EXTENDED REPORT

Alcohol delamination of the corneal epithelium for recalcitrant recurrent corneal erosion syndrome: a prospective study of efficacy and safety

Ravinder P Singh, Dev Raj, Anupama Pherwani, Ruby Lagnado, Asiya Abedin, Habibullah Eatamadi, Manu Mathew, Harminder S Dua

A video clip of the method is available as a supplementary file online at <http://bjophthalmol.com/supplemental>

See end of article for authors' affiliations

Correspondence to: Professor H S Dua, Division of Ophthalmology and Visual Sciences, B Floor, Eye Ear Nose Throat Centre, University Hospital, Queen's Medical Centre, Nottingham NG7 2UH, UK; harminder.dua@nottingham.ac.uk

Accepted 2 February 2007
Published Online First
14 February 2007

Br J Ophthalmol 2007;91:908–911. doi: 10.1136/bjo.2006.112912

Aim: To investigate the safety and efficacy of alcohol delamination of the corneal epithelium for recalcitrant recurrent corneal erosion syndrome (RCE) in a prospective non-comparative interventional case series.

Methods: Patients with RCE who remained symptomatic despite topical lubrication and 3-month use of an extended wear (bandage) contact lens were included. The intensity of pain on a scale of 1 to 10, and duration and frequency of attacks were recorded. Patients were treated with alcohol delamination and followed up at 1 week, 1 month and then at 12 months, which was the minimum follow up time. Success was defined as a resolution of symptoms after 1 month of treatment, and partial success as a significant reduction in symptoms manageable with topical lubricants, and failure where symptoms were unchanged or worsened.

Results: 20 eyes of 20 patients with RCE caused by trauma ($n = 14$), anterior basement membrane dystrophy ($n = 5$) or idiopathic (1) were studied. The mean age of patients was 44 years and mean follow-up 24 months. Two eyes were lost to follow-up. 15 (83%) eyes were qualified as successes, 3 as partial successes and no failures were seen. No intraoperative complications were observed. 1 patient developed transient subepithelial haze that resolved with topical steroid, 1 had a change in refraction and 1 developed herpetic stromal keratitis 2 months postoperatively, which was successfully treated. No loss of vision was observed in any of the patients.

Conclusion: Alcohol delamination of the corneal epithelium is a safe and effective method for treating patients with recalcitrant RCE.

Recurrent corneal erosion (RCE) is a painful condition, which can seriously affect the comfort and lifestyle of patients.¹ Fortunately, mild episodes can often be successfully managed with topical lubrication alone. However there are cases in which such conservative measures fail. A number of treatments have been advocated for this group of patients, all of which report a high degree of success. These include using high water content bandage-soft contact lens (BCL),^{2–4} anterior stromal puncture,^{5–6} neodymium-doped:yttrium aluminium garnet (ND:YAG) laser puncture,^{7–8} superficial keratectomy with a diamond burr^{9–10} and phototherapeutic keratectomy.^{11–13} These treatments have all been used successfully, but are limited by potential for scarring over the visual axis, refractive change, or cost and availability. Alcohol delamination of the corneal epithelium (ADCE) has been reported in a retrospective case series as a novel but effective alternative for treating RCE.¹ We present the first prospective case series of a cohort of patients with RCE treated with ADCE, and report on the results and complications of treatment.

PATIENTS AND METHODS

Patients were prospectively enrolled into the study from a tertiary referral cornea service. Institutional ethics committee approval was obtained before the commencement of the study, and all patients provided written informed consent. The inclusion criterion was any patient with recurrent corneal erosion syndrome from any cause in whom symptoms were not controlled by conservative treatment. Conservative treatment was initially topical lubrication with non-preserved hypromellose

0.3% during the day and paraffin-wax-based lubrication at night (Lacrilube, Allergan, Irvine, California, USA). If symptoms were persistent, a high water-content BCL was used (Focus Dailies, CIBA vision, Southampton, UK) and topical lubricants continued. The BCL was changed every month and worn for 3 months. Patients were warned about the symptoms of infective keratitis and instructed to present immediately if they occurred. Failure of conservative therapy was defined as persistent symptoms despite topical lubrication and BCL usage, or recurrence of symptoms on discontinuation of BCL after 3 months.

A total of 20 eyes of 20 patients were enrolled into the study. The average age of the patients was 44 years (range 32–77 years). In all, 12 (60%) of the patients were male. RCE was secondary to previous corneal trauma in 14 (70%) cases, anterior basement membrane dystrophy was present in five cases and 1 (5%) case was idiopathic. Patients were asked to grade the severity of pain they experienced during an attack on a scale from 1 to 10 on a visual analogue pain score chart (1 being no pain and 10 being severe pain), and the average frequency and duration of pain ascertained pretreatment. A visual analogue pain score, although subjective, effectively compares pain scores for an individual before and after treatment.¹⁴ After treatment, all patients were given a chart to record the occurrence and duration of each

Abbreviations: ADCE, alcohol delamination of the corneal epithelium; BCL, bandage-soft contact lens; BSS, balanced salt solution; ND:YAG, neodymium-doped:yttrium aluminium garnet; PTK, phototherapeutic keratectomy; RCE, recurrent corneal erosion

Figure 1 Photograph of patient treated with alcohol delamination of the corneal epithelium. (A) Preoperative photograph demonstrating macroform erosion. (B) Fluorescein photograph demonstrating erosion. (C) Clinical appearance 1 week after the operation. (D) Fluorescein photograph 1 week after the operation.

episode of pain and grade its severity. Preoperative and post-operative visual acuities were recorded, as were complications during or after treatment.

Procedure

During an attack, the site of corneal erosions was documented with a diagram or digital photograph with fluorescein instillation and cobalt-blue light. Only areas of erosion were treated. All procedures were carried out under an ophthalmic surgical microscope, in a clean procedure room, under a topical anaesthetic and after instillation of 5% betadine into the conjunctival sac followed by sterile draping and insertion of a lid speculum.

A solution of 100% alcohol was diluted with sterile water to a 20% solution in a 1 ml syringe. A circular well (optical zone marker 4–6 mm in diameter, Bausch and Lomb, Kingston-upon-Thames, Surrey, UK) of diameter sufficient to encompass the area of erosions was placed onto the cornea and held with firm downward pressure. A few drops of the alcohol solution were then placed inside the well so that the entire treatment area was covered, and left for a duration of 30–40 s. The alcohol was then drained from the well with a surgical sponge (K-Sponge-Katena Products, Denville, New Jersey, USA) and the well removed from the cornea. The surface of the eye was irrigated with balanced salt solution to wash away residual alcohol.

Using a fresh dry surgical sponge, the treated area of corneal epithelium was completely debrided from the corneal surface as a single sheet. The corneal surface was gently irrigated again with balanced salt solution and a BCL inserted. The patient was treated with chloramphenicol 0.3% (Minims preservative free, Bausch and Lomb, Surrey, UK) antibiotic drops four times a day and seen 1 week later. The BCL was removed at follow-up, and the wound examined with fluorescein to assess healing. If there was still an epithelial defect, the BCL was replaced and antibiotics continued for a further week. In all patients, healing of the denuded area was complete in 2 weeks and the BCL was discontinued (fig 1). Patients were encouraged to continue using topical lubrication regardless of the resolution of symptoms. Patients were reviewed 1 month later to examine the cornea and assess symptoms. If patients were asymptomatic and no abnormality was seen on examination, they were seen 12 months later for their follow-up appointment for the study. Longer follow-up times were obtained where possible after the 12-month appointment to document

further the safety and efficacy of treatment for the purposes of our study. All patients were asked to keep a record of any recurrence on the follow-up chart provided.

Outcome measures

Success was defined as complete resolution of symptoms after 1 month of treatment, and partial success was defined as a subjective experience of reduction in patients' symptoms to the extent that they were able to manage their attacks with topical lubrication alone. Failure was defined as no improvement in or worsening of symptoms following treatment.

RESULTS

Table 1 summarises the age, sex, aetiology and symptom severity before and after treatment for each patient in the study. Of the 20 eyes studied, 2 (10%) were lost to follow-up. Mean follow-up time of the eyes studied was 24 months (range 12–38).

In all, 15 eyes of 18 patients (83%) remained free of symptoms from RCE at follow-up after treatment with ADCE and were classified as a "success", and 3 (17%) patients had persistent symptoms that were much less severe and were managed with lubricants and so were qualified as a "partial success". No failures were seen in the study.

All the three patients who still had symptoms (patients 1, 14, 18—table 1) reported them to be much less severe and less frequent than their original symptoms. Patient 1 experienced reduced symptoms for 9 months after treatment, which resolved completely thereafter. Patient 14 had persistent symptoms, but found them to be much reduced in severity and more manageable with topical lubrication alone (severity 2/10, frequency 1 per month, duration 1 h after the operation, compared with 6/10, 2 per month, duration 18 h before the operation). Patient 18 also experienced symptoms that were less severe and managed her symptoms with lacrilube alone before sleep (severity 5/10, duration 2 h, frequency once per week after the operation, compared with 8/10, duration 2 h, frequency every night before the operation). All three patients were satisfied with the reduction in severity of their symptoms, and, on specific questioning, did not feel that they required any further form of treatment to control their symptoms. Of the five patients with anterior basement membrane dystrophy, one had recurrence of symptoms (patient 18).

Table 1 Clinical details of patients

No.	Age/sex	Aetiology	Pre-op pain score (severity, duration, frequency)	Follow up (months)	Persistent symptoms (severity, duration, frequency)	Comments
1	53/F	Trauma	10/10, 3 h, 2/week	12	4/10, 1 h, 1/month	Had complete resolution of symptoms 9 months post-op
2	38/M	Trauma	8/10, 3 days, 1/week	NA	NA	Lost to follow-up
3	52/F	Trauma	8/10, 2 days, 1/month	22	Nil	—
4	36/F	Trauma	10/10, 3 h, every day	18	Nil	—
5	41/M	Trauma	8/10, 1–2 h, 2/month	24	Nil	—
6	77/M	ABMD	7/10, 30 min, 5/week	12	Nil	—
7	47/M	Trauma	8/10, 12 h, 2/month	12	Nil	Experienced fluctuation in refraction, which stabilised after 3 months with no loss of BSCVA
8	58/M	ABMD	8/10, “constant” symptoms	NA	NA	Lost to follow-up
9	42/M	Trauma	7/10, 1 h, 2–3/week	21	Nil	—
10	54/M	Trauma	8/10, 2 h, every day	21	Nil	—
11	52/F	ABMD	8/10, 5 min, every day	12	Nil	Herpetic disciform keratitis post-op successfully treated with no recurrence or loss of BSCVA to date
12	30/M	Trauma	10/10, 3–4 h, every day	26	Nil	—
13	65/F	Idiopathic	5/10, few minutes, every night	37	Nil	—
14	27/F	Trauma	6/10, 18 h, 2/month	22	2/10, 1 h, 1/month	Patient reported a marked improvement in ocular comfort and manages symptoms with topical lubrication
15	37/F	Trauma	10/10, 24 h, 1/week	38	Nil	—
16	37/M	Trauma	5/10, 1 h, 1/2 months	38	Nil	Transient subepithelial haze post-op; resolved with topical steroid, no loss of BSCVA
17	32/M	Trauma	7/10, 30 min, 1/week	38	Nil	—
18	33/F	ABMD	8/10, 2 h, every night	26	5/10, 2 h, 1/week	Subjectively much more comfortable and manages symptoms with lubrication
19	44/M	ABMD	10/10, 1–2 days, 1/month	27	Nil	Persistent microcysts at treatment site but no symptoms
20	33/M	Trauma	9/10, 12 h, 1/week	23	Nil	Persistent microcysts at treatment site but no symptoms

ABM, anterior basement membrane; ABMD, anterior basement membrane dystrophy; BSCVA, best spectacle corrected visual acuity; F, female; M, male; NA, not available; pre-op, pre-operation; post-op, post-operation.

Pre-operative and, where relevant, post-operative pain scores and comments pertaining to each individual patient are given.

Among the 20 eyes that underwent the procedure, no intraoperative complication was observed and no patient developed infective keratitis following BCL insertion. No loss of best spectacle corrected visual acuity (BSCVA) was recorded in any of the patients. Of all the patients examined at follow-up, two had persistent epithelial microcysts at the site of treatment (patients 19 and 20), none of whom had recurrent symptoms.

Patient 7 experienced fluctuating vision postoperatively because of an unstable refractive error. Her initial refraction was +1.5/−1.0×140, which eventually stabilised at −0.5/−2.0×5 over a 3-month period. Her BSCVA remained stable. Patient 11 developed herpetic disciform keratitis 2 months postoperatively, which responded to topical steroids and acyclovir treatment. No recurrence or loss of vision was recorded in the follow-up period. Patient 16 developed transient subepithelial haze in the first month postoperatively, which resolved with a course of topical fluoromethalone 0.1% four times a day for 1 week, with no loss of vision.

DISCUSSION

RCE can be an extremely painful condition that significantly affects patients' quality of life and ability to work. There are several theories about its pathogenesis, including the presence of weak hemidesmosomes, reduplication of the corneal epithelial basement membrane and activation of matrix metalloproteinases, implicating an inflammatory component in the disease.^{15–16}

Many treatment modalities have been put forward for treating this painful condition, with topical lubrication usually

being the first-line treatment. Failing this, there are numerous other treatment modalities available.

Use of a high-water-content BCL to cover the cornea while allowing time for more secure attachment between corneal epithelial cells and underlying basement membrane to occur can be effective, but risks complications such as infective keratitis and corneal neovascularisation.³ Anterior stromal puncture and ND:YAG laser puncture are also effective treatments that work by encouraging scar tissue formation, which promotes adhesion between the basement membrane and corneal epithelium.^{5–8} The scarring, however, may degrade visual acuity if used for erosions near the visual axis. Phototherapeutic keratectomy (PTK) has also been used to treat recalcitrant RCE successfully, with success rates varying between 60%–100%.^{13–17–19} In cases where patients initially had recurrence of symptoms after PTK, re-treatment with PTK, has been associated with a high rate of resolution of symptoms, but has the potential to induce a hyperopic shift.¹¹

Successful medical treatments for RCE have included topical steroid and oral tetracycline (doxycycline) as inhibitors of matrix metalloproteinase-9²⁰ and topical autologous serum drops.²¹ ADCE has the advantage of being a one-off treatment in the majority of cases compared with medical modalities. Holzer *et al*²² used PTK to treat RCE and used autologous serum eye drops as a postoperative lubricant, achieving 80% success in symptom eradication; in the remaining patients, 80% of the symptoms were controlled using autologous serum drops alone, without the need for further surgery.

Despite the effectiveness of PTK for treating RCE, its high cost and lack of widespread availability limit its application in

general ophthalmic practice. In contrast, ADCE only requires standard minor-operations, ophthalmic equipment and resources. It was originally described in a retrospective case series and shown to be a safe and effective treatment for RCE by Dua *et al.*¹ Histology and transmission electron microscopy of debrided sheets of epithelium revealed intraepithelial microcysts and abnormal hemidesmosomes in the basal epithelial layer. In addition, a subcellular amorphous non-fibrillar proteinaceous material was observed on transmission electron microscopy, which resembled thickened basement membrane on light microscopy. It is possible that alcohol-assisted debridement of the epithelium removes such subepithelial debris and any potentially noxious stimuli that encourage weakening of the attachment of the corneal epithelium to its underlying basement membrane.

The results of the first prospective case series of ADCE to treat recalcitrant RCE suggest that it is effective at eliminating symptoms in the majority of patients and has a good safety profile. The remaining patients had much less pain severity, duration and frequency than before, and were comfortable enough with lubricants alone to feel they did not need further treatment. It would be interesting to see whether complete resolution of their symptoms could have been achieved with re-treatment with ADCE as seen in patients re-treated with PTK for RCE.¹¹ Alternatively, recurrent symptoms may have arisen from a new area on the cornea not covered by the initial treatment. Of the four patients with anterior basement membrane dystrophy who were followed up, three were free of symptoms (75% success in this subgroup). It is difficult, however, to draw conclusions on a small sample of patients, and further study with ADCE in a larger group of patients with anterior basement membrane dystrophy would help better determine its efficacy in treating this subset of patients with RCE. Cavanagh *et al.*¹² demonstrated an 86.2% success in treating RCE in patients with anterior basement membrane dystrophy with PTK.

No visually lasting complications were observed in the study. The one patient who developed herpetic disciform keratitis did not have a history of herpes keratitis. It is not certain whether a definite cause-effect relationship was present. Transient subepithelial haze was observed in one patient, and subsided with topical corticosteroids without adverse visual sequelae. One patient had a fluctuating refractive error which eventually stabilised without any loss of BCSVA.

Patients had a mild amount of discomfort following the procedure, despite a BCL placed in situ, and this was managed with topical lubricants, antibiotics and oral analgesia as required. This mild discomfort diminished as the epithelium healed. It has been observed in two patients, subsequent to the closure of recruitment for this study, that the BCL in itself can be a cause of discomfort and pain after treatment because of an inadequate fit. Patients who present with severe pain in the immediate postoperative period with a BCL in situ should be assessed for problems related to fit, as well as for other causes, including microbial keratitis. Inadequate fit and poor oxygenation from limbal ischaemia can also retard the healing response of the corneal epithelium.

ADCE is a promising treatment for RCE not responsive to conservative treatment. Its safety and efficacy is comparable to that of PTK, but it has the advantage of being much

more widely available and much less expensive to perform. Re-treatment could also be considered in cases where symptoms recur. A prospective trial comparing patients with RCE treated with ADCE with those treated with other techniques would, however, be the best way to compare the relative safety and efficacy of the treatment techniques available. The lack of a control group is a potential limitation of this study.

Authors' affiliations

Ravinder P Singh, Dev Raj, Anupama Pherwani, Asiya Abedin, Habibullah Eatamadi, Manu Mathew, Harminder S Dua, Division of Ophthalmology and Visual Sciences, University of Nottingham, University Hospital, Queen's Medical Centre, Nottingham, UK
Ruby Lagnado, Huddersfield Royal Infirmary, West Yorkshire, UK

Competing interests: None.

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