Accepted Manuscript

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PII: S0039-6257(16)30201-6
DOI: 10.1016/j.survophthal.2017.09.005
Reference: SOP 6754

To appear in: Survey of Ophthalmology

Received Date: 11 October 2016
Revised Date: 8 September 2017
Accepted Date: 11 September 2017


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Treatment of Acute Ocular Chemical Burns

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Conflicts of interest: None

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Abstract

Ocular chemical burns are an ophthalmic emergency and are responsible for 11.5% to 22.1% of ocular injuries. Immediate copious irrigation is universally recommended in acute ocular burns to remove the offending agent and minimize damage. Conventional medical therapy consists of the use of agents that promote epithelialization, minimize inflammation, and prevent cicatricial complications. Biological fluids such as autologous serum, umbilical cord blood serum, platelet-rich plasma, and amniotic membrane suspension are a rich source of growth factors and promote healing when used as adjuncts to conventional therapy. Surgical treatment of acute ocular burns includes the debridement of the necrotic tissue, application of tissue adhesives, tenoplasty, and tectonic keratoplasty. Amniotic membrane transplantation is a novel surgical treatment that is increasingly being used as an adjunct to conventional treatment to promote epithelial healing, minimize pain, and restore visual acuity. Various experimental treatments that aim to promote wound healing and minimize inflammation are being evaluated such as human mesenchymal and adipose stem cells, beta-1,3 glucan, angiotensin-converting enzyme inhibitors, cultivated fibroblasts, zinc desferrioxamine, anti-fibrinolytic agents, antioxidants, collagen cross-linking, and inhibitors of corneal neovascularization.

Keywords: acute ocular burns, amniotic membrane transplantation in acute ocular burns, ocular chemical burns, ocular alkali burns, umbilical cord serum in acute ocular burns, autologous serum in acute ocular burns
I. Introduction

Acute ocular chemical burns are an ophthalmic emergency and require immediate diagnosis and prompt management. They are responsible for 11.5% to 22.1% of ocular injuries. A recent epidemiologic survey reported that children aged 1 to 2 years are at a significantly higher risk of sustaining ocular chemical injuries than other age groups. Ocular burns may occur accidentally at the workplace, laboratories, home, or be intentional as a result of assault or vitriolage. A majority of ocular chemical burns occur at residential locations in the lower socioeconomic groups. The various types of chemical agents that cause ocular burns include alkalis and acids; alkalis are responsible for 60% of ocular burns.

The clinical course of an ocular chemical injury may be divided into the immediate, acute, early reparative, and late reparative phases. The immediate phase begins at the moment of contact of the chemical agent with the ocular surface. The initial 7 days after chemical eye injury constitute the acute phase of recovery. This is followed by the early reparative phase, which is the transition period of ocular healing and lasts 8-21 days after the injury. Herein, we describe the treatment modalities in the initial immediate, acute, and early reparative phases. For the purpose of this review, the term “acute ocular burns” refers to burns with duration of less than 3 weeks.

Ocular chemical burns may result in extensive long-term damage to the ocular surface and limbal stem cells. Limbal stem cell deficiency may lead to severely dry eyes, corneal neovascularization, and corneal opacity. The potential cicatricial sequelae of ocular chemical burns include lid margin abnormalities, symblepharon, ankyloblepharon, and trichiasis.
Conventional management of acute ocular burns focuses on the promotion of epithelialization, reduction of inflammation, and prevention of progressive corneal melt and cicatricial complications.\textsuperscript{9,218} The various medical therapies that have been used to treat ocular burns include ascorbic acid,\textsuperscript{20,107,144} citrate,\textsuperscript{144} tetracycline,\textsuperscript{140,156,180} corticosteroids,\textsuperscript{50} and medroxyprogesterone.\textsuperscript{218} The surgical treatment of acute ocular burns includes the debridement of necrotic tissue, application of tissue adhesives,\textsuperscript{58} tenoplasty,\textsuperscript{206,165} and tectonic keratoplasty, if required.\textsuperscript{158}

Growth factors play an important role in corneal epithelial wound healing and repair.\textsuperscript{116} Amniotic membrane is a rich source of growth factors and is increasingly being used in the treatment of acute ocular burns.\textsuperscript{78,87,109,154,187,196,126,202} It has anti-inflammatory and anti-fibrotic properties that promote the restoration of a stable ocular surface. Other biological agents that are rich sources of growth factors and have been used topically in acute ocular burns include autologous serum, umbilical cord serum, and autologous platelet-rich plasma.\textsuperscript{108,134,186,187,181}

II. Classification

Acute ocular chemical burns may be classified on the basis of limbal, corneal, and conjunctival involvement at the time of injury. Various classification systems have been proposed to help prognosticate the outcome of acute ocular burns. The Roper-Hall and Dua classification systems are commonly used.\textsuperscript{52,174} The Roper-Hall classification system was initially proposed by Ballen in 1964 and was subsequently modified by Roper-Hall in 1965.\textsuperscript{8,174} The extent of tissue damage is assessed by the degree of corneal haze and the amount of limbal ischemia and is used to determine the prognosis following ocular surface
injury (Table 1); however, it classifies all cases with 50%-100% limbal ischemia as grade IV burns, even though not all such cases have a poor prognosis. The Dua classification system is based on the limbal involvement in clock hours as well as the percentage of bulbar conjunctival involvement (Table 2).\textsuperscript{52} It re-classifies Roper Hall grade IV burns into grade IV, V, or VI burns, and the prognosis is determined by the extent of limbal and conjunctival involvement. This is based on the fact that the limbal epithelial stem cells and the fornical stem cells of the conjunctival epithelium may help in the restoration of an intact ocular surface and wound healing.\textsuperscript{52} Intact limbal anatomy of even one clock hour may promote re-epithelialization and healing after ocular surface injury and an intact conjunctival epithelium may grow over the denuded cornea and promote the natural repair mechanism while minimizing stromal melt. Hence, only eyes that have 12 clock hours of limbal involvement and 100% of conjunctival involvement are classified as grade VI burns, with a very poor prognosis.

Dua’s classification also incorporates an analogue scale that allows for a continuous score to be assigned to the limbal and conjunctival involvement in addition to the step-wise gradation of the severity of ocular injury.\textsuperscript{52} The analogue scale enhances the flexibility of the classification system by allowing crossover between the grades of chemical injury in different clinical scenarios and can accurately reflect the daily progress and healing following acute burns, even if the grade of injury remains the same. Dua’s classification helps in more precise definition of the extent of ocular surface injury and a better prediction of injury outcomes.\textsuperscript{52}

III. Medical Management
Medical management aims at the removal of the offending agent, copious irrigation, the promotion of epithelialization, the minimization of ulceration, and controlling inflammation. Topical biological fluids are increasingly being used in acute ocular burns as a source of growth factors in order to promote corneal wound healing and repair. The role of oxygen therapy is being evaluated in experimental animal as well as in human studies to assist wound healing.\textsuperscript{73,183,184}

A. Emergency treatment

Prompt institution of emergency treatment in cases of acute ocular chemical burns is the keystone in management and helps in the prevention of long-term debilitating cicatricial sequelae. Removal of particulate matter and irrigation are well-established modalities to minimize further ocular damage. The benefit of paracentesis in cases of acute ocular chemical injuries is controversial.

1. Irrigation

Immediate copious irrigation of the ocular surface in acute ocular burns is universally recommended to minimize the potential ocular injury.\textsuperscript{23,128,25,98,112} In experimental alkali-burned porcine corneas, minimal changes were observed in the intraocular pH of eyes that had been rinsed immediately after the induction of an alkali burn.\textsuperscript{169} Irrigation should be continued until neutralization of the ocular surface pH is achieved. A minimum of 30 minutes of irrigation is recommended using 1-3 liters of fluid. The pH should be checked every 15-20 minutes during irrigation. Continuous irrigation systems have been developed for the emergency management of acute ocular burns.\textsuperscript{223} Irrigating contact lenses such as the Morgan lens (MorTan, Inc., Missoula, MT, USA) may be used to deliver a continuous stream of the irrigating fluid. Following
copious irrigation, the lids should be everted and a comprehensive ocular surface examination should be undertaken to remove any remnant particulate matter and to document the extent of the injury. Double eversion of the lid should be performed if needed. The chemical particles are removed from the ocular surface with a moist cotton tip or fine-tipped forceps.

The rinsing solutions that have been used for irrigation include water, normal saline, Ringer’s lactate, phosphate buffer, Diphtherine® (Prevor, Cologne, Germany), and Cederroth® eye wash (Cederroth Industrial Products, Upplands Vasby Sweden). Clean tap water is an effective rinsing solution in emergency situations when none of the physiological solutions are available. Immediate copious irrigation with clean tap water may reduce the severity of ocular burns and shorten the healing time. Hypo-osmolarity of the tap water may lead to corneal edema. The subsequent enlargement of the diffusion barrier and intracorneal dilution inhibits elevated intracameral pH levels. Iso-osmolar saline is less efficacious than tap water as an irrigating agent for ocular burns. Amphoteric solutions that have a non-specific binding with bases and acids are also useful in emergency situations. Diphtherine is a hypertonic, polyvalent, amphoteric substance with buffering capacity comparable to that of phosphate buffer. Cederroth eye wash is a borate buffer solution. A comparative evaluation of different irrigating solutions reported that both Diphtherine and Cederroth eye wash solutions are superior to tap water in lowering intracameral pH following experimental alkali burns; however, saline and isotonic phosphate buffer are not effective in buffering intraocular pH. Prompt commencement of irrigation is more important than the choice of irrigating solution.
2. Paracentesis

The role of paracentesis and anterior chamber irrigation in acute ocular chemical burns is not well established owing to a paucity of clinical studies. Paracentesis and anterior chamber irrigation lowered the intracameral pH in experimental animal studies when instituted within 1-30 minutes of chemical injuries. We do not recommend the use of paracentesis or anterior chamber irrigation in acute ocular chemical burns.

B. Promotion of epithelialization

The agents that promote epithelialization following acute ocular burns include artificial tears, fibronectin, epidermal growth factor, retinoic acid, and sodium hyaluronate. The role of fibronectin, epidermal growth factor, retinoic acid and sodium hyaluronate is experimental, with no conclusive studies in human subjects to determine their efficacy in cases of acute ocular burns.

1. Artificial tears

Artificial tears are the mainstay of treatment in cases of acute ocular chemical injuries and are routinely administered to promote epithelialization. Preservative-free tear substitutes may ameliorate persistent epitheliopathy, reduce the risk of recurrent erosion, and accelerate visual rehabilitation.

2. Fibronectin

Fibronectin promotes corneal wound healing following acute ocular burns in experimental animal studies. Increased expression of fibronectin and laminin has been observed in rat corneal alkali burns as early as 7 hours following an alkali burn. It enhances epithelialization and prevents secondary breakdown of the
regenerating epithelium in alkali burns induced in rabbits. Fibronectin helps preserve a stable, intact ocular surface by decreasing the peeling back of the healing epithelium and promoting re-epithelialization in experimental animal burns; however, the role of fibronectin in acute ocular burns is still experimental, and its usage is not recommended routinely.

3. **Epidermal growth factor**

Epidermal growth factor (EGF) plays an essential role in wound healing in tissues such as the skin, cornea, and gastrointestinal tract. It stimulates the proliferation of keratocytes in the early stages of wound healing and promotes re-epithelialization in experimental animal alkali burn models. The safety and efficacy of EGF in acute ocular chemical burns has not been established in human studies, and its routine use is not recommended.

4. **Retinoic acid**

Vitamin A is necessary for normal epithelial growth and differentiation. Vitamin A deficiency leads to the loss of goblet cells, increased epidermal keratinization, and squamous metaplasia of the mucous membranes, including the cornea and conjunctiva. Retinoic acid stimulates the conversion of limbal stem cells to transient amplifying cells, inhibits the proliferation of corneal and limbal transient amplifying cells, and prevents abnormal terminal epithelial differentiation in experimental studies. It promotes transdifferentiation of the conjunctival epithelium into the corneal epithelium following severe chemical injury. Theoretically, it may be useful following severe chemical injury in promoting goblet cell recovery, tear film stabilization, and improved ocular surface wetting. Kim et al. demonstrated that 1500 IU/ml of retinyl palmitate eye drops
administered 4 times a day for 3 days can inhibit vascular endothelial growth factor-A (VEGF-A), activate thrombospondin 2, and improve conjunctival impression cytologic findings in experimental corneal alkali burns in rats. 84 Toshida et al. demonstrated accelerated wound healing in experimental ocular chemical burns in rabbits after administering 1500 IU/ml of retinol palmitate 6 times a day for 11 days; 208 however, there is a paucity of human studies and retinoic acid is currently not advocated in the routine management of acute ocular chemical burns.

5. Sodium hyaluronate

Hyaluronic acid (HA) is a high-molecular-weight glycosaminoglycan and extracellular matrix component that promotes cell proliferation. High-molecular-weight HA modulates biosynthetic pathways, cell migration, cell outgrowth, and protein degradation to stimulate wound healing and prevent cell death. 222 Histochemical analysis of animal corneas following acute ocular burns demonstrates the presence of hyaluronic acid in the healing epithelium, repopulating keratocytes/fibroblasts and the cells forming the retrocorneal membrane. 56 Topical HA (1% and 2%) promotes corneal epithelial wound healing in experimentally induced ocular burns. 38,40,7,224 Topical 1% HA may enhance the formation of hemidesmosomes during the early healing phase in n-heptanol-induced experimental corneal wounds. 41 The routine use of HA is not recommended in cases of acute burns because of lack of definitive literature in humans.

C. Support repair and minimize ulceration

Ascorbate, tetracyclines, and collagenase inhibitors support repair and minimize ulceration following acute ocular burns. Both topical and systemic ascorbate, as well as
tetracycline, exert a beneficial effect in the acute phase of wound healing. The role of collagenase inhibitors is experimental with no studies on human subjects.

1. **Ascorbate**

   Alkali injury to the ciliary epithelial transport processes and the ciliary body vasculature may result in a decrease in the aqueous humor ascorbate levels to one-third the normal values. The scorbutic state results in the failure of the fibroblasts to synthesize collagen for repair. Immediate treatment with systemic or topical ascorbate to reverse this deficiency significantly decreases the incidence of subsequent corneal ulceration and perforation in experimental animal models. Topical administration is more effective than systemic administration, since the latter has inadequate penetration in the anterior segment of the injured eye as observed in experimental studies. Transmission electron microscopy has demonstrated the presence of basal lamina under the regenerating epithelium in rabbit eyes with alkali burns following treatment with 10% sodium ascorbate. Topical ascorbate also potentiates the effect of topical citrate in preventing corneal ulceration.

   A majority of the experimental studies demonstrate a definite benefit of topical and systemic sodium ascorbate in the management of acute ocular chemical burns. Even in studies that do not show any significant difference in outcome, a trend toward the beneficial effect of ascorbate is evident as there is a decrease in the perforation rates, rapid healing, and a shift of the adenosine triphosphate (ATP)/adenosine diphosphate (ADP) ratio.

   Based on our clinical experience and the available literature, we recommend the administration of 500 mg of oral ascorbate 4 times a day, along with 10% topical...
ascorbate eye drops every 2 hours, in the initial 4 weeks, followed by tapering the dose over 1 month in cases of grade III-VI (Dua classification) acute ocular burns.

2. **Tetracyclines**

Tetracyclines prevent collagenolytic degradation of the cornea after ocular chemical injury. Increased tetracycline levels in the ocular tissues decrease the likelihood of ulceration in alkali burn-induced rabbit eyes. Tetracyclines inhibit matrix metalloproteinases through multiple mechanisms involving the restriction of gene expression of neutrophil collagenase and epithelial gelatinase, suppression of alpha-1-antitrypsin degradation, and scavenging of reactive oxygen species. The anticollagenolytic mechanism is independent of the anti-microbial mechanism of tetracyclines. Oral tetracycline, 250 mg 4 times a day; doxycycline, 100 mg twice a day; or minocycline, 100 mg twice a day may be used alongwith topical tetracycline preparations (1% suspension or 3% ointment) in cases of acute ocular burns. Both topical and systemic tetracycline have beneficial effects in cases of acute ocular burns. Doxycycline is more potent than minocycline or tetracycline in preventing collagen ulceration, and the effect is not reversible by an excess of cationic calcium. However, all the referenced studies are experimental animal studies, and there is an absence of well controlled human studies showing clinical benefit.

3. **Collagenase inhibitors**

N-acetyl cysteine (10-20%) and synthetic inhibitors of metalloproteinases (SIMP) significantly delay or prevent the ulceration of alkali-injured corneas by influencing collagen degradation. In addition to collagenase inhibition, SIMPs also cause a significant reduction in the accumulation of polymorphonuclear leukocytes
(PMNL) in alkali-injured corneas. The dual effect of the inhibition of PMNL chemotaxis and collagenase activity make SIMP a potential drug for combating ulceration in alkali-injured corneas.\textsuperscript{143,22} An experimental study did not observe any beneficial effect of n-acetyl cysteine in cases of acute alkali burns.\textsuperscript{145} The role of collagenase inhibitors is not well established with a paucity of human studies; hence, they are not recommended for routine clinical use in cases of acute ocular chemical burns.

D. Control of inflammation

The agents that have been used to control inflammation include corticosteroids, progestational steroids, non-steroidal anti-inflammatory drugs, and citrate.

1. Corticosteroids

Corticosteroids have traditionally been the mainstay of therapy for the reduction of tissue injury related to acute or chronic inflammatory conditions. They reduce inflammatory cell infiltration and stabilize PMNL cytoplasmic and lysosomal membranes.\textsuperscript{80,106} Corticosteroids can be used intensively during the first week following an alkali burn without increasing the risk of corneal melting. Topical prednisolone 1% and topical dexamethasone 0.1% may be used in the acute phase after ocular burns; however, they should be rapidly tapered in 10-14 days to minimize their deleterious effects.

The use of topical steroids for more than 6 days after ocular chemical injury increases the incidence of corneoscleral melting in experimental animal models.\textsuperscript{50} The mechanism for enhancement of corneal ulceration is not a direct augmentation of collagenase activity, but probably involves the inhibition of the repair process.\textsuperscript{50} Vitamin
C has been used in conjunction with topical steroids for prolonged periods without an increase in corneoscleral melting.\textsuperscript{48}

In an experimental animal study, corneas treated with 0.1\% dexamethasone alone for the first week maintained a well-preserved basement membrane for as long as 4 weeks after the initial damage without enhancement of the inflammatory cell infiltration.\textsuperscript{39} In another experimental study, topical administration of 0.1\% dexamethasone deterred endothelial healing during the early period and prevented secondary endothelial breakdown. The total repair process of the endothelium was accelerated by the dexamethasone treatment and it may have therapeutic potential in the management of endothelial healing after corneal alkali injury.\textsuperscript{42}

Conjunctival damage in alkali burns results in the loss of goblet cells in the acute post-injury period. A deficiency in goblet cells and mucin is associated with both short- and long-term ocular sequelae. Topical steroids in the acute phase of ocular chemical burns are also beneficial in suppressing goblet cell loss in experimental animal models.\textsuperscript{39} We recommend the institution of topical prednisolone 1\% or topical dexamethasone 0.1\% every 2 hours in the acute phase of ocular burns in conjunction with topical and oral ascorbate. The topical steroids are tapered in 10-14 days.

2. \textbf{Progestational steroids}

Progestational steroids have less potent anti-inflammatory properties compared to corticosteroids; however, they have a minimal inhibitory effect on stromal repair and collagen synthesis.\textsuperscript{152} The mode of action is related to the suppressive effect of progestational steroids on the production of tissue collagenase, as indicated by the considerable reduction in collagenolytic activity by living explants of the treated
corneas. They may have the potential to substitute corticosteroids after 10-14 days of acute ocular chemical burns in inflamed eyes.

The incidence of perforation and deep ulceration in experimental alkali-burned rabbit corneas is reduced by the topical or parenteral administration of medroxyprogesterone, however, further clinical studies in humans are required to definitely establish the clinical role of medroxyprogesterone in acute ocular chemical burns.

3. Citrate

Sodium citrate significantly inhibits the development of corneal ulcers after alkali injury. It inhibits collagenase activity as well as PMNL infiltration of the cornea following alkali burns. Citrate acts by chelating calcium and magnesium. This has been supported by an experimental study in which the addition of calcium and magnesium annulled the favorable effect of 10% topical citrate in alkali-injured rabbit eyes. Sodium citrate-induced collagenase inhibition is also reversible by excess calcium cations. Topical citrate 10% was observed to be superior to 10% ascorbate, 20% acetylcysteine, or Adsorbotear in reducing the incidence of corneal ulceration and perforation after experimental alkali burns. The combination of citrate and ascorbate is superior to citrate alone in preventing corneal ulceration. A retrospective 11-year review of ocular burns observed a trend toward rapid healing in grade III burns (Roper-Hall classification) with the use of topical citrate. We recommend the use of topical 10% citrate every 2 hours in the acute phase of ocular chemical burns, followed by tapering after the initial 4 weeks in grade III-VI (Dua classification) burns.

4. Non-steroidal anti-inflammatory drugs (NSAIDs)
NSAIDs and experimental lipogenase and leukotriene inhibitors are effective inhibitors of PMN leukocytes. Anti-inflammatory non-steroidal therapy combined with free radical scavengers may be a potential alternative to corticosteroid treatment in cases of chemical injuries. Pretreatment with aspirin or indomethacin abolishes the increase in intraocular pressure and the elevation of prostaglandin-like activity in the aqueous humor following experimentally induced corneal burns; however, further clinical studies in humans are required to establish the clinical role of NSAIDs in acute ocular chemical burns.

E. Adjuvant therapy

The use of prophylactic topical antibiotics is warranted during the initial treatment stages to prevent the occurrence of secondary infection, especially in the presence of epithelial defect.

Severe ocular chemical burns (Roper-Hall grade III or IV) are more likely to be associated with glaucoma and require surgical management for the control of intraocular pressure (IOP). Elevated IOP generally occurs within 1 week in such eyes. Topical aqueous suppressants are advocated to reduce IOP secondary to chemical injuries, both as an initial therapy and during the later recovery phase, if IOP is high (>30 mm Hg). Systemic anti-glaucoma drugs are advocated to control IOP. This also minimizes epithelial toxicity that may occur due to the use of topical aqueous suppressants. Glaucoma-filtering surgery and drainage devices may be needed in cases of severe chemical burns with uncontrolled IOP.

Topical cycloplegic agents are required to manage the ciliary spasm and oral analgesics may be required in some cases initially to control pain.
Preservative-free topical medications are preferred to prevent exacerbation of the ocular surface injury and secondary drug-induced toxicity. Oral medications may be considered when appropriate to further spare the ocular surface.

F. Topical biological fluids

Biological fluids that have been used to promote epithelialization and accelerate wound healing in cases of acute ocular burns include autologous serum, umbilical cord serum, amniotic membrane suspension, and autologous platelet-rich plasma (Table 3). They also find an application in various other ocular surface disorders such as dry eyes, persistent epithelial defects, neurotrophic ulcers, recurrent erosion syndrome, and superior limbic keratoconjunctivitis.

1. Biological properties

The rationale for the use of biological fluids in acute ocular burns stems from the presence of various growth factors in serum. Autologous serum contains growth factors such as epidermal growth factor, acidic fibroblast growth factor, basic fibroblast growth factor, platelet-derived growth factor, hepatocyte growth factor, transforming growth factor-beta, insulin-like growth factor-1, and nerve growth factor. It also contains vitamin A, substance P, fibronectin, immunoglobulins, and serum anti-proteases such as alpha-2-macroglobulin, which promote wound healing and re-epithelialization. The composition is similar to natural tears, with a higher concentration of vitamin A, transforming growth factor-beta-1, insulin-like growth factor-1, nerve growth factor, fibronectin, and lysosyme than tears. Autologous serum eye drops are superior to
artificial tears in treating dry eyes\textsuperscript{27} and have the additional advantage of being preservative free.

The constituents of umbilical cord serum are similar to autologous serum; however, the concentrations of growth factors are several times higher in umbilical cord serum than in peripheral blood serum.\textsuperscript{229,231} Vitamin A and insulin-like growth factor-1 concentrations are higher in autologous serum compared to cord blood serum.\textsuperscript{229,231}

Autologous platelet-rich plasma contains platelets in addition to the growth factors and cytokines. The platelets contribute to the prolonged release of growth factors and cytokines.\textsuperscript{122}

Amniotic membrane is a rich source of growth factors, with additional anti-inflammatory and anti-scarring properties.\textsuperscript{68,86,89} Topical amniotic membrane suspension obviates the need for a surgical procedure as required in amniotic membrane transplantation.\textsuperscript{108}

2. Outcomes

The efficacy of amniotic membrane suspension, autologous serum, and umbilical cord serum in acute chemical burns has been demonstrated in various experimental animal studies.\textsuperscript{35,72,132,176,182} Undiluted autologous serum eyedrops promoted the epithelial healing process in experimental corneal alkali wounds induced in rabbits.\textsuperscript{176} Umbilical cord serum was superior to peripheral blood serum and artificial tears in promoting wound healing and decreasing the corneal haze in a mouse model of ocular chemical burns.\textsuperscript{132} Amniotic membrane suspension promoted faster epithelial healing than autologous serum in a rabbit model of alkaline corneal injury.\textsuperscript{182} Amniotic membrane
suspension promotes epithelial healing and decreases corneal haze, neovascularization, and inflammation in cases of alkali burns.\textsuperscript{36,72}

Only a few human studies exist evaluating the role of different biological fluids in cases of acute ocular burns. A prospective study assessed the role of 50% autologous serum in various ocular surface disorders including chemical burns.\textsuperscript{181} Fifteen eyes with grade II-III chemical injury (Dua classification) received 50% autologous serum drops 5-6 times per day in addition to conventional therapy. The autologous serum was introduced 7 days after the corticosteroid therapy in patients with persistent inflammation, epithelial defects, or any type of ocular surface instability. The dose was reduced to 3 times daily after 1 month and continued until the absence of symptoms for at least 3 more months without supportive therapy. At the end of a mean follow up of 16±5.86 weeks, all patients with chemical injury experienced symptomatic relief and an average gain of 4 lines of Snellen acuity. Epithelial integrity was achieved in all cases, with a decrease in inflammation and corneal opacity.

Two randomized control trials compared the efficacy of umbilical cord serum in acute ocular burns.\textsuperscript{186,188} The first prospective randomized control trial compared the role of umbilical cord serum, autologous serum, and artificial tears in acute ocular chemical burns.\textsuperscript{186} A total of 33 eyes of 32 patients with grade III, IV, or V burns (Dua classification) were randomized to receive either 20% umbilical cord serum (n=12), 20% autologous serum (n=11), or artificial tears (n=10) administered 10 times per day. The patients were followed up for 3 months. Patients receiving umbilical cord serum experienced significantly more pain relief at day 7 compared to autologous serum and artificial tears. Umbilical cord serum was superior in terms of epithelial defect healing,
corneal clarity, decrease in vascularization, and limbal involvement at the end of 3 months. No significant difference was observed between the groups with regard to symblepharon formation.

Another randomized controlled trial compared the efficacy of topical umbilical cord serum drops and amniotic membrane transplantation (AMT) in acute ocular chemical burns. A total of 45 eyes with acute chemical burns of grade III, IV, and V (Dua's classification) presenting within the first week of injury were randomized into 3 groups to receive either 20% umbilical cord serum with medical therapy, AMT with medical therapy, or conventional medical therapy alone. Umbilical cord serum and AMT were found to be equally efficacious in terms of time to corneal re-epithelialization and both were superior to medical therapy alone. Umbilical cord serum achieved faster improvement in corneal clarity, better pain control, and helped avoid surgery in inflamed eyes.

A retrospective interventional comparative case series compared umbilical cord serum (20%, 10 times/day) with AMT and conventional management in 55 eyes with moderate (grade II-IV Dua classification) acute ocular burns. Both umbilical cord serum and AMT were superior to conventional management in healing the epithelial defect. Umbilical cord serum was superior to AMT in terms of a healthy ocular surface; furthermore, there is an additional advantage of avoiding surgery in inflamed eyes.

A prospective case series evaluated the use of topical amniotic membrane extract in 14 eyes of 11 patients with acute chemical burns. Amniotic membrane extract was instilled hourly for the first 4 weeks, then every 2 hours for 2 weeks and tapered slowly until the inflammation subsided. Symptomatic relief and epithelial defect healing were
reported in all cases. Improvement in visual acuity and a reduction of inflammation was observed, with a greater efficacy in mild to moderately acute cases.\textsuperscript{108}

Panda et al. randomly assigned 20 eyes with grade III-V (Dua classification) acute chemical injury into 2 groups. Group I (10 eyes) received autologous platelet-rich plasma eye drops 10 times per day along with standard medical treatment, and group II (10 eyes) received standard medical treatment alone. At the end of 3 months of follow up, the group receiving the autologous platelet-rich plasma demonstrated faster healing of epithelial defects and better corneal clarity.\textsuperscript{134}

A single case controlled study evaluated the role of subconjunctival application of regenerative factor-rich plasma for the treatment of ocular alkali burns in 35 eyes. A significant reduction in the corneal and conjunctival epithelialization times and healing times was reported in cases of moderate burns receiving the regenerative factor-rich plasma.\textsuperscript{121}

We recommend the instillation of topical biological fluids 10-12 times per day for the initial 4 weeks followed by slowly tapering the dose until the inflammation subsides in all cases of grade III-VI (Dua classification) ocular burns (Figure 1). Umbilical cord serum is preferred over autologous serum and topical amniotic membrane suspension.

G. Oxygen therapy

Oxygen therapy has been used to assist wound healing for many years. Multiple mechanisms have been proposed to explain the beneficial effect of the hyperoxia induced by hyperbaric oxygen. Hyperbaric oxygen therapy induces vasoconstriction and promotes fibroblast
proliferation and also increases bacterial killing by the recruitment of leukocytes and facilitates
toxin inhibition and antibiotic synergy.102

Two animal studies have studied the role of oxygen therapy in acute ocular burns. Hirst et al.
did not report any beneficial effect of hyperbaric oxygen in preventing corneal perforation in 24
rabbit eyes with experimental alkali burns;73 however, Sharifipour et al. observed a delay in the
onset of ulceration and a decreased incidence of corneal perforation in 28 rabbit eyes receiving
5L/min oxygen therapy for 1 hour daily.184

A pilot study evaluated the effect of the systemic administration of oxygen in cases with
acute ocular burns in a nonrandomized prospective comparative study.183 A total of 24 eyes of 22
patients with grade III-IV burns (Roper-Hall classification) were administered 100% oxygen at
flow rates of 10 L/min for 1 hour twice a day. The eyes receiving oxygen therapy had
significantly faster corneal epithelialization and vascularization of the ischemic areas with a
better mean visual acuity. The use of oxygen may salvage the partially injured ischemic limbal
stem cells, thereby promoting the restoration of an intact transparent ocular surface and
preventing the development of sight-threatening complications. No case receiving oxygen
developed corneoscleral melt or had symblepharon.

Large-scale studies are needed to further elucidate the effects of systemic oxygen therapy
in acute ocular burns so that a therapeutic regimen describing the specific dosage and duration
may be formulated. Currently, we do not recommend the routine use of oxygen therapy in acute
ocular chemical burns.

IV. Surgical Therapy
The surgical therapy in cases of acute ocular burns consists of debridement of the necrotic tissues, amniotic membrane transplantation, use of tenoplasty if required, and keratoplasty.

A. Debridement

Debridement of the necrotic epibulbar tissue removes inflammatory debris from the ocular surface. Necrotic tissues act as a site for the accumulation of polymorphonuclear neutrophils and leukocytes that release detrimental proteolytic enzymes, further aggravating the damage.\(^{160,161}\)

B. Amniotic membrane transplantation

1. Biological properties

The amnion is the innermost layer of fetal membranes and consists of the epithelium, basement membrane, and stroma.\(^{47}\) Bourne described 5 layers in the amnion, namely the epithelium, basement membrane, compact layer, fibroblast layer, and spongy layer.\(^{16}\) The epithelium consists of a single layer of cuboidal cells that are attached to the underlying basement membrane with the help of numerous hemidesmosomes. The basement membrane consists of collagen IV and VII, fibronectin, and laminin 1 and 5. The laminin isoforms in the amniotic membrane promote adhesion and the spread of corneal epithelial cells onto the amniotic membrane.\(^{28,97}\) The stroma contains loose connective tissue that provides tensile strength to the amniotic membrane. The epithelium and stroma act as sources of growth factors and cytokines, which serve to maintain the microenvironment of the stem cells of the corneal epithelium. They help maintain undifferentiated epithelial phenotype when culturing the limbal stem cells. Epidermal growth factor, transforming growth factor-alpha, keratinocyte growth factor, hepatocyte growth factor, basic fibroblast growth factor, and
transforming growth factor beta-1 and beta-2 are some of the growth factors that have been demonstrated in the amniotic membrane epithelium and stroma.\textsuperscript{89} The basement membrane provides the framework for epithelial cell migration and also induces their differentiation. It strengthens adhesion on the basal cells and prevents apoptosis.\textsuperscript{14,15} The stromal matrix inhibits cicatization through the downregulation of transforming growth factor beta signalling.\textsuperscript{210} It suppresses corneal, conjunctival, and limbal fibroblast proliferation and differentiation and reduces subconjunctival fibrosis. The mRNA of antiangiogenic and anti-inflammatory proteins has been demonstrated in the amniotic membrane; additionally, protease inhibitors that reduce stromal inflammation and ulceration are also present.\textsuperscript{58,86} The stromal matrix traps and induces apoptosis of the inflammatory cells and reduces neovascularization.\textsuperscript{86} Antimicrobial properties have also been demonstrated in amniotic membrane in a few studies.\textsuperscript{157,172}

2. Preparations of amniotic membrane

Various types of amniotic membrane preparations have been used for acute ocular burns. The most commonly used preparation is cryopreserved amniotic membrane,\textsuperscript{78,87,109,154,187,196,202,203,205,207,126,131,235} followed by fresh amniotic membrane\textsuperscript{6,30,214,235} and sutureless amniotic membrane (PROKERA®, Bio-Tissue, Inc., Miami, FL, USA).\textsuperscript{82,201} Dried amniotic membrane (amnioplastin) was historically used in initial trials of amniotic membrane transplantation in acute ocular surface burns.\textsuperscript{193,194}

a) Fresh amniotic membrane

Before delivery, fresh amniotic membrane is obtained during elective caesarean section from the placenta of women who are seronegative for hepatitis B, hepatitis C,
syphilis, and HIV. The amniotic membrane is separated from the placenta under sterile conditions and irrigated with copious sterile salt solution.\textsuperscript{214} It is stored in normal saline solution containing 50,000 IU penicillin and 1g streptomycin per 400 ml saline at 4\textdegree{}C.\textsuperscript{6} Fresh amniotic membrane should be used within 24 hours of retrieval. Fresh amniotic membrane, although more biologically active, is not preferred because of the potential risk of microbiological transmission.\textsuperscript{125}

b) **Cryopreserved amniotic membrane**

Most surgeons use cryopreserved amniotic membrane in cases of acute ocular burns.\textsuperscript{78,87,109,187,196,202,203,205,207,126,235} Cryopreserved amniotic membrane is prepared in accordance with the method described by Kim and Tseng,\textsuperscript{85} with minor modifications. Amniotic membrane is harvested from placentas procured through elective caesarean section of a seronegative donor. The serology of the donor is done to exclude hepatitis B and C viruses, HIV, and syphilis during pregnancy or at the time of delivery. The serology is repeated 3 to 6 months after delivery when the membrane is cryopreserved to account for any infections at the time of initial screening. Meller et al. additionally tested the donors for human T cell lymphotropic virus (HTLV).\textsuperscript{126} The original method described by Kim and Tseng includes washing the membrane under a lamellar flow hood to remove the blood clots, followed by dissecting the amnion bluntly from the chorion.\textsuperscript{85} This amnion is flattened onto nitrocellulose filter paper with the epithelium/basement membrane side up, and then washed 3 times with buffered phosphate saline containing 1000U/ml penicillin, 20 mg/ml streptomycin, and 2.5 mcg/ml amphotericin B. The resulting membrane is cut into 1.5 cm diameter disks and stored at 4\textdegree{}C in 100% glycerine.
Lee and Tseng made minor modifications in the above technique. The placenta is cleaned of the blood clots under a lamellar flow hood using Earle’s balance salt solution containing 50 µg/ml penicillin, 50 µg/ml streptomycin, 100 µg/ml neomycin, and 2.5 µg/ml amphotericin B. The amnion is flattened onto nitrocellulose filter paper (0.45 micron pore size) and cut into small disks of 3×4 cm. It is cryopreserved at -80°C in a sterile vial containing Dulbecco’s modified Eagle’s medium and glycerol at a ratio of 1:1 (v/v). A similar method has been described by Dua and Azuara-Blanco that involves washing the placenta with physiological saline or 0.01 M phosphate buffered saline (PBS) containing 100 mg of dibekacin sulphate. Tamhane et al. placed the amnion-chorion complex in sterile solution of normal saline (540 ml), dexamethasone (8mg), gentamicin (80 mg), and heparin (5000 IU) after retrieval.

c) PROKERA

PROKERA (Bio-Tissue, Inc., Miami, FL, USA) contains cryopreserved amniotic membrane clipped onto a symblepharon ring-like concave polycarbonate dual-ring structure. The ring has an inner diameter of 15 mm (for pediatric patients) or 16 mm (for adult patients) and adheres to the corneal and limbal surface like a contact lens. It is a class II medical device that the FDA approved in 2003 for use as a temporary amniotic membrane patch that is easy to insert and remove and obviates the need for sutures. It acts as a biological bandage, with the stromal side of the amniotic membrane in contact with the ocular surface and the symblepharon ring-like structure fitting snugly in the fornices holding the amniotic membrane in place.
3. Surgical techniques

Meller et al. initially performed cryopreserved amniotic membrane transplantation (AMT) in accordance with the technique described by Brown et al. The amniotic membrane was placed on the eye covering the entire ocular surface from the upper lid margin to the lower lid margin and anchored using interrupted episcleral and lid margin bites with 9/10-0 vicryl sutures. Fornix formation was done with 6-0 silk sutures passing through the amniotic membrane and newly formed fornices brought out through the lid and tied over the skin with bolsters. In a few cases with less extensive damage, the amniotic membrane was used as a graft to cover only the damaged area. The sticky stromal side was in contact with the corneo-conjunctival surface; however, in some studies, the amniotic membrane with the stromal side up was also transplanted.

Variations in the technique of AMT have been described based on the orientation, size, and layers of the amniotic membrane. Various modifications to decrease the dislodgement of the amniotic membrane have been described, such as the use of a bandage contact lens, symblepharon ring, fibrin glue, and modification of the suturing technique.

a) Amniotic membrane layers and orientation

Most studies have transplanted a single layer of amniotic membrane onto the damaged ocular surface, with a few studies using multilayered amniotic membrane with the epithelial side facing upward. A few studies have also placed the amniotic membrane with the sticky stromal side facing upward, and the epithelial side in contact with the ocular surface.

b) Size of amniotic membrane
Depending on the severity of injury, the amniotic membrane either covers the whole ocular surface stretching until the lid margins or may act as a graft covering only the localized area of damaged corneoconjunctiva.\textsuperscript{126}

c) Permanent versus temporary amniotic membrane transplantation

Amniotic membrane may be allowed to cover the ocular surface post transplantation until its spontaneous dissolution or it may be removed after a few days, acting as a temporary patch in that period.\textsuperscript{82,87,109,193,194,126,203}

d) Modification in suturing technique

Kobayashi et al. introduced the technique of using running a nylon suture to anchor the amniotic membrane to the lid margin and a purse string suture 1-2 mm from the limbus to anchor the amniotic membrane to the episclera. This reduces redundant amniotic membrane, decreasing the risk of infection and detachment.\textsuperscript{87}

e) Use of fibrin glue

We routinely use fibrin glue (TISSEEL VH fibrin sealant, Baxter AG, Vienna, Austria) to anchor the amniotic membrane to the ocular surface. The amniotic membrane is placed stromal side down on the ocular surface, and 4 8-0 vicryl stay sutures are placed in the perilimbal area. This is followed by injecting fibrin glue beneath the amniotic membrane after drying the ocular surface. A symblepharon ring is then placed, and the redundant amniotic membrane is trimmed.

f) Use of symblepharon ring

Tamhane et al. anchored the amniotic membrane with perilimbal and lid margin interrupted 8-0 vicryl sutures, and used a symblepharon ring to spread the amniotic membrane on the ocular surface.\textsuperscript{202} The symblepharon ring was removed after the
amniotic membrane was anchored with vicryl sutures along the lid margins, and sutures applied after removing the ring. A similar technique was used by Sharma et al. in their recent study.\textsuperscript{187} Tejwani et al. placed a symblepharon ring after suturing amniotic membrane graft with interrupted 10-0 nylon perilimbal sutures and interrupted 8-0 vicryl episcleral sutures, which was removed after 1 week after surgery.\textsuperscript{205} Thanikachalam et al. placed a pediatric scleral shell after AMT.\textsuperscript{207} Liang et al. fabricated a modified symblepharon ring made of polymethyl methacrylate (PMMA), obviating the need for suturing the amniotic membrane.\textsuperscript{109} The modified symblepharon ring was made by creating an impression of the anterior ocular surface on PMMA conformers using an ocular prosthesis. The resultant 1 mm thick PMMA device had a 30-35 mm inner diameter, 35-38 mm outer diameter horizontally, and 35-40 mm outer diameter vertically, with a gap in the lowest part of the fornix of the device. The amniotic membrane was placed epithelial side down covering the entire ocular surface, and the modified symblepharon ring was placed on it, followed by trimming of the redundant amniotic membrane.

\textbf{g) Use of bandage contact lens}

Arora et al. used a bandage contact lens in addition to the symblepharon ring.\textsuperscript{6} Bandage contact lenses following AMT have been used by others to ensure the safety of the transplanted amniotic membrane.\textsuperscript{114,115,196,126,214} Ucakhan et al. kept the bandage contact lens in situ until the completion of epithelialization.\textsuperscript{214} We prefer to keep the bandage contact lens over the amniotic membrane as this prolongs the duration the amniotic membrane remains in situ.

\textbf{h) PROKERA insertion}
PROKERA (Bio-Tissue, Inc., Miami, FL, USA), a device for sutureless AM delivery, is inserted under topical anesthesia in adult patients on an outpatient basis. The patient is asked to look down and the PROKERA is inserted in the superior fornix, followed by the inferior fornix. It is removed after healing.\textsuperscript{82,201}

4. Outcomes

After AMT, the patients were followed up over a 30-960 day period.\textsuperscript{201} A majority of patients experienced symptomatic relief after amniotic membrane transplantation.\textsuperscript{6,82,87,114,115,126,202,205,188,214} Following AMT, an improvement in visual acuity and faster epithelialization was noted in most studies, with grade II-III burns (Roper-Hall classification) healing better than grade IV burns.\textsuperscript{6,82,87,109,114,115,126,187,193,194,196,202,203,205,214}

a) Symptoms

Most patients undergoing amniotic membrane transplantation experienced a resolution of pain, photophobia, and tearing in the immediate postoperative period.\textsuperscript{6,82,87,114,115,126,205,188,214} Tejwani et al. reported symptomatic relief in 100\% of patients with acid injuries compared to 94.44\% of patients with alkali injuries.\textsuperscript{205} There was immediate reduction in light sensitivity and foreign body sensation, and the patients were more comfortable.

b) Visual acuity

Following AMT in cases of acute ocular burns, an improvement in visual acuity has been noted in most studies.\textsuperscript{6,82,87,109,114,115,126,187,193,194,196,202,205,214,220} Liang et al. reported a gain in visual acuity in 46.15\% of patients undergoing sutureless AMT using...
the modified symblepharon ring compared to 41.67% of patients in the sutured AMT group.\textsuperscript{109} Grade II-III (Roper-Hall classification) of ocular burns had more mean improvement in visual acuity compared to grade IV ocular burns;\textsuperscript{6,126,202} however, no improvement in visual acuity was reported in grade IV (Roper-Hall classification) ocular burns undergoing AMT in few studies, with worsening of visual acuity in some cases.\textsuperscript{6,78,202} In a case series by Joseph et al, all four eyes had a visual acuity of no perception of light at the end of two years.\textsuperscript{78} In two randomized control trials, there was no significant difference in the visual outcome amongst patients undergoing AMT or those receiving conventional medical management.\textsuperscript{188,203}

c) Time to epithelialization

After AMT, the time taken for restoration of stable ocular surface was variable, ranging from less than one week to more than three months.\textsuperscript{87,114,115,187,193,194,214} Faster epithelial defect healing was noted in grade II-III (Roper Hall classification) ocular surface burns compared to grade IV burns.\textsuperscript{126,202,214} On histopathological examination, faster re-epithelialization and better epithelial and stromal regeneration was observed following AMT compared to conventional medical therapy in moderate alkaline burns.\textsuperscript{114,115} On comparison of sutureless AMT with conventional sutured AMT, faster epithelialization was noted in the sutureless group, with 71.79% of eyes achieving complete epithelialization compared to 47.22% eyes in the sutured group.\textsuperscript{109} In a randomized control trial comparing conventional medical treatment with AMT, faster epithelial healing with AMT occurred compared to conventional medical treatment in grade II-III (Roper Hall classification), but not grade IV ocular surface burns.\textsuperscript{202} In another randomized control trial comparing the role of umbilical cord serum and amniotic
membranes as adjuncts in cases of acute ocular burns, faster epithelialization was observed in both the AMT group and cord serum group when compared to conventional medical therapy alone. Few studies have also reported persistent epithelial defects and failure of amniotic membrane transplantation to restore stable ocular surface in grade IV burns.

5. Complications

The most common sequelae occurring after AMT were symblepharon formation, corneal vascularization, and limbal stem cell deficiency. In a randomized control trial that compared sutureless AMT using a modified symblepharon ring with sutured AMT, symblepharon was significantly less in the sutureless group (38.46%) compared to the sutured group (61.11%). Another randomized control trial evaluated AMT vs conventional medical management and found less tendency toward symblepharon formation in eyes undergoing AMT compared to conventional medical therapy in moderate grade II-III burns (Roper-Hall classification); however, the same did not hold true for severe burns (grade IV Roper Hall classification). A few studies did not report any cicatricial complications. Grade IV (Roper-Hall) injuries usually had persistent limbal stem cell deficiency despite AMT, with a poorer prognosis than grade II-III burns.

Additional procedures such as limbal stem cell transplant, keratolimbal allograft, or conjunctival limbal autograft are often needed to treat limbal stem cell deficiency. Dislodgement of the graft in the postoperative period necessitating a regraft has been reported, usually caused by frequent eye rubbing. Persistent epithelial defects may
lead to corneal perforation that eventually requires a penetrating keratoplasty.\textsuperscript{6,7,8,12,15,42,235} Granuloma pyogenicum, infective keratitis, and recurrent ulceration were also infrequently observed.\textsuperscript{6,15,4,20,21} Corneal scarring, corneal melt, and lid abnormalities have also been observed in few cases.\textsuperscript{7,8,12,6,15,4,20,41,19,6,23,5,20,3}

Contraction of the conjunctival sac and fornices have also been observed in severe grade V-VI burns (Dua classification).\textsuperscript{109} Less than 1\% of eyes were lost from uncontrolled inflammation, phthisis bulbi, autoevisceration, or exenteration.\textsuperscript{7,8,14,6} Although transplantation of fresh amniotic membrane is associated with a theoretical risk of transmission of infection, no such case has been reported following AMT.

Repeat amniotic membrane transplantation was the most common additional surgical procedure required post AMT (74.2\%) for persistent epithelial defect after dissolution of the initial amniotic membrane.\textsuperscript{7,8,12,6,15,4,19,3,4,20,4,19,6,23,5,20,3,5,22,3} Dislodgement of the previous graft and increased corneal staining were additional reasons for regraft.\textsuperscript{12,6,19,3}

Although symblepharon is a common complication, symblepharon release was performed in only 2.2\%.\textsuperscript{20,5,21,7,8,12,6,15,4} Additional procedures for limbal stem cell deficiency, such as limbal stem cell transplant, conjunctival autograft, and large diameter lamellar keratoplasty and keratolimbal allograft were required in 16.5\% cases, where amniotic membrane alone was not sufficient to restore the limbal anatomy.\textsuperscript{12,6,23} Fornix formation and lid reconstruction were infrequently required.\textsuperscript{7,8,20,5} Tectonic penetrating keratoplasty was carried out in a few cases of progressive corneal melt and perforation.\textsuperscript{7,8,12}

Conjunctival flap and tenoplasty have also been carried out in poor prognosis cases with recalcitrant epithelial defects not amenable to repeat AMT.\textsuperscript{7,8,12}

6. Conclusion
A Cochrane systematic review did not find enough evidence to recommend AMT in acute ocular chemical burns in the first 7 days following injury. It included only 1 randomized control trial and highlighted the lack of high-quality evidence supporting the use of AMT in acute ocular burns. Future well-designed randomized control trials are needed to conclusively establish the guidelines for the use of AMT in acute ocular chemical burns. However, a majority of studies have observed a beneficial effect of AMT in acute ocular chemical burns.

Both umbilical cord serum and AMT are superior to conventional management in promoting epithelialization. In cases of acute ocular burns, the use of cord serum as an adjunct has an additional advantage of avoiding surgery in already inflamed eyes. However, umbilical cord serum is a scarce biological resource and may not be available at all centers. Therefore, the use of AMT is an effective alternative in cases where umbilical cord serum is not readily available (Figure 2).

We recommend AMT in all cases of grade III-VI (Dua’s classification) acute ocular burns. Grade I-II (Dua’s classification) ocular chemical burns are mild and may be effectively managed with conventional medical therapy alone. Although the role of AMT in severe ocular chemical burns (grade IV-VI, Dua’s classification/grade IV, and Roper-Hall classification) is controversial, we recommend AMT based on our clinical experience. In our experience, AMT provides symptomatic relief and promotes healing in grade IV-VI (Dua’s classification) ocular chemical burns, although the benefits are not as pronounced as in grade III burns. The surgical procedure should be undertaken as soon as possible after providing emergency care. Cryopreserved or fresh amniotic membrane may be used. PROKERA is preferred in pediatric patients and systemically unstable patients.
due to the ease of insertion of the device even at bedside. The high cost of the device and the limited availability of PROKERA may limit its widespread usage, especially in developing countries.

C. Tenoplasty

Tenoplasty is based on the principle of re-establishment of the limbal blood supply in cases of severe ocular burns to potentially prevent late complications. A vital connective tissue of orbit is used to cover the damaged ocular surface.

The technique of tenoplasty first described by Teping and Reim requires initial debridement of all necrotic tissue from the conjunctiva and sclera. The tenon is then bluntly separated from the extraocular muscles and the equatorial region of the globe, taking care to preserve the vascular supply of the tenon tissue. After the preparation of a smooth tenon flap, it is advanced to the limbus and sutured to the sclera, thus providing a revascularization of the denuded sclera and the limbus region.

Tenoplasty helps in the resolution of scleral ulceration and prevents anterior segment necrosis in eyes with severe chemical and thermal burns. It shortened the period of intensive inpatient treatment in a series of 24 eyes with severe chemical burns. The conjunctival epithelium regenerated in 10-50 days, and the corneoscleral ulceration healed in all cases. In 14 of 24 eyes, the denuded corneal stroma was covered with an artificial epithelium. Keratoplasty was performed in 11 cases. Although some cases developed symblepharon, corneal opacity, and neovascularization, tenoplasty laid the foundation for further reconstructive surgeries.

Augmentation of the tenoplasty may be needed with glued-on contact lenses, amniotic membrane, or lamellar corneal patch graft.159,165,206
Cyanoacrylate tissue adhesive augmented tenoplasty has been successfully tried in a case of progressive corneolimboscleral ulceration after grade IV chemical burns.\textsuperscript{185} The cyanoacrylate tissue adhesive is directly applied to the ulcerated corneoscleral surface to augment the tenoplasty. It results in fibrous tissue proliferation and the formation of leucomatous corneal opacity with symblepharon. The ocular integrity was preserved and the final visual acuity was 6/36.

D. Tissue adhesives

Tissue adhesives may be used in the management of impending or actual perforations following sterile corneal ulcerations in acute ocular burns. They provide tectonic support and promote re-epithelialization. When used in conjunction with a contact lens, they prevent further ulceration by inducing fibrovascular scarring and minimizing the stromal infiltration of polymorphonuclear leukocytes.\textsuperscript{81}

Both fibrin and cyanoacrylate tissue adhesives are effective for the closure of corneal perforations up to 3 mm in diameter. Fibrin glue is associated with less corneal inflammation and neovascularization, and there is no need for removal of the glue.\textsuperscript{217,190,53,13}

The direct application of cyanoacrylate tissue adhesive on the ulcer bed followed by the placement of a bandage lens helps prevent progressive corneal melt.\textsuperscript{58} The cyanoacrylate glue is left in situ until it loosens spontaneously with the progress of re-epithelialization. It can be removed with forceps 6 to 8 weeks after inflammation has subsided and neovascularization has eliminated the risk of recurrent ulceration.

Tissue adhesives have been used in conjunction with amniotic membrane for small corneal perforations.\textsuperscript{53,204,199} They may help to delay penetrating keratoplasty for treating corneal perforations, especially in acute cases with an increased risk of graft rejection.\textsuperscript{53}
combined with amniotic membrane transplantation helps the rapid restoration of corneal and conjunctival surfaces, thus preventing late stage cicatricial sequelae. In severe burns, it arrests corneoscleral melting and restores the conjunctival surface and anterior segment blood supply, but does not restore the integrity of the corneal surface.  

E. Keratoplasty

Corneoscleral ulcerations and perforations are severe complications of ocular burns. An emergency full thickness keratoplasty may be required to provide tectonic support and maintain the integrity of the globe.

1. Lamellar keratoplasty

The role of deep anterior lamellar keratoplasty (DALK) has been evaluated in acute ocular chemical burns alone or in conjunction with AMT or a conjunctivo-limbal graft. DALK alone or combined with AMT helps to restore ocular integrity and has been reported to result in excellent graft transparency in 86% of cases and improvement in visual acuity in 100% of cases with acute chemical burns. Eyes with grade II and grade III ocular burns experience more improvement than grade IV burns (Roper-Hall classification). DALK leads to a faster resolution of symptoms and epithelial healing compared to the control group. The incidence of symblepharon, corneal perforation, and the severity of vascularization decreased in cases that underwent DALK.

2. Penetrating keratoplasty

An emergency therapeutic keratoplasty may be needed in acute ocular burns with large perforations. The prognosis for graft survival is poor because of the co-existent limbal stem cell dysfunction. A large diameter keratoplasty also provides limbal stem cells along with tectonic support.
A large keratoplasty 11-12 mm in diameter has been successfully tried in 8 eyes with widespread progressive corneal ulcerations and deep stromal defects. Six grafts remained clear with a healthy epithelial layer but an early rejection within 3 months was experienced in 2 cases. Large keratoplasties may help achieve long-lasting healing and rehabilitation in very severe ocular burns with total corneal melts. Restoration of an intact limbal anatomy is essential for graft survival.94

A retrospective analysis of keratoplasty with scleral rim undertaken in cases of severe ocular burns evaluated the putative role of surgery as a globe-salvaging procedure. Twelve keratoplasties with a scleral rim were undertaken in 9 eyes with severe corneal burns. Three eyes needed a repeat keratoplasty. Keratoplasty with a scleral rim can potentially save the eye in cases with extensive corneoscleral ulceration or perforation. Nevertheless, visual rehabilitation may not be achieved in most cases because of imminent graft failure. Only 2 grafts in the study remained clear, with failed grafts in the remaining 10 cases. Incomplete eyelid closure, severe vascularization, corneal scarring, and poor epithelial healing may contribute to graft failure.158

V. Investigational Agents

A. Stem cells

Human adipose-derived stem cells and mesenchymal stem cells inhibited inflammation and angiogenesis and promoted corneal wound healing in experimental ocular chemical burns in animal models.

1. Human adipose-derived stem cells

Human adipose-derived stem cells promoted cell renewal and healing in experimental rabbit models of ocular chemical injury.110,54 Human adipose-derived stem
cells overlaid on a scleral contact lens (SCL) carrier reduced inflammation and corneal haziness in severe ocular alkali burns in rabbits.\textsuperscript{54} Eyes receiving human adipose-derived stem cells had smaller epithelial defects and less corneal opacities and neovascularization compared to eyes receiving SCL alone. Untreated corneas melted in 2 weeks and developed severe symblepharon.

Subconjunctival injection of human adipose-derived stem cell suspension (1.3 \times 10^5 \text{cells}/0.2 \text{mL}) in rabbits with acute ocular chemical burns resulted in faster wound healing than in the control group. Transplantation of cultured human adipose tissue-derived stem cells in acute corneal chemical burns promotes cell renewal and assists in damage repair.\textsuperscript{110}

2. Mesenchymal stem cells

Subconjunctivally administered mesenchymal stem cells (MSCs) promote corneal wound healing in the acute stage of alkali burns.

Subconjunctival injection of MSCs significantly enhanced the recovery of the corneal epithelium and decreased the corneal neovascularization area in experimental ocular alkali burns in rats. These effects are related to a reduction of infiltrated CD68 (+) cells and the downregulation of MIP-1\textalpha, TNF-\textalpha, and VEGF.\textsuperscript{225}

Human MSCs have also been transplanted into rat corneas using the amniotic membrane as a carrier 7 days after chemical burns. They lead to the successful reconstruction of the damaged corneal surface. The therapeutic effect of transplantation may be associated with the inhibition of inflammation and angiogenesis rather than epithelial differentiation from MSCs.\textsuperscript{118}
B. Beta 1,3 glucan

Beta 1,3 glucan promotes invitro epithelial wound healing and suppresses the acute inflammatory reaction in experimental corneal alkali burns in rats. Laminarin and beta 1,3 glucan increased the in vitro epithelial cell migration of immortalized human corneal epithelial cells (HCECs) and hyaluronic acid (HA) conjugated beta 1,3 glucan demonstrates enhanced the migration rate more than beta 1,3 glucan alone.\(^{37}\)

Forty rats with experimentally induced alkali burns were divided into 4 groups receiving 200 \(\mu\)g/mL topical laminarin (n = 10), beta 1,3 glucan (n = 10), beta 1,3 glucan HA (n = 10), or no treatment (n=10). The highest wound healing ratio and the lowest opacity score were observed in the beta 1,3 glucan-HA group. Tissue sections revealed relatively fewer polymorphonuclear leukocyte infiltrates in the corneal stroma in the beta 1,3 glucan and beta 1,3 glucan-HA groups compared to the injury-only group.\(^{37}\)

C. Anti-fibrinolytic agents

Anti-fibrinolytic agents such as epsilon-aminocaproic acid (EACA) and tranexamic acid (TXA) competitively inhibit plasmin through binding at the serine site, blocking the catabolic function of plasmin. They inhibit plasmin-mediated catabolism of fibronectin on the basilar membrane surface attachment of the epithelial cells. These agents also promote the activation of plasmin from plasminogen, thereby depleting the pool of available plasminogen.\(^{130}\) Fibronectin establishes a supportive base for the migrating epithelium by anchoring the regenerating epithelial cells to the underlying stroma. The anti-fibrinolytic agents inhibit fibronectin catabolism and are hypothesized to increase the rate of initial re-epithelialization of the corneal epithelium immediately.
following the induction of epithelial defects by alkali burn. They have shown a significant improvement in the treatment of persistent epithelial defect in rabbits.

Both EACA and TXA increased the rate of re-epithelialization compared to an untreated control in the cultured corneas of rat alkali burn models. EACA was up to 35% more efficacious than TXA.\textsuperscript{46}

D. Angiotensin converting enzyme inhibitors

The local renin-angiotensin system activity determines the microcirculation in the eye, and an increase in the activity of angiotensin-converting enzyme (ACE) has been found in conjunctival ischemia. Instillation of the ACE inhibitor in rabbit eyes within 2 weeks of experimental alkali burns resulted in a reduction in ACE activity and an earlier recovery of microcirculation in the area of conjunctival ischemia. ACE inhibitor facilitates the maintenance of a high level of tear antioxidant potential and may have a positive effect on the course of reparative processes after ocular burns.\textsuperscript{34}

E. Allogenic fibroblasts cultivated in collagen gel

Transplantation of allogenic fibroblasts cultivated in collagen gel promoted wound healing and corneal regeneration in an experimental model of acute alkali corneal burns in rabbits.\textsuperscript{120}

F. Zinc desferrioxamine

Topical zinc desferrioxamine (220 microM 7 times a day for 4 weeks) was effective in decreasing the severity of ulceration in acute corneal alkali burns in rabbits. It may be an adjunctive treatment in protecting the cornea against alkali injury.\textsuperscript{189}

G. Hydroxypyridine derivatives
Emoxypine promoted healing of the corneal epithelial defect at the stage of epitheliocyte migration to the defect area in experimental alkali burns in rabbits. Mexidol also promoted epithelialization at the stage of epitheliocyte proliferation was is more effective than emoxypine in decreasing the area of conjunctival ischemia. Antioxidant activity and the content of products of nitric oxide metabolism in tear fluid decreased after chemical burns, which may be restored by Mexidol.33

H. Antioxidant therapy

Antioxidant therapy may be considered as a complementary treatment in the pharmacological modulation of acute corneal inflammation. Topical treatment with antioxidants such as 0.2% superoxide dismutase and 0.5% dimethylthiourea (DMTU) reduced inflammation, improved corneal transparency, and promoted healing in experimental studies.4

I. Collagen cross-linking

Collagen cross-linking allows covalent bonds to be formed between the collagen fibrils, thus promoting thickening of the collagen fibrils through the deposition of structural molecules such as proteoglycans.2

The effect of riboflavin-ultraviolet-A-induced cross-linking (CXL) was evaluated in 10 eyes with experimentally induced corneal alkali burns in rabbits. CXL-treated eyes demonstrated significant decrease in the size of epithelial defect with a smaller extent of corneal opacity compared to the control group. Histopathological evaluation of the CXL-
treated eyes showed the presence of collagen bridges linking the collagen fibers. CXL may have the potential to improve the prognosis of acute corneal alkali burns.\textsuperscript{44}

J. Inhibitors of corneal neovascularization

Corneal neovascularization (CNV) results from an imbalance between the angiogenic and antiangiogenic factors and can lead to corneal scarring, edema, lipid deposition, and inflammation.\textsuperscript{226,29} One of the most common causes of visual impairment, CNV leads to a loss of the immunologic privilege of the cornea and is a high-risk factor for rejection after allograft corneal transplantation.\textsuperscript{10,71,104,233,142} The role of various inhibitors of CNV in preventing the debilitating long-term sequelae of ocular burns is being evaluated.

1. Endostatin

The antiangiogenic activities of lipid-mediated subconjunctival injection of endostatin have been evaluated in a rabbit model of neovascularization. Both native endostatin and a modified human endostatin gene containing a RGDRGD (arginine-glycin-aspartic-arginine-glycin-aspartic) motif significantly inhibit CNV by suppressing the expression of vascular endothelial growth factor (VEGF). Modified endostatin with an RGDRGD motif is a more effective inhibitor of angiogenesis than native endostatin.\textsuperscript{62}

2. Canstatin

Recombinant canstatin protein administered intraperitoneally (5-10mg/kg body weight once a day for up to 14 days) suppresses corneal neovascularization in an alkaline burn-induced mice model. Expression of VEGF and TNF-\(\alpha\) significantly decreased in canstatin-treated corneas. It may be used as an inhibitor of angiogenesis to treat neovascularization-related corneal diseases.\textsuperscript{219}

3. Subconjunctival angiostatin
Subconjunctival injection of recombinant adeno-associated virus (rAAV)-angiostatin in alkali burn-induced rats reduced corneal angiogenesis. Ocular gene therapy involving the subconjunctival injection of adenovirus-associated gene transfer of angiogenesis inhibitors may be a simple and safe treatment modality that can achieve therapeutic levels and long-lasting effects in the treatment of corneal neovascularization induced by ocular surface disorders. 

4. AMD3100

AMD3100 is a CXCR4 antagonist and rapid stem cell-mobilizing agent. Locally administrated AMD3100 reduced the number of alkali burn induced corneal neovascularization in mice. The expression of endothelial progenitor cells marker proteins VEGFR2 and CD34 is decreased by the subconjunctival administration of AMD3100.

5. Chondrocyte-derived extracellular matrix

Chondrocyte-derived extracellular matrix (CDECM) suppresses corneal neovascularization by inhibiting nuclear factor-kappa B (NF-κB) activation by blocking the PKC- and Akt-signaling pathways. CDECM markedly decreased corneal thickness, neovascularization, and opacity when transplanted onto the corneal surface in experimental alkali-burned rabbit corneas. It improved corneal healing by disrupting corneal epithelial proliferation and reducing fibrotic changes of the stroma.

6. Anti-angiogenic multigene therapy

Angiogenesis is a complex process, and therapy targeting a single anti-angiogenic gene cannot block corneal neovascularization completely. Anti-angiogenic activity of multiple genes targeting endostatin (mEndo), murine-soluble vascular endothelial growth
factor receptor-2 (msFlk-1), or murine-soluble Tie2 (msTie2) have been evaluated to inhibit alkaline burn-induced corneal neovascularization in mice. Overexpression of these putative anti-angiogenic proteins inhibits the in vitro proliferation and migration of human umbilical vein endothelial cells. The subconjunctival injection of retroviral particles of mEndo and msFlk-1 resulted in the most significant inhibition of CNV in a murine corneal neovascularization model. The combination of multiple anti-angiogenic genes might be necessary for effective therapy of corneal neovascularization.  

7. **Bevacizumab**

VEGF stimulates corneal neovascularization, and both VEGF and its receptors are present in higher concentrations in human corneas with neovascularization. Bevacizumab (Avastin) is a recombinant humanized murine monoclonal antibody that binds to and inhibits the biological activity of all human VEGF-A isoforms. Subconjunctival bevacizumab (2.5-5mg/ml) reduced corneal neovascularization as well as VEGF levels in animal rabbit models of alkaline burns. It significantly decreased the total neovascularization area, the circumference involved, and the longest neovascular pedicle length. Bevacizumab (1.25 mg/0.05 ml) also decreased inflammatory cell infiltration in chemically burned rat corneas. The levels of inflammatory cytokines such as IL-2, IFN-gamma, and IL-6 were also decreased in rats receiving bevacizumab injections.

Subconjunctival bevacizumab (5mg/day) associated with dexamethasone (4mg/day) may have an advantage over monotherapy with bevacizumab alone in causing the involution of corneal neovascularization after corneal alkali burn.
Combination therapy of topical doxycycline temperature-sensitive hydrogel (DTSH) and bevacizumab is more effective in inhibiting corneal neovascularization than topical bevacizumab or DTSH alone. DTSH combined with bevacizumab significantly accelerates corneal wound healing by inhibiting the expression and activity of MMPs, VEGF, phosphorylated VEGFR1, VEGFR2, and the production of iNOS and IL-1β.  

Conclusions

The principle of treatment of acute ocular burns is to prevent further damage, promote wound healing, and hinder visually debilitating cicatricial sequelae. The management of acute ocular chemical burns is summarized in Figure 3. Emergency management constitutes copious irrigation and conventional medical agents—including ascorbic acid, citrate, tetracycline, and corticosteroids.

Growth factors have been shown to play an important role in wound healing. Topical biological fluids that are a rich source of growth factors include umbilical cord serum, autologous serum, platelet-rich plasma, and amniotic membrane suspension. Amniotic membrane is also a rich source of growth factors, with inherent anti-inflammatory, anti-angiogenic, and anti-fibroblastic properties. Topical biological fluids and amniotic membrane are increasingly being used in acute ocular burns, where timely intervention is the key to preventing future cicatricial complications and preserving visual function. AMT has been shown to provide immediate symptomatic relief, promote epithelial healing, and improve visual acuity in cases of acute ocular burns; however, its efficacy is limited to moderate burns and the results have not been encouraging in severe grade IV (Roper-Hall classification), possibly because the associated severe limbal ischemia negates the regenerative effects of AMT. Topical biological fluids are convenient methods of delivering growth factors to the
eye without the need for surgical intervention. They have been shown to effectively relieve symptoms and promote healing, although limited evidence is available.

Various experimental treatments that promote wound healing and inhibit corneal neovascularization are being evaluated, such as beta 1,3 glucan, angiotensin converting enzyme inhibitors, cultivated fibroblasts, zinc desferrioxamine, anti-fibrinolytic agents, antioxidants, collagen cross-linking, and inhibitors of angiogenesis. They may play an important role in the future in preventing cicatricial complications in cases of acute ocular burns.

**Method of Literature Search**

The literature search was performed in Medline using the following keywords: acute ocular burns, amniotic membrane transplantation in acute ocular burns, ocular chemical burns, ocular alkali burns, umbilical cord serum in acute ocular burns, and autologous serum in acute ocular burns. The relevant references cited in those articles were also searched. Abstracts of relevant non-English articles were used. All articles that described the use of biological fluids (autologous serum, umbilical cord serum, platelet-rich plasma, and amniotic membrane suspension) were reviewed. Regarding amniotic membrane transplantation in acute ocular burns, all articles were reviewed since the first use of amniotic membrane in ocular burns in 1986. For statements that are frequently mentioned in the literature, we chose the earliest publication and other important articles.
References


Abbreviations

Epidermal growth factor (EGF)
Hyaluronic acid (HA)
Synthetic inhibitors of metalloproteinases (SIMP)
Polymorphonuclear leukocytes (PMNL)
Non-steroidal anti-inflammatory drugs (NSAIDs)
Human Immunodeficiency Virus (HIV)
Amniotic membrane transplantation (AMT)
Phosphate buffered saline (PBS)
Dimethylsulfoxide (DMSO)
Deep anterior lamellar keratoplasty (DALK)
Conjunctival limbal autograft (CLAU)
Scleral contact lens (SCL)
Mesenchymal stem cells (MSCs)
Human corneal epithelial cells (HCECs)
Dulbecco's modified Eagle's medium (DMEM)
Epsilon-aminocaproic acid (EACA)
Tranexamic acid (TXA)
Angiotensin-converting enzyme (ACE)
Collagen cross linking (CXL)
Vascular endothelial growth factor (VEGF)
Chondrocyte-derived extracellular matrix (CDECM)
Doxycycline temperature-sensitive hydrogel (DTSH)
Figure legends:

Figure 1: Grade V (Dua’s classification) acute ocular chemical burn receiving topical umbilical cord serum in addition to conventional treatment (a) at presentation (b) one month after receiving topical umbilical cord serum

Figure 2: Grade IV (Dua’s classification) acute ocular chemical burn undergoing AMT (a) preoperative (b) one month postoperative

Figure 3: Management of acute ocular chemical burns
Table 1: Roper-Hall classification for the severity of ocular surface burns

<table>
<thead>
<tr>
<th>Grade</th>
<th>Clinical Findings</th>
<th>Conjunctiva/Limbus</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Corneal epithelial damage</td>
<td>No limbal ischemia</td>
<td>Good</td>
</tr>
<tr>
<td>II</td>
<td>Corneal haze, iris details visible</td>
<td>&lt;1/3 limbal ischemia</td>
<td>Good</td>
</tr>
<tr>
<td>III</td>
<td>Total epithelial loss, stromal haze and iris details obscured</td>
<td>1/3-1/2 limbal ischemia</td>
<td>Guarded</td>
</tr>
<tr>
<td>IV</td>
<td>Cornea opaque, iris and pupil obscured</td>
<td>&gt;1/2 limbal ischemia</td>
<td>Poor</td>
</tr>
</tbody>
</table>
Table 2: Dua classification for severity of ocular surface burns

<table>
<thead>
<tr>
<th>Grade</th>
<th>Clinical Findings</th>
<th>Conjunctival Involvement</th>
<th>Analogue Scale (Clock hours of limbal involvement/ % bulbar conjunctival involvement)</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>0 clock hours limbal involvement</td>
<td>0%</td>
<td>0/0%</td>
<td>Very good</td>
</tr>
<tr>
<td>II</td>
<td>≤3 clock hours limbal involvement</td>
<td>≤30%</td>
<td>0.1-3/1-29.9%</td>
<td>Good</td>
</tr>
<tr>
<td>III</td>
<td>&gt;3-6 clock hours limbal involvement</td>
<td>&gt;30-50%</td>
<td>3.1-6/31-50%</td>
<td>Good</td>
</tr>
<tr>
<td>IV</td>
<td>&gt;6-9 clock hours limbal involvement</td>
<td>&gt;50-75%</td>
<td>6.1-9/51-75%</td>
<td>Good to guarded</td>
</tr>
<tr>
<td>V</td>
<td>&gt;9-&lt;12 clock hours limbal involvement</td>
<td>&gt;75-&lt;100%</td>
<td>9.1-11.9/75.1-99.9%</td>
<td>Guarded to poor</td>
</tr>
<tr>
<td>VI</td>
<td>Total (12 clock hours) limbal involvement</td>
<td>100% (Total)</td>
<td>12/100%</td>
<td>Very poor</td>
</tr>
</tbody>
</table>
Table 3: Biological Properties and Dose of Topical Biological Fluids used in Treatment of Acute Ocular Chemical Burns

<table>
<thead>
<tr>
<th>Biological Fluid</th>
<th>Constituents</th>
<th>Source</th>
<th>Concentration</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autologous Serum</td>
<td>Growth factors, Vitamin A, Substance P, Fibronectin, Immunoglobulins Serum</td>
<td>Patient’s whole blood</td>
<td>20%, 50%, 100%</td>
<td>10 times/day for 4 weeks. Slow taper till inflammation subsides</td>
</tr>
<tr>
<td>Umbilical Cord Serum</td>
<td>Similar to Autologous serum</td>
<td>Umbilical cord blood</td>
<td>20%</td>
<td>10 times/day for 4 weeks. Slow taper till inflammation subsides</td>
</tr>
<tr>
<td>Platelet Rich Plasma</td>
<td>Platelets, Growth factors, Cytokines</td>
<td>Patient’s whole blood</td>
<td>-</td>
<td>10 times/day for 4 weeks. Slow taper till inflammation subsides</td>
</tr>
<tr>
<td>Amniotic Membrane Suspension</td>
<td>Growth factors, Cytokines, Additional anti-scarring, anti-inflammatory properties</td>
<td>Amniotic Membrane</td>
<td>30%, 50%</td>
<td>Hourly for first 4 weeks, then 2 hourly for 2 weeks and taper slowly till inflammation subsides</td>
</tr>
</tbody>
</table>

*Most commonly used concentration of autologous serum

Abbreviations: IGF-1: Insulin like growth factor-1