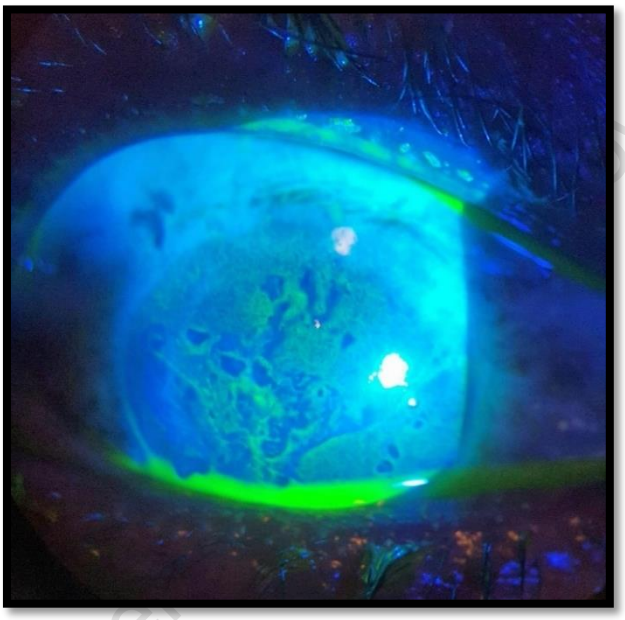
Master of Medicine in Ophthalmology

University of Cape Town

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



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Contents

Declaration

I, Daemon Bruce McClunan, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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Abstract

Purpose: The aim of the study was to evaluate the outcomes of corneal manual epithelial debridement (MED) for the treatment of painful bullous keratopathy (BK).

Methods: In a prospective interventional case series, 15 eyes of 15 consecutive patients presenting with painful BK of varying aetiology underwent MED. Patients were followed up at 10 days, 1 month, 2 months, 3 months and 6 months post procedure. Outcome parameters evaluated include numeric rating pain score (NRS), visual acuity (VA), corneal transparency and size of corneal bullae.

Results: The mean NRS was significantly decreased from its baseline value of 7.2 +- 1.7 at all follow-up visits ($p < 0.02$). Mean VA and corneal transparency remained stable for the duration of the study. In most patients the average size of corneal bullae was initially reduced, but returned to baseline by the end of the study.

Conclusion: MED reduces mean pain scores and temporarily reduces the size of corneal bullae in BK. MED may be considered as a simple, low cost alternative for reducing pain in patients awaiting corneal transplant. Further studies are required to evaluate MED for the treatment of BK and compare outcomes against other palliative treatment options.

Keywords: Bullous keratopathy, Corneal epithelial debridement

Note: The abstract has been prepared in the publication ready format

Acknowledgements

I would like to acknowledge the input from my supervisor with regards to formulation of the research methodology, clinical support for patient management during the study and assistance with compiling this thesis. I would also like to acknowledge our co-author Dr Pollock who assisted with the research methodology and the literature review.

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Table of abbreviations

Table 1: Abbreviations in alphabetical order

ABK	Aphakic bullous keratopathy
AM	Amniotic membrane
AMT	Amniotic membrane transplant
ASP	Anterior stromal puncture
BCL	Bandage contact lens
BK	Bullous keratopathy
CCT	Central corneal thickness
CXL	Corneal collagen cross-linking
FED	Fuch's endothelial dystrophy
IK	Infective keratitis
MED	Manual corneal epithelial debridement
KP	Keratoplasty
NRS	Numeric rating pain score
NSAIDS	Non-steroidal anti-inflammatory agents
PBK	Pseudophakic bullous keratopathy
PTK	Phototherapeutic keratectomy
RCE	Recurrent corneal erosion syndrome
SEF	Sub-epithelial fibrosis
VA	Visual acuity
VAS	Visual analogue pain score

Word count

Excluding abstract, tables, figures and references:

- Literature review: 5426 words
- Manuscript: 2192 words

Note: the manuscript has been compiled to be as short and concise as possible to improve the likelihood of publication. This was advised by the study supervisor and co-author. The literature review section has therefore been expanded to make up for the lower word count in the manuscript.

Chapter 1: Introduction and Literature review

1. Introduction

A review of the literature on bullous keratopathy with a view to exploring epithelial debridement as a novel treatment option.

1.1 Summary

Bullous keratopathy (BK) is a painful condition characterised by blisters on the corneal surface. The gold standard of treatment is corneal transplant. Unfortunately, transplant may be contraindicated or patients may wait long periods prior to transplant.

Many alternative treatment options which aim to reduce discomfort in patients with BK have been described in the literature with mixed outcomes and opinions.

There is evidence to suggest that epithelial debridement performed during corneal crosslinking (CXL), amniotic membrane transplant (AMT) and phototherapeutic keratectomy (PTK) plays a significant role in the pain reduction afforded to patients with bullous keratopathy.

Epithelial debridement as a stand-alone procedure for the treatment of painful BK has not yet been described in the literature and may be a novel treatment option.

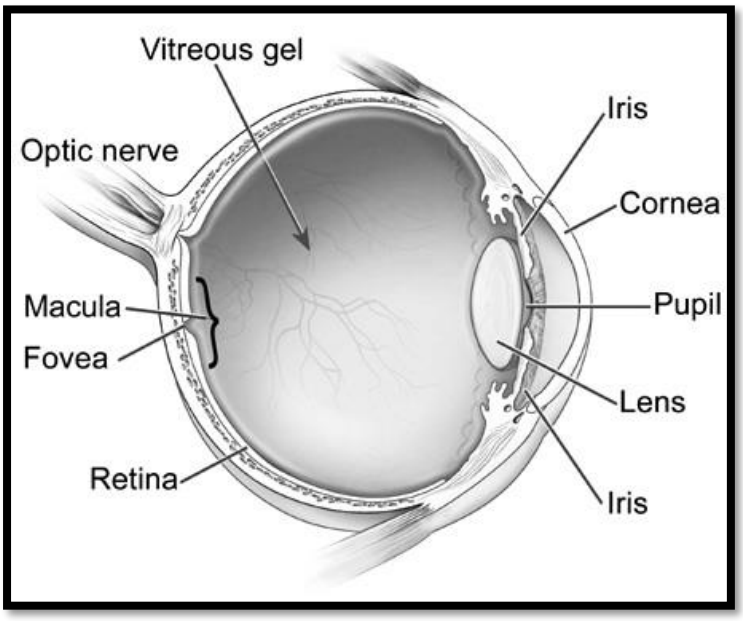

Figure 1: Anatomy of the eye

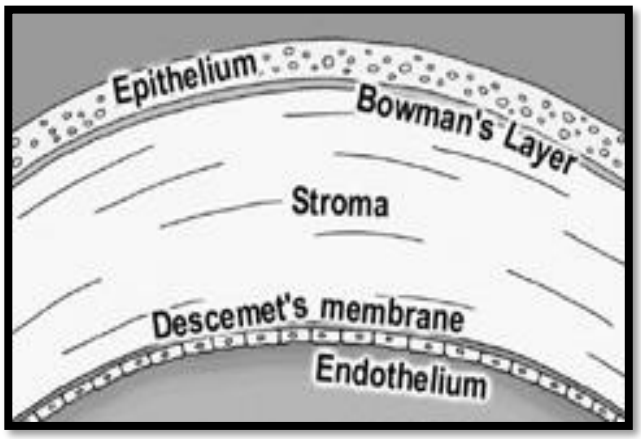

Figure 2: Layers of the cornea

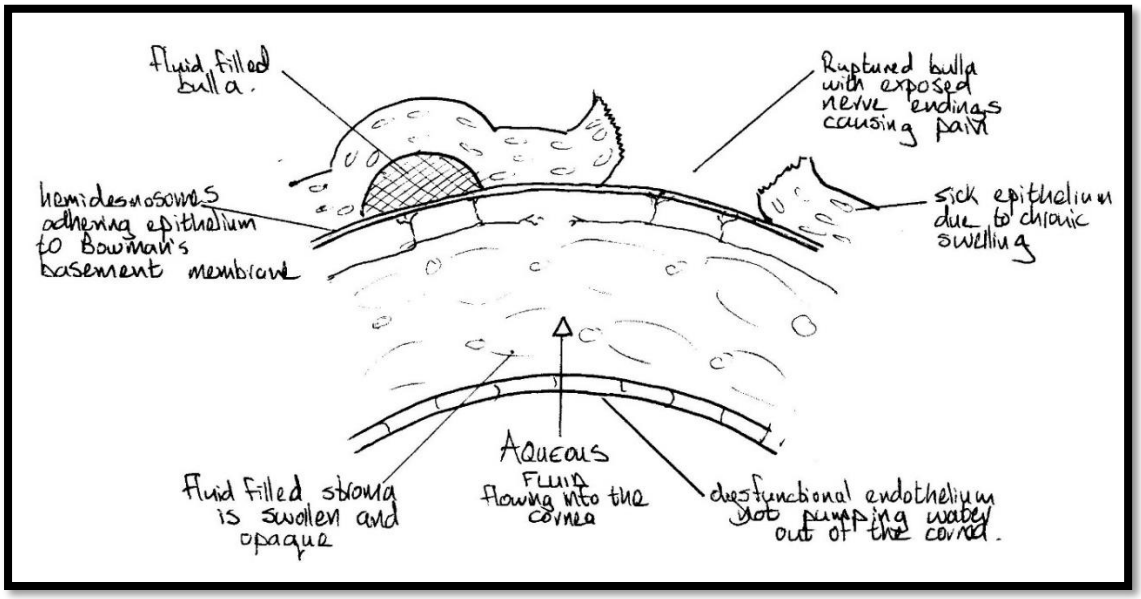

Figure 3: Bullous keratopathy

2. Objectives of the literature review

The literature review aims to be comprehensive in its analysis of the literature relevant to BK. The core objective of the review is to compare the methods and outcomes of the prevailing surgical treatment options for patients who are not suitable for, or are awaiting corneal transplant. This sets the scene for introducing the proposed critical research question. The review therefore aims to achieve the following:

- Identify relevant and core articles.

- Highlight the prevailing treatment trends, scientific theories, connections and contradictions in the literature.
- Critique relevant arguments by highlighting the main supporting and opposing findings.
- Discuss and compare outcomes of relevant studies.
- Make comment on the quality of core studies.
- Attempt to synthesize findings to give guidance on the topic.
- Uncover scientific gaps and opportunities for further research in the field.

Through this process the review sheds light on the following questions:

- What is the magnitude of disease caused by BK?
- What are the central theories related to the pathology of BK?
- What treatment practices have evolved over time?
- What are the demographics across patient study groups?
- Are the treatment methods standardised?
- What pain score is used to assess pain in BK?
- How effective are the various treatment options in reducing pain?
- What are the strengths and weaknesses associated with each treatment option?
- What are the qualities which would define the ideal treatment option?
- Is Manual corneal epithelial debridement (MED) safe?
- Is there evidence to support the theory that MED may reduce pain in BK?
- What is the accepted method of MED?
- What are the gaps in the literature and opportunities for further research

3. Literature review search strategy

3.1 Methods

Data collection

- The search aimed to be semi-exhaustive in identifying journal articles related to the treatment of pain in patients with BK.
- A systematic review of the literature was conducted by performing a broad search of Pubmed and Google scholar.
- The following keywords, wildcards, brackets and operators were used in various combinations and truncations to identify relevant articles:

1. Keywords: Corneal, Bullous, Keratopathy, Endothelial, Decompensation, Cross linking, Phototherapeutic, Keratectomy, Amniotic membrane, Transplant, Stromal puncture, Debridement, Polishing, Scraping, Delamination, Erosion.
2. Operators: AND, OR, NOT.
3. Brackets: ( )
4. Wildcards: *

- A strategy of preview → overview → inview was employed:
  - Search results were screened for potentially relevant articles.
  - Abstracts of potentially relevant articles were reviewed to assess relevance.
  - Full texts of articles deemed relevant were acquired and bibliographies were screened for further potentially relevant articles.
- This process was repeated until it was felt that a reasonable effort had been made to identify all relevant articles.

Data organisation

- Articles were grouped thematically as follows:
  - BK
    - Pathology
    - Management
      - Corneal cross linking
      - Phototherapeutic keratectomy
      - Anterior stromal puncture
      - Amniotic membrane transplant
      - Medical
      - Other
  - Recurrent corneal epithelial erosion syndrome
  - Corneal epithelial debridement
  - Ocular pain
  - Corneal wound healing

Data evaluation

- Core articles were broken down to populate tables for data analysis

Table 2: Data organisation and analysis

Study				
Validity				
Year				
Journal				
Bias				
Methods				
Study design				
Pain score				
Variables				
Participants				
Aetiology				
Inclusion criteria				
Exclusion criteria				
Surgical technique				
Post op treatment				
Follow up times				
Results				
Demographics				
Pre-op pain				
Mean pre CCT				
Mean pre-VA				

Table 2 continued: Data organisation and analysis

Symptom duration				
Pre-op Rx				
Aetiology				
Pain outcome				
VA outcome				
CCT outcome				
Bullae outcome				
Vessels outcome				
Side-effects / Complications				
Statistical analysis				

CCT, Central corneal thickness; VA, Visual acuity

3.2 Inclusion criteria

- Type: Peer reviewed journal article.
- Method: Human, animal, laboratory study.
- Scope: Minimum 8 patients (core articles).

3.3 Exclusion criteria

- Language: No English language version.
- Availability: Not available on the University of Cape Town (UCT) electronic journal database or library.
- Chronology: Older than 20 years.
- Quality: Unacceptably low quality.

4. Quality criteria

4.1 Study design

- Study question or hypothesis
- Methods
- Level of evidence
- Validity
    - Bias and confounding
    - Precision of measurements
    - Effect size and clinical importance
    - External validity

4.2 Manuscript

- Peer review
- Date of publication
- Author credentials
- Organisation and structure
- Analysis, reasoning and conclusions
- Relevance, scope and context
- Graphs and illustrations
- References

5. Analysis of the literature

5.1 Pathology of bullous keratopathy

5.1.1 Introduction

It is not disputed that the primary pathology causing BK is failure of the corneal endothelial pump with subsequent fluid accumulation. If epithelial bullae occur, the term BK is used.

5.1.2 Visual loss

Swelling of the corneal stroma causes folds and irregular lamellae in descemet's membrane. This results in light scatter and early loss of Visual acuity (VA).[1,2]

Fluid also accumulates in the sub-epithelial space, detaching the epithelium from its basement membrane. These fluid filled spaces coalesce to form macrobullae. This irregularity of the corneal surface causes refractive aberrations with further loss of VA[3-6].

Following longstanding BK, Sub-epithelial fibrosis (SEF) occurs which causes late deterioration in VA.[1,2]

5.1.3 Ocular discomfort

The conventional understanding is that pain in BK is caused by exposure of corneal nerve endings. This follows rupture of bullae during microtrauma. Almost all authors agree that this is the main mechanism for the ocular discomfort experienced by patients with BK.[3,5,7,8] One histological study showed that superficial corneal stromal nerves were in fact reduced or absent in BK.[9] This suggests evidence which conflicts with the above conventional understanding.

Some authors also mention stretching of corneal nerves by epithelial bullae as a mechanism for pain. [9]This cannot be explained anatomically as corneal nerves do not extend into the epithelium, but rather terminate in the superficial stroma.

5.1.4 Complications

Chronic BK results in the collection of abnormal collagen structures above the Bowman layer which correspond to SEF. Morishige found that SEF was only detected in specimens from individuals with a duration of stromal oedema of at least 12 months.[1] Longstanding BK also predisposes to corneal vascularisation, infection and scarring, which may complicate the condition and compromise future surgical outcomes.[2,8,10]The potential risk of infection in BK has been quoted as 4.7%.[7]

5.1.5 Aetiology

The popularity of cataract surgery has made this the most common cause of BK; aseudophakic bullous keratopathy (PBK)/aphakic bullous keratopathy (ABK) over the last 30 years. Corneal graft failure is another important secondary cause of BK. Fuch's endothelial dystrophy (FED) is the most common primary cause of BK.

Other less common causes referenced in the literature include:

- Trauma
- Vitreoretinal surgery
- Other endothelial dystrophies
- Congenital anterior segment dysgeneses
- Refractory glaucoma
- Laser therapy
- Chronic inflammation

5.2 Treatment of BK

5.2.1 Overview

The primary goal of treatment in BK is to alleviate ocular discomfort. The secondary goal is to improve visual function. It is generally agreed that keratoplasty (KP) remains the gold standard of treatment in patients with good visual potential as it relieves pain and also provides visual rehabilitation.[2,4,7,8,11,12,13] BK is quoted as the most common indication for KP as well as for re-grafting worldwide.[3,7,11]

KP might not be indicated for certain patients due to poor visual potential, ocular / systemic contra-indications or a lack of corneal transplant facilities. Where KP is indicated and resources are available, patients may wait many months before receiving transplant, especially in resource poor settings.[2,5,6,14]

5.2.2 Alternatives to transplant

Various alternative medical and surgical treatment options which attempt to alleviate pain and improve vision in BK patients have been described. They may be indicated as palliative treatment, or as temporising measures for patients awaiting transplant.

5.2.3 Medical treatment

Topical Lubricants, hypertonic saline, non-steroidal anti-inflammatory agents (NSAIDS), steroids, cycloplegics and bandage contact lens (BCL) may be useful to relieve symptoms in early disease. Topical Rho-associated kinase (ROCK) inhibitors is an emerging potential treatment option. Advanced disease usually requires surgical intervention.[2,9,15,16]

5.2.3.1 Lubricants, cycloplegics, steroids and NSAIDS

Although these are often quoted as a treatment option, there are no studies quantifying the effect which they have on pain or VA in patients with BK. There is also concern over potential side-effects of steroids [Delayed epithelial healing, Infective keratitis (IK)] and NSAIDS (Corneal melt).[17]

5.2.3.2 Hyperosmotic solutions

Results of a prospective comparative study of 70 eyes of 55 patients showed that hypertonic saline was only useful in early disease for improving VA and reducing central corneal thickness (CCT), but not in more advanced disease. Hypertonic saline is simple to use, but not all patients can tolerate the drops due to stinging. [2]

5.2.3.3 Bandage contact lens

BCL has been shown to improve corneal epithelial healing.[17,18] One prospective comparative study showed significantly improved comfort scores in BK patients using 3 different types of BCL.[16]

Unfortunately BCL requires 2 weekly follow up for lens exchange, is known to be the most significant risk factor for IK and may cause corneal vascularisation.[10,19]

5.2.4 Surgical treatment

Multiple surgical treatment options were described in the literature with varying frequency and differing levels of evidence.

Frequently described treatment options with good levels of evidence, in chronological order, include:

1) Phototherapeutic keratectomy (PTK) [10,12, 23]
2) Amniotic membrane transplant (AMT) [4, 7, 8, 9, 13, 23]
3) Anterior stromal puncture (ASP) [9,11,22]
4) Corneal crosslinking (CXL) [5, 6, 24, 25]

Less common treatment options mentioned in the literature [2,4,10,12,20,21,22], in alphabetical order, include:

1) Annular keratotomy
2) Autologous perichondrium transplantation
3) Corneal surface thermal or laser cautery
4) Cultured endothelial cell injection
5) Diamond burr polishing
6) Enucleation or evisceration
7) Epikeratophakia
8) Gunderson flap
9) Intrastromal silicone oil/hydrogel lens insertion
10) Posterior corneal cryopexy
11) Retrobulbar alcohol

All the commonly used treatment modalities aim to reduce the presence of bullae by one of the following mechanisms:

1) Allowing a fresh layer of epithelium to cover the corneal surface: CXL, PTK, AMT
2) Increasing adhesion between the epithelium and the underlying basement membrane (Bowman's): ASP

3) Preventing corneal stromal swelling: CXL

5.3 Analysis of the core literature

Table 3: Core studies by intervention and first author

PTK	AMT	ASP	CXL
Lin[12]	Chawla[23]	Gomes[22]	Ghanem[5]
Maini[10]	Pires[4]	Sridhar[11]	Gharaee[24]
Chawla[23]	Espana[7]	Paris[9]	Arora[6]
	Chansanti[8]		Sharma[25]
	Georgiadis[13]		
	Paris[9]		

AMT, Amniotic membrane transplant; ASP, Anterior stromal puncture; CXL, Corneal collagen cross-linking; PTK, Phototherapeutic keratectomy

5.3.1 Are patients comparable across studies?

5.3.1.1 Demographics

The mean age of study patients ranged from 50 to 83 and the average mean age was 66 years of age. There were no children included in any studies. All studies included both men and women and there were roughly equal numbers of each in total. Differences in age or sex which may have been present are unlikely to have affected study outcomes.

Racial demographics were not recorded by any studies. This may be important to note due to racial differences in wound healing response.[26,27]

5.3.1.2 Inclusion and exclusion criteria

VISUAL POTENTIAL

In the studies related to PTK and AMT only patients with poor visual potential were included in the study. In the ASP studies Gomes[22] and Paris[9] also included patients with good visual potential. It appears all the patients included in the CXL studies had good visual potential, although Sharma[25] does not make specific mention of this.

Patients with poor visual potential often have a history of glaucoma, trauma, diabetic retinopathy or other ocular disease which may affect study outcomes. Ideally sub-analysis should be performed between those with and without visual potential. Unfortunately, this is usually not possible due to limited study participant numbers.

INTRAOCULAR PRESSURE

Elevated intraocular pressure may worsen the symptoms of BK. These patients should therefore be excluded or analysed separately. This confounding factor was unfortunately seriously under reported, with only the studies by Arora[6] and Paris[9] citing this in their exclusion criteria.

5.3.1.3 Aetiology of BK

In FED the epithelial basement membrane has been shown to display dystrophic features.[28,29] In graft failure, there may be issues with adhesion of the host epithelium to the underlying donor stroma. Both these factors may negatively affect epithelial adhesion.

PBK was the most common cause of BK across the studies. Studies by Maini[10], Chawla[23], Ghanem[5], Arora[6] and Sharma[25] included only patients with PBK. Other studies included patients with BK of varying aetiologies. Failed graft was a common cause of BK in the PTK studies and in the study by Gharaee[24]. Espana[7], Paris[9] and Sridhar[11] were the only studies which included patients with FED.

Unfortunately, there was no sub-analysis performed between patients with differing aetiologies in BK, thus comment cannot be made as to whether there were differences in outcome.

5.3.1.4 Severity and duration of BK

CCT is a good indicator of the severity of BK whereas duration of symptoms has been shown to be an indicator of the risk for sub-epithelial fibrosis[30]. Both have been shown to affect treatment outcomes. These are therefore important clinical variables to indicate whether outcomes between patient study groups can be compared.

Unfortunately, pre-intervention CCT was only mentioned in 8 of the 16 studies and duration of symptoms in 4. In some patients CCT was un-recordable due to the severity of corneal oedema. This may result in a falsely low mean CCT. A normal CCT is 550 µm, the mean CCT of the study participants ranged between 725-872 µm. This shows that there was significant variation across studies with mean CCT ranging between 30% and 60% above normal.

Table 4: Pre-intervention CCT and duration of symptoms

Study	Intervention	CCT	Mean duration of BK
Maini[10]	PTK	Mean 762 µm (range 588–969 µm)	NA
Chawla[23]	PTK+AMT	Mean 730 µm (range 610–922 µm)	17 months (range 3–48)
Paris[9]	AMT+ASP	Mean 814 µm (range 463–1725 µm)	27 months (range 2–96)
Pires[4]	AMT	NA	23 months (range 0–240)
Espana[7]	AMT	NA	12 months (range 1–36)
Chansanti[8]	AMT	NA	16 months (range 5–24)
Gomes[22]	ASP	Mean 854 µm (range 672–1029 µm)	NA
Ghanem[5]	CXL	Mean 747 µm (range 630–837 µm)	NA
Gharaee[24]	CXL	Mean 872 µm (range 710–1040 µm)	NA
Arora[6]	CXL	Mean 813 µm (range unknown)	NA
Sharma[25]	CXL	Mean 725 µm (range 650–800 µm)	NA

AMT, Amniotic membrane transplant; ASP, Anterior stromal puncture; BK, Bullous keratopathy; CCT, Central corneal thickness; CXL, Corneal collagen cross-linking; NA. Not analysed; PTK, Phototherapeutic keratectomy

The mean duration of symptoms varied between 12 and 27 months. There was a large inter-individual range of between 0 and 240 months. Morishige showed that SEF was only present on histology after a symptom duration of 12 months or more. The effect which SEF has on treatment outcomes has not been evaluated. It may well play an important role.

These results show that there is a large variation in the mean severity and duration of BK which makes it difficult to directly compare study outcomes.

5.3.2 Are the study methods standardised?

5.3.2.1 Study design and scope

All studies consisted of prospective interventional clinical trials except for the studies by Espana,[7] Sridhar[11] and Sharma[25] which were performed as retrospective reviews and therefore may constitute lower levels of scientific evidence. There were only two randomised comparative clinical trials. The first by Chawla[23] compared outcomes between AMT and PTK and the other, by Paris,[9] compared outcomes following AMT and ASP.

The number of patients in each study varied between 8 and 85.

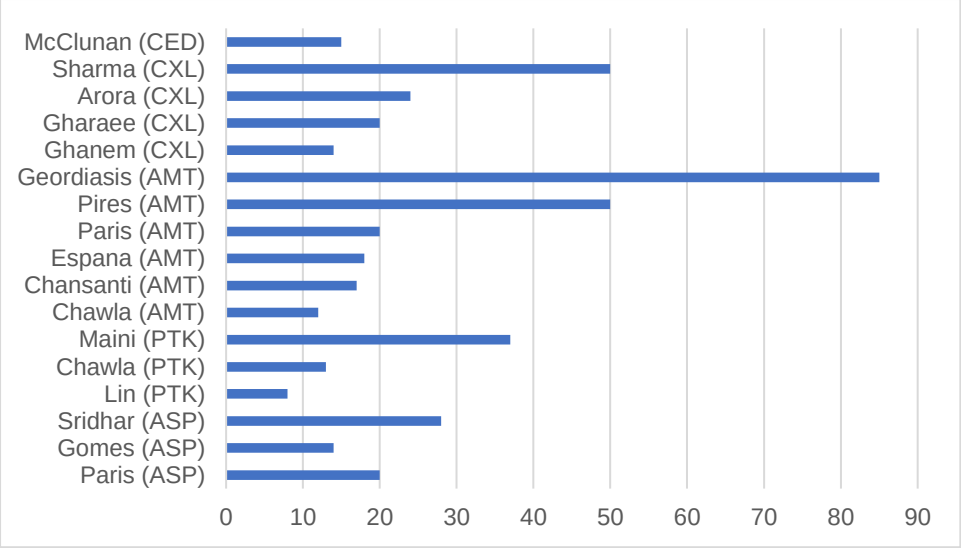

Figure 4: Number of study participants

5.3.2.2 Medical treatment

Only 4 studies made note of what medical treatment patients were using prior to intervention. These included artificial tears, lubricants, hypertonic saline solution, bandage contact lens.[4,6,8,13] Unfortunately, it was not stated whether this treatment was continued or discontinued following surgical intervention.

The medical treatment given to patients following surgical intervention also varied significantly both within and between studies. Of importance is the inconsistent use of, and duration of treatment with, BCL's. Some authors inserted BCL for patients only until corneal epithelialisation had occurred (Chawla,[23] Gharaee[24]) whereas Lin exchanged the BCL every 2–3 weeks for a period of 3 months. Pires[4] inserted a BCL in 62% of patients, and not in the remaining 38%.[12]

Medical treatment is a confounding factor which may skew the results and therefore needs to be accurately controlled and recorded. The following are suggested guidelines which may assist in minimising this bias:

- Medical treatment being used prior to intervention should either be stopped for at least one month prior to intervention or should be continued afterwards.
- New medical treatment given post intervention should be kept to a minimum as required and should stopped as soon as possible.
- Any outcomes recorded while medical treatment is still being administered should be noted as such.

5.3.2.3 Surgical intervention method

PTK: In all studies, manual corneal epithelial debridement was performed under topical anaesthetic which was followed by laser keratectomy. All the studies varied in terms of the size of central and peripheral ablation areas created and there was also no standard depth to which the stroma was ablated.

AMT: All studies performed manual epithelial debridement followed by AMT using fresh frozen amniotic membrane (AM). All authors attached the AM with the basement membrane side up. The most common method of applying the AM was using the “inlay” method. Here the AM is sutured onto the cornea over the epithelial defect. This was used by in five of the six studies. In three studies the AM was sutured directly onto the cornea whereas the other two sutured the AM into lamellar pockets created in the peripheral cornea. Espana[7] further used a second AM graft sutured over the first. Georgiadis[13] used a novel method whereby the AM was sutured onto the limbal conjunctiva thereby forming an epithelial “overlay” rather than an “inlay”.

ASP: Gomes[22] and Paris[9] applied roughly 100 punctures using a 25G needle whereas Sridhar[11] used 200 punctures using a 26G needle.

CXL: All studies used the standard Dresden protocol which consists of:

1. Manual corneal epithelial debridement following topical anaesthetic.
2. Riboflavin (0.1%) eye drops applied repeatedly for 30 min.
3. Corneal cross-linking through application of UVA (370 nm, 3 mW/cm2) for 30min while continuing to apply riboflavin drops.

There was variation in the surgical technique used in all the intervention methods besides for CXL, where set guidelines were followed. Ideally all the procedures should be standardised so that outcomes are not affected by variation in surgical technique.

5.3.2.4 Visual acuity recording

All authors used the Snellen VA grading system. Arora[6] and Sharma[25] later converted this to LogMAR for statistical analysis.

Visual acuity before and after intervention was recorded in all studies besides Maini[10]. Chawla,[23] Gomes[22] and Paris[9] commented on, but did not quantify the change in VA. Pires,[4] Espana[7] and Sridhar[11] only quantified the VA’s of patients in whom vision had improved. All the CXL studies quantified the pre and post intervention VA’s. They further calculated whether the change in VA was statistically significant.

Accurately recorded visual acuities before and after intervention are important for evaluating the effect an intervention has on this clinically relevant outcome. Unfortunately, most patients with advanced BK have very low VA and changes in VA are more difficult to quantify. A tool for accurately measuring and comparing visual function in patients with severe visual loss would be useful in these patients.

5.3.2.5 Pain score used

The methods used to qualify and quantify pain were poorly standardised which makes it difficult to compare outcomes between studies. The pain scoring methods which were used include:

Multivariate pain scores

- Qualitative ocular symptom questionnaire: Espana,[7] Gharaee[24]
    - Presence of pain, photophobia, tearing, and foreign-body sensation recorded.
- Quantitative ocular symptom scale/questionnaire:
    - Gomes:[22] Questionnaire with foreign-body sensation (0 to 3), pain intensity (0 to 3), photophobia (0 to 3), and insomnia related to pain.
    - Chawla:[23] Ocular symptom scale: Asymptomatic (0), minimal (1), mild (2), moderate (3), severe (4).
- Pain duration score: Paris[9]
    - Total duration and the duration of the worst episode of pain experienced by the patient was recorded in the preceding month was recorded as <30 min, ≤4 h or >4 h.

Univariate pain scores

- Binomial description of ocular pain as worse or better: Lin,[12] Maini,[10] Pires[4], Chansanti,[8] Srhidar. [11]
- Numeric rating score: Paris,[9] Sharma[25]
    - Patients asked to score the maximum intensity of pain experienced in the preceding 1 month period on a scale of 1–10 (1=minimal pain and 10=unbearable pain).
- Visual analog pain score (VAS): Ghanem,[5] Arora[6]
    - Patients asked to mark on a line, from 1 to 10, the point they believe represents their perception of pain. The VAS score was determined by measuring from the left-hand end of the line to the point marked by the patient in millimetres. (0=no pain, 10=unbearable pain).

Ocular symptom questionnaires are important for qualitative data capturing the complexity of patient discomfort and fluctuations in symptoms [31]. They unfortunately make it difficult to compare study outcomes and to evaluate the statistical significance of changes in symptoms following an intervention.

To determine the magnitude of pain relief afforded by an intervention quantitative pain scores are preferable. The numeric rating pain score (NRS) and VAS are both valid, easy to administer and have been shown to be highly correlated with one another. The VAS has been shown to have superior sensitivity to changes in pain score whereas the NRS has been shown to be have high test-retest reliability in patients with chronic pain conditions. The verbal numeric pain score has the advantages of being simpler for patients to perform and can be recorded telephonically.[32]

5.3.3 Study outcomes

5.3.3.1 Pain

For the PTK, AMT and ASP studies which used binomial outcomes or questionnaires, outcomes at the end of the study can be grouped into one of three categories: “No pain”, “Significantly reduced pain” or “Pain similar to baseline”. “Significantly reduced pain” refers to a reduction in pain which study participants subjectively considered as “Significant”.

Table 5: Pain outcomes and mean duration of follow up after PTK, AMT and ASP

Study	Intervention	Pain free	Significantly reduced pain	Pain similar to baseline	Mean duration of follow up
Lin[12]	PTK	88%	NA	NA	11 months
Maini[10]	PTK	NA	73%	22%	8 months
Chawla[23]	PTK	90%	10%	0%	8 months
Chawla[23]	AMT	80%	20%	0%	8 months
Pires[4]	AMT	90%	6%	4%	8 months
Espana[7]	AMT	73%	22%	NA	6 months
Chansanti[8]	AMT	NA	82%	NA	14 months

Table 5 continued: Pain outcomes and mean duration of follow up after PTK, AMT and ASP

Georgiadis[13]	AMT	88%	22%	0%	21 months
Gomes[22]	ASP	64%	7%	29%	5.5 months
Sridhar[11]	ASP	71%	29%	0%	9.5 months

AMT, Amniotic membrane transplant; ASP, Anterior stromal puncture; NA, Not analysed; PTK, Phototherapeutic keratectomy

All studies showed that the greatest proportion of participants either had no pain or a significant reduction in pain at the end of the study. Only Maini[10] and Gomes[22] report a significant number of patients with pain outcomes similar to baseline following PTK and ASP respectively. Unfortunately, there were large differences in the duration of follow up which may have affected outcomes as pain scores are likely to change over time.

The CXL studies assessed pain outcomes quantitatively using visual analog and verbal numeric pain scores. There was also better standardisation of follow up intervals. These factors allow for better comparison of CXL outcomes when compared with other studies.

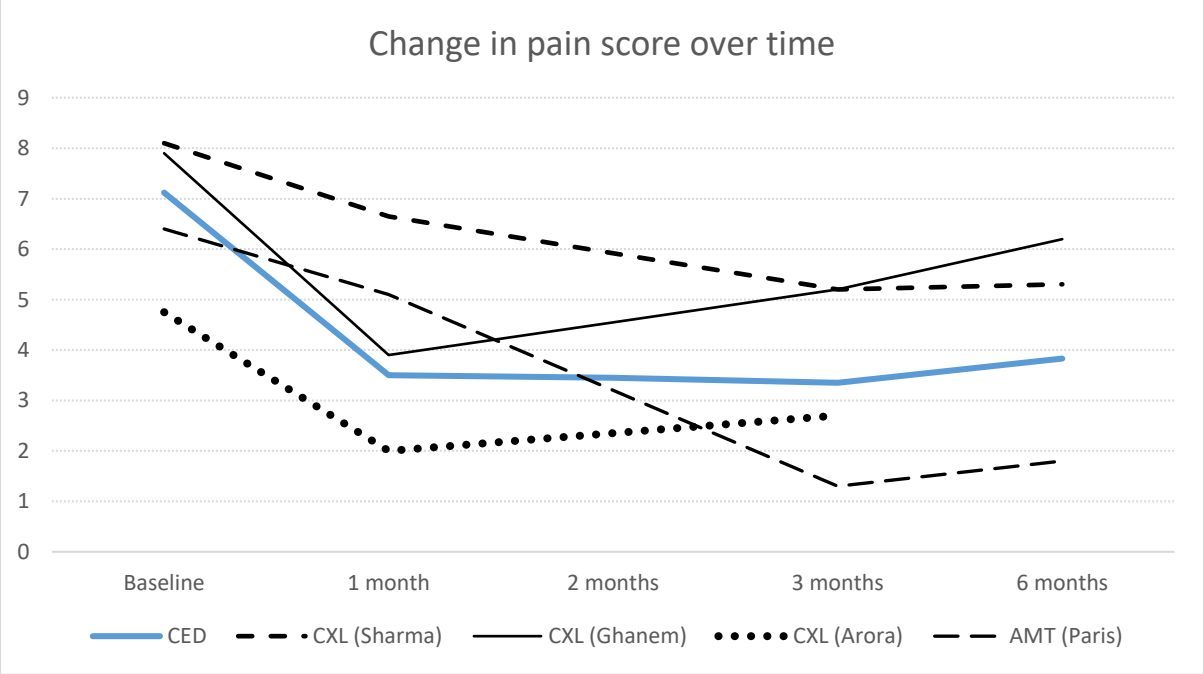

Figure 5: Changes in pain score with time following CXL

If a drop in pain score of 2 or more is considered as significant then the reduction in pain at the end of the study was significant in all except for the CXL study by Ghanem.[5] Pain scores

showed a late trend towards a return to baseline in all studies except for pain following ASP in the study by Paris.[9]

5.3.3.2 Visual acuity

For the PTK, AMT and ASP studies outcomes at the end of the study can be grouped into one of three categories: “VA unchanged”, “VA improved” or “VA decreased”.

Table 6: VA outcomes and mean duration of follow up after PTK, AMT and ASP

Study	Intervention	VA Unchanged	VA improved	VA Decreased	Duration of follow up
Lin[12]	PTK	75%	25%	0%	11 months
Chawla[23]	PTK	85%	15%	0%	8 months
Chawla[23]	AMT	92%	8%	0%	8 months
Pires[4]	AMT	76%	18%	6%	8 months
Espana[7]	AMT	77%	17%	6%	6 months
Georgiadis[13]	AMT	79%	17%	4%	21 months
Sridhar[11]	ASP	32%	25%	43%	9.5 months

AMT, Amniotic membrane transplant; ASP, Anterior stromal puncture; PTK, Phototherapeutic keratectomy; VA, Visual acuity

The number of patients who showed a significant improvement in their VA was similar across the various interventions and on average 18% of patients had improvement. 43% of participants had significantly decreased VA following ASP in the study by Sridhar[11]. This is likely due to the corneal scarring which is a well described side effect of ASP.

For the CXL studies change in VA over time can be classified as either “Statistically significant improvement” or “No significant change.”

Table 7: VA changes with time following CXL

Study	Intervention	VA at 1-2 weeks	VA at 1 month	VA at 3 months	VA at 6 months
Ghanem[5]	CXL	NA	Significant improvement	NA	No change
Gharaee[24]	CXL	NA	NA	NA	No change
Arora[6]	CXL	Significant improvement	Significant improvement	No change	NA
Sharma[25]	CXL	Significant improvement	No change	No change	No change

CXL, Corneal collagen cross-linking; NA. Not analysed; VA, Visual acuity

Although some studies showed significant improvement in VA during the first month after intervention this was not sustained and no significant change in VA was seen by 3 months.

5.3.3.3 Recurrence of bullae

All studies showed some recurrence of bullae although there was wide variation from 10% following AMT to 79% following CXL.

There appeared to be a trend towards recurrence of bullae over time in the study by Sharma[25] where bullae were seen in 6% of participants at 1 month, 24% at 3 months, and 44% at 6 months after CXL.

Table 8: Recurrence of bullae and duration of follow up

Study	Intervention	Recurrence of bullae	Duration of follow up
Lin[12]	PTK	13%	11 months
Maini[10]	PTK	24%	8 months

Table 8 continued: Recurrence of bullae and duration of follow up

Chansanti[8]	AMT	41%	14 months
Pires[4]	AMT	10%	8 months
Paris[9]	AMT	22%	6 months
Paris[9]	ASP	38%	6months
Sridhar[11]	ASP	43%	9.5 months
Ghanem[5]	CXL	79%	6 months
Sharma[25]	CXL	44%	6 months

AMT, Amniotic membrane transplant; ASP, Anterior stromal puncture; CXL, Corneal collagen cross-linking; PTK, Phototherapeutic keratectomy

5.3.3.4 Other outcomes

Corneal clarity scores were only used in the CXL studies. A similar scoring system was used in 3 of the CXL studies. Corneal clarity was graded from 1 to 4 by assessing the clarity of the iris details as viewed through the cornea. Arora[6] used an alternative grading system from 1 to 4 which graded the clarity by looking for features of progressive BK such as stromal oedema, bullae and fibrosis.

Anterior segment photographs were used by Espana[7] and Paris.[9] Photographs were used to assess the number and size of corneal bullae which may give an objective indication of disease severity. Photographs also allowed the degree of vascularisation of the cornea to be assessed which is important as vascularisation may affect KP outcomes.

Corneal sensitivity readings were recorded by Paris[9] and Gomes.[22] Both used a Cochet and Bonnet aesthesiometer.

5.3.3.5 Severe complications

3 incidences of IK were reported. One following PTK in the study by Lin[12] and 2 following AMT in the studies by Chawla[23] and Espana.[7]

5.4 Analysis of the literature on MED

5.4.1 Arguments for and against MED as a method of treating BK

The results of CXL are not full explained by the process of stromal cross linking. Although CXL has proven to provide increased resistance to stromal swelling,[33] it is not clear whether this translates into a reduced drive towards corneal epithelial oedema.

MED has been used effectively in the treatment of Recurrent corneal erosion syndrome (RCE) by increasing epithelial adhesion. Studies showed that interventions which also remove the underlying basement membrane such as Diamond burr polishing or PTK are superior to MED alonein the treatment of RCE.[19,31,32] BK differs to RCE in that the basement membrane is not inherently abnormal and therefore its removal is likely not necessary in BK, as it is in RCE.

In the study by Sharma[25] he comments: “Epithelial debridement may itself be causing a temporary effect on corneal thickness and other study variables such as pain score and BCVA”. [34]

5.4.2 Method of MED: Manual vs Alcohol assisted

The literature suggests that Alcohol delamination of the epithelium for the treatment of RCE may be superior to manual debridement.[34,35] There are however grounds for concern over the potentially toxic effects of alcohol on the endothelium.[36]

Alcohol delamination has not yet been described as part of the management of BK whereas manual debridement is well described as part of AMT, PTK, and CXL.

The evidence therefore suggests that manual debridement may be the safer method of MED in BK.

5.5 Summary of the literature

Keratoplasty remains the gold standard of treatment for BK. Anterior stromal puncture, AMT, PTK or CXL should be considered for the management of painful BK in patients with poor visual potential or without access to early keratoplasty.

ASP, AMT and PTK appear to provide long term pain relief. There was much however much variation in study methodology and the pain scores used do not allow for accurate cross analysis. This brings the study findings into question. CXL studies were better standardised and treatment was shown to provide short-term pain relief. ASP was shown to cause corneal scarring which reduced VA and may affect outcomes of future lamellar keratoplasty.

There is a feeling amongst many authors that there is still a need for a safe, cheap and effective treatment option for relieving pain in patients with bullous keratopathy. The literature suggests that corneal epithelial debridement may fulfil this requirement and indicates a need for well-constructed studies which evaluate this possibility further.

6. Identification of gaps and opportunities for further research

6.1 Gaps

1. There is a lack of long term clinical trials which compare the safety and efficacy of available treatment options.
2. Standardised surgical methods are required for ASP, PTK and AMT.
3. There is a need for a grading system to classify the severity of corneal bullae in BK.

6.2 Potential future research questions / studies

1. Is MED alone effective for reducing pain in BK?
2. MED vs CXL/PTK/AMT.
3. What is the best pain score to use when assessing patients with BK.
4. Does the number/area of corneal bullae correlate with pain score.
5. Does the CCT correlate with pain score.
6. Does lowering normal intraocular pressure reduce pain score.
7. The effect of surgical treatments on subsequent keratoplasty.
8. ROCK inhibitors and cultivated endothelial cells for the treatment of bullous keratopathy not caused by FED.
9. Alcohol debrided vs mechanically debrided MED in BK.
10. Histopathological study: Does epithelial-on CXL reduce fluid accumulation in the sub-epithelial space or only in the stroma.
11. UV exposure and safety threshold when applied to sick endothelium in BK.

7. Proposed research

7.1 Introduction

There is a gap in the literature with regards to the safety and efficacy of MED for the treatment of BK and this comprises the critical research question. This dissertation makes a meaningful contribution to knowledge in the field by establishing a new line of theory that epithelial debridement alone may be effective in reducing pain in BK. This study aims to

provide early evidence and statistical data which pave the way for further research in the field.

7.2 Primary research aims

- To evaluate the safety and efficacy of MED in the management of pain in patients suffering from symptomatic bullous keratopathy.
- To evaluate the effect of MED on visual acuity, number of corneal bullae, corneal transparency and central corneal thickness.

7.3 Secondary research aims

- Compare MED outcomes with those of other palliative treatment options.
- Serve as a pilot study for future randomised controlled trials.

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Chapter 2: Publication-ready manuscript

Authors

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Introduction

Bullous keratopathy (BK) is a disabling condition caused by failure of the corneal endothelial pump function. Stromal and epithelial oedema occurs in early disease. In later disease, sub-epithelial fluid collections produce corneal bullae. These bullae are the primary cause of discomfort and the characteristic features of BK [1-4]. In longstanding disease sub-epithelial fibrosis replaces the fluid-filled spaces[5].

The gold standard of treatment is corneal transplant, which offers both pain relief and visual rehabilitation. Unfortunately, patients may not be suitable for transplant or may not have access to transplant facilities. Many palliative surgical procedures, which aim to reduce pain in BK patients, have been described. Three of the four most widely studied interventions corneal crosslinking (CXL), amniotic membrane transplant (AMT), phototherapeutic keratectomy (PTK) and anterior stromal puncture (ASP), employ manual corneal epithelial debridement (MED) as part of the surgical procedure.

MED has been used safely and effectively in the treatment of recurrent corneal erosion syndrome[6] and has been shown to increase epithelial adherence to the underlying Bowman's membrane.[7] It follows that MED performed in the presence of BK may prevent fluid influx into the sub-epithelial space and therefore limit the formation of painful bullae. This suggests that the MED performed as part of CXL, AMT and PTK may play a significant role in the pain reduction these interventions afford to patients with BK.[8]

Materials and methods

Consecutive patients who presented to the Groote Schuur Hospital Eye Clinic with painful BK between May and December 2016 were considered for the study. Vulnerable patients, patients not willing to consent and patients with significant ocular surface disease or intraocular pressures 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. 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.

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 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 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.

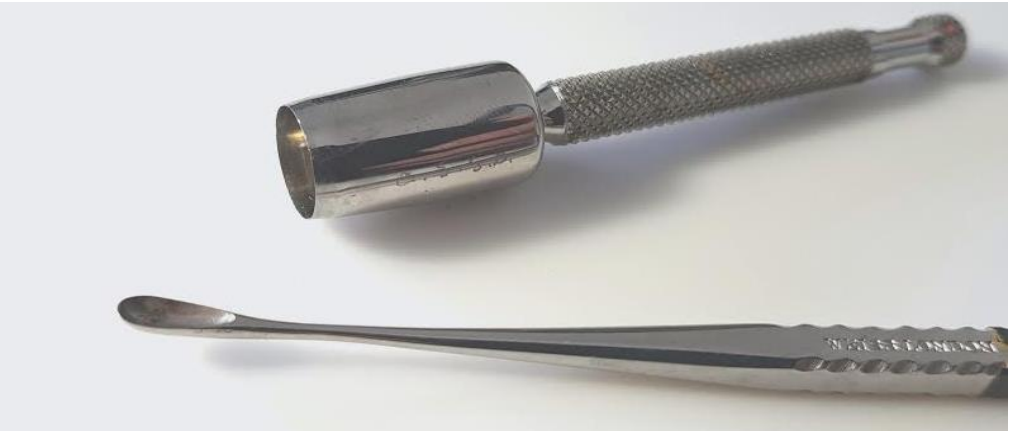

FIGURE 1: Ophthalmic spoon and 10 mm trephine used to perform MED

Oral analgesia and a topical antibiotic drop (Ofloxacin “OCTIN”, Cipla, Mumbai, India) qid were prescribed. Patients were followed up 10 days later where BCL was removed and a steroid / antibiotic combination drop (Dexamethasone / Chloramphenicol “SPERSADEX COMP”, Novartis, Basel, Switzerland) was prescribed qid for a period of 1 week. Patients were followed up again at 1 month, 2 months, 3 months and 6 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.

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 +- standard deviation. 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.

Results

A total of 15 eyes of 15 patients were included in the study. The average age of participants was 63.3 years +- 12.2 (range, 34-80 years). There were 4 men and 11 women. BK was due to trauma in 1 patient, graft failure in 2 patients, Fuch’s endothelial dystrophy in 2 patients and pseudophakic BK in the remaining 10 patients. The average duration of disease was 24 months +- 33 (range, 2-136 months).

The average pain score at time of presentation was 7.2 +- 1.7 (range, 5-10). Average pain scores were significantly decreased at all follow up visits as follows: Day 10 = 4.4 +- 2.6 (range, 1.5-9.5, $p = 0.0015$); 1 month = 3.5 +- 2.4 (range, 1-9, $p = 0.0004$); 2 months = 3.5 +- 2.4 (range, 1-8, $p = 0.0016$); 3 months = 3.4 +- 2.1 (range, 1-8, $p = 0.0003$); and 6 months = 3.8 +- 2.4 (range, 1-7.5, $p = 0.0005$). There was 1 patient lost to follow up after 1 month. A further 2 patients were excluded from statistical analysis, one after 2 months and another

after 3 months due to worsening ocular pain which required rescue treatment with hypertonic saline, lubricants, oral analgesia and BCL insertion. One patient excluded from the study defaulted her follow-up visit. She subsequently presented with an IK complicated by endophthalmitis after wearing her BCL continuously for 8 weeks. The other patient excluded from the study went on to receive penetrating keratoplasty

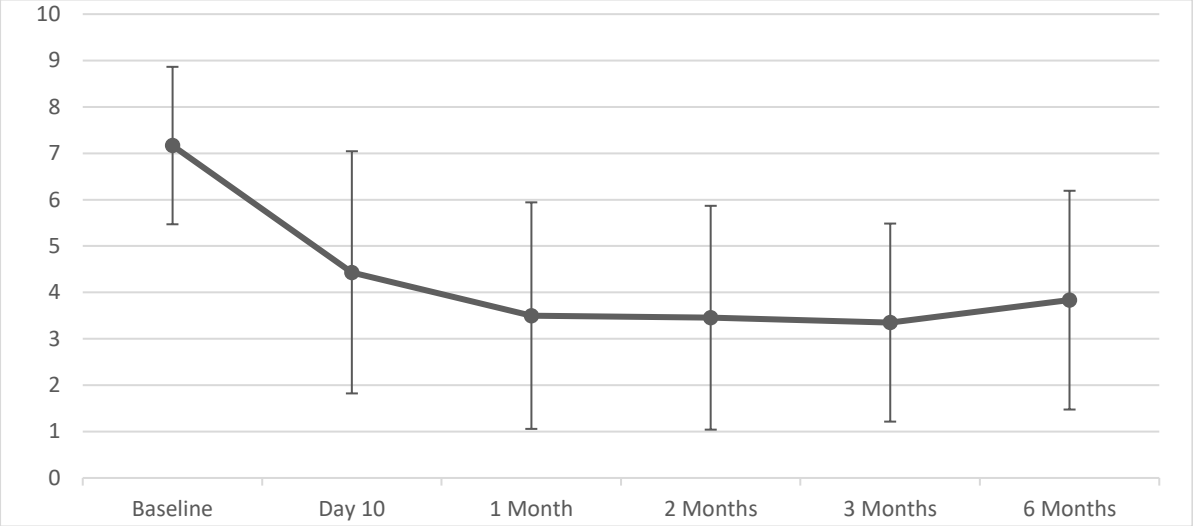

FIGURE 2: Change in NRS pain score over time following MED in BK

The average CCT was 667 µm on presentation, but this parameter was only recordable in 7 of the 15 patients. CCT was therefore excluded from further analysis.

The average corneal transparency at presentation was 2.5 +- 0.5 (range, 2-3). Baseline transparency improved in 2 patients and decreased in 1 patient at all visits following MED. There was no significant change in average corneal transparency throughout the study ($p < 0.02$).

The VA at presentation was CF in 9 patients, HM in 3 patients and NLP in 3 patients. VA improved from HM to CF at all follow-up visits in 2 patients. VA decreased from HM to NLP in one patient at the 3 months follow-up visit. Central retinal artery occlusion was suspected as the cause of visual loss due to the presence of new vessels on the iris. There was no significant change in average VA found during the study ($p < 0.005$).

At 1 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 6 months however, the size of corneal bullae remained reduced in only 30% of patients and had returned to baseline size in the other 70%.

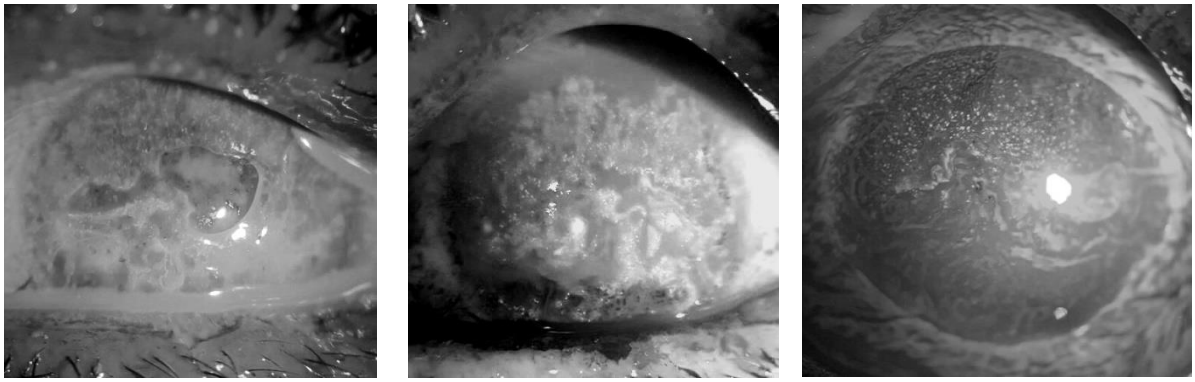

FIGURE 3: Anterior segment photography showing the size of corneal bullae in a patient at baseline, 1 months and 6 months after MED. Bullae appear as discrete or coalescent dark mounds surrounded by lakes of fluorescein.

No persistent epithelial defects were noted. One patient presented with a scleritis type picture at 2 weeks post debridement. The pain responded well to a short course of oral prednisone. No other complications were noted.

Discussion

CXL[4,8,9,10], AMT[2,3,11-14] and PTK[14,15,16] 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. 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, we found that MED was effective in reducing the mean pain score over a period of 6 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]

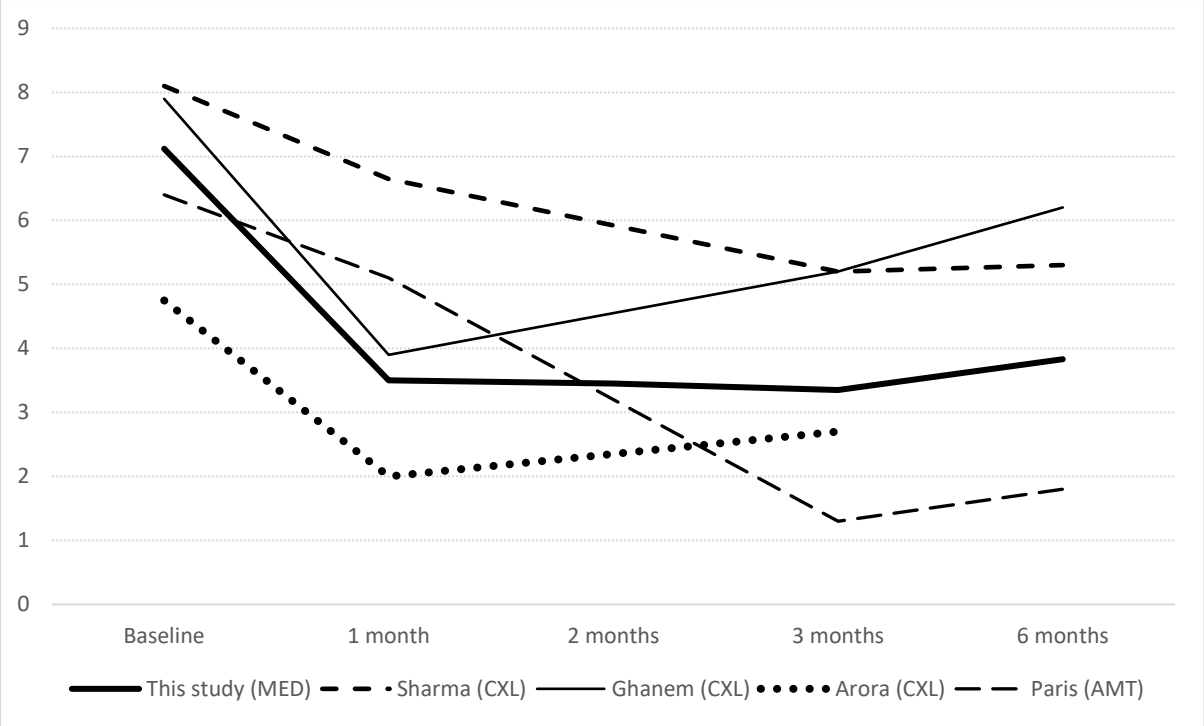

FIGURE 4: Comparison of pain score outcomes following MED, CXL and AMT for BK

All studies showed early improvement in pain scores with a late trend towards regression. AMT appears to be more effective than both CXL and MED in reducing pain scores beyond 2 months. A confounding factor in our study was that 2 patients, whose pain scores remained high at the 2 and 3 months follow-up visits, were excluded from future statistical analysis due to the initiation of rescue treatment. The pain scores at 3 and 6 months may therefore be falsely low. One patient, who had been excluded from the study, developed IK after failing to replace her BCL. This highlights the fact that contact lens wear remains the most significant risk factor for developing IK.[17] For this reason, BCL should be used with caution in the treatment of BK.

In other studies, 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”.

The PTK and AMT 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 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.

TABLE 1: Comparison of pain outcomes following PTK and AMT for BK.

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

AMT, Amniotic membrane transplant; NA, Not analysed; PTK, Phototherapeutic keratectomy

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 our patients prior to intervention was 24 months. This is the second longest duration of symptoms quoted in the relevant literature.

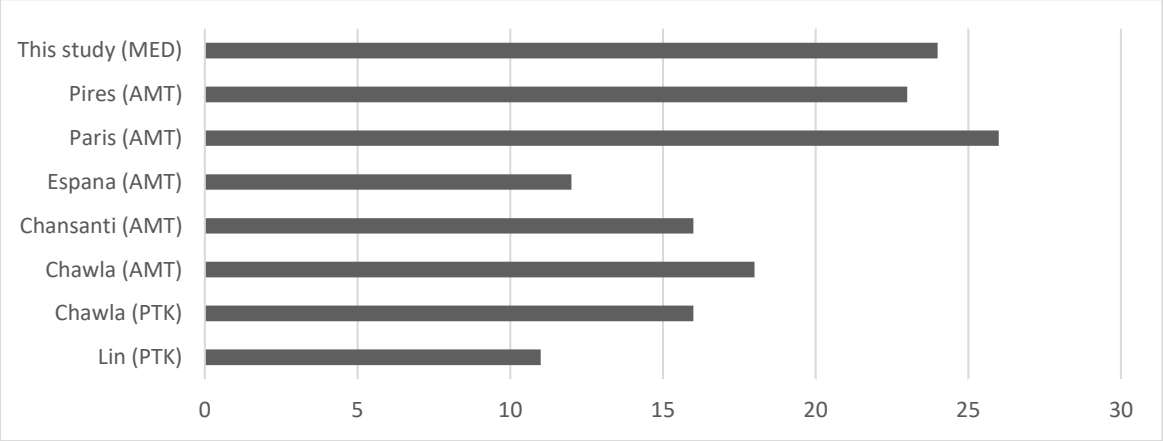

FIGURE 5: Duration of BK symptoms in months prior to MED, AMT and PTK

CCT was unrecordable in 8 of our study patients. In these patients, the odds were 4 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. However, our small study size reduces the reliability of the chi-squared test. The lack of corneal opacity following MED is desirable because eyes remain suitable for endothelial keratoplasty.

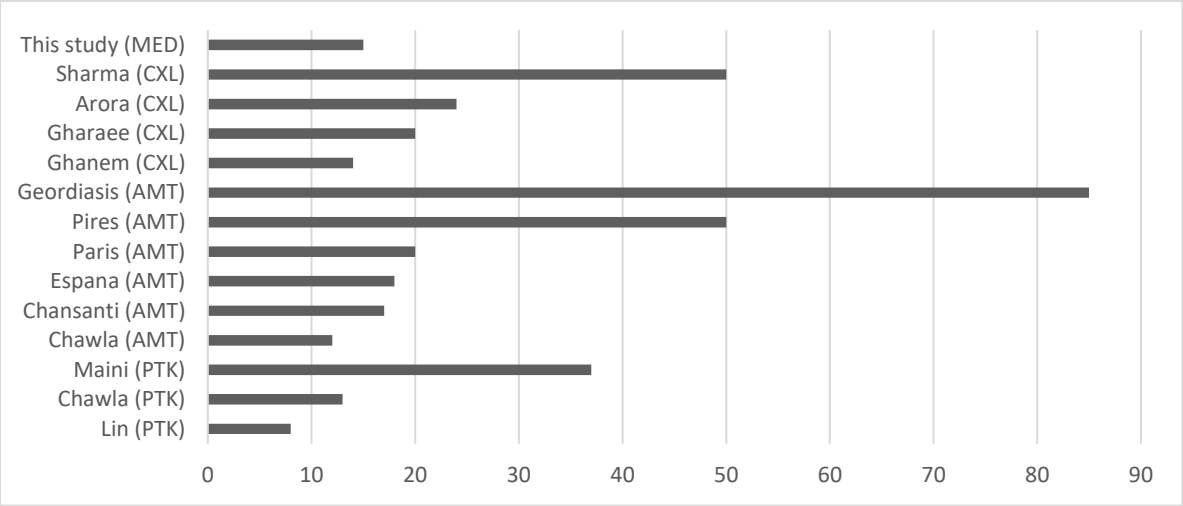

FIGURE 6: Number of participants in studies evaluating MED, CXL, AMT and PTK for BK

The size of corneal bullae, although reduced at the 1 month follow up in a large percentage of patients, returned to baseline size by 6 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.

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 6 months. MED also temporarily reduced the size of corneal bullae in most patients and shows promise as a method for treating patients who are not suitable for, or are awaiting transplant. However, our study numbers were small and there appeared to be a tendency towards regression in pain scores by 6 months. Larger and more long-term studies are required to further evaluate MED and compare it against other procedures used in the palliative management of BK.

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Appendices

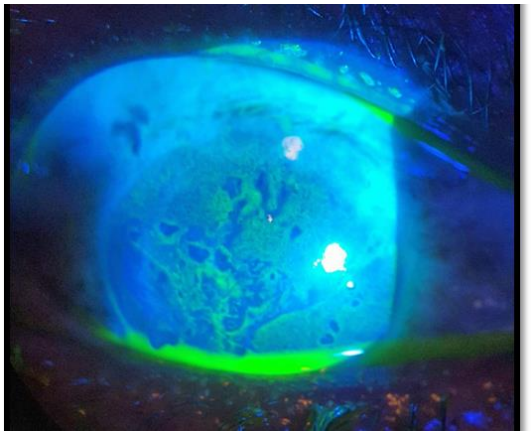
Appendix A: Informed consent

Why is this study being done?

- We would like to study whether a procedure called “Epithelial debridement”, which is helpful in another eye condition similar to yours, will work for your condition as well
- We want to test whether the procedure will decrease the pain you are experiencing
- We need to make sure the procedure is safe

Why are you being asked to take part?

- You have an eye condition called “Bullous keratopathy”. This is when blisters form on the front of the eye because of swelling in this area. These blisters cause the pain and scratchiness which you are feeling



How many people will take part in the study?

- We aim to have at least 15 people take part

How long will the study last?

- The study will be done over a period of one year from 1 May 2016 to 31 March 2017.
- You will be followed up for six months after the procedure has been done.
- At the end of these six months you and the doctor will discuss how your condition is doing and decide on what plan will be best for you going forward.

What do we do to decide if you are eligible to be take part?

- Doctor will make sure that you do have the condition known as Bullous keratopathy
- Doctor will make sure you don't have signs of other eye conditions which could put you at higher risk of having problems from the procedure
- Doctor will discuss the study with you and make sure you are happy to take part

Do you have to take part in the study?

- No. It is completely up to you whether you would like to take part in the study
- If you decide not to take part you will be treated as usual with eye drops
- You can decide to pull out of the study at any point

What will happen if you decide to take part in the study?

- After discussing any questions you have with the doctor you will need to sign this form to show that you have agreed to take part
- The procedure will be done on the earliest day that suits you and where doctor is available
- Doctor will record some information regarding your condition and also take photos of your eye
- After this the procedure will be done in the minor procedures room at the eye clinic
- You will need to return to the Groote Schuur eye clinic for check-ups at ten days, one month, two months, three months and six months after the procedure. Doctor will again record some information and take photos of your eye during these check ups

What does the procedure involve?

- The doctor will put drops in your eye for 5 minutes which will kill any germs in your eye and numb the eye so you won't feel pain during the procedure.
- Doctor will use an instrument to keep your eyelids open for you and then will rinse the eye clean.
- You will need to lie down on a bed and keep still for about five minutes while the doctor is working on your eye through a microscope
- The blisters will then be cleaned off the eye using a blunt spoon and a small sponge
- The eye will be rinsed again
- A soft contact lens will be placed on your eye to protect it while it is healing
- You will be given a follow up date

- Doctor will explain that you should come to the Groote Schuur emergency area urgently if you experience any Redness, Sensitivity to the light, decreasing Vision or worsening Pain (RSVP)
- You will go to the pharmacy to collect some pain tablets and drops which you will need to put in the eye four times a day
- You can expect the eye to become painful about thirty minutes after the procedure and this could last for around one week
- It is important that you use the drops as prescribed and keep the eye clean for the first week after the procedure. This means no swimming. You can still bath or shower but you should avoid getting water into the eye. Don't rub the eye or put your fingers into your eye. If the contact lens falls out, don't put it back in. Keep it in a container or piece of clean tissue paper and contact the doctor.

What are the benefits to you for being in the study?

- We expect the procedure to make the pain in your eye less for a period of three to six months. Note that we do not expect the pain to go away completely but only to become less.
- There is a chance that the procedure could improve your vision for a while as well
- You will be helping us to understand your condition better which may help other patients in future

What are the risks of this study?

- The biggest risk is that you could get an eye infection called "Infective keratitis" after the procedure. We will do everything possible to prevent this, but if you do get this infection you will need to be admitted to the hospital for treatment. Treatment usually means drops onto the eye every hour. If the drops don't work you might need to go for an operation.
- The other risk is that we expect that the procedure will make your pain worse for the first week after the procedure while the eye is healing
- There is also a chance that the procedure might not actually decrease your pain. Because this is an experimental procedure we cannot be sure that it is going to work.

What happens if you get hurt taking part in this study?

- This research study is covered by an insurance policy taken out by the University of Cape Town

- If you suffer a bodily injury because you are taking part in the study the insurer will pay for all reasonable medical costs required to treat your bodily injury, according to the SA Good Clinical Practice Guidelines 2006 (or latest version), which are based on the Association of the British Pharmaceutical Industry Guidelines. The insurer will pay without you having to prove that the research was responsible for your bodily injury.
- You may ask the study doctor for a copy of these guidelines.
- The insurer will not pay for harm if, during the study, you:
    - Use medicines or other substances that are not allowed
    - Do not follow the study doctor's instructions
    - Do not tell the study doctor that you have a bad side effect from the study procedure or medicines
    - Do not take reasonable care of yourself and your study medicines
- If you are harmed and the insurer pays for the necessary medical costs, usually you will be asked to accept that insurance payment as full settlement of the claim for medical costs. However, accepting this offer of insurance cover does not mean you give up your right to make a separate claim for other losses based on negligence, in a South African court.
- It is important to follow the study doctor's instructions and to report straightaway if you have a side effect from the study medicine.

What other choices do you have?

- There are drops which you can use which might help make your pain less, but often they don't help when the condition has become advanced.
- There are other surgery procedures which can be done but we don't use them here at Groote Schuur because they haven't been shown to work as well as we would like.
- The best treatment for this condition is to replace the area of the eye that is affected with the same part from another person who has died. This is called a "Corneal transplant". If you want to have it done at Groote Schuur you will be put on a waiting list. If you want to have it done sooner you can have it done at a private eye specialist.

What will happen when the study is over?

- You and the doctor will discuss how your condition is doing and decide on what treatment will be best for you afterwards.
- We will let you know what the results of the study were if you would like to know

Who will see the information which is collected about you during the study?

- Only the doctors involved in the study will see the information collected but the results of the study will be made available to the public

Who do I contact if I have any questions, comments, complaints or problems during the study?

- You can contact Dr McClunan via cell: 0846047600 or E-mail dae.mcc@gmail.com
- Alternatively you can visit the UCT Human Research Ethics Committee at the Old Main Building of Groote Schuur Hospital, Floor E52, Room 23 or phone: 021 406 6626
- If you have an emergency please go to the Groote Schuur emergency area to be seen by the casualty doctor who can then contact Dr McClunan after you have been examined

X	X	X
Doctor	Patient full name and signature	Witness (If patient Illiterate)

Appendix B: Data collection pro-forma

Day of debridement		Code
Date	/ /2016	-
Phone number		-
Age	years	-
Sex	Male / Female	
Race	African / Mixed / Indian / Asian / White	
Diagnosis	Pseudo / Fuchs / Graft / Trauma Other:	
Other important findings		
Duration of symptoms	Years Months	-
Unilateral/bilateral	Right / Left / Bilateral	
Eye with most discomfort	Right / Left	
Current treatment	BCL / Lubricants / Hypertonic Saline	
Exclusion criteria Specify	No / Yes	
Snellen visual acuity		
Pain score	/10	
Micro bullae / Macro bullae	Micro / Macro	
Corneal transparency	1 / 2 / 3 / 4	
Goldmann intra-ocular pressure	mmHg	
Central corneal thickness	µm	-
Anterior segment photo taken	Yes / No	
Discharge medication	Antibiotic drops / Paracetamol	-
Follow up date	/ / 2016	-
RSVP symptoms explained	Yes	-
Notes:		-

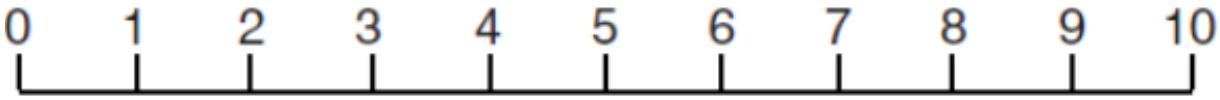
Follow up appointment: 10 days		Code
Folder number		-
Date	/ / 2016	-
Patient used antibiotic drops	Yes / No	
Average pain score	/10	
BCL in situ	Yes / No	
BCL removed	Yes	
Snellen visual acuity		
Infective keratitis	Yes / No	
Micro bullae / Macro bullae	Micro / Macro	
Corneal transparency	1 / 2 / 3 / 4	
Anterior segment photo taken	Yes / No	
CCT		
Discharge medication	SpersadexCo Other:	-
Follow up date	/ / 2016	-
Notes:		-

Follow up appointment: 1 month		Code
Folder number		-
Date	/ / 2016	-
Patient used antibiotic/steroid drops	Yes / No	
Average pain score	/10	
Snellen visual acuity		
Infective keratitis	Yes / No	
Micro bullae / Macro bullae	Micro / Macro	
Corneal transparency	1 / 2 / 3 / 4	
Anterior segment photo taken	Yes / No	
CCT		
Discharge medication	Nil Other:	-
Follow up date	/ / 2016	-
Notes:		-

Follow up appointment: 2 months		Code
Folder number		-
Date	/ / 2016	-
Average pain score	/10	
Snellen visual acuity		
Infective keratitis	Yes / No	
Micro bullae / Macro bullae	Micro / Macro	
Corneal transparency	1 / 2 / 3 / 4	
Anterior segment photo taken	Yes / No	
CCT		
Discharge medication	Nil Other:	-
Follow up date	/ / 2016	-
Notes:		-

Follow up appointment: 3 months		Code
Folder number		-
Date	/ / 2016	-
Average pain score	/10	
Snellen visual acuity		
Infective keratitis	Yes / No	
Micro bullae / Macro bullae	Micro / Macro	
Corneal transparency	1 / 2 / 3 / 4	
Anterior segment photo taken	Yes / No	
CCT		
Discharge medication	Nil Other:	-
Follow up date	/ / 2016	-
Notes:		-

Follow up appointment: 6 months		Code
Folder number		-
Date	/ / 2016	-
Average pain score	/10	
Snellen visual acuity		
Infective keratitis	Yes / No	
Micro bullae / Macro bullae	Micro / Macro	
Corneal transparency	1 / 2 / 3 / 4	
Anterior segment photo taken	Yes / No	
CCT		
Follow up date	/ / 2016	-
Discharge plan:		-



No pain	Moderate pain	Severe pain
Geen pyn	Maatige pyn	Erge pyn
Akukho ntlungu	Intlungu kancinci	Intlungu ezininzi

Appendix C: Instructions to authors

Journal of choice: Cornea

See instructions for authors at http://edmgr.ovid.com/cornea/accounts/ifauth.htm.

For the purpose of this thesis:

- The title page and abstract have been omitted
- Figures and tables are included in the text
- The text formatting differs

Appendix D: Ethics approval letter

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: sumayah.ariefdien@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

30 May 2016

HREC REF: 201/2016

A/Prof N Du Toit
Division of Ophthalmology
Ward D 4-Surgery
NGSH

Dear A/Prof Du Toit

PROJECT TITLE: EPITHELIAL DEBRIDEMENT: IS IT AN EFFECTIVE INTERVENTION TO DECREASE OCULAR PAIN IN PATIENTS SUFFERING FROM BULLOUS KERATOPATHY (MMED CANDIDATE - DR D McCLUNAN)

Thank you for your response letter dated 16 May 2016, addressing the issues raised by the Human Research Ethics Committee (HREC).

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study:-

1. The HREC note that the one old reference that suggest racial differences may affect wound healing. This of interest was not in your initial references listed in the protocol.
2. Please remove in the informed consent document under 'What other choices" the cost of Corneal transplant by a private eye specialist. This may be correct but is deemed coercive for vulnerable State participants.

Approval is granted for one year until the 30 June 2017.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

We acknowledge that the student, Dr Daemon McClunan will also be involved in this study.

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval before the research may occur.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI),and Declaration of Helsinki (2013) guidelines.
The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

HREC 201/2016