AN OBSERVATIONAL STUDY ON THE OUTCOME OF CORNEAL CROSS-LINKING FOR KERATOCONUS AT GREYS TERTIARY HOSPITAL, PIETERMARITZBURG

by

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The thesis is submitted in partial fulfilment of the requirement

for the degree of

Masters in Medicine (Ophthalmology)

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Durban
2018

PLAGIARISM DECLARATION

I, **NOLUTHANDO PUPUMA** declare that:

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DEDICATION

I dedicate this thesis to my husband and children for all the time they patiently allowed for me to complete this degree.

ACKNOWLEDGEMENTS

I would like to acknowledge Dr Carl-Heinz Kruse (my supervisor) from the Department of Ophthalmology at Greys Hospital and Prof Reitze Rodseth whose dedication made it possible for this MMed research degree to be analysed.

OVERVIEW

The purpose of this observational study was to evaluate the efficacy of corneal cross-linking for keratoconus, beginning when the procedure was performed up to a year after the procedure in patients at Greys Hospital in Pietermaritzburg, South Africa between January 2010 and December 2015.

Keratoconus is a progressive, non-inflammatory ectatic corneal disorder characterised by a progressive corneal thinning that causes irregular astigmatism and decreasing visual acuity. It is often associated with allergic conjunctivitis and seems to also have a degree of familial inheritance. Onset is during the first decade and is progressive until the third decade of life when it often seems to stabilise. Amongst the corneal ectatic diseases it remains the most common cause of debilitating progressive visual impairment during childhood and adulthood. Individuals with keratoconus form a significant proportion of patients for a practitioner specialising in corneal diseases, yet it is a disease in which the pathogenesis is poorly understood and until recently there has been no treatment (apart from corneal transplantation) that could be offered that was curative or capable of slowing the progression of the disease. Collagen cross-linking treatment using riboflavin and UV light was developed in an attempt to address this need and the initial results were promising.

Charts from a sample of 54 eyes from 49 patients aged between 13 and 35 years with keratoconus treated once with corneal cross-linking, were reviewed from the time of the procedure until 1 year after the procedure or for three consecutive follow-up visits after the procedure. Although less successful than similar studies on Caucasian patients, there was significant stability in the keratometric and pachymetry measurements. The results show that the cross-linking procedure for keratoconus is a useful conservative treatment modality to stop the progression of keratoconus. This also means that the need for corneal graft procedures is significantly reduced. The fairly minimal costs involved in this procedure compared to corneal graft procedures are also an important point to consider. More study is required to elicit whether corneal cross-linking is less successful in African patients than in Caucasians.

1 INTRODUCTION

1.1 Literature review

The cornea is the transparent anterior portion of the fibrous coat of the eye (8). In humans the cornea averages 0.52 mm in thickness at the centre and is about 0.65 mm thick at the periphery (9,10,11). The human cornea traditionally consists of five layers: epithelium, Bowman's membrane, stroma, Descemet's membrane and endothelium (9,10,11). The newly discovered Dua's layer will not be discussed. The stroma makes up approximately 90% of the thickness of the cornea and is the major structural component. The cornea's strength, shape and transparency can be attributed to the anatomic and metabolic properties of the stroma (9,10). The stroma consists of collagen, glycosaminoglycans, keratocytes and nerves. Two to three percent of the stroma consists of cellular components (keratocytes). Collagen makes up approximately 70% of the dry weight of the cornea. Type I collagen makes up the majority of the collagen in the stroma with types III, IV and VI also being present (10).

Keratoconus is a well-known ectatic condition of the cornea. *Cline et al* (6) defined keratoconus as, "a developmental or dystrophic deformity of the cornea in which it becomes cone-shaped due to a thinning and stretching of the tissue in its central area". It is the most common corneal dystrophy affecting one in 2000 people. It is an ectatic corneal disorder characterised by a progressive corneal thinning that causes irregular astigmatism and decreasing visual acuity (10). It is often associated with allergic conjunctivitis and seems to also have a degree of familial inheritance. It usually manifests itself during puberty, is usually bilateral and is more common in women than men.

A clinical description of keratoconus might include the following, a non-inflammatory, bilateral, asymmetric progressive ectasia of the cornea associated with thinning, protrusion and distortion of the cornea (12,13,14). Clinical signs of keratoconus include, Vogt's striae, Fleischer's ring, corneal thinning, corneal scarring, increased visibility of corneal nerves, characteristic topographical changes, protrusion and rupture/folding in the area of Descemet's membrane (13,14,15).

Keratoconus has a prevalence of between 50 and 230 people per 100 000 of the population depending on the criteria used to diagnose the condition (7). Its patho-physiology is undetermined, thought to include biochemical, physical and genetic factors and probably the final common pathway for several different disorders (22-24).

Aspects of keratoconus that are perhaps not clear are the clinical characteristics of the condition that are common to a particular keratoconic population of patients. For instance, what is the prevalence of Vogt's striae in that clinic population? In how many patients is it not possible to get any reliable measurements of refractive state, keratometric or topographical data? How many patients present with corneal scarring? What are the locations of the cones? The answers to the above questions are not obvious. Onset is during the first decade and the disease progresses until the third decade of life when it often stabilises.

The treatment of keratoconus can be subdivided in several entities:

1. Optimizing visual acuity with visual aids; a. Spectacle correction b. Regular contact lens fitting c. Advanced (scleral) contact lens fitting
2. Surgically by using the following methods: a. Intracorneal ring segment implantation b. Phakic toric implant lenses c. Corneal grafting procedure
3. Restoring the clarity of the scarred cornea after corneal scarring;
4. Prevention of disease progression by corneal cross-linking.

Yet, it is a disease where the pathogenesis is poorly understood and until recently there has been no treatment (apart from corneal transplantation) that could be offered that was curative or even capable of slowing the progression of the disease (1). The cross-linking of collagen refers to the ability of collagen fibrils to form strong bonds with adjacent fibrils. In the cornea, collagen cross-linking occurs naturally with aging due to oxidative deamination reactions that take place within the end chains of collagen (28). Collagen cross-linking treatment using riboflavin and UV light was developed in an attempt to address this need, and the initial results were promising. This method of therapeutic cross-linking was developed in Germany by researchers at the University of Dresden; it was later called the Dresden Protocol. The exact mechanism is not known but it is believed that riboflavin causes the release of oxygen radicals that in turn induces an oxidation reaction to create new bonds between the collagen fibrils(2).

In a first phase (until 2003) different methods of cross-linking were experimentally compared regarding efficacy and safety. The most promising method of treatment comprised UVA (370 nm) and riboflavin as a photo-mediator and was tested in pilot studies on human eyes with progressive keratoconus. Stromal keratocytes were killed up to 320 microns deep in the stroma but the delicate endothelium appeared unaffected. In 2003, the first results of these pilot studies were published (2). Surprisingly, not only a halt in progression was found, but also in more than half of the eyes treated, a regression towards a more regular shaped cornea took place.

So far, very few complications have been reported. Progression in keratometry value of 2D or more (corneal steepening), the need for a new contact lens fit, or, "patient reports of decreasing visual acuity" parameters were used in following and monitoring keratoconus progression referenced in the German study by C. G. Carus (3). The sustained effect of cross-linking as a treatment of keratoconus was proven in the later Siena Eye cross study (4) and again in the Australian study of keratoconus (5) using the three parameters, k–values, visual acuities and pachymetry.

In a resource-constrained environment such as KwaZulu-Natal, South Africa, corneal cross-linking seemed to be the ideal treatment option to prevent expensive and resource intensive corneal transplantation in keratoconic eyes. The first public facility in KwaZulu-Natal to offer cross-linking was Grey's Hospital in Pietermaritzburg. The patient profile in the first few years was mostly black African, but with time, Caucasian, Indian and patients of mixed race were all included. This will be the first study to evaluate the effectiveness of corneal cross-linking in keratoconus in this patient group.

1.3 Hypothesis

To prove that the corneal cross-linking procedure is an effective method of treatment in patients with progressive keratoconus.

2 PUBLICATION READY MANUSCRIPT

Abstract

Background: Keratoconus is a progressive non-inflammatory corneal disorder where the normally spherical corneal structure progressively assumes a cone shape, thereby distorting vision and decreasing the quality of life from a young age. Cross-linking remains the only procedure for keratoconus that can be used to halt the progression of the disease. Greys Hospital is one of the few KwaZulu-Natal government hospitals that offers cross-linking and has shown good results preventing blindness from keratoconus.

Evaluate: the outcome of corneal cross-linking in Greys Hospital in patients between the ages of 13 and 35 years.

Setting: Patients from the Greys Hospital clinical records of cross-linking procedures performed for keratoconus.

Methods: An observational, descriptive quantitative chart review study was conducted on charts for patients who had corneal cross-linking for keratoconus between January 2010 and December 2015.

Results: A total of 54 eyes from 49 patients were analysed from the records, 2 eyes progressed post cross-linking on both K-max and pachymetry values. 12 eyes showed an increase on K-max readings only and 16 showed progression on pachymetry only.

Conclusion: The study showed that cross-linking for keratoconus is a safe and effective method of treating progressive keratoconus but seems less effective than in comparative studies done in the first world.

Introduction:

Keratoconus is an ectatic non-inflammatory corneal disorder characterised by progressive corneal thinning that causes irregular astigmatism and decreasing visual acuity. It is often associated with allergic conjunctivitis and seems to also have a degree of familial inheritance. Onset is during the first decade and it progresses until the third decade of life when it often stabilises. Amongst the corneal ectatic diseases it remains the most common cause of debilitating progressive visual impairment in the childhood and young adult phases of life.

Individuals with keratoconus form a significant proportion of patients for an eye practitioner managing corneal diseases. Yet, it is a disease where the pathogenesis is poorly understood and until recently there has been no treatment (apart from corneal transplantation) that could be offered that was curative or even capable of slowing down the progression of the disease (1). Collagen cross-linking treatment using riboflavin and UV light was developed in an attempt to address this need and the initial results were promising (2).

Until 2003, different methods of cross-linking were experimentally compared regarding efficacy and safety. The most promising comprised of UVA (370 nm) and riboflavin as a photo-mediator and was tested in pilot studies on human eyes with progressive keratoconus. Stromal keratocytes were killed up to 320 microns deep in the stroma but the delicate endothelium appeared unaffected.

In 2003, the first results of these pilot studies were published (2). Surprisingly, not only a halt in progression was found, but in more than half of the eyes treated regression toward a more regular shaped cornea occurred. So far, very few complications have been reported. Progression of 2D or more keratometry value (corneal steepening), the need for a new contact lens fit, or “if a patient reports of decreasing visual acuity" were used in following and monitoring keratoconus progression in the German study by C.G. Carus (3).

The sustained effect of cross-linking as a treatment of keratoconus was proven in the later Siena Eye cross study (4) and again in the Australian study of keratoconus (5) using the three parameters; k–values, visual acuities and pachymetry.

Meiri Z et al. [19] did a review and meta-analysis of the efficacy of collagen cross-linking where they found that there was an improvement in Snellen Chat visual acuity of 1 to 2 lines at 3 months or more post corneal collagen cross-linking. They further found some topography parameters also improved by 0.6 – 1 D in 12 to 24 months post collagen cross –linking. Meiri et al. made an interesting discovery of decreased endothelial cell density by 225 cells per square millimetre in the first 3 months and thereafter returned to normal. Corneal thickness was reduced by 10 – 20 nm in the year following corneal cross-linking but not after 12 months. It was then concluded that corneal collagen cross-linking is a safe and effective method for halting the progression of keratoconus, while slightly improving visual acuities.

In a resource-constrained environment such as KwaZulu-Natal, South Africa, corneal cross-linking seemed to be an ideal treatment option to prevent expensive and resource intensive corneal transplantation in keratoconic eyes. The first public facility to offer cross-linking in KwaZulu-Natal was Grey's Hospital in Pietermaritzburg. The patient profile in the first few years was mostly black African but Caucasian, Indian and patients of mixed race were included. This will be the first study to evaluate the effectiveness of corneal cross-linking in keratoconus across the different population groups. In this study, the researcher hopes to show that corneal cross-linking is a safe and effective method of treating keratoconus.

Research methods and design

Charts from all patients with keratoconus, treated once with corneal cross-linking were reviewed from the time of the procedure up to 1 year after the procedure. The patients were taken from recorded data from the Greys Hospital keratoconus clinic. Each eye was treated as an "individual" and was given a unique study number. Preoperative readings were compared with visits taking place within 180 days (early) of the procedure and visits taking place 180 days after the procedure (late). The reasons for dividing the visits into early and late groups are as follows:

1. Visits for the different patients did not occur at regular intervals. Some patients complete three visits within the first six months then default further follow-up, while others might only come late due to transport and other reasons.
2. The researchers wanted to see the difference between pre-treatment and end-result but also whether further changes occur in this population later than six months after the treatment.

The inclusion criteria included, keratoconic eyes that had received a corneal cross-linking procedure done in Grey's Hospital, Pietermaritzburg between January 2010 and December 2015.

The sample consisted of both males and females between the ages of 13 and 35.

The following patients were excluded:

1. Patients who had less than 3 follow up dates since the procedure, irrespective of the time after treatment.
2. Cross-linking done in patients for any other indication other than for keratoconus.
3. Ocular or central nervous system disease other than keratoconus which prevents good vision.

The study looked at the corneal steepness, keratometry, K-values (D) and pachymetry (μm) as primary outcome indices to determine whether corneal cross-linking improves corneal stability in the profile of patients.

- A pachymetric failure-of-treatment is defined as a loss of at least 25 μm in thickness from baseline thinnest area of the cornea.
- A keratometric failure-of-treatment is defined as a gain of at least 2 dioptres steepening in the K-maximum.

The researchers used the Liu method to determine the optimal cut-points. When looking at the data for prediction the researchers were searching for variables before the corneal cross-linking procedure that could predict treatment failure. The age was tested, pre-treatment keratometry and pre-treatment pachymetry readings using logistic regression. The analysis aimed to predict combination (pachymetry + keratometry) as well as failure-of-treatment of the individual indices (pachymetry fail or keratometry fail separately).

Permission to conduct the study was granted by Greys Hospital, the KwaZulu-Natal Department of Health and the BREC committee in the University of KwaZulu-Natal. BREC permit number – BR489/15

Results:

54 eyes of 49 patients were found to fulfil the criteria for entrance into the study.

Follow-up times in the study cohort were not regular therefore all follow up visits were divided into one of two time frames: < 180 days (early) and > 180 days (late). This also allowed us to get an idea whether stabilisation of the cornea keeps increasing more than six months after the treatment.

The average age in the "early group" of visits was 22.3 years with a standard deviation (SD) of 4.94 years pre-surgery, the average keratometry was 57.1 D (SD= 3.89 D), and average corneal thickness was 425.94 µm, with an average follow-up of 114.19 days. The average post-surgery keratometry was 56.93 dioptre and the pachymetry was 415.06 µm. The Wilcoxon sign rank test shows that there is no difference between these two groups for dioptres (p = 0.582) or pachy (p=0.4367) values pre and post procedure. Only 5 eyes out of 42 showed worsening of dioptre values and 4 out of 36 showed further thinning based on pachymetric values. Of the above eyes that worsened only one eye failed to stabilise on both indices.

Variable	Obs	Mean	Std. Dev.	Min	Max
age	42	22.14286	5.53733	13	39
pred	42	50.1631	3.890907	43.3	58.9
prep	42	428.7619	45.59622	304	523
follow	42	121.4048	39.70136	31	185
postd	42	50.9481	5.035051	43.2	70.95
postp	42	415.0714	50.40538	297	498
dchange	42	.7850002	2.925887	-5.100002	12.05
pchange	42	-13.69048	46.23349	-160	82

Figure 1: Summary of population in the group with early follow-up

The “late group” had an average age of 21 years at first visit (SD= 4.95 years). Average baseline keratometry was 56.78 D (SD= 5.8 D), and pachymetry was 425 µm.

The changes in pachymetry and keratometry post procedure was 11.73µm and the dioptre change was -0.373, both the changes are not significant. (pachy p = 0.0551 and keratometry p = 0.3747)

Variable	Obs	Mean	Std. Dev.	Min	Max
age	41	21.31707	4.951964	13	29
pbase	41	425	42.57229	327	543
dbase	41	56.77805	9.022625	44.6	81.4
dlong	41	57.15122	8.566216	47.5	79.8
plong	41	413.2683	40.88889	331	513
pchange	41	11.73171	36.00766	-62	109
dchange	41	-.3731707	3.447827	-8.2	9.4

Figure 2: Summary of population in the group with more than 180 days follow-up

3.2 Failure rates

An analysis of the failure rate of treatment in the long term group revealed that looking at the overall failures on this group it was observed that when it comes to keratometry there were 7 eyes out of out of 41 that failed and 12 out of 41 eyes continued to progress on pachymetry, only one eye failed on both.

3.2.1 Combination failure

Results using age, pre-treatment dioptre and pre-treatment pachymetry readings gave no variables to use as predictors for combined indices failure.

For the outcome on dioptre failure only the dioptre baseline value is a statistically significant variable. When looking at the outcome of pachymetry failure on its own, the baseline pachymetry seems to be most important but is not statistically significant.

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. tabulate combofail
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combofail	Freq.	Percent	Cum.
0	23	56.10	56.10
1	18	43.90	100.00
Total	41	100.00	

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. roctab combofail age
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Obs	ROC Area	Std. Err.	Asymptotic Normal [95% Conf.	Interval]
41	0.5435	0.0931	0.36100	0.72595

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. roctab combofail pbase
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Obs	ROC Area	Std. Err.	Asymptotic Normal [95% Conf.	Interval]
41	0.5459	0.0978	0.35414	0.73765

Fig. 3 ROC prediction curves

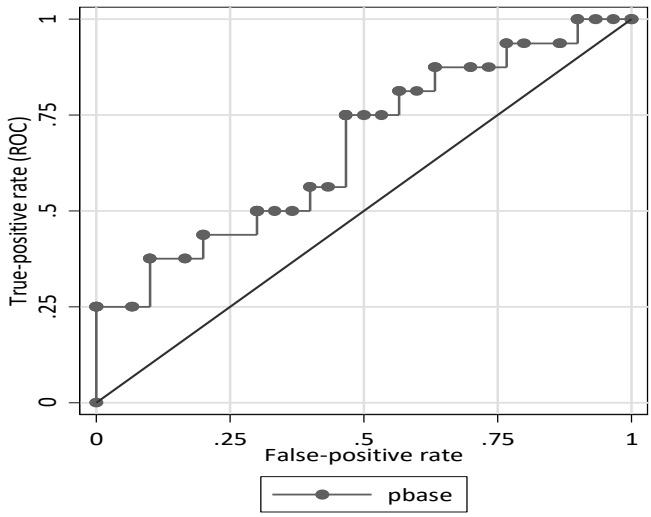

Fig 4. **ROC prediction curves displaying the predictive effect of baseline pachymetry on treatment failure.**

The optimal discrimination point for pachymetry in this study is at 450µm thickness and is the value that best separates the study population into two groups – failure and success. This implies that stability is more likely to occur with an initial corneal thickness of more than 450µm than with thinner corneas. The age of 20.5 years is also a threshold but not nearly as powerful as pachymetry in predicting treatment failure and probably has no significance in clinical practice. The sensitivity at cut-point was determined at 0.44 and the specificity at 0.78.

There was overall stability in the keratometry and pachymetry measured between the three time periods. Stabilization or improvement was seen in 28 out of the 36 eyes in the early follow-up group and in 23 out of 41 patients in the late follow-up group. Failures generally occurred in only one of the indices and only one patient had a treatment failure on both thinning and steepening of the cornea.

Discussion:

The main finding in this study was that only 8 eyes had failed out of the sample group of 36 and 7 eyes out of the 41 who had a longer follow up period. There was no statistical difference of treatment failures between the two groups. In this study, therefore, the cornea did not seem to increase or decrease in stability more than six months after the treatment.

We found that most failures came from the continued thinning of the cornea whilst the dioptres were still steady. This was considered as statistically significant for this study. Of the above numbers only one eye progressed in both the k-max and pachymetry parameters. This was considered statistically significant for the study. Age did not seem to have a significant contribution in terms of those who seemingly progressed but perhaps that also speaks to the criteria that the patients were only between the ages of 13 and 35 and not falling within the paediatric age bracket.

Chunyu et. al [32] did a meta-analysis where they concluded that cross-linking for keratoconus in patients followed for 1 year showed a statistical significance at 12 months post procedure. In the current study, the above behaviour was seen with a significant stabilisation in K- max and pachymetry values.

A study of 23 patients by Wollensak et al. (2) on collagen cross-linking showed that in *all* treated eyes, the progression of keratoconus was at least stopped. 16 eyes (70%) showed regression of the ectasia with a reduction of the maximal keratometry readings by at least 2 dioptres and improvement of the refractive error by 1.14 dioptres was found. These results are substantially better than the results on the current study population group.

In a study done by Hersch and Greenstein (4) the results of cross-linked eyes showed that maximum K-value worsened between baseline and 1 month, followed by improvement between the first and third month and stabilization thereafter. The above phenomena were also observed in the current study aligning with previous findings in studies done on the subject. Similar observations were made by Raiskup-Wolf et al (3) who showed that the best corrected visual acuity (BCVA) improved significantly (≥1 line) in 53% of 142 eyes in the first year, 57% of 66 eyes in the second year and 58% of 33 eyes in the third year or remained stable (no lines lost) in 20%, 24% and 29% respectively.

A significant number of the patients seen with keratoconus at Greys Hospital also have allergic conjunctivitis or vernal keratoconjunctivitis as it has been found that there is a proven association between keratoconus and chronic ocular allergies [30]. Amongst the points of concern the researchers speculated whether keratoconus and ocular allergies in the African population give the same outcomes as other populations where there is less ocular allergy involved. In the study researchers suggested that atopy, positive family history and smoking are not independent factors affecting corneal cross-linking outcomes.

The outcome of this study was not as favourable as the other prominent studies although the results were significant enough to support the hypothesis. Poli et. al [31] conducted a study in which they looked at patients who had cross-linking for keratoconus and showed that from 1 month up to 6 years in some patients the results may not be as favourable as one expects. They noted that after 1 year moving towards the 6 year period there was a notable improvement in the patients' parameters including visual acuity. The above study prompts for a study looking at long term effects of corneal cross-linking on these current patients.

Meiri Z. et al [19] also noted in his study that corneal thickness in some individuals who have had corneal cross as a mode of treatment for keratoconus tend to decrease in thickness up to a period of 24 months but not beyond. This is perhaps the same phenomena observed in the current study, hence a longer period of observation could reveal more on the corneal behaviours post cross-linking.

Limitations and strengths

Greys Hospital is the only hospital that offers corneal cross-linking for the Uthungulu district and it is a referral hospital. This study is the first conducted to assess the outcome of cross-linking in patients from the Ethekwini and Uthungulu districts.

Despite many challenges including late referrals, poor transport systems, financial constraints and staff shortages the team at Greys Hospital continues to manage keratoconus to the above mentioned districts.

Limitations for this study included having a fairly small sample group with varying dates for follow up, therefore the comparison between them is not as accurate as the researchers desired it to be. Dividing the visits into early and late visits aimed to standardise the data more effectively.

The sample included patients who had cross-linking done using the hypotonic riboflavin solution and there is no indication of how many of these patients were included in the study. All patients, however, had "epi-off" cross-linking, where riboflavin is administered to the cornea after a portion of the epithelium had been removed.

Another limitation is that the data from the patients during the time of consultation and examination was taken by different medical officers that worked in the department at the time, therefore, there is a chance of positional variations on the parameters depending on the skill of the officer. Most data, however was taken directly from the Pentacam equipment which adds a degree of objectivity.

Some patients that had the procedure done had mild to moderate ocular allergies and they were marked during the period of the procedure or collection to see if the presence of ocular allergies made a difference in the outcome of cross-linking in those individuals.

Lack of visual acuities as a measure of the procedure outcome is possibly the biggest limitation of this study since our aim in treating is to preserve/ improve visual function in our patients.

Implications and recommendations:

Corneal cross-linking for keratoconus is still a safe and valid means of halting progression of the disease. A longer follow up study to determine the behavioural pattern post procedure will reveal more in terms of the outcome.

The threshold of 450µm corneal thickness in predicting stability after treatment is, at least partly, to be expected since thicker corneas should logically be more stable from the outset. It might, however, be prudent when counselling patients about the relative success of corneal cross-linking depending on initial corneal thickness.

This study leaves us with many questions in terms of contributors to the rate of success or failure in the African setting. It would be of interest to look at the effect of ocular allergies and the outcome of cross-linking in the African population as a research topic in the future. The effect of earlier referral, larger age differences, treatment with hypotonic vs. isotonic riboflavin, and "epi-on" corneal cross-linking still require researching in a South African population.

Conclusion:

These results show that cross-linking for keratoconus is a useful conservative treatment modality to halt the progression of keratoconus. The need for corneal graft procedures is subsequently significantly reduced. The fairly minimal costs involved in this procedure compared to corneal graft procedures are also an important point to consider. Results in African patients might, however, be poorer than in Caucasian eyes for as yet unknown reasons.

Acknowledgements:

Statistical support by Prof R. Rodseth is greatly acknowledged.

Competing interests:

The authors declare that they have no financial or personal relationships which may have inappropriately influenced them in writing this article.

Authors' contributions:

Dr N Pupuma (University of KwaZulu-Natal) was principal investigator in this study and was responsible for conceptualisation of the study, acquisition of the data and the writing of the manuscript. Prof R. Rodseth was responsible for the analysis of the data. Dr C-H Kruse (University of KwaZulu-Natal) reviewed and edited the manuscript. All authors read and approved the final version of the manuscript.

Funding: No funding was received for this study

Disclaimer: The views expressed in this article are my own and are not an official position of the University of KwaZulu-Natal.

References

1. Ashwin PT, McDonnell PJ. Collagen cross-linkage: a comprehensive review and directions for future research. Br J Ophthalmol. 2010 Aug; 94(8):965–70.

2. Wollensak G, Spoerl E, Seiler T. Riboflavin/ultraviolet-a-induced collagen cross-linking for the treatment of keratoconus. Am J Ophthalmol. 2003 May; 135(5):620–7.

3. Raiskup-Wolf F, Hoyer A, Spoerl E, Pillunat LE. Collagen cross-linking with riboflavin and ultraviolet-A light in keratoconus: long-term results. J Cataract Refract Surg. 2008 May; 34(5):796–801.

4. Hersh PS, Greenstein SA, Fry KL. Corneal collagen cross-linking for keratoconus and corneal ectasia: One-year results. J Cataract Refract Surg. 2011 Jan; 37(1):149–60.

5. Wittig-Silva C, Whiting M, Lamoureux E, Lindsay RG, Sullivan LJ, Snibson GR. A randomized controlled trial of corneal collagen cross-linking in progressive keratoconus: preliminary results. J Refract Surg Thorofare NJ 1995. 2008 Sep; 24(7):S720-725.

6. Rabinowitz YS ; Keratoconus. Survey of Ophthalmology 1998;42, 297 - 319

7. Cline D, Hofstetter HW, Griffin JR. Dictionary of visual science. Boston: Butterworth-Heinemann, 1997.

8. Warwick R. Eugene Wolff's anatomy of the eye and orbit. London: HK Lewis and Co, 1976.

9. Fatt I, Weissman BA. Physiology of the eye: an introduction to the vegetative functions. Stoneham: Butterworth-Heinemann, 1992.

10. Krachmer JH, Mannis MJ, Holland EJ. Cornea 2nd ed Vol I Fundamentals, diagnosis and management. London: ElsevierMosby, 2005.

11. Ruskell GC. Anatomy and physiology of the cornea and related structures. In: Contact lenses 3rd ed. Eds: Phillips AJ, Stone J. London: Butterworths, 1989.

12. Arffa R. Graysons diseases of the cornea 4th ed. St Louis: Mosby, 1997. 7. Nelson DC, Cox MM. Principles of biochemistry 4ed. New York: WH Freeman and Co, 2005

13. Woodward EG. Contact lenses in abnormal conditions: kerataconus. In: Phillips AJ, Stone J. eds. Contact lenses 3rd ed. London: Butterworths, 1989 pp748-757.

14. Khachikian SS, Belin MW. Clinical characteristics of keratoconus. In: Wang M. ed. Keratoconus and keratoectasia. New Jersey: Slack incorporated, 2010 pp 3343.

15. McMahon TT, Szczotka-Flynn LB. Contact lens applications for ocular trauma, disease and surgery. In: Bennett ES, Weissman BA. Eds. Clinical contact lens practice. Philadelphia: Lippincott Williams and Wilkins, 2005 pp568571.

16. Harminder S. Dua: MD, PhD; Lana A. Faraj, MD MSc; Dalia G. Said, MD, FRCS; Trevor Gray, MSC, James Lowe, MD FRC-Path: Human corneal anatomy redefined, Dua's layer.

17. Epstein RI, Chiu YL, Epstein GL: Pentacam HR criteria for curvature change in Keratoconus and post – op LASIK ectasia.

18. Meiri Zohar BMedSc, Keren, Shay MD, Rosenblatt, Amir MD, Sarig. : Efficacy of corneal collagen cross-linking for the treatment of Keratoconus; a systematic review and meta-analysis. *Cornea.2016 Mar;35(3) : 417 – 28*

19. Kanellopoullos, Asimellis G.; Anterior segment OCT; assisted topographic corneal epithelial thickness distribution imaging keratoconus patient. *Cornea,Nov.2013.Vol 13 issue 11 p 1493 -1498*

20. Jing Jing Li, Peng Ji, Xiaoti Lin: Efficacy of Corneal for treatment of keratoconus, Meta- analysis of randomized controlled trials.

21. Javadi MA, Motlagh BF, Jafarinasab MR, et.al; Outcomes of penetrating keratoplasty in patients with keratoconus. *Am J Ophthalmol 2005 ; 24:941 - 6*

22. Reeves SW, Stinett S, Adelman RA, et al. : Risk factors for progression to penetrating keratoplasty in patients with keratoconus.*Am J. Ophthalmol 2005; 140: 607 – 11*

23. Mamalis N., Anderson CW, Kreisler KR et al. ; Changing trends in the indication for penetrating keratoplasty *Arch Ophthalmol 1992 ; 110 : 1409 – 11*

24. Joshua K. Duncan, Michael W Bein and Mark Borgstrom: Assessing progression of keratoconus; novel tomographic determinants. *Eye and Vision journal ; 2016 : 3 – 6*

25. Barbara R, Castllo JH, Hanna R, Berkowitz E, Tiosano B, Barbara A ; Keratoconus Expert meeting, London : 2014. *J Kerat EctCor. Dis 2014 : 3(3) : 141 – 8*

26. Sykakis E, Karim r, Evans JR, Bunce C, Amissah – Arthur KN, Patways S et al. : Corneal cross –linking to halt progressionof keratoconus. *Cochrane Database System Rev. 2015; 3 :CD010121*

27. Emma Davies, MD, Kathryn Colby,MD, PhD : Controversies Corneal Collagen Cross – linking ; *International Ophthalmology clinics : October 2015 –Volume 55, Issue 4 p.1-11*

28. Hasan Razmjoo, Alireza Peyman, MD and Hoda Jafari Modrek : Corneal collagen cross-linking for keratoconus : a comparison between accelerated an conventional methods*; Advbiores.net,Nov 2017,IP:50.7.155.93*

29. Hidenaga Kobashi and Shi Song Rong: Corneal Collagen Cross-Linking for Keratoconus: Systematic *Review ; Published 11 June 2017 Hindawi BioMed Research International*

30. Namrata Sharma,[1] Kavita Rao,[2] Prafulla K Maharana,[1] and Rasik B Vajpayee, : Ocular allergies and Keratoconus ; Indian Journal of Ophthalmology ; I*ndian J Ophthalmol. 2013 Aug; 61(8): 407–409.*

31. Poli M, Lefevre A, Auxenfans C, Burillon C. : Corneal collagen cross-linking for the treatment of progressive corneal ectasia: 6-year prospective outcome in a French population. *Am J Ophthalmol. 2015;160(4):654.e1–662.e1*

32. T. Chunyu, P. Xiujun, F. Zhengjun, Z. Xia, and Z. Feihu, "Corneal collagen cross-linking in keratoconus: a systematic review and meta-analysis*," Scientific Reports, vol. 4, article 5652, 2014.*

6. APPENDICES

6.1 THE FINAL STUDY PROTOCOL

UNIVERSITY OF KWAZULU-NATAL
COLLEGE OF HEALTH SCIENCES
SCHOOL OF CLINICAL MEDICINE

Title: The outcome of corneal cross-linking for keratoconus in Greys Hospital, Pietermaritzburg

Degree: MMed(Ophth)

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EXECUTIVE SUMMARY

Statement of purpose:
The purpose of this observational study is to understand the 6-month efficacy of corneal cross-linking for keratoconus in patients at Greys Hospital in Pietermaritzburg between January 2010 and December 2015.

This study is necessary because aims to help health workers understand the process and effect of corneal cross-linking for keratoconus in the South African patient population. Trials on keratoconus have been done mostly in first world countries with Caucasian patients. Data and trials that include South African patient populations and how they respond to this type of treatment is still lacking

The study will be conducted in the following way:

I am going to collect the records of patients who have had corneal cross- linking for keratoconus. I will find patients between the ages of 13 and 30. The following data will be collected comparing the values before corneal cross-linking with the 2 consecutive values after the procedure K-values (steepest, flattest and average) Pachymetry

The output from this project will mainly be for my MMed thesis research. Improved patient care and health care recommendations are the desired products of my study.

THE PROTOCOL

1. DEFINING THE RESEARCH PROBLEM

Keratoconus is a progressive eye disease in which the normally round cornea thins and begins to bulge into a cone-like shape. This cone shape deflects light as it enters the eye on its way to the light-sensitive retina, causing distorted vision.

Keratoconus usually starts in the teenage years. It can, however, begin in childhood or in people up to about age 30. It is possible in people aged 40 and older, but this is less common. The changes in the shape of the cornea can happen quickly or may occur over several years. The changes can result in blurred vision, glare and halos at night and the streaking of lights. The changes can stop at any time, or they can continue for decades. There is no way to predict how the condition will progress. In most people who have keratoconus, both eyes are eventually affected, although not always to the same extent.

Keratoconus is the spontaneous weakening and stretching of the cornea and usually develops in one eye first and then later in the other eye. With severe stretching the back of the cornea can tear, swell and take many months for the swelling to go away. This often results in a large corneal scar. Treatment of early keratoconus is eyeglasses. If eyeglasses do not provide adequate vision, then contact lenses, usually rigid gas permeable contact lenses, may be recommended. Eventually, the cornea can become so thin and scarred that a corneal transplant is required – unless there is a method to stop progression of the disease.

A treatment called corneal collagen cross-linking is effective to help prevent progression of keratoconus. Performing cross-linking on these corneas can also avoid the change in lifestyle associated with loss of vision, corneal transplant and the limitations thereof.

2. LITERATURE OVERVIEW AND

MOTIVATION

Background and Literature:

Individuals with keratoconus form a significant proportion of patients for a practitioner specialising in corneal diseases. Yet it is a disease where the pathogenesis is poorly understood and until recently, there has been no treatment apart from transplantation that could be offered that was curative or even capable of slowing the progression of the disease. [1] Collagen cross-linking treatment using riboflavin and UV light has been developed to address this need and the initial results are promising. [6]

During the first phase, (until 2003) different methods of cross-linking were experimentally compared regarding efficacy and safety. As the most promising compromise the use of UVA (370 nm) and riboflavin as a photo mediator was tested in pilot studies on human eyes with progressive keratoconus. In 2003, the first results of such pilot studies were published. Surprisingly, not only a halt in progression was found but in more than half of the eyes treated a progression towards a more regular cornea took place. So far, very few complications have been reported. Keratocytes are killed up to 320 microns deep in the stroma but the delicate endothelium appears unaffected. Worldwide, nine cases of therapy-refractory corneal melting were treated by means of UVA/riboflavin cross-linking and in 8 of the 9 cases the melting process was stopped.

The sustained effect of cross – linking as a treatment of keratoconus were proven in the Siena Eye cross study[4] and again in the Australian study [5]of keratoconus using the same parameters as k–values and pachymetry.

KEY REFERENCES:

P T Ashwin, P J McDonnell. Collagen cross-linkage: a comprehensive review and directions for future research. Br J Ophthalmol 2010; 94:965-970

Wollensak G, Spoerl E, Seiler T. Riboflavin/ultraviolet-a-induced collagen cross-linking for the treatment of keratoconus. Am J Ophthalmol. 2003 May; 135(5):620-7.

Raiskup-Wolf F, Hoyer A, Spoerl E, Pillunat LE. Collagen cross-linking with riboflavin and ultraviolet-A light in keratoconus: long-term results. J Cataract Refract Surg. 2008 May; 34(5):796-801.

Hersh PS, Greenstein SA, Fry KL. Corneal collagen cross-linking for keratoconus and corneal ectasia: One-year results. J Cataract Refract Surgery. 2011 (37): 149-160 Wittig-Silva, C; Whiting M, Lamoureux E, Lindsay RG, Sullivan LJ, Snibson GR. A Randomized Controlled Trial of Corneal Collagen Cross-linking in Progressive Keratoconus: Preliminary Results. Journal of Refractive Surgery. 2008 (24): S720 - S725. Am J Ophthalmol. 2003 Klin Monbl Augenheilkd. 2007 Sep; 224(9):700-6.

AIMS AND OBJECTIVES

AIM

To evaluate the outcomes of corneal cross- linking in a public tertiary hospital setting in South Africa.

OBJECTIVES

To study the pre-procedural values of K-readings and pachymetry.
To look and compare the post procedural values of the same parameters at 2 consecutive values after the procedure.
To prove that the corneal cross-linking procedure is an effective method of treatment in patients with progressive keratoconus.

4. METHODS

STUDY DESIGN

This study is a descriptive, quantitative chart review project.

SETTINGS

The study will be conducted at Greys Tertiary Hospital in the Ophthalmology clinic.

Permission to conduct a study granted by the medical manager at Greys Hospital, an application sent to the KwaZulu-Natal department of Health and the BREC office.

PARTICIPANT SELECTION

Source: Outpatients

Age: Adolescent (13-17 years) and Adult (18 – 35 years)

Numbers: Indicate the number of participants in each of the above study-groups.

Adolescent: ±60 Adults: ±40, this number was chosen because the number of patients seen at Greys hospital who had the corneal cross –linking procedure fell into the younger age group.

There were no control groups for this study.

Detail inclusion and exclusion criteria:

Inclusion:
Keratoconic patients who have had the corneal cross-linking procedure done in Grey's Hospital, Pietermaritzburg.
Males and females between the ages of 13 and 35 years.

Exclusion:
Patients who had less than three follow up routine visits post the cross-linking procedure.
Cross-linking done for any other indication other than keratoconus.
Ocular or central nervous system disease other than keratoconus which prevents good vision.

MEASUREMENTS

K-values: Steepest, flattest and average curvature of the cornea measures in mm radius by Pentacam (the smaller the value the steeper the cornea).
Pachymetry (corneal thickness) measured as thinnest point by the Pentacam and/or anterior segment OCT (in microns).

DATA SELECTION AND STATISTICAL ANALYSIS

Data will be entered into SPSS version 21 (Statistical Packages for the Social Sciences) for analysis. A p value <0.05 will be considered as statistically significant. A descriptive statistical analysis of the data (means, standard deviations, ranges, frequencies and percentages, etc.) will initially be conducted. Analysis of Variance (Anova) will be used to assess the changes on the Pentacam and Visual acuity scores.

SAMPLE

Adolescent (13-17 years) and Adult (18 – 30 years)
Numbers: Indicate the number of participants in each of the above study-groups. Total number of patients = ±100 (estimation – all treated patients are to be included)
adolescent: ±60 Adults: ±40

This number was chosen because the number of patients seen at Greys hospital who had the corneal cross –linking procedure fell into the younger age group.

5. ETHICAL CONSIDERATIONS

This is a retrospective study which will not include direct contact with the patient. Data will be kept anonymous: no identifying numbers, name or specific birth dates will be included in the final presentation. Data will be linked to the specific patient file by random number assignment and kept separately from the data storage: Raw data as well as the identifying list will be kept in an electronic database, encrypted and stored for five years. After this period the information will be securely destroyed. Results as well as the original patient files will be preserved.

6. BUDGET (including Funding obtained)

No additional funding is needed for this study.

TIME LINES AND PROJECT MANAGEMENT

	Nov.2015 – Nov. 2016	Dec– Jan.2017	Feb. 2017	March –April 2017
Data capture				
Analysis				
Write-up				
Publication				

8. CONTRIBUTORS AND AUTHORSHIP

Name	Department	Contribution	Author or acknowledgement
Noluthando Pupuma	Ophthalmology	Entire Project	Author
Carl-Heinz Kruse	Ophthalmology	Intellectual guidance and projects drafting	Author
Dr W Sibanda	Statistics	Data analysis	Acknowledgement
Prof R. Rodseth	Anaesthetics	Data analysis	Author

8. APPENDICES

1. Supervisor's report
2. Data sample sheet
3. University of KwaZulu-Natal ethics committee approval
4. KwaZulu-Natal Department of Health Ethics approval
5. Greys Hospital (Pietermaritzburg) study approval
6. GCP certificate

Study #	Pt. age	Visit1	k-flat (D)	K-ave (D)		Time	Visit2	K-steep	k-flat	K-ave	Pachy	Time (months)	Visit3	K-steep	k-flat	K-ave	Pachy
KC - 001	34	05.03.12	42,0 46.5	44.25	397	3	08.06.12	41.7	46.6	44.15	397	8	07.02.13	42.6	47.1	44.9	409
KC 002	43	07.05.12	48.4 54.6	51.5	403	4	18.09.12	49.4	55.1	52.3	353	2	19.11.12	48.9	55.3	52.0	372
KC 003	23	11.06.12	50.8 56.5	53.5	379	4	16.10.12	49.5	50.9	50.2	461	12	01.10.13	50.4	53.1	51.7	418
KC 004	27	23.01.12	48.9 53.4	51.15	398	4	28.05.12	48.3	53.1	50.7	415	4	21.09.12	49.0	53.8	51.4	408
KC 005	27	23.01.12	48.2 53.0	50.6	405	4	28.05.12	48.1	52.5	50.3	406	4	21.09.12	49.6	51.8	50.7	443
KC 006	28	23.01.12	48.3 53.4	50.85	436	4	28.05.12	47.0	51.5	49.25	470	5	23.10.12	47.0	50.6	48.8	423
KC 007	25	09.07.12	61.6 67.6	64.6	327	7	18.02.13	61.1	66.7	63.9	308	6	08.08.14	60.5	68.9	64.7	364
KC – 008	17	09.07.12	45.4 49.6	47.5	460	5	10.12.12	45.4	49.9	47.65	468	5	06.05.13	45.0	49.5	47.25	473
KC – 009	18	06.05.13	43.7 46.2	44.95	432	7	13.01.14	45.2	46.9	46.05	414	9	05.10.14	44.6	46.7	45.65	402
KC – 010	48	13.08.12	51.1 55.2	53.15	418	8	22.04.13	51.4	54.7	53.05	415	6	07.10.13	53.7	56.6	55.15	389
KC – 011	24	14.09.12	50.9 54.2	52.55	380	6	18.03.13	52.9	56.2	54.55	387	6	22.09.14	55.6	54.2	54.9	361
KC - 012	13	01.09.14	44.1 46.8	45.45	406	4	27.01.15	44.3	47.1	45.7	407	2	02.03.15	44.5	47.3	45.9	435
KC - 013	13	01.09.14	44.4 47.3	44.85	398	4	27.01.15	43.3	46.2	44.75	330	2	02.03.15	43.3	46.9	45.1	375
KC - 014	17	28.10.14	50 52.2	51.1	456	4	02.02.15	50.0	51.7	50.85	440	5	27.07.15	49.8	51.7	50.75	447
KC - 015	17	28.10.14	46 46.6	46.3	479	4	02.02.15	46.4	47.1	46.75	495	5	27.07.15	45.1	46.6	45.85	460
KC 016	10	10.11.14	54.2 58.9	56.55	443	1	17.12.14	54.8	57.9	56.35	370	2	26.02.15	56.9	61.2	59.1	422
KC - 017	10	10.11.14	52.4 56.8	54.6	423	1	17.12.14	52.2	56.0	54.1	399	1	16.01.15	52.7	55.7	54.2	365
KC - 018	45	26.03.14	51.3 52.5	51.9	456	11	10.02.15	51.7	52.7	52.2	444	3	10.05.15	51.0	52.7	51.9	406
KC - 019	18	07.04.14	45.4 50.2	47.8	395	8	09.12.14	45.1	50.5	47.8	395	5	17.05.15	45.4	50.1	47.8	381
KC - 020	37	27.10.14	49.8 52.6	51.2	437	2	17.12.14	49.9	52.9	51.4	428	2	05.02.15	49.3	53.5	51.4	430
KC - 021	37	27.10.14	47.5 49.3	48.4	450	2	17.12.14	47.3	48.8	48.05	431	2	05.02.15	47.8	49.1	48.45	454
KC - 022	14	19.05.14	42.5 45.1	43.8	425	7	03.12.14	42.9	44.5	43.7	379	1	25.01.15	42.9	46.1	44.5	432
KC - 023	14	19.05.14	44.4 55.3	49.9	381	8	26.01.15	42.4	58.6	50.5	378	5	14.06.15	45.0	59.5	52.25	364
KC - 024	17	28.10.14	46 46.6	46.3	479	4	02.02.15	46.4	47.1	46.75	495	5	27.07.15	45.1	46.6	45.85	460
KC - 025	17	28.10.14	50 52.2	51.1	456	4	02.02.15	50.0	51.7	50.85	440	5	27.07.15	49.8	51.7	50.75	447
KC - 026	24	14.09.12	50.9 54.2	52.55	380	6	18.03.13	52.9	56.2	54.55	387	6	22.09.14	55.6	54.2	54.9	361
KC – 027	17	28.10.14	50.0 52.2	51.1	456	4	02.02.15	50.0	51.7	50.85	440	5	27.07.15	49.8	51.7	50.75	447
KC – 028	25	21.05.12	49.3 53.7	51.5	415	3	27.08.12	49.6	54.1	51.9	416	9	07.05.13	49.7	53.2	51.5	401
KC - 029	17	21.05.12	52.8 56.6	54.7	417	6	07.11.13	59.3	59.7	59.5	395	2	28.01.14	59.4	64.7	62.1	400
KC - 030	17	16.04.12	46.0 47.0	46.5	469	5	25.09.12	45.3	46.9	46.1	418	12	30.09.13	47.0	47.8	47.4	403
KC - 031	34	05.03.12	42.1 46.9	44.5	416	13	07.02.13	41.9	47.5	44.7	387	10	09.12.13	44.0	49.0	46.5	387
KC - 032	24	24.03.14	51.1 53.4	52.25	462	1	01.04.14	51.5	52.9	52.2	474	6	21.10.14	50.1	52.3	51.2	401
KC - 033	19	12.08.13	46.6 65.4	56.0	523	5	27.01.14	49.2	67.9	58.6	367	6	27.7.14	46.4	49.7	40.05	478
KC - 034	19	12.08.13	45.7 48.8	47.3	488	5	27.01.14	46.2	50.5	48.5	456	6	24.07.14	46.7	50.7	48.7	453
KC - 035	26	09.03.15	50.1 53.1	51.6	458	1	15.04.15	48.8	52.9	50.9	448	3	13.07.15	49.4	53.4	51.4	420
KC - 036	31	20.10.12	48.8 50.3	49.5	406	3	07.01.13	47.6	50.0	48.8	417	5	13.06.13	47.0	49.2	48.1	425
KC 0037	29	21.11.13	50.8 56.6	53.7	353	5	17.04.14	49.5	54.4	52.0	377	4	17.08.14	52.4	54.8	52.4	390
KC 0038	15	08.07.13	49.2 52.2	50.7	457	4	21.11.13	53.6	65.3	59.2	297	6	22.05.14	49.8	54.3	52.05	390

KC 0039		30	15.01.12	41.4	45.2	43.3	462	3	03.04.12	43.7	44.0	43.9	476	1	25.05.12	42.7	43.6	43.2	471
KC 0040		24	10.09.13	55.7	62.1	58.9	411	1	03.10.13	58.1	62.1	60.1	382	2	12.12.13	62.8	79.1	70.95	306
KC 0041		14	10.09.13	46.1	51.2	48.7	442	1	03.10.13	49.7	52.4	51.2	403	1	06.11.13	49.2	52.5	50.9	413
KC 0042		15	17.01.11	42.2	44.6	43.4	487	19	10.07.12	42.2	46.0	44.1	491	37	11.08.15	42.9	48.7	45.8	417
KC 0043		24	21.05.15	51.9	57.7	54.8	426	2	08.07.15	51.5	57.7	54.62	420	13	08.08.16	49.9	55.4	52.65	470
KC 0044		27	19.03.15	46.8	47.2	47.0	402	0	19.03.15	47.1	65.1	56.1	448	4	22.07.15	46.2	84.4	65.3	505
KC 0045	?		03.02.11	49.6	52.1	50.9	459	0	14.02.11	48.7	52.4	50.6	457	5	18.07.11	49.5	52.2	50.85	449
KC 0046	?		03.02.11	44.3	48.3	46.3	471	0	14.02.11	44.8	48.5	46.65	474	5	18.07.11	45.2	47.7	46.45	468
KC 0047		19	04.12.12	56.4D	60D	58.2D	394	5	30.05.13		58 61.4	59.7	401	8	28.01.14		60 60.9	60.45	388
KC 0048		16	09.12.13	46.9D	56.5D	51.7D	408	1	07.01.14	45.8	56.9	51.4	397	1	04.02.14	45.9	47.3	46.6	351
KC 049		26	18.08.14	38.2	48.7	43.5	451	6	02.02.15	48.1	52.1	50.3	457	2	16.04.15	45.2	49.4	47.3	513
KC 0050		31	28.03.11	53.6	59.6	56.6	406	4	25.07.11	54.2	59.7	56.95	388	9	02.04.12	53.4	58.0	55.7	394
KC 0051		18	03.10.11	47.2	49.3	48.3	334	5	30.05.11	46.6	48.7	47.65	372	7	16.01.12	47.5	49.8	48.65	356
KC 052		27	17.01.11	43.6	45.4	44.5	458	3	11.04.11		44 45.5	44.75	453	9	13.12.11	43.8	46.2	45.0	449
KC 0053		14	30.05.11	39.6	41.7	40.65	475	9	06.02.12		38 43.9	40.95	441	10	06.12.12	41.8	45.	43.6	495
KC 0054		27	17.01.11	42.2	46.2	44.2	433	3	11.04.11	44.7	48.6	46.65	478	8	13.12.11	42.8	47.4	45.1	419
KC 0055		29	28.05.13	46.3	49.4	47.9	456	7	19.11.13	47.2	50.5	48.85	426	4	20.03.14	47.1	50.5	48.8	414
KC 0056		8	24.10.13	55.2	57.0	56.1	320	1	18.11.13	54.7	58.1	56.4	366	2	30.1.14	52.8	57.4	55.1	382
KC 0057		12	19.08.13	43.2	48.0	45.6	404	2	19.10.13	43.2	48.1	45.65	438	1	19.11.13	45.7	49.6	47.7	398
KC 0058		48	03.03.14	55.2	57.5	56.4	470	2	26.05.14	53.2	54.6	53.9	464	9	10.02.15	53.3	55.8	54.5	391
KC 0059		25	10.09.10	41.7	44.2	42.3	443	8	09.05.11	42.2	44.2	43.2	445	9	20.02.12	42.1	45.5	43.8	436
KC 0060		25	10.09.10	40.0	45.4	42.7	434	8	09.05.11	40.6	45.8	43.2	425	9	20.02.12	40.6	46.1	43.35	423
KC 061		24	10.09.13	44.1	47.7	45.9	402	12	14.09.14	46.7	49.0	47.9	360	6	19.03.15	47.2	47.7	47.5	347
KC 062		24	10.09.13	44.5	45.4	44.95	428	12	14.09.14	46.1	47.2	46.7	376	4	15.01.15	46.3	47.6	46.95	398
KC063		12	24.10.13	54.1	58.0	56.1	358	1	18.11.13	55.8	50.6	53.1	319	2	30.01.14	53.1	50.9	51.7	329
KC 064		27	14.07.14	50.1	53.9	52D	375	1	22.08.14	47.4	56.1	51.8	377	3	17.11.14	50.5	54.4	52.45	375
KC 065		20	08.04.13	43.1	46.3	44.7	500	1	15.05.13	41.8	46.7	44.25	501	1	05.06.13	42.3	47.5	44.9	498
KC 066		23	05.09.11	45.0	53.0	49.0	460	5	06.02.12	44.8	54.6	49.7	403	8	30.10.12		47 51.4	49.2	469
KC 067		21	26.03.12	52.7	53.9	53.3	416	1	30.04.12	52.8	53.6	53.2	402	4	27.08.12	52.1	53.2	52.7	411
KC 068		21	30.04.12	48.6D	51.9D	50.3D	471	4	27.08.12	47.4	50.3	48.9	428	1	27.09.12	47.4	50.3	52.9	428
KC 069		26	09.01.12	42.5	53.0	47.75	422	0	30.01.12	42.4	54.3	48.4	423	4	10.05.12	45.0	57.6	51.2	412
KC 070		26	09.01.12	46.3	57.4	51.85	419	0	30.01.12	46.6	57.0	51.8	427	4	10.05.12	41.7	53.9	47.8	398
KC 071		9	15.09.14	46.8	54.4	55.6	366	1	19.10.14	47.0	54.9	50.9	386	3	30.03.15	45.6	54.5	50.05	386
KC 072		28	16.08.10	47.9	50.0	48.95	386	38	03.10.13	52.4	54.3	53.4	326	3	17.02.14	53.4	55.4	54.4	347
KC 073		12	24.11.14	57.5	62.3	54.9	358	5	27.04.15	58.1	63.3	60.7	387	1	28.05.15	58.1	63.3	60.7	387
KC 074		18	04.03.13	56.8	52.8	54.8	373	1	04.04.13	58.7	53.8	56.3	385	16	25.08.14	54.7	57.5	56.1	394
KC 075		19	22.08.11	52.0	58.4	55.2	410	9	28.05.12	52.3	59.2	55.8	439	9	11.03.13	51.9	53.4	52.7	418
KC 076		22	28.11.11	42.5	43.8	43.2	543	9	06.08.12	44.0	45.8	44.9	478	13	16.09.13	43.9	45.5	44.7	434
KC 077		25	28.10.13	47.1	58.4	52.8	389	8	02.06.14	46.4	57.3	51.8	353	10	16.04.15		48 56.3	52.2	372

KC 078	39	15.04.13	54.2	55.3	54.7	304	1	16.05.13	49.3	58.7	54.0	299	3	15.08.13	51.4	56.9	54.1	309
KC 079	19	22.08.11	44.3	51.0	47.7	449	9	28.05.12	44.4	51.5	47.9	449	9	13.02.13	44.6	51.6	48.1	444
KC 080	18	04.03.13	59.6	54.7	57.2	375	10	09.01.14	61.6	73.1	67.3	331	3	24.04.14	67.1	73.3	70.2	194

Please note that these 80 are the original data before exclusion criteria were applied.
Once all relevant individuals were excluded we were left with only 54 data sets.

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

DIRECTORATE:
Health Research & Knowledge Management

Physical Address: 330 Langalibalele Street, Pietermaritzburg
Postal Address: Private Bag X9051
Tel: 033 395 2805/ 3189/ 3123 Fax: 033 394 3782
Email:
www.kznhealth.gov.za

Reference: 68/16
KZ_2015RP29_46

Date: 15 March 2016

Dear Dr N. Pupuma
Email: n.olu@hotmail.com

Approval of research

1. The research proposal titled **'The outcome of corneal cross-linking for keratoconus in Greys Hospital, Pietermaritzburg'** was reviewed by the KwaZulu-Natal Department of Health.

   The proposal is hereby **approved** for research to be undertaken at Greys' Hospital.

2. You are requested to take note of the following:
   a. Make the necessary arrangement with the identified facility before commencing with your research project.
   b. Provide an interim progress report and final report (electronic and hard copies) when your research is complete.

3. Your final report must be posted to **HEALTH RESEARCH AND KNOWLEDGE MANAGEMENT, 10-102, PRIVATE BAG X9051, PIETERMARITZBURG, 3200** and e-mail an electronic copy to hrkm@kznhealth.gov.za

For any additional information please contact Mr X. Xaba on 033-395 2805.

Yours Sincerely

Dr E Lutge
Chairperson, Health Research Committee
Date: 15/03/16

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

GREYS HOSPITAL
OFFICE OF THE CEO
Private Bag X 9001, Pietermaritzburg, 3200
Town Bush Road, Chase Valley, Pietermaritzburg, 3201
Tel.:033 – 897 3321 Fax.: 033 - 8973398

To:	**Dr. N. Pupuma** **10 Kembali, 1 Craigie Drive, Montrose, PMB, 3201**
From:	**Dr. K. B. Bilenge** **CEO - Greys Hospital**
Date:	**29 January 2016**
Re:	**Request for permission to conduct research at Grey's Hospital:** ***The outcome of corneal cross-linking for keratoconus performed at Grey's Hospital, Pietermaritzburg***

Dear Dr. Pupuma

Your request to conduct research at Grey's Hospital refers.
Permission to conduct the above study is hereby granted under the following conditions:

- Your provisional ethics approval and research protocol are assumed to be valid and final ethics approval is a prerequisite for conducting your study at our hospital. Once obtained, please submit a copy of the full ethics approval;
- You are also required to obtain approval for your study from the Provincial Department of Health KZN Health Research Unit prior to commencing your study at Grey's Hospital. You will find more information on their website: *http://www.kznhealth.gov.za/hrkm.htm*
- Confidentiality of hospital information, including staff and patient medical and/or contact information, must be kept at all times; Patient records are **not** to be removed from the hospital premises nor are you allowed to photocopy/ photograph them.
- Your research must comply with National Health Act Regulation R719 of 2014 stipulations.
- You are to ensure that your data collection process will not interfere with the routine services at the hospital;
- You are to ensure that hospital resources are not used to manage your data collection, e.g. hospital staff collating data; photocopying; telephone; facsimile, etc.;
- Informed consent is to be obtained from all participants in your study, if applicable;
- Policies, guidelines and protocols of the Department of Health and Grey's Hospital must be adhered to at all times;
- Professional attitude and behaviour whilst dealing with research participants must be exhibited;
- The Department of Health, hospital and its staff will not be held responsible for any negative incidents and/or consequences, including injuries and illnesses that may be contracted on site, litigation matters, etc. that may arise as a result of your study or your presence on site;
- You are required to submit to this office a summary of study findings upon completion of your research.
- You are requested to make contact with the **HoD of the Ophthalmology Department – Dr. Kruse,** at Grey's Hospital once you are ready to commence data collection.

Recommended by:

Dr L. Naidoo
Senior Manager: Medical Services

Approved by:

Dr. K. B. Bilenge
Hospital CEO

Zertifikat

Certificado

Certificat

Certificate

Promouvoir les plus hauts standards éthiques dans la protection des participants à la recherche biomédicale Promoting the highest ethical standards in the protection of biomedical research participants

Clinical Trials Centre
The University of Hong Kong

Certificat de formation - Training Certificate

Ce document atteste que - this document certifies that

Noluthando Pupuma

a complété avec succès - has successfully completed

Good Clinical Practice (GCP)

du programme de formation TRREE en évaluation éthique de la recherche
of the TRREE training programme in research ethics evaluation

June 18th, 2015
CID : HI3tlH96FF

Professeur Dominique Sprumont
Coordinateur TRREE Coordinator

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[REV : 20140328]

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

17 March 2016

Dr N Pupuma (201295547)
Discipline of Ophthalmology
School of Clinical Medicine
n.olu@hotmail.com

Dear Dr Pupuma

Protocol: The outcome of corneal cross-linking for keratoconus in Grey's Hospital, Pietermaritzburg.
Degree: MMed
BREC reference number: BE489/15

EXPEDITED APPLICATION

The Biomedical Research Ethics Committee has considered and noted your application received on 20 November 2015.

The study was provisionally approved pending appropriate responses to queries raised. Your responses dated 16 March 2016 to queries raised on 20 January 2016 have been noted and approved by a sub-committee of the Biomedical Research Ethics Committee. The conditions have now been met and the study is given **full ethics approval.**

This approval is valid for one year from **17 March 2016.** To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2015), South African National Good Clinical Practice Guidelines (2006) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx.

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The sub-committee's decision will be **RATIFIED** by a full Committee at its meeting taking place on **12 April 2016.**

We wish you well with this study. We would appreciate receiving copies of all publications arising out of this study.

Yours sincerely

Professor J Tsoka-Gwegweni
Chair: Biomedical Research Ethics Committee

cc supervisor: ruraleye@gmail.com
cc postgraduate office: konar@ukzn.ac.za