Comp Clin Pathol (2010) 19:357–362
DOI 10.1007/s00580-009-0877-9

ORIGINAL ARTICLE

Effects of sutureless amniotic membrane patching with 2-Octyl cyanoacrylate (Dermabond) on experimental corneal alkali burn in dogs

M. Abbaszadeh · S. J. Aldavood · A. R. Foroutan · M. Azizzadeh · M. Selk Ghaffari

Received: 16 March 2009 / Accepted: 4 June 2009 / Published online: 24 June 2009

Abstract This study was performed to evaluate the surgical technique required and the clinical usefulness of tissue adhesive (2-Octyl cyanoacrylate) combined with amniotic membrane (AM) patching in the treatment of experimental corneal burn in dogs. Alkali wounds were inflicted on the central corneas of dogs by applying a round filter paper, 6.0 mm in diameter, soaked in 1 M NaOH for 60 s. Only one eye in each dog was used. A total of 15 dogs were divided into three groups of five animals each: (1) uncovered—control, (2) covered by AM with the amnion cell side down and secured with 10–0 nylon sutures to the cornea around the wound area—AM+suture, and (3) covered by sutureless AM patching secured with 2-Octyl cyanoacrylate (Dermabond)—AM+glue. The operating time was compared between both treatment groups. Clinical outcome was monitored by evaluation of epithelial defects, corneal opacity, duration of blepharospasm, time of AM persistence, corneal vascularisation, and duration of ocular discharge. The mean surgery time in AM+suture group was significantly longer than AM+glue group. AM persistence in AM+glue group was significantly greater than AM+suture group. The duration of ocular discharge and corneal vascularisation in AM+glue group was significantly lower in comparison with control group. Epithelial healing was faster in the AM+glue group than in controls. In conclusion, sutureless AM patching with 2-Octyl cyanoacrylate (Dermabond) as a dressing on a corneal alkali burn, used for the first time in this research, may induce rapid epithelial healing with less vascularisation and be a much faster and useful technique in dogs.

Keywords Dog · Amniotic membrane · 2-Octyl cyanoacrylate · Dermabond · Corneal alkali burn

The work was completed at the Internal Medicine Research Center, Department of Clinical Sciences, University of Tehran, Iran and was not supported by any grant.

M. Abbaszadeh · S. J. Aldavood (✉)
Department of Clinical Sciences, Faculty of Veterinary Medicine,
University of Tehran,
Tehran, Iran
e-mail: sja@ut.ac.ir

A. R. Foroutan
Department of Clinical Sciences, Eye Research Center, Iran
University of Medical Sciences,
Tehran, Iran

M. Azizzadeh
Department of Clinical Sciences, Faculty of Veterinary Medicine,
Ferdowsi University,
Mashhad, Iran

M. Selk Ghaffari
Department of Clinical Sciences, Faculty of Veterinary Medicine,
Islamic Azad University-Karaj Branch,
Karaj, Iran

Introduction

An alkali burn of the cornea causes a recalcitrant keratitis characterised by frequent blister formation, recurrent epithelial breakdown, stromal cell death, inflammatory cell infiltration, and endothelial dysfunction (McCulley 1994). Despite many clinical treatments being advocated, moderate and severe alkali burns remain difficult to treat and frequently lead to a protracted treatment course with various sight-threatening complications. Several proteinases released from the alkali-injured cornea might account for the ulcerative process.

Amniotic membrane (AM) consists of a thick basement membrane and an avascular stroma that has shown anti-inflammatory, anti-microbial, anti-vascularisation, and anti-fibrosis effects on various ocular problems (Kim and Tseng 1995; Lee and Tseng 1997; Shinozaki et al. 1995; Hao et al. 2000; Park et al. 2008). It can provide good cell-basement membrane interaction that is critical for epithelial proliferation and differentiation (Kurpakus et al. 1992). For the first time, Sorsby and Symons (1946) successfully promoted healing with the use of AM as a patch for treating acute ocular burns. For reasons still not clear, the use of AM disappeared from the literature. Recently, several reports disclosed the use of AM in various ocular surface diseases (Kim and Tseng 1995; Lee and Tseng 1997; Park et al. 2008).

Since Kim and Tseng (1995) reported the effectiveness of AM transplantation in an experimental alkali burn model, many clinical reports have been published in regard to this treatment (Chen et al. 2000; Hanada et al. 2001; Honavar et al. 2000; Kim 2000; Kruse et al. 1999; Meller et al. 2000; Tsai et al. 2000). In those reports, two ways of AM transplantation were demonstrated: graft and patch. In the former, in which the epithelium grows on the AM, the AM is used as an anti-scarring material for the conjunctiva, while in the latter, in which the epithelium expands under the AM, the AM is applied as a bandage material to the cornea. The main purpose of the patch seemed to be to enhance epithelial healing of the damaged cornea. On the other hand, an AM patch applied over an excimer laser-ablated cornea has been shown not only to enhance epithelial healing but also to reduce corneal haze (Wang et al. 2001; Woo et al. 2001).

The most common current method of attaching AM is by means of suturing. The use of sutures requires a high degree of surgical skill and is associated with several disadvantages, including prolonged operating time and suture-related complications, such as suture abscesses, granuloma formation, and tissue necrosis (Chen et al. 1995; Koranyi et al. 2004; Sridhar et al. 2002; Ti et al. 2000). Moreover, corneal irritation, scarring, graft loss due to membrane shrinkage, the need for subsequent suture removal, post-operative pain, and discomfort due to foreign body sensation and tearing with ocular surface reconstruction are significant problems for patients (Uy et al. 2005). Replacement of sutures by bioadhesives might be an advantageous alternative.

Cyanoacrylate is an adhesive that results from the chemical reaction between formaldehyde and the esters of cyanoacetate. The monomer can then be modified by altering the ester group of the molecule to obtain compounds of different chain lengths. These products have been used in plastic surgery, gastrointestinal tract surgery, and in oral and maxillofacial surgery. They have also been applied in kidney, liver, and bone lesions and on animal and human blood vessels (Singer and Thode 2004; Toriumi et al. 1998; Vote and Elder 2000).

Cyanoacrylate enhances skin wound healing by decreasing inflammatory response (Eriksson 1976) and preventing collagenase production (de Almeida Manzano et al. 2006; Eiferman and Snyder 1983). Cyanoacrylate glues have been successfully applied in ophthalmology to repair corneal perforations (de Almeida Manzano et al. 2006). Watte et al. (2004) used butyl-2-cyanoacrylate adhesive combined with conjunctival grafts in the management of canine and feline corneal disease. Different types of cyanoacrylate adhesive have been used in surgery (Lauto et al. 2008). Dermabond (2-octylcyanoacrylate) is much more pliable and tissue compatible than its predecessors; it has less toxicity and almost four times the strength of N-butyl-2-cyanoacrylate (Schwade 2002). In 2001, Taravella and Chang reported the successful use of 2-Octyl cyanoacrylate (Dermabond) to seal a corneal perforation (Taravella and Chang 2001).

The aim of this study was to evaluate the surgical technique required and the clinical usefulness of tissue adhesive (2-Octyl cyanoacrylate) combined with AM patching in the treatment of an experimental corneal burn in dogs.

Materials and methods

All experimental procedures in this study were performed simultaneously. This project was approved by the Iranian laboratory animal ethics framework and under the supervision of Iranian Society for the Prevention of Cruelty to Animals. Fifteen mixed-breed adult male and female dogs with normal eyes, weighing about 15 kg, and 1–2 years old were divided into three groups of five animals each. Prior to the study, complete physical examinations, complete blood counts, and ophthalmic examinations including, indirect ophthalmoscopy, slit lamp biomicroscopy, Schirmer tear test, and fluorescein staining of both eyes were performed. Animals were anaesthetised by acepromazine (0.1 mg/kg), ketamine (10 mg/kg), and diazepam (0.2 mg/kg). The corneal alkali burn was made by placing a 6-mm diameter circular piece of filter paper soaked in 1 M NaOH on the central cornea for 60 s. Only one eye in each dog was used. The cornea was rinsed with 2 ml of physiological saline immediately after alkali exposure. Five dogs without AM patching after the alkali burn were designated as the control group (group 1). In group 2 (AM+suture), human AM (AmniDress®) was placed on the rinsed cornea with the basement membrane side facing down and sutured around the corneal wound area in a single interrupted pattern using 10–0 nylon sutures (Fig. 1). In group 3 (AM+glue), the AM was attached (basement membrane side down) using 2-Octyl cyanoacrylate (Dermabond®, Ethicon, Somerville,

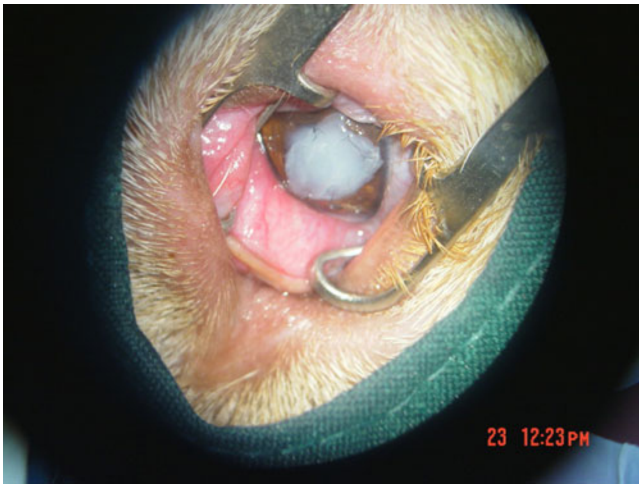

Fig. 1 Human amniotic membrane placed on the corneal ulcer with the basement membrane side facing down and sutured around the corneal wound area in a single interrupted pattern using 10–0 nylon sutures (AM+suture group)

NJ, USA; Fig. 2). In the post-operative period, dogs received ciprofloxacin eye drops four times daily on the corneal alkali burn.

The operation time in the AM+suture and AM+glue groups was recorded. The eyes were examined daily by slit lamp biomicroscopy for 21 days. Clinical outcome was monitored by evaluating epithelial defects, corneal opacity, duration of blepharospasm, duration of AM persistence, corneal vascularisation, and duration of ocular discharge.

The severity of corneal opacity was graded 0–3 by an investigator unaware of which group each case came from (Pfister and Pfister 1997). Grade 0 represents completely clear cornea, grade 1 represents faint corneal haze, grade 2 represents blurs iris detail, and grade 3 represents pupil not visible. Corneal vascularisation was graded 0–3 (Kozak et al. 2002). Grade 0 represents no vascularisation, grade 1 represents superficial focal vascularisation, grade 2 represents superficial diffuse vascularisation, and grade 3 represents deep vascularisation.

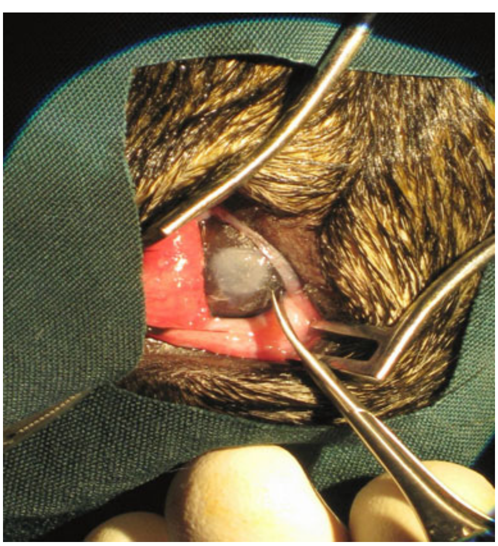

Fig. 2 Sutureless attachment of AM (basement membrane side down) on corneal chemical burn by using of 2-Octyl cyanoacrylate (Dermabond; AM+glue group)

Statistical analysis for corneal opacity and corneal vascularisation was performed on days 3, 6, 10, 15, and 21. The corneal burns were examined, stained with 2% fluorescein, and photographed once daily (after the AM had fallen off). To evaluate corneal epithelial defects, the photographs were analysed with image analysis software (NIH ImageJ v.1.33u), and the area of the stained lesion was measured by counting pixels.

Statistical analysis for operation time, AM persistence, and duration of stainable cornea (days) was performed by Mann–Whitney *U* test. Statistical analysis for duration of ocular discharge, duration of blepharospasm, corneal oedema, corneal vascularisation, and epithelial defect was performed by Kruskal–Wallis test. Pairwise comparison between groups was performed. *P* values of <0.05 were considered to be significant.

Results

Analysis of mean operation time in groups AM+suture and AM+glue was performed. The mean operation time in AM+suture group was significantly longer than AM+glue group ($P < 0.001$). AM persistence in AM+glue group was significantly longer than AM+suture group ($P = 0.023$). AM rejection occurred faster in AM+suture group in comparison to AM+glue group.

Comparison between groups showed that the AM+glue group had significantly lower ($P = 0.041$) discharge days in comparison with control group (group 1). Duration of blepharospasm revealed no significant statistical differences ($P > 0.05$).

Corneal oedema was most prominent in the first week after surgery in all groups. Corneal opacity revealed no significant statistical differences on days 3, 6, 10, 15, and 21 ($P > 0.05$).

There was no corneal vascularisation in any group on day 3. Although there were no significant statistical differences between corneal vascularisation in any group at days 6 and 10, corneal vascularisation was less in AM patching groups than control group, but corneal vascularisation revealed significant differences between groups on days 15 ($P = 0.018$) and 21 ($P = 0.040$; Fig. 3). Pairwise comparison determined that the AM+glue group had a significantly lower degree of corneal vascularisation than the control group (Fig. 4).

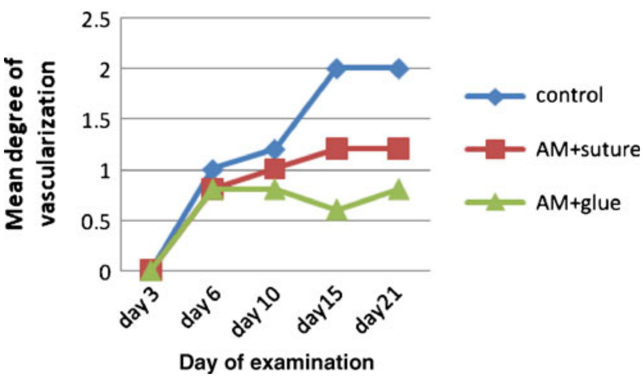

Fig. 3 The graph demonstrates the vascularisation trend based on mean degree of vascularisation. AM patching groups show lower vascularisation compared with the uncovered group at days 15 and 21. Among the AM patching groups, the AM+glue group showed the best result ($P<0.05$)

Corneal epithelial defects were compared, after the AM fell off, using fluorescein staining. Statistical analysis was performed on day 7 comparing all corneas except for two dogs in the AM+glue group as the AM was still in place in these animals at this time point. Healing of the corneal epithelial defects revealed significant differences between the AM+glue group and the control group after 7 days. Epithelial defects healed faster in the AM+glue compared with the control group over time ($P = 0.038$).

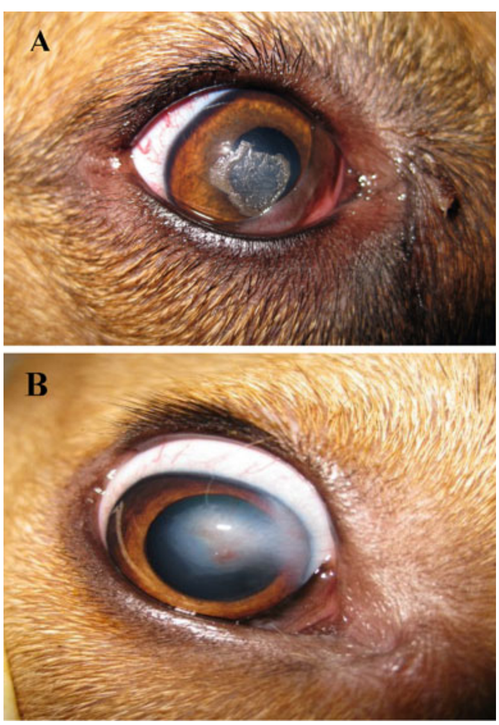

Fig. 4 **a** Day 17 AM+glue eye (AM fell off on day 6), some glue remaining on corneal surface; no corneal opacity or vascularisation observed. **b** Day 17 control eye; opacity, vascularisation, and granulation tissue on central cornea

The duration of stainable cornea (days) after the AM fell off was compared. None of the corneas in the AM+glue group were stained after AM rejection. Duration of stainable cornea (days) in AM+suture group was shorter than control group, but statistical analysis of these two groups revealed no significant statistical differences ($P > 0.05$).

Discussion

The repair of the severely ulcerated cornea is a challenge for ophthalmologists. Alkali burns are the most serious of chemical injuries to the anterior segment of the eye (Meller et al. 2000). Several correction methods and materials have been described in the last few years for defects in the cornea (Chen et al. 2000; Hanada et al. 2001; Kim and Tseng 1995; Kruse et al. 1999; Lee and Tseng 1997; Meller et al. 2000; Shimazaki et al. 1997; Tsai et al. 2000; Wang et al. 2001; Watte et al. 2004; Woo et al. 2001).

The lack of any published data on the effects of sutureless AM patching on corneal ulcer healing with 2-Octyl cyanoacrylate (Dermabond) in dogs prompted this investigation.

The mean operation time in the AM+suture group was significantly longer than the AM+glue group ($P < 0.001$). This could be explained by the fact that using sutureless AM patching on corneal alkali burns can reduce anaesthetic complications by reducing operating time.

Corneal opacity is related to oedema due to water capture and disarrangement of the normal pattern of collagen lamellas of the stroma and is very common in alkali burns in the cornea (Waring 1984). In this study, the opacity was most prominent during the first week after surgery in all groups, and there were no significant statistical differences during the study. Although in some research AM alone did not remove corneal opacities (Kozak et al. 2002), AM patching has reduced oedema and opacity in many studies (Lee and Tseng 1997; Hao et al. 2000; Park et al. 2008). Blepharospasm is often found in the presence of suture thread or strange bodies on the cornea (Slatter 2008). In our study, blepharospasm was observed in all groups, and its duration revealed no significant statistical differences during the study. This was probably due to the pain of the corneal alkali burn, sutures, and irritation due to cyanoacrylate.

In the events following the corneal alkali burn, polymorphonuclear leukocyte (PMNs) enter the wound from limbal capillaries and migrate through the stroma, and there are recurrent epithelial defects (McCulley 1994). Kim (2000) showed that AM patching in corneal alkali burns in rabbits blocks PMN infiltration, preventing a local inflammatory response and thereby enhancing wound healing. Lee and Tseng (1997) used AM for the treatment of persistent epithelial defects, and results showed the efficacy of AM patch in the improvement of epithelialization that may be attributed to inhibition of collagenase by AM and supplementation of the basement membrane and growth factors. The basement membrane of AM promotes epithelial growth and differentiation, reinforces the adhesion of basal epithelial cells, and prevents epithelial apoptosis (Park et al. 2008). Here, this concept was supported as epithelial defects healed faster in the AM+glue group than in the control group over time, and the epithelial wound sizes of the AM patching groups were statistically smaller than that of the control group at the same time point. In addition, none of the corneas in the AM+glue group stained after AM rejection. Inhibition of ulceration and enhancement of the healing process with AM patching in this study and similar studies (Kim 2000; Shimazaki et al. 1997) suggests that the protection mechanisms of AM in the alkali-injured eye might help the healing process. Sutures are associated with several disadvantages such as interfering with the healing process and tissue necrosis (Koranyi et al. 2004; Sridhar et al. 2002; Ti et al. 2000; Uy et al. 2005). On the other hand, cyanoacrylate may support stromal ulceration and has anti-microbial effects (Slatter 2008) and prevents collagenase production (de Almeida Manzano et al. 2006; Eiferman and Snyder 1983).

Neovascularisation, mainly superficial, was observed in the control group more than the other groups. The dogs in AM+glue group had significantly less corneal vascularisation than the control group on days15 and 21. The corneal vascular neoformation appears due to persistent, infected, or destructive stromal lesions in order to improve the tropism of the injured site and to carry inflammatory mediators (Slatter 2008). Lee and Tseng (1997) showed the efficacy of AM patching in the improvement of corneal epithelial defects and the probability of the role of AM in the inhibition of collagenase and supplementation of the basement membrane and growth factors. Some investigators identified anti-angiogenic (e.g., endostatin and thrombostatin-1) and anti-inflammatory (e.g., interleukin-1 receptor antagonists) factors in human AM (Kim 2000; Hao et al. 2000). It is assumed that in this study, a combination of these factors in the AM in addition to the use of a sutureless technique with 2-Octyl cyanoacrylate, and its anti-inflammatory, anti-collagenase (de Almeida Manzano et al. 2006), and anti-microbial effects (Slatter 2008) helped rapid healing and reduction of corneal vascularisation. The minor neovascularisation in the AM+glue group suggests that a rapid organisation of the corneal stroma has occurred in the absence of infection, thus, without needing inflammatory mediators.

In this study, the advantages of using AM and 2-Octyl cyanoacrylate to create a sutureless technique resulted in less ocular discharge, less corneal vascularisation, and better healing compared to the control group. These results indicate that use of sutureless AM patching with Dermabond (2-Octyl cyanoacrylate) adhesive offers the clinician a good, fast, and effective method for the treatment of corneal wounds without the need of highly specialised surgical skills, at the same time, reducing operating time and suture-related complications. Thus, it can be recommended as an important option in the treatment of alkali burn-induced corneal ulcers.

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