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Management of ocular surface chemical burns

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Severe forms of ocular surface chemical burns are responsible for conjunctivalisation and neovascularisation of the cornea often associated with recurrent corneal erosions.[1] This hallmark of limbal stem cell deficiency (LSCD) can be associated with a variable destruction of the corneal stroma leading to heavy scarring or perforation in the worst cases. Conjunctival lesions can also be responsible for severe sequelae such as symblepharons and dry eyes. The prognosis of severe forms has improved during the last decade as a result of amniotic membrane transplantation (AMT) and the use of auto-[2] or allo-[3] limbal stem cell transplantation (LSCT). The severity of ocular surface chemical burns varies with the causative agent and the duration of exposure. The penetration depth in the anterior segment correlates with the pH, especially for alkalis.

Acid burns (pH<4): strong acids such as sulfuric acid, found in car batteries, or chlorhydric acid, used for swimming-pool cleaning, will denature, precipitate and coagulate corneal proteins. Protein coagulation generally acts as barrier preventing deeper penetration. It is responsible for a 'ground glass' appearance of the cornea.

Alkali burns (pH>10): strong bases such as baking soda or ammonia are lipophylic. They dissociate into a hydroxyl ion and a cation, and will destroy the epithelium, the stroma and the endothelium while they saponify cell membrane fatty acids.[1] Hydroxyl ions will denature the collagen matrix. Penetration will keep occurring long after the initial exposure. In 5–15 min, strong bases can reach the anterior chamber and damage the iris, lens, iridocorneal angle and ciliary body.

Hydrofluoridric acid, a weak acid found in antirust solutions, is an exeption. In its nonionised form, it behaves like an alkaline substance, penetrating the corneal stroma and leading to extensive anterior segment lesions. When it becomes ionised it will combine with intracellular calcium and magnesium ions, and form insoluble complexes, responsible for potassium ion movements, leading to nervous stimulation and extreme pain. Once fluoride ions are released in the systemic circulation, gastro-intestinal, neurological, cardiovascular and respiratory manifestations will appear, associated with a severe hypocalcaemia.[4]

After initial first aid therapy consisting of profuse irrigation of the eyes and removal of particulate matter, the involvement of the eye(s) must be graded according to a prognostic classification. The goal of the different classifications is to evaluate in a simple way the extent of the initial lesions in order to make a precise prognosis that will help in choosing the right treatment strategy. The most commonly used classification was that of Ballen[5] modified by Roper-Hall.[6] It has four grades of increasing gravity based on the corneal appearance and the extent of limbal ischaemia. The modern management of ocular surface chemical burns, including AMT and ocular surface reconstruction techniques, has changed the prognosis of severe cases. However, Joseph *et al* noticed that the clinical outcome of patients with a Grade IV of Roper-Hall who had received similar treatments was highly variable.[7] Based on this, Dua *et al* drew the conclusion that Roper-Hall lacked precision and proposed a new classification on an 'analogue scale' expressed as the number of clock hours of limbal involvement and percentage of conjunctival involvement, which could be broken down into six grades.[8] Conjunctival involvement is of major importance. Even if the limbus is entirely destroyed, if a sufficient amount of conjunctiva remains, it will still be able to re-epithelialise the corneal surface, prevent stromal perforation and secure the ocular surface for possible secondary LSCT at a later date.

Dua's Classification recommends that the analogue grade be recorded on a daily basis in the acute stages, as the clinical situation evolves. The Roper-Hall Classification was proposed before the concept of limbal stem cell transplantation was introduced and does not take into consideration the involvement of the conjunctiva.

In this issue of *BJO*, Gupta *et al* reported the results of a prospective, randomised study, comparing the predictive outcome of ocular burns, in two groups of 50 patients, using the Roper-Hall and Dua Classification systems.[9] Although these authors were not the first to report the results of such a comparison, they are the first to publish a controlled clinical trial of this magnitude. The initial study by Dua *et al* had been carried out in 67 patients (35 retrospective and 32 prospective).[8] Gupta *et al* reported that there was a significant difference in extent of corneal neovascularisation between Grades IV, V and VI. They also found that patients who benefited from AMT in Grade IV burns had clearer corneas and a better final best-corrected visual acuity than those with Grades V and VI. Based on these results, they were able to confirm that Dua's Classification, by providing further subclassification of the Grade IV in three separate grades, had a superior prognostic predictive value.

It is crucial to remove the inciting chemical with an immediate, copious and prolonged irrigation, better achieved by using a lid speculum, after tetracaine topical anaesthesia. Ideally, the irrigation solution should be balanced salt solution or Ringer's lactate solution. In alkali burns, some authors recommend the use of an amphoteric solution such as diphoterine. This helps to obtain a faster corneal re-epithelialisation in Roper-Hall Grades I and II than with physiological serum.[10] Patients with Dua Classification Grades I and II will receive a topical treatment consisting of non-preserved tear substitutes (promoting the re-epithelialisation in a context in which the tear film is abnormal due to the destruction of goblet cells),[11] a cycloplegic agent (tropicamide or atropine 1% that will relieve pain and minimise the risk of iris lens synechiae/phenylephrine hydrochloride and other adrenergic drugs should not be used, owing to their vasocostrictive action leading to the worsening of limbal ischaemia) and non-preserved broad spectrum antibiotic eye-drops.

Paracetamol with or without dextropropoxyphen should be taken orally.

Patients with Grade III to VI should be hospitalised. In addition to the precited medical treatment, they should receive pain medication (corneal nerve inflammation and damage being responsible for extreme pain).

Topical mucomimetic agents such as sodium hyaluronate should be used in order to increase the wetability of the

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surface and the tear-film stability. This also reduces conjunctival fibrosis.[11] Topical steroids should be first instilled on an hourly basis in order to prevent a secondary destruction of the surrounding tissues. They will limit the inflammatory processes by diminishing chemotaxis of inflammatory cells and by stabilising cellular and lysosomal membranes of polymorphonuclear leucocytes.[11] For a long time, steroids were considered to be a contraindication for fear of provoking corneal perforations by countering the action of tissue inhibitors of metalloproteases. Recent studies have contradicted this dogma.[12] After the acute phase, steroids may slow down the re-epithelialisation process as well as healing of the collagen matrix. They should be stopped after 7–10 days but can be reintroduced 6 weeks after the burn, in order to reduce chronic ocular surface inflammation.[11]

The antioxidant properties of vitamin C eye-drops limit the effects of free radicals released after an ocular surface chemical burn. They also play a role as a collagen cofactor (endogenous vitamin C being secreted physiologically in the aqueous humour by the ciliary body and quickly depleted after a severe chemical burn). Its use is recommended for the treatment of Grade II burns and over. Systemic vitamin C does not have a proven efficacy.[13]

Tetracyclines inhibit collagenases. Systemic administration should be preferred. N-Acetylcysteine is supposed to have anticollagenase properties, but its efficacy remains controversial.[11] Soft hydrophilic bandage contact lenses with a high oxygen permeability can be used. They relieve pain, by acting as a bandage, and enhance re-epithelialisation. However, they increase the risk of infection.[10] AMT can be a suitable alternative.[14 15] Systemic acetazolamide helps to control raised intraocular pressure after chemical injuries (cyclodestruction should be avoided because it is unpredictable, adds extra inflammation and carries a risk of secondary phytis bulbi).

Patients with burns of Grade IV and higher will benefit from AMT.[15 16] The amniotic membrane (AM) is avascular and acellular. It will facilitate epithelial healing acting as a basement membrane (it shares commons collagen isoforms with the conjunctival basement membrane).[14] It is also rich in growth factors such as transforming growth factor β2 (TGF β2), transforming growth factor β1(TGF β1), hepatocyte growth factor (HGF) and epithelial growth factor (EGF). Their combined action with other cytokines is supposed to stimulate epithelialisation and inhibit fibrosis.[14 17] The AM can be used as a patch, epithelial side down, for a maximum concentration of growth factors in contact with the remaining LSC.[14 17] The AM will also act as a barrier against the efflux of immune cells, by tempering the immune response and displaying antiangiogenic properties.[14] AMT alone can help restore the corneal epithelial surface only in moderate chemical burns.[16] In more severe cases, it will not prevent partial or total LSCD.[7] However, it may help prevent corneal perforation and provide a suitable environment for LSCT in the future. AMT has also been shown to be very useful to reduce the often intolerable pain observed after chemical burns; this is indispensable, especially in children.[14] LSCT is not indicated during the acute phase.[15] However, a preventive treatment of LSCD by sequential sectoral conjunctival epitheliectomy is indicated in mild to moderate burns. Performed under topical anaesthesia, a repeated removal of the conjunctival epithelium invading the corneal surface will help a healthy corneal epithelial epithelium prevail.[18]

In Dua Classification Grades V and VI, with extensive conjunctival necrosis leading to limbal ischaemia, after the excision of necrotic conjunctiva a viable Tenon sheet from the orbital region can be prepared and advanced up to the limbus, to cover the ischaemic or ulcerating sclera with healthy vascularised tissue. It may not prevent the development of LSCD but can prevent scleral perforation, thus leaving open the possibility of a LSCT in the future.[19] In cases in which LSCD affects the optical axis, LSCT (auto or allo) is required.[20–22] When limbal explants are used as a graft, there will be an 'in vivo' expansion of epithelial cells. If limbal progenitors or cells from oral mucosa are cultivated prior to grafting, they are referred to as 'ex vivo' expansion.[23 24] Some authors in bilateral cases have replaced limbal tissue with fragments taken from oral mucosa biopsies. After ex vivo expansion on denuded AM, they obtained an epithelium phenotypically close to the corneal epithelium.[25] The AM can also be used as a patch for its anti-inflammatory and epitheliotrophic properties.[14] Once a stable corneal epithelium has been obtained, a keratoplasty (either lamellar or penetrating) is often needed in order to restore corneal transparency.[26]

In conclusion, the modern management of ocular surface burns guided by Dua Classification, with judicious use of steroids and AMT during the acute phase and of ocular surface reconstruction techniques once the inflammation has settled, has greatly enhanced the prognosis of severe ocular surface burns. Ex vivo expansion techniques look promising and may become the new gold standard in the near future. Nevertheless, they are not yet standardised across laboratories, introducing an important variable in evaluating clinical efficacy. Randomised controlled trials are still needed in order to prove their superiority.

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