Corneal manual epithelial debridement for the treatment of painful bullous keratopathy: a pilot study

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Abstract

Background: Bullous keratopathy (BK) is a painful condition requiring corneal transplant. Patients in resource-poor settings often wait many months before receiving transplant.

Aims: The purpose of the study was to evaluate corneal manual epithelial debridement (MED) in the treatment of painful bullous keratopathy.

Settings and design: In a prospective interventional case series, consecutive patients presenting to Groote Schuur Hospital Eye Clinic, Cape Town, South Africa, with painful BK between May 2016 and December 2016 were considered for the study.

Methods and material: Fifteen eyes of 15 patients underwent MED. Patients were followed up at ten days, one month, two months, three months and six months post procedure. Outcome parameters evaluated included: numeric rating pain score (NRS), visual acuity (VA), corneal transparency, and size of corneal bullae. Pain score and corneal transparency were analysed statistically using the paired t-test. VA was analysed using the chi-squared test.

Results: The mean NRS was significantly decreased from its baseline value of 7.2 ± 1.7 at all follow-up visits ($p<0.02$) as follows: day ten = 4.4 ± 2.6 (range 1.5–9.5, p=0.0015); one month = 3.5 ± 2.4 (range 1–9, p=0.0004); two months = 3.5 ± 2.4 (range 1–8, p=0.0016); three months = 3.4 ± 2.1 (range 1–8, p=0.0003); and six months = 3.8 ± 2.4 (range 1–7.5, p=0.0005). Mean VA and corneal transparency remained stable for the duration of the study. In most patients, the size of corneal bullae assessed via subjective anterior segment photography was initially reduced, but returned to baseline by the end of the study.

Conclusions: MED reduces mean pain scores and temporarily reduces the size of corneal bullae in BK. MED may be considered as a simple, low-cost treatment alternative for reducing pain in patients awaiting transplant in a resource-poor setting.

Key words: amniotic membrane transplant (AMT), bullous keratopathy (BK), corneal crosslinking (CXL), corneal manual epithelial debridement (MED), phototherapeutic keratectomy (PTK)

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Conflict of interest: No conflicts of interest to declare.

Introduction

Corneal bullae are the main cause of the disabling pain experienced by patients with bullous keratopathy (BK).[1-5] The gold standard of treatment is corneal transplant. Patients in resource-poor settings often wait many months before receiving transplant. Corneal crosslinking (CXL), amniotic membrane transplant (AMT) and phototherapeutic keratectomy (PTK) have been described as palliative treatments. Manual corneal epithelial debridement (MED) is the first step in these procedures. There is evidence that MED plays a role in preventing the recurrence of painful bullae.[6,7] The primary aim of the study was to evaluate MED as a treatment for painful BK.

Subjects and methods

Consecutive patients who presented to the Groote Schuur Hospital Eye Clinic with painful BK between May 2016 and December 2016 were considered for the study. Children, prisoners, pregnant women, intellectually impaired persons, patients with blepharitis, conjunctivitis, keratitis, entropion, ectropion, pannus, severe dry eye or intra-ocular pressure above 30 mmHg were excluded.

Patients included in the study underwent a complete ophthalmological history and examination prior to the procedure. The aetiology of BK, duration and severity of symptoms and current medical treatment were recorded. Pain score was evaluated using the verbal numeric rating scale (NRS). Patients were asked to grade the severity of their average ocular pain on a scale of 0 to 10 according to subjective pain perception, with 0 representing no pain and 10 the worst pain imaginable.

Anthropometric parameters evaluated at baseline included Snellen visual acuity (VA),

central corneal thickness (CCT) measured by ultrasonic pachymetry (Alcon OcuScan), average size of corneal bullae and corneal transparency by subjective assessment of anterior segment photography.

Average size of corneal bullae was assessed using anterior segment photographs taken post instillation of fluorescein. Corneal transparency was graded according to a known system used in the CXL studies by Ghanem *et al.* and Sharma *et al*:[4,8]

0 – clear cornea
1 – mild oedema with minimal loss of transparency
2 – moderate oedema with iris details visible
3 – severe oedema with iris details obscured
4 – opaque cornea with no iris details visible

In patients with bilateral disease, MED was performed in the eye with the highest pain score. The procedure was performed under sterile conditions in the minor procedures room of the Groote Schuur Hospital Eye Clinic, as follows:

1. Benoxinate hydrochloride topical anaesthetic drop instilled every minute for 5 minutes
2. Epithelial area to be debrided marked using a 10 mm circular trephine
3. Epithelium manually debrided with an ophthalmic spoon
4. Debris cleaned from basement membrane using a cotton bud
5. Bandage contact lens (BCL) inserted

Oral analgesia and a topical antibiotic drop (Ofloxacin) qid were prescribed. Patients were followed up ten days later where BCL was removed and a steroid/antibiotic combination drop (dexamethasone/chloramphenicol) was prescribed qid for a period of one week. Patients were followed up again at one month, two months, three months and six months post procedure. At each follow-up visit, patients underwent an ophthalmic examination with repeat measurement of the study parameters and documentation of any complications. The average size of corneal bullae was assessed as being unchanged, reduced or increased, as agreed by the authors. Pre-existing topical treatment, such as lubricants or hypertonic saline, were continued throughout the study period.

The study methodology complies with the principles described in the declaration of Helsinki and was approved by the University of Cape Town Human Research Ethics Committee (ethics reference #201/2016).

Statistical analysis

Pre-operative values were used as controls, and outcomes were compared against these baseline values at each follow-up visit.

Quantitative data are expressed as mean ($\bar{x}$); ±standard deviation (±SD). Qualitative data are represented as a proportion or percentage. Data analysis was performed using IBM SPSS version 24. Normality was assessed using the Shapiro-Wilk test. Pain score and corneal transparency were analysed using the paired t-test.

Associations of pain and corneal transparency scores over time were assessed using Pearson correlation. VA was analysed using the chi-squared test. Statistical significance was determined as p-value <0.05.

Results

For this pilot study, 15 eyes of 15 patients were included. The mean age of participants was 63.3 years ± 12.2 (range 34–80 years). There were four men and 11 women. BK was due to trauma in one patient, graft failure in two patients, Fuch's endothelial dystrophy in two patients and pseudophakic BK in the remaining ten patients. The mean duration of disease was 24 months ± 33 (range 2–136 months).

The mean pain score at time of presentation was 7.2 ± 1.7 (range 5–10). Mean pain scores were significantly decreased at all follow-up visits as follows: day ten = 4.4 ± 2.6 (range 1.5–9.5, p=0.0015); one month = 3.5 ± 2.4 (range 1–9, p=0.0004); two months = 3.5 ± 2.4 (range 1–8, p=0.0016); three months = 3.4 ± 2.1 (range 1–8, p=0.0003); and six months = 3.8 ± 2.4 (range 1–7.5, p=0.0005). A total of three patients were excluded from the study. One patient was lost to follow-up after one month. Two patients were excluded, one after two months and another after three months due to worsening ocular pain which required rescue treatment with hypertonic saline, lubricants, oral analgesia, BCL insertion and penetrating keratoplasty in one case. The patient not treated with penetrating keratoplasty defaulted follow-up and later presented with an infective keratitis complicated by endophthalmitis after wearing her BCL continuously for eight weeks (*Figure 1*).

The mean CCT was 667 µm on presentation, but this parameter was only recordable in seven of the 15 patients. CCT was therefore excluded from further analysis. The mean corneal transparency at presentation was 2.5 ± 0.5 (range 2–3). Baseline transparency improved from grade 2 to grade 3 in two patients and decreased from grade 3 to grade 2 in one patient at all visits following MED. There was no significant change in mean corneal transparency throughout the study: day ten = 2.6 ± 0.5; one month = 2.6 ± 0.5; two months = 2.7 ± 0.5; three months = 2.6 ± 0.5; six months = 2.7 ± 0.5.

The VA at presentation was count fingers (CF) in nine patients, hand movements (HM) in three patients and no light perception (NLP) in three patients. VA improved from HM to CF at all follow-up visits in two patients. VA decreased from HM to NLP in one patient at the three months follow-up visit. Central retinal artery occlusion was suspected as the cause of visual loss due to the history of sudden complete loss of vision and the presence of new vessels on the iris. There was no significant change in VA found during the study.

At one-month follow-up, the average size of corneal bullae was reduced in 75% of patients, unchanged in 17% and increased in 8% of patients when compared with baseline. By six months however, the size of corneal bullae remained reduced in only 30% of patients

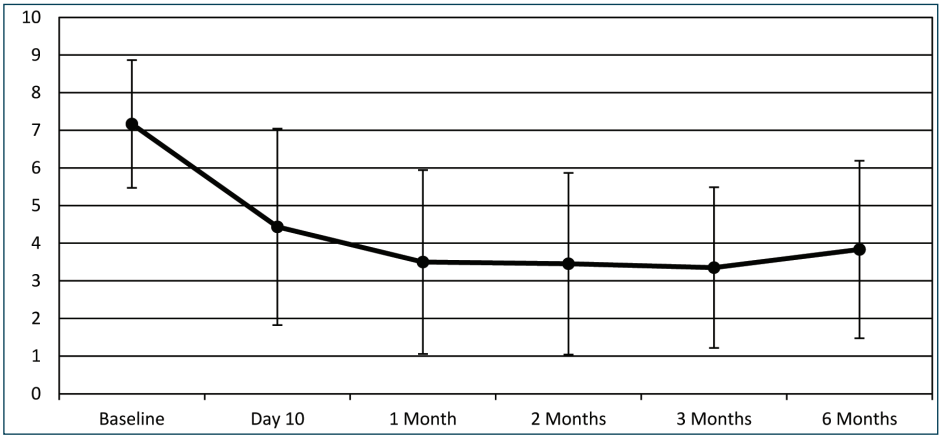
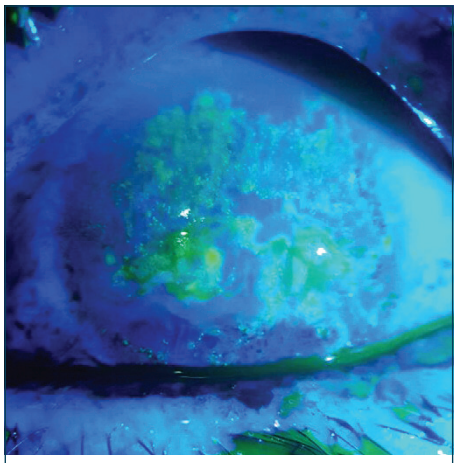
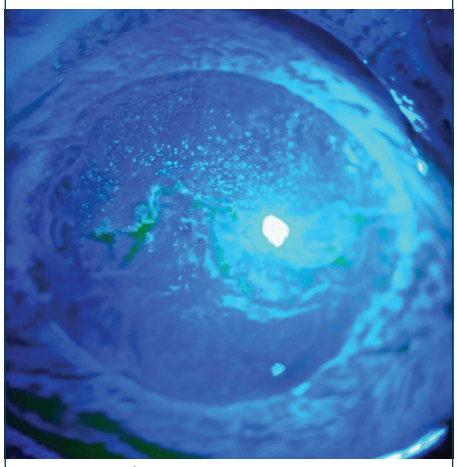


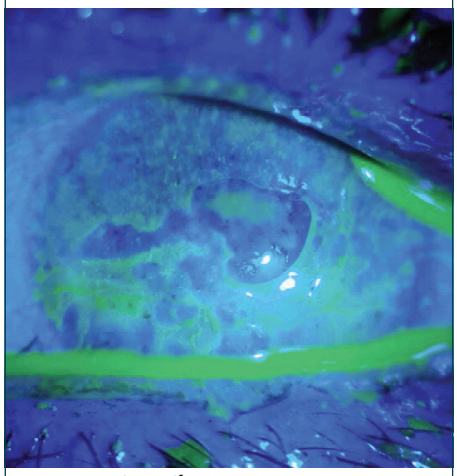
Figure 1. Change in NRS pain score over time following MED in BK



Cornea at one month



Cornea at six months



Cornea at baseline

Figure 2. Anterior segment photography showing the size of corneal bullae in a patient at baseline, one month and six months after MED
*****Bullae appear as discrete or coalescent dark mounds surrounded by lakes of fluorescein***

and had returned to baseline size in the other 70% (*Figure 2*).

No persistent epithelial defects were noted. One patient presented with scleritis at two weeks post debridement. The pain responded well to a short course of oral prednisone. No other complications were noted.

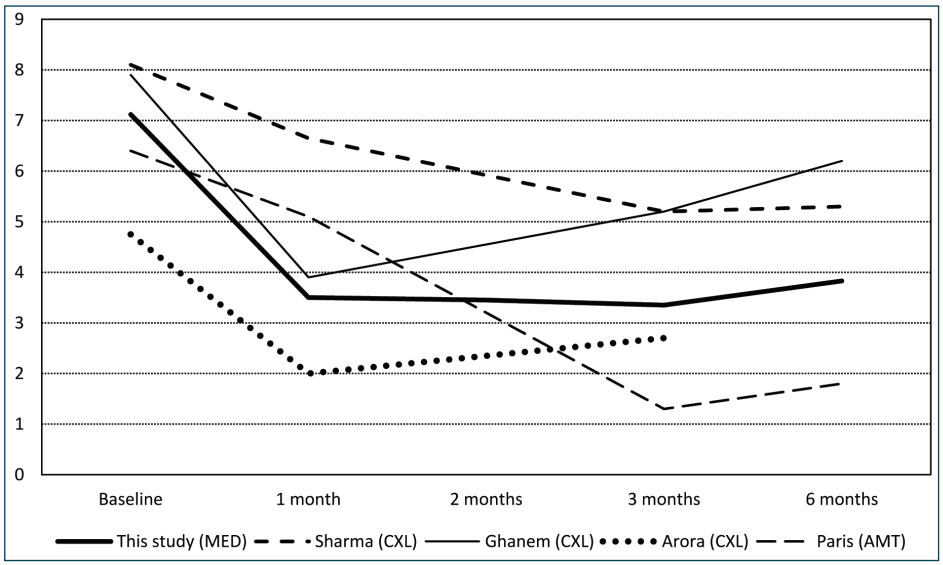


Figure 3. Comparison of pain score outcomes following MED, CXL and AMT for BK

Discussion

CXL,[4,8-10] AMT[2,3,11-14] and PTK[14-16] for the palliative treatment of BK have been relatively well described. The literature suggests that they are all effective options for reducing pain in patients with BK. Unfortunately, these procedures are time-consuming and expensive. CXL, AMT and PTK all employ MED as the initial step in the surgical procedure. MED is simple, inexpensive and has been used safely and effectively for reducing pain in recurrent corneal erosion syndrome.[6,7] There are, however, no other studies which evaluate MED as a means for reducing pain in BK and no studies comparing MED vs CXL, AMT or PTK for the treatment of BK.

In this study, the authors found that MED was effective in reducing the mean pain score over a period of six months in patients with BK. Subjective numeric pain scores were also used in the CXL studies by Sharma,[8] Ghanem[4] and Arora,[9] as well as in the AMT study by Paris.[13]

All studies showed early improvement in pain scores with a late trend towards regression (*Figure 3*). AMT appears to be more effective than both CXL and MED in reducing pain scores beyond two months. A confounding factor in our study was that two patients, whose pain scores remained high at the two- and three-month follow-up visits, were excluded from future statistical analysis due to the initiation of rescue treatment. The pain scores at three and six months may therefore be falsely low. One patient, who had previously been excluded from the study, developed infective keratitis after failing to replace her BCL for over six weeks. This highlights the fact that contact lens wear remains the most significant risk factor for developing infective keratitis.[17] For this reason, BCL should be used with caution in the treatment of BK.

In other studies[2,3,10-12,14-16] numerical pain scores were not used. The severity of pain experienced by patients at the end of the study was reported broadly, as either 'no pain', 'significantly less pain' or 'pain like baseline'.

Table I indicates that the PTK[14-16] and AMT[2,3,11-14] studies had a longer follow-up than the CXL studies. They report that the greatest proportion of participants either had no pain, or a significant reduction in pain at the end of the study. It therefore

Table I: Comparison of pain outcomes following PTK and AMT in BK

Study author	Intervention	Pain free	Significantly reduced pain	Pain similar to baseline	Study duration (months)
Lin[16]	PTK	88%	NA	NA	11
Maini[15]	PTK	NA	73%	22%	8
Chawla[14]	PTK	90%	10%	0%	8
Chawla[14]	AMT	80%	20%	0%	8
Pires[12]	AMT	90%	6%	4%	8
Espana[2]	AMT	73%	22%	NA	6
Chansanti[3]	AMT	NA	82%	NA	14
Georgiadis[11]	AMT	88%	22%	0%	21

AMT: amniotic membrane transplant; BK: bullous keratopathy; PTK: phototherapeutic keratectomy; NA: not analysed

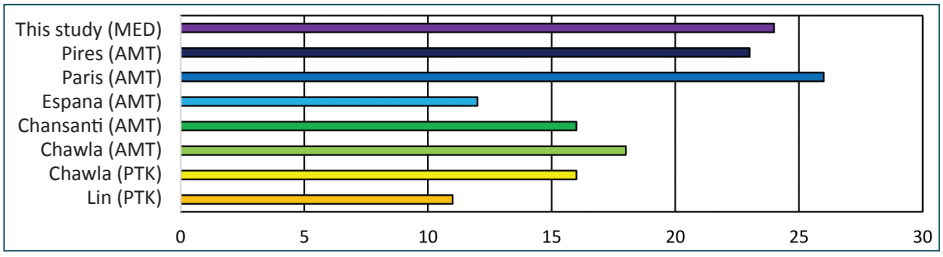


Figure 4. Duration of BK symptoms in months prior to MED, AMT and PTK

appears that PTK and AMT may be more effective than CXL and MED for reducing pain over longer periods of time. Long-term comparative studies are required to confirm whether this is true. The onset of sub-epithelial fibrosis in BK has been associated with at least 12 months history of symptoms.[5] The mean duration of symptoms experienced by the study participants prior to intervention was 24 months. This is the second longest duration of symptoms quoted in the relevant literature (*Figure* 4).

CCT was unrecordable in eight of our study patients. In these patients, the odds were four times higher that they had a symptom duration of 12 months or more compared with patients where CCT was recordable. Our mean CCT may therefore be falsely low because of missing data from patients with advanced disease. Sub-epithelial fibrosis may have contributed to our difficulty in obtaining CCT measurements in these patients.

MED did not significantly affect VA or corneal transparency in our study group. This makes MED an attractive option over anterior stromal puncture (ASP) for patients who may be eligible for endothelial keratoplasty in future. However, our small study size reduces the reliability of the chi-squared test (*Figure 5*).

The size of corneal bullae, although reduced at the one-month follow-up in a large percentage of patients, returned to baseline size by six months in most patients. The correlation between size of corneal bullae and patient pain score has not been evaluated in the literature. There is also no grading system described which quantifies the severity of corneal bullae. These could be useful tools for statistical analysis, but larger studies are required to determine these parameters.

Conclusion

MED is fast, simple and inexpensive to perform. In our study MED was found to be safe and effective in reducing subjective pain scores over a period of six months. MED also temporarily reduced the size of corneal bullae and shows promise as a method for managing patients who are not suitable for or who are awaiting transplant in a resource-poor setting. However, our study numbers were small and there appeared to be a tendency towards regression in pain scores by six months. Larger and more long-term studies are required to evaluate long-term outcomes of MED and compare MED against other procedures used in the palliative management of BK.

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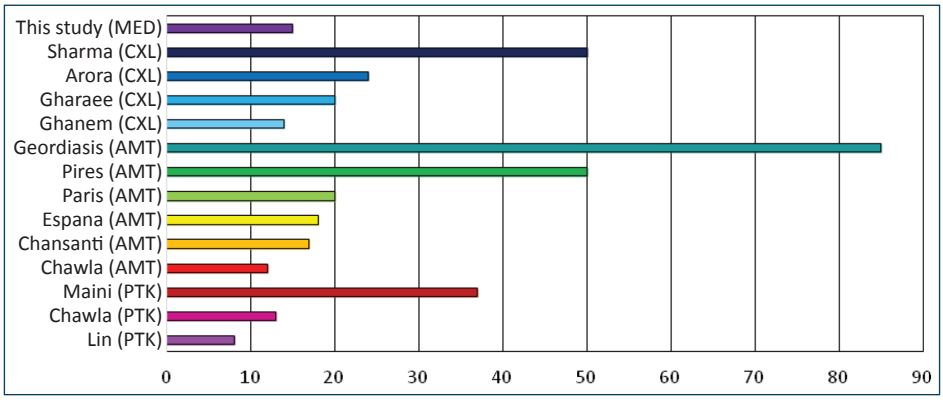

Figure 5. Number of participants in studies evaluating MED, CXL, AMT and PTK for BK

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