Adjunctive Use of Intravitreal Dexamethasone in Presumed Bacterial Endophthalmitis

By

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Declaration

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

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Special Acknowledgement

I hereby acknowledge that this dissertation is based upon a trial conceptualised by Dr. J. Richards who designed and initiated the trial, obtained ethics approval and started the database. Dr T. Pollock then supervised the clinical work in Dr. Richards' absence. I appreciate Drs Richards and Pollock's permission to use this work as a basis for the dissertation.

Abstract

AIM: To evaluate the use of intravitreal dexamethasone as adjunctive therapy in the treatment of presumed bacterial endophthalmitis.

DESIGN: Prospective randomised placebo-controlled clinical trial.

METHODS: All patients with suspected endophthalmitis were divided into 3 groups; post cataract surgery (PC), bleb related endophthalmitis (BRE), and other (O) including endogenous, trauma and post vitreo-retinal surgery. All patients requiring vitrectomy or suspected to have fungal endophthalmitis were excluded. Within each group, patients were randomly assigned by pharmacy to receive intravitreal ceftazidime (2.225mg/0.1ml), vancomycin (1mg/0.1ml) and either dexamethasone (0.4mg/0.1) or placebo using masked labels. All vitreous biopsies and aqueous samples were sent for microbiological analysis. Patients were evaluated and if deemed necessary the injections were repeated after 48 hrs. Snellen visual acuity was measured on presentation, within the first 14 days post injection, and at 2-4 months as the primary outcomes measure.

RESULTS: 62 patients were recruited and completed the protocol from 2001 to 2005. 30 patients received intravitreal dexamethasone and 32 received intravitreal placebo. Preliminary analysis reveals no statistically significant difference in the visual acuity outcomes of either group with an average of 2.79 Snellen lines improvement of the intravitreal dexamethasone group versus 1.8 lines improvement of the placebo group. However subgroup analysis suggested a clinical trend to better visual acuity in the Post Cataract Steroid Subgroup with average of 4.1 lines improvement versus 2.7 in the placebo group ($p = 0.33$). No adverse events attributable to the dexamethasone were reported.

CONCLUSIONS: Intravitreal dexamethasone appears safe and may be of benefit in post cataract presumed bacterial endophthalmitis.

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Chapter 1:

Introduction and Literature Review

Endophthalmitis is defined as inflammation of the contents or cavity of the eye and usually represents an infection of the vitreous, although it may represent sterile inflammation.

It may be divided into endogenous and exogenous depending on the source of the infection. In endogenous or metastatic endophthalmitis the bacteria have spread haematologically from an infective site elsewhere in the body to the eye. Sites of infection often include septic meningitis, endocarditis, pneumonia, osteitis etc. In exogenous endophthalmitis the infection has breached the outer structure of the eye in order to enter and infect the cavity of the eye. Exogenous can further be classified into its various causes: post cataract surgery, post penetrating trauma, post glaucoma surgery or other intraocular surgery, and spread from other infection such as keratitis or sinusitis.

The causative organism can be bacterial, viral, fungal or protozoal. The most common bacteria in post cataract surgery are gram positive (60%) such as Staphlococcus epidermidis, Staphlococcus aureus, Streptococcus species, as well as gram negative (30%) such as Proteus and Pseudomonas species. The most common bacteria in endophthalmitis following glaucoma surgery include Haemophilus species and Streptococcus species [1].

Once the structural integrity of the eye has been breached the sensitive intraocular structures are very vulnerable to both the infective organism, its toxins as well as the inflammatory response. The neural retina is particularly sensitive to toxins while the vitreous is particularly prone to long-term fibrosis resulting in tractional retinal detachments.

Therefore since both the infective organism as well as the subsequent immune response is thought to be pivotal in the disease process, it has been theorised that any effective treatment should aim at treating both arms of the pathological process. Hence intravitreal antibiotic injections are the mainstay of treatment. However, the role of any steroid either orally or intravitreally has been debated in the literature again and again. It was first experimented with as far back as 1974 [2].The advantages of adding the intravitreal steroid at the time of intravitreal antibiotics is to provide a high anti-inflammatory concentration at the pathological site and limit systemic side effects especially in our typical elderly patient profile and in diabetic patients.

This adjunctive use of intravitreal steroids needs to be proven as a safe and effective form of adjunctive therapy, before justifying changing our current use of intravitreal antibiotics alone.

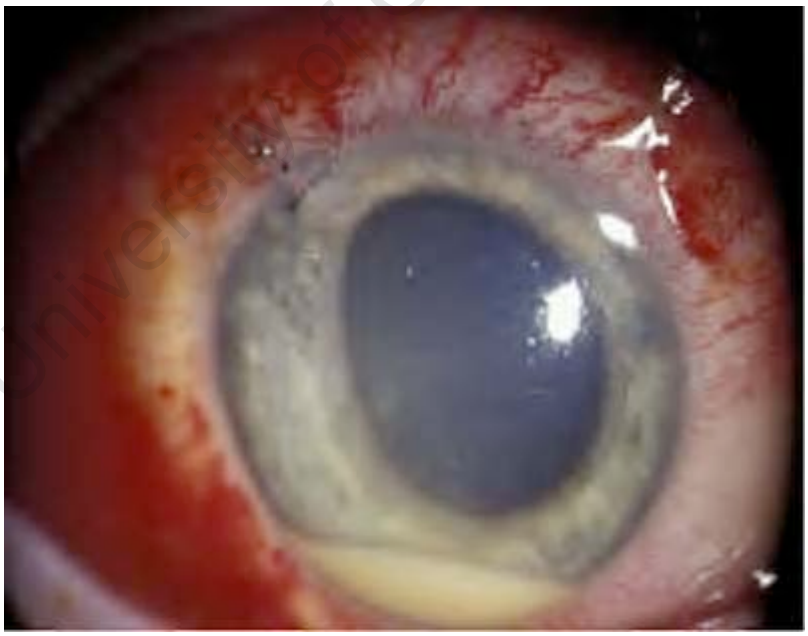


Figure 1. Post Cataract Endophthalmitis

A Pubmed, Medline, Ovid and ScienceDirect search of the literature reveals that the issue of using intravitreal steroid as adjunctive therapy is still controversial. Most authors seem to be of the opinion that steroids reduce inflammation, but as yet, no one has shown a clinically significant difference in the visual outcome and hence no standard accepted regime is in use. A survey, performed over 12 months from October1999 to September 2000, of all post cataract endophthalmitis in the United Kingdom [3] showed that of the 213 patients, only 17% received intravitreal steroids while Moorfields Eye Hospital [4] reported their routine use of oral steroids on day one and others report the use of subconjunctival steroids. This demonstrates the wide clinical practice within one country. The Bascom Palmer Eye Institute in Florida [5] reported their 10 year post cataract surgery endophthalmitis experience in which they report their standard initial management consists of intravitreal vancomycin, ceftazidime and intravitreal dexamethasone. Other authors such as Chaudhry [6] in Connecticut reported their standard treatment includes intravitreal antibiotics and subconjunctival steroids. This again highlights the wide spectrum of clinical practice. This scope of practice reflects the lack of clear guidelines from the literature.

In 2002 Elder and Mortlett [7] gave a very useful summary of the evidence for and against the use of steroids under the title "Clinical Controversy". In essence they mention there have been six rabbit studies that have shown a benefit in reducing the inflammation and four rabbit studies showing no significant benefit. They mention three clinical trials. The most significant is that of Das et al [8], which was a prospective randomised clinical trial treating 63 cases of endophthalmitis with vitrectomy, intravitreal antibiotics and then either intravitreal dexamethasone or placebo. They showed a reduction in inflammation, but no independent influence on visual outcome. Elder and Mortlett concluded that there was no clear evidence either for or against the adjunctive use of intravitreal steroids.

Other authors have reported differing results. Shah et al [9] in 2000 reported a retrospective nonrandomized comparative trial of 57 postoperative endophthalmitis cases comparing those who received intravitreal steroids to those who received only intravitreal antibiotics. They concluded that those who received steroids had a

significantly reduced likelihood of obtaining a 3-line improvement and felt this provided no support for the routine use of intravitreal steroids.

Also in 2004 Pollack et al [10] attempted to demonstrate the use of intravitreal dexamethasone on its own to reduce intraocular inflammation in experimental Bacillus cereus endophthalmitis in 36 rabbit eyes. The rabbits were randomised to receive intravitreal Bacillus with or without intravitreal dexamethasone. They concluded that a standard dose of intravitreal dexamethasone does not appear to attenuate the intraocular inflammatory response and suggested alternative options such as vitrectomy to reduce the endotoxin load.

The most recent randomised trial by Gan et al [11] reported in December 2005 is a prospective randomised placebo controlled clinical trial of 29 postoperative endophthalmitis cases, who received either intravitreal dexamethasone (13/29) or placebo (16/29) in addition to the intravitreal antibiotics. Their small study demonstrated a trend towards a better visual acuity in the dexamethasone group. This is the first study to demonstrate such a finding, justifying further investigation.

In 2006 Pathengay et al [12] from India, reported the use of intravitreal triamcinolone acetonide for bacterial endophthalmitis as an interventional pilot case series. Triamcinolone is known to remain active in the vitreous for up to three months. They treated five patients with culture positive bacterial endophthalmitis with intravitreal antibiotics and then after 48-72 hrs injected intravitreal triamcinolone. All patients also received oral ciprofloxacin. In all five cases they reported complete resolution of the inflammation, which suggested a beneficial response to intravitreal steroids.

In 2007 Ermis et al [13] reported on the use of intravitreal moxifloxacin with and without intravitreal dexamethasone in a randomised rabbit model of Staphylococcus aureus endophthalmitis and compared the outcomes with those of a control group as well as to a group receiving only intravitreal vancomycin. They concluded that all three treatment options were comparable.

Rehak et al [14] in 2007 reported a six-year experience with postoperative endophthalmitis in which 32 of 34 patients underwent immediate vitrectomy, intravitreal antibiotics as well as intravitreal steroids. They concluded that immediate vitrectomy with intravitreal steroids and antibiotics resulted in good visual outcomes in 79% of cases. They also mentioned that systemic steroids seemed to be associated with a better final visual acuity.

Saleh et al [15] in 2008 reported the potential advantage of early intravitreal dexamethasone specifically in Staphylococcus epidermidis endophthalmitis, but again concluded that a randomised clinical trial is still required.

De Kasper et al [16] reported in 2008 on a trial of induced Staphlococcus aureus experimental endophthalmitis in rabbits. They were randomised to receive intravitreal vancomycin, amikacin and either placebo or dexamethasone. They demonstrated reduced clinical inflammation, improved ERG readings and reduced histological inflammation in the group receiving both antibiotics and dexamethasone. Again confounding the interpretation is the routine use of intravenous imipenem for four days and small numbers with only five in each group. The results of this study suggest that further investigation is warranted.

In 2008 Liu et al [17] reported an experimental Bacillus endophthalmitis in rabbits where the rabbits were divided into two groups, each injected with Bacillus colonies and then 24 hours later divided into intravitreal balanced salt solution and intravitreal antibiotic group versus intravitreal dexamethasone and intravitreal antibiotics. They reported significant reduction in inflammatory scores, including histology, in the group receiving intravitreal dexamethasone.

The dose of intravitreal dexamethasone seems to have become standardised since the report of Kwak et al [18] in 1992 which histologically suggested increasing disorganisation of the Muller cells at doses above 440 micrograms.

There have also been conflicting reports regarding the alteration of the pharmacodynamics of the antibiotics in the intravitreal injection by adding dexamethasone. Some reports initially suggested a decreased intravitreal concentration of vancomycin [19] while others have reported a decreased elimination of the intravitreal vancomycin [20]. Most recently in 2005, Gan [21] reported no effect of intravitreal dexamethasone on the intravitreal concentration of vancomycin in a prospective trial of postoperative endophthalmitis.

The role of immediate primary vitrectomy is also debated and the Endophthalmitis Vitrectomy Study in 1995[22] suggested that systemic antibiotics are not indicated and patients with visual acuity of perception of light or less fared better with immediate vitrectomy. Although techniques and instrumentation have improved, no randomised study has been repeated and this is often debated with some authors suggesting that any infective vitreous should always be removed surgically.

Conclusion:

From a review of the literature, it is difficult to come to a clear conclusion as to the benefit or otherwise of including intravitreal dexamethasone in the management of endophthalmitis. The constraints include the small sample sizes in most of the studies and the different treatment regimens used including vitrectomy, different antibiotics, different organisms etc.

The only prospective randomised trial is that reported by Gan [11] et al, which showed a beneficial trend but no statistically significant difference because of the small sample size.

There is merit in conducting another prospective randomised clinical trial, if only to provide additional data for a future meta analysis.

Chapter 2:

Methods

Study Design:

A prospective randomised clinical trial comparing the adjunctive use of intravitreal dexamethasone versus placebo in addition to standard intravitreal antibiotics in presumed bacterial endophthalmitis was undertaken.

Ethical Approval:

Approval from the University Of Cape Town Research Ethics Committee, Faculty Of Medicine was formally granted on 09/02/2001 REC REF: 226/2000. Patients were recruited from January 2001 to December 2005.

Participants:

All patients with presumed bacterial endophthalmitis presenting to Groote Schuur Hospital were considered for inclusion. They were divided into 3 etiological groups by the admitting clinician: post cataract (PC), bleb related endophthalmitis (GB) and other (O), which included post penetrating injuries, metastatic endophthalmitis and post pars plana vitrectomy. This was to identify post cataract endophthalmitis as a priority subgroup, which could then be compared to other similar trials.

Sample Size:

It was planned to recruit 80-90 subjects over a five year period, of which about 35 would be in the post cataract group.

Exclusion Criteria:

1. All patients with suspected fungal endophthalmitis.

2. Patients with perception of light vision if the vitreo-retinal surgeons elected to perform a primary vitrectomy. Due to the lack of a full time vitreo-retinal surgeon at the time of the trial we could not always follow the Endophthalmitis Vitrectomy

Study's (EVS) [22] recommendation of performing an immediate primary vitrectomy if the vision was worse than hand movements. Therefore, patients were excluded if they underwent primary vitrectomy.

Intervention:

On presentation, patients were admitted, counselled, informed consent was obtained and intravitreal antibiotics and dexamethasone/placebo ordered. Pharmacy randomised the patients within the 3 groups using standard computer generated randomisation tables, to receive either dexamethasone 0.4mg/1ml together with the standard vancomycin 1mg/0.1ml and ceftazidime 2.225mg/0.1ml or placebo 0.1ml balanced salt solution. Penicillin allergic patients would receive amikacin 0.4mg/1ml in place of ceftazidime. A standard double-blinding label (dex/placebo) masked the dexamethasone/placebo injection so that both the surgeon and patient were unaware which drug was injected. Pharmacy kept the randomisation tables with the corresponding folder number until the end of the trial so that the clinicians at follow up would still be masked. When patients presented after hours a sealed envelope was given to the ward sister who mixed the steroid/placebo injection to keep the surgeon masked and pharmacy kept the correlating randomisation table numbers.

Patients underwent standard vitreous biopsy as per surgeons' preference with either local or general anaesthesia, with injection of the intravitreal antibiotics and dex/placebo injection. Vitreous and aqueous samples were sent for microbiological analysis and culture. A subconjunctival injection of vancomycin (25mg/0.5ml), ceftazidime (50mg/0.5ml) and celestone (1.5mg/0.5ml) was also administered at the end of the procedure.

Injection Technique:

The technique used was -

Topical anaesthetic instilled

5% betadine wash

Lid speculum

Subconjunctival lignocaine injection for local anaesthetic cases.

Anterior chamber tap (0.1 mls) with 23-gauge insulin syringe

Transconjunctival vitreous tap (0.3mls) 3.5 mm from limbus in pseudophakic patients, 4mm in phakic patients, and then leave needle in situ and detach syringe.

Intravitreal injection (0.425mls) from separate syringes of

- Vancomycin (0.1ml)
- Ceftazidime(0.25 mls)
- Dex/placebo (0.1mls)

Post injection, patients received topical ofloxacin (or equivalent fluoroquinolone) and topical dexamethasone hourly for 24 hours, then 2 hourly for two days, then 6 hourly. Patients were reviewed daily in the ward and if initial therapy was deemed unsuccessful, patients were considered for repeat injection or vitrectomy.

Criteria for repeat injection/vitrectomy (as per EVS recommendations):

If all of the following were present, the injection was repeated:

1. Visual acuity between counting fingers at 1 metre and perception of light
2. Absent red reflex or increased opacification from presentation
3. One of the following:
    - 1 mm increase in hypopyon
    - corneal ring infiltrate
    - worsening pain

Patient Review:

Patients were reviewed in the first 10 days and at 3 months. A separate endophthalmitis pack with prepared forms was designed and used to facilitate administrative issues, to standardise both treatment and record keeping (see addendum).

Outcomes:

The primary outcome measure was the visual acuity using standard Snellen chart and visual acuity worse than 6/60 was graded using no perception of light, perception of light, hand movements, and count fingers at 1 metre. The visual acuity was then grouped into the following categories for comparison:

Group 1: 6/6 – 6/18

Group 2: 6/24-6/60

Group 3: <6/60

The visual acuities at presentation and at 3 months as well as the number of lines improvement on the Snellen chart were recorded.

The secondary outcome measures were any adverse events and any side effects to the medication.

Statistical Analysis:

On completion of the study the pharmacy master records were collected and unmasked, and the data collected from the folders on a standard data form.

Data was entered using a custom designed template in Microsoft Excel.

Data was analysed using the statistical programme Stata Version 9.0. The analysis was on an intention to treat basis. The analysis was stratified according to the underlying cause of the endophthalmitis. Variables were described using means, medians and proportions, as appropriate. Bivariate comparisons were based on student t test (for means), Wilcoxon sum rank test (for medians), and Chi squared or Fisher's exact test (for proportions). The main analysis focussed on describing the difference in the visual acuity outcome in the two groups. All statistical tests were two sided at a= 0.05.

CHAPTER 3

RESULTS

A total of 62 were patients were identified from the pharmacy master records between January 2001 and December 2005 who met the criteria and followed the protocols.

Diagram 1: Study Flow Diagram

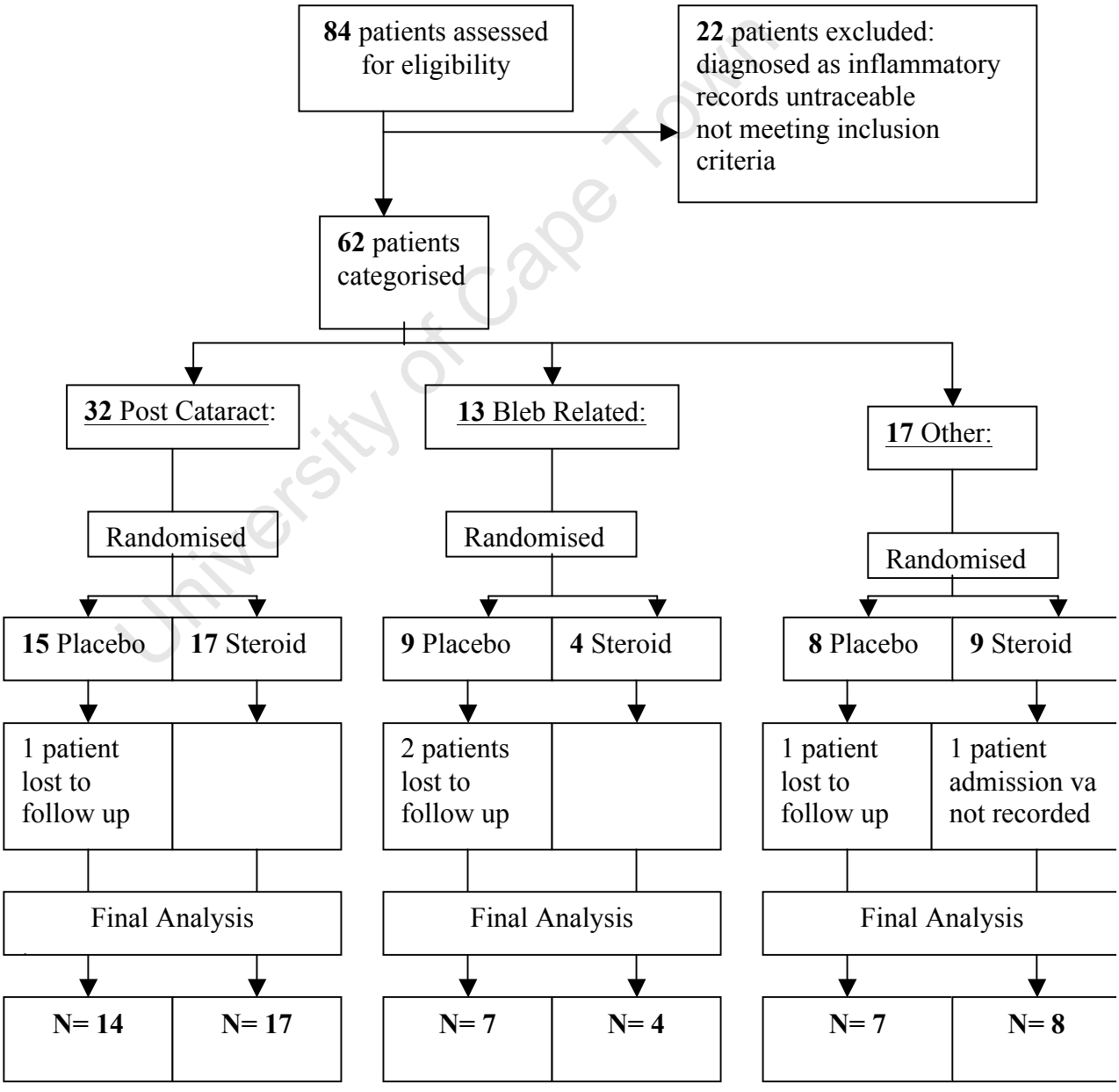


Table 1 compares some of the characteristics of the two groups. There were no significant differences in any of the characteristics between the two groups.

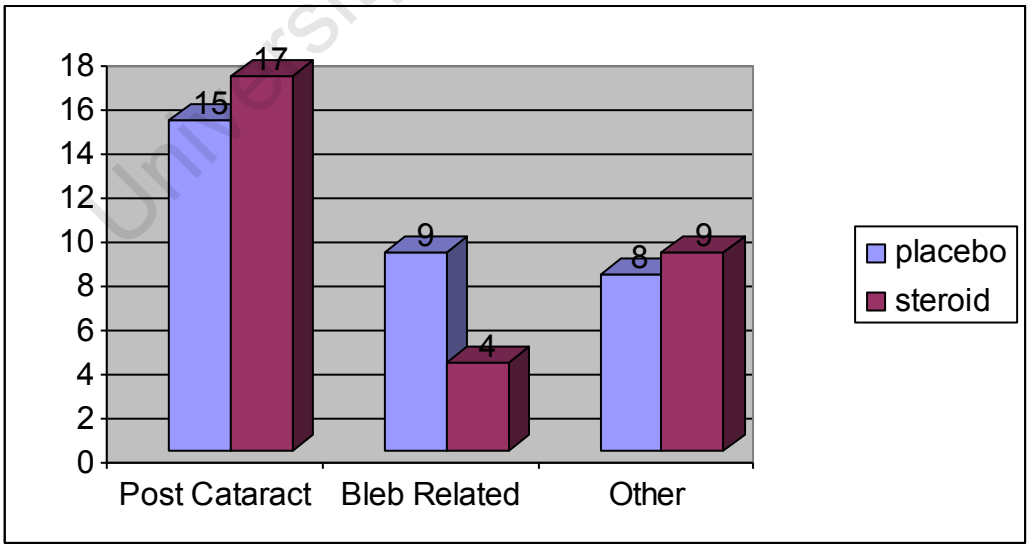
Table 1: Baseline Demographic

	Steroid	Placebo	P Value
Mean Age	59 (29-91)	61 (20-83)	P >0.5
Gender	Male 11 (36%) Female 19 (63%)	Male 18 (56%) Female 14 (54%)	0.137
Group: Post Cataract Post Bleb Other	17 (56%) 4 (13%) 9 (30%)	15 (47%) 9 (28%) 8 (25%)	0.974
Systemic Co morbidity Yes No	 12 (40%) 18 (60%)	 15 (47%) 17 (53%)	0.585
Diabetes mellitus Yes No	 6 (20%) 24 (80%)	 11 (34%) 21 (66%)	0.260
Hypertension Yes No	 4 (13%) 26 (87%)	 6 (19%) 26 (81%)	0.733
HIV Yes No	 1 (3%) 29 (97%)	 1 (3%) 31 (97%)	0.999
Ocular Co morbidity Yes No	 10 (33%) 20 (66%)	 15 (46 %) 17 (54%)	0.311
Glaucoma Yes No	 5 (17%) 25 (83%)	 11 (34%) 21 (66%)	0.150
Diabetic Retinopathy Yes No	 5 (17%) 25 (83%)	 2 (6%) 30 (94%)	0.249
Cataract Yes No	 2 (7%) 28 (93%)	 1 (3%) 31 (97%)	0.607
ARMD Yes No	 0 30 (100%)	 2 (6%) 30 (94%)	0.492
Corneal Disease Yes No	 0 30 (100%)	 1 (3%) 31 (97%)	0.999

Of the 62 patients, 30 received intravitreal steroid while 32 received intravitreal placebo (balanced salt solution). The largest subgroup was the post cataract surgery group (PC), which comprised 32 of the total 62 patients of which 15 received intravitreal placebo and 17 received intravitreal steroid. There were 13 patients with bleb related endophthalmitis of which 4 patients received intravitreal steroid while 9 patients received intravitreal placebo/balanced salt solution. Seventeen patients were classified as other: 8 trauma related with 4 receiving intravitreal steroids and 4 receiving intravitreal placebo, 3 endogenous endophthalmitis of which 1 received intravitreal steroid and 2 received intravitreal placebo, 6 endophthalmitis following pars plana vitrectomy of which 4 received intravitreal steroids and 2 received intravitreal placebo.

Graph 1 shows the breakdown of the subgroups within the steroid and placebo group. Unfortunately the numbers in the bleb related endophthalmitis and other groups are too small to derive statistical information within their respective groups, but they do contribute to the total number.

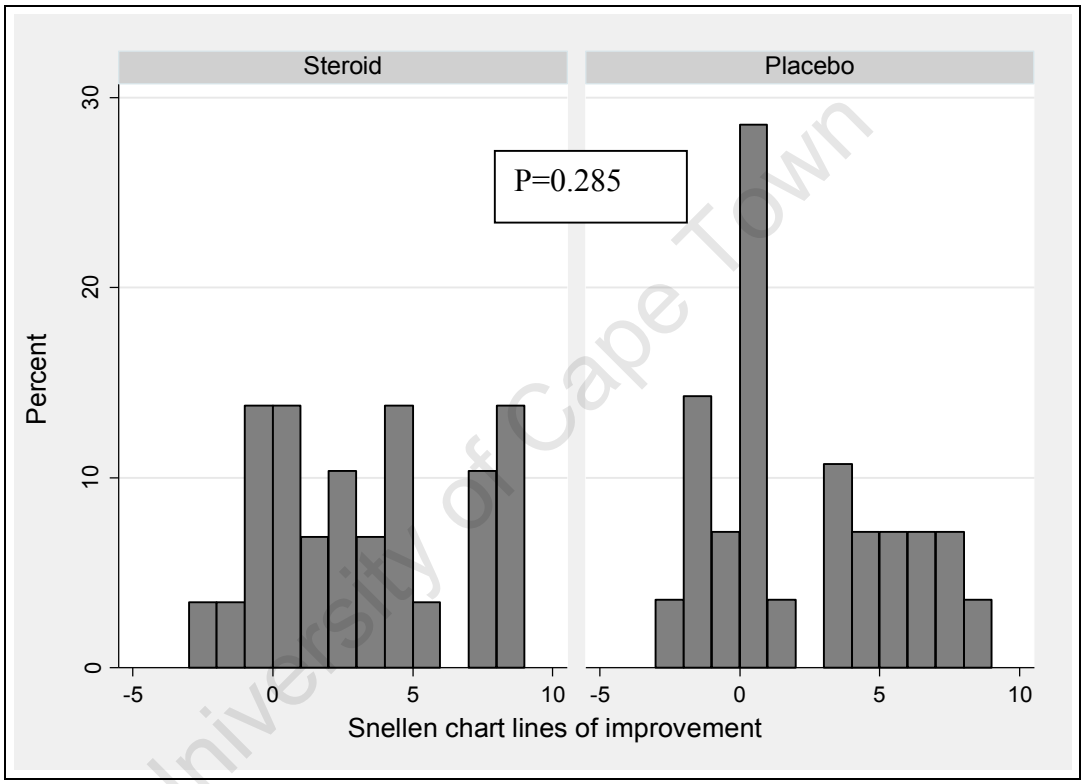
Graph 1: Subgroups of Steroid and Placebo:



The primary outcome measured was the Snellen visual acuity on admission and at 3 months. The number of lines improvement on the Snellen visual acuity chart was compared. This ranged from –3, i.e. lost 3 lines, to 9 i.e. gained 9 lines which

includes lines of No Perception of Light, Perception of Light, Hand movements and Count Fingers as well as the standard Snellen visual acuities. The mean improvement in the placebo group was 1.79 lines (-3 to 9) compared to the steroid group, which showed 2.76 (-3 to 9) lines of improvement (Student's t test P=0.285). This is displayed as a histogram in graph 2.

Graph 2: Snellen Chart No of lines of improvement Steroid vs Placebo



To compare visual outcomes between the 2 groups the Snellen visual acuities were also grouped into 3 categories according to the World Health Organisation classification:

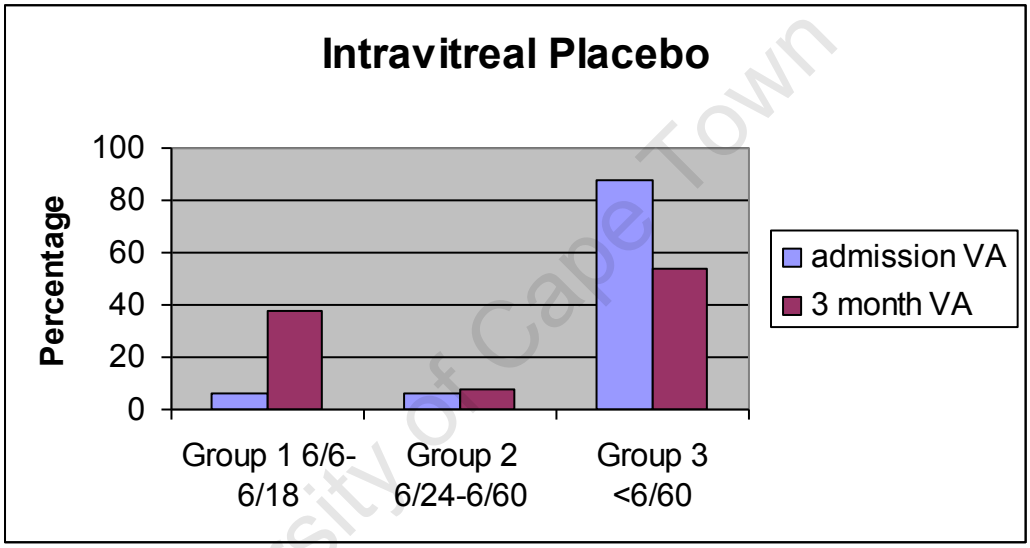
Group 1: Good visual outcome 6/6 – 6/18

Group 2: Visually impaired: 6/24-6/60

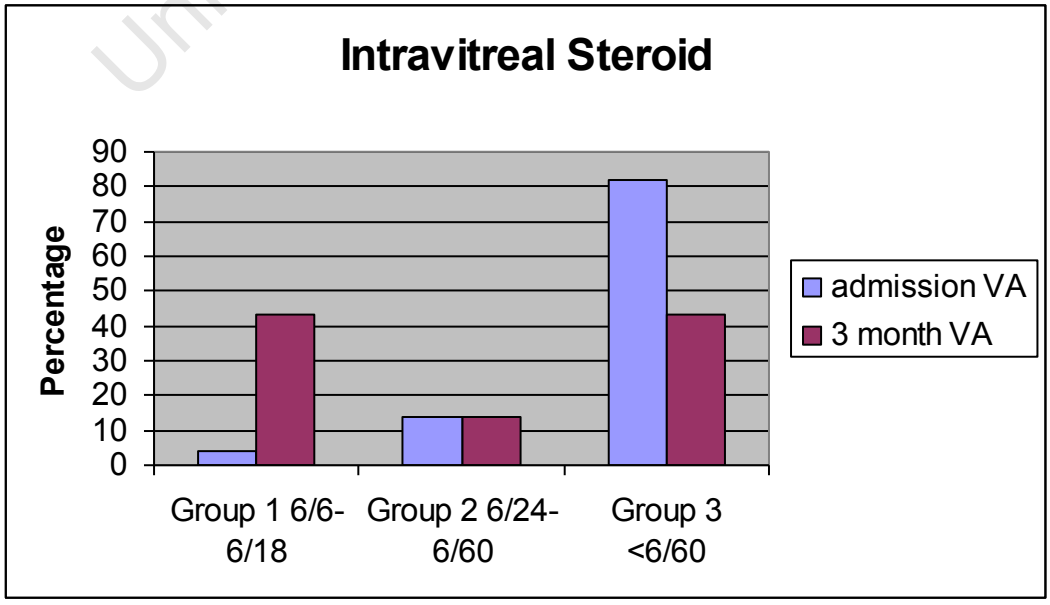
Group 3: Severe visual impairment and Blindness: less than 6/60 i.e. Count Fingers to No Perception of Light.

This shows that of those patients who received intravitreal placebo, 88% had a visual acuity of less than 6/60 on admission. At 3 months 54% of these patients still had a visual acuity of less than 6/60. However, of patients who received intravitreal steroid, 82 % had a visual acuity of less than 6/60 on admission and at 3 months only 43 % had a visual acuity of less than 6/60. In the placebo group 38% of patients had a final visual acuity of 6/18 or better while in the steroid group 43 % had a 3-month visual acuity of 6/18 or better. This is demonstrated in graphs 3 and 4.

Graph 3 Visual Acuity of the Placebo group: Admission vs 3 month:

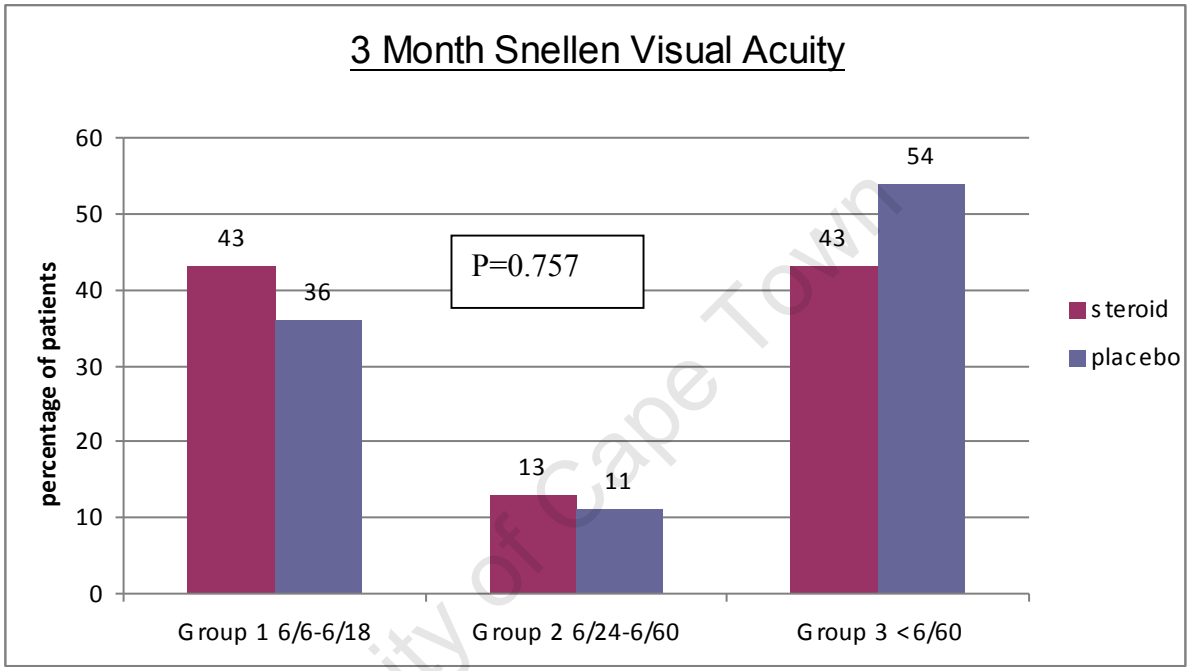


Graph 4 Visual Acuity of the Steroid group: Admission vs 3 month:



Graph 5 shows the comparison between the visual outcomes at 3 months of the total steroid and the total placebo group with a p value of 0.757 (Fishers exact test)

Graph 5: 3-Month Visual Acuity comparison between Placebo vs Steroid

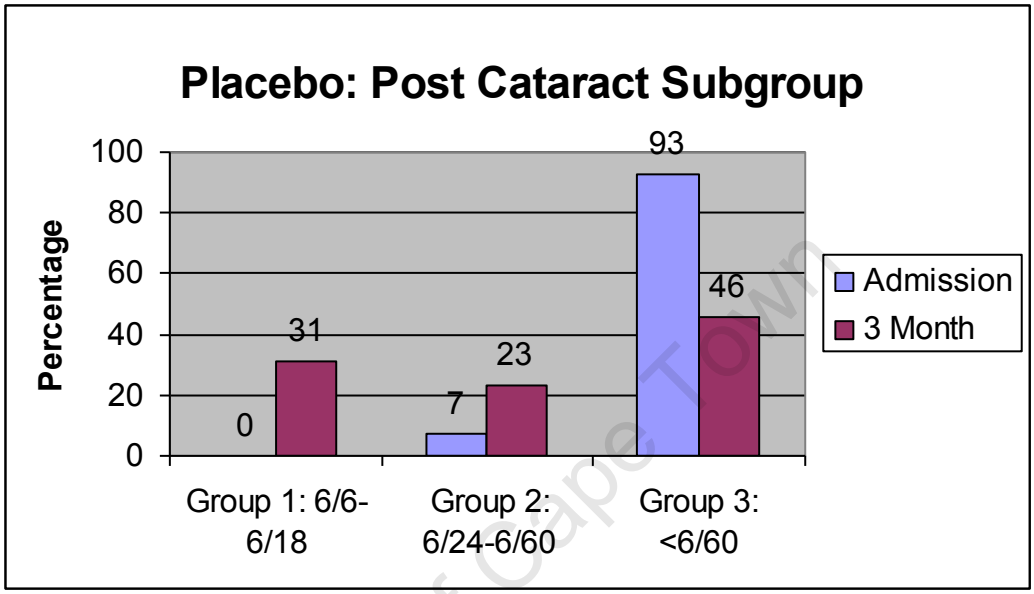


Analysis of the post cataract group, consisting of 17 steroid patients and 15 placebo patients, was also conducted. Only 1 of the 3-month visual acuities in the placebo group was unavailable. The average lines improvement on the Snellen visual acuity chart was 2.7 (-3 to 9) for the placebo group compared to 4.1 (-3 to 9) for the steroid group (Student's t test, p = 0.330).

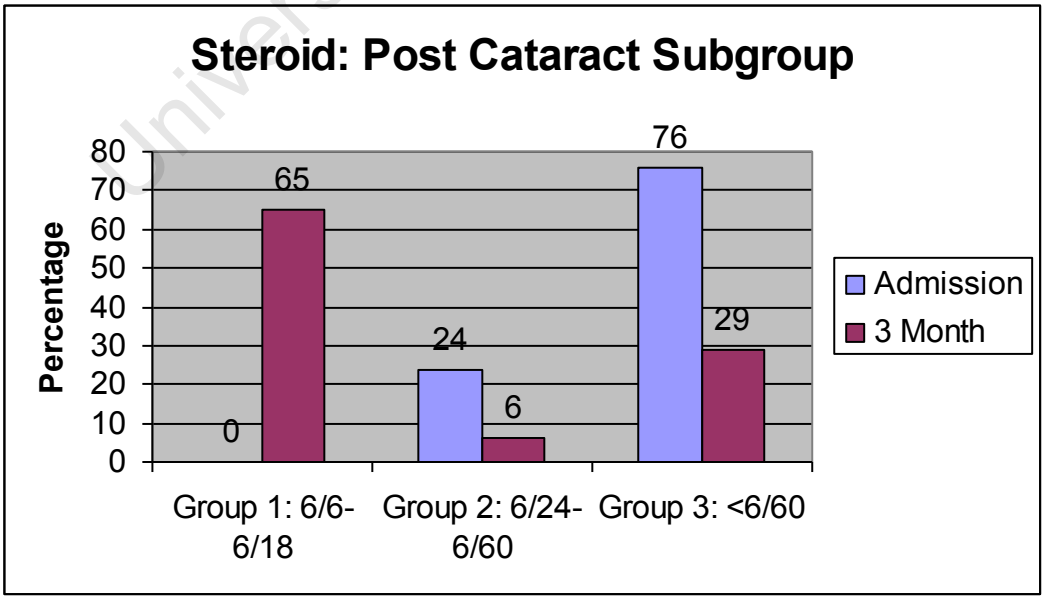
In the post cataract placebo group 93 % (14/15) presented with a visual acuity of less than 6/60 while at the 3 month visit only 46 % (6/13) had a visual acuity of less than 6/60. In the post cataract steroid group, 76% (13/17) presented with a visual acuity of less than 6/60 and at the 3 month visit only 29 % (5/17) retained a visual acuity of less than 6/60. Of the placebo group 31% (4/13) had a good visual outcome with a visual acuity of 6/18 or better compared to the steroid group where 65% (11/17) had a visual acuity of 6/18 or better. This is shown in Graphs 6 and 7, while graph 8

shows the 3-month comparison in Snellen category between the placebo and steroid patients in the post cataract subgroup, which shows a p value of 0.214 (Student's t test).

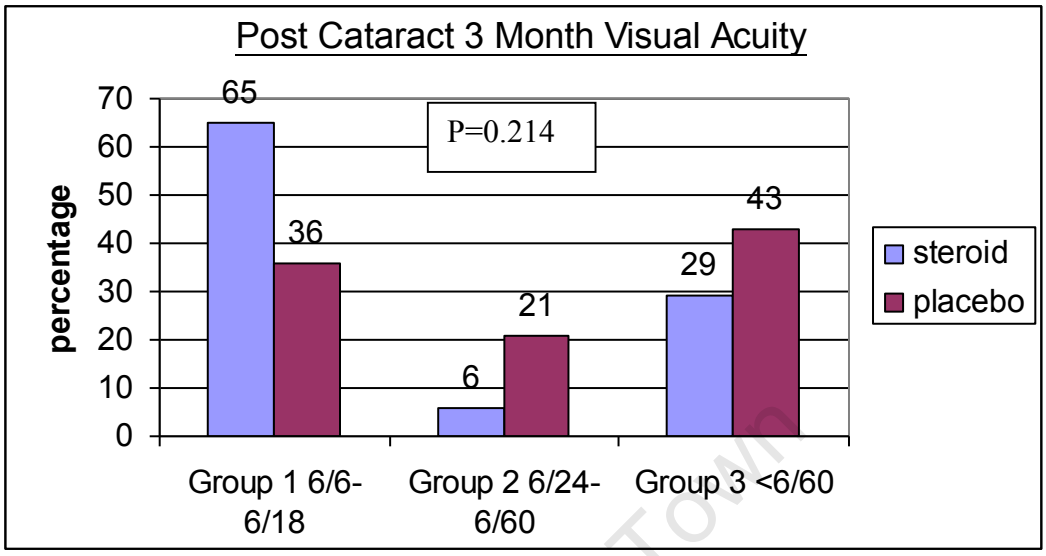
Graph 6: Visual Acuity of the Placebo Post Cataract on Admission vs 3-Month



Graph 7: Visual Acuity of the Steroid Post Cataract on Admission vs 3-Month



Graph 8: Post Cataract 3-Month Visual Acuity Placebo vs Steroid



In the bleb related endophthalmitis group, 9 patients received intravitreal placebo, of whom 2 patients did not attend for follow up and 4 received intravitreal steroids. The mean number of lines improvement on the Snellen visual acuity chart for this placebo subgroup was 0.85 lines compared to the steroid subgroup, which was 1.25 lines (Student's t test, p=0.95).

Of those patients who were classified as "other":

a) 8 were trauma related endophthalmitis of which 4 received steroid and 4 received placebo.

b) 3 were due to endogenous endophthalmitis of which 1 received steroid and 2 received placebo.

c) 6 were post pars plana vitrectomy of which 4 received steroid and 2 received placebo.

The mean number of Snellen lines improvement in the "placebo: other" subgroup was 0.714 lines compared to the "steroid: other" subgroup which was 0.625 lines. (Student's t test, p = 0.851)

The vitreous and aqueous taps yielded a 52.5 % positive culture rate. The most common organism cultured was Staphylococcus epidermidis, which was cultured in 23% of all cases followed by Staphylococcus aureus and Streptococcus species (including pneumonia, mitis, oralis, constellatus, viridans, and intermedius). Unfortunately 5 results were lost with the installation of a new hospital information system.

Table 2 shows the organisms in each group.

Table 2: Microbilogy Culture Results

Organism	Post Cataract	Bleb Related	Other
Coagulase Neg. Staph.	7	4	3
Staph. aureus	4	0	1
Streptococcus species	5	2	1
Bacillus	0	0	2
Rhodococcus species	1	0	0

The only adverse events were 3 retinal detachments. All three patients were post cataract patients who received intravitreal steroids. One patient developed a total rhegmatogenous retinal detachment 5 days after the injection with a break noted at 12h00. The injection site was recorded at 07h00. The patient had complicated cataract surgery with posterior capsular tear and anterior vitrectomy. An external retinal detachment repair was performed successfully but the 3-month visual acuity remained counting fingers.

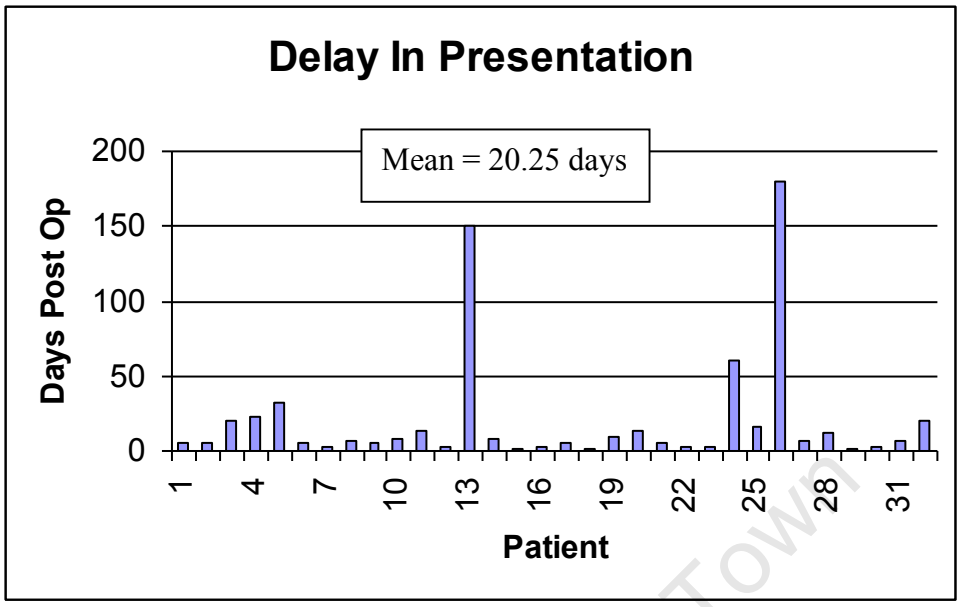
The second patient had undergone a lens washout for blunt traumatic cataract and developed a rhegmatogenous retinal detachment in the area of injection with severe proliferative retinopathy. A pars plan vitrectomy with insertion of silicone oil was performed, but the cornea decompensated and the vision remained hand movements at 3 months.

The third patient also had complicated cataract surgery with posterior capsular tear and anterior vitrectomy. After intravitreal injection at 07h00 the visual acuity recovered to 6/9, but 6 months later developed an inferior rhegmatogenous retinal detachment with a break recorded at 04h00.

No adverse reactions directly attributable to the intravitreal steroid were recorded.

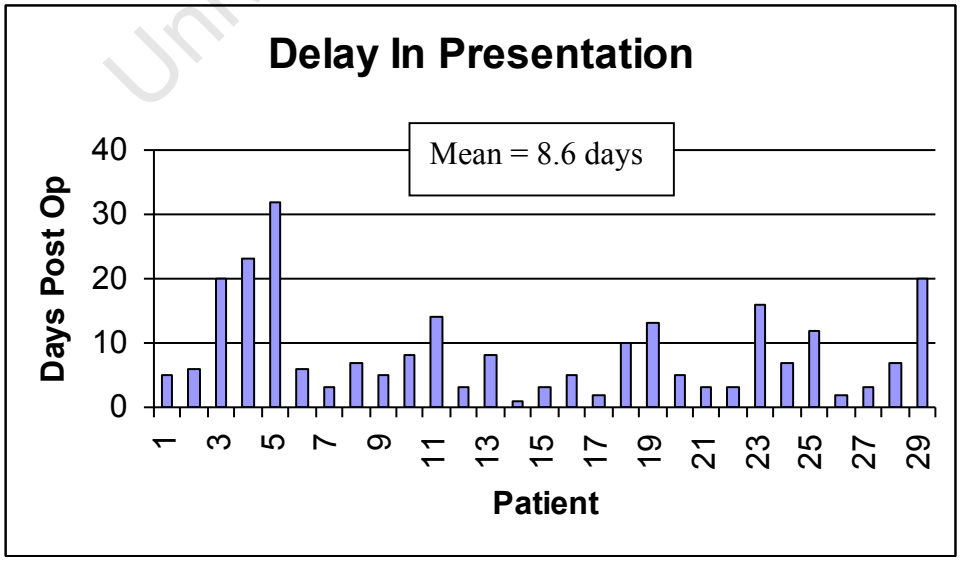
We also noted a delay in the presentation of the post cataract patients. The time between the surgery and the day of presentation was recorded and is shown in graph 9

Graph 9: Delay In Presentation of all Post Cataract Endophthalmitis



Therefore 3 patients presented with a chronic form of endophthalmitis: 1 at 2 months, 1 at 5 months and 1 at 6 months. The mean delay in presentation is 20.25 days, but if the 3 chronic cases are removed then the mean delay is reduced to 8.6 days and is displayed in graph 10.

Graph 10: Delay In Presentation of Acute Post Cataract Endophthalmitis



Chapter 4

Discussion

The most important limitation of the study is the small sample size. Prior to the start of the study our department had experienced an increased incidence of all forms of endophthalmitis including referrals from secondary units. We planned to be able to recruit approximately 100 subjects over a five-year period. However, we were only able to recruit 62 subjects, of whom 32 had endophthalmitis following cataract surgery. There could have been merit in conducting a multi-centre study, to increase the sample size.

A second weakness of our study is the difficulty we experienced in keeping accurate records in our busy understaffed clinic. Ideally, accurate records should have been kept on all patients considered for the trial and their reason for exclusion, as recommended by the Consort [23] statement. This does not affect the outcome in any way, but would improve the transparency of the reporting and thereby the confidence the reader has in evaluating the trial, especially in evaluating for any selection bias. The most common reason for exclusion was postoperative inflammation where the patient would be admitted for observation with intensive topical steroids and intravitreal injections ordered. However, if there was clinical improvement then the diagnosis was changed to post operative uveitis. Other exclusions included lost hospital records. A few patients who presented after hours were also excluded as they did not follow the correct protocols and subsequently were not randomised. The precise details of these patients were not recorded and should have been documented and displayed in flow diagram 1.

A separate endophthalmitis trial pack (see appendix 1) was used on each patient to facilitate ease of record keeping, but in a few cases it replaced the master notes and some visual acuity records were missing. This highlights the need for any trial records to be separate from the main hospital record to ensure continuity of patient records, especially for medico-legal reasons.

A third weakness is the use of Snellen visual acuity charts, which is the only type of chart available in our clinics. Dr J. Holladay described the most accurate method of comparing visual acuities using the geometric equivalent as a logmar in order to compare geometric means etc. of different groups [24]. The conversion tables (see appendix 2) are dependant on each line having the same number of letters such as on the EDTRS charts or Bailey –Lowe charts. Otherwise, each line would ideally require a separate conversion equation. However, he also points out that there is no logmar or geometric equivalent for visual acuity of Light Perception or No Light Perception, as they do not represent a measurable angle, but merely the detection or absence of a light stimulus. Thus he suggests that these patients are reported separately. In our study, this means that 22 (35 %) patients would be analysed separately, which would make the logmar analysis of the remaining visual acuities meaningless.

A further difficulty encountered by all researchers interested in presumed bacterial endophthalmitis is the diagnosis. The gold standard is an appropriate vitreous or aqueous tap culture result. Our 52.5 % positive culture result is in keeping with the international standard, but this does always raise the question of the accuracy of differentiating infectious endophthalmitis from inflammatory uveitis especially in the early postoperative period. However if the sample size is adequate then this confounding variable should be neutralised by the successful randomisation. The baseline comparative demographics (Table 1) reveal no significant difference between the two groups which shows the success of the randomisation. We would hence expect this potential confounding variable to affect each group equally.

Using the visual acuity at 3 months as a final acuity also has its drawbacks. Three months is a compromise between improving the follow up rate, which is traditionally very poor, and allowing sufficient time for the vision to finally stabilise and allowing for late complications to develop. It could be argued that the early anti-inflammatory effect of the steroids may mean quicker recovery but no difference in final vision if measured at either 6 or 12 months. Conversely, it may be argued that the placebo group may be at higher risk for long-term complications such as tractional retinal

detachments, which may be missed at the 3-month mark. The only way to know this would be to have a longer follow up period.

The visual outcome in comparing the total steroid to the total placebo group showed no significant difference, which is in keeping with other studies. It did not show a detrimental effect, which has been previously shown by Shah's group [9]. However these studies are usually limited to only post cataract endophthalmitis patients. In comparing the priority subgroup of the post cataract patients to other studies the results become more interesting. Firstly a beneficial trend was demonstrated despite the small numbers with the average number lines improvement being 4.1 in the steroid group compared to 2.7 with the same range (-3 to 9). Although the p value is only 0.330 due to the small numbers, this still appears clinically significant and is significantly different from Shah's results of a non-randomised postoperative endophthalmitis study where they showed a reduced likelihood of a 3-line improvement in the steroid group [9]. Our results are more in keeping with Gan's result, which was also a randomised trial with 30 patients and showed a trend to better visual acuity in the steroid group [11]. Thus the only two randomised trials of similar design both show a beneficial trend for the intravitreal steroid group in post cataract endophthalmitis patients. Similarly our study, as seen in Graph 8, shows a non-statistically significant trend towards better visual outcome for post cataract patients in the steroid group.

The results of the bleb related endophthalmitis group and the other endophthalmitis group all show p values of nearly 1 due to the very low numbers in each group. The comparison of the number of lines improvement and the visual categories has no clinical significance. Therefore the role of intravitreal steroid in these clinical situations cannot be commented on.

The 52.5% positive vitreous/aqueous tap culture rate is in keeping with published literature and the cultured organisms were as expected. The most common was Staphylococcus epidermidis, Staphylococcus aureus and Streptococcus species, which is in keeping with the literature. The 2 Bacillus species cultured were in

trauma related cases and the only unusual organism was the Rhodococcus species. This was cultured in a post cataract patient who presented on day 1 post surgery with a fulminant endophthalmitis that did not respond to treatment. The presenting visual acuity of no light perception did not improve. This organism is usually found in rural farming communities and the patient was a farm labourer.

No adverse reactions or side effects were directly attributed to the intravitreal steroids. The only adverse events were the 3 rhegmatogenous retinal detachments. All 3 patients had complicated cataract surgery with posterior capsule rupture and vitreous loss. The retinal surgeons confirmed only 1 of the detachments as a definite consequence of the intravitreal injection with the site of the injection and the proliferative retinopathy anatomically correlating.

It was of interest to note the delay in presentation. Traditionally [25] it is thought that there are 3 peaks of incidences in postoperative endophthalmitis: a day 2-4 peak of fulminant cases, days 5-7 less fulminant cases usually Staph. epidermidis and then the chronic cases usually presenting months after surgery. Therefore our mean delay of 20.25 days was surprising and even removing the 3 most chronic cases still left a mean delay of 8.6 days. This raises the question of why our patients present later than expected. Unfortunately the time between onset of symptoms and the time of presentation was not recorded which would have been helpful. We know in our setting the difficulty that patients have in attending the regional hospital, especially after hours with little or no public transport available. In addition the education and understanding of some of our patients might be limited. A further problem might be from the referring secondary hospital where cataract surgery is performed but there is no after hours ophthalmology service available and patients are meant to attend their regional hospital, but are generally ill informed of this. We know that any delay has a significant impact on visual outcome.

Chapter 5

Conclusion

The results of our study must be viewed in context of the small sample size. There is no statistically significant difference between the two groups. However, the patients who received intravitreal steroid showed a trend towards improved visual acuity compared with those who received intravitreal placebo, and this trend might be considered as clinically significant.

This finding is the same as that of Gan and others, who also found a trend towards better visual outcome with intravitreal steroid. With the controversy that exists regarding the use of intravitreal steroids in the treatment of endophthalmitis, it is noteworthy that these two small randomized controlled trials show similar results. The results from these studies might be included in a future meta-analysis. The results highlight the need for a larger trial.

We would recommend that consideration is given to including intravitreal dexamethasone in the treatment of post-operative endophthalmitis. It has been shown to be safe and most likely beneficial in two very similar studies.

A further recommendation from our study is to highlight patient education regarding the symptoms of endophthalmitis and to encourage patients to seek medical attention as soon as possible if they develop symptoms of endophthalmitis. We have adapted our standard post-cataract surgery data sheets to include a tick box which both reminds the surgeon to highlight the dangers to the patient, as well as to document that the patient has been informed (see appendix). In addition, an improved referral system from our secondary level units performing high volume cataract surgery has also been implemented.

Bibliography

1. Ness T, Pelz K, Hansen LL. Endogenous endophthalmitis: microorganisms, disposition and prognosis. *Acta Ophthalmol Scand*. Dec 2007; 85(8): 852-6.

2. Graham RO, Peyman GA. Intravitreal injection of dexamethasone. Treatment of experimentally induced endophthalmitis. *Arch Ophthalmol*. 1974 Aug; 92(2):149-54.

3. Kamalarajah S, Silvestri G et al. Surveillance of endophthalmitis following cataract surgery in the UK. *Eye* 2004 Jun; 18(6): 580-7.

4. Okhravi N, Towler HM et al. Assessment of a standard treatment protocol on visual outcome following presumed bacterial endophthalmitis. *Br. J. Ophthalmol*. 1997; 81: 719-25.

5. Lalwani GA, Flynn HW Jr. et al**.** Acute-onset endophthalmitis after clear corneal cataract surgery (1996-2005). Clinical features, causative organisms, and visual acuity outcomes. *Ophthalmology*. 2008 Mar; 115(3): 473-6.

6. Chaudhry NA et al. A cluster of patients with acute-onset endophthalmitis following cataract surgery. *Ophthalmic Surg Lasers Imaging*. 2005 May-Jun; 36(3): 205-10.

7. Elder MJ, Morlet N. Clinical controversy. *Clin and Exp Ophthalmol* (2002); 30: 394-398.

8. Das T, Jalali S et al. Intraviteral dexamethasone in exogenous bacterial endophthalmitis: results of a prospective randomized study. *Br J. Ophthalmol* 1999; 83: 1050 –55.

9. Shah GK et al. Visual outcomes following the use of intravitreal steroids in the treatment of postoperative endophthalmitis. *Ophthalmology*. 2000 Mar; 107(3): 486-489.

10. Pollack JS et al. Failure of intravitreal dexamethasone to diminish inflammation or retinal toxicity in an experimental model of Bacillus cereus endophthalmitis. *Curr Eye Res.* 2004 Oct-Nov; 29(4-5): 253-9.

11. Gan IM et al. Intravitreal dexamethasone as adjuvant in the treatment of postoperative endophthalmitis: a prospective randomized trial. *Graefes Arch Clin Exp Ophthalmol*. 2005 Dec; 243 (12): 1200-5.

12. Pathengay A et al. Intravitreal triamcinolone acetonide in the management of exogenous bacterial endophthalmitis. *Am J Ophthalmol.* 2006 May;141(5):938-40.

13. Ermis SS et al. Effects of intravitreal moxifloxacin and dexamethasone in experimental Staphylococcus aureus endophthalmitis. *Curr Eye Res.* 2007 Apr; 32(4): 337-44.

14. Rehak M et al. [Primary vitrectomy with intraocular antibiotic application in postoperative endophthalmitis]. *Ophthalmologe.* 2007 Nov; 104(11): 958-64.

15. Saleh M et al. [Advantages of corticosteroids in managing acute bacterial postoperative endophthalmitis.] *J Fr Ophtalmol.* 2008 Oct; 31(8): 825-33.

16. De Kaspar HM et al. Effects of intravitreal corticosteroid in the treatment of Staphylococcus aureus-induced experimental endophthalmitis. *Retina.* 2008 Feb; 28(2): 326-327.

17. Liu F et al. The efficacy of intravitreal vancomycin and dexamethasone in the treatment of experimental bacillus cereus endophthalmitis. *Curr Eye Res*. 2008 Sep; 33(9): 761-8.

18. Kwak HW et al. Evaluation of the retinal toxicity and pharmacokinetics of dexamethasone after intravitreal injection. *Arch Ophthalmol*. 1992 Feb;110(2): 259-66.

19. Smith MA et al. Effects of intravitreal dexamethasone on concentration of intravitreal vancomycin in experimental methicillin-resistant Staphylococcus epidermidis endophthalmitis. *Antimicrob Agents Chemother*. 1991 Jul; 35(7):1298-302.

20. Park SS et al. Intravitreal dexamethasone effect on intravitreal vancomycin elimination in endophthalmitis. *Arch Ophthalmol.* 1999 Aug; 117(8): 1058-62.

21. Gan IM et al. Effect of intravitreal dexamethasone on vitreous vancomycin concentrations in patients with suspected postoperative bacterial endophthalmitis. *Graefes Arch Clin Exp Ophthalmol*. 2005 Nov; 243(11): 1186-9.

22. Doft BH et al. The endophthalmitis vitrectomy study. *Arch Ophthalmol*. 1991 Apr; 109(4): 487-9.

23. Moher et al. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. *The Lancet.* 2001 April; 357: 1191-94.

24. Jack T.Holladay. Guest Editorial: Visual acuity measurements. *J Cataract Refract Surg*. 2004 February; 30: 287-290.

25. Endophthalmitis Vitrectomy Study Group. Microbiologic factors and visual outcome in the endophthalmitis vitrectomy study. *Am J Ophthalmol*. Dec 1996; 122(6): 830-46.

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Changes to Dissertation:
18/11/2009

Pg 3 line 5: "…post cataract surgery (PC), **b**leb related endophthalmitis (BRE) and **o**ther (O), including…" – do not use upper case B and O as it was not used for "post cataract"

Pg 4 bottom: "Appendix" should read "Appendices" as there are 2

Pg 6 last paragraph, second line: "…infective organism, its toxins…" – no apostrophe after "its"

Pg 8, second paragraph, third line: "…studies that have shown a benefit…" - not showed

Pg 9, paragraph 3, third line: "…of 29 postoperative endophthalmitis **cases or patients**, who received…"

Pg 9 last paragraph, second line: "…model of Staph**y**lococcus aureus…" – **y** omitted

Pg 12 third paragraph: "…clinician: **p**ost cataract (PC), **b**leb related endophthalmitis (**BRE**) and **o**ther (O), …" – to correspond to abstract wording

Pg 14 third line: "…anaesthetic inst**i**lled" – not installed

Pg 19 sixth line: "**Seventeen** patients…" – you should not start a sentence with a number

Pg 31 second last sentence – there are 2 "also's" in the sentence. Rather start the sentence with "**In addition**…"

Pg 33 second paragraph first line: "…of Gan and …" without the **h** in Ghan

On pg 8, first paragraph an article is incorrectly quoted (reference nr 3). The sentence currently reads: "A survey of **all** post cataract endophthalmitis in the United Kingdom showed that of the 213 patients, only…" That is not correct - there are a lot more than 213 patients in the UK who developed post cataract surgery endophthalmitis! The sentence should read: "A survey, **performed over 12 months from October 1999 to September 2000**, of post cataract endophthalmitis in the United Kingdom showed that of the 213 patients, only…"