# EFFECT OF POST OPERATIVE TIMOLOL 0.5% ON THE FIRST DAY POST OPERATIVE INTRAOCULAR PRESSURE AFTER UNCOMPLICATED SMALL INCISION CATARACT SURGERY

A STUDY CARRIED OUT IN PART FULFILLMENT FOR THE DEGREE OF MASTER OF MEDICINE IN OPHTHALMOLOGY IN THE UNIVERSITY OF NAIROBI

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**Declaration**

This dissertation is my origional work and has not been presented 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**

Dedicated to my wife Sosan Haile kiros for her tremendous contribution since the inception of my career.

**Acknowledgement**

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## List of Abbreviations

**CBM** - CHRISTIAN BLIND MISSION

**CSR** - CATARACT SURGERY RATE

**ECCE** - EXTRA CAPSULAR CATARCT EXTRACTION

**HDL** - HIGH DENSITY LIPOPROTEIN

**HPMC** - HYDROXY PROPYL METHYLCELLULOSE

**ICCE** - INTRACAPSULAR CATARACT EXTRACTION

**IAPB** - INTERNATIONAL AGENCY FOR THE PREVENTION OF BLINDNESS

**IOL** - INTRAOCULAR LENS

**IOP** - INTRAOCULAR PRESSURE

**KNH** - KENYATTA NATIONAL HOSPITAL

**MAP** - MEAN ARTERIAL PRESSURE

**OR** - OPERATION ROOM

**OVD** - OPHTHALMIC VISCICOSURGICAL DEVICES

**PCEA** - PRESBYTERIAN CHURCH OF EAST AFRICA

**UON** - UNIVERSITY OF NAIROBI

**WHO** - WORLD HEALTH ORGANIZATION

## Definition of Terms

3.1 Post operative Intra ocular pressure Spike is an intraocular pressure ≥30 mmHg following surgery.[1]

3.2 Perfusion pressure: mean arterial pressure – intraocular Pressure

3.3 Experienced surgeon: a surgeon who has done more than three hundred cataract surgeries.[45]

## Abstract

**Background**:-Raised intraocular pressure is the most common postoperative complication of cataract surgery which is multi factorial .[14] In most cases it is transient and return to normal in 95.7% of non glaucomatous patients with or without treatment with in 24hours[2]

**Aim**:- To determine the effect of post operative timolol 0.5% on first day post operative intraocular pressure in uncomplicated small incision cataract surgery.

**Design**:- A double masked prospective randomized Clinical trial at Kikuyu Eye Unit.

**Methods**:-With ethical approval, patients who underwent uncomplicated small incision cataract surgery from September to October 2011 were randomly assigned in the two arms of the study.All of the measurments of the the intraocular pressure were done by the investigator with a Tonopen. The data was analysed using SPSS version 17.

**Results**: - A total of 98 patients were included in the study out of the 126 initially recruited. Two( 2%) patients in the intervention group developed post operative IOP greater or equal to 30mmHg and 4.1% in the control groups' (P= 1.00). 10.2% in the intervention and 20.4% in the control groups developed post operative high intraocular pressure (IOP > 21mmHg) (p=0.161). The mean Pre-operative intraocular pressure was 14.6mmHg (SD 4.6) and that of postoperative was found to be 15.5mmHg (SD 6.3) for all patients (p= 0.144), which showed no statistically significance difference. The mean post operative intraocular pressure in the intervention group was 15.1mmHg (SD 5.8) and in the control group 15.9mmHg (SD 6.8) and there was no statistically significant difference between the intervention and the control groups (p= 0.544).

**Conclusion**: - Post operative prophylactic Timolol 0.5% has no any effect on first day post operative intraocular pressure after uncomplicated small incision cataract surgery as compared to placebo. Uncomplicated small incision cataract surgery does not cause significant post operative intra ocular pressure spikes.

**Recommendation**: There is no need to start anyone on Timolol 0.5% post cataract surgery for preventing post operative IOP rise after uncomplicated small incision cataract surgery but further studies with larger sample sizes are recommended.

# CHAPTER ONE

# INTRODUCTION AND LITRATURE REVIEW

## 1.1. Background

Despite the progress made in surgical techniques in many countries during the last ten years, cataract (47.9%) remains the leading cause of visual impairment in all areas of the world, except for developed countries.[2]

According to World Health Organization estimate and other population based surveys, 1.2% of the entire population of Africa is blind, of which 36% caused by cataract .This translates to 6,000,000 blind in Africa with 2,000,000 blind from cataract. Despite this burden the average number of cataract operations done annually by each ophthalmologist in Africa is very low-120[3]. In Kenya, of the 300,000 people living with blindness, approximately 43% is due to cataract, with an added annual incidence of more than 14,500 new cases[4, 5] .That is why one of the basic VISION 2020 activities in Kenya is to Create and upgrade the "right to sight" eye units which will spearhead the intended increase Cataract Surgery Rate (CSR) and improvement of quality of cataract surgery[5].

The cataract surgical rate (CSR) is the number of cataract operations done per million populations each year. This output indicator is used to measure the progress of cataract services in a country or district.[6] Targets for the cataract surgical rate in order to eliminate avoidable blindness by the year 2020 vary globally from 2000-5000. By 2005, only 9 of 46 countries in Sub-Saharan Africa had a CSR greater than 500.Currently the CSR in most sub Saharan countries remains less than 500. Kenya's Cataract Surgery Rate is estimated by World Health Organization to range from 500-999[7]. The Kenyan society for the blind in 2010 reported that thousands of people becoming blind from a preventable disease cataract which costs only US$60 which is similar to the report of Lewallen et al Who estimated the cost of cataract surgery in eastern Africa to be US$40 to 60. (Lewallen et al. 2006) A study done in Kenya, Bangladesh and the Philippines revealed that cataract surgery has a positive socioeconomic implications by increasing time spent

on productive activities and reducing assistance following cataract surgery among older adults in low-income settings and has a large contribution in poverty alleviation.

Most recent studies have shown that the prevalence of cataract related blindness may be on the rise due to cataract surgery related complications which may convert some of the" curable blind" to" incurable blind"[10,11] Performing enough surgeries alone is not enough to reduce the prevalence of blindness due to cataract. The quality of the surgery should also be of such a standard that the majority of patients have no visual impairment after surgery. It is estimated that 25% of the cataract surgery performed in the developing world results in poor acuities.[12] Poor outcomes decrease demand and lower volume. Even a single bad outcome can dissuade many from undergoing cataract surgery[13].

Raised intraocular pressure is the most common postoperative complication of cataract surgery which is multi factorial[14]. In some patients it can cause worsening of preoperative vision impairment and dissatisfaction of the patient with the surgery because patients' perceptions of the benefit of surgery are related to their subjective assessment of vision[14]. Other complications include posterior capsule tear, vitreous loss, hyphema and rarely retinal detachment in approximately one half of one percent, endophthalmitis occurring in 0.03 percent while choroidal haemorrhage usually occurs in older patients who have high blood pressure or have glaucoma.

### 1.2. Post Operative Intraocular Pressure Spike

Cataract extraction is one of the most commonly performed and successful surgical procedures with raised intraocular pressure being the most commomn complication following cataract surgery[16-19]. In some cases it requires specific treatment.Commomnly it presents in the first 24 hours after surgry[20-23].

Gomez was the first to report the issue of elevated IOP one day after cataract surgery in 1950s in the history of ophthalmology[24] and later Rich, in 1968 discovered patients who had water tight closure of the incision site were having elevated IOP following cataract extraction. He reported a mean IOP elevation of 39.5mmHg 7 hours after uncomplicated ICCE.[25] Hildebrand et al also noted as many patients may experience an IOP greater than 28 mm Hg following cataract surgery with the peak most commonly occur 8 to 12 hours after surgery[10] and Thomas G bomer, reported the maximum post operative intraocular pressure occurs at 5-7 hours after phakoemulsification.[27]

Even though modern cataract surgery techniques have many advantages like rapid wound healing, fast visual recovery time, high patient satisfaction and low post operative complications, the phenomena of elevated intraocular pressure following surgery is still predominant.[1, 10] .In most cases this post operative IOP spikes is transient and return to normal in 95.7% of non glaucomatous patients with and without treatment with in 24hours[28].

A similar result was also reported by Tomoda T et al where they found an IOP in all treated and untreated patients with ocular hypertension on the first day following surgery returned to normal within three days.[29] But in some patients without glaucoma pressure can rise to high levels and leads to complications like anterior ischemic optic neuropathy and corneal oedema[30]. Hayreh noted from 13 cases that developed anterior ischemic optic neuropathy following cataract surgery, 11 of which had high post op intraocular pressure.[30] Tranos P et al also observed 4.3% of patients who had no previous glaucoma develops secondary Glaucoma following post operative IOP spikes. [28]

Radius R.et al found post operative intraocular pressure rise up to 80 mm Hg,which causes only transient visual field defects that fully resolve on normalization of IOP[31] .So the risk of permanent damage from postoperative pressure spike is likely dependent on the duration and

degree of hypertension as well as local susceptibility. The long-term clinical significance of transient IOP spike in otherwise healthy eye is not clear.[32,33]

A significant and sustained rise in intraocular pressure following cataract surgery may necessitate timely and specific management in several circumstances. If left untreated uncontrolled postoperative intraocular pressure spike results in pain, corneal oedema, glaucomatous nerve damage and anterior ischemic optic neuropathy[34,35]. The increase in IOP causes a reduction of the perfusion pressure resulting in significant compromisation of the blood supply in the optic disc, especially in eyes with a vulnerable optic nerve head circulation.[36]

### 1.3 Causes of post operative Intra Ocular pressure spikes

It is assumed that several factors affect the flow of aqueous humour through the trabecular meshwork and result in intraocular pressure elevation.

Initially limbal incision and suture may result in damage to the trabecular meshwork. Corneoscleral sutures have a greater risk for IOP rise than corneoscleral tunnels because of micro leakage from the tunnel, direct suture-related trauma, or distortion of the trabecular meshwork that results in outflowobstruction.[36, 37]

Retained viscoelastic material such as, hyaluronate retained in the eye after cataract surgery, is frequently responsible for postoperative IOP elevation. Even when it is removed from the anterior chamber at the conclusion of surgery, viscoelastic material can be sequestered in the posterior chamber or behind the lens implant. Mixtures of chondroitin and hyaluronate have been advocated to reduce the risk of this occurrence; however, even these combinations are associated with elevated IOP in certain patients. Experimental studies show that hyaluronate can cause rapid, marked outflow impairment [37, 38] This effect can safely be reversed by intracameral hyaluronidase.[37, 39, 49] so viscoelastic-related outflow obstruction can be reduced but not entirely prevented by careful and complete removal.[37]

The mechanism of viscoelastic related outflow obstruction is generally thought to involve the trabecular meshwork. However, it is possible that viscoelastic material also affects uveal outflow
or leads to the formation of capsulocortical and iridocortical seals that result in aqueous misdirection phenomena[37]. So once viscoelastic material is used during cataract surgery it is advisable to gently rock the IOL to promote release of all visible viscoelastic material from behind the lens rather than direct retrolenticular aspiration. viscoelastic material may remains in the posterior chamber, trapped between the iris, ciliary body, capsule, zonular fibres, and anterior hyaloid, as well as in the trabecular meshwork and capsular bag, leading to delayed release into the anterior chamber.[37]

In 1983, Berson et al reported that sodium hyaluronate caused a substantial decrease (55% to 60%) in the outflow of aqueous humour when injected into the anterior chamber.[37] Later Arshinoff S after studying different types of ophthalmic viscicosurgical devices (OVDs) i.e. the cohesive and dispersive OVDS, concluded if not completely removed all OVDs will cause Post cataract surgery Intraocular pressure rises. He also noted a high-viscosity OVDs are associated with a higher postoperative IOPs compared with lower-viscosity OVDs as the particles of low-viscosity OVDs are considered dispersive because they do not adhere to one another like they do in high-viscosity OVDs. [41, 42]

Release of serum protein and Iris pigment during traumatic surgery can lead to obstruction of the trabecular meshwork. [43]

Inflammation of the trabecular meshwork by the dissipated ultrasound energy is also another factor for intraocular pressure spikes after phacoemulsification[43, 44]

Surgeon's experience: A study done by Thomas G Bomer, et al revealed that the surgeon's experience is an important factor for the postoperative intraocular pressure rise. The mean pressure rise in eyes operated by experienced surgeons was about half the

pressure rise in eyes operated by beginners. This finding is not surprising, as beginners often perform intraocular surgery in a more traumatising manner than experienced surgeons. A greater trauma leads to a more pronounced release of serum proteins and iris pigment into the anterior chamber and also to a greater direct damage to the trabecular meshwork.[45]

Supine positioning: Gutave N.Alberti etal ,reported supine positioning and auto regulatory mechanisms were assumed to have the greatest effect on IOP changes. They noted a 9mmHg difference between supine positioning in the operation room and preoperative clinic IOP.[46]

Other causes of elevated Intraocular pressure after cataract surgery includes, hyphema or red blood cells, infection, ciliary block, pre-existing glaucoma, speculum usage, pupillary block, or peripheral anterior synechiae, uveitis ,inflammatory cells, expulsive haemorrhage, aqueous misdirection and epithelial in growth. Risk factors for vision loss secondary to IOP spikes includes advanced glaucomatous cupping ,patients prone to anterior ischemic optic neuropathy(AION) ,disc at risk, systemic hypertension, diabetes mellitus, dys- lipidemia ,collagen vascular disease, nocturnal hypotension, anaemia ,sleep apnoea, syndrome.[47]

**1.4 Medical Management of Post operative IOP spikes**

There is a dispute in the literature as to whether medications which reduce aqueous secretion are more effective in controlling postoperative IOP spikes or those that increase aqueous outflow. Arshinoff found that aqueous secretion inhibitors, such as alpha agonists and beta blockers, are ineffective in treating postoperative IOP spikes because they delay washout of residual viscoelastic from the eye; miotics and prostaglandin analogs increase aqueous washout, effectively lowering postoperative IOP spikes.

Conversely, Lewis RA found that prostaglandin analogs were less effective in the immediate postoperative setting because they required a more prolonged onset of action and additionally may induce anterior segment inflammation[48]. Besides possibly worsening the postoperative

anterior segment inflammation, prostaglandin analogs may cause or exacerbate cystoids macular oedema, which is a well known potential postoperative complication following uncomplicated or complicated cataract extraction. Both sides appear to have strong arguments and until a study proves which drugs definitively work the best, the choice of IOP lowering medication postoperatively is left to patient contraindications and clinician preference.

### 1.5 Surgical Management of post operative IOP spikes

Marked IOP elevation in the early postoperative period may be managed expeditiously by anterior chamber decompression which is by releasing a small amount of aqueous humour with gentle pressure on the posterior lip of a pre-existing paracentesis. A study by Hildebrand et al found that decompression is an effective way of controlling post operative IOP rise .They noted a mean decrease in IOP of 4.3mmHg immediately after decompression, though they reported a rebounce rise of IOP to high level half an hour after decompression, which has a transient effect.[11]Arshinoff recommended multiple attempts at side port drainage which is decompression hourly for three hours plus anti glaucoma treatment for two days.[4]

### 1.6 Prophylaxis of post operative IOP spikes

Since the discovery of the phenomena of post operative IOP spikes, many treatment strategies of blunting it have been proposed, including use of prophylactic intracameral cholinergic agents and anti glaucoma medication, [49,50,51,52] Todate there is no definitive recommendations regarding the type of agent or the need for their use in cataract surgery .[1] A study by Usha et al in United Kingdom revealed , that there is a wide variation in prophylaxis practice for IOP rise among ophthalmologists whereby; 20.6% surgeons indicated that their practice was based on evidence , 43.3% based it on personal

experience, and 17.6% based it on their unit policy . [53] Gross JG et al, noticed extracapsular cataract extraction with nucleus expression was associated

with higher postoperative pressure rises than cataract extraction by phacoemulsification. Hence, the effect of prophylactic, intraocular pressure lowering medication could be more pronounced in patients under going extracapsular cataract extraction. [54]

Many researchers have conducted several studies on the prophylactic effect of either preoperative or postoperative ocular hypotensive agents, such as timolol[55],brinzolamide,[56] brimonidine,[57]travoprost,[58] acetazolamide,[59] latanoprost,[60] apraclonidine,[61] dorzolamide,[62] to reduce the incidence of postoperative IOP spikes, a significant reduction in postoperative IOP has been shown with most agents including timolol , but no ocular hypotensive agent has completely prevented the postoperative rise in IOP. Interestingly a number of clinical trials studying the effect of pre and post-operative prophylaxis use of common topical agents such as timolol and apraclonidine have shown opposing results.[63-67]A study by Ermis SS and his collegues revealed a significant difference in post cataract surgery IOP among patients who had received prophylaxis anti ocular hypertensive eye drops and those who did not receive.[58]

Lai JSM et al reported that Timolol is more effective in reducing postoperative IOP than Latanoprost. All patients receiving one drop of timolol at the end of surgery had a mean decrease in IOP of 4.77 mm Hg and 2.99 mm Hg at 4 and 24 hours respectively[55], however timolol is less effective as compared to intra cameral carbachol.[68] Obstbaum SA et al reported that instillation of timolol 0.5% immediately after cataract surgery is prophylactic as well as therapeutic. The difference in IOP between the control and experimental groups was statistically significant ($p = 0.01$) .[41] However Tomoda T et al reported the mean IOP on the first day following surgery was 20.0 mm Hg in the timolol group and 20.7 mm Hg in the control group concluding that timolol, therefore, had no

effect on acute postoperative pressure elevation following ECCE and posterior chamber lens implantation.[29]

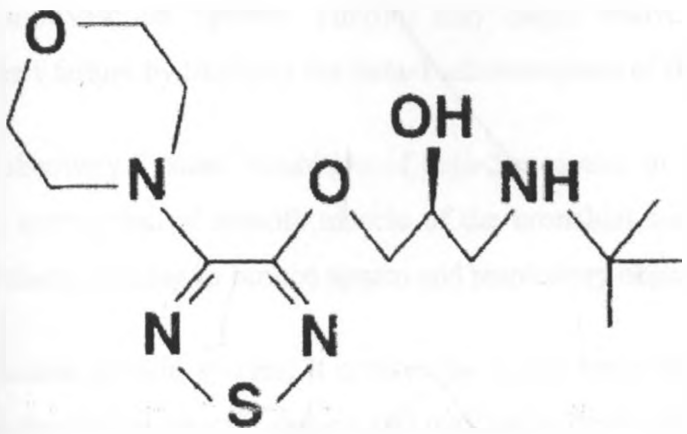
A study by Barak A, also reported that prophylactic timolol does not eliminate post operative IOP spikes and its effect is negligible compared to a placebo.[69-72] Rainer et al also compared a fixed dorzolamide-timolol combination with latanoprost. The fixed combination reduced postoperative IOP more effectively, and it prevented any increase in IOP to greater than 30 mm Hg.[73]Anothertudy comparing a dorzolamide-timolol combination to placebo found the fixed combination to produce a clinically significant reduction in postoperative IOP. But, did not completely prevent pressure spikes greater than 30 mm Hg.[74]

Hani Levkovitch-Verbin, et al reported that treatment with timolol maleate 0.5% significantly changed postoperative IOP over time in the glaucomatous eyes ($P$ =0.003), but it made no difference in the normal eyes ($P$= 0.5080). The mean IOP in the glaucoma group was reduced (from 26.7_2.9 mmHg to 17.8_1.3 mmHg) with treatment at 4 hours postoperatively, even though the IOP spike was still there[76].

## 1. 7. TIMOLOL

Timolol: Is a non cardio selective beta-adrenergic antagonist, without intrinsic sympathomimetic activity .It was the first ocular β blocker marketed; therefore, all of the newer ophthalmic β blockers are compared with timolol for safety and effectiveness.[77] .It was approved by the FDA for ocular use in 1978.

The molecular formula of timolol is Formula C13H24N4O3S and its structural formula




As a Beta-blocker, timolol competes with sympathomimetic substances for binding to receptors. Antagonism of the β2 adrenoreceptor at the cilliary epithelium of the eye is primarily responsible for the ocular hypotensive effect of timolol. It effectively lowers IOP by decreasing the production of aqueous. Some studies have shown that it has a slight effect on the facility of outflow.[78, 79] the precise mechanism of this effect is not known.

Timolol causes a mean decrease in intraocular pressure of 26 % and maximal efficacy of 0.25% and 0.5% timolol is similar.[80] the onset of action is within 30 minutes and lasts for up to 24 hours. [81]It was found to be the most effective eye drop for reducing IOP spikes among normal patients who underwent extra capsular cataract extraction.[76]

### 1.7.1. Adverse effects[80, 81, 82]

The most common ocular adverse events associated with timolol therapy include: - conjunctiva hyperaemia, burning, stinging, or superficial punctuates dermatitis. Most ocular side effects resolve after the medication is discontinued.

Systemic side effects associated with topical beta-blockers may be more serious. Topical application of beta-blockers can lead to systemic absorption through conjunctiva and lacrimal drainage system.

Cardiovascular System: Timolol may cause bradycardia, arrhythmia, and congestive heart failure by blocking the beta-1 adrenoceptors of the heart

Pulmonary System: inhibition of beta-2 receptors in the bronchi and bronchioles results in contraction of smooth muscle of the bronchial tree from unopposed parasympathetic activity, leading to bronco spasm and respiratory obstruction

Central nervous system: It crosses the blood–brain barrier and blocks serotonin receptors in the central nervous system and may cause depression, weakness, fatigue, memory loss, decreased libido and impotence.

Metabolic Problems: Topical beta-blockers may decrease plasma high density lipoprotein (HDL) levels. Several reports have demonstrated that the use of topical beta-blockers may negatively impact patients' quality of life by causing exercise intolerance, sexual dysfunction, and respiratory difficulty.

**1.7.2 Drug Interaction**

A report by Valuck et al [83] found that 30.2%–45.7% of topical beta blocker users surveyed had a concurrent prescription for one or more medications used to treat depression, congestive heart failure, or chronic obstructive pulmonary disease. Timolol like other topical beta-blockers may exacerbate all of these chronic conditions. The concomitant administration of systemic and topical beta-blockers is inadvisable because of the potential for systemic additive effects and reduced ocular hypotensive efficacy. Caution must also be used when prescribing it to patients using calcium antagonists, catecholamine-depleting drugs, digitalis, calcium antagonists, and quinidine.

**1.7.3 Preparations:** Timolol comes in ophthalmic solution of 0.25%, 0.5% as well as a gel of 0.25% and 0.5% concentration.

**1.7.4 Dosing:** The usual dose is one drop into the affected eye twice daily. Concentration or dosages exceeding one drop of timolol 0.5% Bid do not produce further significant decreases in IOP Timoptic-XE gel forming solution usually is used once daily. Mono ocular administration of timolol has resulted in equal bilateral IOP reduction.[84]

**1.7.5 Contraindications:** Although there are no human studies that have examined the effects of oral timolol on the foetus, animal studies have shown adverse effects. Therefore, the physician must weigh the potential risks to the foetus against the potential benefits to the mother

**1.7.5.1 Pregnancy:** Although there are no human studies that have examined the effects of oral timolol on the foetus, animal studies have shown adverse effects. Therefore, the physician must weigh the potential risks to the foetus against the potential benefits to the mother.

**1.7.5.2 Nursing Mother:** Concentrations of timolol in breast milk can be three times those in the mother's blood after oral administration .A breast milk sample taken One and half hours after topical administration of one drop of timolol 0.5% revealed a concentration of 5.6ng/mL. With a concomitant plasma concentration of 0.93ng/mL. It should be used cautiously in nursing mother.[77]

## CHAPTER TWO

## STUDY JUSTIFICATION

Cataract surgery is the most frequently performed ocular surgery. A rise in intra ocular pressure is one of the most common and immediate complications of cataract surgery.[11-16]

One of the common practices which have been used in preventing and treating such complications is to instil a drop of Timolol 0.5% immediately after completion of surgery while the patient is on the table.[41] So far studies done on the effectiveness of the use of Timolol have shown differing conclusions.[37-40]

Considering the fact that published research done on this region of Africa are lacking and there is no a clear consensus whether to use Timolol as prophylaxis to prevent post op IOP rise, there is an equipoise which necessitates a local trial.

# CHAPTER THREE

## OBJECTIVE

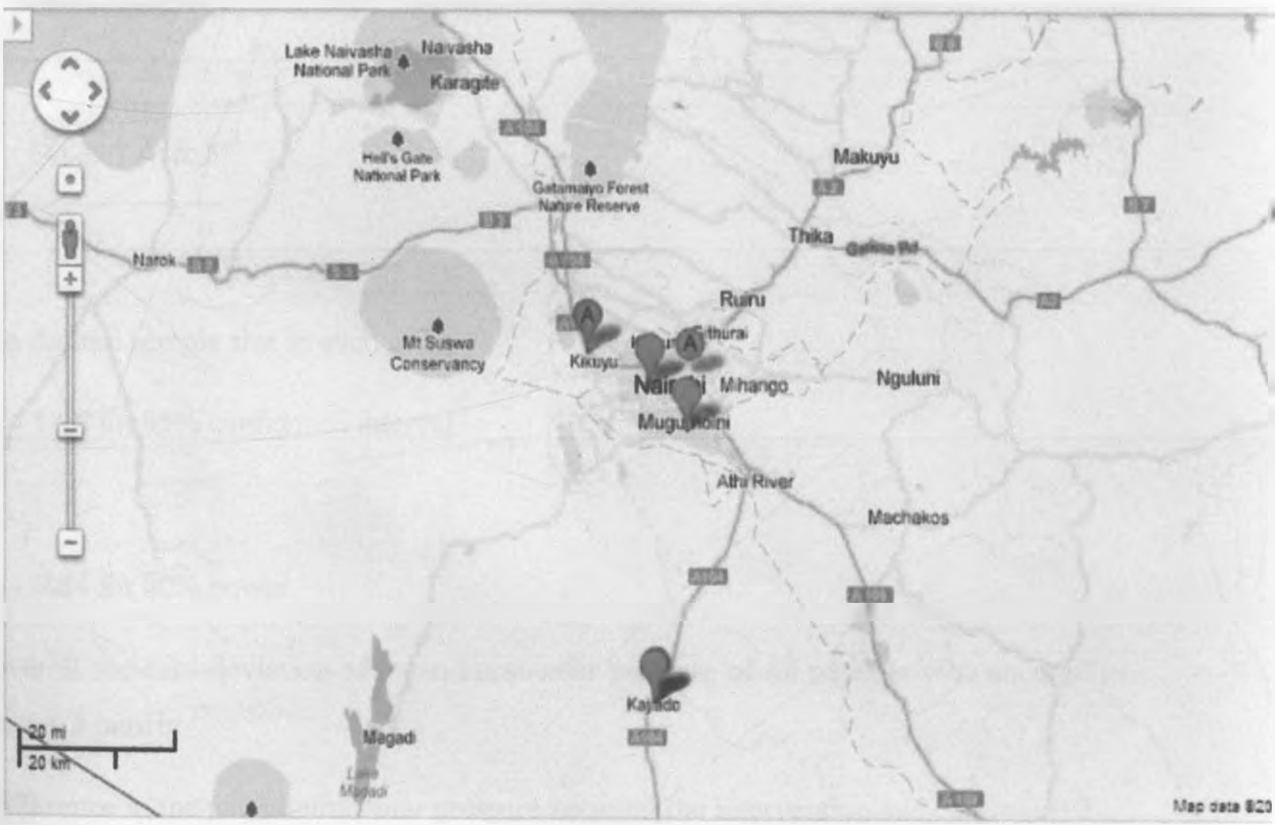
To evaluate the effect of timolol 0.5% eye drop on the first day post-operative IOP following small incision cataract surgery.

# 4. METHODOLOGY

## 4.1 Study Design

A Double Masked Prospective Randomized Clinical trial

## 4.2 Study Setting




The Kikuyu Eye Unit, located in kikuyu town (green arrow), is 20 Kilometres from Nairobi city. it was started by the Christopher Blinden Mission (CBM) in 1975. It is a referral centre for East African Region. The Kikuyu Eye Unit clinic attends up to 60,000 clients per year.[48]

referral centre for East African Region. The Kikuyu Eye Unit clinic attends up to 60,000 clients per year.[48]

### 4.3 Study Period

6th September to 4th Ocotober , 2011

### 4.4 Source Population

patients attending Kikuyu Eye Unit during the study period.

### 4.5.Sample Size Calculation

$$n = \frac{(Z_{1-\alpha/2} + Z_{1-\beta/2})\sigma^2}{\delta^2}$$

n – the desired sample size in each group

$Z_{1-\alpha/2}$ – 1.96 for 95% confidence interval

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$Z_{1-\beta/2}$ – 0.84 for 80% power

σ – overall standard deviation of mean intraocular pressure of all patients who undergo cataract = 5 mmHg [15]

δ – difference in the mean intraocular pressure between the intervention and controls = 2 mmHg

when substitued in the formula

n = 49 for each group

### 4.6 Sampling method

Patients were randomly divided into two groups: group 1 who had received a drop of Timolol 0.5% eye drop immediately after surgery(intervention group) and group 2 , the control group, who had received a drop of Artificial tear(Hypromellose 0.7%), a placebo .Every day two empty KSB bottles were prepared ,labelled and coded as "A" and "B" by the pharmacist at Kikuyu eye unit. The contents of these two bottles were not disclosed even to the investigator till the end of the study. Every day the first patient on the list received a drop from bottle "A" and the second patient a drop from bottle "B" throughout the study till the required sample size was achieved.

### 4.7 Inclusion criteria

1- Patients who underwent uncomplicated suture less cataract surgery with posterior chamber IOL implantation

2- Patients who gave a written informed consent.

### 4.8 Exclusion criteria

1- Patients with a history of glaucoma or ocular hypertension
2- Patients with a base line IOP of 22 mmHg or more
3- Active intraocular infection or inflammation,
4- Previous intraocular surgery in the index eye
5- Corneal opacity – thickened scarred corneas lead to error in IOP recording and corneal oedema will be difficult to assess

6- Corneal abnormality precluding Tonopen and patients on systemic medication which might have secondary effects on IOP, e.g. beta blockers, acetazolamide or other carbonic anhydrase
7- Patient in whom timolol is contraindicated e.g. patients who have pulmonary or cardiac problems.

**4.9 Procedure**

The small incision cataract surgery was carried out by two experienced surgeons through a 5.5mm scleral tunnel. The scleral tunnel was extended to allow an introduction of the intraocular implant (IOL). Each eye at surgery received 1ml viscous agent hydroxyl propyl methylcellulose (PMC) IP 2% w/v in a balanced salt solution to maintain anterior chamber depth and facilitate IOL implantation. The HPMC was washed out following IOL implantation. Immediately after surgery the eye was dried with dry gauze and either a drop of Timolol 0.5% on the intervention or Artificial tear (Hypermellose 0.7%) on the control group was instilled.

All measurement of the IOP was checked using a Reichert Tonopen-iPac$^{TM.}$ with acceptable standard deviation of 5% by the investigator who was unaware of the drops used. Baseline IOP was recorded one day prior to surgery. The second measurement of IOP was taken 24 hours after surgery. Every patient with high post operative intraocular pressure, i.e. IOP > 21mmHg was treated with timolol eye drops twice a day and followed up like any other post cataract surgery patients in the hospital.

**4.10 Data Analysis**

All collected data was recorded in a questionnaire, coded and entered into a computer and later analysed using statistical package (SPSS version 17). The baseline characteristics was summarised and presented as means/medians and proportions. The

difference between the two groups in terms of the baseline characteristics was determined using appropriate statistical tests. The mean and proportions of participants who developed raised IOP in the intervention and control group were compared using Student's t test. All statistical tests were performed at 5% level of significance (95% confidence interval). The results of the study were presented in forms of tables and histograms.

# CHAPTER FIVE

## 5.1 ETHICAL CONSIDERATION

Ethical approval was obtained from UON/KNH Ethics, Research and Standards Committee prior to the commencement of the study.

Permission was obtained from Kikuyu eye unit.

A written informed consent was obtained from all study participants.

All patients' records were handled confidentially and only the researcher had access to the data.

## 5.2 STUDY LIMITATION

As it is the first study in the region, getting representative sample size was difficult .A study done in Europe was used to compute sample size as there is no any comparable data in Africa. We did not analyse the post operative IOP among different ethnic groups as all patients involved in the study are black Africans .We also did not analyse the post operative IOP among different age groups as there was no statistically significant difference in the two groups preoperatively.

## 5.3 RESULTS

A total of 126 black African patients were recruited initially, 17 of them were excluded because the base line IOP was greater than 21mmHg, 6 patients who had sutured wound and 5 patients who had posterior capsular tear intra operatively were also excluded to get 98 patients who were included in the study. Females constituted 57.1% of the study participants.

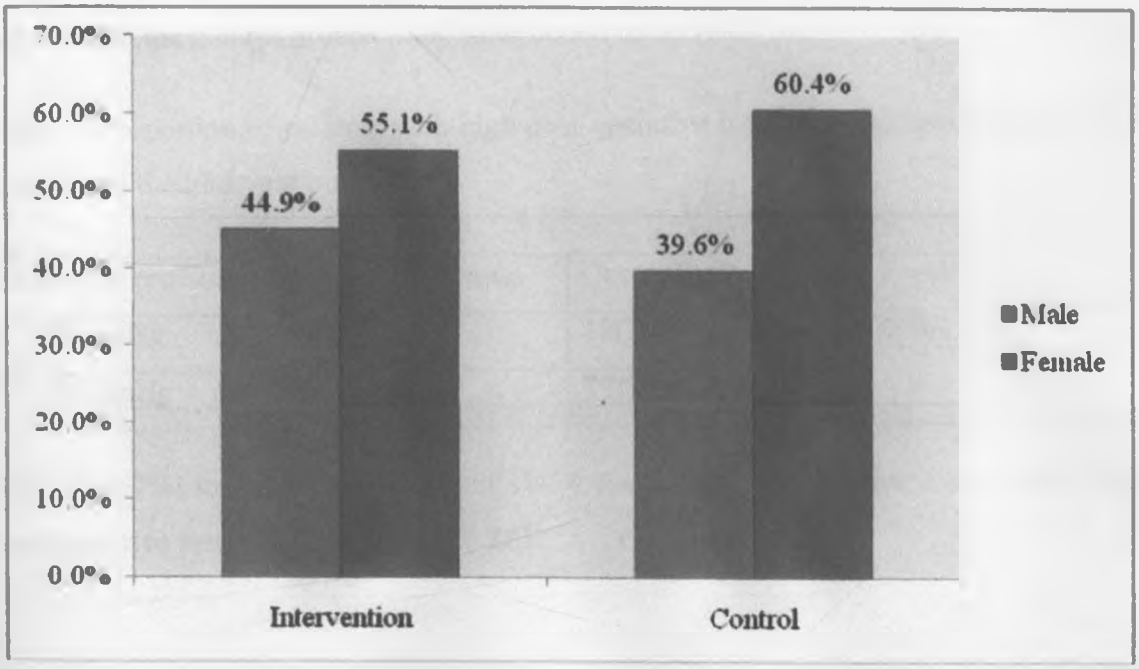
Table1: Base line Characteristics of both the intervention and control groups (n=98)

| Variable | | Intervention group | Control group | OR (95% CI) | P value |
|---|---|---|---|---|---|
| Mean Age | | 63.6(13.8) | 65.2(12.8) | - | 0.556 |
| Blood Pressure | Systolic | 134.0(26.4) | 130.6(22.20) | - | 0.493 |
| | Diastolic | 80.8(14.5) | 80.6(8.7) | - | 0.939 |
| Preoperative IOP | | 14.8(4.6) | 14.3(4.5) | - | 0.584 |
| CCT | | 522.6(25.6) | 519.6(23.9) | - | 0.585 |

Both the intervention and control groups were similar in the above base line characteristics.

The mean preoperative IOP in the intervention group was 14.8mmHg (4.6) and 14.3mmHg (4.5) in the control groups. No significant difference noted between the two groups (p, 0.584)

Figure 1. Distribution of patients by sex in the intervention and control groups.




Of all patients 42(42.9%) were male and 56(57.1%) female. Among the intervention group 22(44.9%) were males and 27(55.1%) females while in the control group20 (39.6%) and 29(60.4%) respectively, with an odds ratio 0f 1.2(0.6-2.8) and p value found to be 0.596.

Table 2.proportion of patients with post operative intraocular pressure spikes between the control and the intervention group

| **Intraocular pressure** | **Intervention group** | **Control group** | **P-value** |
|---|---|---|---|
| ≥30mmHg | 1(2%) | 2(4.1%) | 1.00 |
| < 30 mmHg | 48(98%) | 47(95.9%) | |

Only few patients developed post operative IOP spikes in groups, 2% in the intervention and 4.1% in the control groups'. P-value found to be 1.00.

Table 3. Proportion of patients with high post operative intraocular pressure between the control and the intervention group

| Intraocular pressure | Intervention group | Control group | P-value |
|---|---|---|---|
| ≥ 22mmHg | 5(10.2%) | 10(20.4%) | 0.161 |
| < 22 mmHg | 44(89.8%) | 39(79.6%) | |

Only 5(10.2%) in the intervention and 10(20.4%) in the control groups developed high post operative pressure at p-value of 0.161.

Table 4. Comparison of the mean IOP for the prevalence of high IOP and IOP spikes between the two groups.

| Post-operative IOP | Intervention group | Control group | P value |
|---|---|---|---|
| ≥22 mmHg | 25.9 (6.9) | 28.4 (4.5) | 0.478 |
| ≥30mmHg | 36.0(7.1) | 37.5 (9.1) | 0.916 |

The mean post operative high IOP in the intervention group was 25.9mmHg and 28.4mmHg in the control with a p-value of 0.478.The mean post operative IOP spike in the intervention and control were 36mmHg and 37.5mmHg (P-value 0.916).

Table 5. The mean post operative intraocular pressure comparison between the two groups (n=98)

| Variable | Intervention group | Control group | OR(95% CI) | P-Value |
|---|---|---|---|---|
| Postoperative IOP in mmHg | 15.1(5.8) | 15.9(6.8) | | 0.544 |

No significant difference in post operative intraocular pressure between the intervention and the control groups P=0.544

Table 6. Preoperative and post operative IOP comparison of all patients (n=98)

| Groups | Pre-operation | Post-operation | P value |
|---|---|---|---|
| Overall group n=98 | 14.6 (4.6) | 15.5 (6.3) | 0.144 |
| Intervention group, n=49 | 14.8 (4.6) | 15.1 (5.8) | 0.737 |
| Control group, n=49 | 14.3 (4.5) | 15.9 (6.8) | 0.109 |

No significant difference noted in the mean pre and post operative intraocular pressure of the two groups.

Table 7. Comparison of corneal oedema with post operative IOP between the two groups

| **Grades of corneal oedema** | **Post operative mean IOP in mmHg** | | **P-value** |
|---|---|---|---|
| | Intervention group | Control groups | |
| Oedematous cornea | 19.9(5.8) | 20.1(6.2) | 0.868 |
| Clear cornea | 11.4(4.2) | 12.2(4.8) | |

No significant relation noted between corneal oedema and post operative intraocular pressure between the two groups.

## 5.4 DISCUSSION

Raised intraocular pressure is one of the most common complications following cataract surgery, requiring specific treatment. In order to minimize postoperative IOP rise, prophylaxis may be adopted. Currently, there are no specific guidelines for IOP rise prophylaxis in uncomplicated cataract surgery. The exact mechanism of elevation in IOP postoperatively is not known. It is attributed to many reasons.[54 55 71] The IOP elevations are statistically more common and generally high in glaucoma patients[88].

A total of 98 black African patients with age related cataract were selected for the study based on the inclusion and exclusion. Of these 98 patients ,49 patients were then randomly assigned to each arm i.e,49 for the intervention and 49 for the placebo group . Of all patients 42(42.9%) were male and 56(57.1%) female.which is almost similar to the kenyan national male to female ratio of 1:01(2000 estimate)(Fig.1) .Among the Intervention group 22(44.9%) were males and 27(55.1%) females. And for the control group 20(39.6%) were males and 29(60.4%) females. The mean age for the intervention groups was 63.6 years and that of the control groups was 65.2years that supports our choice of patients with age related cataracts ,which are almost the same age group of patients studied by P D sharma et al[89] .(Table 1 )

The mean blood pressure in the intervention group was 134/80.8mmHg and that of the control group was 130.6/80.6mmHg which are within a normal range as hypertension is a major risk factor for Glaucoma and post operative high IOP.The mean preoperative Intraocular pressure for the intervention group was 14.8mmHg (4.6) and that of the control group was 14.3mmHg (4.5).The P-value for the mean preoperative Intraocular Pressure for the two groups was found to

Be 0.584, which shows no statistically significant difference between the two groups. The mean central corneal thickness (CCT) for the intervention group was 522.6(25.5) micrometers and that of the control group was 519.6(23.9) micrometers, which coincides with the normal CCT value for Africans (520 – 540 micrometers) which makes our IOP

measurement free from the influence of CCT,as thinner corneas underestimate IOP while thicker ones overestimate it [90,91]. Generally the two groups are similar in base line characteristics that made the two arms to be comparable (P-value >0.05 in all parameters.).(Table.1)

The mean post operative intraocular pressure in the intervention group was 15.1mmHg(5.8) and that of the controll groups found to be 15.9mmHg(6.8) with a P-value of 0.544. We noted that 2% in the intervention and 4.1% in the control groups developed post operative IOP spikes.P-value found to be 1.00(Table.2) .Five patients(10.2%) in the intervention and of ten(20.4%) in the control group developed post operative high IOP with a p-value of 0.161(Table.3). The mean post operative high IOP in the intervention group was 25.9mmHg and 28.4mmHg in the controls with a p-value of 0.478.The mean post operative IOP spike in the intervention and control groups were 36mmGh and 37.5mmHg(P-value 0.916)(Table.4).We also found no significant difference in the mean preoperative and post operative intraocular pressure between the two groups with a p-value of 0.544(Table.5 & 6).

The fact that we did not find any significant rise in IOP post surgery can be explained by the experience of the surgeons.It has been noted that the mean pressure rise in eyes operated by experienced surgeons is about half the pressure rise in eyes operated by beginners.[45] Small incision cataract surgery is also associated with low post operative IOP due to microleakage through the corneoscleral tunnel unlike extracapsular cataract extraction with nucleus expression which is associated with higher postoperative pressure rises as it was reported by Gross JG et al[53] . The absence of a limbal incision and suture also avoid possible damage to Trabecular meshwerk and tight wound closure.[45,89]

Even though Ermis SS and his collegues revealed a significant difference in post cataract surgery IOP among patients who had received prophylaxis anti ocular hypertensive eye drops and those who did not receive[58] ,in our study there was no statistical difference in the post operative intraocular pressure in the two arms which is similar to the findings by Tomoda T et al[29] as well as Hani Levkovitch-Verbin et al[76] ,

Barak A et al and[69] Ruiz RS et al[68] who found no significant difference between the intervention and controll groups. Like wise Parag A ,et al[85] and Lewis RA.[48] reported that there is no difference in post operative IOP in the controll and intervention groups.

We also found there was no significant associations between the corneal edema and post operative IOP in both arms(P=0.868).This may be due to the fact that Tonopen is the least affected by corneal edema making it preferable for post operative IOP measurment.[87]We noted 15 patients(30.6%) in the intervention and 22 patients(44.9%) in the controll group has developed corneal edema but no statistical difference between the two groups(P = 0.442).(Table .7).

## 5.5 CONCLUSION

1 - There is no significant post operative intra ocular pressure spikes noted in both groups ,i.e. mean post operative IOP in the intervention and control group was 15.1(5.8) and 15.9(6.8)mmHg respectively

2 - Intra operative prophylactic Timolol 0.5% has no any effect in first day post operative intraocular pressure after uncomplicated small incision cataract surgery as compared to placebo.

## 5.6 RECOMMENDATION

1. There is no need to start anyone on Timolol 0.5% post cataract surgery for preventing post operative IOP rise after uncomplicated small incision cataract surgery.

2. Further studies with large sample size are recommended as this is the first Randomized clinical trial in this Area in Africa.

**APPENDICES**

**APPENDIXI: QUESTIONAIRRE**

Name----------Age---------Sex----------

Place of Residence----------Date---------- Code----------

I-History

1- Do you have any known medical illness----------Yes----------No-------

2- If the answer is yes,what is the problem----------

3- Are you on treatment for any medical illness----------

4- If yes which medication are you on?----------

5- Have you ever had any eye problem----------Yes----------No----------

6- If yes, when was that ?----------And now?----------

7- Do you know the diagnosis----------Yes----------No----------

8- Have you ever gotten any treatment----------

9- If yes ,What kind of treatment ? Medication--------Surgery----------

10- What kind of medication----------

11- What kind of surgery----------

12- What was the outcome----------

## II- PHYSCICAL EXAMINATION

General appearance----------

Vital Signs: Blood Pressure----------

Temprature----------

Ocular examination

Visual Acuty RE-------LE----------

EOMM RE---------LE----------

IOP (base line) RE---------LE----------

| | **Right Eye** | **Left eye** |
|---|---|---|
| Lid | ---------- | ---------- |
| Conjuctiva | ---------- | ---------- |
| Cornea | ---------- | ---------- |

A/C---------- ----------

Iris---------- ----------

Pupil---------- ----------

Lens---------- ----------

Fundus---------- ----------

Gonioscopy---------- ----------

CCT---------- ----------

Name and signature of examiner----------date----------

Code----------

**INTRAOPERATIVE NOTES**

Name----------Age----------

Diagnosis----------

Type of Operation----------

RE / LE----------

Type of tunneling----------

Type of OVDS used----------

Any complication noted----------

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Types of eye drops used---Code=A----------Code=B----------

Date of Operation----------Time of operation----------

Name of the surgeon---- ----------date----------

First post operative day Notes Date---------- Code----------

**PHYSCICAL EXAMINATION**

General appearance----------

Vital Signs: Blood Pressure----------

Temprature----------

Ocular examination

Visual Acuty RE---------LE----------

EOMM RE---------LE----------

IOP (1st post op) RE---------LE----------

| | **Right Eye** | **Left eye** |
|---|---|---|
| Lid | ---------- | ---------- |
| Conjuctiva | ---------- | ---------- |
| Cornea | ---------- | ---------- |
| A/C | ---------- | ---------- |
| Iris | ---------- | ---------- |
| Pupil | ---------- | ---------- |
| Lens | ---------- | ---------- |
| Fundus | ---------- | ---------- |

Name and signature of examiner----------date----------

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