STUDY OF TREND OF INTRAOCULAR PRESSURE VARIATION IN SUPPURATIVE CORNEAL ULCERS IN A SOUTH INDIAN TERTIARY CARE CENTRE - AN OBSERVATIONAL STUDY

DISSERTATION SUBMITTED TOWARDS FULFILMENT

OF THE RULES AND REGULATIONS FOR

THE M.S. BRANCH III OPHTHALMOLOGY EXAMINATION OF THE

TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY

TO BE HELD IN APRIL, 2016

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SUBMITTED BY

Dr. BINDU THOMAS

CHRISTIAN MEDICAL COLLEGE

VELLORE

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BONA FIDE CERTIFICATE

This is to certify that this dissertation entitled "Study of trend of intraocular pressure variation in suppurative corneal ulcers" towards fulfilment of the requirements of the Tamil Nadu Dr MGR Medical University, Chennai for MS Branch III Ophthalmology examination to be conducted in April 2016, is the bona fide original work of Dr.Bindu Thomas, Post Graduate student in Ophthalmology, Christian Medical College, Vellore.

Dr. Andrew David Braganza, MS,

Professor and Head of the Department,

Department of Ophthalmology,

Christian Medical College,

Vellore-632001.

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Dr.Sanita Mary George Korah DO, MS, DNB Ophthalmology

Professor, Department of Ophthalmology,

Christian Medical College,

Vellore-632001

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Dr.Bindu Thomas,

Post Graduate Student,

Department of Ophthalmology,

Christian Medical College,

Vellore

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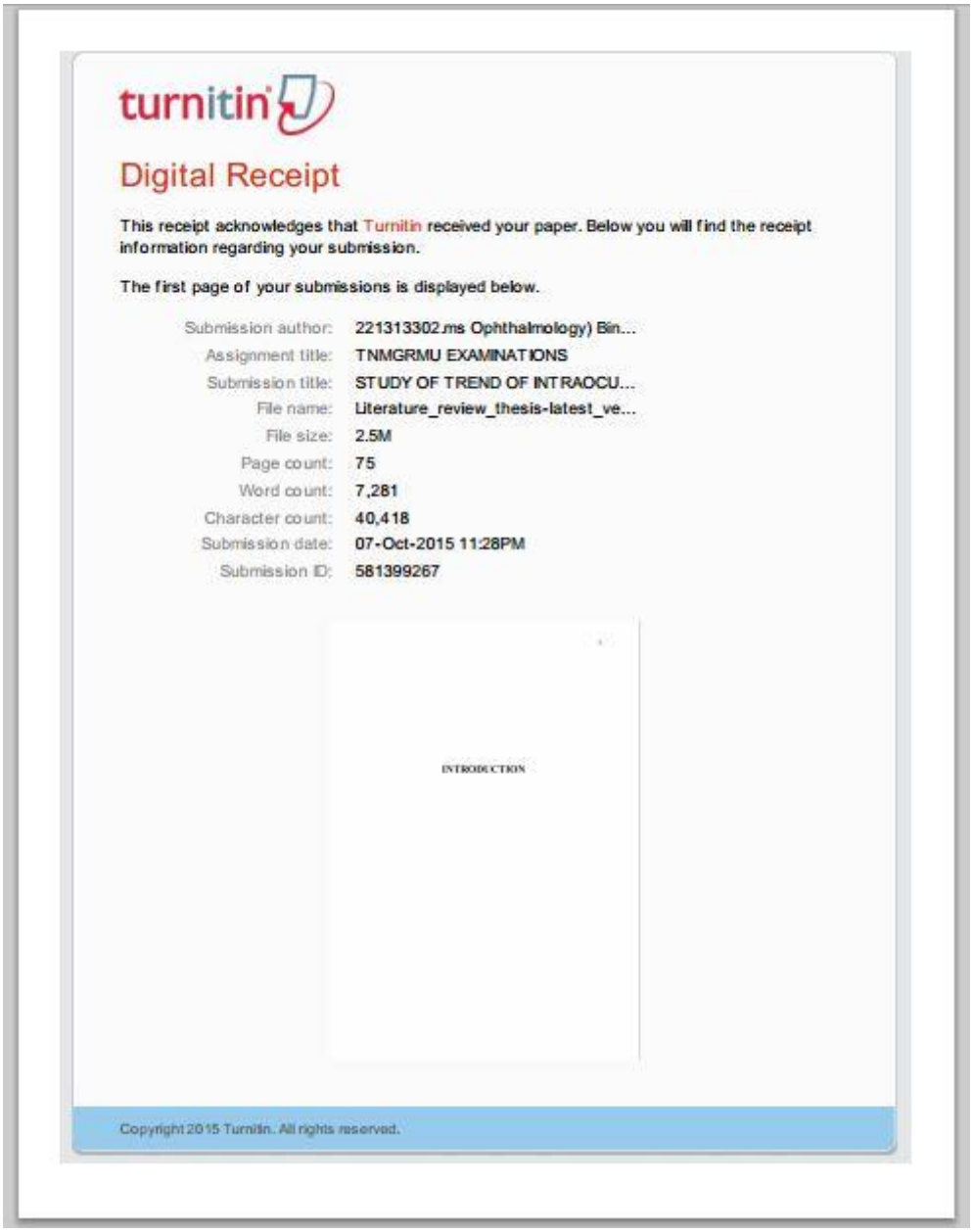

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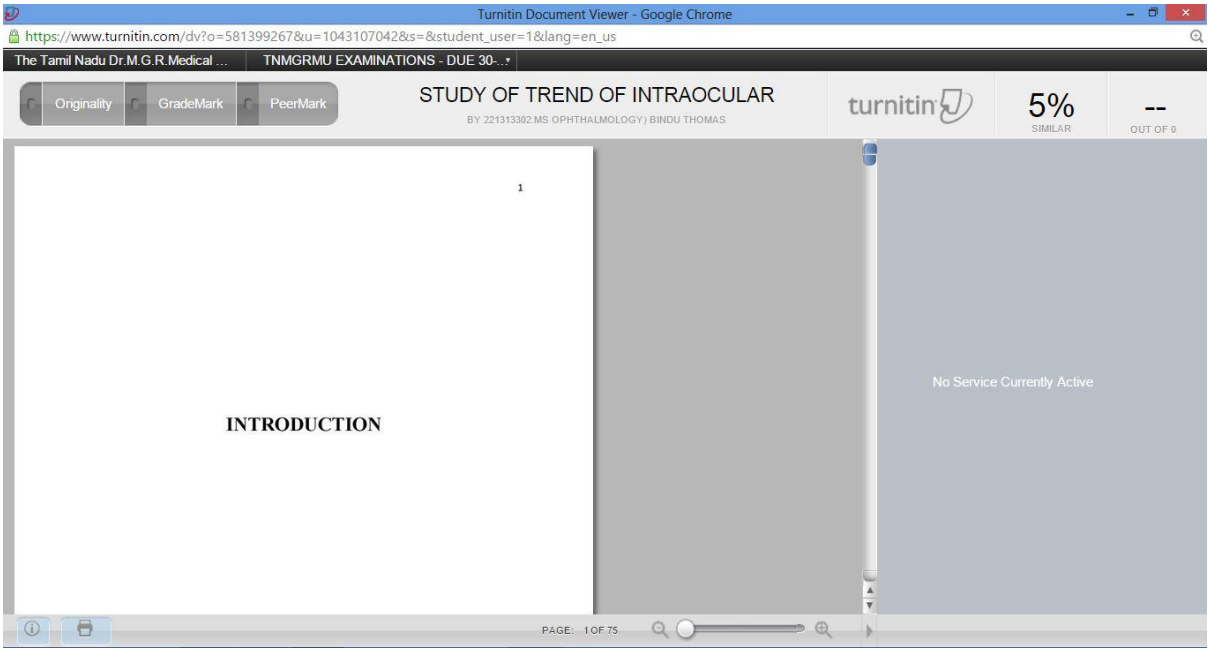
INTRODUCTION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INTRODUCTION

The cornea is the transparent, dome shaped tissue covering the front of the eye. It is a powerful refracting surface and provides 65 to 75 % of the focusing power of the eye.

Corneal injury can result in loss of this transparency, while the rest of the eyeball is structurally and functionally intact. This causes decreased vision, a condition termed "Corneal Blindness"(1).

Corneal injury and corneal ulceration result in about 2 million new cases of corneal blindness annually(1)**.** Infectious keratitis, or corneal ulcer, is characterized by a corneal epithelial defect with underlying stromal inflammation and destruction caused by multiplying organisms and their toxins. Associated uveal tissue and anterior chamber inflammation also occur, with an outpouring of leucocytes into the anterior chamber, which can then form a hypopyon. (2–4)

Microbial keratitis is a leading cause of ocular morbidity and blindness worldwide.(1) Delayed or inappropriate treatment of infectious keratitis can lead to significant visual loss in as many as 50% of cases (1,5). A large number of fungi, bacteria, protozoa, and viruses have been identified and implicated as infectious agents in microbial keratitis(5)

All microbial keratitis requires aggressive management to stop the disease process and reduce the extent of scarring which lead to loss of vision(1,6,7)

Treatment of corneal ulcers includes the specific antimicrobial treatment as well as adjunctive treatment to reduce pain and inflammation, including cycloplegic agents to reduce ciliary body spasm, and anti inflammatory pain killers.**(8,9)**

In addition to the above, treatment guidelines have generally mentioned antiglaucoma medication (Tab. Acetazolamide) as part of this adjunctive treatment. The rational is that the intraocular pressure (IOP) would be expected to increase in the presence of inflammation and inflammatory cells within the anterior chamber . This rise in intraocular pressure may cause increase in pain, as well as prolong the time to healing of the ulcer, leading to poorer outcomes. (10–12)

Currently, the side effects of Acetazolamide(13) have become more clear, and the American Academy of Ophthalmology advises anti glaucoma medication only in those patients where IOP is found to be raised. (14)

The applanation tonometer, which is the gold standard instrument used to check IOP in normal patients, (15)cannot be used in this situation because of the absence of a smooth corneal surface in patients with corneal ulcer(15). The easiest method in this situation to check for raised IOP, is digital palpation over the eyelid(16). This method is however highly inaccurate in this situation due to the presence of the often severe lid edema associated with corneal ulcers, leading to frequent under-estimation of the IOP(17).Additionally, this method proves to be painful in the patent who is already in severe pain due to the ulcer.

There are now newer instruments available, e.g. the Tonopen, the I-Care system, etc which can be used to get an objective assessment of the IOP for such patients [28] [18] However, these instruments are not readily available, are expensive, and incur a recurring expense due to the need for caps or disposable tips (to prevent cross-infection). (18)

Thus in a developing country such as ours, where the population that is most affected by this health problem is the lower socio-economic sections of society, (19–21) these instruments cannot be used for every patient indiscriminately.

Recently, there have been reports in the literature, that there may be a specific group of patients with corneal ulcers who may be expected to experience a raise in IOP.(4)We plan to study prospectively, the intra-ocular pressure profile in our population of patients with corneal ulcer, to determine if there is indeed a specific group of patients, in whom regular objective intraocular pressure monitoring is indicated. We hope to be able to propose patient and ulcer specific treatment management protocols, so that indiscriminate, and unwarranted anti-glaucoma medication may be avoided.

Thus we feel that this prospective study is highly warranted in our country, where the corneal ulcer load is much higher than in the West (22) and where the extra expenses involved in checking intraocular patients in all patients may not be a viable option

AIM AND OBJECTIVES

AIM

Study of the intraocular pressure trends in patients with infective corneal ulcers presenting to a tertiary center in South India

OBJECTIVES

Primary Objective:

To compare the Intraocular Pressure prospectively in the affected eye of patients with infective corneal ulcers with the opposite unaffected eye of the same patient.

Secondary Objectives:

1) To determine if rise in IOP leads to prolongation of Time to Heal.

2) To determine the IOP trend with respect to microbiological profile of patients with corneal ulcers.

3) To determine if initial presenting size of the ulcer has any influence on IOP.

LITERATURE REVIEW

A corneal ulcer is defined as an epithelial defect, with a stromal infiltrate with or without a hypopyon (5,22) . Infectious corneal ulcer or microbial keratitis is caused due to the multiplication of microorganisms which includes bacteria,fungi, parasites and virus along with inflammation of the corneal tissue. **(5)**It is sight threatening if not appropriately treated.

In developing countries like our own, bacterial and fungal corneal ulcers are more common than in the West.(5) (22)

A study done in Aravind Eye Hospital in South India showed 63% of ulcer were due to fungal aetiology, while 35.7% were due to bacterial eitiology**(23)**. Fusarium was the most common fungus isolated (42.3%) and Streptococcus pneumoniae was the most common bacteria followed by Pseudomonas aeruginosa and Nocardia.

The ocular surface has got mechanisms of its own for defence which includes the following:(5)

1) Intact corneal epithelium

2) Eye lid closure : reflexive or even just normal blinking

3) Tear film components like Immunoglobulin A, Lysozymes, Lactoferrin, Betalysins, orosomucoid , ceruloplasmin, complements (5,24)(both classic and alternative pathway), corneal epithelial cells which can phagocytose, subepithelial mucosal associated lymphoid tissue (MALT), and normal conjunctival flora with both sessile and planktonic bacteria that help prevent the growth of pathogenic microorganisms.

The commonest normal flora of ocular surface seen in descending order of prevalence are Staphylococcus epidermidis, Staphylococcus aureous, Micrococcus species, Corynebacterium spp, Propionibacterium species, Sreptococcus spp, and Haemophilus influenza.(1-5)

Dry eye due to autoimmune disorders as well as mucin and lipid deficiency of in tear film are predisposing factors for the development of corneal ulcers. Most commonly found fungi in healthy eyes include Aspergillus , Candida spp, Penicillium, and Cladosporium species. (1,3) They need organic compounds for growth.

Risk factors of fungal ulcers include corneal surgeries,steroid use,chronic keratitis ,topical anaestheitic use,topical moxifloxacin use,immunosuppression.Usually fungal ulcers have an indolent course, with starting symptoms of foreign body sensation with slow onset of pain,blurred vision.

Signs of fungal keratitis are the follows:

<u>Non specific</u>

Suppuration,Conjunctival injection

Epithelial defect, stromal infiltraton

Anterior chamber reaction

<u>Non specific</u>

Infiltrates have feathery margins

Gray brown pigmentation suggestive of demetiaceous fungi)

Elevated edges ,raised slough

Rough texture

Satellite lesions

Intact epithelium with deep stromal infiltrate seen.

Bacterial ulcers-Types

1)Staphylococcal ulcers

Most common gram positive bacteria, seen as part of normal ocular flora. It grows as pearly white colonies in routine culture. Keratitis occurs in compromised cornea like bullous keratopathy, keratoconjunctiitis sicca , ocular rosacea. They show rapidly progressive infiltration with the presence of endothelial plaque or hypopyon. The ulcer is round or oval with dense infiltration and a distinct border. Stromal microabscess is also noticed in some cases

Coagulase negative staphylococcus ulcers are mainly opportunistic infection with slow progression

2) Streptococcal ulcers

Mostly occur after trauma, dacryocystitis, filtering bleb infections. Ulcers are purulent and rapidly progressive .There is severe anterior chamber reaction with retrocorneal fibrin coagulation. Perforation is common

3) Pseudomonas ulcers

Pseudomonas the most common gram negative pathogen isolated. Commonly seen in soft contact lens users.Corneal ring infiltrate can be seen.

4)Neisseria ulcers

Obligate intracellular gram negative cocci .Infiltrate associated with hyperpurulent conjunctivitis and chemosis

5) Bacillus ulcer

Bacillus cereus is a gram positive bacillus which can cause devastating keratitis. Intraocular extension is caused by exotoxin

6)Nocardia ulcers

The infiltrates has a ring like appearance, pinhead like infiltrates with a wreath pattern. There can be associated satellite lesions.

PATHOGENESIS OF CORNEAL ULCER (5,25,26)

1)Bacterial adherence: In most cases damage to the corneal epithelium is a prerequist for bacterial adherence. Bacterial pili or fimbriae enable attachment of the bacteria to the glycocalyx of the injured corneal tissue.

2) Bacterial invasion : Starts within hours and may peak in 2 days. Polysaccharides in the capsule can stop the activation of the alternate complement pathway. Lipopolysaccharides can activate inflammatory mediators and some bacterial exotoxins can result in corneal cell necrosis. Proteolytic enzymes that are produced by the bacteria lead to destruction of corneal stroma and collagen fibrils.

Some bacteria like Neisseria meningitides, Neisseria gonorrhoea, C.diphtheria , Haemphilus aegypticus , Shigella and Listeria monocytogenes care able to penetrate intact corneal epithelium. (5,27)

3) Corneal inflammation:This occurs through the kinin forming , clotting and fibrinolytic system. Immunoglobulins as well as complement componenets, vasoactive amines, neuropeptides and cytokines (EGF,TGF beta S,Hepatocyte growth factor in tears) also contribute to this.

NATURAL COURSE OF CORNEAL ULCERS (1,4,6)

Patients can present with pain, photophobia, decreased vision, conjunctival congestion and anterior chamber reaction with or without hypopyon.

Clinical signs of active corneal ulcers are as follows:

1) Epithelial defect

2) Suppurative corneal stromal infiltrate with distinct edges, edema and white cell infiltration in surrounding stroma

3)Anterior chamber reaction with or without hypopyon.

Severe lesions, with an infiltration diameter of more than 6mm and those involving deeper than one third of corneal thickness can have rapid progression to perforation and sclera involvement

In the last few years, there has been comparatively little published on corneal ulcers since practically nothing new has developed on this subject. Evans(28) states that out of 700 elderly blind people, 45 were blind because of corneal opacities. Most of the corneal opacities were caused by corneal ulcers. Considering the huge number of corneal opacities that are caused by corneal ulcers which produce partial or total blindness, the necessity for further study in the management of this disease becomes clear.

The behavior of the human cornea in health, disease as well as injury has been quite well established by several investigators, and although there are still a few conditions that are not completely undertood, there has been progress leading to a satisfactory understanding of the healthy as well as the diseased cornea. (1,3,6,7)

Clinical signs of healing of ulcers (5)

1. Reduction of edema and inflammatory cells in the cornea
2. Reduction in the anterior chamber inflamation
3. Re-epithelialization
4. Halting of thinning of cornea.
5. Blunting of the edges of corneal infiltrate and decrease in the density of the infiltrate

As part of investigation almost aii patients will undergo scraping. Done for initial debridement of microbes and sloughed epithelium. Scraping is done from the leading edges and not from base of ulcer.But Moraxella can be well detected when scraping is done from the base of ulcer. Scraping material is inoculated into the solid media (Blood agar, Chocolate agar, and Sabourad's dextrose agar) as well as smeared to the microscopic slide

STANDARD TREATMENT PROTOCOL IN CORNEAL ULCERS

Corneal ulcers are one of the few true Ophthalmological emergencies. (5)

The treatment of corneal ulcers cannot be delayed, as this will worsen the already poor visual prognosis further.

There are different approaches in the initiation of treatment in corneal ulcers

Empirical approach (5,11,29)

In places where investigations are not possible, immediate broad spectrum topical antibiotics can be started without corneal scraping. It is always convenient and cost effective. However, in situations where the organism is an unusual one, or is resistant to conventional antibiotics, valuable time will be lost, and a poor result obtained.

Microbiological Culture - guided approach:(30)

Even though this is more costly, it is the more scientific approach, providing a definite eitiologic diagnosis. Antibiotic sensitivity profiles can be studied, so that effective medication can be administerd so that progression of the ulcer is halted and healing of the ulcer occurs as rapidly as possible.

inflammation.This is strictly contraindicated in fungal ulcers.

TREATMENT OPTIONS IN COMPLICATED CORNEAL ULCERS

1)Cyanoacrylate tissue adhesives→To treat corneal thinning,descematocele,and corneal perforation.

2)Therapeutic soft contact lenses→To facilitate epithelial healing

3)Conjunctival flap→ For recalcitrant microbial keratitis

4)Penetrating Keratoplasty→ In old age,delay in referral,excessive steroid use, previous surgery in eye, large size of ulcer and centrally locating ulcers.

INTRAOCULAR PRESSURE IN CORNEAL ULCERS

Our literature search revealed only one study which looked at intraocular pressure measurements in patients with active cornea ulcers . (4)This report, from Jules Stein eye institiute,California , was a retrospective study where 184 patients with culture positive microbial keratitis were studied. Those patients with intraocular pressure (IOP) more than 22 mmHg or higher in the affected eye were taken as the cases (52 of 184 patients – 28%) and those with intraocular pressure less than 22 mmHg in the affected eye were the controls. They found that the mean intraocular pressure in the High IOP group was 29.1 mmHg (range: 22 – 51).

They also found that the “time to healing” (ulcer resolution) was longer in the high IOP group (mean 50.1 + / - 53.2 days) than in the control group(mean, 31.6 + / - 42.0 days; P=0.005).

Final visual acuity of 20/40 or better was achieved by more patients in the control group (47%) than in the high IOP group (20%;P<0.001).

They therefore concluded that elevated IOP is present in a significant proportion of patients with active keratitis and that raised IOP was associated with poorer out comes. Hence a recommendation that routine IOP measurement is essential in all cases of corneal ulcers to avoid possible optic nerve damage secondary to high pressure was made.

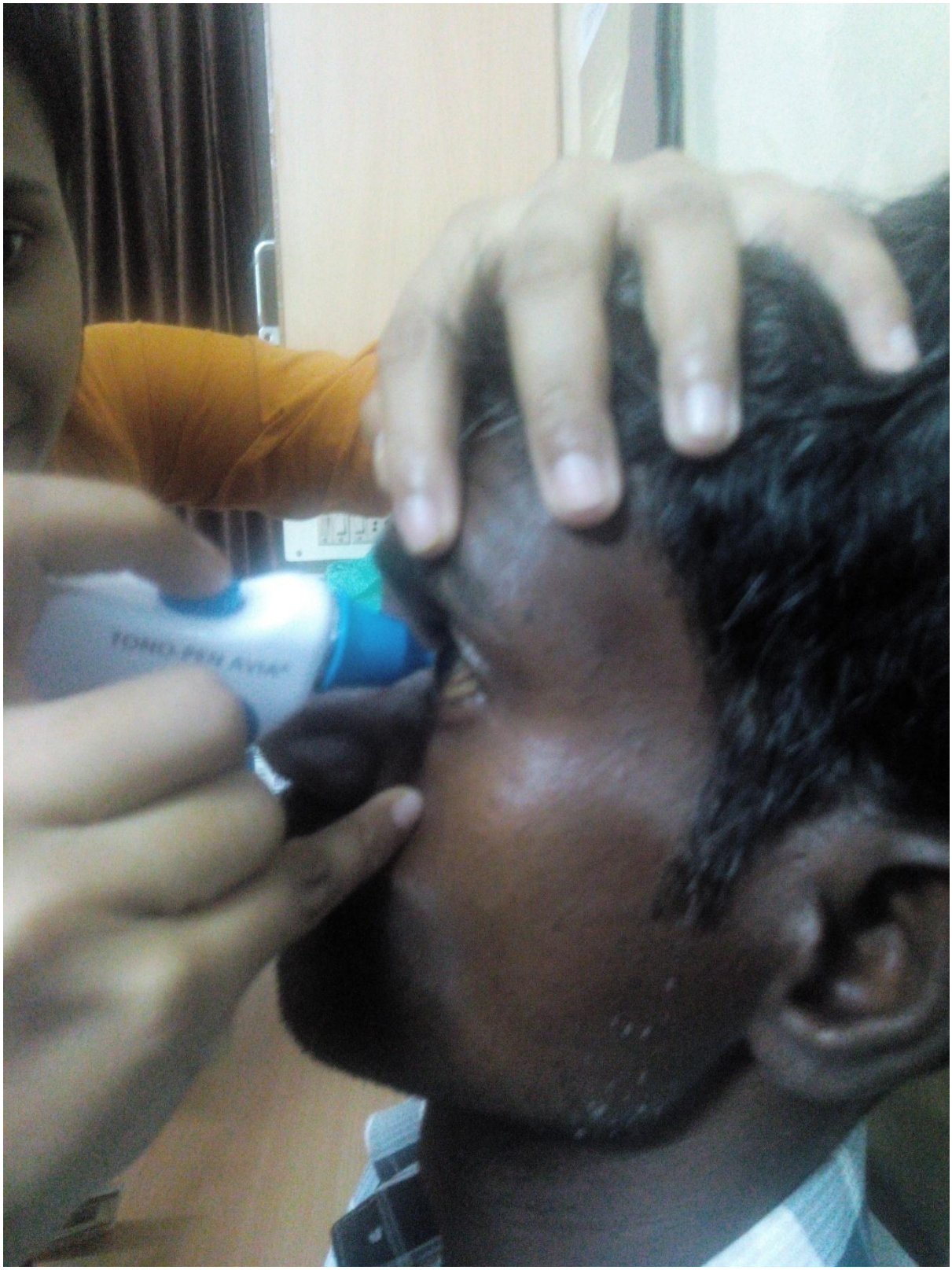
In 1997-1998, a preliminary prospective study was conducted in our department (unpublished data) on corneal ulcer patients and it was found that there were probably at least two subgroups of patients who tended to have raised IOP i.e; in patients with pneumococcal ulcers and patients with fungal ulcers with hypopyon.

TONOPEN

The Tonopen is an instrument that has been documented to be useful in recording intraocular pressure in eyes having scars or ulceration of the cornea. (15) The Tonopen is an easy to use, handheld instrument that uses micro strain gage technology and a 1 mm transducer tip.(31,32).The tip is covered with a new thin sterile disposable latex cap before each use.

After checking the caliberation, topical anaesthetic agent (paracaine 1% eye drops) is instilled into the eye. The tip of the instrument is then touched momentarily (feather light touch) to the cornea lightly and then withdrawn .The tip must be kept perpendicular to the centre of cornea. Over-intendation of the cornea can cause falsely high IOP readings. The measurement is digitally displayed each time a valid reading is obtained. After 4 readings the final bleep will sound and the average measurement will appear on the LCD along with the single bar denoting statistical reliability (coefficient of variation) . A reliable reading will show a coefficient of variation 5%. Three reliable readings are taken and the average of these values of IOP at that point of time is obtained. Other causes of error and unreliable readings that should be avoided incorrect tip cover tension , wrong caliberation, dirt over the transducer tip. Some people can have allergy to latex which causes local and systemic reaction which can affect the readings.(33)

Tonopen used for intraocular pressure mesurement



Measurement of intraocular pressure in one of our study subjects

IOP MEASUREMENT IN CORNEAL ULCERS

Objective measurement of IOP is not performed routinely in patients with infective corneal ulcers, as special instruments like the Tonopen is required . But growing evidence suggests that there is a subgroup of corneal ulcer patients who experience a rise in IOP which may result in poorer outcome [2].

The cause of IOP elevation in acute ucerative keratitis in a subset of people is not actually understood clearly. This may be due to multiple factors .

Non-infectious uveitis usually presents with decreased or normal IOP [3,4]. In infectious uveitis e.g. viral uveitis, an increase in IOP is noted. (4)Microbial keratitis may have a similar pathophysiology.

The anterior chamber reaction causes "blood-aqueous barrier" breakdown with the release of inflammatory polymorphonuclear cells and proteins. These can block the trabecular meshwork. (4)Prostaglandins released during inflammation in the eye may also play a role in the increase of IOP.(4) Microbial toxins have also been described to cause an increase in IOP.(3,4) None of the studies retrieved from our literature search so far has suggested evidence of a specific organism or microbial toxin which by itself may cause an increase in IOP.

IOP elevation in corneal ulcers may be caused by both angle closure and open angle mechanisms.

Angle closure is caused by inflammation and anterior or posterior synechiae formation. A specific type of pupillary block glaucoma, called "Malignant Glaucoma" has been described in Fungal ulcers.(34) It is caused by a mushroom – shaped growth of fungal elements from the anterior chamber, through the pupil, into the posterior chamber. This causes pupillary block, which has to be adressed surgically.

Open angle mechanisms of glaucoma, as described previously, are possibly due to increased inflammatory cells, exudation of high-molecular wieght protiens, as well are micro-organism toxin liberation into the anterior chamber (9)

INCLUSION CRITERIA

1) All suspected suppurative corneal ulcers more than 2mm size who have undergone microbiological scraping for smear and culture (including fungal and bacterial)

2) All patients 18yrs or above who are able to give consent

EXCLUSION CRITERIA

1. Perforated corneal ulcers
2. Ulcers clinically diagnosed as immune – related peripheral keratitis
3. Patients on anti-glaucoma medication within 48 hours of presentation to this department
4. Patients with bilateral ulcers
5. Patients presenting with descemetocoel
6. One – Eyed patients

Withdrawal of the patients from study after recruitment:

Patients initially recruited and undergoing standard medical therapy will be withdrawn from the study if:

1. They undergo any surgical intervention e.g. intracameral injections, therapeutic keratoplasty during the course of their treatment in this hospital.

2. Intraocular pressures are found to be raised to 50mmHg for more than 72 hrs.

Guidelines for treatment of acute / temporary elevations of IOP are not available for infective keratitis. We therefore decided to use the guidelines published for the management of blunt trauma patients with hyphema (Blood in the anterior chamber).An intraocular pressure of 50mmHg for more than 4 days requires intervention to bring down the IOP in order to prevent pressure-related optic nerve damage.[5]

However, patients with raised IOP will be closely followed for development of any evidence of posterior segment vascular or optic nerve compromise, and if any risk is perceived, earlier intervention will be performed.

Those patients who require interventions will be started on anti-glaucoma medication as indicated (Oral/topical/intravenous). These patients will be taken out of the "Time to Healing " analysis. All such patients will be analyzed separately. The IOP trend and differences as compared to the normal (unaffected) eye will be recorded and analyzed.

All known glaucoma patients with normal IOP on regular treatment will be included in the study. These patients can be continued with their antiglaucoma medication.

OUTCOMES USED FOR STUDY

1. **IOP variation:** Trend of IOP variation in suppurative corneal ulcers ulcer eye (study eye) compared to unaffected normal eye (control eye) of the patient.

2. **Time to Healing:** Time from start of symptoms, to healing.

The "Time to Healing" in patients with raised IOP will be determined and compared with the "Time to Healing" of those patients who do not get a raised pressure.

3. **Clinical Outcome**: A poor clinical outcome has occurred if a complication such as corneal perforation, emergency corneal transplant or evisceration has ensued.

Healing of corneal ulcer: End point – Complete closure of the epithelial defect with complete resolution of infiltrate

Non - healing of corneal ulcer:

- Complication of ulcers with descematocele,perforation, evisceration or atrophy/phthisis of eyeball
- Ulcers for which therapeutic keratoplasty was done

METHODOLOGY

Study design:

Case control design : IOP in case or ulcer eye compared to IOP in control of unaffected eye

Secondary objectives :

Observational study for correlation with microbiological profile and ulcer size at presentation.

SAMPLE SIZE CALCULATION

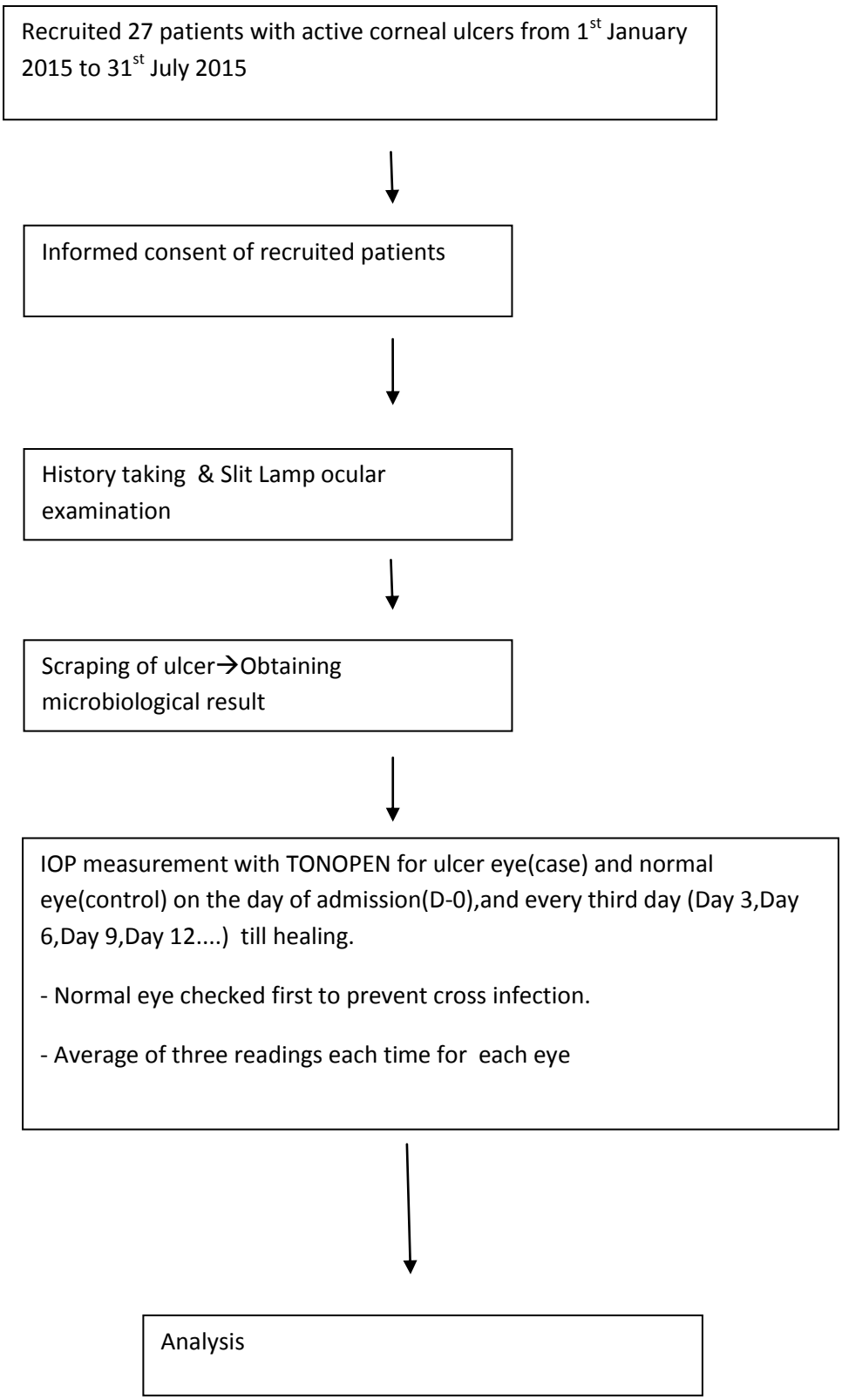
This was purely an observational study done in our hospital and all those patients who presented to us who satisfied the inclusion and exclusion criteria during the duration of the study were recruited.

In this study, out of the 92 patients who presented to our department from January 1st 2015, to July 31st 2015 with corneal ulcers, 46 patients who satisfied the study criteria were recruited. Of these patients, 19 patients were withdrawn due to need for surgical intervention as outlined above. No patient was removed due to prologed elevated intraocular pressure.

In all, 27 patients were included in the study.

This study protocol was approved by the institutional review board and ethics Committee of Christian Medical College, Vellore as per the ICMR guidelines required for any study conducted in this institution. A written informed consent was obtained from everyone who underwent this study.

Methodology: WORK-FLOW CHART



Materials & Methods

Patients who presented to the out-patient and casualty departments of our hospital with active corneal ulcer during the study period were assessed for eligibility for this study.

27 patients were finally included in this study.

Detailed history including hospital number , name, age, sex, address, contact number, date and time of presentation, symptoms with which they present are taken. History of medications prior to presentation and systemic illness also taken. Visual acuity at presentation was noted down in both eyes.

After this all patients underwent slit lamp examination during which the following parameters were assessed:

- Site and size of infiltrate
- Size of epithelial defect
- Location (involving visual axis or not)
- Depth of involvement

- Thinning in percentage

- Corneal sensation

- Endothelial plaque

- Previous scars

- Vascularisation

- Presence or abscence of hypopyon

- Satellite lesions

After examination all patients underwent corneal scraping under aseptic conditions for microbiological testing. For those patients who were already on some other antibiotic drops from elsewhere a waiting period of 6 hours from the time last instillation was given, and then scraping done .

Gram staining for bacteria and Lacto-Phenol Cotton Blue smears for fungus were done. In addition, Calcofluor White Fluorescent microscopy was performed in cases where both the above smears are negative.

For culture , specimens were inoculated into blood agar, chocolate agar and Sabouraud dextrose agar (SDA) media and they were incubated in the microbiology department for a total of 10 days to 2 weeks, depending on the media .

Smear-based medical therapy was started in all patients, which was modified as required once the sensitivity reports were available.

Treatment of all the corneal ulcers was according to our standard therapy protocols as follows.

Gram negative bacteria in smear/ smear negative for bacteria or fungus:

-Fortified Gentamycin eye drops (1.45%) + Cefazoline drops(50mg/ml)

Gram positive bacteria in smear:

Crystalline Penicilline 1 lac units/ml + Fortified Gentamycin drops

Fungal hyphae in smear: Natamycin eye drops 5%

+/- Tablet Ketoconazole 200 mg twice daily (based on depth of ulcer).

All drops were started at hourly intervals.

For other suspected organisms e.g. Acanthamoeba / Nocardia , specific culture media and therapy as per department protocols were followed.

Additional supportive therapy:

Atropine sulphate eye drops 1% to reduce pain because of ciliary muscle spasm.

-Antiinflammatory pain killers

or perforation - glue and contact lens

METHOD OF INTRAOCULAR PRESSURE RECORDING IN ULCERS

On the day of admission the intraocular pressure was noted in both eyes using the Tonopen as follows.

An anaesthetic drop (Paracaine 1%) was instilled in both eyes. A thin sterile disposable latex cap was used on the tip of the Tonopen before each use. Recordings of IOP were taken, first from the normal eye and then from the study (ulcer) eye. An average of three recordings, each with a coefficient of variation of of 5% were taken. The IOP in the normal (control) eye was recorded first to prevent cross-infection.

Intraocular pressures at an interval of 3 days were then taken in both eyes. Further recordings were taken as per the duration of admission at 3 day intervals. All efforts were made to take

IOP between 4pm and 8pm for each patient, to minimize the effect of diurnal variation of IOP.

Figure showing measurement of Intraocular pressure with Tonopen in our institution

As per our department protocol, when the ulcer showed good improvement with treatment, the patient was discharged and followed up in the “Septic OPD”, till complete healing occurred.

The signs of healing and the response to therapy noted at each visit were:

1. Decrease in corneal edema and inflammation of endothelium
2. Reduction in anterior chamber inflammation
3. Re - epithelialisation
4. Cessation of thinning of cornea
5. Decrease in infiltrate size and density

The time taken for the ulcer to heal was noted.

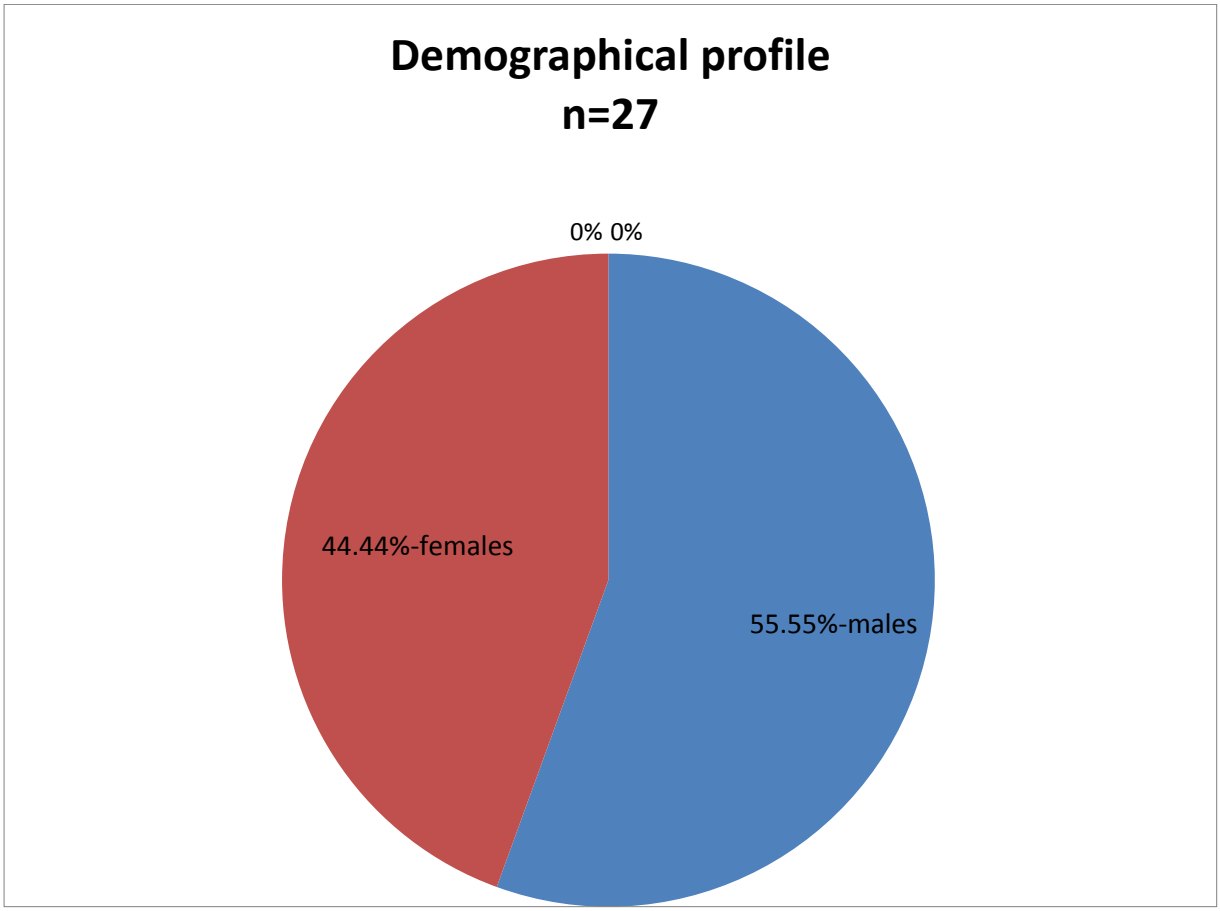
RESULTS

This was case control study which was carried out the Department of Ophthalmology, Christian Medical College Vellore 1st January 2015 to 31st July 2015. A total of 47 patients were recruited, of which 20 patients were excluded for the above said reasons; 27 patients remained for final analysis

1. DEMOGRAPHIC PROFILE OF ALL PATIENTS RECRUITED

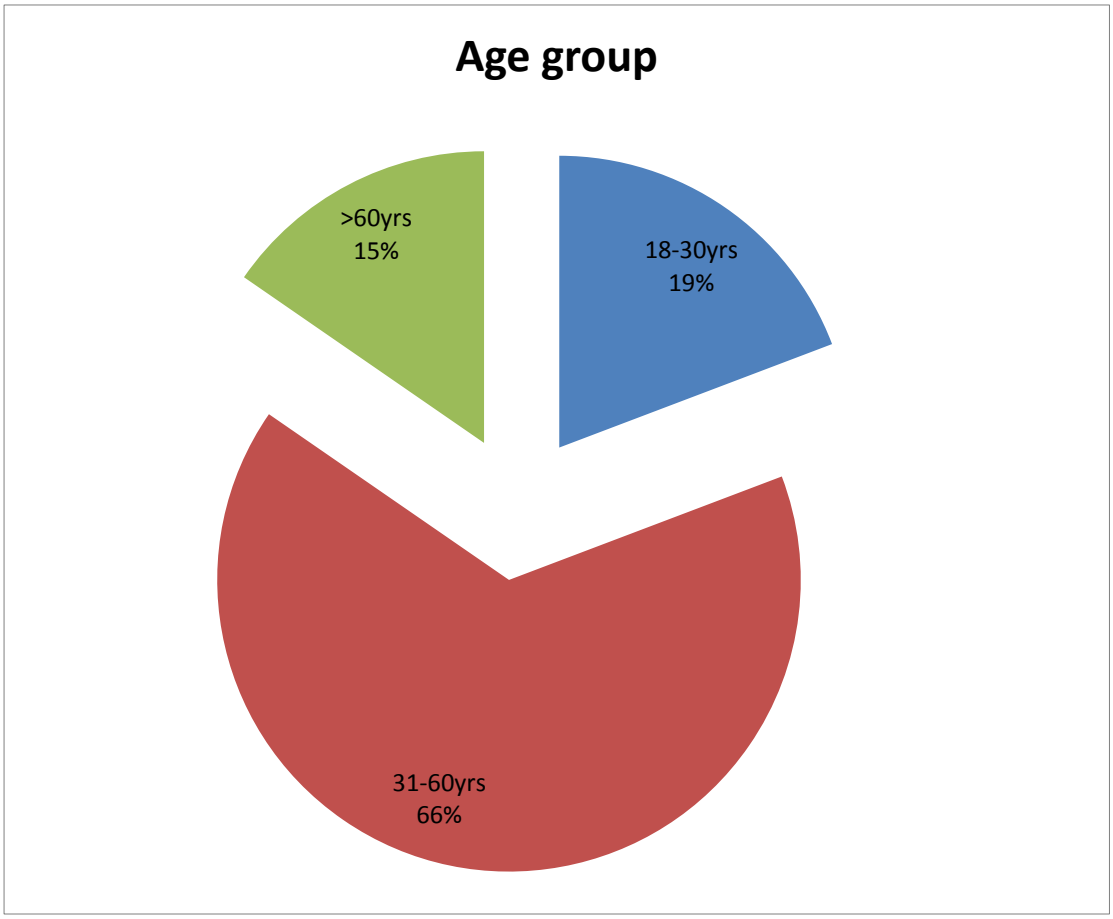
The average age of the study population was 20 to 80 years(Min to Max). When sub-classified, majority of the patients belonged to the mid age, aged between 31 to 60 years(17 patients). Most of the patients belonged to the Southern states of India with majority coming from Tamil Nadu. Among the 27 patients only 1 patient had systemic risk factor of Diabetes Mellitus who was on treatment from elsewhere, at the time of presentation. Nearly 50 % (14 patients) had some sort of topical treatment at the time of presentation to our hospital.

Pie chart 1 : Gender distribution of cases



There was almost equal representation of males and females in our cohort of patients.

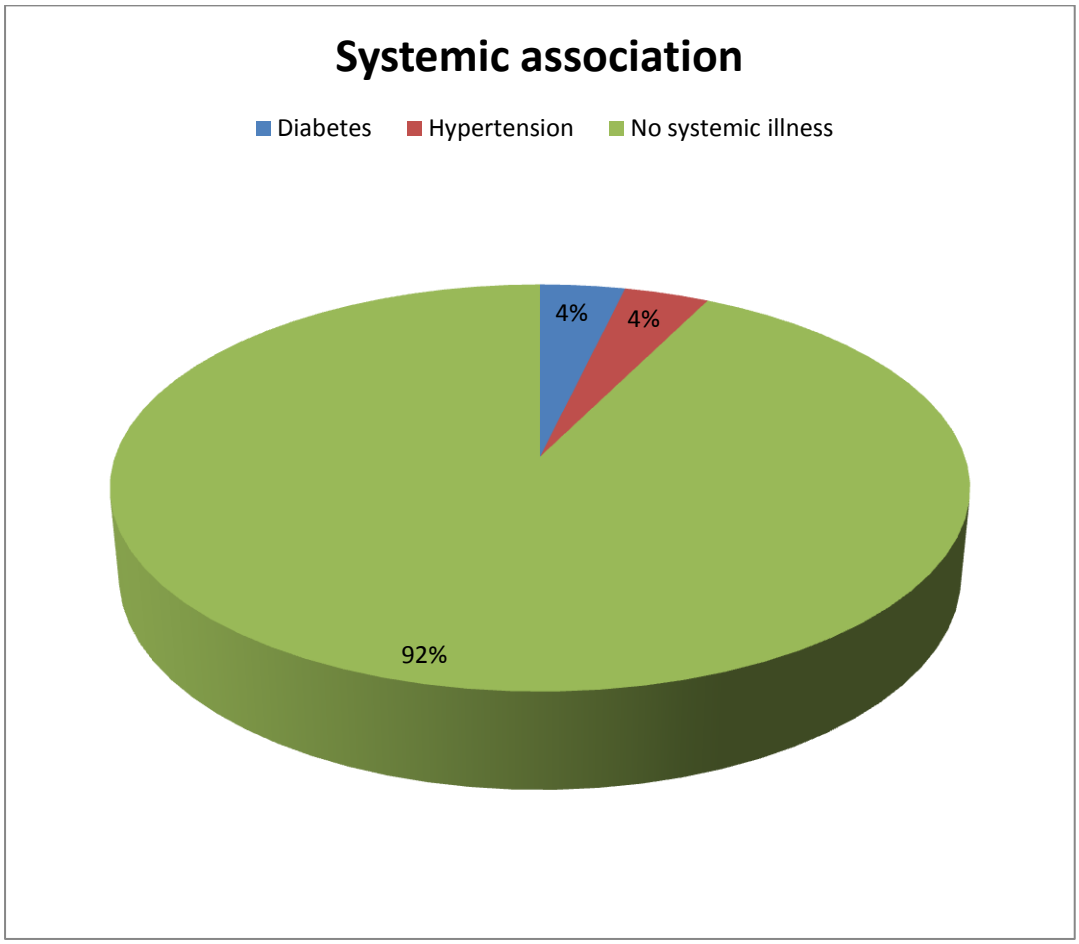
Pie chart 2: Age group affected:



The maximum number of patients fell in the 31 – 60 year age group. This is representative of the population who are in the working age group who would be susceptible to trauma to the eye.

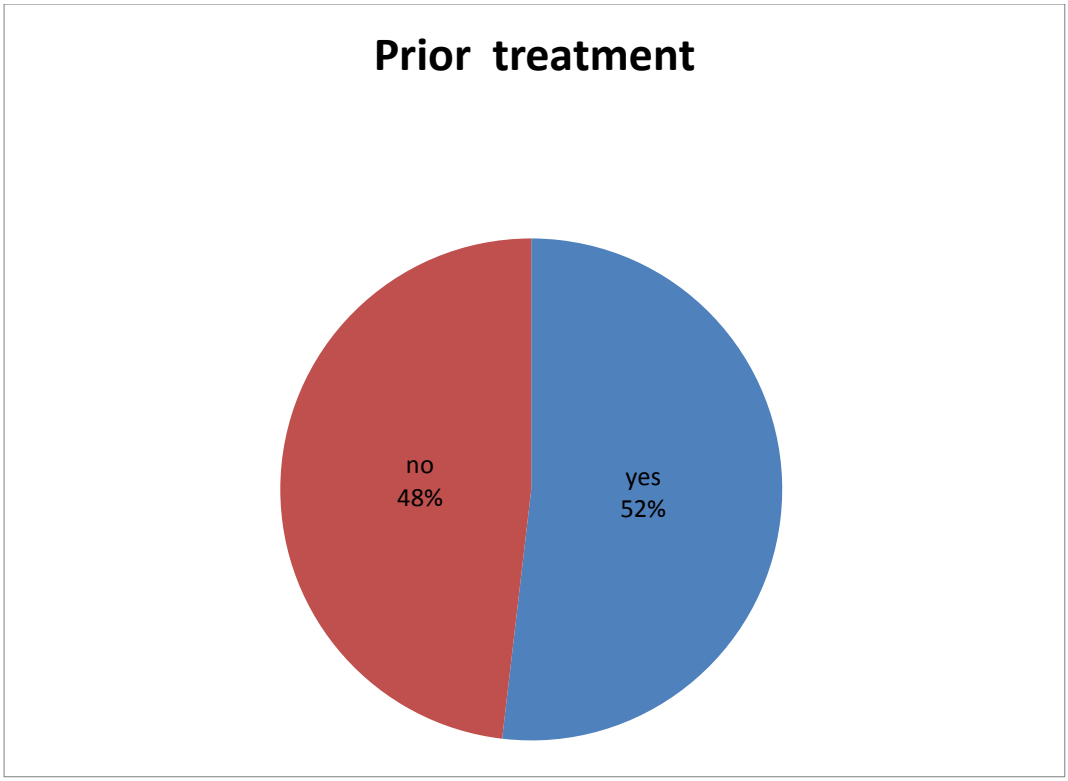
2. PATIENT CHARACTERISTICS

Pie chart 3: Systemic illness



Only one patient each were found to be diabetic and hypertensive in the cohort of 27 study patients.

Pie chart 4: Prior Treatment from Elsewhere



Almost equal numbers of patients had sought treatment from centres other than our own before presentation, as compared to those who presented in our department primarily.

3. ULCER CHARACTERISTICS

In our study population (n = 27), the majority were proven fungal ulcers (10 patients) followed by 7 patients with bacterial growth, Nocardia (2 Patients) and Acanthamoeba (1 Patient). A significant number of patients (7 / 27 or 25.9 %) did not have any growth identified in the routine culture.

Graph 1: Microbiological Profile of the organisms grown (n=27)

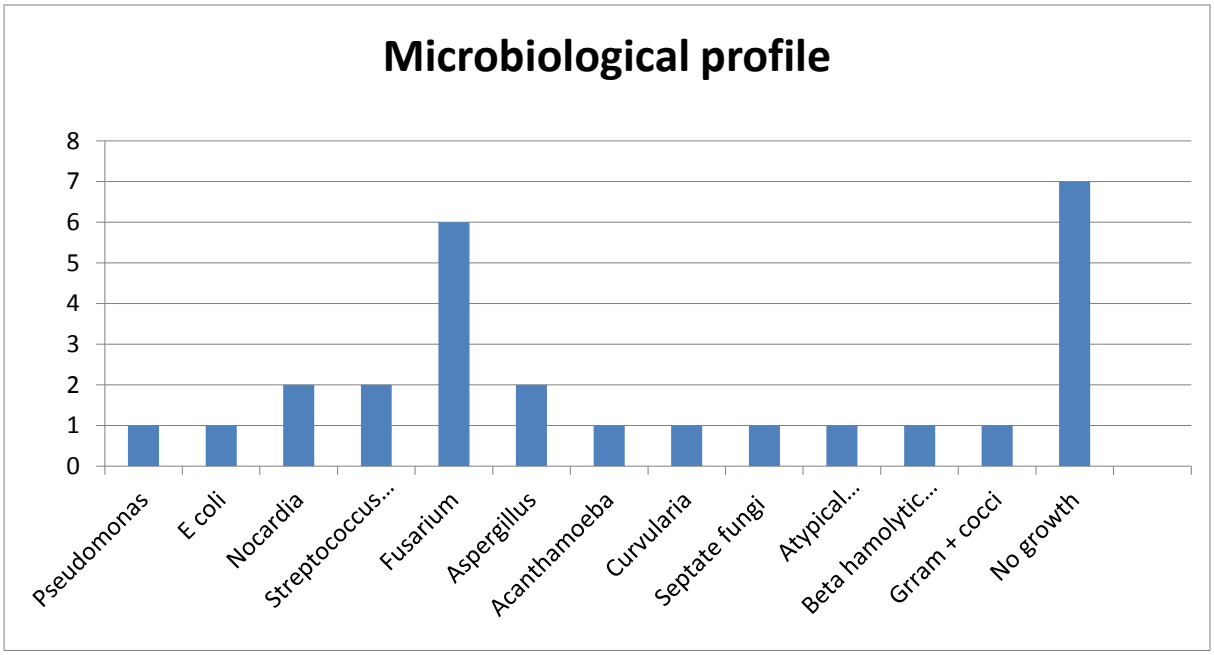
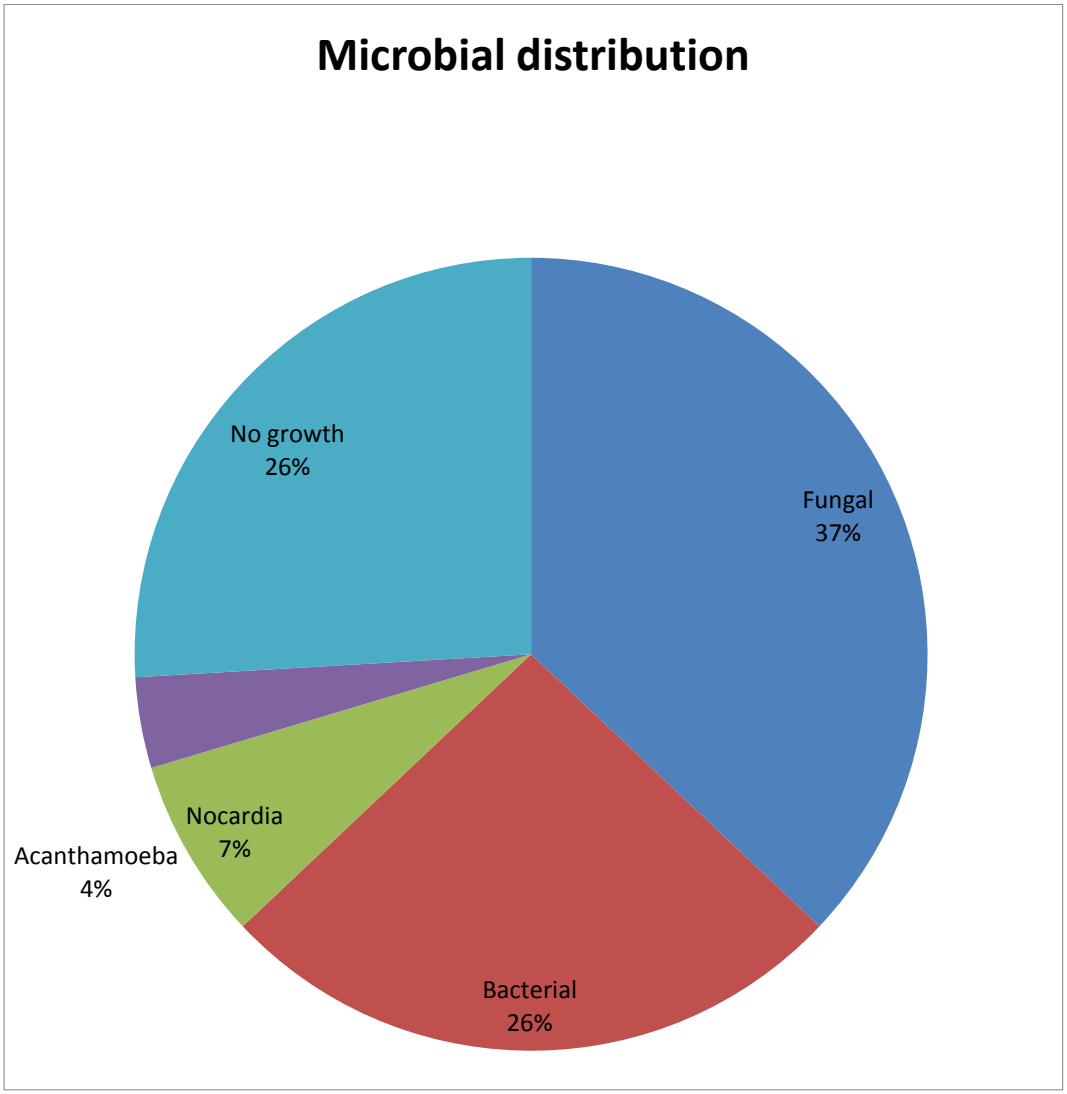


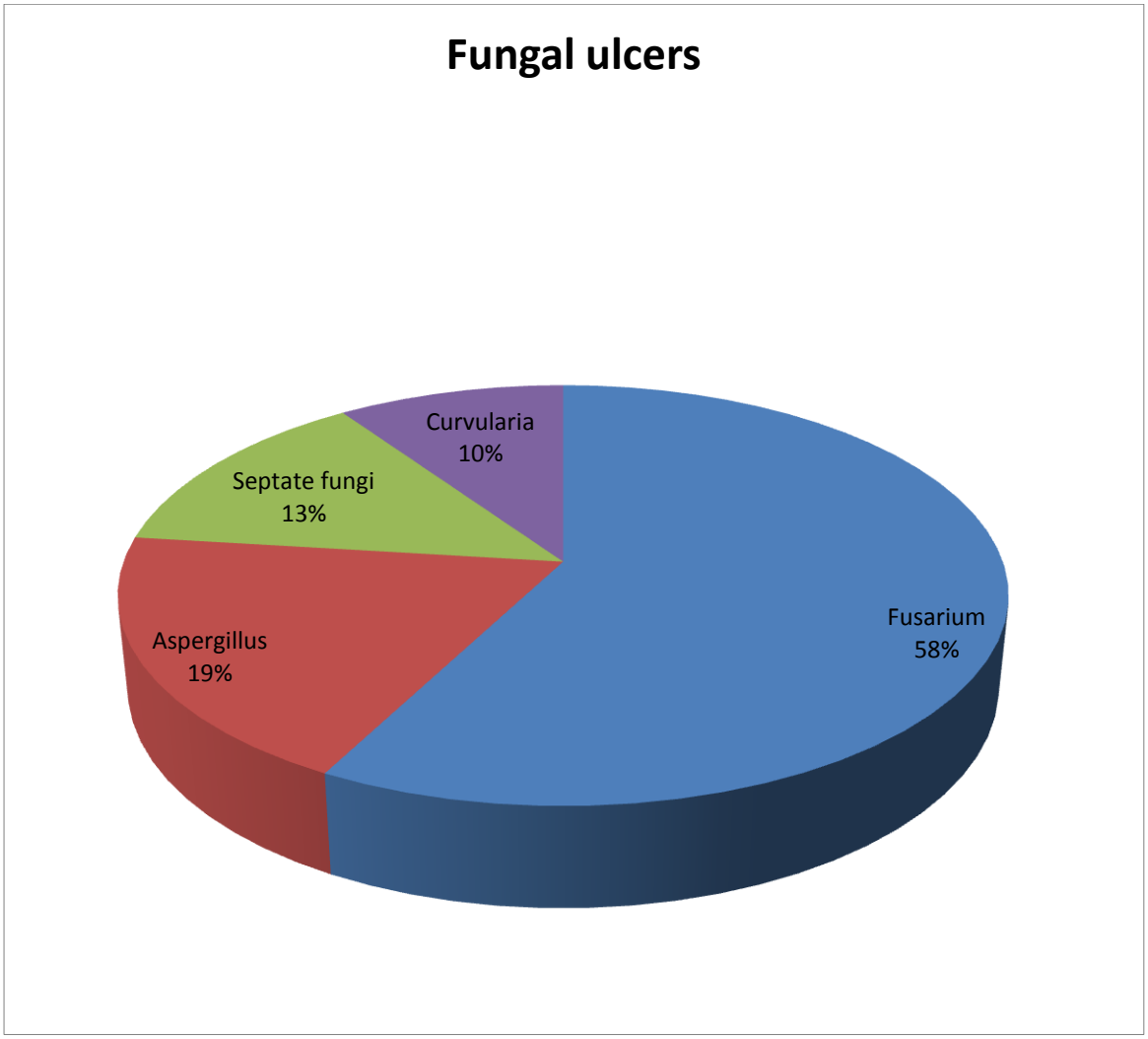
Table 1: Microbiological Profile numbers

Fungal Ulcer	10
Bacterial Ulcer	7
Nocardia	2
Acanthamoeba	1
No Growth	7

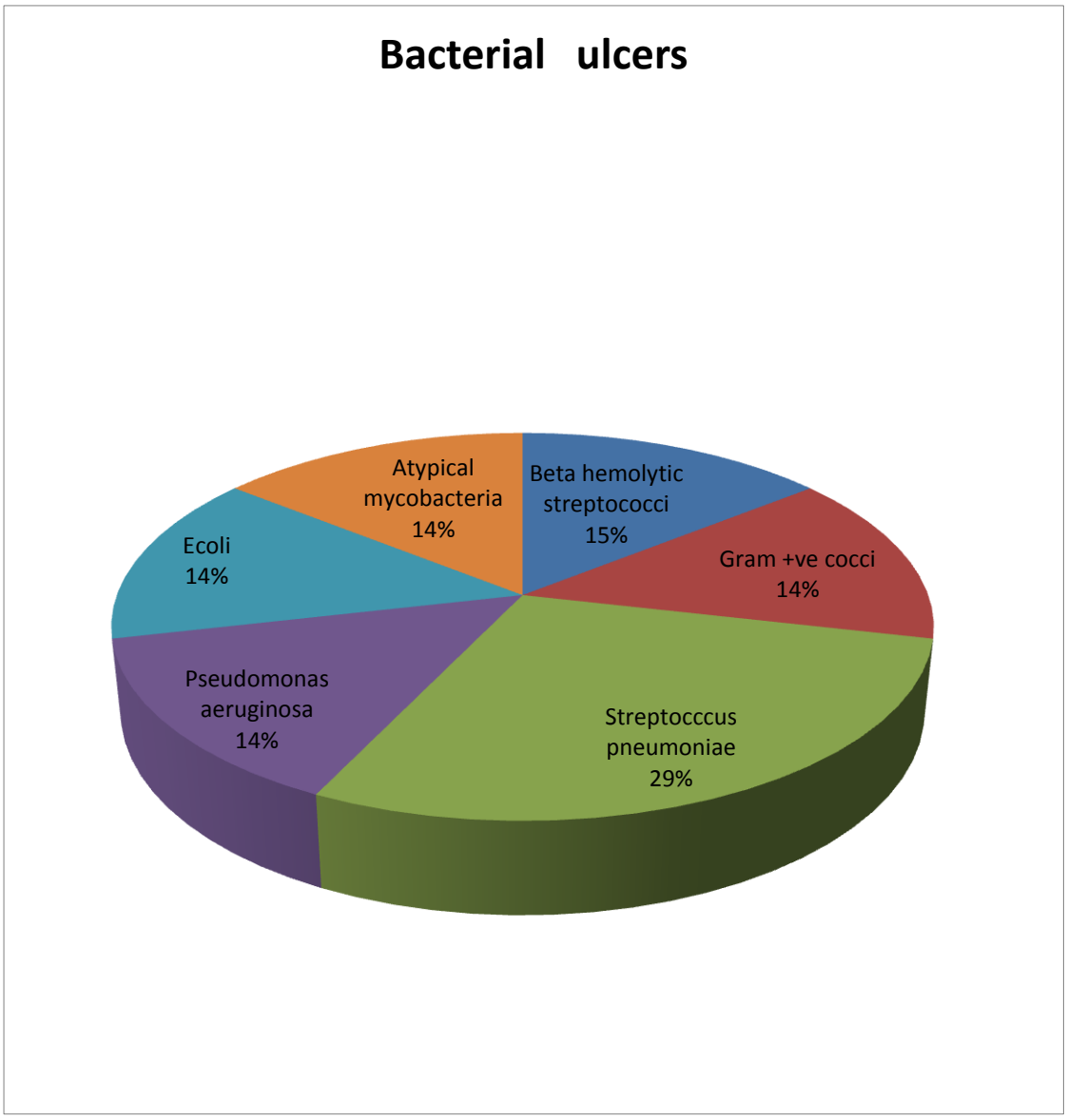
Pie Chart 5 : The microbiological profile



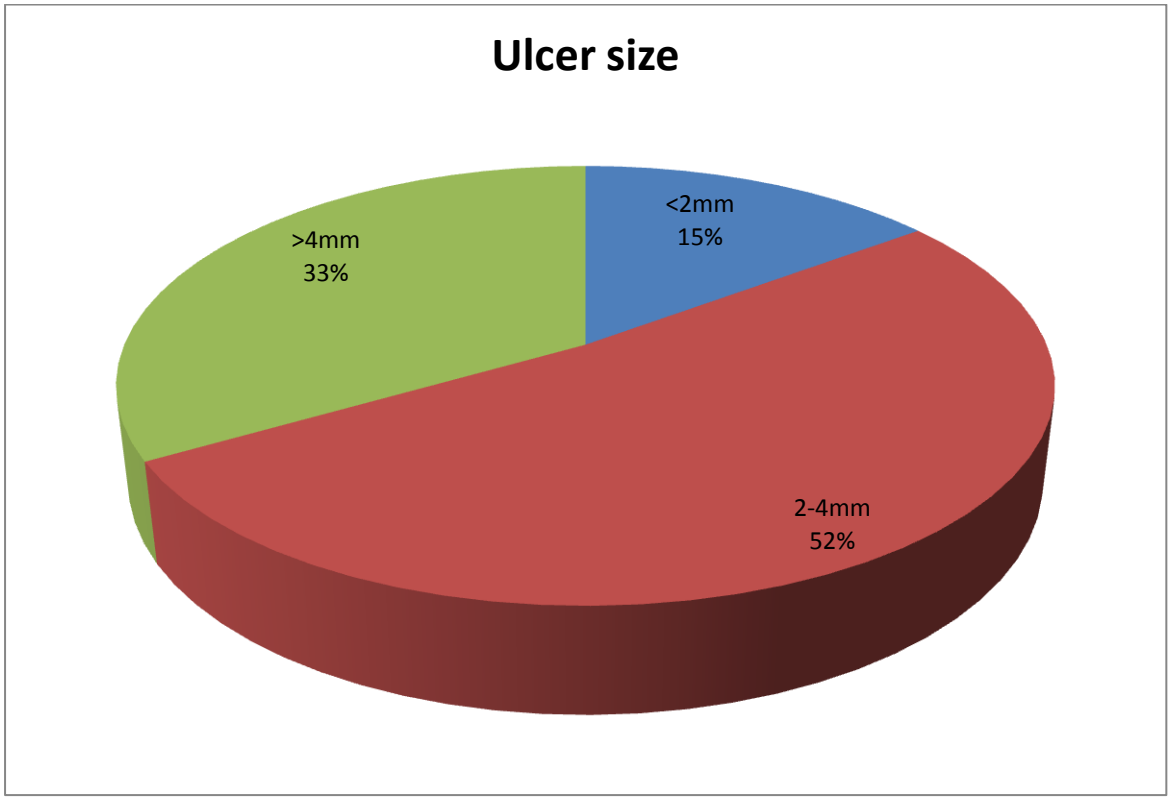
Pie chart 6: Species distribution of fungi grown



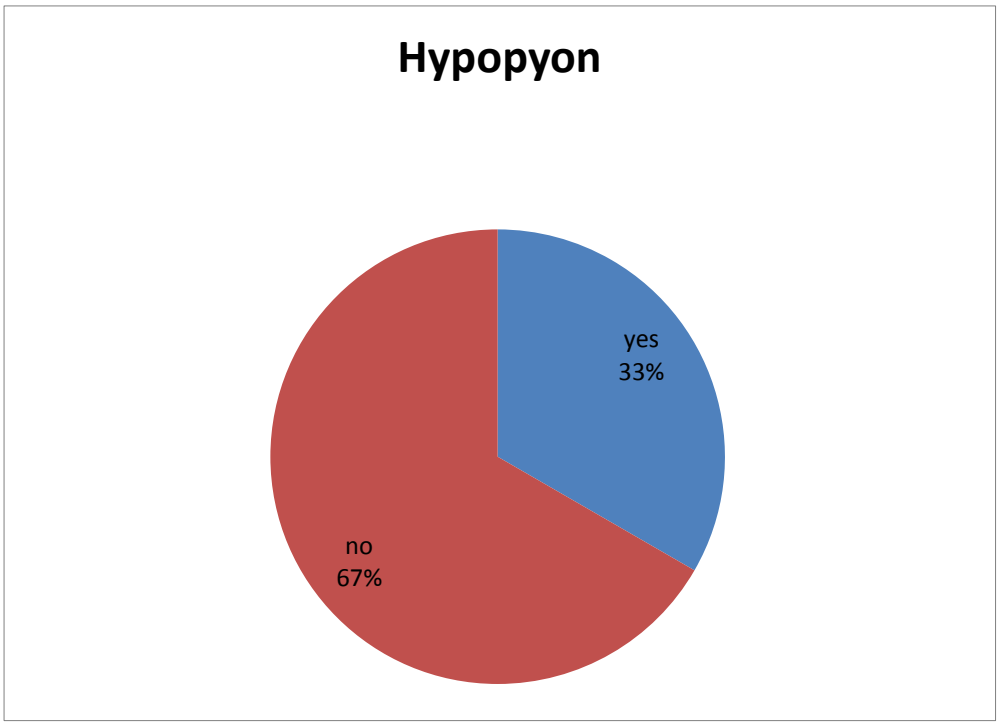
Pie chart 7: Species distribution of bacteria grown



Pie Chart 8: Size distribution of the Ulcers studied



Pie chart 9: Hypopyon at presentation



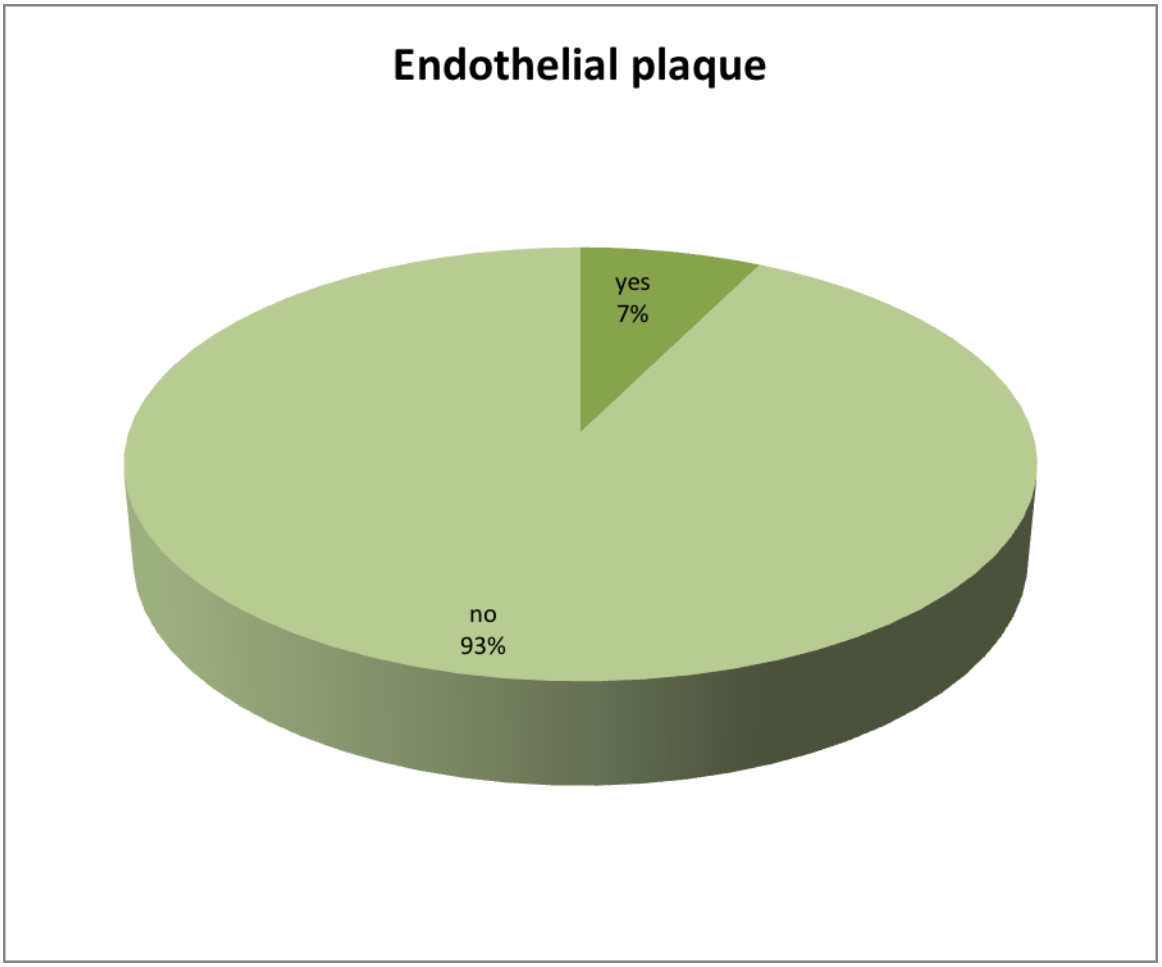
9 among 27 (33%) patients presented with hypopyon.

The following table depicts the distribution of the ulcers that presented with hypopyon.

Table 2: Table depicting the distribution of hypopyon among the ulcers

TYPE OF ULCER	BACTERIAL	FUNGAL	NO GROWTH	NOCARDIA	ACANTHAMOEBA
NUMBER	2	4	2	1	0

Pie chart 10: Endothelial plaque at presentation

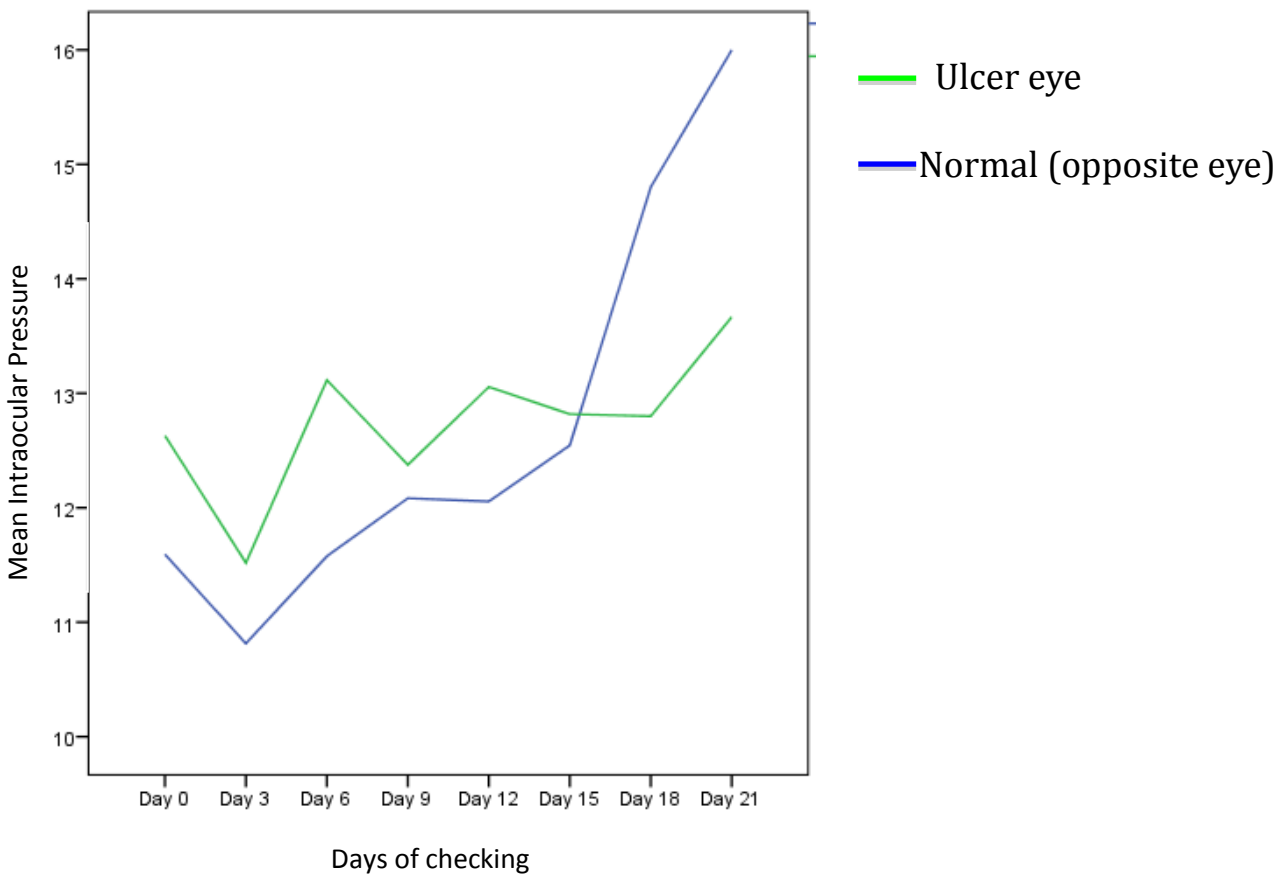


Only 7% (2/27) of all the ulcers had an endothelial Plaque at presentation.

The endothelial plaque was present in one patient with a bacterial ulcer, and in one patient where there was no growth of any organism.

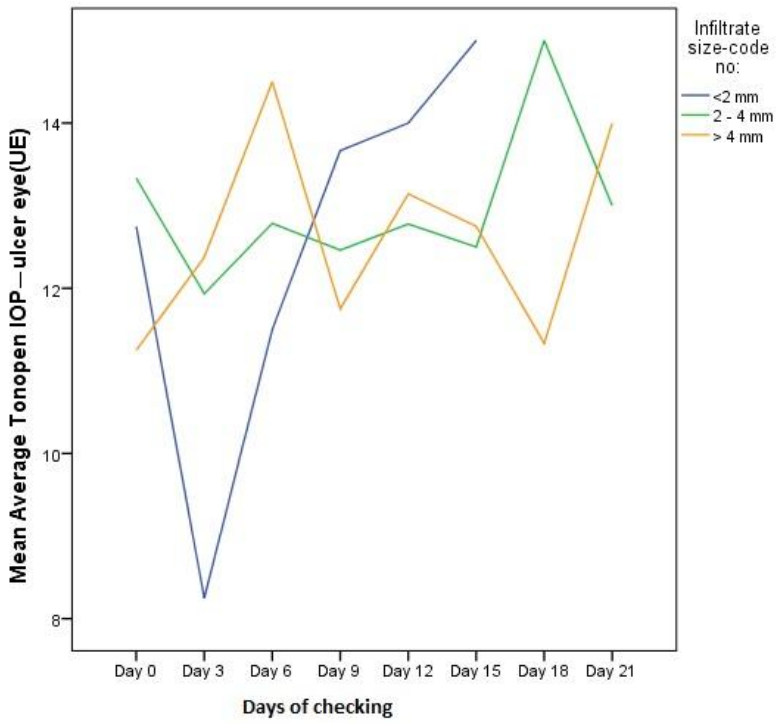
4. ANALYSIS OF INTRAOCULAR PRESSURE TREND IN ULCER EYE

Graph 2: Intra ocular Pressure trend in Ulcer Eyes and Normal Eyes



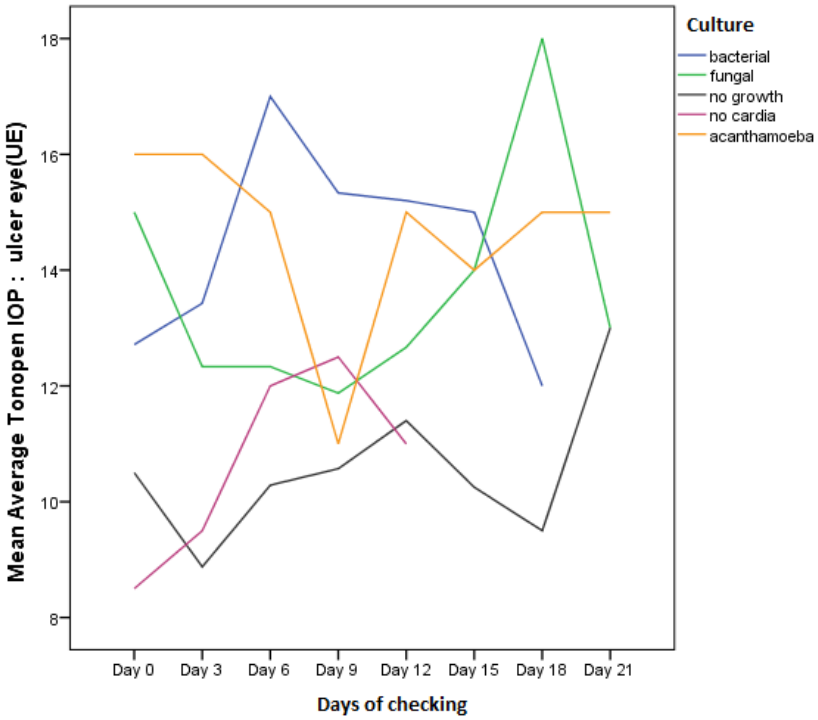
This graph depicts the trend of the intraocular pressure of the Ulcer Eye and the normal opposite eye . It can be seen that in the early part of the ulcer course, the intraocular pressure is higher than the opposite eye. However, beyond the 15th day, this trend reverses, with the normal eye showing higher pressure.

Graph 3: Intraocular pressure Trend in Ulcer Eye versus size of ulcer



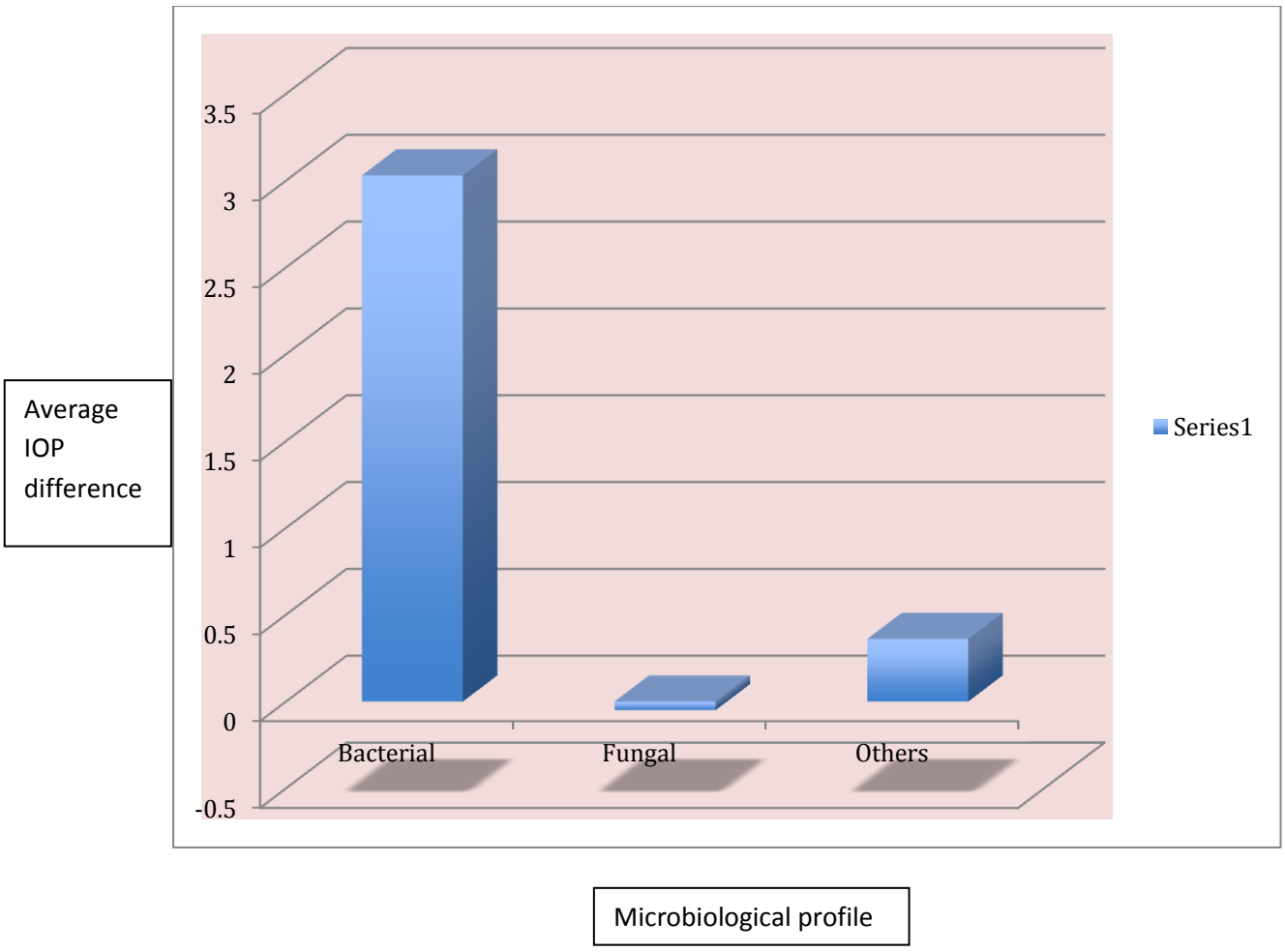
This graph reveals that there is no specific effect of size of the infiltrate on the intraocular pressure. On day 3, the smaller ulcers seem to have a dip in the intraocular pressure.

Graph 4: Intraocular pressure Trend in Ulcer Eye versus Etiology of ulcer



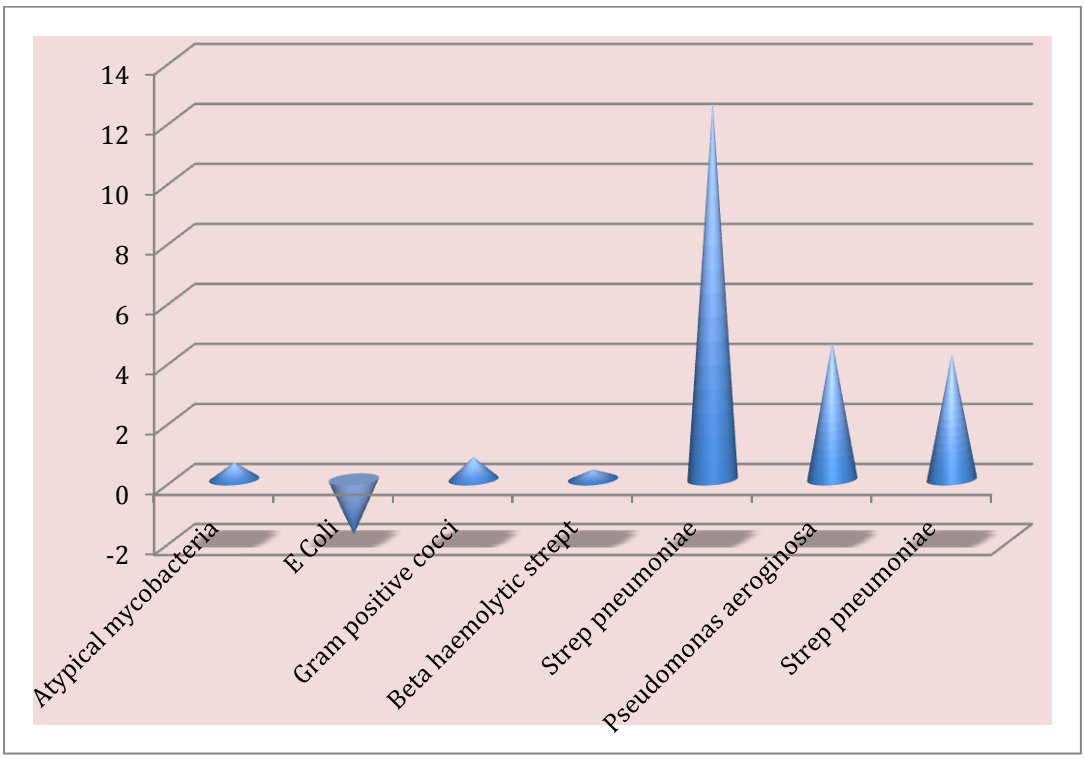
This graph demonstrates that the bacterial ulcers show a trend for a higher intraocular pressure as compared to the other ulcers

Graph 5: Graph depicting the average IOP difference between the ulcer eye and the normal eye in Bacterial, Fungal, and Others ulcers (includes no growth- 7, Nocardia -2, and Acanthamoeba-1)



This graph shows that in general, the ulcer eye had a higher average IOP in the "Bacterial" and "Others" groups, with the "Fungal" ulcers being almost equal to the opposite unaffected eye. However, interestingly, the bacterial ulcers had a statistically significant higher IOP (P value:0.01) compared to the other groups.

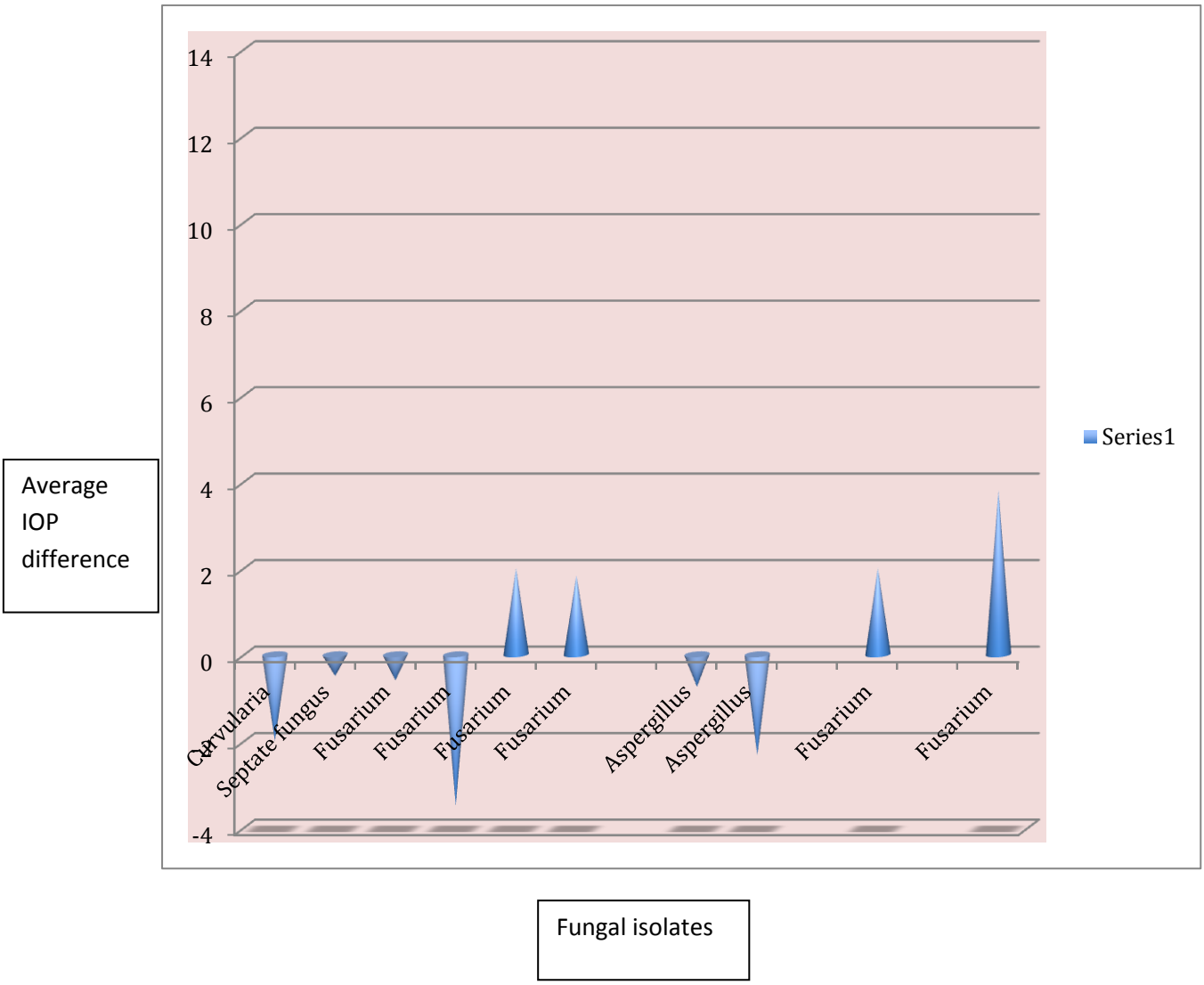
Graph 6: Graph depicting the average IOP difference between the ulcer eye and the normal eye in the 7 bacterial isolates



This graph(graph 6) shows the tallest spike in a patient with Streptococcus pneumonia. Out of the 7 bacterial ulcers showed a higher IOP in the ulcer eye compared to the normal eye.

In contrast, the following plot shows on the same scale, that the average IOP difference between the ulcer eye and the normal eye in the 10 patients with fungal isolates (Graph 7), was much smaller. 6 out of the 10 patients had lesser IOP in the ulcer eye as compared to the normal eye.

Graph 7:


Average IOP difference
14
12
10
8
6
4
2
0
-2
-4
Curvularia
Septate fungus
Fusarium
Fusarium
Fusarium
Fusarium
Aspergillus
Aspergillus
Fusarium
Fusarium
Series1
Fungal isolates

6. ANALYSIS OF "TIME TO HEALING" IN ULCER EYE

The average Time To Healing of the 27 ulcers included in this study was 24 days.The subanalysis based on IOP,size of ulcer and microbiological isolate given below.

1. MEAN TIME TO HEALING OF ULCER EYE WITH RESPECT TO INTROCULAR PRESSURE

For this part of the analysis, a mean INCREASED intraocular pressure of 4mmHg (Mean IOP difference > +4mmHg) or more in the ulcer eye as compared to the control eye was considered as the exposure, called the "High IOP Eyes. The ulcer eyes in which the mean IOP of the ulcer eye was less than 4mmHg higher than, equal to or less than the control eye (Mean IOP difference < 0mmHg / = 0mmHg / <+4mmHg)were considered "Normal IOP Eyes"

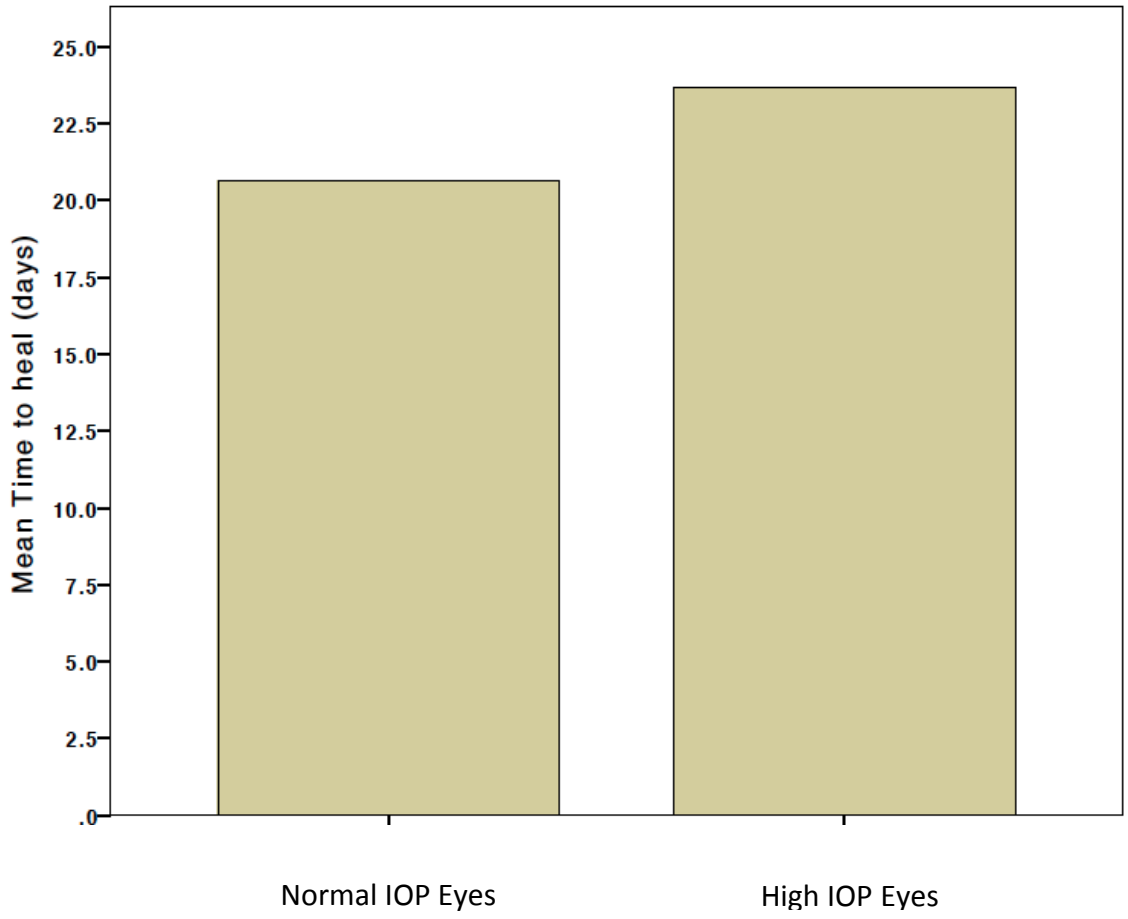
Table 3: Mean Time to Healing of Ulcer eye with respect to Introcular pressure

	Mean Time to Heal (Days)	Standard Deviation
Normal IOP Eyes (n = 21)	20.62	7.35
High IOP Eyes (n = 6)	23.67	8.04

The “Time to Healing” was marginally higher in the “High IOP Eyes” group with a “p” value of 0.58. This difference was not statistical significant.

The following is a bar graph depicting this.

Graph 8: Difference in Mean Time to Healing of Ulcer eyes with “Normal IOP” and “High IOP”



3. MEAN TIME TO HEALING OF ULCER EYE WITH RESPECT TO SIZE OF THE ULCER.

For this analysis, the ulcers were grouped into 3 groups as follows:

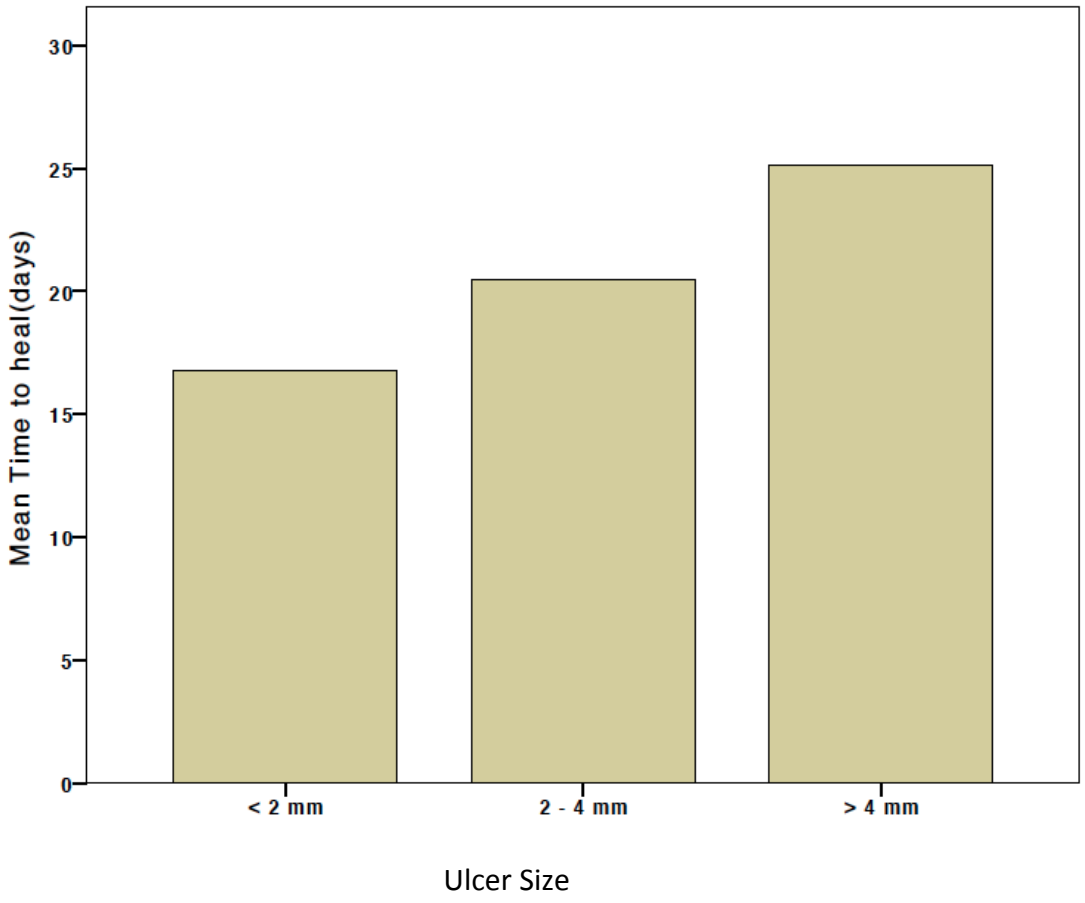
<2mm size, 2 – 4 mm size and > 4mm size. The following table displays the results.

Table 4: Time to Healing with respect to size of ulcer.

	Time to Healing (Days)	Standard Deviation
Ulcer size <2mm (n = 4)	16.75	7.27
Ulcer size 2 – 4 mm (n = 15)	20.47	8.17
Ulcer size > 4mm (n = 8)	25.13	4.52

This is depicted in the following graph.

Graph 9: Mean Time to Healing in eyes with increasing size of Ulcer



The above table and graph demonstrates that the Time to Healing increases as the size of the ulcer increases. However the differences did not reach statistical significance (p = 0.23).

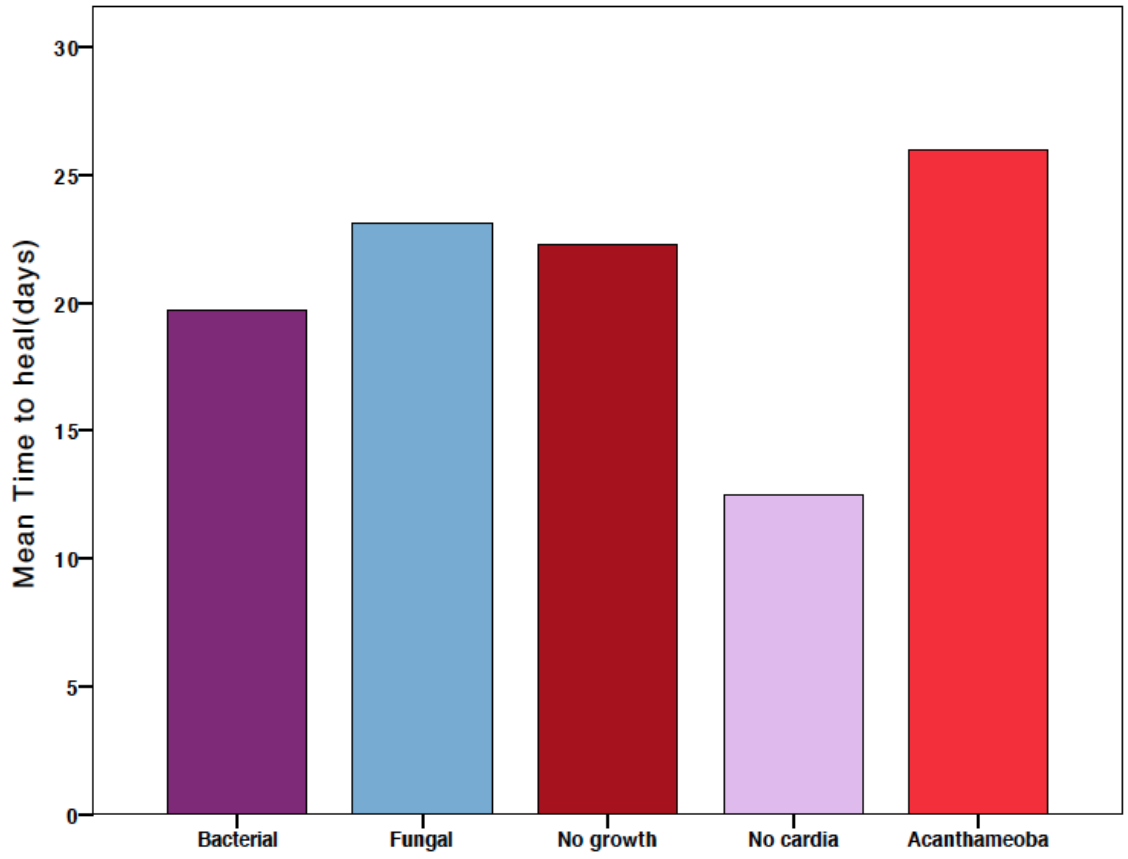
4. MEAN TIME TO HEALING OF ULCER EYE WITH RESPECT TO THE MICROBIOLOGICAL PROFILE OF THE ULCER

Table 5: Mean Time to Healing with respect to microbiological profile

	Time to Healing (Days)	Standard Deviation
Bacterial Ulcers (n = 7)	19.71	6.95
Fungal Ulcers (n = 10)	23.11	6.57
No Growth (n = 7)	22.25	9.00
Nocardia Ulcers (n = 2)	12.50	3.54
Acanthamoeba Ulcer (n = 1)	26.00	5.24

The following displays the above data in graphical form.

Graph 10: Time to Healing with respect to microbiological profile



The differences noted above did not reach statistical significance (p = 0.27

DISCUSSION

Infectious keratitis is caused due to the proliferation of microorganisms like bacteria, fungi, virus and parasites, which leads to the destruction of corneal tissue. The proteases produced by bacteria causes destruction of the stromal collagen and proteoglycans. Additionally, exotoxins produced by some bacteria like Streptococci, Staphylococci, and Pseudomonas aeruginosa can cause corneal cell necrosis.(5)

Normal conjunctival flora can also become opportunistic pathogens in immunocompromised eye. (35)

Most of the bacterial corneal ulcers develop at the site of epithelial defect in cornea. However, there are some organisms e.g. N. gonorrhoeae, N.meningitidis, Corynebacterium diphtheria, Haemophilus aegypticus and Listeria monocytogenes, Shigella spp; which can invade intact epithelium of cornea.

Central corneal ulcers after healing cause significant visual impairment because of the scar that is produced by the healing process.

Fungal corneal ulcers usually show an indolent course. The patient may present with foreign body sensation in eye with slow onset of pain and blurred vision

It is difficult to distinguish between infectious and non infectious ulcers and they need to be treated with anti-inflammatory medications. Most of the presenting cases are infective in aetiology.

A patient with a corneal ulcer ideally undergoes a battery of microbiological investigations inluding Smears for bacteria (Grams-stain) and Fungus (Potassium hydroxide- KOH, or Lactophenol Cotton Blue –LPCB), and culture plating in Blood agar, Saboraud Dextrose Agar and Chocolate Agar. If Acanthamoeba is suspected, Non-nutrient agar with E coli overlay is also used. Based on the results of the smear, and later the culture and sensitivity profile, appropriate topical medication is started and modified as required. Systemic anti-microbial medication is not used except in fungal ulcers where there is suspicion of hyphae infiltrating through the corneal endothelium into the anterior chamber.

Even with all these measures, the lack of vascularity of the cornea, the tight junctions of the epithelial and endothelial cells, as well as the lipid solubility/aqueus solubility issues of the medications used, results in difficulty in healing of the ulcer, usually necessitation weeks of in-patient care to get the ulcer under control.

In our population, any additional factor that prolongs hospital stay is detrimental to the patient’s socio economic status.

Hence any factor which impedes the healing process like dry eyes, trichiasis, etc have to be treated sideby side.

Healing of the ulcer depends upon many factors.

1. The presenting size of the ulcer has a significant role in the time to heal. In this study also, the larger size ulcers showed a signific longer time to heal than a smaller sized one.The outcome of a corneal ulcer always depends on how early the ulcer is diagnosed and treated. Those ulcers which are small , superficial,mostly limited to the anterior most cornea, which are treated with appropriate topical antibiotic drops will heal faster. But at the same time the ulcer in a compromised cornea which is large in size will take more time to heal.

2. The organism causing the ulcer may respond rapidly to the medication used. However, some organisms may be resistant to the medications that are used, or the organism may be one that causes indolent ulcers e.g. Non tuberculous mycobacteria.

3. The role of raised intraocular pressure (secondary glaucoma) in prolonging the time taken for the ulcer to heal is currently. This aspect of corneal ulcers has been very sparsely studied. A study(4) published in 2011 has however highlighted this, and it was found that the raised IOP is infact associated with an increased time to healing.

The reasons for this may be:

a. Inflammation of the anterior chamber associated with inflammation of the trabecular meshwork in the ulcer eye i.e. associated trabeculitis.

b. Blockage of the trabecular meshwork by infalmmatory debris in the anterior chamber

c. Pupillary block due to inflammatory membranes across the pupil. Pupillary block due to growth of fungal elements across the pupil causing “malignant glaucoma” has been documented. (36)

d. Inflammatory cytokins and molecules released by certain bacteria may cause increased inflammatory reactions and trabeculitis. This may be one of the reasons that addition of steroids in the treatment of some bacterial ulcers helps with the healing of these ulcers.(30,37)

In a preliminary unpublished study conducted in our department in 1996- 1999, a definite trend for raised IOP in corneal ulcers with Streptococci pneumoniae isolated was detected. These ulcers heal faster with reduction of IOP when steroids are added to the treatment protocol.

Once the patient starts showing signs of healing like decrease in pain, redness, blunting of the perimeter of infiltrate and resurfacing of the epithelial defect , the frequency of the topical antibiotics should be reduced to avoid the potential side effects .

About present study:

In this study, conducted in Schell eye hospital , CMC, from 1st January 2015 to 31st July 2015, 46 patients with active ulcers were enrolled initially. Among those 46 patients 5 patients had descematocele formation , 6 patients had perforation, and 8 underwent ocular interventions. A total of 27 patients were included for the analysis. Most of them were from Vellore district and mostly from rural areas. Most of them were agricultural workers as their main occupation.

The majority of the patients who presented were in the age group 31-60 years, which represents the working group in the society.

Among the 27 patients there was one with hypertension and one with diabetes mellitus. None of the rest patients were not known to have any systemic illness .This may represent the lack of knowledge about there own health as the people from villages were not aware about the importance of routine health checkups.

Out of 27 patients 14 patients received some sort of ophthalmic treatment prior to presentation to our hospital.

All patients who underwent scraping and were admitted here, were started on topical medication according to the smear and culture reports as per standard hospital protocols detailed above.

Intraocular Pressure Recording

Intraocular pressure was checked with Tonopen after caliberation, with he normal eye IOP being checked first so that no transfer of infection occurred. The difference between the IOP was also noted between two eyes. The same procedure is repeated at three day intervals. Great efforts were taken to make sure IOP was recorded at almost the same time (4pm – 8pm) in all patients, to avoid bias due to diurnal variation of intraocular pressure.

In our study, we found that bacterial ulcers had a higher IOP in the ulcer eye as compared to the unaffected opposite eye. On an average after 9 days, the IOP of the ulcer eye started to become stabilized. In many of the ulcers, the IOP in the ulcer eye

was lower than that of the unaffected eye. This is what is usually seen in patients with non infectious anterior uveitis.

It is extremely interesting to note that in our study, the average IOP difference in the bacterial ulcers (higher IOP in the ulcer eye) was larger than the average IOP difference in the fungal ulcers, and the other ulcer (no growth / nocardia / acamthamoeba) groups. This difference was statistically significant.

Additionally, on break down of the individual IOP difference for each bacterial isolate obtained, the highest IOP diference (higher IOP in the ulcer eye) was found for Streptococcus pneumoniae isolate. However, the sample size is too small to make any kind of generalization about this finding.

Analysis of the “time to healing “ was done for

1. IOP difference between the ulcer eye and the opposite normal eye: the exposure being a **higher** IOP in the ulcer eye:

Patients who had a difference in IOP between the study eye and the normal eye of (a) More than + 4mmHg i.e. IOP in the ulcer eye 4mmHg or more higher than the normal opposite eye compared to

(b) those with difference in IOP less than 4mmHg (higher in the ulcer eye) and those with IOP less in the ulcer eye than in the normal eye.

The results of this analysis was not statistcally significant. Hence our study could not show that the time to healing was influenced in any way by the IOP in the ulcer eye. This maybe due to the small sample size studied.

2. Size of the infiltrate:

Here, the results of our analysis did not show a statisticaly significant difference in the "time to healing" between the 3 sub groups studied. There was however a clear trend demonstrating a longer time taken to heal as the ulcer size increased. This seems intuitively plausible.

3. Microbiological Profile:

Here as well, the results of our analysis did not show a statisticaly significant difference in the "time to healing" between the different microbiological isolates obtained.

SUMMARY

Infectious keratitis is an ocular emergency as it is a sight threatening condition worldwide, which is a major public health issue. The age group mostly affected is the middle age group. Most of the patients in our population are from rural areas and majority are agriculturalists as occupation.

All the 27 patients who were included in the study after microbiological scraping were started on standard therapy as per department protocol. Those who were selected for this study additionally had intra ocular pressure (IOP) measurements taken at intervals of 3 days, between 4pm and 8pm, with the Tonopen.

Healing time of the ulcer was considered as the time between presentation to us and closure of the epithelial defect with resolution of the infiltrate.

The main objective of the present study was to study the trend of intraocular pressure variation between the ulcer eye and the normal eye. The secondary objectives were to determine if "Time to Healing" was affected by a raised IOP in the ulcer eye, the size of the ulcer at presentation, and the microbiological profile of the patients.

The average "Time to Healing" of all the ulcers included in this study was found to be 24 days.

The analysis of the results of the IOP monitoring did not show show a clear trend of IOP in the ulcer eye of the population studied, except for a suggestion that bacterial ulcers may tend to have a higher IOP in the ulcer eye than the unaffected eye, and that

perhaps Streptococcus pneumoniae ulcers have an IOP spike that should be monitored for and treated appropriately.

Additionally, this study does not show a significant difference in the “Time to Healing” based on raised intraocular pressure in the ulcer eye, size of the ulcer and microbiological isolate profile.

LIMITATIONS OF THE STUDY

1) The sample size is not adequate to comment about the IOP trends and correlation of IOP, size of ulcer and microbiological profile with the healing time.
2) Some of the eligible patients who were recruited initially had to be withdraw from the study due to surgical interventions
3) A few patients did not come for follow up for the complete study course.
4) A large number with " no growth "in culture limited the scope of large scale microbiological analysis

CONCLUSION

This study does not show a clear trent of IOP in the ulcer eye of the population studied, except for a suggestion that bacterial ulcers may tend to have a higher IOP in the ulcer eye than the unaffected eye, and that perhaps Streptococcus pneumoniae ulcers have an IOP spike that should be monitored for and treated appropriately.

Additionally, this study does not show a significant difference in the time to healing based on raised intraocular pressure in the ulcer eye, size of the ulcer and microbiological isolate profile. However, there is a sugestion that increasing ulcer size leads to increasing time for healing to occur.

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APPENDIX A

IRB APPROVAL LETTER

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. Alfred Job Daniel, D Ortho, MS Ortho, DNB Ortho
Chairperson, Research Committee & Principal

Dr. Nihal Thomas,
MD., MNAMS., DNB (Endo), FRACP (Endo), FRCP (Edin), FRCP (Glasg)
Deputy Chairperson
Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

December 30, 2014

Dr. Bindu Thomas
PG Registrar
Department of Ophthalmology
Christian Medical College, Vellore 632 001

Sub: **Fluid Research Grant Project:**
Observational study of intraocular pressure (IOP) patterns in patients with infective corneal ulcers presenting to a tertiary center in South India.
Dr. Bindu Thomas, P.G Registrar, Dr. Sanita Korah, Dr. Satheesh Solomon, T Selvin, Ophthalmology, CMC, Vellore.

Ref: IRB Min No: 9151 [OBSERVE] dated 12.11.2014

Dear Dr. Bindu Thomas,

I enclose the following documents:

1. Institutional Review Board approval 2. Agreement

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

With best wishes,

Dr. Nihal Thomas
Secretary (Ethics Committee)
Institutional Review Board

Dr. NIHAL THOMAS
MD, MNAMS, DNB (Endo), FRACP (Endo), FRCP(Edin), FRCP(Glasg)
SECRETARY - (ETHICS COMMITTEE)
Institutional Review Board,
Christian Medical College, Vellore - 632 002.

Cc: Dr. Sanita Korah, Ophthalmology, CMC, Vellore.

OFFICE OF RESEARCH
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CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA.

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December 30, 2014

Dr. Bindu Thomas
PG Registrar
Department of Ophthalmology
Christian Medical College, Vellore 632 001

Sub: **Fluid Research Grant Project:**
Observational study of intraocular pressure (IOP) patterns in patients with infective corneal ulcers presenting to a tertiary center in South India.
Dr. Bindu Thomas, P.G Registrar, Dr. Sanita Korah, Dr. Satheesh Solomon, T Selvin, Ophthalmology, CMC, Vellore.

Ref: IRB Min No: 9151 [OBSERVE] dated 12.11.2014

Dear Dr. Bindu Thomas,

The Institutional Review Board (Blue, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project entitled "Observational study of intraocular pressure (IOP) patterns in patients with infective corneal ulcers presenting to a tertiary center in South India." on November 12th 2014.

The Committees reviewed the following documents:

1. IRB Application format
2. Curriculum Vitae' of Drs. Bindu Thomas, Sanita Korah, Satheesh Solomon, T Selvin.
3. Informed Consent form (English & Tamil)
4. Information Sheet (English & Tamil)
5. No of documents 1-4

The following Institutional Review Board (Blue, Research & Ethics Committee) members were present at the meeting held on November 12th 2014 in the CREST/SACN Conference Room, Christian Medical College, Bagayam, Vellore 632002.

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

Dr. B.J. Prashantham, M.A., M.A., Dr. Min (Clinical)
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Chairperson, Ethics Committee.

Dr. Alfred Job Daniel, D Ortho, MS Ortho, DNB Ortho
Chairperson, Research Committee & Principal

Dr. Nihal Thomas,
MD., MNAMS., DNB (Endo), FRACP (Endo), FRCP (Edin), FRCP (Glasg)
Deputy Chairperson
Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

Name	Qualification	Designation	Other Affiliations
Dr. Chandra Singh	MS, MCH, DMB	Professor, Urology, CMC, Vellore	Internal, Clinician
Dr. Ranjith K Moorthy	MBBS M Ch	Professor, Neurological Sciences, CMC, Vellore	Internal, Clinician
Dr. Bobby John	MBBS, MD, DM, Ph D, MAMS	Professor, Cardiology, CMC, Vellore	Internal, Clinician
Dr. Benjamin Perakath	MBBS, MS, FRCS	Professor, Colorectal Surgery, CMC, Vellore	Internal, Clinician
Dr. Rajesh Kannangai	MD, Ph D,	Professor & In-charge Retrovirus Laboratory (NRL under NACO), Department of Clinical Virology, CMC, Vellore	Internal, Clinician
Dr. Anup Ramachandran	Ph. D	The Wellcome Trust Research Laboratory Gastrointestinal Sciences, CMC, Vellore	Internal, Basic Medical Scientist
Dr. Anand Zachariah	MBBS, PhD	Professor, Medicine, CMC, Vellore	Internal, Clinician
Dr. Simon Pavamani	MBBS, MD,	Professor, Radiotherapy, CMC, Vellore	Internal, Clinician
Dr. Visalakshi. J	MPH, PhD	Lecturer, Dept of Biostatistics, CMC, Vellore	Internal, Statistician
Dr. T. Balamugesh	MBBS, MD(Int Med), DM, FCCP (USA)	Professor, Pulmonary Medicine, CMC, Vellore	Internal, Clinician

OFFICE OF RESEARCH
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CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA.

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MD., MNAMS., DNB (Endo), FRACP (Endo), FRCP (Edin), FRCP (Glasg)
Deputy Chairperson
Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

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
Mrs. Pattabiraman	B. Sc, DSSA	Social Worker, Vellore	External, Lay Person
Dr. Denise H. Fleming	B. Sc (Hons), PhD	Honorary Professor, Clinical Pharmacology, CMC, Vellore	Internal, Scientist & Pharmacologist
Dr. Anuradha Rose	MBBS, MD	Assistant Professor, Community Health, CMC, Vellore	Internal, Clinician
Mrs. Emily Daniel	MSc Nursing	Professor, Medical Surgical Nursing, CMC, Vellore	Internal, Nurse
Mrs. Sheela Durai	MSc Nursing	Addl. Deputy Nursing Superintendent, Professor of Nursing in Medical Surgical Nursing, CMC, Vellore	Internal, Nurse
Mr. C. Sampath	BSc, BL	Legal Expert, Vellore	External, Legal Expert
Dr. Jayaprakash Muliyil	BSC, MBBS, MD, MPH, Dr PH (Epid), DMHC	Retired Professor, Vellore	External, Scientist & Epidemiologist
Rev. Joseph Devaraj	B. Sc, BD	Chaplaincy Department, CMC, Vellore	Internal, Social Scientist

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

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MD., MNAMS., DNB (Endo), FRACP (Endo), FRCP (Edin), FRCP (Glasg)
Deputy Chairperson
Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

Dr. Nihal Thomas,	MD, MNAMS, DNB(Endo), FRACP(Endo) FRCP(Edin) FRCP (Glasg)	Professor & Head, Endocrinology. Additional Vice Principal (Research), Deputy Chairperson, IRB, Member Secretary (Ethics Committee), IRB	Internal, Clinician

We approve the project to be conducted as presented.

The Institutional Ethics Committee expects to be informed about the progress of the project, any **adverse events** occurring in the course of the project, any **amendments in the protocol and the patient information / informed consent**. On completion of the study you are expected to submit a copy of the **final report**. Respective forms can be downloaded from the following link: http://172.16.11.136/Research/IRB_Polices.html in the CMC Intranet and in the CMC website link address: http://www.cmch-vellore.edu/static/research/Index.html.

Fluid Grant Allocation:

A sum of 86,250/- INR (Rupees Eighty Six Thousand Two Hundred and Fifty only) will be granted for 9 months.

Yours sincerely,

Dr. Nihal Thomas
Secretary (Ethics Committee)
Institutional Review Board

Dr. NIHAL THOMAS
MD.,MNAMS.,DNB(Endo),FRACP(Endo),FRCP(Edin),FRCP(Glasg)
SECRETARY - (ETHICS COMMITTEE)
Institutional Review Board,
Christian Medical College, Vellore - 632 002.

Cc: Dr. Sanita Korah, Ophthalmology, CMC, Vellore.

IRB Min No: 9150 [OBSERVE] dated 12.11.2014

APPENDIX – B

PATIENT INFORMATION SHEET AND CONSENT FORM

INFORMATION SHEET

Christian Medical College, Vellore

Department of Ophthalmology

Study to determine the variation of intraocular pressure in active infective corneal ulcers : An observational study in a tertiary eye care centre

Study number: **Date:**

Name of participant:

Hospital number:

You are being requested to participate in a study to determine the variation of intraocular pressure in infective corneal ulcers. After a detailed history and examination, the IOP in both eyes will be taken with a Tonopen.

Tonopen is a surface contact instrument that produces a digital recording of the IOP. The tip of the instrument is covered with a thin sterile, disposable latex cap before each use.After calibration, topical anaesthetic drops are instilled into the eye, and the tip of the instrument is touched momentarily to the cornea lightly and briefly, then withdrawn.

A minimum of four recording of IOP will be taken :at the day of admission, and then at intervals of 3 days and at last follow up. Three readings with SD 5% will be taken and averaged to get the value of the IOP for that eye at that time. You will be followed up till the ulcer heals. We hope to include about 150 patients from this hospital for this study.

Can you withdraw from this study after it starts?

Your participation in this study is voluntary. Not giving consent for participation in the study will not affect your treatment in this hospital.

What are the potential risks to participants in this study?

Since, it is an observational study, there are no potential risks in participating in this study. The history taking and examination will be according to standard protocol for all patients coming with active corneal ulcers

Will your personal details be kept confidential?

The results of this study will be published in a medical journal but you will not be identified by name in any publication or presentation of results. However, your medical notes may be reviewed by people associated with the study, without your additional permission, should you decide to participate in this study.

If you have any further questions, please ask Dr.Bindu Thomas (Tel: 04163071201 , 9488816051) or email: binzthomas06@gmail.com

INFORMED CONSENT

Informed Consent form to participate in a research study

Study Title:

Study Number: _____

Subject's Initials: _____ Subject's Name: _____

Date of Birth / Age: _____

(Subject)

(i)I confirm that I have read and understood the information sheet dated _____ for the above study and have had the opportunity to ask questions related to the procedure.I confirm that I have been given the option of undergoing intraocular pressure checking in my ulcer eye and normal eye using an instrument called Tonopen during my admission in this hospital.The procedure of using Tonopen has been explained to me in my own language and i have understood that this procedure may or may not have any benefit on my corneal ulcer. [ ]

(ii) I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. [ ]

(iii) I understand that the Sponsor of the clinical trial, others working on the Sponsor's behalf, the Ethics Committee and the regulatory authorities will not

need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published.I accept to share the data obtained during analysis in the faith that it will be used only for scientific purposes. [ ]

(iv) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s). [ ]

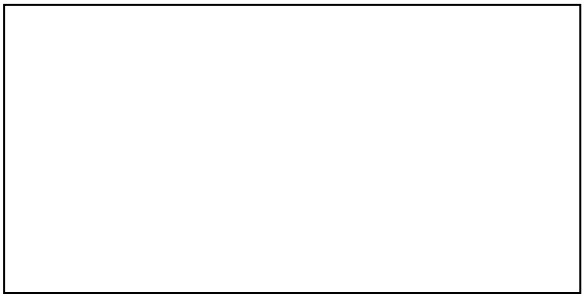
(v) I agree to take part in the above study. [ ]

Signature (or Thumb impression) of the Subject/Legally Acceptable

Date: _____/_____/_____

Signatory's Name: _____ Signature:

Or



Representative: _____

Date: _____/_____/_____

Signatory's Name: _____

Signature of the Investigator: _____

Date: _____/_____/_____

Study Investigater's Name: _____

Signature or thumb impression of the Witness: _____

Date: _____/_____/_____

Name & Address of the Witness: _____

தகவல் தாள் / பிரதி

(1)

கருவிழியின் புண்களில் உள்ள உள் விழி அழுத்தத்தை வேறுபட்ட சாதனங்கள் மூலம் கண்டறிதல்

ஆய்வு எண் : தேதி :

பங்கேற்பாளரின் பெயர் மருத்துவ அட்டை எண் :

உங்கள் கருவிழி புண்களில் உள்ள உள் விழி அழுத்த வேறுபாட்டை தீர்மானிக்க நீங்கள் இந்த ஆய்வில் பங்கேற்க வேண்டும் என கேட்டுக் கொள்கிறோம்.

உங்களிடம் சில விவரங்கள் மற்றும் சில பரிசோதனைகள் செய்த பின்பு உங்கள் கண்களில் உள்ள உள் விழி அழுத்தத்தை டோனோபென் என்னும் கருவிக் கொண்டு அளவிடப்படும்.

டோனோபென் என்னும் கருவியின் மேற்பரப்பில் உள்ள ~~அண்ணளவல்~~ ஒரு தொடர்பு கருவி, உள் விழி ~~அழுத்தத்தை டிஜிட்டல் (எண்ணியல், இலக்கவியல்) கொண்டு பதிவு~~ அளவை அழுத்தத்தின் அளவை டிஜிட்டல் (எண்ணியல், இலக்கவியல்) பதிவு செய்யப்படும். இந்த கருவியின் முனையில் மெலிதான இரப்பர் மரப்பால் ஆன ஒரு முறை மட்டும் பயன்படுத்தக் கூடிய மூடி இருக்கும். கருவி ~~சுத்தப்படுத்~~ ~~பகு~~தியை ஆயத்த நிலைக்கு வர செய்து, பரிசோதிக்கப்பட வேண்டிய கண்ணில் சோதிக்கப்பட வேண்டிய இடத்தில் / பரப்பில் உணர்ச்சி மயக்கமூட்டுகிற ~~மருந்து~~ சொட்டு மருந்தை தனித்தனியாக ஒரு சொட்டு விட்ட பிறகு கருவியின் ~~மேல்~~ முனையினால் ~~கண்~~ ~~தொட~~ விழி வெண்படலத்தில் தொட்ட பிறகு திரும்ப கருவியை எடுத்துவிட வேண்டும்.

(சேர்க்கப்பட்ட பங்கேற்பாளர் / நோயாளி அனுமதிக்கப்பட்ட அன்று குறைந்தபட்சம் 4 முறை உள் விழி அழுத்தத்தை அளவிடப்பட வேண்டும். பிறகு தொடர்ந்து 3 நாட்கள் ~~அன்று~~ இடைவெளியில்

(2)

உள் விழி அழுத்த நோய்

இடைவெளியில் மீண்டும் அளவிட வேண்டும்
நிலையானது 5% வரை மக்கள்தொகையில் காணப்படுகிறது
அளவீடுகள்
இதை உள்விழி அழுத்தத்தின் அளவீடாக
கண்டறிந்து கொள்ளலாம் செய்யலாம்
புள்ளிகள் அழுத்த அழுத்தத்தை கண்காணித்து
கூடும்
இந்த சிகிச்சை தொடர்ந்து வேண்டும் சொட்டு மருந்துகள்
வேண்டும். இந்த மருத்துவமனையில் இருந்து 150
நோயாளிகள் பங்கேற்பாளர்கள் என நம்புகிறோம்

இந்த ஆய்வு தொடங்கிய பிறகு விலகிக் கொள்ள முடியுமா?

இந்த ஆய்வில் பங்கேற்பது என்பது உங்களுடைய சொந்த விருப்பத்தின் பேரில் தான். நீங்கள் பங்கேற்க விரும்பவில்லை என்றாலும் உங்களுக்கு வழங்கப்படும் / சிகிச்சையும் சிகிச்சையில் எந்த பாதிப்பும் இருக்காது.

இந்த ஆய்வில் பங்கேற்பதால் என்னென்ன பாதிப்புகள் நேரும்?

இது ஒரு பின் நோக்கு / முன்னோட்ட ஆய்வு, எனவே எந்த வித பாதிப்பு / ஆபத்து ஏற்படாது. கண்விழி புள்ளிகளின் சிகிச்சைக்கு வரும் நோயாளிகளிடம் அவரைக் குறித்த விவரங்கள் மற்றும் பரிசோதனைகள் ஒரே வழிமுறைகள் கொண்டது.

உங்களைக் குறித்த விவரங்கள் பாதுகாக்கப்படுமா?

இந்த ஆய்வின் முடிவுகள் மருத்துவ இதழ்களில் வெளியிடப்படும் உங்களைக் குறித்த அடையாளங்கள் எந்த இதழ்களிலும், முடிவுகளிலும் வெளியிடப்படாது. உங்களின் மருத்துவ விவரங்கள் இந்த ஆய்வை சார்ந்தவர்கள்

(5)

உங்கள் அனுமதியின்றி ~~பயன்படுத்தப்படமாட்டாது~~ பயன்படுத்திக் கொள்வார்கள். நீங்கள் இந்த ஆய்வில் பங்கேற்க முடிவு செய்ய வேண்டும்.

மேலும் விவரங்களுக்கு டாக்டர் பிந்து தாமஸ் என்பவரை 0416-3071201 மற்றும் 9488816051 என்ற ~~எண்களிலும்~~ நம்பரில் தொடர்பு கொள்ளவும்

மின் அஞ்சல் : binuthomas06@gmail.com

இந்த ஆய்வில் பங்கேற்பவரின் ஒப்புதல் படிவம்

ஆய்வின் தலைப்பு :

ஆய்வு எண் : மருத்துவ பட்டை எண் :

பங்கேற்பாளரின் முதல் எழுத்து : பங்கேற்பாளரின் பெயர் :

பிறந்த தேதி / வயது :

1) ________ ஆகிய எனக்கு கொடுக்கப்பட்ட தகவல் தாளில் ~~கொடுக்கப்பட்ட~~ இந்த ஆய்வின் செய்முறை குறித்து படித்து, அதில் எனக்கு ஏற்பட்ட சந்தேகங்கள் ~~கேள்வி~~ கேட்க எனக்கு வாய்ப்பு கொடுக்கப்பட்டது. என்னுடைய ~~கண்~~ கருவிழியில் ஏற்பட்ட புண்களின் காரணத்தினால் மருத்துவமனையில் அனுமதிக்கப்பட்ட நாட்களில் இருந்து ~~இந்த~~ பாதிக்கப்பட்ட மற்றும் பாதிக்கப்படாத கண்களில் இருந்து ~~ஒரு~~ பரிசோதனை ~~செய்ய ஒப்புக் கொள்கிறேன்.~~ போலவே நானும் கருவிழியை கொண்டு பரிசோதனை செய்ய ஒப்புக் கொள்கிறேன்

(4)

போனோபைன் என்ற கிரீமை எப்படி பயன்படுத்துவது என்பதைக் குறித்து என்னுடைய தாய் மொழியில் விளக்கமாக கூறினார்கள். மேலும் இந்த செய்முறைகளால் எனக்கு என்னுடைய சிகிச்சையில் ஏற்பட்ட பக்கவிளைவுகள் / நன்மைகள் பெறலாம் அல்லது பெறாமலும் இருக்கலாம் என்றும் அறிவேன்.

ii) இந்த ஆய்வில் பங்கேற்பது என்னுடைய தன்னார்வத்தின் பேரில் என்றும், எந்த நேரத்திலும் நிபந்தனையின்றி விலகிக் கொள்ளலாம் என்றும் இதனால் எனக்கு வழங்கப்படும் சிகிச்சையும், என்னுடைய மனித உரிமையும் பாதிக்காது என்றும் அறிவேன்.

iii) இந்த ஆய்வை நடத்துபவர் அல்லது அவரது பிரதிநிதிகள், நன்னெறிக் குழு உறுப்பினர்கள் மற்றும் நிர்வாக அதிகாரிகள் என்னுடைய அனுமதியின்றி என் மருத்துவ விவரங்களை இந்த ஆய்வுக்கும் மற்றும் சில ஆராய்ச்சிக்கும் நான் இந்த ஆய்வில் விலகினாலும் பயன்படுத்திக் கொள்ளலாம் என்றும் அறிவேன். என்னுடைய அடையாளங்கள் யாருக்கும் தெரிவிக்கவோ அல்லது வெளியிட மாட்டார்கள் என்றும் அறிவேன். இந்த ஆய்வில் இருந்து பெறப்பட்ட விவரங்கள் அறிவியல் தேவைகளுக்கு மட்டும் பயன்படுத்தப்படும் என்றும் அறிவேன்

iv) இந்த ஆய்வின் மூலம் பெறப்பட்ட விவரங்கள் அறிவியல் பயன்பாட்டிற்கு பயன்படுத்த தடையில்லை என்று நான் சம்மதம் தெரிவிக்கிறேன்.

v) இந்த ஆய்வில் பங்கேற்க சம்மதம் அளிக்கிறேன்

(5)

சமயபுரி வடமாக ஏதாவது கொள்ளை படவரின்
கையெழுத்து / கைரேகை பதிவு

தேதி :

கையொப்பமிடுபவரின் பெயர் : _____ அதிகாரப்பூர்வ : _____

or

பாஸ்போர்ட் புகைப்படம்
தாள் இல்

தேதி : _____

கையெழுத்திடுபவரின் பெயர் : _____

அதிகாரியின் கையொப்பம் : _____

தேதி :

அதிகாரியின் பெயர் : _____

சாட்சியின் கையொப்பம் : _____
அல்லது கைரேகை பதிவு

தேதி : _____

சாட்சியின் பெயர் மற்றும் : _____
முகவரி

APPENDIX C

CLINICAL RESEARCH FORM

PROFOMA

Serial number:

Schell no

CMC no(if present)

Name:

Age (yrs)

Sex: M/F

Address

Tel No:

Date and Time of presentation: / (OPD / Casualty -Put tick mark)

Date of starting of symptoms:

Date and time of admission: /

SYMPTOMS

Is he/she a known glaucoma patient

YES	NO

ANY MEDICATION /PREVIOUS CONSULTATION FROM OUTSIDE

Yes(Mention the medication)	No	Not sure

SYSTEMIC ILLNESS

Diabetes	**Hypertension**	**IHD**	**Asthma**
Others			

EXAMINATION

VISUAL ACUITY → Right eye: Left eye:

In the ulcer eye

- Size of infiltrate →
- Size of epithelial defect →
- Location(involving visual axis or not) →
- Depth of involvement →
- Thinning (%) →
- Corneal sensation →
- Hypopyon +/- →
- Endothelial plaque+/- →

- Satellite lesion +/- →
- Previous scars →
- Vascularization(deep/superficial) →

INTRAOCULAR PRESSURE (with tonopen)

	Normal eye	Ulcer eye	Difference
Day of admission			
Day 3			
Day 6			
Day 9			
Further IOP's			

Final IOP at healing

INVESTIGATION

CORNEAL SCRAPING

1)Smear report

2)Culture report

3)Organism identified

Bacteria	Fungus	Culture negative/suspected viral ulcers	Others

4)Sensitivity pattern

Sensitive	Resistant	Intermediate

5)Indication for antiglaucoma medication:

6)Antiglaucoma medication started :

7)Date of discharge from septic opd (at healing):

8)Total time to healing:

9)Outcome:

-Healed

-Perforated

-Eviscerated

-Therapeutic PKP

-Others

Treatment done :

Total no. of OPD attendance:

Date of discharge:

APPENDIX D

EXCEL DATA SHEET

No	Schell no	Name	Age(yrs)	Sex(M=1/F=2)	Previous Treatment(yes(1)/no(2)
1	476264s	Roja	24	2	1
2	476133s	Ezhumalai	30	1	1
3	456331s	Laksmi	35	2	2
4	477008s	Salman	21	1	1
5	481122s	Akbar	36	1	2
6	486277s	Thangaivel	69	1	1
7	909002e	Chitty Babu	43	1	1
8	492002s	Nithyanandam	20	1	2
9	485091s	Amuda	50	2	2
10	492195s	Veerapandian	50	1	02-01-1900
11	485686s	Jeevarathnam	57	2	1
12	317052s	Varathammal	74	2	02-01-1900
13	485363s	Saraswathy	60	2	02-01-1900
14	477219s	Lakshmi	35	2	1
15	473183s	Ganesh	34	1	1
27	297177s	Sampangi	42	1	
16	473195s	Parvathy	30	2	1
17	434903s	Dayalan	61	1	2
18	483954s	Munisamy	52	1	2
19	484155s	Govindamma	38	2	1
20	487055s	Shanti C	54	2	1
21	500000s	Nageswar Yadav	37	1	1
22	495419S	Rajaraman	46	1	2
23	492206s	Rangasamy	85	1	02-01-1900
24	478266s	Paneerselvam	42	1	2
25	473686s	Valliammal	59	2	1
26	480443s	Muthammal	42	2	2
27	354457s	Rajammal	59	2	2

Systemic illness	Size of infiltrate(mm)	Size of epithelial defect(mm)	Location	corneal sensation(=/-)
0	2.1 * 2.1 mm	2.4* 2.1mm	2	+
0	7.5*8mm	7.5*8mm	1	+
0	2.5*2.5mm	2.5*2.6mm	1	+
0	2.3*2.2	1.8*2mm	2	+
0	1.9*1.3mm	1.8*1.3mm	1	+
0	3mm*3mm	2.9*3mm	1	+
0	4.5*5mm	4.5*5mm	1	+
0	3*3mm	3*3mm	1	+
0	4*8mm	4*8mm	1	+
0	1.5*1.6mm	1.5*1.5mm	2	+
		3*3.5mm		+
0	1.8*1.8mm	3.2*3mm	1	+
0	5*7.3mm	5*7mm	1	+
0	3*4mm	3*4mm	1	+
0	1.8*2mm	2*2mm	2	+
0	2.3*1.3mm	1.5*1.4mm	1	+
	2.5*2.5mm	2*2.5mm	1	+
0	2*2.1mm	3.4*3.5mm	1	+
0	7.5*5mm	7.6*5mm	1	+
0	3*4mm	1*2mm	1	+
1	5.8*5.8mm	5.8*5.8mm	1	+
0	1.5*1.5mm	1*1mm	2	+
0	4*3mm	4*3mm	1	+
0	3.5*3mm	3*3mm	1	+
0	3.5*3.5mm	3*3.5mm	1	+
0	3.0mm*2.9mm	3*3mm	2	decreased
0	5.2*5.8mm	5.2*6.8mm	1	+
2	5.2*4.5mm	4.5*4.8mm	2	+
0	4*4mm	3.4*3.6mm	2	+

Diabetes=1

Hypertension=2

IHD=3

Asthma=4

Nil=0

Central=1

Eccentric=2

Hypopyon(yes=1,no=2)	Endothelial plaque(Y=1/N=2)	Vascularization(y/n)	ulcer eye(RE-1) (LE=2)
2	2	N	2
2	2	N	2
1	2	n	2
2	2	N	1
2	2	n	1
1	2	n	2
2	2	n	2
2	2	n	2
2	2	n	2
2	2	n	1
2	2	n	1
1	2	n	1
1	2	n	2
2	2	n	2
1	2	n	2
2	2	n	2
2	2	n	1
2	2	n	2
2	2	n	1
2	2	n	1
1	2	n	1
1	2	n	2
2	2	n	1
2	2	n	1
1	1	n	2
1	2	n	1
2	1	n	1

Average Tonopen IOP :Day 0 ulcer eye(UE)	Day 0 - control eye(CE)	Day 0-Difference in IOP(*)
9	10	-1
11	12	-1
12	12	0
6	11	-5
15	18	3
7	12	-5
5	11	-6
15	11	4
8	14	-6
15	13	2
11	13	-2
5	8	-3
11	10	1
12	12	0
20	17	3
Re Le		
19	16	3
16	16	0
7	7	0
11	12	-1
10	11	-1
13	17	-4
17	14	3
15	4	11
22	5	17
18	9	9
16	13	3
day 3-CE day 3* 15	day 6-UE day6-CE5	day 6* 10

Day 3-UE

12	15	-3	6	7	-1
6	7	-1	9	8	1
9	6	3			
10	9	1	9	6	3
8	11	3	15	15	0
10	11	-1	10	9	1
11	7	4	13	15	-2
16	17	-1	16	13	3
9	13	-4	16	18	-2
10	15	-5	13	12	1
6	10	-4	7	14	-7
8	9	-1	8	10	-2
9	12	-3	15	12	3
9	6	3	9	8	1
18	16	2	14	15	-1

13,14

18	14	4	18	15	3
16	16	0	15	15	0
12	11	1	11	10	1
14	13	1	9	11	-2
9	8	1	11	10	1
13	15	-2	18	19	-1
15	15	0	15	15	0
13	4	9	19	4	15
7	6	1	7	7	0
17	9	8	17	9	8
18	13	5	29	14	15
8	4	4	12	10	2

day9-UE	day9-CE	day 9*	day 12-UE	day12-CE	day 12*
6	13	-7	7	6	1
8	10	-2	11	7	4
13	11	2			
20	16	4	17	16	1
10	9	1	8	9	-1
12	13	-1	10	13	-3
15	12	3	16	17	-1
12	16	-4	16	15	1
11	10	1	11	13	-2
10	11	-1			
7	9	-2	12	8	4
12	16	-4	11	15	-4
9	10	-1			
15	15	0	15	16	-1
14	12	2	14	13	1
11	12	-1	15	13	2
13	12	1			
10	11	-1			
19	15	4	21	14	7
18	4	16	16	4	12
6	7	1	7	7	0
16	18	-2	16	16	0
18	17	1	12	15	-3
12	11	1			

day15-UE	day15-CE	day 15*	day 18-UE	day18-CE	day 18*	day 21-UE	day 21-CE	day 21 *
7	8	-1						
9	10	-1	12	14	-2			
15	15	0						
12	10	2						
12	13	-1	12	15	-3			
18	14	4						
10	12	-2	7	10	-3	13	15	---2
14	15	-1						
14	16	-2						
14	16	-2	15	16	-1	15	16	-1
16	9	7	18	19	-1	13	17	-4

1
2
3
4
5

	Culture	Size of infiltrate(mm)	Infiltrate size-code no:	Time to heal(days)	Outcome
2	Curvularia	2.1	2	25	
3	No growth	8	3	27	
3	No growth	2.5	2	5	
4	Nocardia	2.3	2	10	
3	No growth	1.9	1	27	
2	Septate fungi	3	2	25	
3	No growth	5	3	23	
1	Atypical mycobacteria	3	2	30	
1	E coli	8	3	20	
2	Fusarium	1.6	1	16	
2	Fusarium	1.8	1	14	
3	No growth	7.3	3	35	
4	Nocardia	4	2	15	
3	No growth	2	2	15	
2	Fusarium	2.3	2	24	
	No growth				Scarred with
2	Fusarium	2.1	2	24	
5	Acanthamoeba	7.5	3	26	
1	Gram+ cocci	4	2	19	
2	Aspergillus	5.8	3	23	
1	Beta hemolytic streptococcus	1.5	1	10	
2	Aspergillus	4	2	20	
2	Fusarium	3.5	2	37	
1	Streptococcus pneumoniae	3.5	2	12	
2	Fusarium	3	2	25	
1	Pseudomonas aeruginosa	5.8	3	24	
1	Streptococcus pneumoniae	5.2	3	23	
3	No growth	4	2	21	

Bacterial
Fungal
No Growth
Nocardia
Acanthamoeba

<2mm= 1
2-4mm=2
>4mm= 3

Outcome:
Healed with
perforated=
Eviscerated=
Therapeutic
Patient did n
Vascularizati
Pthysical=7

Time to heal(days)	Outcome
25	1
27	1
5	1
10	1
27	1
25	1
23	1
30	5
20	1
16	1
14	1
35	1
15	1
15	1
24	1
	Scarred with vascularization and thinning
24	1
26	1
19	1
23	1
10	1
20	1
37	1
12	1
25	1
24	1
23	1

21		1
	Outcome: Healed with scar=1 perforated=2 Eviscerated=3 Therapeutic PKP=4 Patient did not come for further follow up=5 Vascularization with scarring=6 Pthysical=7	