A HISTORICAL PROSPECTIVE OBSERVATIONAL STUDY OF PATIENTS WITH KERATOCONUS TO DETERMINE THE INCIDENCE OF STEROID INDUCED OCULAR HYPERTENSION FOLLOWING COLLAGEN CROSSLINKING

DISSERTATION SUBMITTED AS PART OF FULFILLMENT FOR THE MS BRANCH III (OPHTHALMOLOGY) EXAMINATION DEGREE EXAMINATION OF THE TAMIL NADU DR.MGR MEDICAL UNIVERSITY, TO BE HELD IN MAY 2020

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VELLORE
INDIA

BONAFIDE CERTIFICATE

This is to certify that this dissertation "A Historical Prospective Observational study of patients with Keratoconus to determine the incidence of steroid induced ocular hypertension following collagen crosslinking" done towards fulfillment of the requirements of the Tamil Nadu Dr MGR Medical University, Chennai for the MS Branch III (Ophthalmology) examination to be conducted in May 2020, is a bona fide work of Dr Minu George P, post graduate student in the Department of Ophthalmology, Christian Medical College, Vellore.

Dr. Sanita Korah, MS, DNB
Professor and Guide,
Department of Ophthalmology,
Christian Medical College,
Vellore-632001.

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Dr. Sanita Korah MS,DNB
Professor, Head of the Department,
Department of Ophthalmology,
Christian Medical College ,
Vellore- 632001

Dr. Anna Pulimood
The Principal,
Christian Medical College,
Vellore-632001.

DECLARATION

This is to certify that the dissertation titled "A Historical Prospective Observational study of patients with keratoconus to determine the incidence of steroid induced ocular hypertension following collagen crosslinking" done towards fulfillment of the requirements of the Tamil Nadu Dr MGR Medical University, Chennai for the MS Branch III (Ophthalmology) examination to be conducted in May,2020 comprises my original research work and information taken from secondary sources has been given due acknowledgement and citation.

Dr. Minu George P,
Post Graduate Student,
Department of Ophthalmology,
Christian Medical College,
Vellore- 632001.

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https://www.keratoconuscenter.com/UserFiles/CXLHazePublished.pdf
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Most importantly I thank my parents George Thomas ,C P Suja ,sister Manju , my husband Jintu Mathews and son Evin because of and for whom I am here and I dedicate this to them.

CONTENTS

AIM

To determine the incidence of steroid induced ocular hypertension following corneal collagen crosslinking in patients with keratoconus in a South Indian tertiary hospital setting.

OBJECTIVES

PRIMARY OBJECTIVE:

To determine the incidence of steroid induced ocular hypertension in patients with keratoconus after use of topical steroids following collagen cross linking (CXL)

SECONDARY OBJECTIVES

1. To study the effect of CXL on retarding the rate of progression of keratoconus by measuring change in Keratometry reading before and after CXL

2. To study change in central corneal thickness after CXL.

3. To study change in Visual acuity after CXL.

4. To study the incidence of complications and outcome of CXL

INTRODUCTION

Steroids are routinely used after ocular surgeries to reduce the postoperative inflammation. Steroid use however, has been associated with complications like cataract, ocular hypertension and glaucoma. Some eyes have been found to have an increased tendency for steroid response compared to others. 5-6% of the normal population has been found to be high steroid responders (Intraocular Pressure (IOP) elevation of more than 15mmHg) and about 30% to be moderate responders (IOP elevation of 6-15mmHg).(3)

Many factors have been identified for steroid response, which includes patient risk factors like family history of glaucoma, primary open angle glaucoma, children, type of steroid used, route of administration and duration of steroid use.

Collagen cross linking is a commonly performed procedure to slow the rate of progression of keratoconus. Keratoconus is a progressive degenerative disease of the cornea which can result in loss of vision and need for corneal transplant. Topical steroid drops are always used for a duration of about 3 months following the procedure to prevent post procedure corneal scarring.

This study was performed because we have observed an increased incidence of steroid induced raise in intraocular pressure among patients who have undergone corneal crosslinking for keratoconus as compared to the normal population.

Based on this suspicion we first conducted a retrospective pilot study in our department, studying 10 patients who had undergone CXL. This pilot study revealed that 40% of patients are steroid responders, which is high compared to the normal population receiving steroid therapy (30%). Thus this study was undertaken to report the incidence of steroid induced raise in intraocular pressure among keratoconus patients after cross linking.

This study was a Historical prospective Observational study. Patients with keratoconus who had undergone collagen cross-linking at our hospital were included in the study. Data from hospital records from the year 2013 (when this procedure was introduced to our hospital) till August 2019 was taken. The preoperative intraocular pressure (IOP) and IOP after steroid was used to calculate the incidence of steroid response.

The factors that could affect the response to steroids were also analyzed to determine positive co-relation. Complications like corneal scarring, corneal infection and outcomes following the procedure were also noted.

The effect of CXL on slowing the rate of progression of keratoconus in our patients by comparing the change in corneal curvature, visual acuity and the central corneal thickness after CXL from available hospital records were also studied.

LITERATURE REVIEW

Part 1:

STEROID INDUCED OCULAR HYPERTENSION:

Rise of intraocular pressure (IOP) as a result of systemic steroid therapy was initially described in 1950 by Mc Lean. It was Francois in 1954 who then described elevated IOP following topical corticosteroid therapy.(1)

Steroid induced raise in IOP has since been reported to occur as a consequence of oral, intravenous, inhaled, topical, periocular, or intravitreal corticosteroid therapy. (2) Patients who experience a transient or sustained pressure rise after corticosteroid instillation are referred to as *steroid responders,* or are said to have Steroid Induced Ocular Hypertension. If glaucomatous damage occurs as manifested in the optic nerve or on visual field testing, then they can be said to have Steroid Induced Glaucoma.(2)

STEROID RESPONDER:

Steroid responsiveness is has been defined in several different ways.

Yamamoto et al in 2008 suggested that an elevation of 5 mmHg following steroid therapy should be defined as a steroid response. (Yamamoto et al., 2008).

Others suggested that an IOP above 21 mmHg (Herbert et al., 2004) or 24 mmHg (Heinz et al. 2009) following steroid treatment should be considered as a steroid responder. Yet another group considered the combination of both an increase of 5 mmHg and IOP above 24 as a steroid responsiveness. (Levine et al 2002)(4)

Armaly and Becker [3] reported that the normal population could be divided into 3 groups based on their response to the topical administration of Dexamethasone and Betamethasone:

(1) High responders, 4–6% of the population, developed an IOP above 31 mm Hg or a rise of more than 15 mm Hg above baseline

(2) Moderate responders, approximately one third of the population, had IOPs between 20 and 31 mm Hg, or a pressure rise of 6–15 mm Hg

(3) Non-responders, the remaining two thirds, had pressure increases of less than 6 mm Hg and IOPs of less than 20 mm Hg.

The incidence of steroid rsponse increases with higher frequency and longer duration of steroids.(2)

MECHANISMOF STEROID INDUCED OCULAR HYPERTENSION:

Aqueous that is produced by the ciliary processes drains out of the eye via the trabecular meshwork. Inadequate outflow of aqueous will lead to an increase in

the intraocular pressure, which results first, in damage to the optic nerve causing visual field defects, and ultimately, loss of vision.

The mechanism of steroid-induced glaucoma is postulated broadly to be due to aqueous outflow obstruction due to the following causes:

1. Accumulation of extracellular matrix in the trabecular meshwork, decreasing the outflow. The accumulated extracellular matrix (ECM) has the potential to affect both the paracellular (that is, the flow in-between trabecular meshwork endothelial cells) and transcellular (that is, the flow through pores created within a single, and / or between two inner wall Schlemm's canal cells) levels.(5)
2. It has been suggested that corticosteroid use activates molecular myocillin gene production, which alters trabecular meshwork morphology, severing aqueous flow facility. (6)

3. There are physical and mechanical changes seen within the trabecular meshwork causing resistance to outflow. The actin fibres were reorganised as actin networks increasing the outflow resistance. (7)
4. Steroids also inhibit proteases and trabecular meshwork endothelial cell phagocytosis causing a decrease in the breakdown of substances in the trabecular meshwork.(8) Levels of tissue plasminogen activator, stromelysin, and metalloproteases (9,10) have been shown to decrease in trabecular meshwork cultures treated with dexamethasone .

In the normal population, 5–6% of people have been found to develop marked IOP elevation (rise more than 16mmHg) while 30% have a moderate rise in IOP between 5-15 mmHg after 4–6 weeks of topical dexamethasone or betamethasone administration.(11,12)

RISK FACTORS FOR STEROID RESPONSIVENESS:

1. PATIENTS WITH SUSPECTED PRIMARY OPEN ANGLE GLAUCOMA (POAG)

Armaly et al suggest that 90% of patients with primary open angle glaucoma and almost one third of glaucoma suspects are steroid responders. (13) POAG usually occurs in patients greater than 50 years of age.

2. AGE:

There is a bimodal distribution. Older people and children less than 6 years are found to be at risk. In a study by Lam et al 71.2 and 59.2% of children receiving topical dexamethasone 0.1% (four times per day and two times per day, respectively) responded with an IOP rise greater than 21 mmHg.(14)

3. HIGH MYOPIA:

High myopia and steroid response have been associated in a study by Steven et al.(15)

4. CONNECTIVE TISSURE DISORDERS:

A study by Gatson et al on 34 patients with connective tissue disorders showed that 15% of them were dramatic steroid responders and 20% intermediate steroid responders.(16)

5. TYPES OF PREPARATIONS OF CORTICOSTEROIDS:

More potent steroids are found to cause a higher ocular hypertensive response. Acetates are lipophilic and penetrate through the cornea better than phosphates, which are relatively hydrophilic.

In a study by Cantrill et al, Medrysone 1.0% caused a 1.0 mmHg rise in IOP, while more potent steroids such as Prednisolone Acetate 1.0% and Dexamethasone acetate 0.1% caused a 10 and 22 mmHg rise in IOP, respectively.(17)

In a study conducted by Marius et al comparing prednisolone acetate eye drops1% and difluprednate ophthalmic emulsion 0.05% after cataract surgery, there was no significant difference in the mean IOP or proportions showing IOP elevation between eyes using either drops. One month postoperatively, 4 eyes in the prednisolone acetate group and 5 eyes in the difluprednate group had an IOP higher than 21 mm Hg. (18)

6. ROUTE OF ADMINISTRATION:

Intravitreal route of administration i.e. injection of steroids into the vitreous cavity has been found to have the highest incidence of steroid responders. Intravitreal injection of triamcinolone can increase IOP by several mm Hg in about 50% of patients, within 2 to 4 weeks after the start of treatment. (19)

Part 2:

KERATOCONUS:

Keratoconus is a non-inflammatory, bilateral ectasia of the cornea. Progressive corneal thinning and protrusion that results in irregular astigmatism and impairment in visual function characterize it. It usually involves the central two-thirds of the cornea, with the apex of the cone usually centered just below the visual axis.

The onset of keratoconus occurs at about the age of puberty. Typically, over a period of 10 to 20 years, the cornea becomes progressively thinner and, because of its relative weakness, it simultaneously protrudes out and becomes ectatic. As the patient ages, natural crosslinking of the stromal collagen fibers due to sunlight (UV light) exposure increases. This results in increased rigidity, and decreased suppleness of the cornea, causing gradual slowing and then cessation of progression. The severity of the disorder at the time that progression stops can range from very mild irregular astigmatism to severe thinning, ectasia, and scarring, requiring keratoplasty (20)

Keratoconus has no gender predominance. The prevalence in studies can range from 0.3 per 100,000 in Russia (29) to 2300 per 100,000 in Central India (0.0003%-2.3%)(31).

ETIOLOGY OF KERATOCONUS:

The exact etiology is unknown. However a genetic basis is suspected, which has been supported by presence of keratoconus in monozygotic twins. Keratoconus is found to be associated with diseases like atopy, vernal keratoconjunctivitis, Leber congenital amaurosis, retinitis pigmentosa, , hard contact lens wear, eye rubbing, , Down syndrome, mitral valve prolapse, and connective tissue disorders, like Ehlers–Danlos syndrome, and osteogenesis imperfect.

The microtrauma that is associated with eye rubbing and contact lens wear is thought to be one of the major causes of keratoconus. (20)

It has been reported that an up-regulation of degradative enzymes with an associated down-regulation of proteinase inhibitors will result in a degradation of the extracellular matrix of the stroma. (21) Keratocytes extracted from keratoconus corneas possess four times the normal number of interleukin-1 binding sites. Interleukin-1 also plays a role in induction of apoptosis, or controlled cell death, of in vitro stromal keratocytes. (22, 23)

Wilson et al have postulated that the corneal epithelium might release interleukin-1 in response to microtrauma that occurs after rubbing the eyes, or contact lens wear. (24)

PATHOLOGY OF KERATOCONUS:

Every layer and tissue of the cornea can be involved in the pathologic process of keratoconus. There are many observations made in corneas with keratoconus.(20)

- Degeneration of the basal epithelial cells and disruption of the epithelial basement membrane is seen(25)
- Ferritin particles accumulate within as well as between the epithelial cells, especially in the basal epithelium causing the Fleischer ring, a hallmark feature of keratoconus(26)
- In keratoconus, the collagen fibers are of normal size; however, the number of collagen lamellae is abnormally low. The number of lamellae within the cone has been found to be less than half of the number peripheral to the cone. (27)
- Collagen lamellae, which are released from their interlamellar attachments or from their attachments to Bowman's layer, and become free to slide. This results in corneal thinning without collagenolysis.
- Endothelial cell pleomorphism and polymegathism occur in keratoconus. (28)

Smolek has found the interlamellar strength profile in the normal cornea to be significantly weaker inferiorly and centrally. (30) The most common location for

the apex of the cone, in the central or inferior cornea, may be related to this inherent corneal weakness. This may also explain the association of eye rubbing with keratoconus.

DIAGNOSIS OF KERATOCONUS:

Usually, a typical patient with keratoconus presents to the Ophthalmologist in the teens or early twenties with complaints of distortion or blurring of vision and requiring frequent changes of glasses due to changes in refractive error. (32)

- High, irregular myopic astigmatism with a scissoring reflex on retinoscopy is one of the earliest signs of established keratoconus.
- In advanced keratoconus, the corneal protrusion may cause angulation of the lower lid on downgaze - Munson’s sign.
- Slit lamp examination reveals an eccentrically located ectatic protrusion of the cornea.
- Vogt’s striae occur in the posterior stroma, just anterior to Descemet's membrane due to mechanical stress forces on corneal collagen.

- Acute keratoconus or corneal hydrops results from stromal imbibition of aqueous through the breaks in descemets membrane. The edema may persist for weeks or months and is eventually replaced by scarring.

Keratometry measurements from corneal topography evaluations are performed to diagnose kerataconus in addition to the clinical features. Central corneal thickness measurements are recorded periodically to monitor the thinning of cornea.

TREATMENT OF KERATOCONUS:

Initial management requires spectacles or soft toric contact lenses. Rigid gas permeable lenses are used for correction of the astigmatism which shows no improvement with glasses. Specialized contact lenses called the Rose-K lens and Scleral lenses are designed to be accurately fitted, and can provide clear vision even in quite severe cases of keratoconus.

Surgical modalities like intracorneal ring segments can be used to flatten the corneal surface thereby correcting myopic astigmatism. In severe cases penetrating keratoplasty might be needed.

Part 3:

CORNEAL CROSS LINKING:

Crosslinking is a process that has been used in the polymer industry to harden materials. Chemical crosslinking with gluteraldehyde has been used in to make heart valves and UV-A light to strengthen dental fillings.

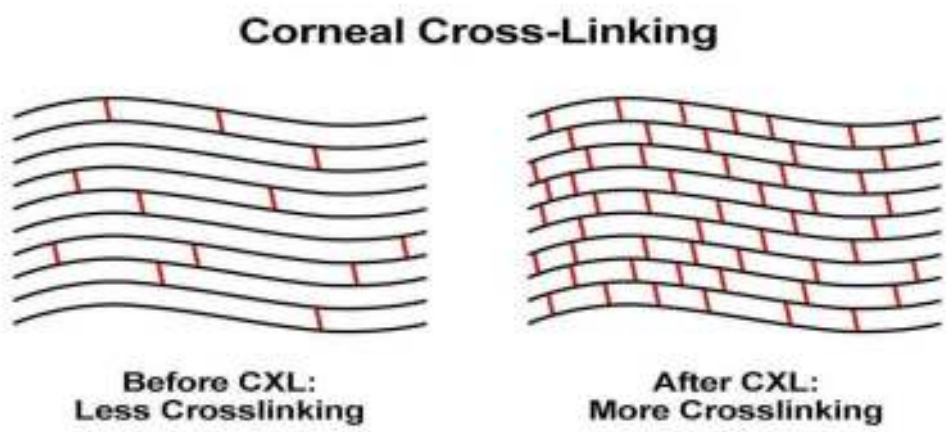
Collagen cross-linking in the cornea is a process that occurs naturally with aging due to an oxidative deamination reaction that takes place within the end chains of the collagen on exposure to sunlight which contains UV light.(38)

Collagen Cross Linking (CXL) was introduced by Gregor Wollensak in 2003 for management of keratoconus and is done to halt or delay the progression of keratoconus.

The principle of CXL is that induction of increased cross-links between the collagen fibrils of the cornea (collagen fibrils form strong chemical bonds with adjacent fibrils) results in stiffening and strengthening of ectatic cornea.

CXL uses UV light and a photosensitizer to enhance the formation of these chemical bonds. Using UVA at 370nm and the photosensitizer riboflavin, the photosensitizer becomes excited into its triplet state thus generating the reactive oxygen species (ROS), mainly singlet oxygen and, to a much lesser degree,

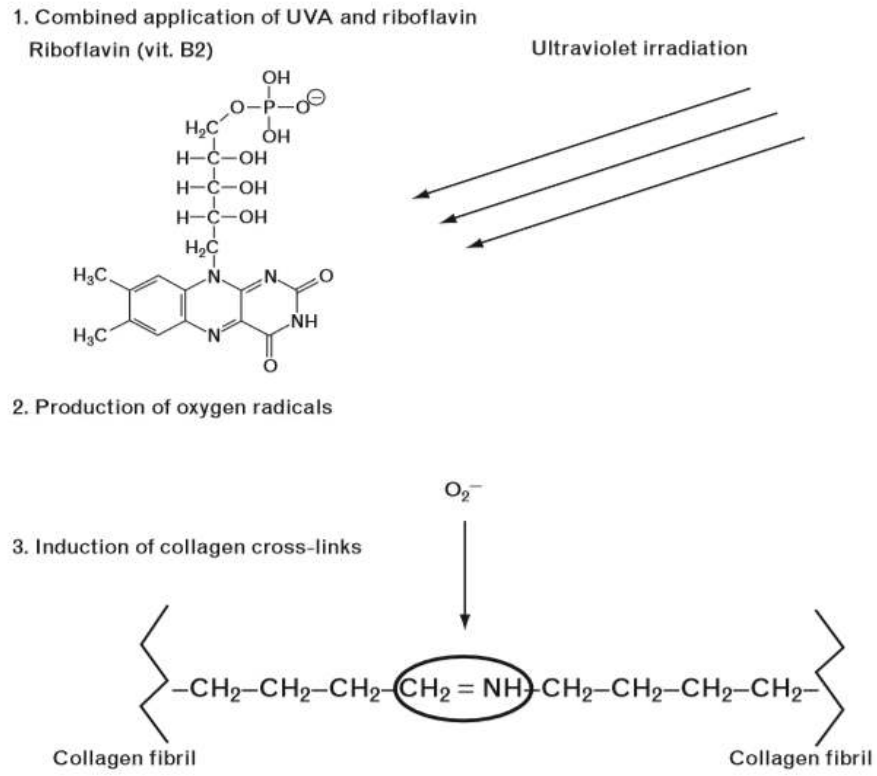
superoxide anion radicals. The ROS reacts with several molecules inducing chemical covalent bonds that bridge amino groups of collagen fibrils (type II photochemical reaction). 370nm was chosen as the wave length of choice because of an absorption peak of riboflavin at this wavelength. (33)

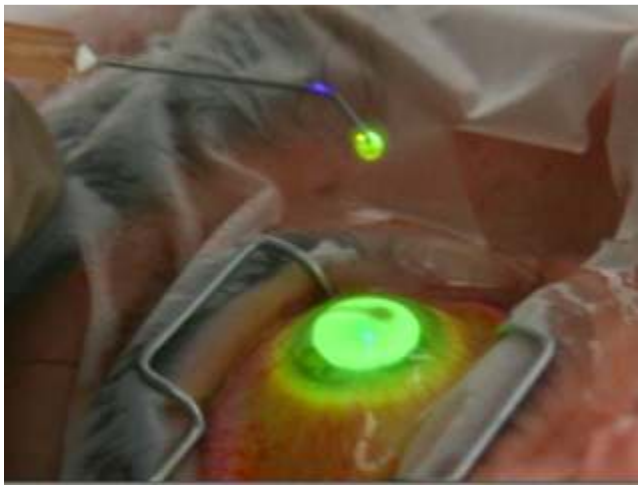


The treatment is conducted under sterile conditions in a room specifically designated for this, or in the operation theatre. The patient's eye is anesthetized with proxymetacainhydrochloride 0.5% drops. Then the central corneal epithelium is removed in a disc of diameter 9mm, to allow better diffusion of riboflavin, the photosensitizer dye, into the stroma.

A 0.1% riboflavin solution (10mg riboflavin-5-phosphate in 10ml dextran 20% solution) is applied every 2 - 4 min starting 30min before the irradiation. The irradiation is performed as per the specifications of the protocol being used. (Standard Dresden Protocol: irradiance of 3mW/cm^2 [equal to a dose of 5.4J/cm2]

for 30 min) using a UVA double diode at 370nm. The required irradiance is controlled in each patient directly before the treatment to avoid a potentially dangerous UVA overdose.(33)



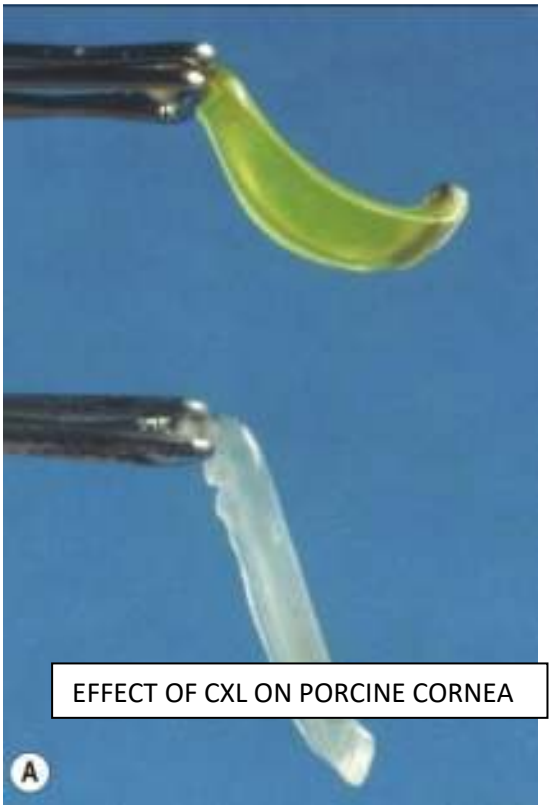


EFFECTS OF CXL:

- Increased corneal rigidity:

Using a microcomputer-controlled biomaterial testing machine, biomechanical stress–strain measurements showed an increase in corneal rigidity of 328.9% in human corneas following CXL. The crosslinking effect is maximal only in the anterior 300mm.(33)

- Corneal collagen fibre diameter is significantly increased. (34)
- Increased resistance against collagenase action has been shown in animal models. (35)



EFFECT OF CXL ON PORCINE CORNEA

Potential Adverse Effects Of CXL:

- Endothelial toxicity: In rabbits, a cytotoxic level for endothelium was found to be 0.36mW/cm2 which would only be reached in human corneas with a stromal thickness of less than 400mm with the standard treatment parameters.(36) Hence it is important to check pachymetry before planning CXL.
- Potential cataract formation with exposure to UVA light. However with the current treatment parameters the lens only receives 0.65J/cm2 which is far below the cataractogenous level of 70J/cm2.(37)

ACCELERATED CXL:

Total treatment time with conventional CXL exceeds 1 hour. According to the rule of Bunsen and Roscoe, a photochemical reaction is directly proportional to the total energy dose, irrespective of the time over which this dose is delivered. (38) The accelerated CXL protocols are those in which CXL is done in a shorter period such as 3, 5, or 10 minutes by using 30, 18, or 9 mW/cm^2 irradiance, respectively, with a cumulative irradiation dose of 5.4 J/cm^2.

Schumacher et al. found equivalent biomechanical responses between the standard Dresden protocol (3 mW/cm^2, 30 minutes) and accelerated (9 mW/cm^2, 10 minutes) treatment protocols (39). Touboul and colleagues compared corneal alterations after standard and another accelerated protocol (30 mW/ cm^2 for 3 minutes) and found accelerated CXL had the most impact on the anterior cornea than conventional CXL.(40) The shorter corneal exposure time of ACXL, might have the potential advantages of reducing the rate of complications such as corneal thinning, haze, infection, and melting. (41)

CXL can also be combined with refractive surgeries like photorefractive keratectomy, phototherapeutic keratectomy, intrastromal corneal ring segments. (42)

STEROIDS AFTER CXL:

Topical steroids are administered after the epithelial defect heals to reduce the postoperative inflammation and also corneal haze post CXL. There is no recommended regimen for steroid use after CXL nor are there studies comparing different potency of steroids with development of corneal haze. A study by Steven et al used topical steroids 4 times a day for 2 weeks found a peak in corneal haze at 1 month and plateauing over 1-3 months. (43) Pang et al suggested that use of

flurometholone with an NSAID Pranoprofen significantly decreased corneal irritation and corneal haze postoperatively. (44)

STEROID INDUCED OCULAR HYPERTENSION IN KERATOCONUS:

A retrospective pilot study conducted at our department, of 10 patients who had undergone CXL, found that 40% of patients are steroid responders with moderate to severe elevation which is very high compared to normal population receiving steroid therapy. Our literature review did not find any studies that looked at the rate of Steroid responsiveness in patients with keratoconus, following plain CXL compared to the normal population.

However, we did find other studies that looked at keratoconus patients undergoing combined CXL and laser procedures, post-keratoplasty or post corneal laser procedures, that found a higher rate of steroid induced ocular hypertension, or steroid induced glaucoma, compared to the normal population.

Kanellopoulos et al performed a retrospective non-randomised case series of 350 keratoconic eyes undergoing a corneal laser procedure, one group without combined CXL, and the other with combined CXL (Group A&B respectively). The same post-operative regimen of topical dexamethasone 0.1 % for at least 1 month was used in both groups.

Both groups were analysed after 4 weeks and ocular hypertension (OHT) was

found to be present in 43.7% of patients with CXL, compared to 27.4% in patients with no combined CXL (49)

It has been proposed that the decreased biomechanical strength in a keratoconic cornea may also be associated with reduced support for the optic nerve at the level of the lamina cribrosa, increasing glaucomatous damage susceptibility.(45) Also the IOP recording is usually difficult due to asymmetrically astigmatic cornea.

A retrospective analysis of 57 eyes with keratoconus who underwent penetrating keratoplasty in a tertiary hospital in New Zealand, showed the incidence of steroid induced glaucoma to be 32%, of which 21% had moderate to severe elevation in IOP ;which is the highest incidence reported among keratoconus patients after penetrating keratoplasty.(46) They had used Prednisolone acetate 1% 2 hourly for first 7 days followed by 4 times a day for 6 months and then slowly tapered.

Other studies conducted on eyes with keratoconus post keratoplasty had significantly lower incidence of steroid induced ocular hypertension like Sihota et al-4% on a study on 26 grafts in India (47),Goldberg et al -15% on 20 grafts(48).

FACTORS AFFECTING IOP MEASUREMENTS IN KERATOCONUS:

- CENTRAL CORNEAL THICKNESS (CCT):

  CCT decreases after collagen cross linking. When CCT is low,it gives a false low IOP value with applanation tonometry. But here we observe a high IOP even in patients with low CCT. In a study by Kasumovic et al (50) CCT was 449 microns before the CXL, but after CXL treatment it reduced to 420 microns 3 months later which was statistically significant, which stabilised at 437 microns 6 and 12 months later.

- METHOD OF MEASUREMENT:

  Tonometry (measurement of IOP) done on keratoconus patients with 4 different tonometers (Goldmann appalanation tonometry (GAT), Tonopen, Dynamic contour tonometry (DCT) and Ocular Response Analyser showed inconsistent readings in advanced stages of keratoconus as compared to early keratoconus.

  A study was done on 202 eyes with various stages of keratoconus to compare the IOP readings with GAT, tonopen, Ocular response analyser and DCT. GAT and Tonopen did not have statistically significant association with CCT. However they gave wrong readings in advanced stages of keratoconus and hence were not ideal to use in keratoconus patients. DCT and Ocular Response Analyser recordings did not show any association with CCT nor the stages of keratoconus and hence were suggested to be ideal for

measurement of IOP in keratoconus. (51)

- CORNEAL RIGIDITY:

  Improved biomechanical properties following CXL may be a factor responsible for a higher IOP reading obtained following CXL which does not acurately reflect the actual IOP. However, the study by Kanellopoulos et al described earlier (49) demonstrated a significant difference in IOP between the 2 groups in 1st month and the 12th month. The 12th month IOP rise could be attributed to the corneal strengthening over time. But the 1st month IOP difference when increased biomechanical strength may not yet be present, was statistically even higher than the 12th month difference, which suggests the role of topical steroids used in the first month after procedure for the IOP rise.

The study by Kasumovic et al (50) on 30 keratoconus eyes with central ectasia showed a rise in IOP after collagen cross linking which they attributed to the increasing corneal rigidity that occurs with time. The pre CXL IOP was 12mmHg, at 3 months post CXL it was 13.5 mmHg, at 6 months 14.0 mmHg and at 12 months 15.0 mmHg.

A similar result was observed in a study by Kymionis et al on 55 eyes with keratoconus after CXL. The IOP was statistically high at 6 months (mean 11.40mmHg) and 12 months (11.35mmHg) compared to pre-CXL (9.95mmHg), which was attributed to the increasing corneal rigidity.(52)

- PREPARTION OF STEROID AND DURATION OF USE AFTER CROSSLINKING:

There are no standard guidelines for type or duration of steroid use after cross linking. It is currently according to surgeon's preference.

PROGRESSION OF KERATOCONUS:

Keratoconus is a progressive degenerative disease. However, defining disease progression in keratoconus can be difficult. Increased steepening of corneal curvature readings (progressively increasing ectasia/protrusion), progressive thinning of the cornea as well as a decline in uncorrected visual acuity (UCVA) or best-corrected visual acuity (BCVA) are all considered as indicators of progression.(55)

Rabinowitz described progression as clinically evident corneal changes such as

stromal thinning, conical protrusion, an iron line at the base of the cone, and fine vertical striae in the deep stroma and Descemet membrane. These corneal changes often begin at puberty, then progress over 10 to 20 years, and usually stop after the third or fourth decade. (55) Progression is also usually asymmetric, with varying rates throughout the disease course, often progressing rapidly during a 3- to 5-year period and then slowing or stopping. Additionally, the changes in a patient's two eyes are also often disparate, again indicating the variability and unpredictability of keratoconus progression even within the same patient.(56)

Hersh et al defined progressive keratoconus in terms of increase in keratometry (corneal curvature) measurements. Thus they defined progression of keratoconus as one or more of the following changes over 24 months: an increase of 1.00 D or more in the steepest keratometry measurement, an increase of 1.00 D or more in manifest cylinder, or an increase of 0.50 D or more in manifest spherical equivalent .(57)

The Collaborative Longitudinal Evaluation of Keratoconus (CLEK) Study, an 8-year multicentre study on 1,988 eyes of 1,062 patients with keratoconus found that keratometry measurements increased by a mean of 0.2D per year for 8 years, with a mean increase of 1.60D over the 8-year study period. 24.1% of

patients had an increase in keratometry greater than or equal to 3.00 D during the 8 years of follow-up. Subjects also had a mean decrease in BCVA of 2.03 and 4.06 letters with high- and low-contrast testing, respectively, over 7 years. (58)

In a study conducted by Sarah et al, 186 patients with keratoconus were studied. Increase in 2 Dioptre average keratometry was taken as progression and study done for 6 months. Only 15% of patients progressed according to their definition and rest were stable.(55)

A systematic review of 41 studies and the largest meta-analysis till date, of 23 studies on 11,529 eyes gives a insight into natural progression of the disease. Younger patients and those with greater K max demonstrated more steepening of K max at 12 months. The meta-analysis for K max included 12 studies and demonstrated a significant increase in K max of 0.7diopters (D) at 12months. Middle-Eastern populations demonstrated a significantly greater K max increase (1.23D) than Europeans (0.75D) and East Asians (0.16D). It was predicted that patients had 0.8 D less Kmax steepening over 12 months for every 10-year increase in age. There was a significant increase in the average K mean of 0.4 D at 12 months. Meta-analysis of 8 studies on pachymetry showed a statistically but not

clinically significant reduction in thinnest pachymetry of 5 micrometre at 12 months with no relation to BCVA or baseline CCT.Analysis of BCVA at 12 months of 12 studies didnot show any statistically significant worsening from baseline (59)

FACTORS AFFECTING PROGRESSION OF KERATOCONUS:

Younger age, poorer BCVA, higher cylinder and keratometry (as measured by topography), thinnest pachymetry, and shorter disease duration have all been proposed as prognosticators of progression in various studies.There is no universal definition of progression and so it is difficult to compare different studies done in this regard.

PROGRESSION OF KERATOCONUS AFTER COLLAGEN CROSS LINKING:

There are mixed results in the literature, with some studies showing significant improvement in keratometry and visual acuity shown in studies with 12 month follow-up.

In a study by Henriquez et al ,maximum keratometry decreased by a mean of 2.66 D at 12 month followup on 10 eyes.(60)

However, beyond this, it appears that there is no further improvement, and infact, many eyes go back to their pre-CXL values.

Henriquez et al studied 44 eyes for 60 months and reported that the vision and keratometry readings did not show any difference from the pre-cross linking values at the 60th month. However, an initial improvement in the first year of study was recorded. (61)

A systematic review of 5 RCTs showed a reduction in K max at one year. Two studies were marginally statistically significant while the other three favored CXL. The thinnest corneal thickness showed no significant difference in the change after one-year follow-up. The change in BCVA showed a significant difference between the CXL and control groups but may not be clinically significant cause the change is less than a line on an eye chart.(62)

The Cochrane systematic review in 2015 analysed 3 RCT s. A total of 219 treated eyes were included. They report that CXL-treated eyes were less likely to progress [an increase of 1.5D or more in maximum keratometry (Kmax)] than sham-treated eyes and that, on average, CXL-treated eyes had less steep corneas and better uncorrected visual acuity at 12 months. However they noticed variations in measuring and reporting outcomes and impreciseness in studies. (63)

A systematic review and meta-analysis on effect of CXL in a pediatric population was conducted which included 13 papers, published between May 2011 and December 2014 examining 490 eyes of 401 patients with a mean age of 15.25 yrs.

There was a significant improvement in UCVA at 6 months and 1 year but this improvement lost significance at 2-year follow-up. There was no significant change from preoperative to 6-month postoperative values of K max in the standard group or at 1 year. However, at 2 years, there appeared to be a greater effect on reduction of K max. Central corneal thickness was statistically unchanged at 6 months and at 1 year in the standard group. At 2-year follow-up, there was an increase in CCT. CXL overall seems to halt progression of the disease in pediatric population (64)

In summary, studies show a modest improvement in topographic measures (average keratometry, Kmax, etc.) and in BCVA by 1 to 2 Snellen lines in the first 12 months post-CXL. The available data for follow-up beyond this time reveals fairly stable measurements and few studies have shown progression after a period of 2 years. However there is heterogeneity observed across studies during meta-analysis and hence the true effect is difficult to analyse.

Comparing standard CXL (SCXL) and accelerated CXL(ACXL), a meta-analysis suggested that SCXL was superior to ACXL in terms of the ability to reduce Kmax. UCVA was equal in both. SCXL might lead to a greater reduction in CCT than ACXL, but RCTs did not support these findings. SCXL created greater endothelial cell loss than ACXL probably due to prolonged UV exposure. (41)

3 RCT s comparing standard CXL and transepithelial CXL (TCXL) were included in a meta-analysis and found that SCXL gives better reduction of Kmax than TCXL. TCXL had better UCVA but BCVA was comparable in both groups. There was no difference in CCT between the 2 groups. (65)

COMPLICATIONS OF CORNEAL CROSSLINKING:

The common complications following CXL are related to removal of epithelium before performing the procedure, and the inflammation that occurs following the procedure. Infective corneal infiltrates or ulcers are disastrous as vision can be lost due to the scar that forms. The procedure is therefore done under strict aseptic conditions. The other complications after CXL are corneal haze, decrease in visual acuity, progression of CXL, corneal oedema, anterior chamber inflammation, and recurrent corneal erosion.

KERATITIS:

Both infectious keratitis and sterile infiltrates have been reported. A systematic review of cases reported between 2003 to 2010 showed that causes of infectious keratitis include gram positive bacteria (Staphylococcus epidermidis, S. aureus, polymicrobial Streptococcus salivarius with S. oralis), gram negative bacteria (Escherichia coli, Pseudomonas aeruginosa), fungi (Microsporidia, Fusarium solani), Acanthamoeba, and herpes simplex virus.(66) Sterile infiltrates were seen

in 7.6% of eyes and 2.8% had central stromal scars and decrease in visual acuity in 2.9% on a study on 117 eyes after CXL (67)

CORNEAL HAZE:

In 2009, Koller et al. prospectively evaluated 117 eyes and found that at the one-month examination, virtually all eyes had anterior stromal haze, which improved in severity within 12 months. They pointed out that cross-linking associated stromal haze is deeper and different than the subepithelial haze associated with photorefractive keratectomy. They reported a 2.9% incidence of stromal scars with corresponding topographic flattening after cross-linking. (67)

The haze after CXL extends into the anterior stroma to approximately 60% depth, which is on average equal to an absolute depth of 300 μm. The corneal haze peaked at 1 month and then plateaued between 1 month and 3 months. Between 3 months and 6 months, the cornea began to clear and a significant decrease in CXL-associated corneal haze was noted which usually does not require treatment except for some low dose steroid medication in some cases. From 6 months to 1 year postoperatively, there continued to be a decrease in haze measurements. (43) The corneal haze can become a permanent scar if steroids are not used in the initial period following cross-linking to control the

inflammation. Steroid dosing and duration are surgeon-dependent, and has been reported as being used for 2-8 weeks by different authors. (42-44)

In a study by Kim et al, the natural history of corneal haze after CXL without use of steroids was studied and they found that corneal haze after CXL is transient with complete clearance by 6 weeks. The role of steroids postoperatively has hence been questioned. (68) However there are no studies comparing corneal haze with and without use of steroids postoperatively in CXL.

ENDOTHELIAL DAMAGE:

In a cornea saturated with riboflavin, exposure to UV-A of 5.4 J/cm2 is recommended only if the minimum corneal thickness is 400 μm to avoid toxic effects to corneal endothelial cells, crystalline lens, and retina. Iatrogenically swelling the cornea with hypotonic riboflavin, resulting in increased temporary corneal thickening may allow for safer CXL in thin corneas. (69)

PROGRESSION AFTER CXL:

The definition of progression of keratoconus following treatment with CXL varies in the literature. A common definition is an increase of more than 0.5–1.0 diopter in maximum keratometry (Kmax) after CXL. Raiskup-Wolf et al. reported less than 1% (2/241 cases) rate of progression 18 months following epi-off CXL, while

Koller et al. reported a higher progression of 7.6% following epi-off cases during the first postoperative year(67,70).

In summary, there are no studies that we found in our literature search that address the issue of steroid induced ocular hypertension in patients following CXL alone (Dresden's protocol or Accelerated procedure (9mW/ 10 mins). Our steroid regimen lasts for 8 weeks in order to minimize permanent post CXL sub-epithelial haze.

Hence this study was undertaken to look at the ocular hypertension rate as well as the occurrence of other complications of CXL. We also intend to analyze by how much the progression of keratoconus was retarded following CXL procedure by comparing increase of keratometry readings for an equal amount of time before and after the CXL.

METHODOLOGY

PRIMARY OBJECTIVE:

To determine the incidence of steroid induced ocular hypertension in patients with keratoconus after use of topical steroids following collagen cross linking (CXL)

SECONDARY OBJECTIVES

1. To study the effect of CXL on retarding the rate of progression of keratoconus by measuring change in Keratometry reading before and after CXL

2. To study change in central corneal thickness after CXL.

3. To study change in Visual acuity after CXL.

4. To study the incidence of complications and outcome of CXL

DESIGN:

Historical prospective Observational study: Patients with keratoconus fulfilling the inclusion criteria treated with collagen cross-linking at our hospital were included in the study. Data from hospital records from the year 2013 (when this procedure was introduced to our hospital) till August 2019.

SETTING**:**

Department of Ophthalmology, Christian Medical College, Schell Campus, Vellore

DATA COLLECTION:

The principal investigator selected the patients fulfilling inclusion criteria from the records available in our operation theatre and medical records department and data was recorded for analysis.

a.) PATIENT SELECTION

INCLUSION CRITERIA:

1) Patients with keratoconus who have undergone CXL in our Department

EXCLUSION CRITERIA:

1) Incomplete records available for analysis
2) Any prior diagnosis of glaucoma
3) Pre-existing other corneal pathology

PREOPERATIVE ASSESSMENT NOTED:

1. Uncorrected and Best-Corrected Visual Acuity

2. Intraocular pressure

3. Central corneal thickness

4. Topography for Keratometry readings

Procedure for Collagen Crosslinking in our Department:

Corneal collagen crosslinking was performed under sterile conditions in the operation theatre. Under topical anesthesia, the epithelium was removed. Riboflavin drops (Riboflavin>0.1% and HPMC 1%) was topically administered to the cornea for a period of 30 minutes at an interval of 3 minutes. This is done to photosensitize the corneal surface. UV irradiation was then performed with a commercially available apparatus (CCL VARIO) using a wavelength of 365 nm and irradiance of 9mW/cm² for a further 10 minutes with topical administration of riboflavin continued during this period at 3 minutes intervals (Accelerated CXL) or irradiance of 3m/W/cm² for 30 minutes with topical administration of riboflavin continued during this period at 3 minutes interval (Dresden protocol)

Isotonic riboflavin is routinely used. Hypotonic riboflavin is used in patients with thinner corneas.

Steroid regimen in our department:

The patient is followed up daily with topical antibiotic drops till the epithelial defect heals (usually takes 3-4 days). Topical Prednisolone Acetate 1% is then started in the involved eye at 2 hourly intervals for first 1 week and then 4 hourly for one week. The patient is reviewed after 2 weeks. The IOP is measured using Goldmann applanation tonometry and patients categorized as steroid responder or non- responder. Topical antiglaucoma medication, Misopt (Dorzolamide 2% and timolol 0.5% combination) is started in the cross-linked eye if the IOP in this eye is higher than 21 mmHg,

The topical steroid (Prednisolone) drops are slowly tapered over the next 2 months. Dexamethasone eye drops have also been used in some patients instead of prednisolone.

The patient is reviewed after the steroid drop course is over and antiglaucoma medications stopped 1 month following this.

The topography, CCT and Visual acuity are recorded at each follow-up in the cornea clinic, till the study period is complete. Thereafter the patient will continue follow up with the cornea consultant as per department protocol.

The medical records of all patients who underwent CXL in our department from 1st June 2013 were assessed for eligibility to be included in the study.

Progression of keratoconus before performing CXL was compared to that following CXL as per records available in the charts.

OUTCOME:

Primary outcome:

Steroid induced ocular hypertension

-IOP more than 21 mmHg in treated eye as compared to untreated eye at 2 weeks following steroid drop initiation.

- IOP difference of more than 5 mmHg in the treated eye as compared to untreated eye at 2 weeks following steroid drop initiation.

Secondary outcomes:

1. Rate of disease progression before compared to after CXL based on the following specific parameters:
    a. Increase in Keratometry readings taken from topography measurements
    b. Reduction in Central corneal thickness

2. Other CXL related complications e.g. corneal infections, corneal haze.
3. Outcomes of CXL

DEFINING PROGRESSION:

KERATOMETRY :

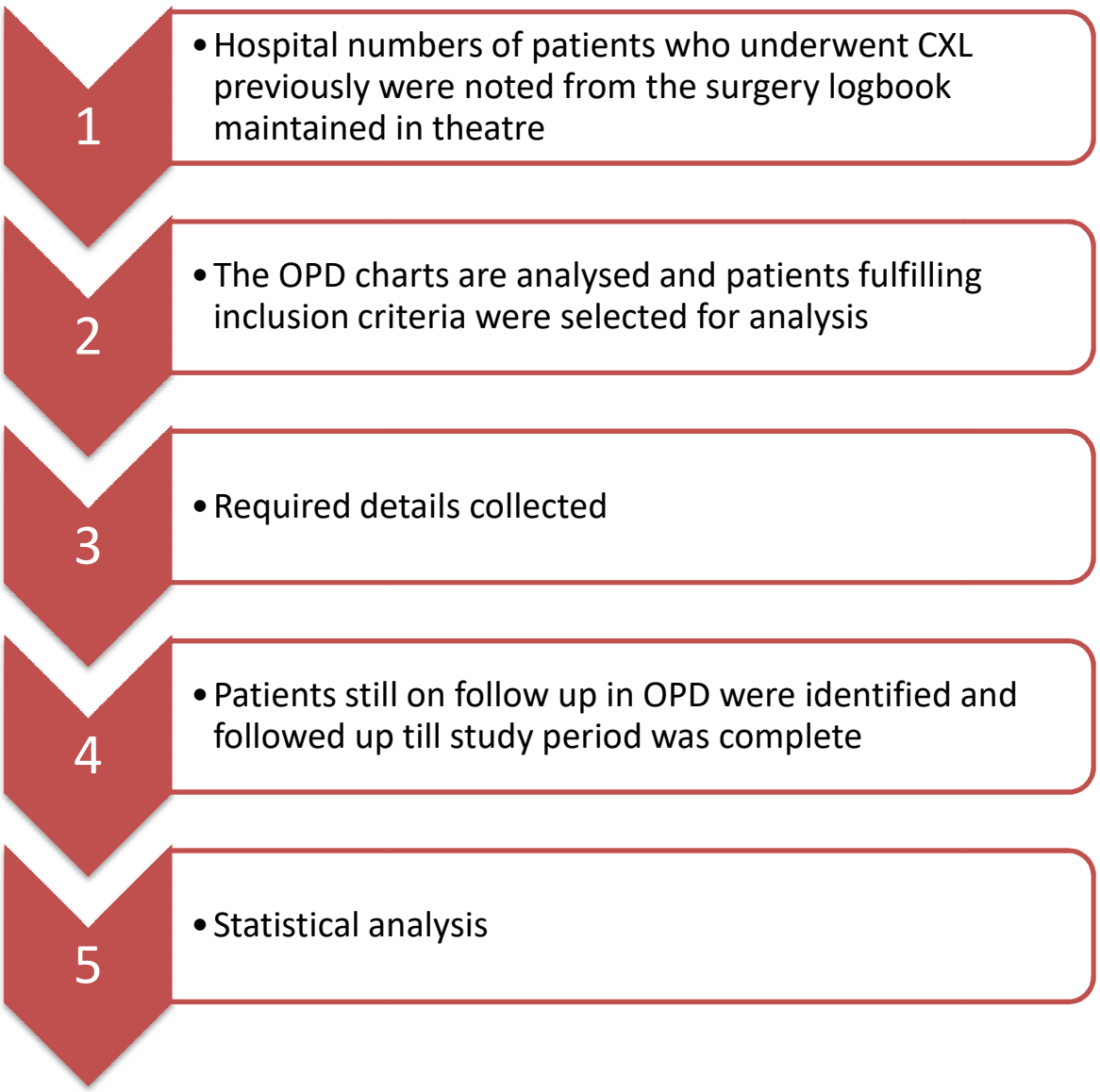
K maximum and K minimum were analysed separately. Maximum and minimum K reading at the final visit of the patient during the study period was taken. A change of K reading within 1 Dioptre of pre-CXL K value was considered 'STABLE'. More than 1 Dioptre reduction was considered 'REDUCTION'. Increase in K by more than 1 Dioptre was considered as 'INCREASED'.

CENTRAL CORNEAL THICKNESS:

CCT was measured pre-CXL and the last CCT available after CXL was noted.

A change of CCT within 10 micrometer (5 above and 5 below) from pre CXL was considered 'STABLE'. An increase in CCT above this was considered 'INCREASED' and a value less than was considered 'DECREASED'.

ALGORITHM:


1
• Hospital numbers of patients who underwent CXL previously were noted from the surgery logbook maintained in theatre
2
• The OPD charts are analysed and patients fulfilling inclusion criteria were selected for analysis
3
• Required details collected
4
• Patients still on follow up in OPD were identified and followed up till study period was complete
5
• Statistical analysis

VARIABLES: Intraocular pressure (IOP), Keratometry (Corneal curvature), Central Corneal Thickness (CCT), Visual acuity, Corneal complications

DATA SOURCES/MANAGEMENT: Direct measurements and Medical records

BIAS: Possible measurement and selection bias may occur.

SAMPLE SIZE CALCULATION:

In order to calculate the sample size for this study, a pilot study was performed using 10 patients. Four patients out of 10 i.e. 40% were found to be steroid responders in this sample.

The following formula was used for sample size calculation.

Formula

$$n = \frac{Z^2_{1-\alpha/2}\, p(1-p)}{d^2}$$

Where,

p : Expected proportion

d : Absolute precision

1- α/2 : Desired Confidence level

Based on our pilot study, the incidence of steroid responders was 40% with 10% precision and 95% confidence interval, the required sample size was calculated as 92. So we need to study nearly 100 subjects.

All patients and medical records that were eligible during the study period based on the study criteria were enrolled**.**

QUANTITATIVE VARIABLES: Intraocular pressure

STATISTICAL METHODS

Qualitative variables were reported using number and percentage. Quantitative variables were summarized using Mean and Standard deviation/Median and Inter Quartile Range (IQR). To check if there was any difference between before and after surgery, Paired t test/Wilcoxon Signed-rank test was used. To study the “over a time change”, repeated measures ANOVA was used. P value at 5% level of significance was considered to be significant. Analysis was carried out using SPSS 21 version.

RESULTS

A total of 102 corneal crosslinking on 87 patients was performed between June, 2013 to August, 2019 . 2 eyes were excluded from the study due to non availability of data.

So a total of 100 eyes of 85 patients were included in the study.15 patients underwent CXL in both eyes.

BASELINE CHARACTERISTICS OF PATIENTS

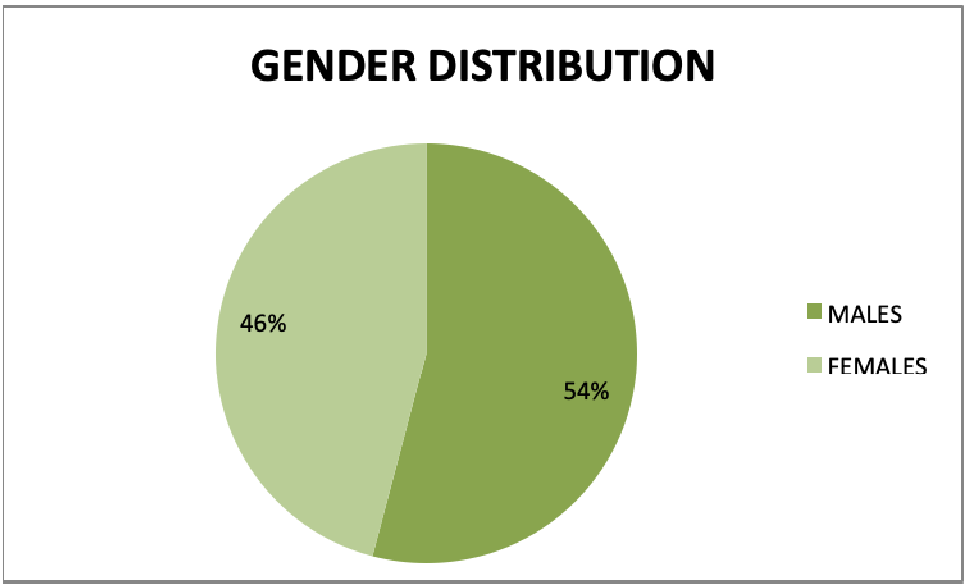
1. GENDER DISTRIBUTION:

Table 1: GENDER DISTRIBUTION

GENDER	FREQUENCY	PERCENTAGE
MALE	46	54
FEMALE	39	46
TOTAL	85	100

Of the 85 subjects included in the study, there were 54% males and 46% females .

Figure 1: GENDER DISTRIBUTION



Males were marginally higher in number than females.

2. AGE DISTRIBUTION:

Table 2: DISTRIBUTION OF AGE (yrs)

Mean	17.071
Median	17.000
Mode	18.0
Std. Deviation	4.0083
Minimum	7.0
Maximum	32.0

The mean age of the 85 patients in the study was 17 years. Most of our patients were in the adolescent age group.There were 2 patients of age 7 which was the minimum age we noted and only 1 patient above 25 years at 32 years(maximum age) who underwent crosslinking.

3. EYE INVOLVED:

Table 3: EYE INVOLVED

EYE	FREQUENCY
RIGHT	51
LEFT	49
TOTAL	100

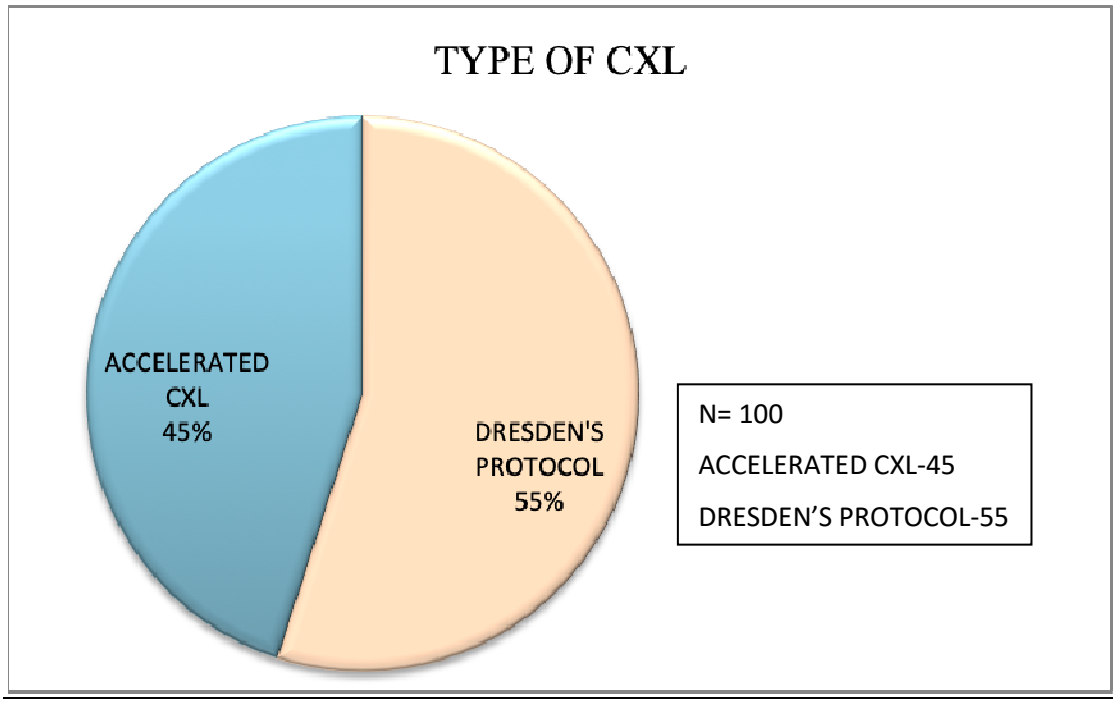
Right and left eyes were almost equally involved. Right eye involved in 51% and left eye in 49%.

4. TYPE OF CXL:

Dresden protocol was followed for CXL at our hospital prior to July, 2017.

Accelerated CXL (9mW/10 mins) is the regimen used in our hospital currently.

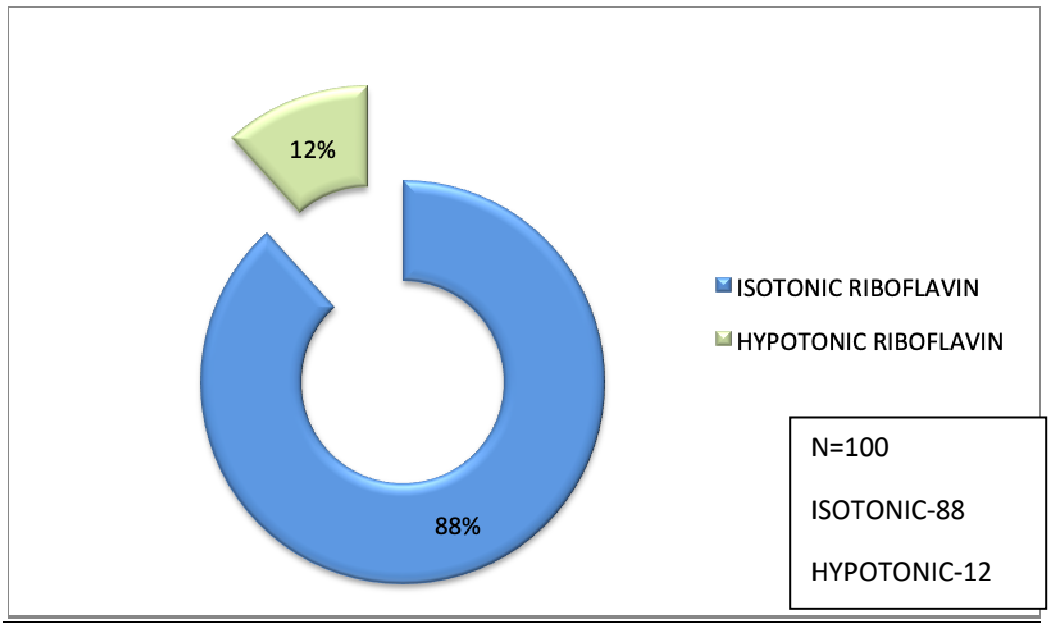
Figure 2 : TYPE OF CXL



Of the 100 patients included in the study, 55 underwent CXL using Dresden protocol and 45 using accelerated CXL protocol.

5. TYPE OF RIBOFLAVIN USED:

Figure 4 : TYPE OF RIBOFLAVIN



Hypotonic riboflavin was used in patients whose central corneal thickness was between 380 micron to 400 microns to prevent endothelial damage. Of the 100 eyes, 12% underwent CXL with hypotonic riboflavin and 88% with isotonic riboflavin.

6. OTHER FEATURES:

Table 4 : OTHER CHARACTERISTICS:

OTHER FEATURES		
Family history of glaucoma		Nil
Connective tissue disorders		Nil
Other associations:	High myopia	1 patient had high myopia with keratoconus
	Retinal detachment	The same patient with high myopia had retinal detachment in one of the eyes
Family history of keratoconus		1 patient had history of keratoconus in mother

One patient had high myopia and subsequently developed retinal detachment in one of the eyes.

There was only one patient with family history of keratoconus in mother.

PRIMARY OBJECTIVE

ASSESSMENT OF STEROID INDUCED OCULAR HYPERTENSION AFTER CXL:

A total of 6 eyes of the 100 were excluded for this part of the study.

2 eyes were excluded due to non availability of IOP data and the other 4 excluded as they were found to be steroid responders when the first eye underwent crosslinking and were therefore started on antiglaucoma medications at the same time as the steroids and hence an IOP assessment in them would not reflect the actual response.

N=94 for the following analysis.

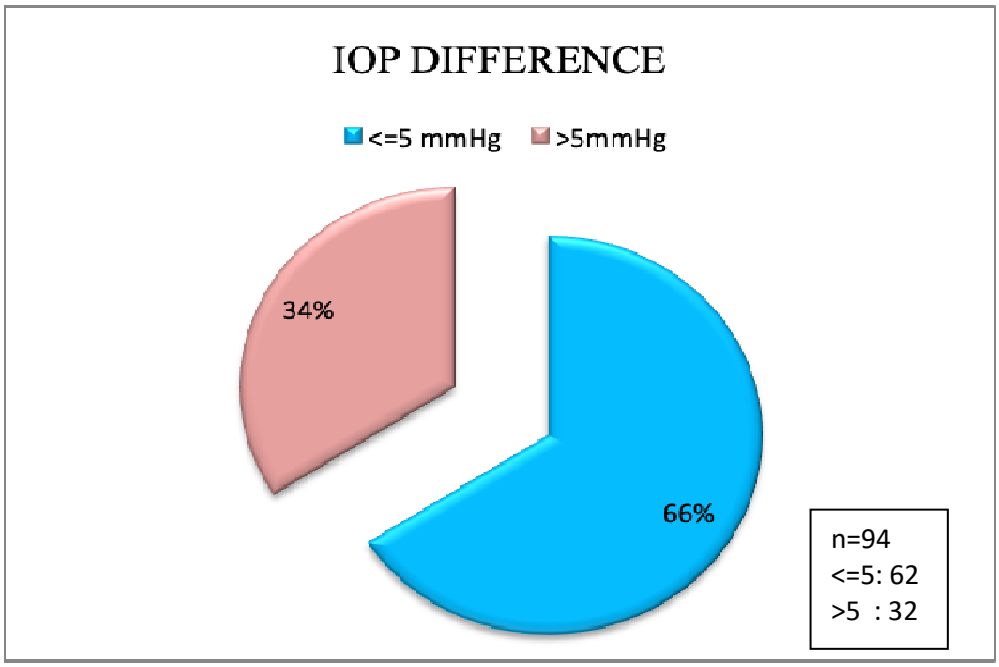
INCREASE IN IOP AFTER CXL AS COMPARED TO PRE-CXL

IOP was analysed by dividing the patients into 2 groups

1. IOP equal to or less than 5mmHg increase as compared to pre-CXL IOP
2. IOP more than 5mmHg increased as compared to pre-CXL IOP.

The following are the results.

Figure 4: IOP DIFFERENCE POST CXL COMPARED TO PRE CXL



Of the 94 eyes studies, 66% had IOP rise <=5mmHg and 34% had IOP rise greater than 5mmHg after CXL compared to pre CXL values.

Table 5: MEAN IOP PRE CXL AND POST CXL

	MEAN mmHg	STD DEVIATION	P VALUE
PREOPERATIVE IOP	11.64	2.55	
POSTOPERATIVE IOP	15.32	4.64	0.00

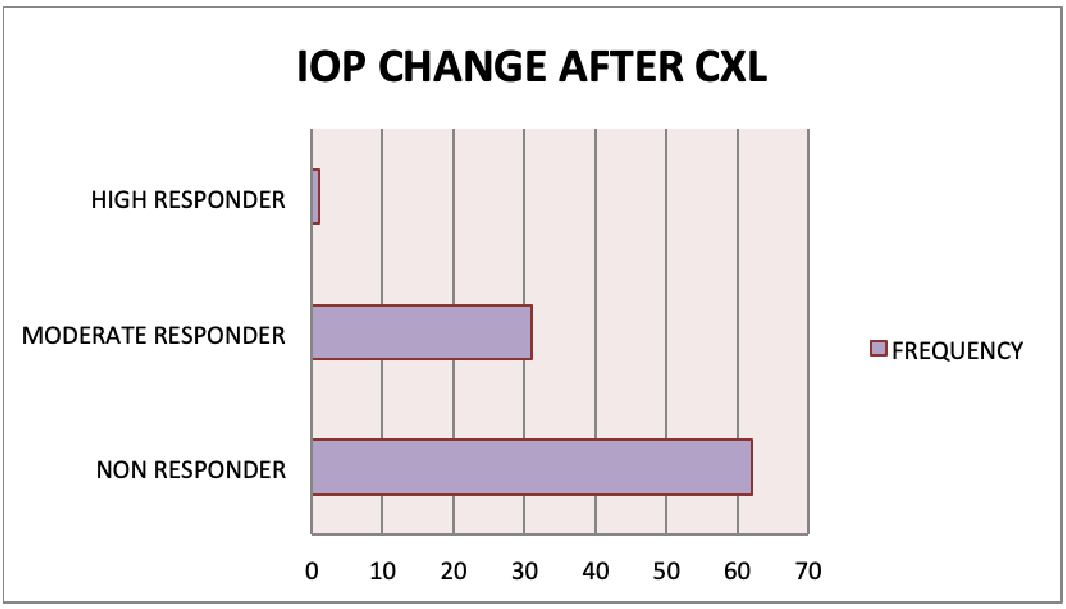
The mean IOP in pre CXL group was 11.6 mmHg and in post CXL group was15.3mmHg. This difference is statistically significant (p=0.000).However, this increase of 4mmHg is not a clinically significant rise in IOP.

Table 6 : DISTRIBUTION OF INCREASE IN IOP POST CXL

IOP (mmHg)	FREQUENCY Nos	PERCENTAGE	CUMMULATIVE PERCENT
<=5	62	66	66
6 - 10	24	25.5	91.5
11 - 15	7	7.4	98.9
>15	1	1.1	100
TOTAL	94	100	

66% were non responders, 25.5% had increase in IOP between 6-10 mmHg, 7.4% had increase in IOP between 10-15mmHg and only 1.1% had marked increase in IOP (>15 mmHg)

Figure 5: DISTRIBUTION OF STEROID RESPONDERS POST CXL



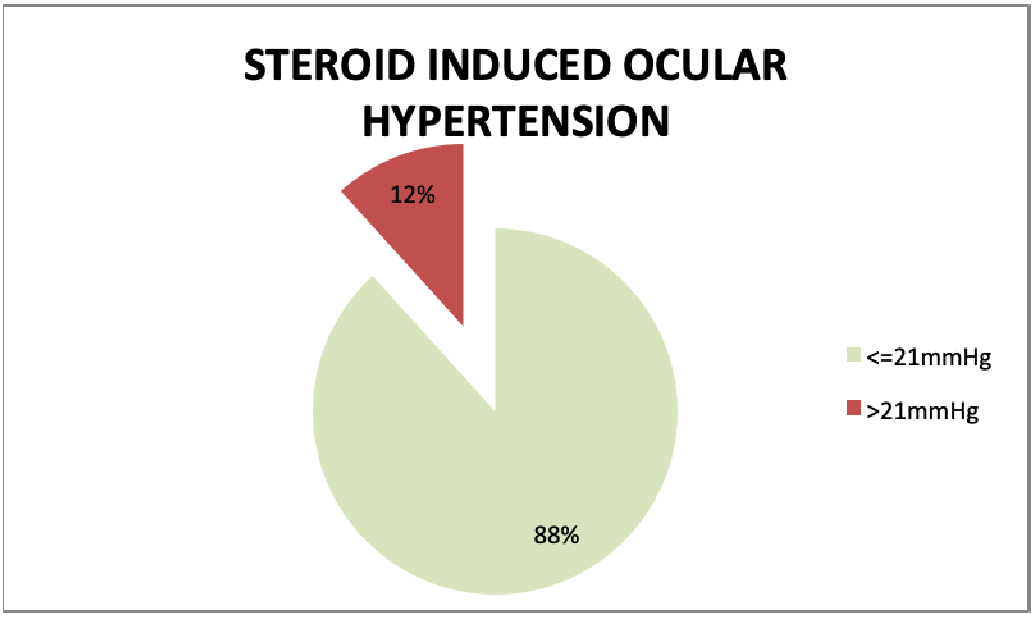
According to Becker's classification of steroid response, only 1 patient was high responder, 31 patients were moderate responders and 62 patients were non responders.

Table 7: INCIDENCE OF STEROID INDUCED OCULAR HYPERTENSION

IOP	FREQUENCY	PERCENTAGE
<=21	83	88.3
>21	11	11.7
TOTAL	94	100

83 eyes out of 94 eyes did not develop an IOP greater than 21mmHg.

Figure 6: STEROID INDUCED OCULAR HYPERTENSION



11 out of 94 eyes (12%) had IOP greater than 21 mmHg post CXL after starting steroids and started on antiglaucoma medications.

CORRELATIONS:

AGE:

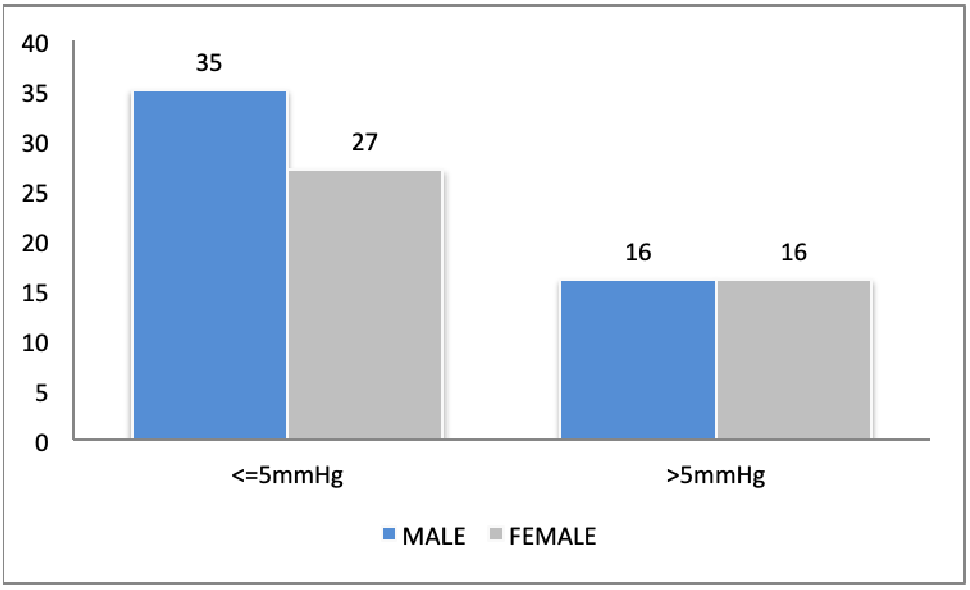
Table 8: CORRELATION OF AGE WITH IOP DIFFERENCE

AGE GROUP	NUMBER	>5mmHg	P VALUE
<=15	31	15	
15-20	47	14	
>20	16	3	0.087
TOTAL	94	32	

The age group was categorised as <=15 years, 15-20 years and >20 years to analyse its association with rise in IOP. The maximum number of patients were in the 15-20 age group(47 patients). There was no statistically significant correlation between age group and rise in IOP greater than 5mmHg (p = 0.087).

GENDER:

Figure 7: ASSOCIATION OF GENDER WITH IOP DIFFERENCE

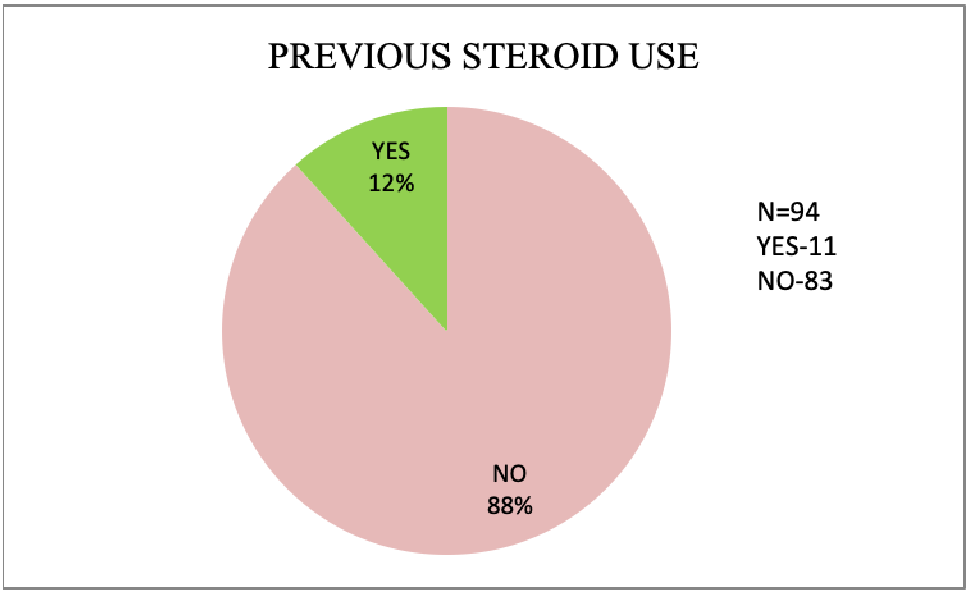


P VALUE-0.552

The male and female ratio in the groups with IOP rise <=5mmHg and >5mmHg did not show any statistical significance (p = 0.552).

PREVIOUS STEROID USE vs IOP DIFFERENCE:

Figure 8: PREVIOUS STEROID USE



11 out of the 94 patients had used topical steroids before; indications being allergic conjunctivitis and post CXL in one eye.

Table 9: ASSOCIATION OF PREVIOUS STEROID USE AND IOP DIFFERENCE

IOP DIFFERENCE VS PREV STEROID USE		FREQUENCY	PERCENTAGE	P VALUE
<=5	**YES**	8	12.9	
	NO	54	87.1	
	TOTAL	62	100	
>5	**YES**	3	9.4	
	NO	29	90.6	0.744
	TOTAL	32	100	

There was no statistical relation between previous steroid use and steroid response among patients after CXL.

PREVIOUS STEROID RESPONSE vs IOP DIFFERENCE :

Among the 94 patients, only 1 had a history of previous steroid response following CXL in one eye but the other eye did not show a increase in IOP after CXL .

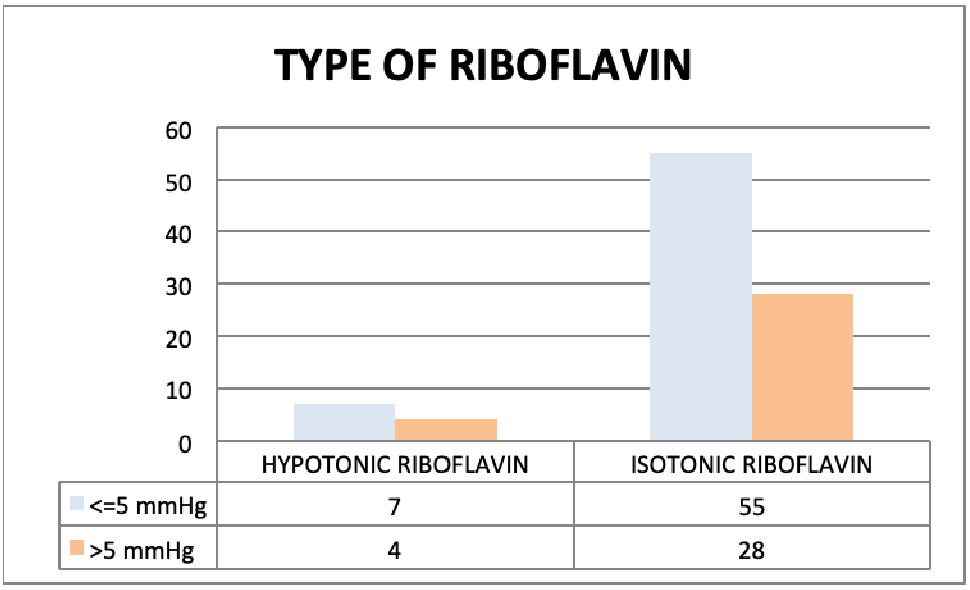
Table 10 : PREVIOUS STEROID RESPONSE RECORDED

IOP DIFF VS PREVIOUS STEROID RESPONSE	PREVIOUS STEROID RESPONSE	FREQUENCY	PERCENTAGE
<=5	YES	1	1.6
	NO	61	
>5	YES	0	0
	NO	32	

The one patient who had a previous steroid response didnot show an increase in IOP >5mmHg during our study.

TYPE OF RIBOFLAVIN vs IOP DIFFERENCE:

Figure 9: TYPE OF RIBOFLAVIN USED AND ASSOCIATION WITH IOP DIFFERENCE



P VALUE-

1.000

The IOP difference in patients treated with isotonic or hypotonic riboflavin was not statistically significant (p=1.00).

66.26% and 33.73% of patients who underwent CXL with isotonic riboflavin had IOP <=5mmHg and >5mmHg respectively. 63.63% and 36.36 % of patients who

underwent CXL with hypotonic riboflavin had IOP <=5mmHg and >5mmHg respectively.

CXL PROTOCOL vs IOP DIFFERENCE:

66% study patients (n=94) had CXL with Dresden protocol and 34% with accelerated CXL protocol.

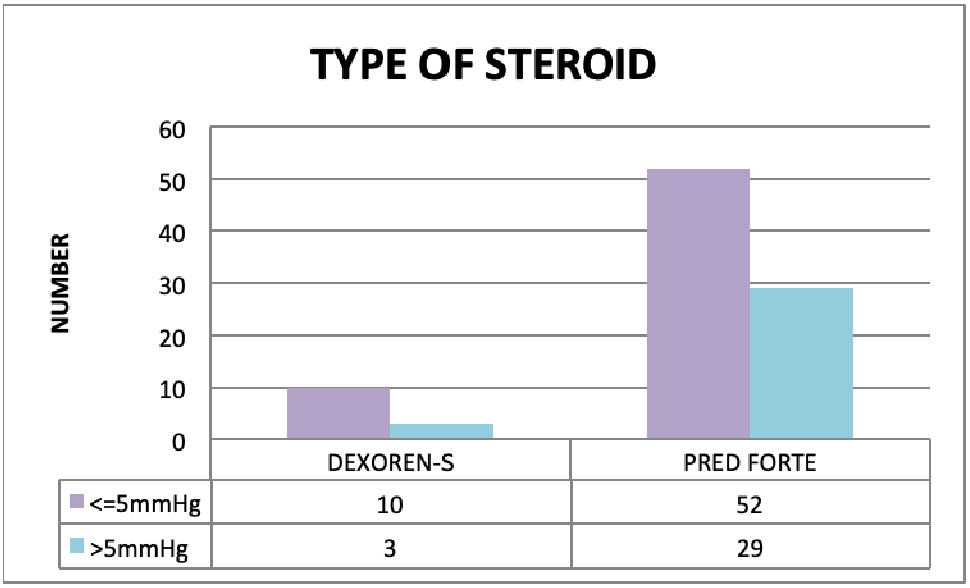
Table 11: TYPE OF PROTOCOL AND ASSOCIATION WITH IOP DIFFERENCE

IOP DIFF VS PROTOCOL		FREQUENCY	PERCENTAGE	P VALUE
<=5	DRESDEN	35	56.5	
	ACCELERATED	27	43.5	
	TOTAL	62	100	
>5	DRESDEN	16	50	
	ACCELERATED	16	50	0.552
	TOTAL	32	100	

Statistical analysis of IOP rise with type of protocol used did not show any statistical significance (p = 0.552).

STEROID USED VS IOP DIFFERNCE:

Figure 10: TYPE OF STEROID USED AND IOP DIFFERENCE



Of the 13 patients who were started on Dexoren-S (Chloramphenicol + Dexamethasone) post CXL, 3 (23.1%) had raise in IOP>5mm Hg. Of the 81 patients started on Prednisolone acetate drops, 29 patients (35.8%) had raise in IOP >5mmHg.

Table 12: TYPE OF STEROID AND IOP DIFFERENCE

IOP DIFF VS	STEROID USED	FREQUENCY	PERCENTAGE	P VALUE
<=5	DEXOREN S	10	16.1	
	PRED FORTE	52	83.9	
	TOTAL	62	100	
>5	DEXOREN-S	3	9.4	
	PREDFORTE	29	90.6	0.532
	TOTAL	32	100	

In the <=5 mmHg group, 83.9% used Prednisolone acetate and in >5mmHg group ,90.6% used Prednisolone acetate eye drops.

Among Dexamethasone eye drops users 30% had raise in IOP >5mmHg where as among prednisolone group there were 56% with raise in IOP >5mmHg. However their numbers are uneven with only 13 in dexamethasone group and 81 in the other group. There was no statistically significant association between type of steroid used and IOP difference (p = 0.532).

PRE CXL CCT vs IOP DIFFERENCE:

Immediate pre-CXL CCT was unavailable in 10 of the study patients - 8 missing in the <=5mmHg group and 2 among >5mmHg group.

Hence 84 patients were included for this analysis.

Table 13: PRE CXL CCT AND ASSOCIATION WITH IOP CHANGE

	N	MEAN CCT PRE CXL	P VALUE
<=5mmHg	54	429.3	
>5mmHg	30	442.5	0.176

The mean of CCT across the 84 patients were taken pre-CXL and compared to post CXL mean CCT. The mean CCT pre and post CXL were 429 and 442 respectively. This was not statistically significant (p = 0.176).

SECONDARY OBJECTIVES:

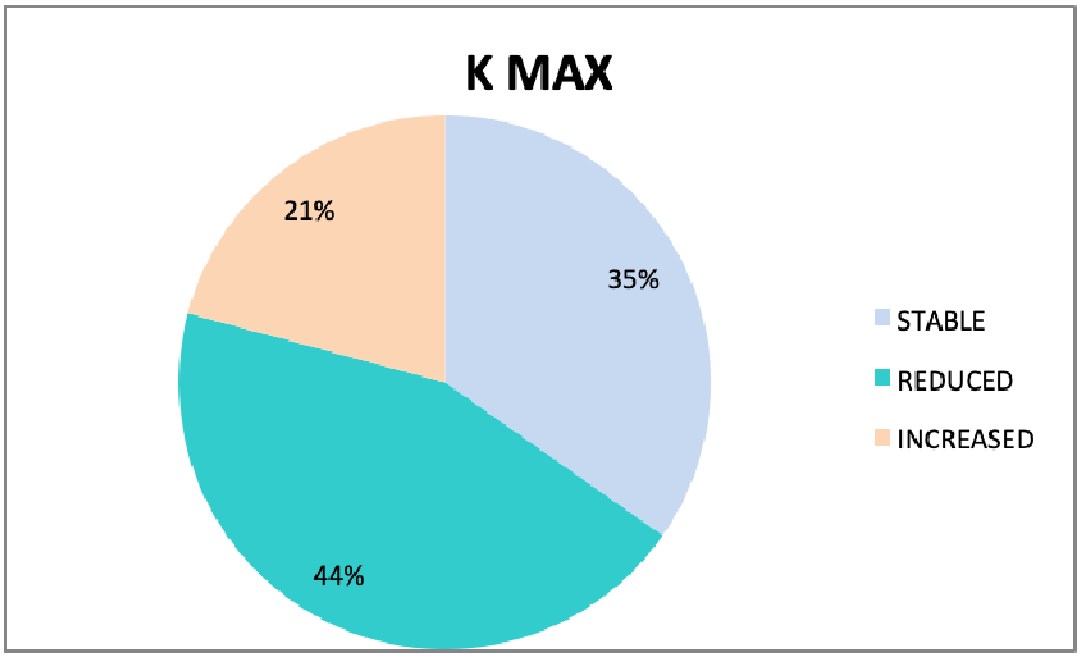
1. K PROGRESSION BEFORE AND AFTER CXL:

72 subjects were included in the analysis of K reading after CXL. The rest were excluded due to non availability of data; either lost to follow up or CXL done within the last 6 months of the study for whom repeat K reading is not yet due.

A difference of K reading within 1 Dioptre of pre CXL value at the final visit during study was taken as stable. If post CXL is >1 Dioptre and <1 Dioptre of pre CXL value ; its taken as increased and decreased respectively.

K MAXIMUM:

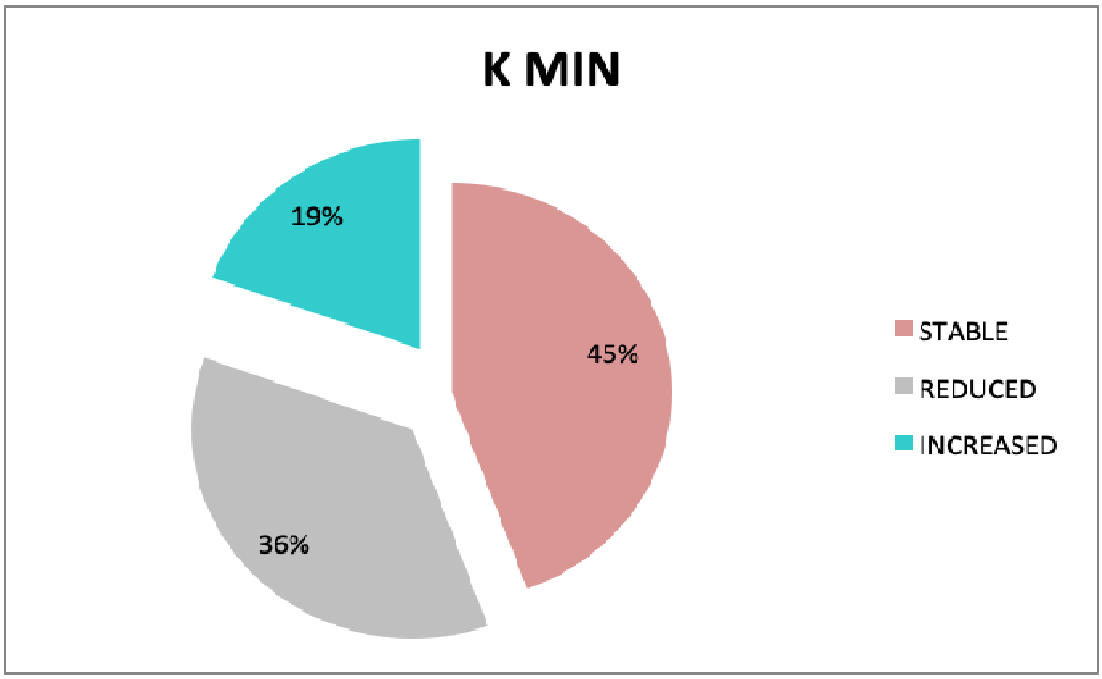
Figure 11: K MAX CHANGE AFTER CXL



K maximum was stable in 35% and reduced in 44% patients. A cumulative percentage of those whose K maximum reading were either stable or reduced was 79%. Only 21% continued to show a progression after CXL.

K MINIMUM:

Figure 12: K MIN CHANGE AFTER CXL

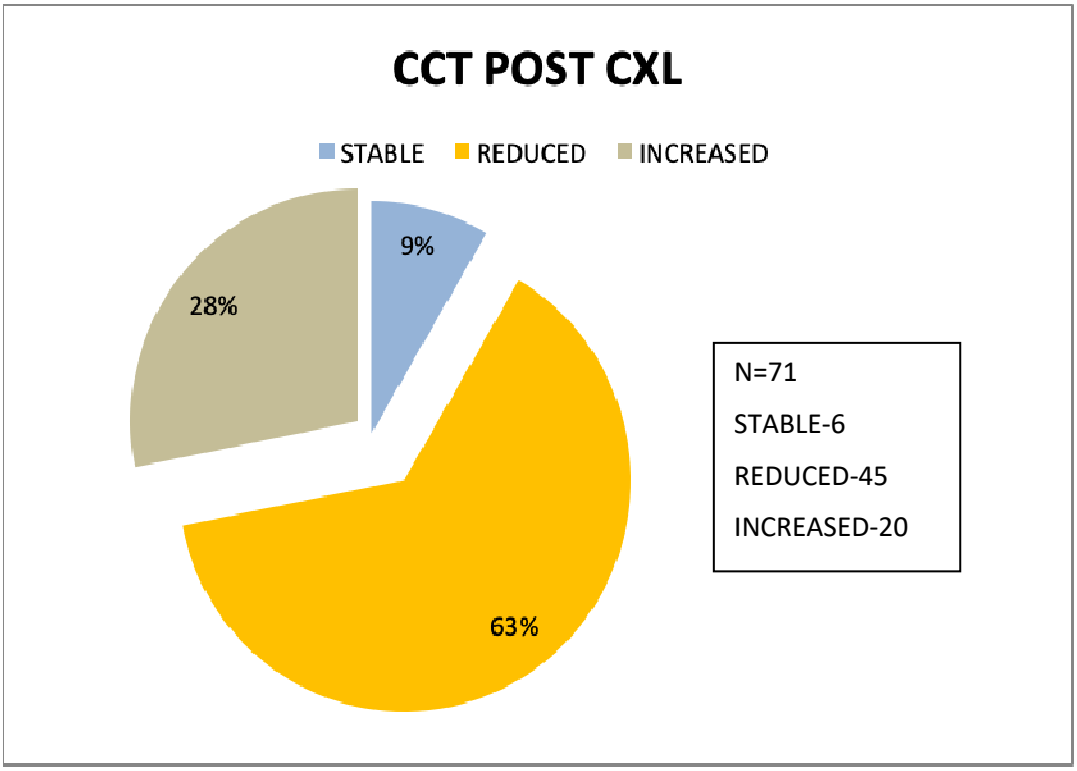


K minimum was stable in 45% and reduced in 36% of patients. A cumulative percentage of patients whose K minimum either stabilised or reduced after CXL was 81% . Only 19% continued to progress.

2. CCT AFTER CXL :

CCT change within 10 microns was considered stable (5 microns above and below the pre CXL value).

Figure 13: CCT CHANGE AFTER CXL



Analysis showed a decreasing trend after CXL in 63%.CCT was stable in 9% and increased in 28%.

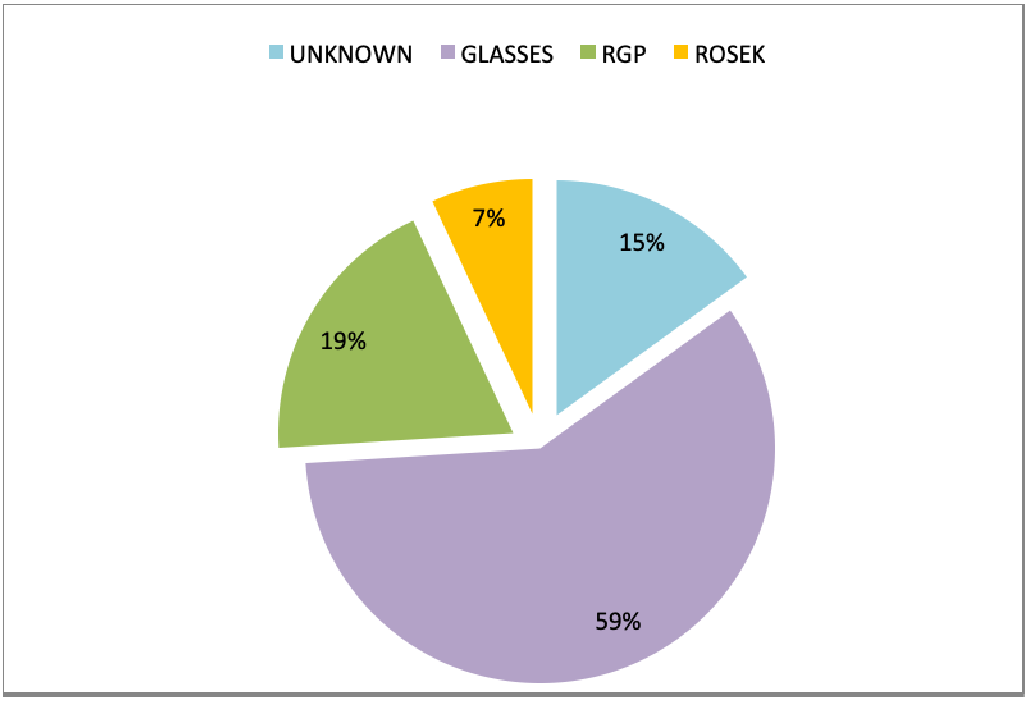
3.VISION AFTER CXL:

Vision after CXL could not be analysed due to lack of uniformity in the method used for assessment of best corrected visual acuity. No patient had a drop in the BCVA following CXL. All patients improved to 6/9 or better when Rose K lenses were trialed on the patient.

4.OUTCOMES:

All 100 patients who underwent CXL are included to study the outcomes of CXL

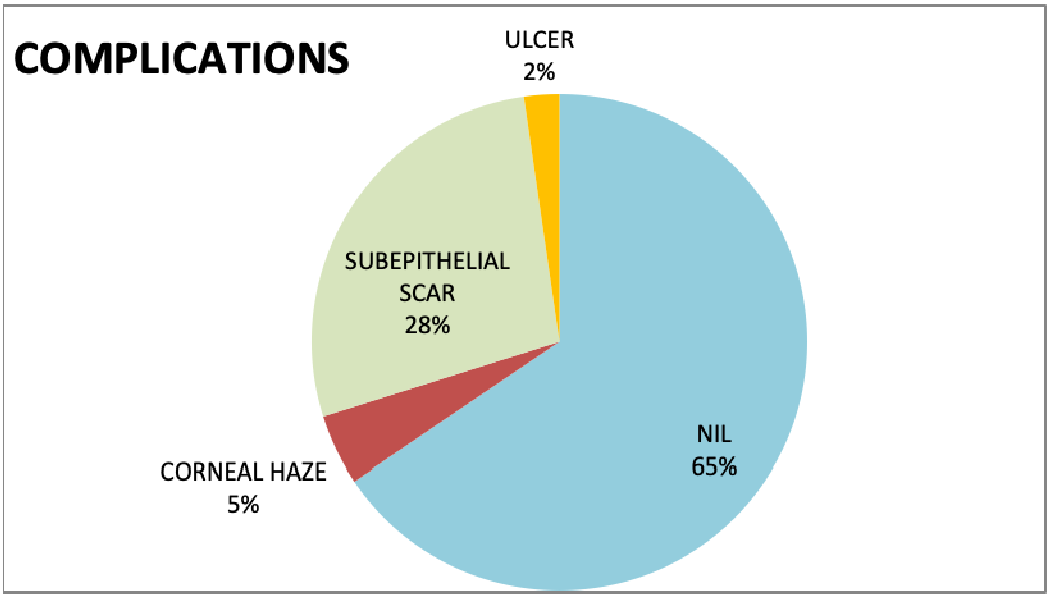
Figure 14: OUTCOMES OF CXL



7% of patients have so far opted for Roses K lenses. 19% of patients are using Rigid Gas Permeable lenses, and the majority (59%) are using glasses. Unknown category included patients who have been lost to followup and as well as those who recently underwent crosslinking and were awaiting final visual assessments.

5. COMPLICATIONS:

Figure 10: COMPLICATIONS OF CXL



65% did not have any complications. 28 % of patients developed a faint subepithelial scar, which was not visually significant. 5% was documented to have a corneal haze. Ulcer developed in 2 patients out of 100 which responded well to treatment.

DISCUSSION

Steroid induced ocular hypertension has to be borne in mind by the surgeons and also explained to the patients while administering topical steroids. It is usually reversible after stopping the steroids but administering anti glaucoma medications along with the steroids is necessary to prevent glaucomatous changes among steroid responders. Steroids are routinely administered after cataract surgery and the steroid response among cataract patients is not as high as that among keratoconus patients post corneal crosslinking. Steroid induced rise in intraocular pressure post keratoplasty and PRK among keratoconus patients have been reported (49) but we did not find reports of steroid induced ocular hypertension among keratoconus patients after corneal crosslinking.

This was a historical prospective study conducted by looking at hospital records between June 2013 and August 2019 .

Most of our study patients were in the adolescent age group. Keratoconus usually progresses in children, adolescents and stabilises as age increases.

STEROID INDUCED OCULAR HYPERTENSION:

IOP measurments were taken with the applanation tonometer. At present there are no reliable normograms for correction of IOP with corneal thickness less than 445 microns as is the case in keratoconus. Hence, for this study, uncorrected IOP has been used. In glaucoma practice a correction factor for IOP measurements has been worked out based on corneal thickness and corneas are classified as either thin, average or thicker The IOP recordings in patients with thinner corneas have been found to be lower than the actual IOP of the patient.

Thus the IOPs recorded in this study may be an under-representation of the actual IOP in these patients with thin corneas.

According to Becker (3), 66% of patients in normal population are non responders (IOP rise <=5mmHg), 29% are intermediate responders (IOP rise between 6-15mmHg) and 5% of them are high responders (IOP rise more than 15mmHg).

In our study , 66% of patients were non responders , 32.9% of patients are intermediate responders and 1.1% was high responders. Thus, this study shows a similar incidence of non-responders as in the general population. The intermediate responders are marginally higher than in the normal population, but this was not statistically significant.

Only 11.7% of the 94 subjects had steroid induced ocular hypertension (IOP >21mmHg) and was started on anti glaucoma medications. Most of the patients who had an increase in IOP of more than 5mmHg, had actual values less than 21mmHg.

The mean IOP of patients pre CXL and post CXL was statistically significant p=0.000.This shows that there is a definite increase in IOP after administration of steroids after CXL and surgeons should carefully look into it.

CORRELATIONS:

There was no association between age of patient and IOP difference. Younger children are generally more prone for steroid response than others but our study did not show any association.

There was no association between gender, previous steroid use, previous steroid response and IOP difference after CXL.There was no association between the type of riboflavin used and the type of protocol used and steroid response. There are no previous studies to compare these data.

Prednisolone acetate and dexamethasone are potent steroids and causes more steroid response than others (17). Our study did not show any statistically

significant difference between the groups who used dexamethasone eye drops and prednisolone acetate eye drops.

SECONDARY OUTCOMES:

Studies have shown a decrease in K reading by 1 year and no change compared to pre CXL by 60th month and overall reduced disease progression (60,61,63). Our study also did show a reduction in K reading after CXL.

A cumulative percentage of 79% patients either had their K max stable or reduced. A cumulative percentage of 81% patients either had their K minimum stabilised or reduced.

CCT change after crosslinking reduced in 63% and was stable in 9% .There was an increase in CCT seen in 28%. Other studies also show a reduction in CCT after CXL at 1 year. (71)

Outcome of CXL - Almost all our patients had at least 6/9 vision with RoseK lenses or conventional RGPs. However due to patient's preference, age and financial status; glasses were the most preferred option for of correction (59%) followed by RGP (19%) and only 7% used RoseK lenses. Rose K lenses have only been introduced in our department in the last 2 years, and are expensive. It was

noted that most of those patients using glasses continue to do so as they have at least 1 eye that corrects reasonably with spectacles.

65% of patients did not have any complications. 28% had a subepithelial faint corneal scar out of which 1 had a pre-CXL scar and 5% had corneal haze persistent. The incidence of stromal scar in study by Koller et al was found to be 2.9% and almost all eyes had corneal haze which cleared off in many by 6 weeks (67). However our study showed a higher percentage of subepithelial scars. This might be because of variability in documentation by the observers and corneal haze / scar would have been used interchangeably. None of our patients had drop in vision post CXL and most had good vision with RGP or Rose K lenses.

Our study shows 2% (2 out of 100) had corneal infiltrates which resolved with topical medications. A study by Koller reported 7.9% infiltrates (67). Ulcers are more prone to develop in epithelium-off CXL; all our cases have been epithelium-off CXL.

Hence, even though there are reports in literature which quote an incidence of steroid induced glaucoma in keratoconus eyes post PKP as 32% (46), 4% (47) and 15%(48) in various studies as well as reports of 43% of steroid induced ocular hypertension when combined CXL with a corneal laser procedure was reported

done (49),there were no previous studies to compare the incidence of steroid induced ocular hypertension post CXL alone.

Hence, we undertook a retrospective study to determine if there was an increased incidence of steroid induced ocular hypertension in such patients.

The results of our study does not show an abnormally high incidence of steroid induced ocular hypertension as compared to the normal population.

CONCLUSIONS

- Incidence of steroid induced ocular hypertension in keratoconus patients post CXL is comparable with the incidence of steroid response in normal population .
- The percentage of intermediate steroid responders and high responders among them are also similar to the normal population.
- There were no associations between rise in intraocular pressure with age , gender, previous steroid use, type of steroid, type of riboflavin or type of protocol used for CXL.
- Keratometry readings and CCT were either stable or reduced after CXL in most patients.
- Serious complications with CXL is not common. Corneal subepithelial scar / haze was the most frequently seen complication .
- Glasses were most preferred among the patients post CXL.
- RoseK lenses and RGP s gave almost all patients vision of 6/9 or better.

LIMITATIONS

1. A change in the CXL technique and protocol used has been implemented in the department over the 6 years study duration.

2. The measurement of IOP has been by multiple observers at different times of the day and hence an inter observer variability and normal diurnal variation would create a bias.

3. The corneal thickness correction to IOP was not done due to unavailability of standard normograms and hence its influence on the result is not known.

4. The trend over the years of the change in Keratometery and Central Corneal Thickness could not be assessed due to non availability of data.

5. Change in best corrected vision before and after CXL could not be assessed due to loss of patients to follow up and non uniformity in data collection.

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ANNEXURES

1.ABSTRACT

2.DATA COLLECTION SHEET

3.IRB APPROVAL FORM

The information sheet and consent form have not been used in the study since it was a retrospective study and hence not attached.

ABSTRACT:

TITLE : A Historical Prospective Observational study of patients with keratoconus to determine the incidence of steroid induced ocular hypertension following collagen crosslinking

DEPARTMENT :Ophthalmology

NAME OF THE CANDIDATE : Minu George P

DEGREE AND SUBJECT : MS Ophthalmology

NAME OF THE GUIDE :Dr. Sanita Korah

OBJECTIVES:

1. To determine the incidence of steroid induced ocular hypertension in patients with keratoconus after use of topical steroids following collagen crosslinking (CXL)

2. To study the effect of CXL on Keratometry reading, central corneal thickness, visual acuity

3. To study the complications and outcome of CXL

METHODS:

This was a historical prospective study done on patients with keratoconus who had undergone CXL in our department. The data from June, 2013 to August, 2019 was collected from the hospital records and the variables noted included preoperative and postoperative IOP measurement, Keratometry reading, central corneal thickness and visual acuity. Outcomes and complications of CXL were also recorded. Data entry was done in Microsoft Excel and analysis done by SPSS software 21 version.

RESULTS:

Incidence of steroid induced ocular hypertension in keratoconus patients post CXL was 34% .There is a statistically significant (p=0.00) rise in intraocular pressure after steroid use. There were no associations between rise in IOP with age, gender, type of steroid, type of riboflavin or type of protocol used for CXL.

Keratometry readings and CCT were stable/reduced after CXL in 80% and 72% respectively. Complications with CXL were corneal subepithelial scar / haze (33%) and corneal infiltrate(2%). Glasses were most preferred (65%) among the patients post CXL. RoseK lenses and RGP s gave almost all patients vision of 6/9 or better.

CONCLUSION:

1. There is no increased incidence of steroid induced hypertension, or steroid response over that of the normal population in patients with keratoconus on topical steroids following had Collagen Crosslinking.
2. The keratometry readings reduced or remained stable for the time duration following CXL that was studied.

The major complications following CXL was Corneal subepithelial scarring. This however, did not affect the vision in any patient.

DATA COLLECTION SHEET

1. STUDY TITLE: A Historical Prospective Observational study of patients with Keratoconus to determine the incidence of steroid induced ocular hypertension and progression of disease following collagen crosslinking

SERIAL NUMBER:

DATE :____/_____/_____ HOSPITAL NUMBER: _____

NAME : _____ AGE :____

SEX : MALE / FEMALE

ADDRESS :

_____

_____

_____

CONTACT NUMBER: _____

HISTORY:

• Eye involved	Right	Left
• Family history of glaucoma	Yes	No
• History of previous/present steroid	Yes	No

use		
• History of steroid response	Yes	No
• Connective tissue disorder	Yes If yes, mention disease	No

Any other comorbidities, Mention:

Prior history of steroid response:

Right

Left

DATE OF CXL:		

CXL: ISOTONIC RIBOFLAVIN ☐ HYPOTONIC RIBOFLAVIN ☐

DRESDEN'S PROTOCOL ☐ ACCELERATED CXL ☐

PART 1:

PRE-OPERATIVE INTRAOCULAR PRESSURE:		
IOP AFTER 2 WEEKS OF STARTING STEROIDS:		

DATE OF STARTING STEROIDS:	
ANTIGLAUCOMA MEDICATION USED	
DURATION OF ANTIGLAUCOMA MEDICATION USE:	

PART 2

TMS

	DATE	RIGHT EYE		LEFT EYE	
		K1	K2	K1	K2
Pre CXL K At diagnosis Last Pre-CXL					
Post CXL 1yr					
Post CXL 2yrs					
Post CXL 3 yrs					
Post CXL 4 yrs					
Post CXL 5 yrs					

Post CXL 6 yrs						

CCT

	DATE	RIGHT		LEFT
Pre CXL CCT At diagnosis Last Pre-CXL				
Post CXL 1yr				
Post CXL 2yrs				
Post CXL 3 yrs				
Post CXL 4 yrs				
Post CXL 5 yrs				
Post CXL 6 yrs				

VISUAL ACUITY

	UNCORRECTED VISUAL ACUITY		BEST CORRECTED VISUAL ACUITY	
	RIGHT	LEFT	RIGHT	LEFT
PRE CXL At diagnosis Last Pre CXL				
Post CXL 1 yr				
Post CXL 2 yrs				
Post CXL 3 yrs				
Post CXL 4 yrs				
Post CXL 5 yrs				
Post CXL 6 yrs				

COMPLICATIONS	Corneal haze / corneal scar / corneal ulcer / Others:
OUTCOME	GLASSES / RGP / ROSE K / PKP

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Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

June 06, 2019

Dr.Minu George P,
PG Registrar,
Department of Ophthalmology,
Christian Medical College.

Sub: **Fluid Research Grant: New Proposal:**
A Historical Prospective Observational study of patients with Keratoconus to determine the incidence of steroid induced ocular hypertension following collagen crosslinking.
Dr.Minu George P, Post graduate registrar, Ophthalmology, Dr. Sanita Korah, Dr. Alo Sen, Department of ophthalmology, Ms. Poornima Sr.Demonstrator, Dept of Biostatistics.

Ref: IRB Min. No. 11678 [OBSERVE] dated 03.12.2018

Dear Dr.Minu George P,

The Institutional Review Board (**Blue**, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project titled "A Historical Prospective Observational study of patients with Keratoconus to determine the incidence of steroid induced ocular hypertension following collagen crosslinking." on December 03rd 2018.

The Committee reviewed the following documents:

1. IRB application format
2. Consent and Assent form and Information Sheet (English, Tamil, Hindi, Bengali)
3. Cv's of Drs. Alo Sen, Sanita, Poornima, Minu George.
4. Data Collection Form
5. No. of documents 1- 4

The following Institutional Review Board (Blue, Research & Ethics Committee) members were present at the meeting held on December 03rd 2018 in the New IRB Room, Bagayam, Christian Medical College, Vellore 632 004.

Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002
Tel: 0416 – 2284294, 2284202 Fax: 0416 – 2262788, 2284481 E-mail: research@cmcvellore.ac.in

OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA

Dr. B.J. Prashantham, M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

Dr. Anna Benjamin Pullmood, M.B.B.S., MD., Ph.D.,
Chairperson, Research Committee & Principal

Dr. Biju George, M.B.B.S., MD., DM.,
Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

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Dear Dr. Minu George P,

I enclose the following documents:-

1. Institutional Review Board approval 2. Agreement

Could you please sign the agreement and send it to Dr. Biju George, Addl. Vice Principal (Research), so that the grant money can be released.

With best wishes,

Dr. Biju George
Secretary (Ethics Committee)
Institutional Review Board

Dr. BIJU GEORGE
MBBS., MD. DM
SECRETARY - (ETHICS COMMITTEE)
Institutional Review Board
Christian Medical College, Vellore - 632 002.

CC: Dr. Sanita Korah, Ophthalmology, Vellore

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Dr. Biju George, M B B.S., MD., DM.,
Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

Name	Qualification	Designation	Affiliation
Dr. Biju George	MBBS, MD, DM	Professor, Haematology, Research), Additional Vice Principal , Deputy Chairperson (Research Committee), Member Secretary (Ethics Committee), IRB, CMC, Vellore	Internal, Clinician
Dr. B. J. Prashantham	MA(Counseling Psychology), MA(Theology), Dr. Min(Clinical Counselling)	Chairperson, Ethics Committee, IRB. Director, Christian Counseling Centre, Vellore	External, Social Scientist
Mr. C. Sampath	BSc, BL	Advocate, Vellore	External, Legal Expert
Dr. Ratna Prabha	MBBS, MD (Pharma)	Associate Professor, Clinical Pharmacology, CMC, Vellore	Internal, Pharmacologist
Mr. Samuel Abraham	MA, PGDBA, PGDPM, M. Phil, BL.	Sr. Legal Officer, CMC, Vellore	Internal, Legal Expert
Dr. John Jude Prakash	MBBS, MD	Professor, Clinical Virology, CMC, Vellore	Internal, Clinician
Dr. Rekha Pai	BSc, MSc, PhD	Associate Professor, Pathology, CMC, Vellore	Internal, Basic Medical Scientist
Mrs. Sophia V	M.Sc Nursing	Addl. Deputy Dean CMC, Vellore	Internal, Nurse
Dr. Ekta Rai	MBBS, MD MRCA	Professor, Department of Anaesthesia, CMC, Vellore	Internal, Clinician
Rev. Joseph Devaraj	BSc, BD	Chaplaincy Department, CMC, Vellore	Internal, Social Scientist
Dr. Inian Samarasam	MS, FRCS, FRACS	Professor, Surgery, CMC, Vellore	Internal, Clinician
Dr. Jayaprakash Muliyil	BSC, MBBS, MD, MPH, Dr PH (Epid), DMHC	Retired Professor, CMC, Vellore	External, Scientist & Epidemiologist

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Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

Mrs. Nirmala Margaret	MSc Nursing	Addl. Deputy Nursing Superintendent, College of Nursing, CMC, Vellore	Internal, Nurse
Dr. Asha Solomon	MSc Nursing	Associate Professor, Medical Surgical Nursing, CMC, Vellore	Internal, Nurse
Dr. Santhanam Sridhar	MBBS, DCH, DNB	Professor, Neonatology, CMC, Vellore	Internal, Clinician
Dr. Ajith Sivadasan	MD, DM	Professor, Neurological Sciences, CMC, Vellore	Internal, Clinician
Mrs. Sheela Durai	MSc Nursing	Professor, Medical Surgical Nursing, CMC, Vellore	Internal, Nurse
Dr. Winsely Rose	MBBS, MD (Paed)	Professor, Paediatrics, CMC Vellore	Internal, Clinician
Dr. Premila Abraham	M.Sc. Ph.D	Professor, Department of Biochemistry, CMC, Vellore	MBBS, MD (Paed)
Dr. Shyam Kumar NK	MBBS, DMRD, DNB, FRCR, FRANZCR	Professor, Radiology, CMC, Vellore	Internal, Clinician
Dr. Vivek Mathew	MD (Gen. Med.) DM (Neuro) Dip. NB (Neuro)	Professor, Neurology, CMC, Vellore	Internal, Clinician
Ms. Grace Rebekah	M.Sc., (Biostatistics)	Lecturer, Biostatistics, CMC, Vellore	Internal, Statistician
Dr. Barney Isaac	MBBS, DNB (Respiratory Diseases)	Associate Professor, Pulmonary Medicine, CMC, Vellore	Internal, Clinician

We approve the project to be conducted as presented.

Kindly provide the total number of patients enrolled in your study and the total number of Withdrawals for the study entitled: "A Historical Prospective Observational study of patients with Keratoconus to determine the incidence of steroid induced ocular hypertension following collagen crosslinking" On a monthly basis. Please send copies of this to the Research Office (research@cmcvellore.ac.in).

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DATA

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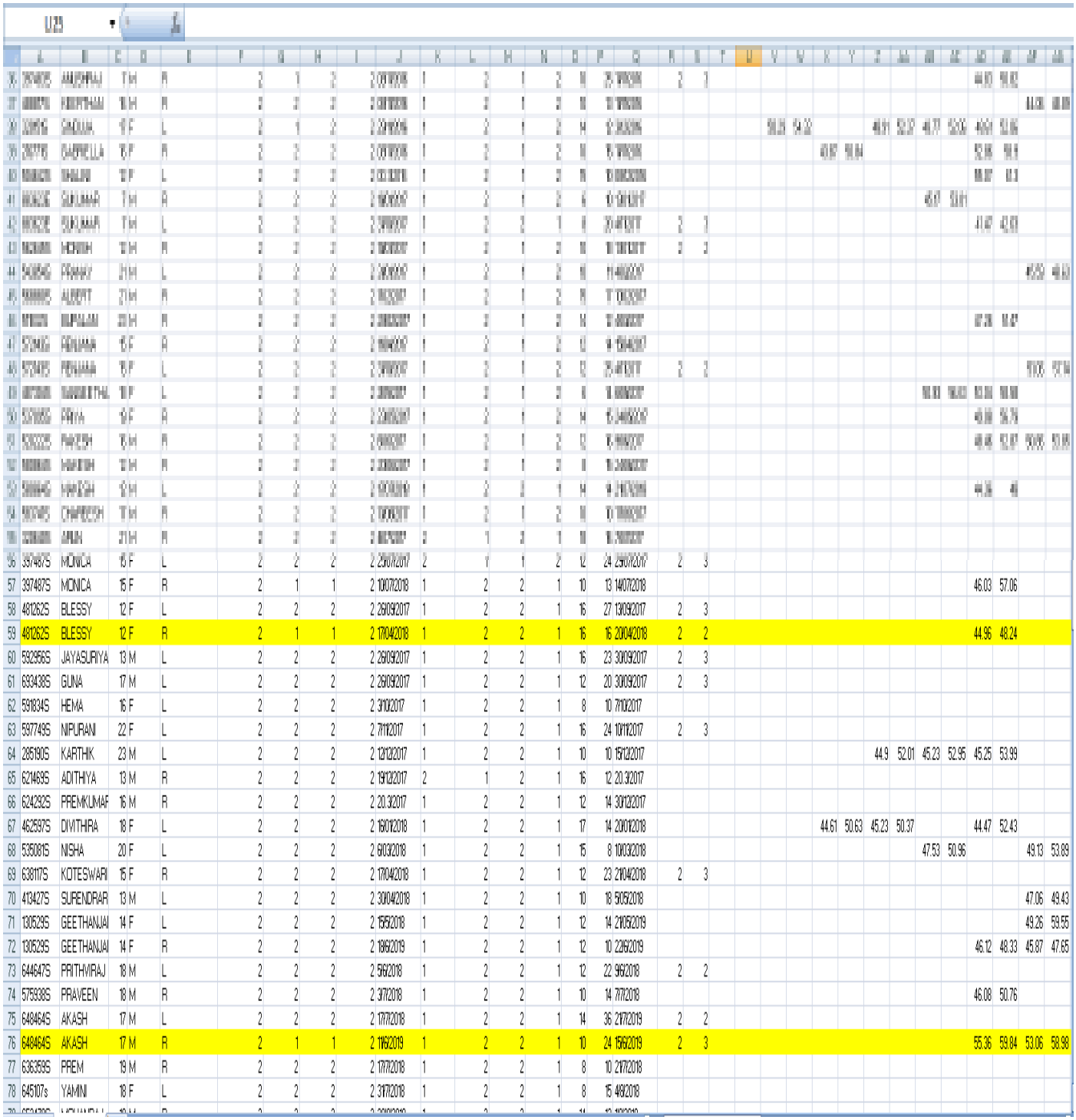
	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W	X	Y	Z	AA	AB	AC	AD	AE	AF	AG
1	HOSP. NO	NAME	AGE	GENDER	EYE INVOLVED	FAMILY HISTORY OF GLAUCOMA	HISTORY OF PREVIOUS PROMINENT STEROID USE	HISTORY OF STEROID RESPONSE	CONNECTIVE TISSUE DISORDER	DATE OF CXL	CXL ISOTONIC RIBOFLAVIN	HYPOTONIC RIBOFLAVIN	DRESDEN PROTOCOL	ACCELERATED CXL	PRE-OPERATIVE INTRAOCULAR PRESSURE	IOP AFTER AVERAGE ?? OF STARTING STEROID	DATE OF STEROIDS	ANTIGLAUCOMA MEDICATION USED	DURATION OF ANTI GLAUCOMA MEDICATION	K PRE CXL		K PRE CXL 5		K PRE CXL 4		K PRE CXL 3		K PRE CXL 2		PRE CXL 1		K PRE CXL [illegible]	
2																			MONTHS	K MIN	K MAX	K MIN	K MAX	K MIN	K MAX	K MIN	K MAX	K MIN	K MAX	K MIN	K MAX	K MIN	K MAX
3	[illegible]	[illegible]	19	F	L	2	2	2	2	[illegible]	1	2	1	2	[illegible]	[illegible]	[illegible]																
4	[illegible]	SUNDER	15	M	L	2	2	2	2	[illegible]	1	2	1	2	[illegible]	10	[illegible]													[illegible]	[illegible]		
5	[illegible]	SUNDER	16	M	R	2	1	2	2	[illegible]	1	2	1	2	[illegible]	11	[illegible]													[illegible]	[illegible]	47.1	[illegible]
6	[illegible]	[illegible]	17	F	L	2	2	2	2	[illegible]	1	2	1	2	[illegible]	20	[illegible]	1	3													[illegible]	[illegible]
7	[illegible]	RAJESH	20	M	R	2	2	2	2	[illegible]	1	2	1	2	[illegible]	[illegible]	[illegible]																
8	[illegible]	[illegible]	11	F	R	2	2	2	2	[illegible]	1	2	1	2	[illegible]	[illegible]	[illegible]															[illegible]	[illegible]
9	[illegible]	[illegible]	11	F	L	2	1	2	2	[illegible]	2	1	1	2	[illegible]	[illegible]	[illegible]					[illegible]	52.1	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]				
10	[illegible]	MONIKA	21	F	R	2	2	2	2	[illegible]	1	2	1	2	14	15	[illegible]									[illegible]	[illegible]	[illegible]	[illegible]				
11	[illegible]	[illegible]	10	F	R	2	1	2	2	[illegible]	1	2	1	2	[illegible]	[illegible]	[illegible]									[illegible]	[illegible]			[illegible]	[illegible]		
12	[illegible]	HARISH	19	M	R	2	2	2	2	[illegible]	2	1	1	2	9	12	[illegible]													[illegible]	[illegible]		
13	460805S	LAVANYA	14	F	L	2	2	2	2	18/11/2014	1	2	1	2	12		29/11/2014																
14	460805S	LAVANYA	14	F	R	2	2	2	2	20/01/2016	2	1	1	2	12		23/01/2016													56.13	58.5	56.87	61.27
15	407032s	diyapriya	16	F	R	2	2	2	2	10/02/2015	1	2	1	2	14	12	20/02/2015											50.5	54.5	49.27	56.32		
16	241489S	REVATHY	20	F	L	2	2	2	2	09/06/2015	1	2	1	2	14	14	12/06/2015					46.78	49.97	47.37	51.5	48.18	51.62	48.26	51.94				
17	428366S	SINDHU	10	F	L	2	2	2	2	28/07/2015	1	2	1	2	10	20	01/08/2015	1	3									45.5	56	48.22	62.52		
18	428366S	SINDHU	10	F	R	2	1	1	2	01/11/2016	1	2	1	2	9	12	05/11/2016	2								44	47.25	46.39	55.95	47.23	59.62		
19	474231S	ANU	18	F	R	2	2	2	2	11/08/2015	1	2	1	2	12	20	13/08/2015	2	4													46.94	51.39
20	491079S	MD GEELANI	17	M	R	2	1	2	2	23/12/2015	1	2	1	2	16	12	20.3/2015															47.68	52.16
21	336473S	AARWIN	22	M	R	2	2	2	2	15/05/2015	1	2	1	2	12	12	16/05/2015									44.89	49.07	44.75	49.25				
22	225178S	SUKUMAR	11	M	L	2	1	2	2	01/07/2012	1	2	1	2	14	14	03/07/2012													47.07	60.1		
23	225178S	SUKUMAR	11	M	R	2	1	2	2	05/05/2015	1	2	1	2	14	15	05/05/2015									41.76	43.6	42.01	43.5	42.86	45.55		
24	459032S	SUBRATHO	16	M	L	2	2	2	2	01/09/2015	1	2	1	2	15	15	03/09/2015													51.5	56.75		
25	498749S	JAGAN	18	M	R	2	2	2	2	13/01/2016	1	2	1	2	10	18	19/01/2016															44.24	50.91
26	328222S	BALAJI	20	M	R	2	2	2	2	27/01/2016	2	1	1	2	6	11	30/01/2016					51.02	64.23			51.73	59.57			57.67	63.7		
27	494242S	RENJITH	32	M	L	2	2	2	2	09/03/2016	1	2	1	2	10	11	12/03/2016													52.35	54.64		
28	424021S	SIMON	22	M	L	2	2	2	2	18/05/2016	1	2	1	2	12	19	21/05/2016													41.9	45.33		
29	424021S	SIMON	22	M	R	2	2	2	2	23/05/2017	1	2	1	2	9	10	26/05/2017											42.44	44.06	42.5	44.01		
30	504644S	VIDYA	16	F	L	2	2	2	2	15/06/2016	1	2	1	2	10	16	18/06/2016															54.48	63.93
31	539786S	SHAWN	13	M	L	2	2	2	2	05/07/2016	1	2	1	2	12	16	09/07/2016																
32	534230S	RAHEEMA	24	F	L	2	2	2	2	09/08/2016	1	2	1	2	10	15	12/08/2016																
33	543544S	SINDUJA	19	F	L	2	2	2	2	20/09/2016	1	2	1	2	10	12	23/09/2016																
34	546466S	DILEP	13	M	L	2	2	2	2	20/09/2016	1	2	1	2	16	20	23/09/2016																
35	545148S	PARTIPAN	19	M	R	2	2	2	2	01/11/2016	2	1	1	2	10	12	05/11/2016																



56	397487S	MONICA	15	F	L	2	2	2	2	2507/2017	2	1	1	2	12	24	2507/2017	2	3														
57	397487S	MONICA	15	F	R	2	1	1	2	19/07/2018	1	2	2	1	10	13	14/07/2018														46.03	57.06	
58	481262S	BLESSY	12	F	L	2	2	2	2	26/09/2017	1	2	2	1	16	27	13/09/2017	2	3														
59	481262S	BLESSY	12	F	R	2	1	1	2	17/04/2018	1	2	2	1	16	16	20/04/2018	2	2													44.96	48.24	
60	592966S	JAYASURIYA	13	M	L	2	2	2	2	26/09/2017	1	2	2	1	16	23	30/09/2017	2	3														
61	693438S	GUNA	17	M	L	2	2	2	2	26/09/2017	1	2	2	1	12	20	30/09/2017	2	3														
62	591834S	HEMA	16	F	L	2	2	2	2	3/10/2017	1	2	2	1	8	10	7/10/2017																
63	597749S	NIPURANI	22	F	L	2	2	2	2	7/11/2017	1	2	2	1	16	24	10/11/2017	2	3														
64	285190S	KARTHIK	23	M	L	2	2	2	2	12/12/2017	1	2	2	1	10	10	15/12/2017														44.9	52.01	45.23	52.95	45.25	53.99	
65	621469S	ADITHYA	13	M	R	2	2	2	2	19/12/2017	2	1	2	1	16	12	20.3/2017																
66	624292S	PREMKUMAR	16	M	R	2	2	2	2	20.3/2017	1	2	2	1	12	14	30/12/2017																
67	462597S	DIVITHRA	18	F	L	2	2	2	2	19/01/2018	1	2	2	1	17	14	29/01/2018														44.61	50.63	45.23	50.37	44.47	52.43	
68	535081S	NISHA	20	F	L	2	2	2	2	6/03/2018	1	2	2	1	15	8	10/03/2018																47.53	50.96			49.13	53.89
69	638117S	KOTESWARI	15	F	R	2	2	2	2	17/04/2018	1	2	2	1	12	23	21/04/2018	2	3														
70	413427S	SURENDRAR	13	M	L	2	2	2	2	30/04/2018	1	2	2	1	10	18	5/05/2018																			47.06	49.43
71	130529S	GEETHANJAI	14	F	L	2	2	2	2	1/05/2018	1	2	2	1	12	14	21/05/2018																			49.26	53.55
72	130529S	GEETHANJAI	14	F	R	2	2	2	2	18/6/2018	1	2	2	1	12	10	23/6/2018																		46.12	48.33	45.87	47.65
73	644647S	PRITHVIRAJ	18	M	L	2	2	2	2	5/6/2018	1	2	2	1	12	22	9/6/2018	2	2														
74	575338S	PRAVEEN	18	M	R	2	2	2	2	3/7/2018	1	2	2	1	10	14	7/7/2018																		46.08	50.76	
75	648464S	AKASH	17	M	L	2	2	2	2	17/7/2018	1	2	2	1	14	36	21/7/2018	2	2														
76	648464S	AKASH	17	M	R	2	1	1	2	1/6/2018	1	2	2	1	10	24	15/6/2018	2	3													55.36	59.84	53.06	58.98
77	636359S	PREM	19	M	R	2	2	2	2	17/7/2018	1	2	2	1	8	10	21/7/2018																
78	645107s	YAMINI	18	F	L	2	2	2	2	31/7/2018	1	2	2	1	8	15	4/8/2018																

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	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	Z	AA	AB	AC	AD	AE	AF	AG
79	[illegible]	MOHANRAJ	19	M	R	2	2	2	2	[illegible]	1	2	2	1	14	12	[illegible]										
80	[illegible]	BHAUPRIYA	16	F	L	2	2	2	2	[illegible]	1	2	2	1	12	14	[illegible]			[illegible]	[illegible]			[illegible]	[illegible]		
81	[illegible]	[illegible]	17	M	L	2	2	2	2	[illegible]	1	2	2	1	12	22	[illegible]	2	2								
82	[illegible]	THENMOZHI	19	F	L	2	2	2	2	[illegible]	1	2	2	1	16	10	[illegible]										
83	[illegible]	SHAHEEN	23	F	R	2	2	2	2	[illegible]	1	2	2	1	14	14	[illegible]									[illegible]	[illegible]
84	[illegible]	SATHISHKUMAR	20	M	R	2	2	2	2	[illegible]	1	2	2	1	12	15	[illegible]										
85	[illegible]	THAMIZHSELVI	15	M	R	2	2	2	2	[illegible]	2	1	2	1	5	16	[illegible]										
86	[illegible]	REVATHI	24	F	L	2	2	2	2	[illegible]	1	2	1	2	12	10	[illegible]							[illegible]	[illegible]		
87	[illegible]	REVATHI	30	F	R	2	1	2	2	[illegible]	1	2	1	2	12	15	[illegible]							[illegible]	[illegible]		
88	[illegible]	POONGODI	19	F	R	2	1	2	2	[illegible]	1	2	1	2	16	22	[illegible]					[illegible]	[illegible]				
89	[illegible]	POONGODI	16	F	L	2	1	1	2	[illegible]	1	2	1	2	14	21	[illegible]					[illegible]	[illegible]			[illegible]	[illegible]
90	[illegible]	PREMKUMAR	18	M	R	2	2	2	2		1	2	2	1	9	15											
91	[illegible]	SOWMIYA	19	M	L	2	2	2	2		2	1	2	1	16	10											
92	[illegible]	NAVEENA	22	F	L	2	2	2	2		2	1	2	1	12	15											
93	[illegible]	BALASUNDAR	17	M	R	2	2	2	2		1	2	2	1	18	18											
94	[illegible]	KANISHKA	12	F	L	2	2	2	2		1	2	2	1	13	12											
95	[illegible]	BISWAJIT	17	M	R	2	2	2	2		1	2	2	1	12	12											
96	[illegible]	[illegible]	15	F	L	2	2	2	2		1	2	2	1	12	16											
97	[illegible]	SAILAJA	11	F	R	2	2	2	2		1	2	2	1	13	14											
98	[illegible]	VALLAM	16	F	L	2	2	2	2		2	1	2	1	12	14											
99	6497545	GOKUL	10	M	L	2	2	2	2		1	2	2	1	12	12											
100	6689365	KOKILA	18	F	L	2	2	2	2		1	2	2	1	16	14											
101	6468655	GUNANIDHI	16	M	R	2	2	2	2		1	2	2	1	14	14											
102	4009145	PRAVEEN	20	M	R	2	2	2	2		1	2	2	1	10	17											
103																											
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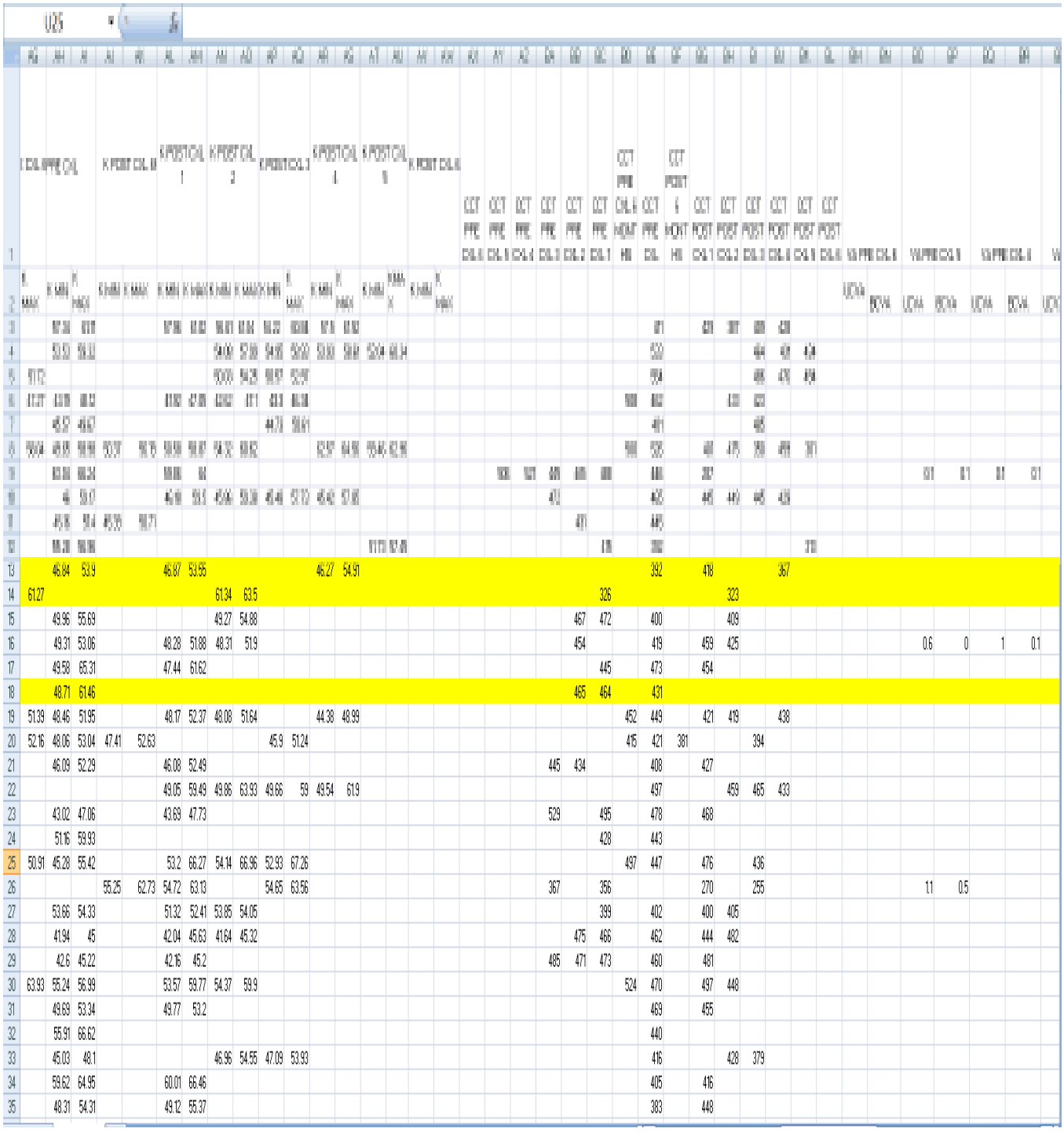

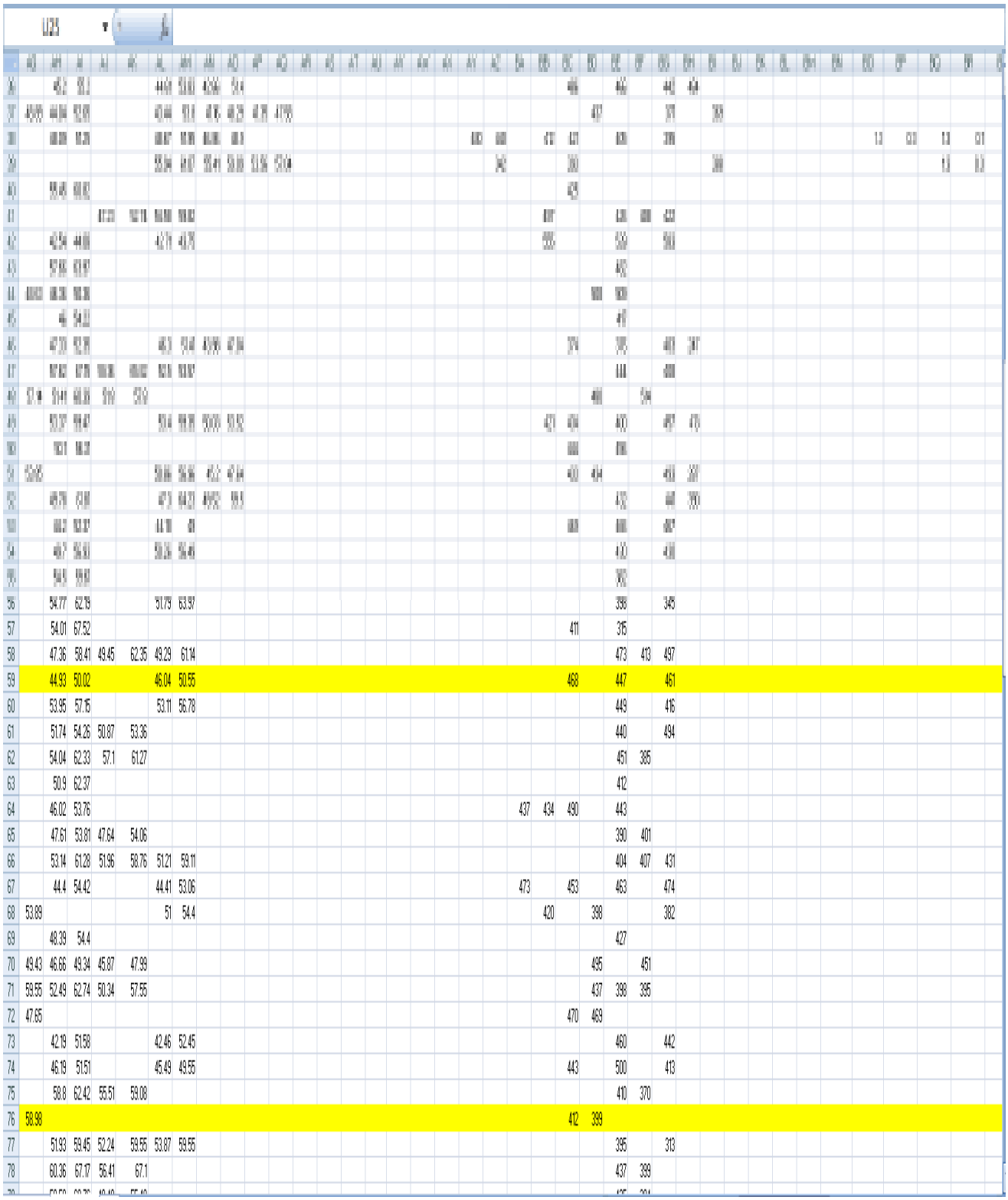

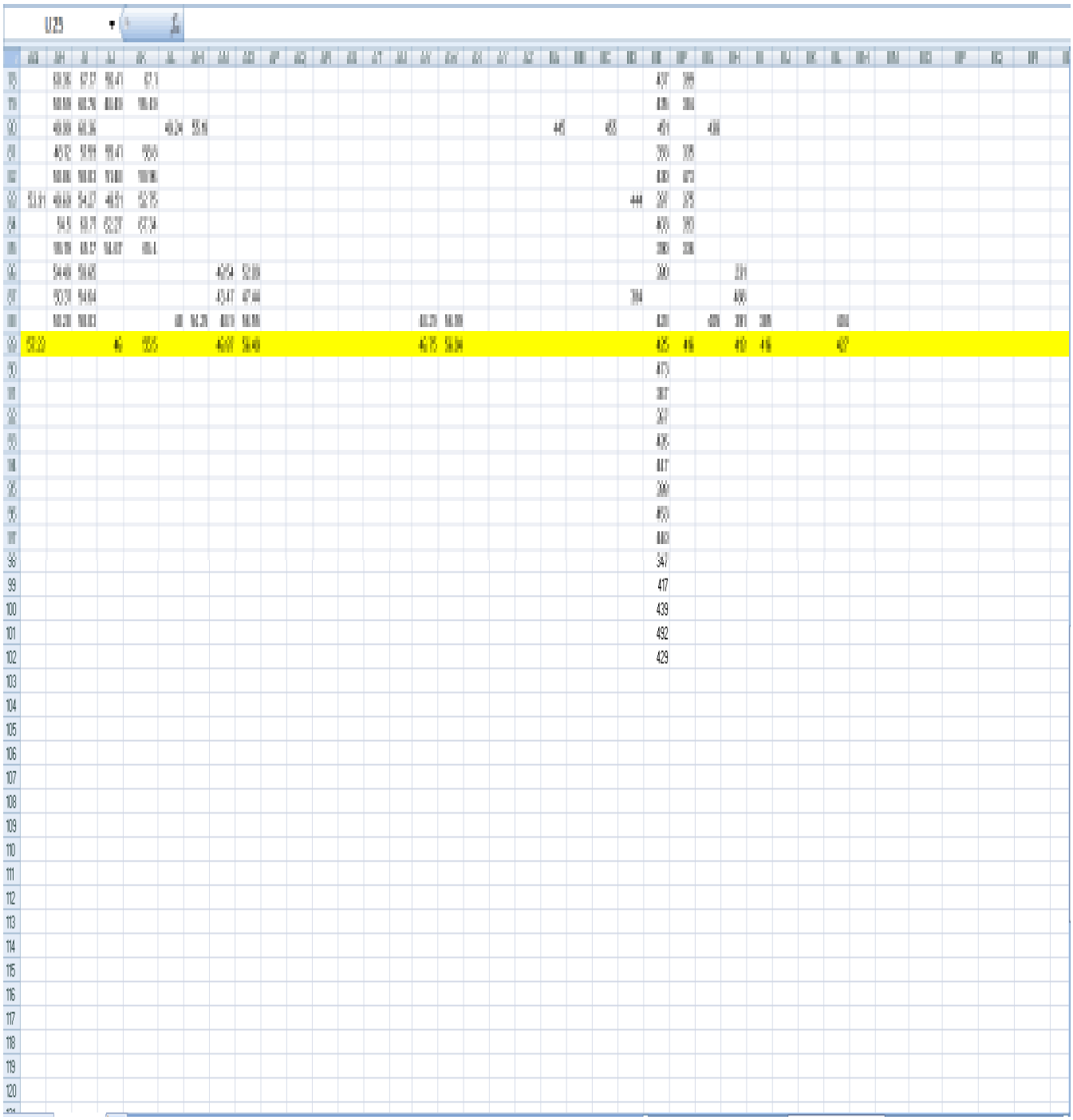

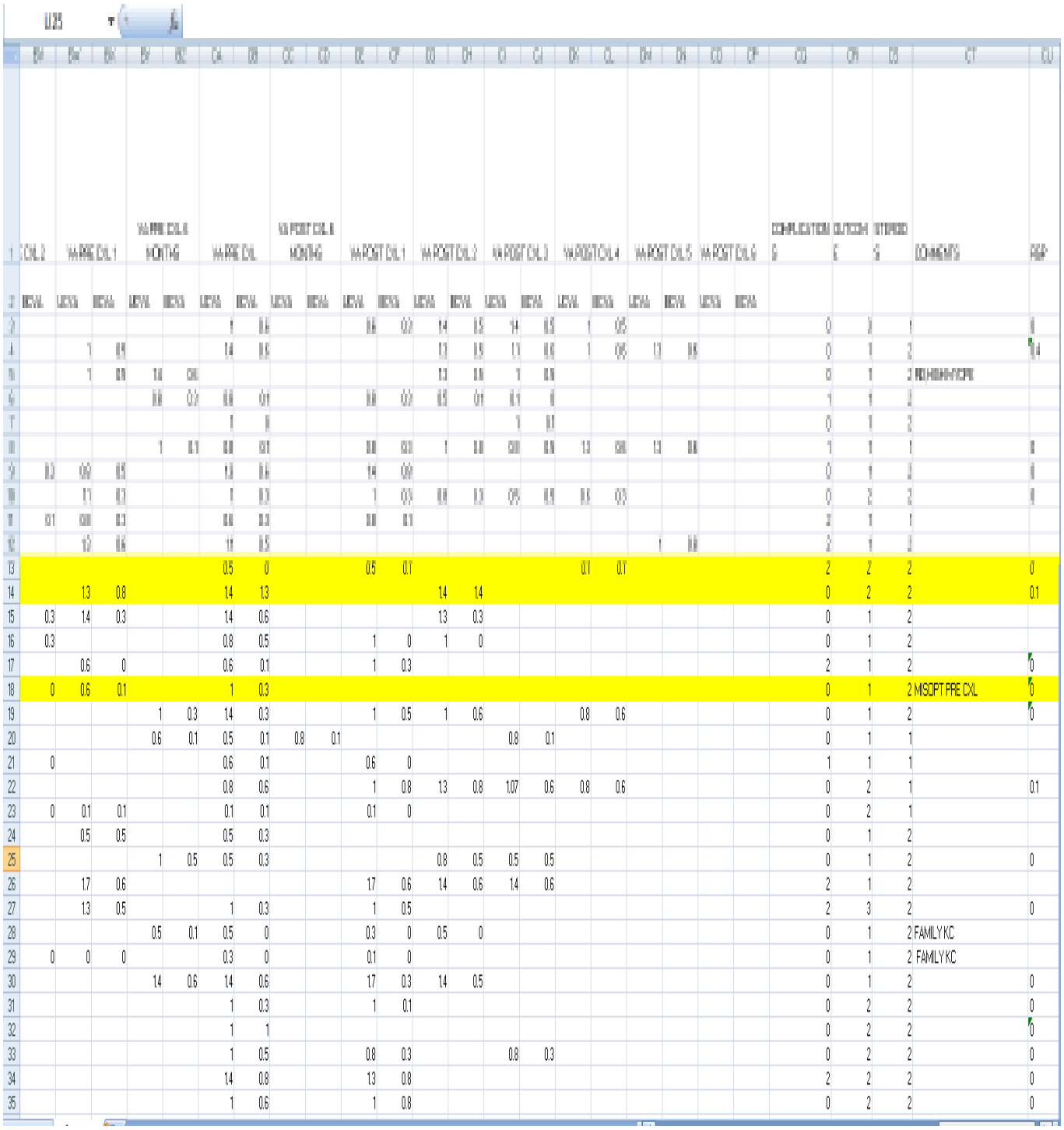

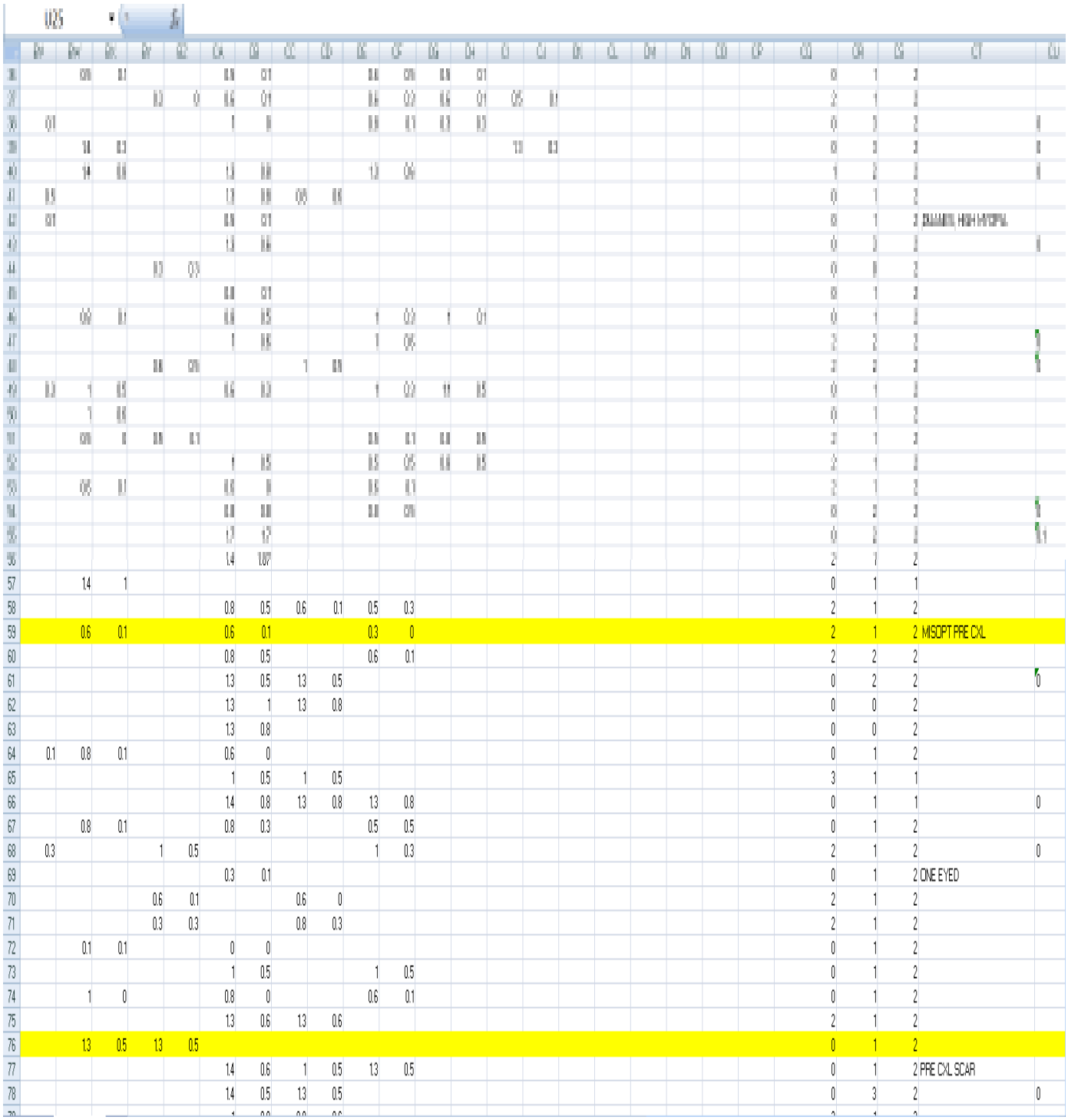

56							1.4	1.07																				2	1	2		
57			1.4	1																								0	1	1		
58							0.8	0.5	0.6	0.1	0.5	0.3																2	1	2		
59			0.6	0.1			0.6	0.1			0.3	0																2	1	2	MISOPT PRE CXL	
60							0.8	0.5			0.6	0.1																2	2	2		
61							1.3	0.5	1.3	0.5																		0	2	2		0
62							1.3	1	1.3	0.8																		0	0	2		
63							1.3	0.8																				0	0	2		
64	0.1	0.8	0.1				0.6	0																				0	1	2		
65							1	0.5	1	0.5																		3	1	1		
66							1.4	0.8	1.3	0.8	1.3	0.8																0	1	1		0
67		0.8	0.1				0.8	0.3			0.5	0.5																0	1	2		
68	0.3			1	0.5						1	0.3																2	1	2		0
69							0.3	0.1																				0	1	2	ONE EYED	
70				0.6	0.1				0.6	0																		2	1	2		
71				0.3	0.3				0.8	0.3																		2	1	2		
72		0.1	0.1				0	0																				0	1	2		
73							1	0.5			1	0.5																0	1	2		
74		1	0				0.8	0			0.6	0.1																0	1	2		
75							1.3	0.6	1.3	0.6																		2	1	2		
76		1.3	0.5	1.3	0.5																							0	1	2		
77							1.4	0.6	1	0.5	1.3	0.5																0	1	2	PRE CXL SCAR	
78							1.4	0.5	1.3	0.5																		0	3	2		0