

Normobaric Oxygen Therapy for Scleral Ischemia or Melt

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Purpose: To investigate the efficacy of normobaric oxygen (NBO) therapy for treatment of scleral ischemia or melt.

Methods: This prospective interventional case series includes 9 eyes of 8 patients with scleral ischemia or melt of diverse etiologies. Following the failure of conventional medical and/or surgical therapy to improve ischemia or upon clinical deterioration, NBO was initiated. All patients received 100% NBO at flow rate of 10 liters/minute by face mask for 1 hour, twice daily until complete vascularization of ischemic areas. Main outcome measures were improvement of scleral ischemia and healing of conjunctival epithelial defects.

Results: NBO therapy led to epithelialization and vascularization of the ischemic sclera in all eyes; the repair process began 3-4 days after NBO had been initiated and was completed in 18.1±4.7 (range, 10-25) days. All patients remained stable over a 9-month follow-up period.

Conclusion: NBO therapy seems effective for treatment of scleral ischemia or melt, and hence can be considered as a non-invasive alternative to surgical intervention in these conditions.

Keywords: Oxygen Therapy; Scleral Ischemia or Melt

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INTRODUCTION

The outermost layer of the eye, the sclera, preserves integrity of the globe. Being composed of compact collagen fibers, elastin and glycoproteins, the sclera is almost devoid of vessels and receives its nutritional supply from choroidal and episcleral circulations.¹

Scleral ischemia and melt may occur in association with systemic or ocular diseases. Predisposing conditions include autoimmune disorders and vasculitides, ocular trauma and surgical procedures i.e. surgically induced

necrotizing scleritis (SINS). Scleral ischemia, thinning and melt may be observed following severe chemical and thermal burns, bare sclera pterygium surgery especially when adjunctive modalities such as beta-radiation or antimetabolites like mitomycin C (MMC) have been used, retinal detachment surgery, and even following cataract and glaucoma procedures.²⁻⁴

Management of scleral ischemia and melt may be challenging. The avascular sclera needs to become vascularized to prevent scleral melting. In line with this strategy, tenoplasty alone or in conjunction with amniotic membrane

transplantation (AMT) has been performed to deliver vessels to the affected area.⁵⁻⁷ For massive scleral necrosis, scleral or corneal patch grafting covered by AMT or a conjunctival flap may correct the condition.⁸⁻¹⁴ The combination of tenoplasty and AMT, with or without lamellar corneal patch grafting using sutures or fibrin glue, have been satisfying in patients with scleral ischemia and/or melt.¹⁵

Hyperbaric oxygen (HBO) therapy has been reported to induce vascularization and healing of the ischemic and necrotic sclera.¹⁶⁻¹⁹ Considering possible side effects of HBO therapy²⁰⁻²³ and the promising results of normobaric oxygen (NBO) therapy for chemical or thermal burns,²⁴ we

conducted a study to evaluate the efficacy of NBO for scleral ischemia or melt.

METHODS

This interventional case series was performed at the Ophthalmology Department of Imam Khomeini Hospital, Ahvaz, Iran; the study adhered to the tenets of the Declaration of Helsinki and was approved by the Ethics Committee of Jundishapur University of Medical Sciences. Written informed consent was obtained from all participants prior to enrollment.

The study included 9 eyes of 8 patients with scleral ischemia or melt of diverse

Table 1. Patients characteristics and results of normobaric oxygen therapy* for scleral ischemia/melt

Case number	Involved eye	Sex/age (yr)	Etiology of scleral ischemia/melt	Extent of scleral ischemia/melt	Epithelial defect: cornea / conjunctiva	Previous treatments	Complete epithelialization and vascularization**
1	OD	F/55	SINS: ECCE (1.5 yr earlier), SB (1 yr earlier), PPV (6 mo earlier)	superior necrosis (4×5 mm)	no/yes	lamellar corneal patch graft and conjunctival flap (2 mo earlier)	10
2	OU	F/39	bilateral bare sclera pterygium excision, intraoperative MMC 0.02% for 3 minutes (3 wk earlier)	nasal ischemia (8×7 mm) with conjunctival inflammation OU, thinning (1.5×2.5 mm) OS	no/yes	medical therapy	22
3	OS	M/29	S/P renal transplantation; large conjunctival mass (SCC) excision, cryotherapy, AMT, MMC eye drop QID/1 mo (37 d earlier)	ischemia (12×6 mm)	no/yes	AMT (37 days earlier)	25
4	OD	M/44	alkali burn (9 d earlier)	ischemia (8×6 mm)	total/yes	medical therapy	14
5	OD	M/40	bare sclera pterygium excision, intraoperative MMC (3 wk earlier)	ischemia (7×6 mm), melt (1.5×2 mm)	no/yes	medical therapy	18
6	OS	M/13	thermal burn (3 wk earlier)	ischemia (360°) up to 7 mm from the limbus	total/yes	medical therapy	21
7	OS	M/46	bare sclera pterygium excision (2 wk earlier)	ischemia (7×6 mm)	no/yes	medical therapy	17
8	OD	M/52	SINS: SB (4 mo earlier), infected buckle extrusion and removal (2 mo earlier)	ischemia, thinning (5×6 mm)	no/yes	conjunctival flap (1 mo earlier)	18

OD, right eye; OS, left eye; OU, both eyes; F, female; M, male; yr, year; mo, month; wk, week; d, day; SINS, surgically induced necrotizing scleritis; ECCE, extracapsular cataract extraction; SB, scleral buckle; PPV, pars plana vitrectomy MMC, mitomycin C; AMT, amniotic membrane transplantation; S/P, status post; SCC, squamous cell carcinoma; QID, four times a day

*Normobaric 100% oxygen was administered at a flow rate of 10 liters/min for 1 hour twice a day; **Days after oxygen therapy.

etiologies in whom previous conventional medical and/or surgical therapy had been ineffective. Medical treatment consisted of topical antibiotics, lubricants, and systemic vitamin C and tetracycline. Surgical therapy on the other hand, included lamellar corneal patch grafting, AMT and conjunctival flap alone or a combination thereof. Patients with SINS underwent a complete systemic work-up to rule out systemic or autoimmune disorders.

All patients received 100% NBO oxygen at flow rate of 10 liters/minute for 1 hour twice daily by face mask in sitting position until total recovery. All patients were examined by a single pulmonologist and none harbored a contraindication for oxygen therapy. Main outcome measures included improvement of scleral ischemia and healing of conjunctival epithelial defects.

RESULTS

A total of 9 eyes of 8 patients, including 2 women and 6 men with scleral ischemia or melt were studied. Mean patient age was 39.8 ± 13.5 (range: 13-55) years.

Epithelialization and vascularization of the ischemic areas began 3-4 days after initiation of NBO and progressed to complete healing at a mean of 18.1 ± 4.7 (range: 10-25) days. Table 1 demonstrates patients' characteristics and the results of therapy. None of the patients experienced any complication at the time of

therapy or afterwards. During a 9-month follow-up period, the condition remained stable in all patients.

Case Presentations

Case #3: A 29-year-old man presented with a large conjunctival mass in his left eye. Due to renal transplantation 2 years earlier, he was receiving cyclosporine A, mycophenolate and prednisolone. Biopsy of the mass revealed a diagnosis of squamous cell carcinoma. The lesion was largely excised, following by cryotherapy and AMT to cover the bare sclera. Treatment was continued with 0.02% MMC eye drops 4 times a day for 1 month. Amniotic membrane degradation was observed after one month, resulting in a 12×6 mm area of ischemic sclera in the nasal quadrant of the left eye (Fig. 1A). No improvement occurred with medical therapy after one week. Four days after starting NBO therapy, small vessels began to grow into the ischemic area leading to complete vascularization of the lesion in 25 days (Fig. 1B). During a follow-up period of 9 months, no recurrence or melting was observed.

Case #4: A 44-year-old man with alkali injury of the right eye and an 8×6 mm area of ischemic sclera was referred 9 days after initial injury. There was complete loss of the conjunctiva, tenon and episclera over the ischemic area and total corneal epithelial defect (Fig. 2A). The patient was on topical antibiotic,

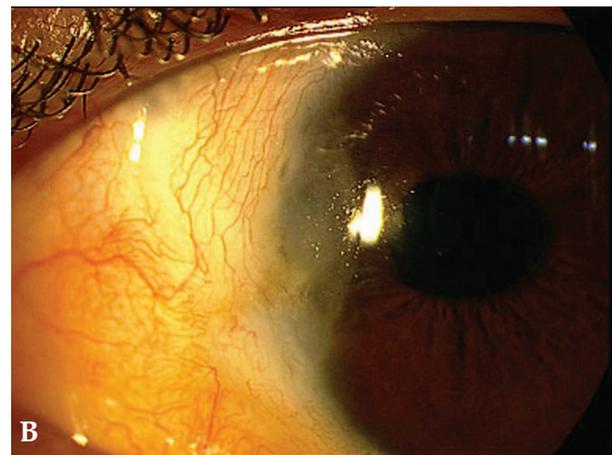


Figure 1. (A) Left eye of case #3; scleral ischemia is apparent following conjunctival mass excision. A 12×6 mm area of scleral ischemia which was unresponsive to amniotic membrane transplantation and medical therapy can be observed. (B) Left eye of case 3; note complete vascularization of the ischemic area 25 days after normobaric oxygen therapy.

lubricants, oral tetracycline and vitamin C. NBO therapy resulted in progressive and complete vascularization of the ischemic area in 14 days (Fig. 2B).

DISCUSSION

The current study illustrated the efficacy of NBO therapy as an adjunctive treatment option in patients with scleral ischemia obviating the need for surgical intervention.

Scleral ischemia may occur due to diverse etiologies and poses a therapeutic challenge. Ischemia may lead to scleral necrosis hence, threatening globe integrity and even lead to loss of the eye. Scleral ischemia may occur with chemical or thermal injuries, following ocular surgery (SINS) or in association with systemic autoimmune diseases.²⁻⁴ Pterygium surgery with adjunctive use of antimetabolite agents such as MMC is a common cause of scleral ischemia and melt.³ Bare sclera pterygium surgery, even without any adjuvant treatment, may also result in scleral melting because the avascular sclera is deprived of the vascular supply of layers which normally provide coverage and nourishment.²

Regardless of the etiology, scleral ischemia should be corrected immediately to prevent progressive melting. For cases of scleral ischemia or melting that arise in the setting of autoimmune diseases, systemic immunosuppressive drugs are an essential part of management.

A commonly used surgical approach to correct scleral ischemia includes conjunctival

flap surgery and tenoplasty to deliver vessels onto the ischemic areas.⁵⁻⁷ For subjects with scleral melting, tissue transplantation may provide tectonic support; these include lamellar corneal grafting, scleral patch grafting together with a conjunctival flap, AMT, or fascia lata transplantation.^{4,8-15}

Oxygen has been employed to assist wound healing for many years, however, there are limited reports regarding its use in ophthalmology.^{16-19,25} Green and Brannen were the first to report the success of HBO therapy in healing beta-irradiation induced scleral necrosis following pterygium excision.¹⁶ The condition had initially failed to respond to conjunctival flap surgery but improved after fourteen sessions of daily HBO therapy for 90 minutes. In a similar report by Bayer et al, scleral necrosis following pterygium surgery and adjunctive MMC for which conjunctival flap surgery had failed twice, responded well to twenty-four sessions of HBO therapy for 90 minutes daily with complete vascularization and healing of the necrotic area.¹⁷

In the current study, new vessels began to grow into the ischemic area 3-4 days after NBO therapy was initiated. Progression of vascularization continued as a wave of branching vessels which reached a remodelling phase after complete healing. In our patients, healing of scleral ischemia or necrosis occurred at a mean of 18.1 ± 4.7 (range: 10-25) days after NBO therapy which is comparable to reports on HBO therapy.

Breathing oxygen increases arterial blood

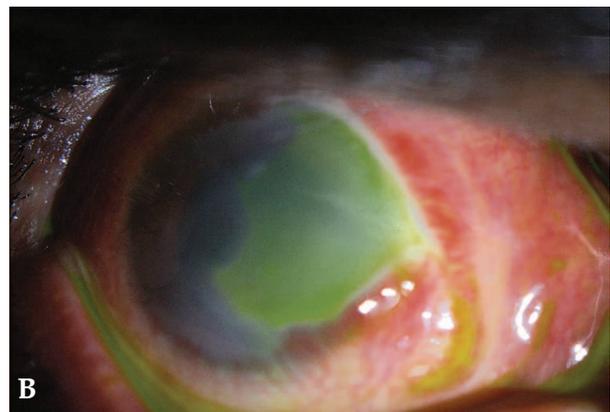
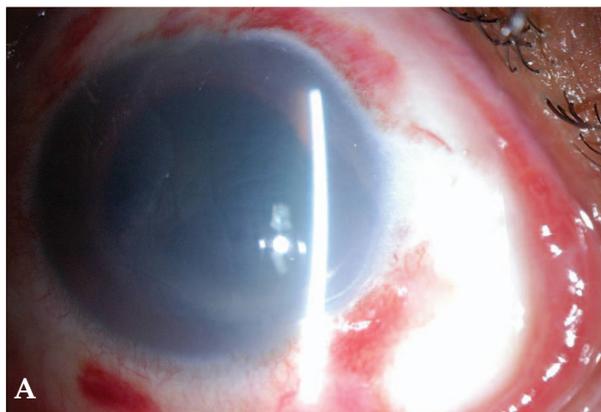


Figure 2. (A) Right eye of case #4 with history of alkali burn; scleral ischemia can be observed 3 days after normobaric oxygen therapy (12th day post-injury). (B) Right eye of case #4 showed complete healing 14 days after normobaric oxygen therapy.

oxygen pressure which in turn elevates tissue oxygen pressure. In ischemic tissues, oxygen pressure is the result of oxygen diffusion from surrounding vessels. Although oxygenation of hypoxic tissues is the primary effect of oxygen therapy in ischemic injuries, oxygen also acts in numerous ways that further assist wound healing even after treatment is terminated and blood oxygen pressures return to pre-treatment levels.

Oxygen influences a number of cytokines and growth factors which are important in the process of wound healing. Under ischemic conditions, HBO up-regulates fibroblast growth factor (FGF).²⁵ Fibroblasts are stimulated to produce and deposit collagen through peroxides. This occurs both in a hypoxic wound and during oxygen therapy.²⁵ Vascular endothelial growth factor (VEGF) is up-regulated by both hypoxia and hyperoxia, but not normoxia, causing angiogenesis. This phenomenon is called the "oxygen paradox". Furthermore, activity of released VEGF is further enhanced during hyperoxia.^{25,26}

Tissue oxygen levels also have a major role in the function of white blood cells (WBCs). Low tissue oxygen pressure (5-15 mmHg) results in diminished ability of WBCs to kill bacteria and decreased collagen synthesis by fibroblasts.^{27,28} Raising tissue oxygen tensions to 30 to 40 mmHg, stimulates fibroblasts to lay down a collagen matrix which supports capillary ingress into avascular areas. Increasing tissue oxygen level improves bacterial killing by WBCs, collagen production by fibroblasts, and angiogenesis.²⁸ Furthermore, the vasoconstrictive effect of oxygen favorably affect wound healing by decreasing edema, thereby reducing the distance across which oxygen diffuses from the vessels to ischemic areas. This, together with a simultaneous increase in blood oxygen pressure, ameliorates tissue hypoxia. In summary, oxygen improves wound healing by up-regulating growth factors, down-regulating inflammatory cytokines, reducing edema and supporting angiogenesis.

HBO therapy has previously been reported to be effective for treatment of scleral necrosis,^{16,17} however regarding favorable outcomes of our

previous study on NBO therapy for management of ocular burns we were encouraged to employ this less complicated modality for scleral ischemia.²⁴

NBO therapy entails certain advantages over HBO therapy especially in terms of safety; NBO is readily available at all medical facilities and appears to have few side effects. HBO therapy, on the other hand, requires specialized and costly equipment and trained specialists; it is much more expensive and poses more side effects and contraindications as compared to NBO.^{19,22,25} For instance, an untreated pneumothorax is an absolute contraindication to HBO therapy. Relative contraindications include impaired pressure equalization, poor cardiac output and severe obstructive pulmonary disease; moreover, HBO therapy is not advised for patients with intraocular gas bubbles.^{19,21} Nevertheless, simple mask oxygen therapy can safely be used in the aforementioned conditions. Common complications of HBO therapy include ear, sinus and pulmonary barotrauma, myopia, cataract, and oxygen toxicity seizures.^{20,22,23}

A major shortcoming of the current study is the absence of a control group. This is due to relative rarity and diverse etiologies of the condition, making selection of similar cases rather difficult. Our observations warrant further studies and possible inclusion of a control group.

This study showed that NBO therapy may be effective for treatment of scleral ischemia and melt. This safe and noninvasive treatment may be considered as an alternative to surgical intervention. Further studies are required to confirm our results and to determine the optimal dosage and frequency of NBO therapy.

Conflicts of Interest

None.

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