Non-healing Corneal Ulcers/Erosions in Animals

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INTRODUCTION

Chronic non-healing superficial corneal ulcers/erosions can be frustrating to the client, patient and veterinarian. These special non-healing lesions may or may not have been initiated by trauma. In many cases it appears that they have arisen spontaneously.

This syndrome can be characterized by the following:

1. A corneal epithelial erosion that tends to remain superficial and is not healing.

2. The presence of a redundant or loose undermined epithelial margin or bleb.

3. Fluorescein stain will undermine the redundant border or pass through a fine epithelial break and be retained under the epithelium beyond the edge of the surface break.

4. The loose epithelial margin may even be rolled or folded upon itself.

5. The eye may not be consistently painful and it usually is intermittently painful.

6. Initially and even chronically there is usually a lack of an inflammatory response characterized by a lack or scarcity of blood vessels.

7. These lesions rarely become infected.

8. They are commonly located in the central or paracentral cornea, yet they can potentially be found anywhere on the corneal surface. Over time some may develop exuberant granulation tissue in the area of non-adherence.

9. The condition can occur in any species of animal, including man. Veterinarians are most often presented with dogs, especially Boxers and middle to older age dogs of any breed or sex, neutered or intact. The syndrome has also been seen in the cat and the aged horse.
Names that have been given to these lesions and this condition are:

Rodent ulcers, Boxer ulcers, indolent ulcers, refractory ulcers, non-healing corneal ulcers/erosions, persistent corneal ulcers/erosions, recurrent ulcers/erosions, recurrent epithelial ulcers/erosions, recurrent ulcers and many others.

The etiology is not precisely known in the majority of the cases. Over the past 15 years much work has been done to investigate this problem. Out of this work a greater understanding about its nature is emerging. References to this syndrome in humans goes back as far as 100 years and nearly forty years in the Boxer dog.

At this time it does seem clear that there is a fundamental lack of adherence of the corneal epithelium to the anterior corneal stroma. After a corneal epithelial break, no matter how proliferative the new epithelium is, there is a failure of the new epithelium to securely fuse with the anterior stroma which allows the shearing force of the eyelid action to elevate this loosely bound epithelium and fold or roll it back upon itself.

In humans, physicians have identified several etiologies. Two common ones are trauma from a sharp superficial cut (paper or fingernail) that can lacerate the epithelium and excise a piece of basement membrane. Some patients then do not replace this lost piece of basement membrane and their lesion becomes indolent.

The second most common etiology is a basement membrane dystrophy of known or unknown etiology or secondary to aging where the basement membrane duplicates with collagen packets in between resulting in abnormal epithelial adhesions.

Some other etiologies in man include microcystic epithelial degeneration complicated by hypotonic tears from closed eyelids during sleep. Diabetes mellitus with basement membrane abnormalities and many other corneal dystrophies that affect the basement membrane have been implicated.

In animals, we recognize that the animals with corneal dystrophy are at greater risk for indolent ulcers. Yet, clinically we see many animals with indolent ulcers that do not have any gross corneal changes that would imply there is a dystrophy. Because of the greater incidence of this problem in older animals an age related basement membrane abnormality may be playing a role. The Boxer definitely has a greater incidence than in any other breed and a microscopic basement membrane dystrophy is involved in these animals.

**In Summary there appears to be a residue or abnormality at the level of the surface of the anterior stroma that prevents adherence of the new epithelium.**
NORMAL ANATOMY AND PHYSIOLOGY

Focusing in at the junction of the anterior stroma with the corneal epithelium, the literature describes an incredibly complex physical chemical bond.

There are not only physical bonds such as hemidesmosomes that bridge the basement membrane and anchor at either end (basal epithelium and anterior stroma) but there are chemical bonds composed of complex macromolecule glycoproteins called fibronectin and laminin.

The physiology of this union is very complex and during normal healing of an epithelial defect these bonds are broken down to allow for epithelial sliding. Normally, once the defect is covered, new firm bonds occur. It has been theorized that in the animals with persistent epithelial defects, this final firm bond does not develop and the non-union persists, irrespective of the proliferative capability of the epithelium.

Certain chemicals such as tissue plasminogen-activator (PA) that normally emerge to temporarily break these bonds to allow for epithelial sliding, may actually persist.

Animals with recognizable subepithelial anterior stromal dystrophies may have a predisposition to these persistent ulcers/erosions, perhaps just due to the anterior stromal and/or basement membrane pathology or residues of previous bonds.

PATHOGENESIS

Initiating factors, such as foreign bodies, trauma, aberrant lashes and cilia, eyelid neoplasms, tear film abnormalities, etc. can cause the original epithelial break. Many animals historically do not appear to have experienced any of the latter initiating factors and perhaps, in these, spontaneous tears may have developed due to the pre-existing poor epithelial bond, or possibly a wrinkle or blister of epithelium that develops, which is then torn open by normal eyelid movement over the corneal surface. Once there is an epithelial defect and the epithelial margins fail to firmly adhere, eyelid movement over the cornea continuously tears back the epithelium in spite of the epithelium’s continued proliferation and sliding to cover the wound.

CLINICAL COURSE

During the clinical course of this syndrome there can be periods of relative ocular comfort when the epithelium has nearly covered the defect, yet is still loose. Clinical signs at this time may consist only of mild ptosis and epiphora. Abrupt acute pain usually results from the shearing forces of the eyelid and movement over the unattached epithelium resulting in the lifting and tearing and/or rolling back of the loose epithelial margins. This cycle may wax and wane for weeks, and even months, without much, if any, corneal neovascularization or inflammation. Medical therapy with antibiotics, sodium chloride ophthalmic ointments, artificial tears, contact lenses, third eyelid flaps, systemic androgens/estrogens, tetracycline, etc. seems to make no
difference. Some will just spontaneously heal on their own, yet most will remain chronic.

**DIAGNOSIS:**

A cardinal sign is a superficial erosion with a loose redundant epithelial margin and lack of a vascular response and no sign of infection (infiltrates) or malacia. Sodium fluorescein applied to the lesion will migrate under the overhanging border of epithelium and stain the anterior stroma up to the point of firm epithelial attachment. **Nonrecurrent ulcers/erosions** will stain only up to the epithelial edge and the stain will not go under the “tight” epithelial margin.

**DIAGNOSTIC CONSIDERATIONS AT THE FIRST VISIT**

Irrespective of the "cardinal" appearance and diagnosis at this point, one must be sure to evaluate the globe and adnexa for any abnormalities that could be causing the persistent epithelial defect (even Boxers), such as foreign bodies, aberrant cilia, etc. (as listed previously).

A swab of the conjunctival cul-de-sac should be taken for bacterial culture early in the examination, prior to the instillation of any drops, in those eyes that exhibit an abnormal discharge other than just a serous tear.

If a Schirmer Tear Test is done, it too should be done at this point prior to topical anesthesia and drops to avoid confusion of the results.

Evaluation of the anterior segment for signs of uveitis should also be done, noting in particular, the size of the pupil and if there is an aqueous flare.

Once the clinician has classified this corneal lesion as one with the potential of being indolent, and has identified any other complicating or predisposing factors; therapeutic modalities and anticipated clinical course can be discussed with the client; the latter being as important as the evaluation and accurate diagnosis.

The client needs to be informed of the potential for a chronic (stubborn) and possibly exacerbated course, with prospects of other modes of therapy being instituted during the course of therapy, if progress is not being made. The therapeutic plan should start conservatively.
THERAPEUTIC MODALITIES

The redundant epithelial border must be removed irrespective of the initial etiology or what other medical or surgical modality is chosen to follow! Included in this debridement should also be the floor of the erosion to include the removal of allegedly abnormal basement membrane and complexes associated with it.

In humans, the clinician tries to separate out the post-traumatic from basement membrane dystrophy cases by slit lamp examination. In my experience with animals, unless the dystrophy is conspicuous, the inciting etiology still remains vague. In either case however, the treatment is usually the same, but the prognosis (especially for the fellow eye) is different. Most physicians begin with patching after instillation of a topical antibiotic and cycloplegic agent. If not successful, a soft Therapeutic Bandage contact lens is placed (i.e: Bausch and Lomb PlanoT Soflens) after debridement. Some cases may require tarsorrhaphy, if only on a temporary basis. Fibronectin appears to be useful in recalcitrant cases. If the epithelial edge of a defect is folded or rolled back, it is often debrided. In patients with recurrent ulcers/erosions and an intact epithelium, micropuncture through the intact epithelium with a sterile bent 27 gauge needle into anterior stroma in multiple locations has been utilized.

Veterinarians have also tried this method, but in a different way. Veterinary reports of epithelial debridement followed by multiple anterior stromal punctures have been made with possibly more rapid healing afterwards.

DEBRIDEMENT OF THE REDUNDANT EPITHELIAL MARGIN, ADJACENT UNSTABLE OR EASILY DEBRIDEABLE EPITHELIUM AND IDEALLY, ANOMALOUS BASEMENT MEMBRANE AND COMPLEXES (cleaning off of the anterior stromal surface) IS THE CLASSICAL INITIAL THERAPEUTIC APPROACH IN VETERINARY MEDICINE

The idea is to remove all of the truncated anomalous complexes and aberrant basement membrane along with the associated loose epithelium back to where the epithelium is firmly adherent and assumed normal. This will allow for the new wave of epithelial migration to cover over a "clean" anterior stroma not cluttered with abnormal basement membrane and complexes, and hopefully subsequently lay down "normal" basement membrane and firm complexes.

All modes of therapy that follow debridement are just methods to make the environment favorable for adhesion of the new sheet of corneal epithelium (PROTECTION).
CORNEAL EPITHELIUM DEBRIDEMENT

Debridement can be accomplished in a variety of ways. All of the following techniques are essentially variations of a superficial keratectomy. There is no one best technique, in general, yet there is a best technique for the practitioner, based on their experience with one, or several of these methods.

In other words, become acquainted with a method, rather than jump back and forth between methods. I prefer to start with one method on the first visit and only change methodology in that particular case to a more aggressive one if the cornea is not responding. Please see flow chart, Figure 1.

Examples of Debridement Methods That Have Been Described

- Mechanical Sterile Cotton Tipped Applicator (CAT’s) debridement.

- Scraping with a corneal spatula (Eximer Spatula BD).
  - #BC585189 5/bx from Cardinal Healthcare 888-444-5440
• Superficial Lamellar Keratectomy with a #15 Bard-Parker blade or #64 Beaver blade under general anesthesia.
  
  o  

• Cross-hatching (scarification) or micropuncture with a 25 or 27 gauge hypodermic needle.
  
  o  

• Chemical (Not routinely used any more)
  
  chemically cleans off anterior stroma
  
  o 2% Tincture of Iodine
  
  o Povidone Iodine Solution: half strength
  
  o Trichloroacetic Acid (TCA)
For example, on the first visit the cornea is debrided with sterile cotton tipped applicators (CTA) followed by cleaning of the anterior stroma with an Excimer Spatula and then the application of a soft contact lens if available and if the fit is OK.

Recheck in one week.

If the eye is comfortable and the contact lens is in place and if the corneal ulcer appears to be healing but has not healed completely (can still see edge to ulcer but tight borders): recheck in one more week.

At the second recheck the contact lens must be removed.

Most of the indolent ulcers respond to the sterile cotton tipped applicator and spatula debridement. A soft contact lens greatly increases the chance of healing after the first debridement but it is not absolutely essential.

If the contact lens comes out and the ulcer has not healed and has loose undermined borders or if it stays in and healing does not occur (loose undermined borders seen under the contact lens); then the process needs to be repeated or an additional method employed (stromal micropuncture or linear keratotomy for example).

Corneal neovascularization during healing is not necessarily a good sign or desirable, as it would be with complicated corneal ulcers. The reason being, that along with these vessels there is epithelial edema, especially when there is a lot of granulation tissue as well.

The epithelial edema (as with microcystic edema in humans) predisposes or makes the epithelium more fragile and easy for the eyelid movement to cause "self debridement."

Therefore in the cases with neovascularization and/or edema, with or without granulation tissue, I find it beneficial to treat the animal with systemic steroids to reduce the keratitis. Do not use topical steroids. Dosing these patients at one-half milligram per pound divided twice daily for 5 days, then tapering the dose down over the next 5 days does not appear to complicate healing like topical steroids could. In fact, some of these vascularized, edematous lesions would not heal if the edema was allowed to persist.

Topical sodium chloride ophthalmic would seem to be beneficial; however, it is yet another drug that needs to be applied which will increase blepharospasm resulting in more frictional irritation to the cornea. 5% sodium chloride can be irritating and it does not treat the primary cause of the edema which is the keratitis. It certainly has a place in some cases where the epithelial edema is producing vesicles or bullae or the edema is not the result of inflammation, and therefore would be helpful.
COTTON TIPPED APPLICATOR DEBRIDEMENT METHOD

Irrespective of the method used, or state of the animal (topical anesthesia or general), the basic idea of debridement is the same. The initially visible loose epithelium is stripped back with dry sterile applicators starting at the central portion of the erosion and wiping toward the periphery. It is usually apparent that more than the initial amount of redundant epithelium strips off. That is OK. Firm, but gentle, pressure with the dry CTA's (exchanging for sterile dry ones as their tips get wet) is all that is usually necessary.

When the loose edge reaches a point where it is more firmly attached, rotate the tip of the swab that is holding the folded over piece of epithelium to coax it to tear off evenly.

Islands of firmly attached epithelium may remain and if they are firm and have tight clean margins, I generally leave them alone.

Too vigorous abrasion will remove even the normal epithelium. There is no need to remove the firmly adherent normal epithelium as well as avoiding the perilimbal epithelium (corneal epithelial stem cells). It is also important to wipe dry applicators over the floor of the erosion to remove the abnormal basement membrane and its complexes. This might be where some of the other techniques are useful in the refractory cases. For example, at this point (after CTA debridement) further mechanical debridement with the Excimer spatula is essential. Concentrate on the “bed” of the erosion/ulcer; clean off the abnormal residue on the anterior stroma.
Post Debridement Therapy

Protection (very important)

Soft Contact Lenses

After the cornea has been debrided the following regimen can be followed. If a soft contact lens is available, it should be used. Be sure reflex tearing is normal (the Schirmer values are greater than 15 mm/min.).

The contact lens will protect the cornea from the movements of the overlying eyelids and splint the new epithelium tight up against the anterior stroma. The fit of the lens needs to be carefully evaluated. Too loose of a fit (large base curve or radius of curvature) will result in lens loss due to wrinkles forming and the eyelid catching on it and lifting it out.

Too tight of a fit (small base curve or radius of curvature) can cause serious corneal damage due to blockage of the normal corneal respiratory cycle. Too small diameter of lens may result in lens loss from the margin of the third eyelid slipping underneath it and lifting it out. The lens should easily be seen to float freely in the tear film without any retained air bubbles or wrinkles.

Most dogs will comfortably wear a 14.5 mm to 15.0 mm diameter lens with a base curve of 8.6 to 8.8.

Bausch & Lomb Plano T Soft Lens: call 800-828-9030 to order

Material: Polymacon
Water Content: 38.6%
FDA Group: I
Oxygen Permeability (Dk): 8.4
Manufacturing Method: Spin-Cast
Diameter: 14.5mm
Base Curve: 8.3
Power: Plano
Center Thickness: 0.17mm

Any sign of increased ocular irritation, corneal cloudiness, etc. is of concern when a contact lens is in place and could mean that the lens is causing a problem (tight lens or blocked pores in the lens) or that there may be foreign material trapped under the lens.

Third Eyelid Flap

Third eyelid flaps are an excellent form of protection and splint for the corneal epithelium during healing. Unfortunately, they require a general anesthetic for placement. Therefore, I usually do not use them initially. If at any time a general anesthetic is required for debridement, I will then take advantage of the anesthetized situation and put a third eyelid flap up. If after the first debridement (or subsequent ones) healing does not occur and further more aggressive debridements are needed, I consider a third eyelid flap after the redundant epithelium is removed, unless a contact lens is available. If a contact lens fails (poor fit or lack of a healing response) I generally then consider a third eyelid flap after debridement. AVOID bilateral third eyelid flaps because, of course, the animal will then be acutely blind while the flaps are in place.
WYMAN MODIFIED THIRD EYELID FLAP

This modification involves suturing the third eyelid directly to the globe to prevent movement of the globe underneath and against the third eyelid which potentially could cause continued abrasion of the new corneal epithelium and result in non-healing.

Under general anesthesia, the third eyelid is grasped and extended in its natural prolapsed direction, toward the superior temporal fornix. The "T" portion of the cartilage is identified and a 4-0 braided nylon (Surgilene-D & G) is passed through the central "T" portion.

The bulbar conjunctiva near the fornix conjunctiva is grasped with a Bishop Harmon forceps or similar small rat-toothed instrument to a depth that feels firm (includes Tenon's and/or rectus muscle) and a wide .75-1 cm bite is deeply taken, avoiding penetration of the globe. The needle then passes out through the "T" portion of the cartilage about 4 mm away from the first bite. The ends are left long and not tied until all subsequent sutures are placed.

Two additional stitches are similarly placed in the wings of the "T", one on either side of the central stitch. Now they can be pulled up and tied. A surgeon's knot should be used. At least six tight throws must be placed on braided nylon, otherwise the knots will untie.

The third eyelid flap is left in place for about ten days. Most animals will tolerate suture removal with only topical anesthesia and physical restraint.
Cyanoacrylate Application

In patients where a contact lens cannot be used because a lens does not fit or one is not available; a thin layer of Cyanoacrylate can be applied to act as a custom contact lens.

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Cyanoacrylate tissue adhesive for treatment of refractory corneal ulceration
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Use Vet-Seal (http://www.jorvet.com/msds.shtml) Jorgensen Laboratory
J299 Vet-Seal® 3 ml, 5 pk. $81.00
Cyanoacrylate tissue adhesive for treatment of refractory corneal ulceration

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Abstract
Isobutyl cyanoacrylate tissue adhesive (BCTA) was used in the treatment of refractory superficial corneal ulcers in 17 dogs, one cat, and one rabbit, present 2 weeks to 7 months (mean 6.8 weeks ± 6.1) prior to referral. Little to no sedation was required in the majority of cases, with only topical anesthetic applied prior to debridement and BCTA application. The presence of the tissue adhesive caused mild discomfort for several days after application, as reported by the owners. The ulcers healed, and the tissue adhesive sloughed in approximately 3 weeks (± 1 week). Mild neovascularization of the cornea resolved with topical corticosteroids. The use of BCTA offers a simple, safe and noninvasive treatment for refractory corneal ulcers.

Key Words: cornea, cyanoacrylate, tissue adhesive, ulceration, vascularization

INTRODUCTION
Previous treatments for refractory superficial ulcers of the cornea (indolent ulcers, ‘Boxer ulcers,’ chronic epithelial erosions) have included repeated epithelial debridement, chemical cautery, niacinamide membrane and conjunctival flaps, superficial keratectomy, hydrophilic contact lenses, punctate or grid keratotomy, epidermal growth factor, and polysulfated glycosaminoglycan. Each treatment modality, used alone or in combination, has varying success.

The use of tissue adhesives in treating corneal ulcers was introduced as early as 1962. Isobutyl cyanoacrylate (BCTA) is a tissue adhesive which hardens by an anionic/polymerization mechanism initiated by water or other weak bases present in the adherent surfaces.

BCTA was applied to experimentally induced superficial and perforating ulcers in rabbits, which were subsequently photographed and studied histologically and ultrastructurally on a weekly basis. Neovascularization was seen to invade the area in 7–14 days. By day 30, the corneal epithelium appeared normal microscopically. The anterior chamber was reformed within minutes of BCTA application in perforated ulcers. The ulcers were healed within 30 days with a vascular response, which regressed by day 40.

Previous reports on the veterinary use of BCTA in clinical cases showed encouraging results in a variety of corneal lesions, including chronic erosions, corneal lacerations, and descemeratoceles.

Isobutyl cyanoacrylate tissue adhesive was applied to selected canine and feline clinical cases for the treatment of chronic and recurrent corneal ulcers. The method of BCTA application, clinical results, and discussion of indications for BCTA use are presented.

MATERIALS AND METHODS
Isobutyl cyanoacrylate (BCTA) was applied to refractory superficial corneal ulcers in 17 dogs (representing 20 eyes), one cat, and one rabbit. The criteria for the diagnosis of refractory superficial ulcer was based on the ulcer being present for more than 10 days, restricted to the epithelium, usually with loose epithelial edges, and no stromal involvement or evidence of infection. Duration of the ulcers prior to referral was 2 weeks to 7 months, with a mean of 6.8 ± 6.1 weeks. The majority of the cases were referred after 4–6 weeks from onset of the ulcers. All ulcerations were unresponsive to previous treatments, consisting of various topical and/or systemic antibiotics, mydriatics, and occasionally topical corticosteroids. Additional treatment modalities included epithelial debridement, third eyelid flaps, chemical cautery, and grid or punctate keratotomies. The mean age of presentation for the patients was 8 years (± 3.4 years), with only four dogs being younger than 7 years. A predominance of female animals were presented (12/17 canines). The Boxer was represented in greater numbers than other breeds (4/17 canines). Several of the animals had concomitant problems (controlled Cushing’s syndrome, endothelial degeneration with bullous keratopathy), which required additional management.

The BCTA (Histacyl® B. Braun Surgical, Melsungen, Germany or Nexaband® Ophthalmic CRX Medical Inc.)
Raleigh, NC, USA) was drawn up into the tip of a 1-mL syringe through a 22-g needle. The needle was manually removed from the syringe and a small amount of BCTA was pushed up to the flattened surface of the syringe tip (Fig. 1). A lid speculum was used to increase exposure of the cornea and prevent accidental gluing of the lids or nictitating membrane. The ulcer was debrided of any devitalized or loose epithelial tissue with a sterile cotton swab. The site to be glued was thoroughly dried with an additional swab. The syringe was then inverted and the BCTA applied to cover the entire ulcerated area with a small amount extending beyond the ulcer edge. The majority of patients allowed the procedure to be carried out with topical anesthetic alone. A few required mild sedation with Ketaset 100 mg/ml (Ketaset, Fort Dodge, Iowa, USA)/diazepam (5 mg/ml; diazepam, Elkins-Sinn, Inc, Cherry Hill, NJ, USA): 1 mL of 50–50 mixture/9 kg or Oxymorphone (1.5 mg/ml; Numorphan®, Endo Pharmaceuticals, Inc., Chadds Ford, PA, USA) 0.1 mg/kg/diazepam (5 mg/mL) (0.4 mg/kg IV) for proper preparation and positioning of the ulcerated area (Fig. 2a, b, and c).

Broad spectrum antibiotic ointment (neomycin, polymyxin, and bacitracin) was used two or three times daily after the procedure. Atropine 1% was also used as required in cases which demonstrated ciliary spasm. Other contributing problems were addressed. Animals with endothelial degeneration received topical hyperosmotic therapy (sodium chloride 5% ointment).

All patients were re-examined 10–14 days after the BCTA application, and then as needed until the tissue adhesive was sloughed and the ulcers healed. Healing was defined as corneal re-epithelialization, with complete sloughing of the glue and negative fluorescein retention. Treatment was continued until resolution of corneal vascular response and for any animals with continuing ophthalmic abnormalities.

RESULTS

All ulcers healed after the application of BCTA. All but one ulceration healed after one application of BCTA. The ulcers epithelialized and the adhesive sloughed off totally in a mean of 3.4 weeks (± 1). Vascular response to the BCTA was seen in almost all cases. The vascularization seen was superficial in nature, and usually extended inward from the limbus toward the glue. Occasionally it would surround the glue and extend under it. In the majority of cases it was mild, and resolved well with the application of a corticosteroid preparation (neomycin, polymyxin, and dexamethasone). Patients that already had some vascular reaction to the refractory ulcer usually had increased vascular response after the BCTA application. The mean time to total resolution of the vascularization, which typically left a small leukoma or subepithelial haziness, was 6.5 weeks (± 2) (Fig. 2a, b, and c).

One dog required additional adhesive application 14 days after the first application when it was noted that there was fluorescein uptake adjacent to the original ulcer. This was probably due to inadequate debridement and BCTA application initially.

The 13-year-old Poodle with controlled Cushings syndrome healed without complication. While the Cushings disease may have played a role in the refractory nature of the ulcer due to increased endogenous cortisol, it did not interfere with the treatment or healing.

One dog with bullous keratopathy due to endothelial degeneration experienced an ulcer in the contralateral eye within 1 year after the first, which responded to BTCA application. This dog, along with the Burmese cat, received hyperosmotic therapy along with the BCTA application. The hyperosmotic was an adjuvant to therapy, and was unlikely to have induced healing of the ulcers by itself, as evidenced by the occurrence of the second ulcer despite continued hyperosmotic therapy.

Owners subjectively reported varying degrees of discomfort for several days after BCTA application, which diminished in 2–3 days. This discomfort was reported as similar to that noted prior to referral and application of the BCTA. However, occasionally a patient displayed mild discomfort until the BCTA was sloughed. A nictitating membrane flap was placed 48 h after BCTA application due to severe blepharospasm in one dog. The flap was left in place 10 days, and the ulcer healed well. This patient’s ulcer had not responded to a flap placed prior to referral, so it is unlikely that the flap, rather than the BCTA was instrumental in resolution of the ulcer.

DISCUSSION

Isobutyl cyanoacrylate tissue adhesive has been used extensively for more than 25 years for the management of corneal ulcerations, offering a simple, noninvasive treatment for corneal ulcers. It is usually applied on an outpatient basis, with little or no sedation required, and is well tolerated. In most cases, the BCTA is spontaneously eliminated in several weeks, facilitating healing, with the end result of a small fibrous scar in the majority of cases. The presence of BCTA on the cornea often creates mild blepharospasm due to foreign body sensation which resolves in 48–72 h. However, its presence also diminishes pain and ciliary spasm associated with ulceration because it covers exposed corneal nerve endings.

Application of BCTA establishes an artificial barrier against polymorphonuclear leukocytes and their enzymes, decreasing stromal melting. Previous studies have shown that
the presence of BCTA decreases the activation of PMN leukocyte neutral collagenolytic protease. The BCTA returns the tear fluid content of the enzyme to normal levels, indicating a decrease in leakage of proteins from conjunctival vessels.\textsuperscript{12,13,15} BCTA also has anti-infectious properties, being bacteriostatic to gram positive organisms.\textsuperscript{15,18,19,20,21}

The ocular toxicity of cyanacrylate tissue adhesive varies according to the chemical composition and quantity of the adhesive used, and is related to the breakdown products (primarily formaldehyde) released during polymerization and degradation. Developmental advances in the chemical formulation has minimized tissue toxicity.\textsuperscript{18} The smaller the amount of BCTA used the better the reaction.\textsuperscript{12,18} Intracorneal and subconjunctival implants of isobutyl CTA induce minimal inflammatory and neovascular reaction, localized around the adhesive, when a small amount of adhesive is used. The extent and intensity of reaction increases with increased amounts of BCTA.\textsuperscript{8,12,15,18}

BCTA polymerizes on contact with moisture.\textsuperscript{13} It is of critical importance to provide a dry, clean bed with adequate epithelial debridement for BCTA application.\textsuperscript{19} Moisture or ophthalmic ointment present in the area leads to inadequate adhesion of the BCTA, increases the tissue inflammatory reaction, and causes more rapid degradation.\textsuperscript{12} Since BCTA expands on polymerization, the smallest amount sufficient to seal the ulceration should be applied.\textsuperscript{13,18}

Previous studies have shown that the hallmark finding in the majority of persistent corneal erosions is nonadherence of dysplastic epithelium to an abnormal underlying stroma (BPA Wilcock, personal communication).\textsuperscript{14-16,24} The basement membrane is either absent or replaced by a thin acellular zone of hyalin collagen. This zone acts as a barrier to epithelial adherence. Only those cases where scar tissue was able to bridge the acellular zone healed.\textsuperscript{24}

BCTA stimulates a mild corneal neovascular reaction when applied in appropriate amounts and is associated with corneal repair.\textsuperscript{11,15,24,25} Subepithelial vascular tissue consisting of both blood vessels and fibroblasts are required for healing to occur. It is postulated that the anchoring fibrils of the migrating epithelium cannot grip the pre-existent defective corneal stroma. This vascular tissue provides the new stroma.\textsuperscript{25}

It has been the author's experience that when no vascular response is evident, the adhesive remains in place longer, leading to prolonged healing time. The amount of neovascular response appears to be associated with the amount of adhesive applied, and the extent of vascularization present prior to its application.\textsuperscript{13,18}

Previous studies have shown variable success in treating refractive ulcers due to corneal endothelial disease.\textsuperscript{4-7} In this study, both the dog and cat with ulcerations associated with corneal edema and bullous keratopathy were successfully treated with the BCTA.

BCTA has also been successfully used in treating chronic ulcers in horses, rabbits, and birds. Limitations in its use are associated with the extent and depth of ulceration. BCTA use in large ulcerations elicits extensive inflammatory reaction related to the amount of adhesive applied. While BCTA has been used with good results for descemetocele, the danger of iatrogenic rupture exists due to the tissue reaction associated with polymerization. It can be used alone, or as an adjuvant to nictitating membrane or conjunctival flaps.

Additional uses of BCTA include its use as an additional seal over sunburned corneal lacerations. Applying a small amount to the edge of a soft contact lens prolongs the time the lens remains in place. It has also been used to perform a temporary tarsorrhaphy.\textsuperscript{70}

In conclusion, the use of BCTA for the management of refractive corneal ulcerations of dogs, cats and rabbits offers a noninvasive treatment modality which is easy to administer, offers little to no risk or adverse effects, and appears to elicit a high rate of healing.

REFERENCES

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TOPICAL OPHTHALMIC MEDICATIONS

When a contact lens is in place

Topical ophthalmic solutions ONLY because ointments will clog pores of lens and reduce or eliminate the passage of respiratory gases, tear components, etc. through the lens.

Corneal edema will result when a lens blocks respiration and serious complications could occur rapidly.

Contact lenses will hold drugs against the cornea much longer than after just topical application and toxic reactions that ordinarily would not occur may be develop or be enhanced. These reactions can be due to the active ingredient and/or its preservative. Therefore, the frequency of application should be reduced to about half of what you would normally use for a particular drug if no lens were available.

Drugs

- Antibacterial: Either a triple antibiotic such as neomycin, bacitracin, polymyxin; gentamicin; or ciprofloxacin.

- Mydriatic-cycloplegic: Mydriatic-cycloplegic such as 1% atropine sulfate should only be used in the face of a uveitis. Occasionally, I will give one or two doses (tropicamide 1%) post-debridement because of the noticeable acute miosis (indicating an anterior uveitis [iritis and potentially cyclitis] secondary to the corneal debridement = axonal reflex involving the fifth cranial nerve and a release of agents by these corneal nerves that mediate release of prostaglandins). Uveitis is not usually a significant component in these cases and therefore it is not necessary to routinely use atropine.

- Elizabethan Collar (use in every case).

  Protects the eye from the animal rubbing at it with its paw. Needs to be used throughout and also for one week after the erosion has healed. This will not stop them from rubbing their head against the furniture.

When a contact lens is not in place

Same as above, except ointments can be used.

The frequency is usually two to three times per day for the antibacterial. The frequency for the mydriatic-cycloplegic, is usually one to three times per day depending on the severity of the uveitis. The frequency for the sodium chloride would be three to four times per day.

In both of the above cases, the technique for application of the ophthalmic medications is important to avoid putting too much pressure against the globe and avoiding frictional
irritation to the cornea by indiscriminate movement of the eyelids against the cornea.

**DO NOT RUB IN THE MEDICATIONS**

Owners always seem to want to rub in the eye medications after their application and this could be disastrous because of the frictional irritation from the movement of the eyelids over the delicate new epithelium.

The head should be stabilized and elevated by placing the muzzle in the area between the owner’s thumb and index finger to act as a crutch while the other hand instills the medication from the medication container. The container should be held between the thumb and index finger while the outside edge of the same hand rests on the animal’s brow. The resulting three finger distance (middle through 5th digit) serves as a comfortable to hold the container tip from the eye during instillation.

The upper eyelid can then be elevated by pulling back on the brow skin with the lateral edge of the instilling hand while tilting the head up. At the same time the lower eyelid can be depressed with the thumb of the other hand, thus avoiding touching the eye and putting pressure against it.

Potential complications from improper medicating techniques include; contamination of the cornea and/or the medication bottle during administration, additional trauma to the cornea from the dropper tip, and painful finger pressure against the globe during treatment which also may also cause excessive eyelid pressure resulting in loss of the contact lens.

When ointments are used a similar instillation technique can be used. The ointment will exit the tube as a strip when the tube is cool and as a semiformed liquid when it is warm. Rate of exit from the tube can be disturbing to the clients and wasteful if the tube has been squeezed excessively prior to removing the cap and therefore handling these tubes as one would with a tube of toothpaste should be avoided. The tip of the tube is round and smooth but could still cause ocular trauma. Keeping the tube tip about a centimeter or two from the eye and allowing a strip or bleb of ointment to fall to the eye works well. Once the ointment strip touches the cornea, simply pull the tube quickly away from the eye. The surface adhesion strength of the ointment to the cornea is greater than the strength of the strip itself, and the ointment will break away from the tube quickly.

**When a third eyelid flap is in place.**

Ointments are preferred. They are carefully applied as a strip over the outer surface of the third eyelid.

There is no need to try to get the medication under the flap.

In most cases treatment with an antibiotic ointment at three times daily is sufficient.
**FLUORESCEIN STAINING**

If a Contact lens is in place - fluorescein will stain the lens and the lens will glow fluorescent green.

At the first (7 day) recheck after a lens has been placed, fluorescein does not need to be used, if:

1. The eye looks comfortable
2. The lens is in place
3. The lens is clear and floating freely
4. The edge of the erosion may or may not be seen but does not look as if it is folded over upon itself
5. The lesion appears smaller.

Therefore in these cases I avoid disturbing the eye and just recheck them in a week.

If the edge of the lesion can not be seen and it appears to have healed, one can either remove the lens at this point or leave it in another 3-7 days and then remove it.

When the lens is going to be removed I:

1. Instill one or two drops of proparacaine.
2. Instill one drop of fluorescein
3. Using a sterile cilia forceps
4. Slide off the lens
   a. Position lens so the edge is over the superior limbus so when the edge is grasped the cornea is not touched.
Do not leave a contact lens in place longer than 14 days!

(due to buildup of protein and mucin material in the lens pores leading to blockage of corneal respiration).

If at any time the eye seems more irritated and there is increased hyperemia and corneal edema, a cloudy contact lens, or the contact lens is not freely floating in the tear film; the lens should be removed and the cornea stained. Foreign material can get trapped under the lens and cause irritation. Warn owners to call you if the eye becomes painful.

If no contact lens was used

fluorescein should be applied **VERY CAREFULLY**

Wet the fluorescein strip with eye wash and allow a drop or two of the fluorescein solution to fall onto the eye.

**DO NOT IRRIGATE THE EXCESS OUT!**

Iatrogenic debridement of the new epithelium could occur at this point if the corneal is irrigated with eye wash. Normal tears will adequately remove excess fluorescein and it should be obvious whether there is retention or not.

**Fully Epithelialized**

Once the lesion has epithelialized it may take up to one month before the epithelium is firmly adherent. Some corneas will rapidly epithelialize and without any keratitis. In these cases, no further treatment is necessary other than advising the owner to keep the Elizabethan Epithelialized corneas (negative fluorescein) exhibiting a mild keratitis with edema, vascularization and granulation tissue will need a topical antibiotic steroid ophthalmic ointment starting at about three to four times per day and tapering the frequency over the next week or two until the keratitis resolves. Significant edema and granulation tissue may necessitate a topical sodium chloride ophthalmic ointment and or systemic steroids as well.

Rapid resolution of the nonulcerative keratitis is essential because the edematous epithelium is very prone to “self-debride” as a result of friction from the eyelids collar on for one additional week.
**Prognosis**

The prognosis is guarded in these cases because it is not uncommon for recurrences to occur any time in the future, in either eye. Especially in high risk animals such as Boxers and middle age or older animals or animals with a noticeable corneal dystrophy. I believe trauma is still the most likely reason for initiation of the problem; the inherent poor healing is however an individual situation.

The response to therapy in each episode may not be the same. Just because the lesion was difficult to resolve the first time does not necessarily follow true with subsequent ulcers/erosions and vice versa.
SUMMARY

This syndrome can be a pleasure to work with, once the clinician has an understanding of the problem, and its natural course or biologic behavior. This especially true when a complete ophthalmic exam has been performed, and a reasonable diagnostic and therapeutic regimen has been followed. Most importantly, counseling the client about the problem at the first visit and in doing so being careful not to make the future look dismal but optimistic because you can reassure them that you know what you are dealing with and what may be expected in the future.

Once a client is aware that these lesions can be problematic and the mode of therapy might change during the span of therapy, there will usually be no client communication problems if the animal requires repeated debridement and/or general anesthesia, surgical debridement and third eyelid flap, etc. Loss of these clients occurs when either the veterinarian has not accurately diagnosed the problem and treats the lesion as simple traumatic erosion; which, if it does not heal as expected, these clients may seek the advice of another veterinarian. Therefore, be ready for animals presented that have been treated elsewhere and are not responding. These animals may have had debridement and still have not healed. There may be a more than usually intense keratitis as well. This inflammation may complicate healing until it can be reduced by means of systemic steroids (making sure that there are no other systemic problems that would contraindicate their use - i.e.: bacterial cystitis, etc.).

I have on occasion seen chronic cases that have been treated elsewhere for a significant period of time. When first presented to me the redundant corneal epithelium is extremely thick and leathery. There also may be a step from the limbus down to the redundant margin due to a "delta" of superficial vessels and granulation tissue. Even if this edge could be removed with a CTA, the step would complicate healing because of the physical drop down to the central cornea. These animals need to be anesthetized and a superficial lamellar keratectomy done to provide a more normal corneal profile. Some of these chronic cases may also develop a calcific plaque (band keratopathy or calcific corneal degeneration) that also requires a superficial lamellar keratectomy under general anesthesia. A modified third eyelid flap should be placed after the keratectomy. Certainly, if the cornea is less than one-half normal thickness after a keratectomy, a consideration of conjunctival flap should be made. These chronic keratitis corneas will also need systemic steroids to reduce the amount of keratitis and granulation tissue during the healing phase.
Some individuals have used a conjunctival flap to cover the superficial corneal ulcers/erosions after debridement, even early in the course of therapy. I personally feel that this is an overzealous plan and unnecessary. It turns out that these conjunctival flaps usually do not adhere to stroma because the new epithelium migrates in so fast. There is a chance that a permanent adhesion could develop when the cornea is vascularized, which would permanently obstruct the visual path.

In contrast to the conjunctival graft/flap used in deep ulcers or complicated deep ulcers which are intended to remain forever.

I would reserve a conjunctival graft for only the most refractory cases that have failed all other modes of therapy and no use it as the first line. In fact prior to a conjunctival graft; application of a cyanoacrylate would be more appropriate.

Dogs that have concurrent endothelial dysfunction can be the most challenging to manage; for, the corneal edema will compromise epithelial adherence due to subepithelial fluid accumulation. Topical hyperosmotic ophthalmic preparations [ointments when a contact lens is not in place and solution when there is a contact lens in place] (5% sodium chloride) are very helpful in these cases.

Aged animals may have endothelial cells that are marginally functional and any corneal inflammation may decompensate endothelial function which would be manifest as increased corneal edema. These cases not only benefit from topical hyperosmotic medications, but also systemic antiinflammatory drugs such as corticosteroids. Reduction in corneal edema will promote adherence of the epithelium. Unfortunately, animals with endothelial dysfunction not secondary to inflammation will not benefit from systemic corticosteroids. Recently oral doxycycline has been shown to be beneficial for
dogs with corneal endothelial degeneration; perhaps it is the anti-inflammatory feature of this drug.

**FUTURE**

In the future, drugs that will enhance or induce the new corneal epithelium to produce a stable adhesion will likely be available. Currently studies are being done with epidermal growth factor, fibronectin, plasmin inhibitors and other agents. Autologous serum used as a topical drop may be beneficial and has appeared to help in a few cases I have tried it in. In addition substances that perhaps could clean the anterior stroma with little to no trauma; ie: eye drop.