graft. Finally, the administration of autologous serum after the surgery provides the nutritional support for vascular and epithelial growth.

To recover scleral revascularization and to prevent graft melting, we aimed to generate a stem cell niche (microenvironment) using stem cell-containing perichondrium and AM on an avascular sclera bed. Thus, AMs were used both beneath and above the perichondrium tissue to protect and improve the microenvironment of stem cell niches. The MSCs niches (microenvironment) generated using perichondrium and AM showed potent proangiogenic and reconstructive potential over the ischemic scleral bed.

Our study has several limitations. First, its design is a non-randomized, noncomparative case series with no control group. The representative conventional materials used for reconstruction included AM as well as preserved sclera. AM has been applied widely because of its therapeutic potential and immunomodulatory features [3]. And AM promotes re-epithelialization and reduces stromal melting, while multilayer transplantation of AM can provide tectonic support. However, there are definite therapeutic limitations to its use. Second, the number of cases included is relatively small, even though this series includes the largest number of cases among published scleral defect case series to date. Third, the latent period in this cases series ranged from 1 to 30 years. In nine cases, PSN occurred within two years after the surgery for pterygium or pinguecula. The use of mitomycin during the previous surgery was confirmed by reviewing the medical records of the cases. Hence, the higher concentration or longer duration of exposure of mitomycin may be associated with relatively short latent periods. In contrast, several cases had a significantly long delay between the timing of the surgery of pterygium or pinguecula and presentation of PSN. We considered the cases as surgically-induced necrotizing scleritis because the location of PSN was on the nasal side in almost cases or the eyes showed no other potential cause. Nevertheless, in cases with a long latent period, this association may not be evident. Moreover, the timing of presentation in patients with scleral melt throughout the long latent period is not clear. Despite these limitations, transplantation of perichondrium and AM showed superior therapeutic potential to conventional surgery, and the structural integrity of the eyeball was maintained to the last follow-up without loss of the eyeball or vision.

5. Conclusions

This study reports the successful performance of transplantation of autologous perichondrium and AM to address PSN. The potent therapeutic potential might be attributed to MSCs and their niches in the perichondrium. We propose that the perichondrium is a physiologically appropriate graft material for scleral reconstructive surgery.

Conflicts of interest

None of the authors has any conflicts of interest to disclose.

Funding

This study was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science, ICT, and Future Planning (NRF-2019R1H1A1035593; NRF-2017R1A2A2A05001128; NRF-2015R1C1A1A01054285). These funding sources had no role in the study design; in the collection, analysis, or interpretation of data; or in the writing of the report.

Acknowledgement

Data included in this manuscript were originally presented as a poster and awarded a best poster at the American Academy of Ophthalmology Annual Meeting, 2017, New Orleans, LA, USA, 11–14 November.
Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jtos.2019.05.004.

References