Intraocular Pressure Changes in Eyes Receiving Intravitreal Triamcinolone Acetonide in Kikuyu Eye Unit

A study carried out in part fulfilment for the degree of Master of Medicine in Ophthalmology in the University of Nairobi

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Declaration

This dissertation is my original work, and it has not been submitted for a degree in any other university

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Approval

This dissertation has been submitted for examination with our approval as University Supervisors.

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Dedication

To mum, Mwoncere M'Mwambia, and dad, M'Mingaine M'Ngaitai

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Abbreviations

ARMD	Age Related Macular Degeneration
BRVO	Branch Retinal Vein Occlusion
CI	confidence interval
CRVO	Central Retinal Vein Occlusion
CMO	Cystoid macula oedema
DMO	Diabetic Macular oedema
ECCE	Extra-capsular cataract extraction
IOP	Intraocular Pressure
IVTA	Intravitreal Triamcinolone Acetonide
KEU	Kikuyu Eye Unit
KNH	Kenyatta National Hospital
max	maximum
mg	milligram
ml	millilitre
mm	millimetre
mmHg	millimetres of Mercury
n	number (in a sample)
p	probability
PDT	Photodynamic Therapy
PGF	Prostaglandin F
PPV	pars plana vitrectomy
SD	Standard deviation
SE	Standard error of the mean
SPSS	Statistical Package for Social Sciences
VEGF	Vascular Endothelial Growth Factor

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Abstract

Objective: To determine the magnitude and pattern of intraocular pressure (IOP) changes in eyes that received intravitreal triamcinolone acetonide in Kikuyu Eye Unit.

Study Design: retrospective interventional case series.

Setting: Kikuyu Eye Unit.

Subjects: Seventy-two eyes (of 61 patients) injected between January 2007 and August 2008.

Methods: Data on IOP, indication for injection, additional procedures (cataract surgery, retinal photocoagulation), and treatment was collected using questionnaires and analysed using SPSS version 11.5.

Results: The mean pre-injection IOP was 16.0 (SD 5.2) mmHg, which increased to 23.8 (SD 11.5) mmHg after intravitreal triamcinolone acetonide injection ($p<0.001$). IOP started increasing significantly within 2 weeks ($p=0.006$). The median post-injection time before IOP peak was 4.6 weeks, and IOP remained high for 24 weeks after injection. Intraocular pressure increase of 5 mmHg or more was found in 39 (54.2%) eyes, while that of 10 mmHg or more was found in 22 (30.1%). Increase of more than a third of pre-injection IOP was noted in 41 (56.9%) eyes. Thirty-three eyes (45.8%) had maximum post-injection IOP beyond 21 mmHg. Twenty-two eyes (30.6%) received treatment for IOP elevation – mostly antiglaucoma medication – and one required cyclophotocoagulation. Eyes with pre-injection IOP of more than 21 mmHg were associated with significantly higher IOP increases ($p<0.001$) and all received pressure-lowering medication. No associations were noticed between age, sex, other procedures, diagnosis and pattern of IOP change.

Conclusions: Intraocular increase was found to be a common complication of intravitreal triamcinolone acetonide, and the increase occurred mostly in the first

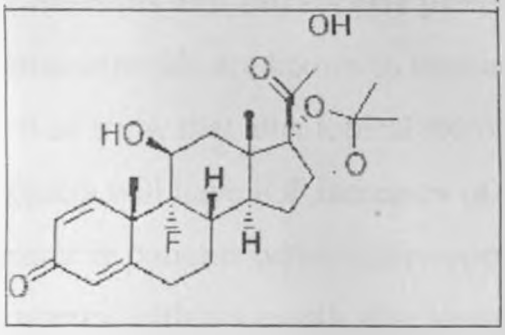
six months. Almost a third of eyes on treatment with Intravitreal triamcinolone acetonide received intervention for increased IOP.

Recommendations: Close follow-up of eyes receiving IVTA is needed, and eyes with IOP over 21 mmHg may benefit from prophylactic antiglaucoma medication immediately after IVTA.

1 Introduction and Literature Review

Triamcinolone acetonide is a synthetic glucocorticoid with intermediate duration of action (15-24 hours) and at least 5-times potency relative to cortisol (hydrocortisone).[1] It is a fluorinated steroid with no mineralocorticoid effect. It is a whitish, crystalline powder that is insoluble in water, and sparingly soluble in alcohol. It is available in oral, inhaled, topical (ointment, cream) as well as injectable forms.[2] The injectable form can be used for intravitreal or posterior sub-Tenon's injections in the eye.[3] Intravitreal forms allow appropriate concentrations of drug to access the retina and choroid without the systemic side effects expected if the drug is given orally or intravenously.

Triamcinolone acetonide



Intravitreal triamcinolone has been used for a number of years[4] now to treat macular oedema due to diabetic retinopathy,[5] central[6] and branch retinal vein occlusion,[7] and uveitis.[8] It is also used for choroidal neovascularisation in age-dependent macular degeneration,[9] and has also been used as adjunctive treatment in neovascular glaucoma.[10] It can also be used as an adjunct to laser and photodynamic therapy (PDT).[4, 5, 9]

Triamcinolone acetonide, when injected into the vitreous, can last in the vitreous cavity for as long as 6 months.[11] Its effects are longstanding, and often patients may just require one injection, occasionally two (though with decreasing efficacy, according to at least one study).[12]

1.1 Mechanism of action

Vessel leakage is a major pathological feature of diabetic retinopathy and macular oedema secondary to central or branch retinal vein occlusion.[4] Vascular Endothelial Growth Factor (VEGF), a 45-kiloDalton protein, mediates breakdown of the blood-retinal barrier leading to increased capillary permeability. Antonetti *et al.*[13] showed that VEGF increases phosphorylation of tight junction proteins like occludin and zonular occluden, thus increasing vessel permeability. Steroids inhibit expression of the VEGF gene.[14] Triamcinolone is particularly useful in reducing neovascularisation.[15]

1.2 Steroids and intraocular pressure

Corticosteroids are known to increase intraocular pressure on prolonged use. Some studies show that after topical steroid use for at least 4 weeks, at least 35% of subjects will have IOP increases of more than 6mmHg, and this can be faster and greater in patients with primary open angle glaucoma.[16] Usually IOP will go back to normal within a month after stopping medication.[17] In susceptible individuals steroids administered via local injection, topical, inhalational and systemic routes will lead to IOP elevation. Diabetics have been found to be particularly susceptible.[18]

A number of theories have been advanced to explain elevation of IOP on steroid use:[19]

- Inhibition of prostaglandins (like $PGF_{2\alpha}$) that enhance outflow, especially uveoscleral aqueous drainage
- Suppression of trabecular endothelial cell phagocytosis
- Alteration of trabecular extracellular matrix components, like proteoglycans and glycoaminoglycans, increasing resistance to outflow
- Increasing cross-linkage of actin in the trabecular meshwork

- Increased expression of cellular tight junction proteins, modifying fluid hydraulic conductivity
- Stabilization of lysosomes, leading to accumulation of hyaluronate or other debris at the trabecular meshwork

Some mechanisms may be active simultaneously or sequentially.

A number of studies investigating IOP changes related to IVTA have been undertaken, though with differing doses of triamcinolone acetonide, and all on Caucasians and Asians. Rhee *et al.* examined a retrospective consecutive case series of 570 eyes of 536 patients receiving a single IVTA 4.0mg (0.1ml), and another set of 43 eyes of 40 patients receiving a second injection.[20] He found out that 53.2% of all eyes had IOP elevation. A baseline IOP of 16mmHg and above was found to be a risk factor.

Jonas *et al.* studied a prospective non-comparative interventional case series of 75 eyes receiving 25mg IVTA, 64 of them for age related macular degeneration and 11 for diabetic macular oedema. Intraocular pressure of more than 21mmHg (from a mean baseline of 15.43mmHg) was noticed in 52% of the eyes two months after the injection.[21] Young age was found to be a positive predictive factor. Intraocular pressure elevation was statistically independent of indication for IVTA, refractive error, or diabetes. This has been corroborated in other studies.[23] All eyes with increased IOP responded to medical therapy except one (which had a pre-injection diagnosis of primary open angle glaucoma and needed filtration surgery). IOP normalised after 6 months without further treatment beyond that duration, and without optic nerve head changes.

Galor *et al.*, in a review of 222 eyes of whom 45 had macular oedema due to uveitis, found out that uveitis was a statistically significant risk factor for adverse IOP events ($p=0.05$).[22]

Studies done in Turkey,[23] South Korea,[24] and Japan,[25] have shown IOP elevations of 20.8% (beyond 22mmHg), 51.4%, and 34.1% (by more than 5mmHg), respectively. The Japanese study by Yamamoto *et al.* corroborated Jonas' finding that young age (younger than 60 years) was a positive predictive factor.

1.3 Dosage of IVTA

The optimal dose of IVTA is not yet decided on. Lam *et al.* randomised 63 patients with clinically significant diabetic macular oedema to receive 4 mg (n = 23), 6 mg (n = 20) or 8 mg (n = 20) IVTA.[26] He found that the mean best corrected visual acuity (BCVA) improvement at 6 months was significantly higher for the 8 mg group compared with the 4 mg group. No statistically significant differences were observed between the three groups for eyes with maximum IOP increased beyond 21 mm Hg (p = 0.27). Nonetheless, the proportion of eyes remaining on treatment for glaucoma at 6 months was higher in the 8 mg group than in the 4 and 6 mg groups (p = 0.05).

Spandau *et al.* compared the effects of 2 mg (n=8), 5 mg (n=10) and 13 mg (n=9) IVTA in patients with diffuse diabetic macular oedema.[27] They used a filtration procedure which is not common in most centres, by removing the solvent agent, benzyl alcohol, and replacing it with Ringer's solution. Their findings showed treatment response may last longer and be more pronounced with a dosage of 13 mg than in lower doses of 5 mg or 2 mg. However, on follow-up, there was no statistically significant association of IOP change with the dosage used (p = 0.77).

Tammewar *et al.* examined records of 51 eyes that had received non-decanted (standard) 4mg IVTA and 41 that received decanted 20mg IVTA. They found out that after follow-up of about 21 weeks, 46% of eyes that had received 4mg had IOPs of 21mmHg and above, compared with 30% of those that received 20mg IVTA, showing that a decanted drug (where sediments have settled and have been

discarded) in higher doses might be better than non-decanted medication. Eyes that underwent vitrectomy had statistically significant lower IOPs than non-vitrectomised eyes.[28]

Das-Bhaumik *et al.* retrospectively examined records of 36 injections that were performed on 33 eyes of 29 patients; intractable cystoid macular oedema was present in 30 eyes and intractable inflammation (panuveitis or vitritis) in eight eyes. All patients received 2 mg non-decanted triamcinolone acetonide (Kenalog®). A postoperative rise in IOP of 5 mmHg or more was measured in 38.8% of eyes and of 10 mmHg or more in 19.4%, but a rise to >21 mmHg (maximum 36 mmHg) was noted in only eight eyes (22.2%). Two eyes with IOP of more than 30mmHg required short-term topical antiglaucoma medication.[29]

1.4 IVTA vs. sub-Tenon's injection of Triamcinolone Acetonide

Posterior sub-Tenon's injection is another way of administering triamcinolone acetonide. Sub-Tenon's dose usually ranges from 20mg to 40mg. Visual outcomes tend to be better with IVTA, but there is no statistically significant difference in the effect on IOP between the two routes.[30] Jea *et al.*[24] in Korea found out that IOP increases earlier with IVTA. Yamamoto *et al.*[25] in Japan observed that IOP increases took longer to reduce to pre-injection levels in those receiving sub-Tenon's injections.

1.5 Studies in Africans

People of African ancestry have been found to have higher proportions of primary open angle glaucoma, compared with Caucasians. Glaucoma also tends to begin earlier in Africans.[31] The Barbados eye studies found out that people of African origin have higher mean IOPs compared with people of mixed descent and Caucasians.[32] They also found a positive relationship between increase in IOP and male sex, hypertension, and diabetes[33]. People of African descent have thinner

corneas than Caucasians. La Rosa *et al.* found most Caucasians in their study to have corneal thickness of between 580 and 600 µm while central corneal thickness in African-American patients ranged from 520 to 540 µm. This could lead to underestimating actual IOPs in people of African descent compared to Caucasians.[34] Wafula *et al.* in Kenya found a mean central corneal thickness of 521.43µm among 261 eyes of Bantus (143), Nilotes (90), and Cushites.[35] Yeshigeta *et al.* in Ethiopia found a mean central corneal thickness of 518.68µm among 300 eyes of Semites, Cushites, and other Ethiopian tribes.[36] Both studies, however, didn't find statistically significant differences in central corneal thickness between specific African ethnic groups.

Diabetes, with the attendant diabetic retinopathy is becoming a common problem in Africa. Kariuki *et al.* in Kenya, found diabetic retinopathy in 49.8% of diabetics attending the Kenyatta National Hospital diabetic clinic, with 40.3% of them having macular oedema.[37] Githeko *et al.* found diabetic macular oedema prevalence of 4.5% in 420 patients attending three peripheral clinics in central Kenya, while 0.4% had proliferative diabetic retinopathy.[38] Nkumbe *et al.* on examining 141 eyes of newly diagnosed diabetics (less than one year), found 8.2% to have macular oedema and 4.3% to have proliferative retinopathy.[39] While IVTA has started being given in Africa, there are no studies done on Sub-Saharan Africans find out how IOP changes on giving IVTA.

1.6 Other complications of IVTA injection

Injection-related complications like haemorrhage or retinal detachment are fairly rare.[40] Jonisch *et al.*, in a review of charts of 554 eyes that underwent IVTA between January 2005 and July 2006, found sterile endophthalmitis of unexplained cause in 11 eyes (1.9%).[41] According to Maia *et al.* this could be related to the preservative used.[42] Maia compared eyes that received preservative-free triamcinolone acetonide (69 injections) and those that received triamcinolone

acetonide with preservative -- Kenalog® (577 injections). Non-infectious endophthalmitis was found more often after Kenalog® injections (p=0.005), but there was no statistically significant difference in IOP increase (above 23mmHg) in both injections (p=0.167).

Progression of cataract is a fairly common complication. Gilles *et al.*, in a randomised clinical trial, found out that 51% of steroid responders (those with IOP elevation of at least 5mmHg) had progression of posterior sub capsular cataract by 2 or more grades using photographic standards from the Age Related Eye Disease Study.[43] In the Turkish study by Ozkiriz *et al.*, 14 (6.6%) of 212 eyes studied had cataract progression and underwent cataract surgery with intraocular lens implantation.[25] Endophthalmitis (coagulase negative *staphylococcus*) developed in one eye (0.5%). Pseudoendophthalmitis occurred in one eye (0.5%), and pseudohypopyon (triamcinolone crystals) was observed in two eyes (0.9%).

1.7 Pupil dilatation and IOP

Some eyes might have had IOP taken after dilatation. This could be a confounding factor. However, Hancox *et al.*, on measuring intraocular pressures of 270 patients attending glaucoma, cataract and retina clinics before and after mydriasis, found a mean increase in IOP of 0.4mmHg for all eyes and 0.8 for those attending the retina clinic. The change also followed a normal distribution curve.[44] Sharp IOP increases were noticed in patients with ocular hypertension and prior diagnosis of glaucoma. Based on that study, all IOPs taken on dilated pupils in this study had 1mmHg subtracted to correct for the dilatation.

2 Study Justification

With the prevalence of diabetes mellitus increasing in sub-Saharan Africa, more patients are expected to develop ocular complications of diabetes such as macular oedema. The use of triamcinolone (IVTA) is gaining popularity as a treatment modality for diabetic macular oedema. Its effects on IOP have not been studied in African patients. African patients may also be at a higher risk of IOP elevation if treated with IVTA. This study will provide important information to fill this knowledge gap.

3 Objectives

3.1 Major:

To determine the magnitude and pattern of intraocular pressure changes in eyes receiving IVTA.

3.2 Specific:

1. To determine the magnitude of IOP change
2. To determine the trend of IOP over time
3. To determine correlates of IOP change e.g. age, sex, previous IOP
4. To describe the association between indication for injection (diagnosis) and IOP change

4 Research Materials and Methods

4.1 Study design

Retrospective hospital based case series.

4.2 Study setting

Kikuyu Eye Unit, located about 20 kilometres from Nairobi city, is a busy eye centre, with an active vitreoretinal service. It is part of a large mission hospital, PCEA Kikuyu Hospital. In Kikuyu Eye Unit intravitreal triamcinolone injections are given for various inflammatory conditions affecting the posterior segment, as well as for macular oedema. Injections are given in theatre under sterile conditions. The IOPs are monitored closely in every subsequent visit, the first usually within 2 weeks. All IOPs are taken using Goldmann's applanation tonometer.
In Kikuyu Eye Unit, patients receive 2mg (0.05ml) of non-decanted Triamcinolone Acetonide (Kenacort®). Initially they were receiving 4mg. The study was conducted in December 2008.

4.3 Sample size

Records of all eyes that received IVTA in Kikuyu Eye Unit from January 2007 to August 2008 were retrieved for analysis.

4.4 Inclusion and exclusion criteria

Eyes that had pre-injection and post-injection IOP records were included in the study. Eyes without pre-injection IOP or at least one post-injection IOP record were excluded.

4.5 Resource personnel

- Registry personnel
- Statistician

4.6 Study materials

- Questionnaire
- Files from the registry for all patients who received IVTA

4.7 Ethical approval

Permission was sought from and granted by the Kikuyu Eye Unit, and ethical approval was obtained from Kenyatta National Hospital Ethical Committee. All information was kept confidential. No patient was identified by name.

4.8 Data analysis and presentation

Data were entered into SPSS version 11.5 and presented using tables, line, bar and pie charts; and statistical analysis was carried out. A mean baseline was calculated for the entire sample as well as for age ranges and for each sex, and for disease entities. Mean post-injection IOPs was compared with pre-injection baselines and described as increases of 5 mmHg and above, 10 mmHg and above, as well as increases by more than a third of baseline IOP and pressures of over 21 mmHg, to facilitate comparison with other published studies. The above proportions were also described for each gender and disease entity. Box plots and tables were used to chart IOP changes with time after injection. Student's *t* tests and χ^2 tests were used to assess associations with sex, age, other procedures, pre-injection IOP, and the diagnosis.

The confidence level was taken as 95% ($p \leq 0.05$).

5 Results

Figure 1: Study flowchart

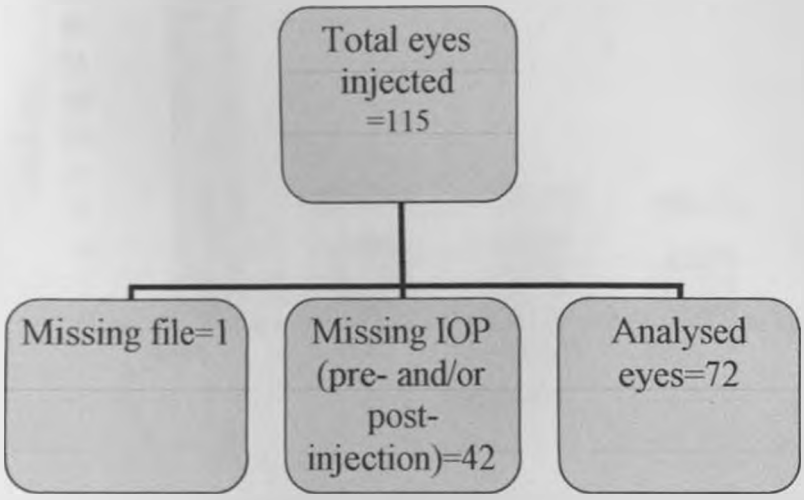
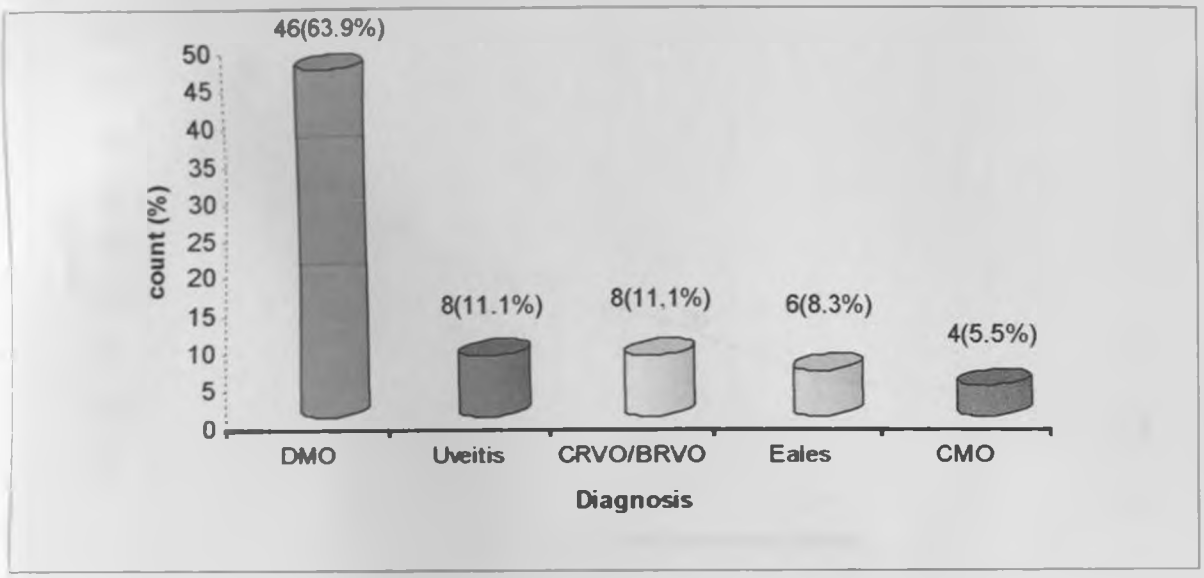


Table 1: Distribution by age and sex (n=61patients)

Factor	Number, (%)	Mean Age (years)	p value
Sex			
• Male	35, (57.4)	57.1	0.709
• Female	26, (42.6)	55.7	
Age ranges (years)			
• < 30	4, (6.6)		
• 30 – 39	6, (9.8)		
• 40 – 49	4, (6.6)		
• 50 – 59	17, (27.9)		
• 60 – 69	21, (34.4)		
• 70+	9, (14.8)		

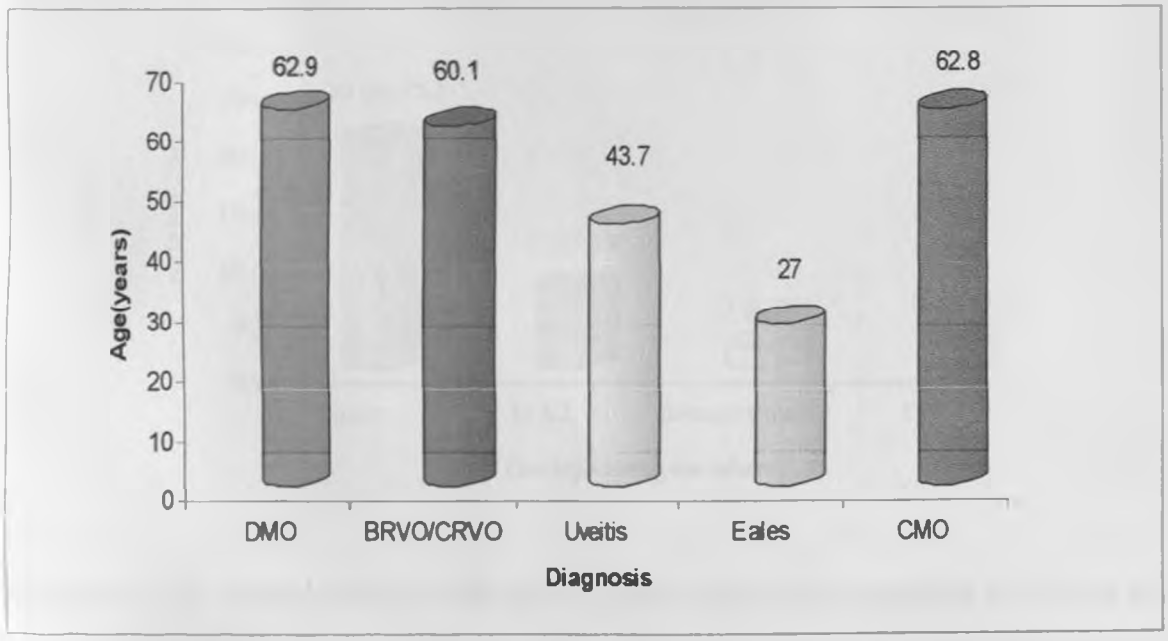
The mean age was 56.5 years, the median was 59 years, and the range was between 21 and 87 years. The mode was 63 years. Majority (77.1%) of patients were aged 50 years and above. Eleven patients had bilateral IVTA. All patients were of African ancestry.

Figure 2: Distribution by diagnosis (n=72 eyes)



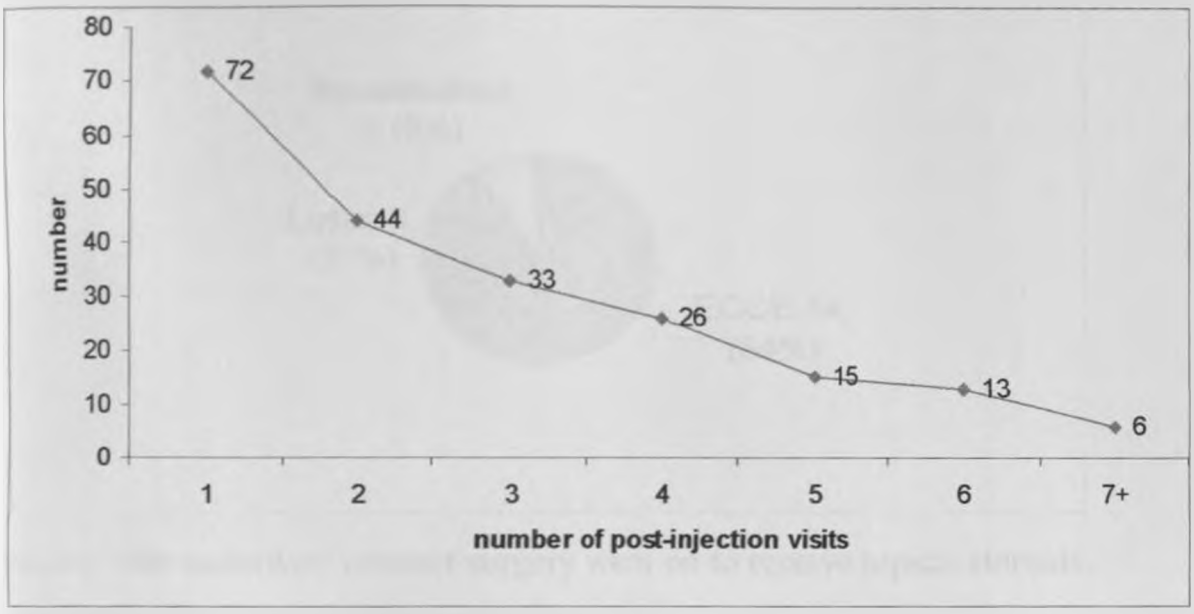
All the eyes with cystoid macular oedema had undergone cataract surgery previously.

Figure 3: Mean age by diagnosis (n=61patients)



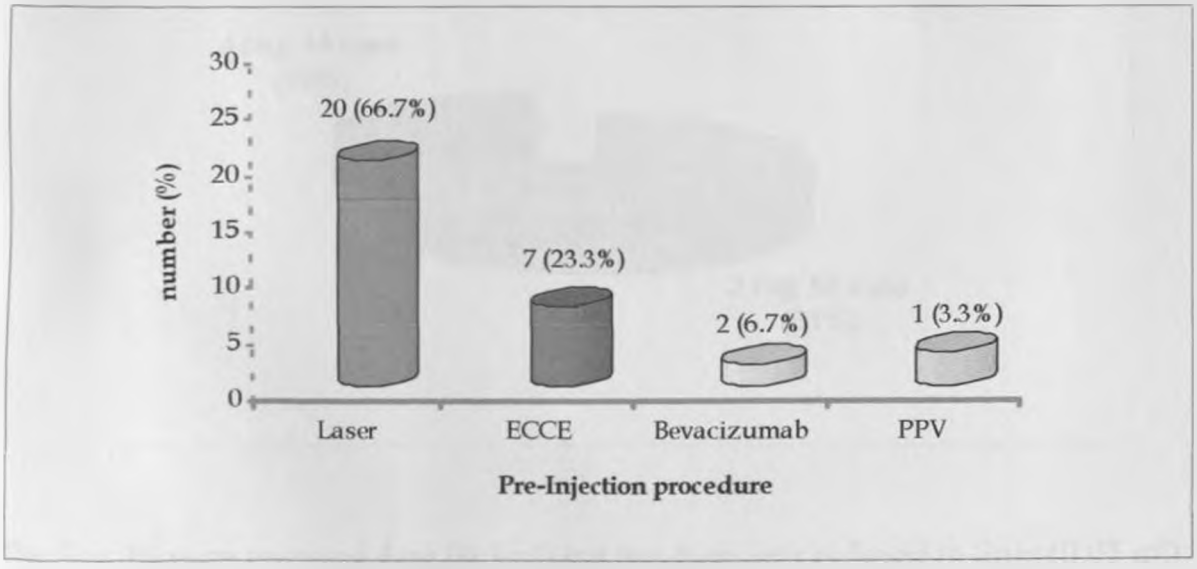
There was a statistically significant association of age with DMO ($p<0.001$), Uveitis ($p=0.003$), and Eales disease ($p<0.001$).

Figure 4: Number of Visits/ Follow-up



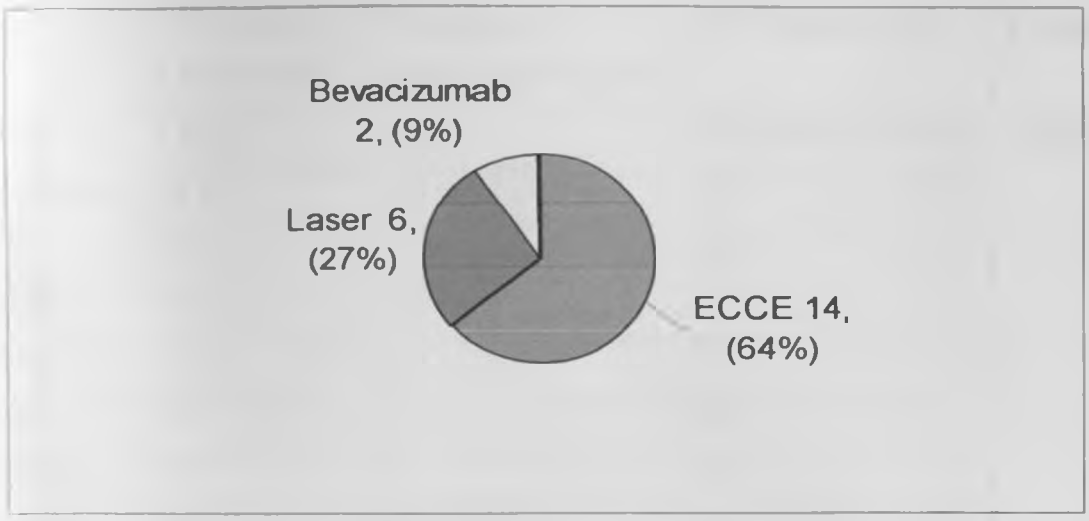
There was fairly high loss to follow-up. Mean duration of follow-up was 25.1 (SD 23.3) weeks.

Figure 5: Pre-injection procedures (n=30)



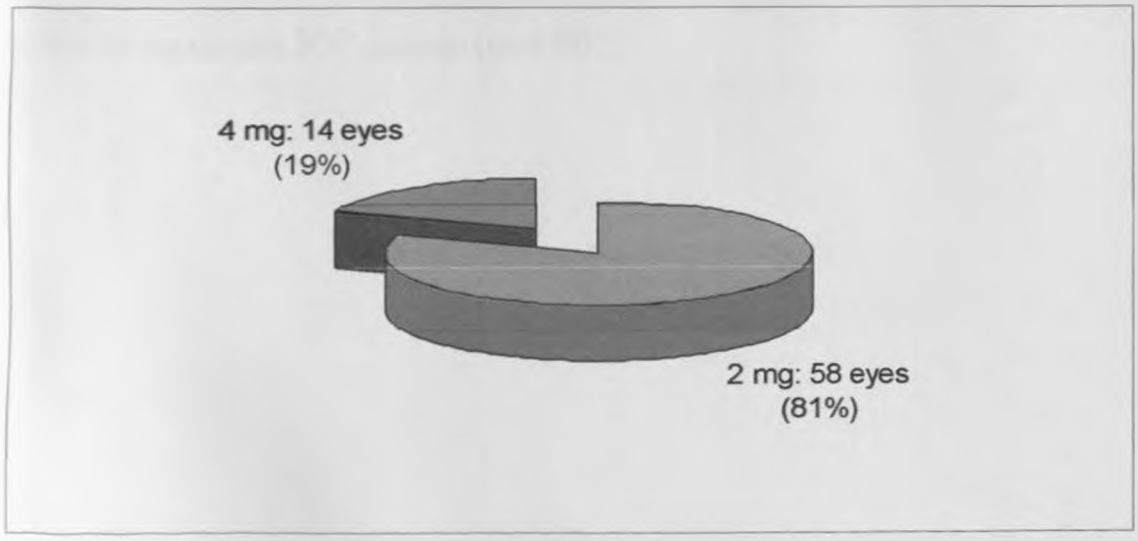
All lasers were retinal photocoagulation. Eight patients had received both oral and topical steroids for durations of more than one month within a month before the injection. All 8 were on treatment for uveitis. One patient had a pre-injection diagnosis of glaucoma but was not on treatment at the time of injection.

Figure 6: Concurrent Procedures (n=22)



Patients who underwent cataract surgery went on to receive topical steroids (prednisolone) for at least two weeks each.

Figure 7: Dosage of IVTA (n=72)



The first 14 eyes received 4mg (0.1ml) but the dose was reduced to 2mg (0.05 ml) after several episodes of central retinal artery occlusion were noted on the operating table and anterior chamber paracentesis had to be performed. Nine eyes had a repeat injection and one had three injections. All repeat injections were of 2mg.

Table 2: **Summary Statistics (IOP in mmHg)**

	Pre-injection IOP (n=72)	Maximum post-injection IOP (n=72)	IOP Change (n=72)	**P-Value**
Mean	16.0	23.8	7.8 (95% CI 5.4-10.2)	**<0.001**
SE of Mean	0.6	1.4	1.2	
SD	5.2	11.5	10.2	
Median	16	20	6	
Mode	12	20	2	
Range	35	57	52	
Minimum	10	8	-11	
Maximum	45	65	41	

Sixty-five (90.3%) of the eyes had IOP between 10 and 21 mmHg, and 7 eyes had IOP beyond 21 mmHg. No eye was on pressure-lowering agents before the injection. There was a statistically significant increase in IOP from pre-injection baseline to maximum IOP change ($p<0.001$).

Table 3: Distribution of Pre-injection IOP by sex, age and diagnosis

Factor	Pre-injection IOP(mmHg)		P-Value
	Mean (SE)	SD	
Sex			
• Male (n=41)	15.8 (0.6)	4.3	0.663
• Female (n=31)	16.3 (1.1)	6.2	
Age			
• < 60 (n=36)	16.5 (1.0)	6.2	0.404
• ≥ 60 (n=36)	15.5 (0.7)	4.0	
Diagnosis			
DMO (n=46)	15 9 (0.6)	4.2	0.865
Uveitis (n=8)	18.8 (3.9)	10.9	0.114
BRVO/CRVO (n=8)	15.6 (1.1)	3.0	0.824
Eales (n=6)	14.3 (1.2)	3.0	0.410
CMO (n=4)	15.0 (2.7)	5.3	0.690

There was no statistically significant difference in pre-injection IOP with different diagnoses, ages and sex.

Table 4: Distribution of maximum Post-injection IOP by various factors

Factor	Post-injection IOP (mmHg)		P-Value
	Mean (SE)	SD	
Sex			
• Male (n=41)	24.0 (1.8)	12.8	0.884
• Female (n=31)	23.5 (2.0)	11.2	
Age			
• < 60 (n=36)	22.8 (2.1)	12.4	0.476
• ≥ 60 (n=36)	24.8 (1.8)	10.5	
Diagnosis			
DMO (n=46)	25.0 (1.7)	11.6	0.232
Uveitis (n=8)	25.5 (6.3)	17.8	0.656
BRVO/CRVO (n=8)	19.6 (1.8)	5.2	0.281
Eales (n=6)	19.0 (3.3)	8.1	0.290
CMO (n=4)	19.8 (4.4)	8.8	0.474
Dosage			
• 2 mg (n=58)	23.7 (1.4)	10.4	0.875
• 4 mg (n=14)	24.2 (4.2)	15.6	
Pre-injection IOP			
<16mmHg (n=35)	22.6 (1.8)	10.7	0.401
≥16mmHg (n=37)	24.9(2.0)	12.2	
Repeat injection (n=9)	16.7 (2.4)	7.1	0.068
Concurrent ECCE (n=13)	27.3 (4.5)	16.3	0.223
Previous ECCE (n=7)	20.4 (2.3)	6.0	0.420
Previous steroid therapy (n=8)	25.5 (6.3)	17.8	0.656
Laser therapy (n=24)	24.9 (2.6)	12.6	0.555

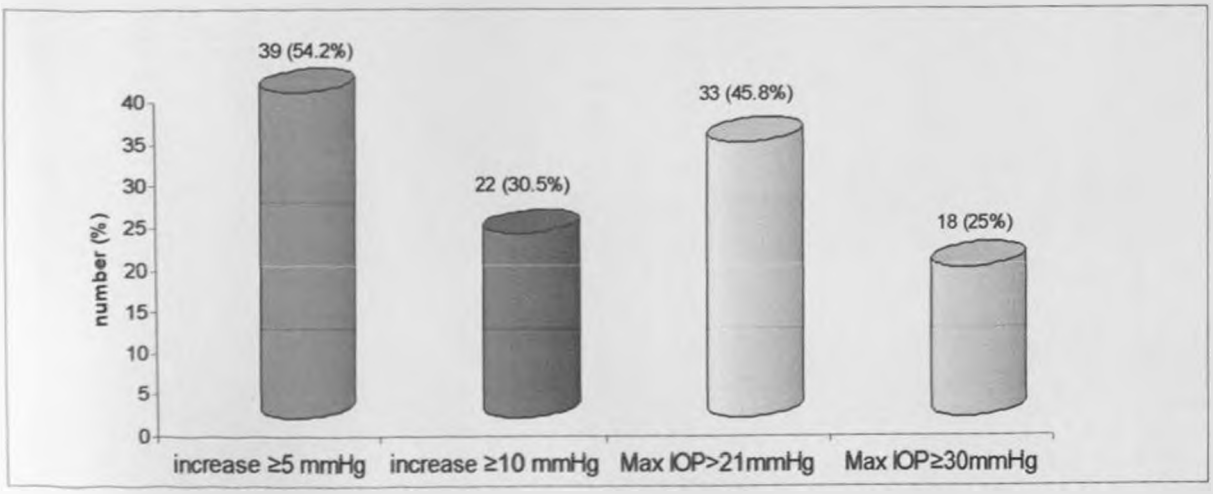
There was no statistically significant association between diagnosis, sex, age and maximum IOP. There was decrease in maximum post-op IOP after a repeat injection, though the difference was not statistically significant.

Table 5: IOP changes for eyes with pre-injection IOP >21 mmHg and IOP≤ 21 mmHg

	Mean (SE) (mmHg)	SD	95% CI of change	P value
pre-injection IOP > 21 mmHg (n=7)				
Pre-injection IOP	26.9 (3.1)	8.1	5.7-20.6	**0.005**
Post-injection IOP	40.0 (5.2)	13.8		
IOP change	**13.1(3.0)**	8.05		
pre-injection IOP ≤ 21 mmHg (n=65)				
Pre-injection IOP	14.9 (0.4)	3.1	4.6-9.3	**<0.001**
Post-injection IOP	22.0 (1.2)	9.8		
IOP change	**7.2 (1.3)**	10.3		

There was a statistically significant difference between the IOP change for eyes with pre-injection IOP>21 mmHg and those with pre-injection IOP≤ 21 mmHg ($p<0.001$).

Figure 8: Maximum IOP increase levels among all eyes (n=72)



Forty-one eyes (56.9%) had IOP increase by more than 1/3 of the baseline IOP.

Table 6: IOP increase levels per sex, age, diagnosis and dose (Pierson χ^2)

Factor/diagnosis	Post-injection IOP increase (mmHg)			
	≥ 5, %, (p-value)	≥ 10, %, (p-value)	≥1/3 of baseline, %, (p-value)	Max IOP > 21, %, (P- value)
Sex male (n=41)	58.5, (0.392)	34.1, (0.447)	58.5, (0.754)	46.3, (0.921)
female (n=31)	48.4	25.8	54.8	45.2
Age *≥ 60 (n=36)	55.6, (0.813)	30.6, (1.000)	61.1, (0.475)	47.2, (0.813)
*< 60 (n=36)	52.8	30.6	52.8	44.4
DMO (n=46)	54.3, (0.967)	34.8, (0.300)	58.7, (0.690)	45.7, (0.967)
Uveitis (n=8)	62.5, (0.616)	37.5, (0.651)	62 5, (0.736)	50.0, (0.802)
BRVO/CRVO (n=9)	55.6, (0.616)	0.00, (0.047)	55.6, (0.736)	33.3, (0.616)
Eales (n=6)	33.3, (0.285)	33.3, (0.877)	33.3, (0.222)	33.3, (0.521)
CMO (n=4)	25.0, (0.228)	25.0, (0.804)	25.0, (0.184)	50.0, (0.863)
Dosage 2mg (n=58)	53.4, (0.808)	32.8, (0.409)	56.9, (0.987)	48.3, (0.397)
4 mg (n=14)	57.1	21.4	57.1	35.7
Pre-op IOP				
≥16mmHg(n=37)	43.2, (0.06)	29.7, (0.876)	43.2, (0.016)	51.4, (0.334)
<16mmHgn=35)	65.7	31.4	71.4	40

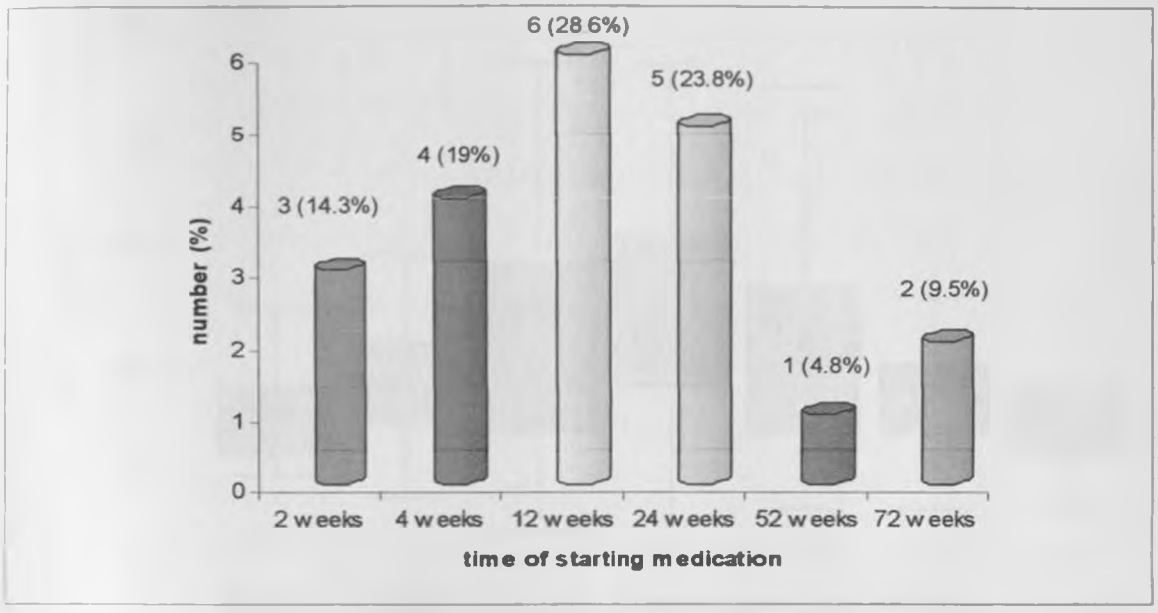
No statistically significant association was found between IOP increase and age, sex diagnosis, or dosage.

Table 7: Intervention given for increased IOP (n=22)

Intervention	Number	Percentage
Timolol alone	8	35
Timolol and acetazolamide	6	27
Timolol and prostaglandin analogue	5	23
Timolol, acetazolamide and Cyclophotocoagulation	1	5
Pars Plana Vitrectomy	1	5
Acetazolamide alone	1	5

Twenty-one eyes received pressure-lowering agents, 52.4% of which needed two drugs. One patient needed cyclophotocoagulation 18 months after the injection. Her pre-injection IOP was 12mmHg. She had been treated with timolol and acetazolamide repeatedly before the cyclophotocoagulation, with IOP of 48 mmHg, and her vision had worsened from 6/60 before injection to perception of light. One patient had PPV five months after the injection, which reduced her IOP. In all, 30.6% of injected eyes received treatment.

Figure 9: Time of starting medication (n=21)



Of the eyes needing medication 61.9% were started on medication within the first 3 months. Twelve eyes (4 eyes still on treatment) had IOP >21mmHg by the time of their last visit. Twelve eyes with IOP > 21 mmHg did not receive treatment. No eye with maximum IOP < 21mmHg received treatment even if the IOP increase was more than 5mmHg. For the eyes that received medication, the IOP rose from a mean of 19.1(SD 7.7) mmHg baseline to a mean maximum of 35.6 (SD 10.4) mmHg, and reduced to a mean of 18.1(SD 4.7) mmHg after therapy (IOP on last visit).

Figure 10: Trend of mean IOP over one year

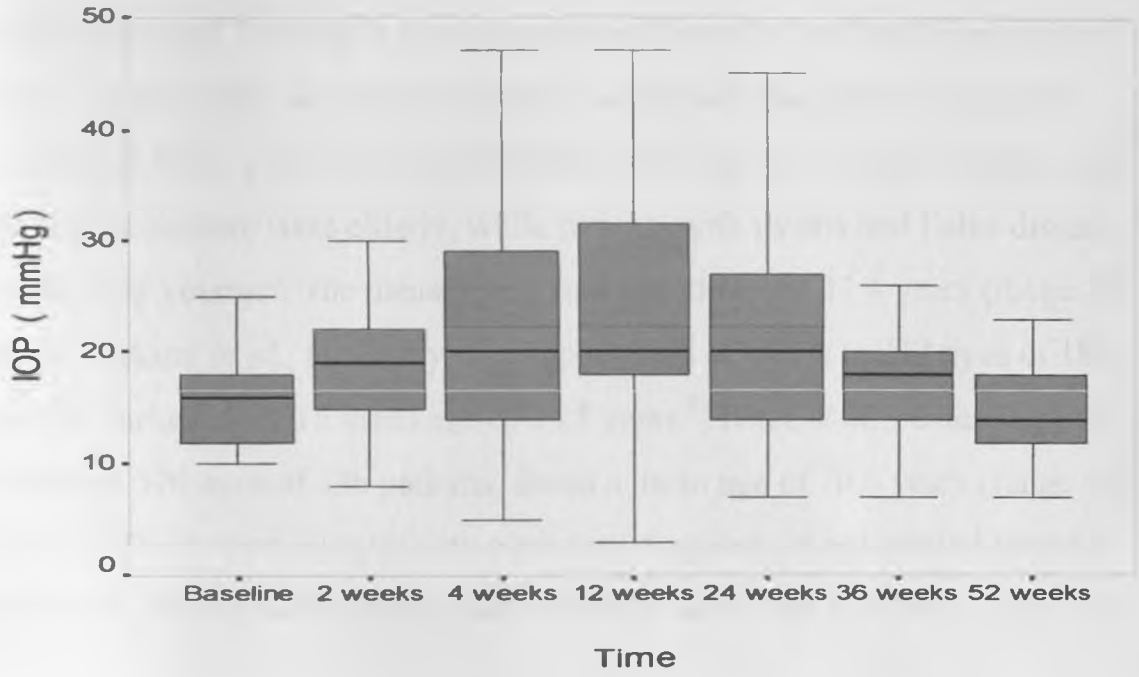


Table 8: IOP change over one year (mmHg)

Time	Mean (SD)	Median	P-value of difference from baseline
Baseline	16.0 (5.2)	16.0	
2 weeks	19.1 (6.4)	19.0	0.006
4 weeks	22.8 (12.2)	20.0	0.001
12 weeks	24.0 (11.0)	20.0	<0.001
24 weeks	22.6 (12.2)	20.0	<0.001
36 weeks	18.0 (7.3)	18.0	0.179
52 weeks	15.3 (5.7)	14.0	0.543

Intraocular pressure started increasing within two weeks of the injection. Mean IOP peaked at 12 weeks (3 months). The mean IOP started going down after 24 weeks (6 months), and at one year it was lower than at baseline. The median duration to maximum IOP was 4.6 weeks.

6 Discussion

Intraocular pressure increase is a common side effect of intravitreal triamcinolone injections. In this study we sought to find its magnitude and pattern in eyes of black patients. Most patients, especially those with diabetic macular oedema and retinal vein occlusion, were elderly, while patients with uveitis and Eales disease were relatively younger. The mean age at first injection was 57.4 years (range 21-87 years). Ozkiriz *et al.*, in a study of complications of IVTA in 212 eyes of 180 patients in Turkey, found a mean age of 54.7 years.[23] Rhee *et al.*, reviewing IOP alterations in 570 eyes of 536 patients, found a mean age of 70.6 years (range 14-95 years).[20] There were no eyes with a primary diagnosis of age-related macular degeneration; these usually receive intravitreal bevacizumab in Kikuyu Eye Unit.,

The mean duration of follow-up of 25.1 weeks (5.86 months) was comparable to that found by Rhee *et al* (5.67 months).[20]

6.1 IOP increase

The mean IOP change was 7.8mmHg. This was from a baseline mean of 16.0 (SD 5.2) mmHg (range 10-45 mmHg, median 16 mmHg) to a mean maximum post-injection IOP of 23.8 (SD 11.5) mmHg (range 8-65 mmHg). Jones *et al* found an increase from 15.43 (SD 3.26) mm Hg (range 8–28 mm Hg) to a mean maximum of 23.38 (SD 8.37) mm Hg (range 13–64 mm Hg) post injection.[21]

More than a half of all eyes (54.2%) had maximal increase of 5 mmHg and above, which also tended to be more than a third of baseline IOP (56.9%). Thirty-three eyes (45.8%) had IOP of more than 21 mmHg. This correlates with other studies using dosages of 4 or 25mg IVTA.[20, 24, 29] In the study by Rhee *et al*, 50.6% of eyes had elevations of at least 30% of their pre-injection IOPs, 45.8% had elevation of 5mmHg or more, with 14.2% having elevations of 10mmHg or more.[20] In a study

by Das-Bhaumik *et al.* where 2mg was used, lower increases were noted – only 22.2% of eyes had IOP>21 mmHg.[29]

6.2 IOP trend

IOP started increasing as early as 2 weeks, peaking in the third month, and remaining high for about 24 weeks (6 months). By the ninth month, the IOP difference from baseline was not statistically significant (p=0.179). This compares with studies by Jonas *et al.* which found that IOPs returned to baseline values approximately 8 to 9 months after injection (p=0.16).[21, 45] Oskiriz *et al.* found statistically significant IOP increase in months 1, 3 and 6, but none in month 9.[23] Since triamcinolone crystals can remain in the vitreous for even six months, its disappearance is probably related to reduction in IOP after that period.[11]

6.3 IOP increase: correlates

Unlike findings in other studies, [21, 25] no relationship was found between young age (under 60 years) and risk of IOP increase. Sex was not a factor influencing IOP change unlike in Yamamoto and associates' findings where IOP increase was associated with female sex.[25] Moreover, no relationship was found between dosage of IVTA and IOP, a finding also observed by other workers.[26, 27] No relation was found between diagnosis and IOP, which is what several other studies have shown.[20, 21, 23-25]

Previous and concurrent procedures like cataract extraction and retinal photocoagulation did not influence the change in IOP. Results of this study imply that cataract surgery can be combined with IVTA without statistically significant risk. Similarly, Jones *et al.* found cataract surgery was not associated with maximal IOP during follow-up (p=0.99) or IOP at the close of follow-up (p=0.06).[46]

Pre-injection IOP, when below 21 mmHg, was not related to post-injection IOP increase, as also noted by Rhee *et al.*[20] However, baseline IOP of 21 mmHg and above led to statistically significant increases in IOP, and all such eyes were put on pressure-lowering medication.

Treatment with topical and oral steroids did not predispose to high post-injection IOPs. Eight of these eyes had uveitis. It's probable that those eyes, already refractory to other modes of treatment, were undergoing ciliary shutdown as most of them showed reduction in IOP with time. Eyes that underwent prior and concurrent ECCE also were put on topical steroids but there was no statistically significant adverse IOP event among them either. Galor *et al.* found a correlation between uveitis and IOP increase.[22]

In this study, repeat injection was not associated with a statistically significant risk of IOP elevation, as found by Rhee *et al.*[20] Chan *et al* did not find any association between a repeat injection and IOP rise (p=0.16).[12]

6.4 Treatment

In this series, 22 eyes (30.6%) received treatment (14.3% within 2 weeks and 61.9% within 3 months). IOP generally stabilised with use of medication, though 52.4% needed two drugs to control the IOP. One patient, however, needed cyclophotocoagulation, and another had PPV. None had filtering surgery.
In Rhee's study, 23.5% of all eyes needed IOP lowering medication, 16.9% of them within the first week.[20] Five eyes (0.9%) needed filtration surgery after refractory increased IOPs beyond 2 months.

6.5 Comparability with other studies in other racial groups

Though most of our patients received 2mg IVTA, the dosage does not seem to affect IOP. Many studies have used dosages ranging from 2 to 25mg.[26-29] A study

to determine the effectiveness of 2mg IVTA in reducing macular oedema or inflammation in our setup is needed, since it has been noted that higher doses may have better visual outcomes.[26, 27] Our findings of IOP increase are fairly similar to those of studies done among Caucasians and Asians.[20, 23, 24]

6.6 Study limitations

A high loss to follow-up, as well as irregular follow-up, was noted. This was a retrospective study with a small sample size. Other limitations inherent in this study are that IOPs were single readings per clinic day, and that some eyes had been dilated prior to IOP measurement.

7 Conclusions

1. Intravitreal injection of triamcinolone acetonide was associated with IOP increase, and the pattern seems to fit that observed among other racial groups.

2. The dosage of IVTA did not affect IOP increases after injection. Neither did age, sex, diagnosis, or concurrent operations.

3. Eyes with a pre-injection IOP of >21 mmHg had statistically significant IOP increases (compared with those with IOP≤21 mmHg).

4. Intraocular pressure started increasing within 2 weeks and had stabilised by the ninth month.

8 Recommendations

1. All eyes receiving IVTA should have close monitoring of IOP preferably beginning immediately and at least from the second post-injection week. Monitoring should continue for at least six months.

2. Eyes with pre-injection IOP>21 mmHg probably could benefit from prophylactic antiglaucoma medication immediately after the injection.

3. A prospective study looking at optic disc and visual field changes will be of benefit, considering nerve changes could occur with normal IOPs (lower than 21 mmHg) due to thinner African corneas. This would also help to assess whether any of the eyes have progressed from ocular hypertension to glaucoma.

4. A study is needed to analyse the cost versus benefit, looking at improvement of macular oedema and visual acuity. The study can evaluate the effect of dosage on macular oedema, inflammation, and visual acuity. Optical coherence tomography would be useful to analyse macular thickness.

Appendix: Questionnaire

Bio data

OPD number	Sex
Age (years) at first injection	

Indication for injection

diagnosis	RE	LE
Diabetic macular oedema		
ARMD		
CRVO		
BRVO		
Uveitis		
Neovascular glaucoma		
Eale's Disease		
Other (specify)		

Pre-injection assessment

		RE	LE
VA			
IOP (pre-injection)	Dilated?		
Pre-op glaucoma?			
Current medication for glaucoma			
Prior surgery?	Nature		
	Duration before injection		
Prior use of steroids?	route		
	Duration before injection		

Injection

Eye injected (tick)	RE	LE
Dose (mg)		
Date of 1st injection		
Date of 2nd injection		
Intra-injection complications		
Remarks		

1st review

Date:		RE	LE
VA			
IOP	Dilated?		
Other abnormality			
Medication/intervention			

2nd review

Date:		RE	LE
VA			
IOP	Dilated?		
Other abnormality			
Medication/intervention			

3rd review

Date:		RE	LE
VA			
IOP	Dilated?		
Other abnormality			
Medication/intervention			

4th review

Date:		RE	LE
VA			
IOP	Dilated?		
Other abnormality			
Medication/intervention			

5th review

Date:		RE	LE
VA			
IOP	Dilated?		
Other abnormality			
Medication/intervention			

6th review

Date:		RE	LE
VA			
IOP	Dilated?		
Other abnormality			
Medication/intervention			

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