How does sevoflurane induction, followed by a ketamine maintenance infusion affect intraocular pressure?

Establishment of a protocol for paediatric glaucoma examinations under anaesthesia.

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Abstract

How does sevoflurane induction, followed by a ketamine maintenance infusion affect intraocular pressure?

Establishment of a protocol for paediatric glaucoma examinations under anaesthesia.

Purpose: 1.To determine the effect of sevoflurane induction, followed by intravenous (IV) ketamine infusion on intraocular pressure (IOP) in the paediatric glaucoma population. 2. To establish the earliest time point at which IOP measurement most closely resembles awake values.

Methods: A prospective, descriptive study of the IOP changes occurring in 25 children requiring IOP measurements at our institution. A standardised anaesthetic technique was employed; sevoflurane induction, intravenous cannulation, ketamine bolus (2mg/kg) and maintenance (4mg/kg/hr) for 15 minutes. IOP measurements and physiological variables were recorded after sevoflurane induction, then every 2 minutes for a period of 10 minutes, one at 15 minutes as well as 5 minutes after ketamine discontinuation.

Results: IOP was measured in 25 patients (50 eyes). Twenty-six eyes (52%) had glaucoma. The mean patient age was 29 months (range 2-88 months). The mean IOP after sevoflurane induction was 3,68mmHg lower than that with ketamine maintenance (sevoflurane eliminated) (95% CI 1,35 to 6,02mmHg) (p=0,002)).
Physiological variables return to baseline at 8 minutes, which correlates with the time taken for sevoflurane to be eliminated from exhaled gas. The difference in IOP between ketamine anaesthesia (time 15 minutes) and near wakefulness was only 0,28 mmHg (95% CI -2,23 to 2,79mmHg) (p=0,826). Mixed effects models showed similar trends but a higher baseline (7,85mmHg (6,19 to 9,51mmHg) (p<0,001)) in those with glaucoma when compared to those without.

Conclusion: Sevoflurane lowers IOP significantly when compared to ketamine anaesthesia. While eyes with glaucoma had a higher baseline than those which did not have glaucoma, both groups follow similar trends in response to the anaesthetic agents. This standardised anaesthetic protocol allows reliable IOP measurement 15 minutes after termination of sevoflurane and commencement of ketamine infusion, with no reported adverse events.

Declaration

I, Jessica Gwendoline van der Walt, hereby declare that the work on which this dissertation/thesis 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.

I empower the university to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

Signature: Dr Jessica van der Walt

Date: 20th November 2015

Format of the Dissertation

As per the UCT Faculty of Health Sciences guidelines, this dissertation is submitted in the 'publication-ready format'. It consists of four interdependent sections:

- Part A includes a brief overview and a focused research protocol
- Part B is a structured review of the extant literature relevant to the topic
- Part C contains a publication-ready manuscript describing the work, formatted for submission to the Journal of Glaucoma
- Part D includes all supplementary and supporting documentation

References are provided at the end of each section in Vancouver Style of referencing.

A detailed contents section as well as lists of tables and figures follows.

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I would like to thank the anaesthetists at Red Cross War Memorial Children's Hospital for their help in alerting us to potential patients for our study as well as their support during data capture.

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Part B: Structured Literature Review

Part C: Publication Ready Manuscript

Abbreviations

Admin: administration

ASA: Anaesthetic Society of Anaesthesiologists physical status classification system

BIS: Bispectral Index

Bpm: beats per minute

CI: confidence intervals

Cisat: cisatracurium

CO_2: carbon dioxide

Dex: dexmedetomidine

EMLA: eutectic mixture of local anaesthetics (lignocaine 2,5% and prilocaine 2,5%)

EUA: examination under anaesthesia

g: grams

GA: general anaesthesia

HR: heart rate

hr: hour

IM: intramuscular

IOP: intraocular pressure

IOPM: intraocular pressure measurements

IV: intravenous

kg: kilogram

l: litre

l/min: litres per minute

LMA: laryngeal mask airway

max: maximum

MBP: mean blood pressure

mcg: micrograms

mcg/kg: micrograms per kilogram

mcg/kg/hr: micrograms per kilogram per hour

mg: milligrams

mg/kg: milligrams per kilogram

mg/lb: milligrams per pound

midaz: midazolam

min: minutes

mmHg: millimetres mercury

mnths: months

N_2O: nitrous oxide

O_2: oxygen

$PaCO_2$: partial pressure of carbon dioxide

PK: pharmacokinetic

Premed: premedication

Remi: remifentanil

SBP: systolic blood pressure

SD: standard deviation

Sevo: sevoflurane

Std dev: standard deviation

yrs: years

Part A: Research Protocol

How does sevoflurane induction, followed by a ketamine maintenance infusion affect intraocular pressure?

Establishment of a protocol for paediatric glaucoma examinations under anaesthesia.

Dissertation for Master of Medicine in Anaesthesiology

Introduction and Overview:

Integral to the management of glaucoma is the accurate measurement of intraocular pressure (IOP). Examination under anaesthesia (EUA) is required for accurate IOP measurement in children under 3 years of age, or the uncooperative child, as awake IOP measurements are poorly tolerated.

Success rates for awake IOP measurements in cooperative, sedated patients is variable. Physiologically these measurements may be elevated in an anxious child due to elevation in central venous pressure, contraction of the extraocular muscles or an increase in the choroidal blood volume(1). Shah et al warn against measurement of IOP in awake patients even if they are cooperative, due to unintentional squeezing of the eyelids(2).

All anaesthetic agents available for sedation or EUA may influence intraocular pressure. Titration of midazolam to clinical effect (drooping of eyelids) causes a significant reduction in intraocular pressure(2). Dexmedetomidine has been shown to reduce intraocular pressure (3-5). Chloral hydrate has been shown not to influence intraocular pressure (6), and has been shown to have a 93,7% success rate for sedation in ophthalmic procedures (7) but is no longer available at our institution as it has been removed from the Essential Drug List. All volatile anaesthetic agents, including sevoflurane, have been shown to reduce intraocular pressure(8) as have the opioid class of drugs(9).

No single best anaesthetic technique has been described for these examinations under anaesthesia. Several confounding factors make the literature difficult to interpret. It is not clear whether results from a population without glaucoma can be extrapolated to those who do have glaucoma. The type of surgery that the study population is undergoing may also influence the results. There are studies reflecting the effects of ketamine induction (intramuscular) followed by sevoflurane(10), sevoflurane vs ketamine(11), ketamine alone(12) and halothane with ketamine(13)

but no studies have looked at the effects on IOP of sevoflurane induction followed by ketamine sedation.

The effect of ketamine on IOP has been widely debated. Recently is has been shown that ketamine, at doses less than 4 mg/kg, doesn't cause a clinical meaningful elevation in IOP(10). This was also suggested by Nagdeve et al (14). They found an increase in intraocular pressure when 6mg/kg of ketamine was administered but not when a lower dose was given.

Rationale and Justification

There is to date no data on the effects on IOP of a standardised anaesthetic technique for EUA using sevoflurane for induction followed by intravenous (IV) ketamine maintenance. Current anaesthetic practise at Red Cross Children's Hospital is varied, with no standardization of technique or timing of intraocular pressure measurements. Common practice is to induce anaesthesia with sevoflurane to allow placement of an IV cannula followed by ketamine to maintain anaesthesia. IV cannulation is notoriously difficult in young children and topical anaesthetic cream is not freely available and takes time to achieve good effect. Furthermore, the sympathetic stimulation caused by a difficult IV cannulation in an awake, uncooperative child may itself elevate intraocular pressure.

Al-abrak et al (15) emphasised that standardisation of all aspects of the anaesthetic is required in order to achieve reliable, repeatable results. Aileen Adams (13) said, 'It would seem wise that any individual child should always be examined under the same anaesthetic agent if truly comparable readings are to be obtained.'

We propose a standardised anaesthetic technique, evaluating changes in IOP over time validating our current clinical practice in order to obtain IOP measurements under EUA that are repeatable and closely reflect awake values.

Aims:

1. To determine the effect of sevoflurane induction, then IV ketamine maintenance infusion on intraocular pressure in paediatric glaucoma EUA.

2. To establish the time point at which IOP measurement most closely resembles awake values.

3. Establishment of a standardised anaesthetic technique for future EUAs at Red Cross War Memorial Children's Hospital.

Method:

A prospective, descriptive, observational study of the IOP changes over time in 25 children (50 eye measurements) requiring IOP measurements using a standardised anaesthetic technique.

Inclusion criteria:

ASA 1-2 children requiring EUA for IOP measurement

Age 0-3 years or unable to cooperate for awake measurements.

Day case surgery

Exclusion criteria:

Contraindication to sevoflurane / ketamine anaesthesia

Difficult airway

ASA 3-4

Standardised anaesthetic technique:

- Normal fasting guidelines: Clear fluids up to 2 hours before surgery, milk/solid food >6 hours before surgery, breastmilk >4 hours before surgery
- No premedication
- Routine intra-operative monitoring & anaesthetic record keeping
- Gas induction with Ayers T-piece, 100% oxygen @ 5 l/min and sevoflurane, gradually increased and limited to 6% until placement of intravenous cannula
- Maintenance of anaesthesia with an IV ketamine bolus: 2 mg/kg followed by an IV ketamine infusion of 4mg/kg/hr for 15 minutes using an Alaris PK syringe driver with a 20ml BD plastic syringe
- Should additional sedation be required further boluses of 1 mg/kg IV ketamine may be given
- Spontaneous ventilation should be maintained with nasal prong oxygen @ 4 l/min with and end tidal CO_2 & sevoflurane measurement.

Alternative & rescue airway management on anaesthetist's discretion

Glycopyrrolate 10 mcg/kg for excessive secretions (on anaesthetist's discretion)

Should ongoing surgery be required, the anaesthetic technique employed should be at the discretion of the attending anaesthetist.

Post-operative recovery and monitoring as per normal practice.

Intraocular pressure (IOP) measurements:

- Single operator
- IOP measurement both eyes, every time, irrespective of whether eye is diseased or normal – 10 seconds/eye
- Perkins applanation tonometer is gold standard

Data Collection and Capture:

- Preoperative demographic data recorded: age (months), weight (kg), pulse(beats per minute), blood pressure(mmHg)
- Time to intravenous cannulation and first IOP measurement
- Total sevoflurane administered (total dose, dose/kg ,dose/kg/min)
- Total ketamine administered (total dose at each measurement time interval, initial bolus, repeat boluses, total infused dose, total dose/kg)
- Heart rate and blood pressure (systolic, mean, diastolic) at each IOP measurement interval to compare with and see at which point they return to pre-operative baseline values
- Assessment intra- and post-operatively for any complications.
- Time of discharge from recovery to be noted.

IOP measurement intervals and data capture:

- Just prior to placing the intravenous cannula with only sevoflurane administered, no possible sympathetic effect of siting cannula or ketamine (Time 0)
- Two minutes after start of ketamine anaesthesia and discontinuation of sevoflurane anaesthetic.
- Every 2 minutes thereafter for 10 minutes, then at 15 minutes.
- After 15 minutes the ketamine infusion is stopped and final measurement is taken at 20 minutes.

Thus IOP measurements taken at 0, 2, 4, 6, 8,10,15,20 min
Please see Part D for Data Collection Form

Proposed Statistical Method

This is a prospective observational study and analysis will be descriptive in nature. The aim is to assess the change in intraocular pressure over time, using a standardised anaesthetic technique. In 3 previous studies, sample sizes were 8, 25 and 30 respectively. In the last study, 2 groups of 15 patients were randomised to two different anaesthetic interventions. In that study, there was no basis for a formal sample size calculation, but the investigators demonstrated significant differences in intraocular pressure at specified time points. Based upon these investigations, a sample size of up to 30 patients (60 eye evaluations) in the current observational study was regarded as likely to provide adequate statistical power. The aim is to plot the physiological variables against time, and obtain an estimate of the effects of the anaesthetic agents on intraocular pressure.

Generalised estimating equations will be used to describe changes in heart rate and blood pressure at each time point (0, 2, 4, 6, 8, 10, 15 and 20 minutes, see Methods, above) from the preoperative values. This will help us to see the effects of our drugs on these variables as well as possibly help identify a point at which our variables are not statistically different from preoperative values. During anaesthesia, the time at which heart rate and blood pressure return to pre-induction levels, will be considered an appropriate time for intraocular pressure values to reflect pre-operative values.

Comparisons will be made between all parameters using the Student's paired t-test should data be normally distributed, and the Wilcoxon signed-rank test in the event

of non-normal distribution. These tests will be used to compare heart rate and blood pressure pre-induction values to those taken when end-tidal sevoflurane concentration returns to zero. The intraocular pressure at this time point will be assumed to approximate preoperative intraocular pressure.

Research Ethics:

Risks and benefits:

Standardization of current practice for paediatric glaucoma patients requiring EUA. No additional risk factors are anticipated, patients may benefit from increased level of observation and presence of additional trained anaesthetic personnel.

Consent:

Consent for surgery and general anaesthesia shall be obtained by the ophthalmic surgeon and anaesthetist performing the procedure as per standard hospital practice. Parental information and consent will be discussed by the investigator present. Adequate time will be given for questions and consideration, written informed consent obtained, and withdrawal permitted at any time prior to induction of anaesthesia. (See Part D – Participant information and consent)

Privacy and confidentiality

Participants will be allocated a study number, indicated on data collection form. All data will be collected on this form protecting patients' privacy. Completed Patient Data Collection Form, and Consent will be securely stored in the Anaesthetic Department. Digital data (Excel spread sheet) will only record study number and will be password protected.

Amendments

On 19 June 2014 aproval was granted from the Human Resources and Ethics Committee to extend our study period beyond 6 months as well as to include children older than 36 months should they be unable to cooperate for awake measurements.

Cost and Budget

No additional time is required for performance of the study, as all data will be collected by investigators during the normal process of providing anaesthesia.

No additional costs as all disposables are used as part of normal clinical practice

Investigators

Study will be conducted at Red Cross War Memorial Children's Hospital, Departments of Anaesthesia and Ophthalmology, University of Cape Town.

Dr Francois Roodt, Specialist Anaesthetist (Principal Investigator)

Dr Jessica Gwendoline Van Der Walt (Senior Registrar and Co-investigator)

Dr Chris Tinley (Co-investigator)

No conflict of interests to declare, no sponsorship from trade.

Original accepted protocol , communication, amendments and study extension, as well as data collections and consent forms can be found in the supporting documentation in Part D.

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Part B: Structured Literature Review

Literature Search Strategy

This literature review was done using PubMed and Google Scholar. Search terms were glaucoma, intraocular pressure, paediatric, anaesthetic agents. Searches were also done using the names of specific agents. Searches were limited to human studies. Adult studies were included due to the small volume of paediatric literature available. Exclusions were animal studies and those where there was not at least an English abstract. Several studies were found from reading references from those studies produced by original searches.

Introduction

Normal intraocular pressure is 16mmHg +/- 5mmHg. It has diurnal variation of 2-3mmHg with pressures peaking in the early hours of the morning(1). In children with no intraocular pathology, intraocular pressure has been shown to be much lower than in adults. These pressures tend to increase with age, reaching normal adult values at around 12 years of age(2).

Maintaining appropriate intraocular pressure is vital as this maintains a constant corneal curvature and a constant refracting index. Intraocular pressure is considered pathological when it is elevated above 25mmHg although there has been a suggestion that since intraocular pressure is generally lower in children, even values of 17-20mmHg are far beyond the physiological limits for this population. (2)

Paediatric glaucoma is a rare condition. Children present with elevated intraocular pressure which may lead to blindness. It can be classified as primary congenital glaucoma or secondary glaucoma.

In primary congenital glaucoma the elevation in intraocular pressure is caused by obstruction to the outflow of aqueous humour resulting from a developmental abnormality of the angle formed between the peripheral cornea and the iris. Secondary glaucoma can be either congenital or acquired and can be related to ocular or systemic diseases such as Sturge-Weber Syndrome.

Accurate measurement of intraocular pressure (IOP) is central to the management of paediatric glaucoma. This is generally surgical in primary congenital glaucoma

and medical in secondary glaucoma. Some of the surgical techniques described include goniotomy in which part of the angle is excised to improve drainage or trabeculectomy to improve filtration of aqueous humour. Medical management includes the use of topical beta-blockers and topical carbonic anhydrase inhibitors (3, 4).

Objectives of Review

This review will briefly examine the physiology and pathophysiology of glaucoma, current measurement strategies, the feasibility of awake measurements and the influence of anaesthetic agents on intraocular pressure.

1. Physiology and pathophysiology of glaucoma

Intraocular pressure is determined by forces within the eye exerted outwardly through the cumulative effects of the aqueous humour volume, choroidal blood volume and the vitreous humour volume. It is also influenced by external forces that exert inward pressure on the globe, including the extraocular muscle tone, compression on the globe, as well as scleral compliance(1).

The volume of aqueous humour is determined by the volume of aqueous humour produced as well as the rate of elimination of aqueous humour from the anterior chamber of the eye. Aqueous humour is produced by the epithelial cells on the ciliary body through an active secretory process involving carbonic anhydrase. This is secreted into the posterior chamber of the globe from where it circulates into the anterior chamber. The aqueous humour leaves the anterior chamber through the trabecular meshwork in the angle between the peripheral cornea and the iris. Drainage through the trabecular meshwork is determined by Hagen-Poiseille's Law.

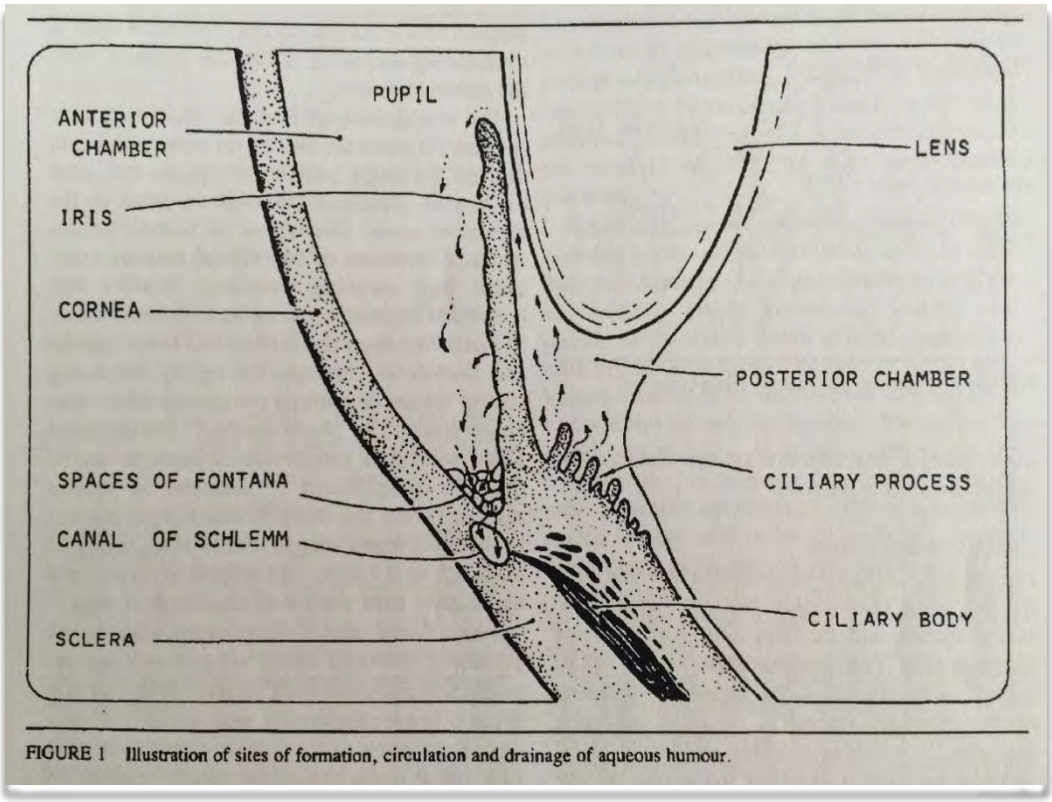

Figure A: Illustration of the sites of formation, circulation and drainage of aqueous humour

This illustration is taken from Cunningham et al's article (1), "Intraocular pressure - physiology and implications for anaesthetic management." Can Anaesth Soc J. 1986;33(2):195-208.

The choroid's blood volume is influenced by autoregulation, blood flow through the choroid will remain constant within a range of perfusion pressures (90 to 130 mmHg). Choroidal blood volume is influenced by hypercarbia, hypoxia, changes in alkalinity and temperature (1).

The tone of the extraocular muscles is controlled neurogenically by the central nervous system, which is in turn influenced by systemic hormonal as well as haemodynamic changes (1).

2. Intraocular Pressure Measurement

Intraocular pressure is measured using applanation tonometry. The principle is that the pressure within a fluid filled sphere is equal to that required to flatten part of its boundary membrane(1). The current gold standard for tonometry is the Goldmann applanation tonometer. A high degree of cooperation is required by the patient as

topical anaesthetic drops are instilled and the patient must supress the natural reflex to move back or blink during the measurement. This can lead to repeated attempts at measurement, prolonged examination times and much distress to both the young patient and their family.

A Perkins' tonometer is a handheld version of the Goldmann applanation tonometer. This is a suitable reference measure for patients in a supine position.

The iCare rebound tonometer is a new handheld device for measuring intraocular pressure. It is more accepted by the paediatric population as no topical anaesthetics are required, it uses minimal force – often not even triggering a blink reflex and takes its measurements within 0.1 seconds. However, there is poor agreement between rebound tonometer measurements and the Goldmann applanation tonometer in children with glaucoma. Rebound tonometry overestimates intraocular pressure, thus while a 'normal' intraocular pressure could be reassuring, children with elevated intraocular pressure would still require more invasive measurements or examination under anaesthesia before dramatic management decisions could be made. (5)

3. The Feasibility of Awake Measurements

One could consider taking these awake in cooperative children. However, physiologically these measurements may be elevated in an anxious child due to an elevation in central venous pressure, contraction of the extraocular muscles and an increase in the choroidal blood volume(3).

Sihota et al (2) determined awake intraocular pressures in 405 cooperative, unsedated children using a handheld Perkins applanation tonometer. Notably, their success rate was only 50-60% in the 1-3 year age group, higher in younger and older children. Some measurements were taken when children were physiologically asleep, others after ensuring ideal conditions of quietness and with the cooperation of a parent who held the child on his or her lap.

Of the 35 patients eligible to be enrolled in Oberacher-Velten et al's study (6) aged 6 months to 2 years, only 5 were able to cooperate for measurement of intraocular pressure with a Perkin's applanation tonometer without sedation. Most recently, Shah et al (15) warn against measurement of intraocular pressure in awake paediatric patients even if they are cooperative.

4. The Effect of Anaesthetic Agents on Intraocular Pressure

A thorough understanding of physiological and pharmacological influences on intraocular pressure are required to provide an anaesthetic with translatable measurements to awake pressures.

Sedation:

Chloral hydrate, one of the oldest sedatives with a well-established safety profile(7) is no longer available at our institution. In a study done by Jaafar et al (8), intraocular pressures were measured in 50 awake, cooperative children with normal eyes and 10 children with glaucoma. The measurements were then repeated after administration of chloral hydrate. No clinically or statistically significant changes in intraocular pressure were noted after chloral hydrate administration in either normal or glaucomatous eyes. A recent review of chloral hydrate sedation for paediatric ophthalmic procedures showed a 94,2% success rate for sedation after a single dose of chloral hydrate(9). Chloral hydrate has a very bitter taste often necessitating rectal administration. Also, it has a long duration of action (up to 8 hours) as well as an active metabolite, trichloroethanol, with a prolonged half-life, reducing its titratability and suitability for outpatient procedures.(6)

Midazolam is the most commonly used drug for procedural sedation in both children and adults. It is a short acting benzodiazepine which provides potent sedation, anxiolysis and amnesia. Many trials have been done confirming the safety and efficacy of this drug(7).

The effects of midazolam on intraocular pressure have been extensively debated. Older trials by Fragen et al (10) as well as Gobeaux et al(11) both found significant reductions in intraocular pressure when intravenous midazolam was given to adult patients without intraocular hypertension.

Oberacher-Velten et al (6) found no significant difference in intraocular pressure when cooperative children were sedated with oral midazolam. In adults, no statistically significant reduction in intraocular pressure was found by either Virkkila et al (12,13) with intramuscular midazolam, or Carter et al (14) with intravenous midazolam used as an anxiolytic.

These findings are in contrast to those recently published by Shah et al(15) where intraocular pressure dropped significantly after titration of midazolam to clinical

effect in awake, cooperative children. Although the average total dose of midazolam is not stated, it would seem that a higher dose of midazolam was used in this study. This study showed a significant reduction in intraocular pressure in cooperative patients after titration of midazolam to clinical effect (eyelid drooping). This has been attributed to complete loss of the squeezing action of the eyelids(15).

A summary of the above trials is documented in Table A.

Table A: Summary of Trials on the Effect of Midazolam on Intraocular Pressure

Study	Year	Population	Number of patients	Ocular pathology	Method	Timing of measurements	Results	Surgical Procedure	Additional drugs used	Topical anaesthesia	IOP assessment tool	Conclusion
Fragen (10)	1981	Adult	30	None	10 patients were induced with IV midazolam 0,15mg/kg; 10 with diazepam and 10 with thiopental	IOP measured before induction,1 and 3 minutes after induction,1 minute after administration of suxamethonium and 1 minute after intubation	Mean IOP reduced from 16,3mmHg to 9,6mmHg after induction				Perkins applanation tonometer	Midazolam reduced IOP (41%) to the same extent as diazepam and thiopentone
Gobeaux (11)	1990	Adult	30	Cataract	Sedation with 0,025mg/kg IV midazolam	IOP measured before and 3 minutes after midazolam	Mean IOP reduced from 17,1mmHg +/- 0,8 to 12,3mmHg +/- 0,7 (p<0,0001)	Cataract Surgery			Perkins applanation tonometer	Midazolam reduced IOP by 29%
Virkkila (12)	1992	Adult	90	Cataract	Premedication with alfentanil (12,5mcg/kg), midazolam (20mcg/kg) or normal saline IM (deltoid) 15 minutes prior to intraocular block	IOP measured in non-operative eye before, 15 and 30 min after premedication	No significant changes in IOP in either group	Cataract Surgery		yes	Schiotz tonometer	No significant change in IOP noted
Virkkila (13)	1994	Adult	90	Cataract	30 patients in each group given either dexmedetomidine (1mcg/kg), midazolam (20mcg/kg) or placebo IM (deltoid) 45 minutes prior to intraocular block	IOP measured in non-operative eye before premedication, 20 and 40 minutes after premedication, 15 minutes after block, after surgery, prior to discharge and 24 hours later.	No statistically significant reduction in IOP in midazolam group when compared to placebo	Day Case Cataract Surgery	Acetazolamide (90/90); Atropine (2/30 dex group); Diazepam(1/30 placebo group); Alfentanil (1/30 placebo group)	yes	Perkins applanation tonometer	Significant reduction in IOP after premed with dexmedetomidine but not with midazolam

Study	Year	Population	Number of patients	Ocular pathology	Method	Timing of measurements	Results	Surgical Procedure	Additional drugs used	Topical anaesthesia	IOP assessment tool	Conclusion
Carter(14)	1999	Adult	40	None	1mg IV midazolam or 1ml normal saline given as a premed (20 in each group)	IOP measured @ baseline, 5,10 and 15 min after admin of midaz or placebo (prior to GA)	No significant differences in IOP between the two groups (p=0,78)	Any patients requiring GA	none		Perkins applanation tonometer	No significant change in IOP noted
Oberacher -Velten(6)	2011	Children; mean age 41,7+/-16,1 months; range 15-72 months	36	Eye disorders not influencing IOP	Oral premedication midazolam (1mg/kg) prior to induction of general anaesthesia	IOP measured before, 15 and 30 min after premedication and 5 and 15 minutes after induction of general anaesthesia	IOP changes of only 0,3-0,5mmHg found under sedation; Not statistically different from baseline a@ 15 min(p=0,195) or @ 30 min(p=0,096)	Patients requiring ophthalmological surgery		0,4% oxybuprocaine	Perkins applanation tonometer	No clinically significant reduction in IOP noted after sedation with midazolam
Shah(15)	2015	Children; mean age 8,5; range 2-15 years	40	Strabismus	0,1mg/kg IV midazolam bolus followed by 0,05mg/kg midazolam every 3 minutes until spontaneous drooping of eyelids was noted(max 2,5mg/kg)	IOP measured awake and then after titration of midazolam to clinical effect. Further drugs and measurements not relevant to this dissertation were also done.	Mean IOP reduced from 19.68+/-4.97 mmHg to 14.79+/-4.31 mmHg after sedation with midazolam (p<0.01)	Strabismus surgery	Atropine 0,01mg/kg		ICare tonometer	A significant reduction in IOP was noted after midazolam administration possibly due to elimination of eyelid squeezing

The unique sedative state produced by dexmedetomidine, a highly selective alpha$_2$ agonist, makes it an attractive option for paediatric procedural sedation with minimal side effects (16).

Dexmedetomidine has clearly been shown to reduce intraocular pressure prior to or without additional general anaesthesia. This is summarized in Table B. Virkkila et al (13) and Abdalla et al's (17) studies were done in adult patients undergoing cataract surgery under regional anaesthesia. Jaakola et al (18) and Mowafi et al (19) found a reduction in intraocular pressure after infusion of dexmedetomidine before induction of general anaesthesia. They also both found that dexmedetomidine blunted the haemodynamic as well as intraocular response to endotracheal intubation. This was confirmed in Lee et al's study (20). Xu Lili et al's study (21), the only paediatric study, demonstrated no difference in intraocular pressures measured after induction with sevoflurane and again 10 minutes after a dexmedetomidine infusion, during which time the patient had received further intravenous drugs and endotracheal intubation had occurred.

Table B: Summary of Trials on the Effect of Dexmedetomidine on Intraocular Pressure

Study	Year	Population	Number of patients	Ocular pathology	Method	Timing of measurements	Results	Surgical Procedure	Additional drugs used	Topical anaesthesia	IOP assessment tool	Conclusion
Jaakola(18)	1992	Adult; age range 18-65 years	30	Cataract	0,6mcg/kg dexmedetomidine iv infusion over 1 minute to 15 patients prior to induction vs placebo	IOP measured 2 min before dexmedetomidine, 2min before induction, 1 min after induction, 1,2 and 5 min after intubation	34%(27-43%) reduction in IOP after dexmedetomidine infusion (P<0,001)	Cataract Surgery	Diazepam (30/30)90 min prior to surgery; Glycopyrronium and Fentanyl prior to induction with Thiopentone and Pancuronium	0,4% oxybuprocaine hydrochloride	Schiotz tonometer	Dexmedetomidine reduces IOP and attenuates sympathoadrenal response associated with intubation
Virkkila(13)	1994	Adult	90	Cataract	30 patients in each group given either dexmedetomidine (1mcg/kg), midazolam (20mcg/kg) or placebo im (deltoid) 45 minutes prior to intraocular block	IOP measured in non-operative eye before premedication, 20 and 40 minutes after premedication, 15 minutes after block, after surgery, prior to discharge and 24 hours later.	Statistically significant reduction in IOP found in dexmedetomidine group only - a reduction in mean IOP from 17,7mmHg to 11,5mmHg (P<0,001)	Day Case Cataract Surgery	Acetazolamide (90/90); Atropine (2/30 dex group); Diazepam(1/30 placebo group); Alfentanil (1/30 placebo group)	Yes	Perkins applanation tonometer	Significant reduction in IOP after premed with dexmedetomidine

Study	Year	Population	Number of patients	Ocular pathology	Method	Timing of measurements	Results	Surgical Procedure	Additional drugs used	Topical anaesthesia	IOP assessment tool	Conclusion
Abdallah(17)	2006	Adult	40	Cataract	20 in each group; dexmedetomidine iv infusion 0,5mcg/kg/hr for 10 minutes then 0,2mcg/kg/hr for 50 min or placebo	IOP measured in non-operated eye before infusion of dexmedetomidine and then after surgery	Statistically significant reduction in IOP in patients treated with dexmedetomidine (p<0,001)	Cataract Surgery		Proparacaine 0,5%	Schiotz tonometer	Significant reduction in IOP after dexmedetomidine infusion
Lee (20)	2007	Adult; age range 18-75 years	60	Vitreoretinal pathology	30 patients in each group randomised to receive dexmedetomidine iv infusion 2,5mcg/kg/hr for 10 minutes then 0,4mcg/kg/hr during GA or placebo	IOP measured before infusion of dexmedetomidine and then 1 minute after intubation	No significant difference in IOP between groups (p=0.567)	Vitreoretinal Surgery	Atropine; Fentanyl; Propofol; Atracurium; Isoflurane	Benoxinate HCl	Tonopen XL	No significant reduction in IOP with dexmedetomidine compared to placebo
Mowafi (19)	2008	Adult <60yrs	40	None	0,6mcg/kg dexmedetomidine iv infusion over 10 minutes to 20 patients prior to induction	IOP measured prior to premed, 10 min after premed, 30s after thiopentone, 30s after succinylcholine, after intubation then every 2 min for 6 min	A significant decrease in IOP after dexmedetomidine compared to placebo (p=0,017)	Non ophthalmic surgery	Thiopentone 5mg/kg; Fentanyl 1mcg/kg; Succinylcholine 1,5mg/kg; Rocuronium 0,6mg/kg; Sevoflurane	Oxybuprocaine hydrochloride 0,4%	Schiotz tonometer	The rise in IOP after succinylcholine and intubation can be blunted with dexmedetomidine

Study	Year	Population	Number of patients	Ocular pathology	Method	Timing of measurements	Results	Surgical Procedure	Additional drugs used	Topical anaesthesia	IOP assessment tool	Conclusion
Xu Lili(21)	2012	Children; age range 3-7 years	60	Vitreoretinal pathology	30 patients in each group received dexmedetomidine (0,5mcg/kg) iv infusion over 10 min or placebo after induction with sevoflurane	IOP measured after induction with sevoflurane and then 10 minutes after dexmedetomidine infusion	No statistically significant difference in IOP between groups (p>0,05)	Vitreoretinal Surgery	Sevoflurane 8% for induction, maintenance 1-2%; Atropine 0,01mg/kg iv; Propofol 2mg/kg iv; Remifentanil 0,5mcg/kg bolus then 0,2mcg/kg/min; Cisat 0,15mg/kg			No significant reduction in IOP from dexmedetomidine

Premedication:

Midazolam can be administered orally or intranasally. Its effects on intraocular pressure have not been conclusively determined. (See earlier notes)

Intranasal dexmedetomidine significantly reduces intraocular pressure. (See earlier notes.)

Oral, intranasal or intramuscular ketamine and anticholinergics are discussed in detail below.

General Anaesthesia:

General anaesthesia is considered for obtaining intraocular pressure measurements in uncooperative patients. This is a review of current knowledge of the influence of volatile anaesthetics, specifically sevoflurane, ketamine and other common anaesthetic adjuvants on intraocular pressure.

It has been well established that volatile anaesthetic agents significantly lower intraocular pressure. The reason for this effect is widely debated. Some suggested mechanisms are depression of the central nervous system's intraocular pressure control centres, relaxation of extraocular muscle tone, effects on the general circulation, ventilation, metabolism and the impact of agents on the balance between the production and outflow of aqueous humour(22, 23). Due to the rapid changes in intraocular pressure after sevoflurane administration, mechanisms other than the effects on aqueous production and outflow are more likely. Artru et al (24) noted a dose dependant decrease in scleral compliance with increasing concentrations of sevoflurane, the effect of which is too small to significantly influence intraocular pressure.

Much early work on the effects of volatile anaesthetic agents on intraocular pressure was done by Ausinsch et al (25). In 1975 they found that intraocular pressure measured under anaesthesia with halothane or isoflurane did not differ significantly from that taken in sedated, cooperative children. Confounding this work however, was the fact that a heavy sedation regime was used to acquire preoperative measurements, including pentobarbital with or without pethidine, which itself was likely to have reduced intraocular pressure. Those who were only sedated with chloral hydrate were uncooperative and did have significantly lower intraocular pressure after administration of volatile anaesthesia.

An overall decrease in intraocular pressure in children with glaucoma under halothane anaesthesia was found by Ausinsch et al in 1977 (26). The response of glaucomatous eyes appeared less predictable than that noted in prior studies on eyes which did not have glaucoma. Three eyes showed no change in intraocular pressure and a slight increase in intraocular pressure was found in 3 eyes. In 5 glaucomatous eyes intraocular pressure decreased below 25mmHg and in one eye below 21mmHg. It was thus noted that the finding of a normal intraocular pressure does not preclude the absence of glaucoma. Once again, the control measurements were taken under sedation with pentobarbital, meperidine and atropine.

When examining studies specific to the paediatric population, awake intraocular pressure measurements are difficult to acquire. Yoshitake et al (27) measured intraocular pressure in children receiving sevoflurane anaesthesia. He found no significant difference in intraocular pressure measured during maintenance of anaesthesia when compared to baseline. However, baseline measurements were taken just after induction and were influenced by sevoflurane. Dominguez et al (28) showed a 10% reduction in intraocular pressure in children given sevoflurane anaesthesia using a linear regression equation. Their recommendation was to read intraocular pressure when the patient is quiet, sevoflurane is almost fully eliminated and the Bispectral Index (BIS) value represents light anaesthesia.

A review by Pun et al (29) describes a series of 679 paediatric patients who received intravenous ketamine anaesthesia for ophthalmic procedures. In this series ophthalmic surgery was carried out safely without need for resuscitation or intubation.

Intramuscular injection of ketamine has been described as the simplest way to provide optimal conditions for measurement of intraocular pressure. Concerns with using this mode of administration include bioavailability, variability of uptake due to variable blood supply at the injection site as well as an inability to titrate the drug to effect. Lei Wu et al (30) found that intramuscular ketamine used for intraocular pressure measurement was strongly associated with increased odds of respiratory complications when compared to intravenous ketamine. (Odds ratio 6,78; p=0,02) It was felt that it is advantageous to be able to titrate intravenous ketamine to adequate anaesthetic depth which overall results in lower doses of ketamine being administered, on average 8mg/kg intramuscularly vs 2,75mg/kg intravenously. Also, the imprecision of intramuscular administration may result in inadvertent

administration of the drug close to a capillary bed resulting in higher than intended peak concentrations due to more rapid absorption of the drug.

The debate as to ketamine's effect on intraocular pressure has been present since the drug was first described as CI-581. The earliest studies showed that ketamine elevated intraocular pressure. Corssen et al (31) found that intraocular pressure was elevated in the paediatric population of their study (15 cases) after administration of ketamine, with a pooled mean increase in intraocular pressure of 3mmHg from control readings.

This study had several limitations. It looked at patients of various ages undergoing general anaesthesia for various types of surgery without standardization of premedications and with considerable variation in pressure readings between eyes, within participants and between participants. Also, measurements were taken 3 minutes after drug administration, inappropriate when the pharmacokinetics of ketamine are considered.

Yoshikawa et al (32) reported that ketamine elevated intraocular pressure in children. Interestingly, they managed to take awake pressure readings by 'training' their patients for three days prior to surgery to relieve their anxiety.

Adams (33) described an elevation in intraocular pressure when 10mg/kg of ketamine was administered intramuscularly to children who had initial readings taken under halothane anaesthesia. Adams (33) also noted that the changes in glaucomatous eyes were inconsistent, there was a slight rise in intraocular pressure in 2 of the 9 children with glaucoma but in the other 7 children intraocular pressure fell or remained the same. Adams (33) concluded that intraocular pressure under ketamine may be closer to awake values than that taken under inhalational anaesthesia, which is associated with muscle relaxation.

Others have found that ketamine has very little effect on intraocular pressure, particularly if patients are well premedicated. Both Peuler et al (34) and Badrinath et al (35) examined intraocular pressure in premedicated adult patients undergoing elective non-ophthalmic surgery after induction with 2mg/kg intravenous ketamine. Both found an early decrease in intraocular pressure after ketamine administration with a return to awake values as the effect of the drug diminished. The mean intraocular pressure dropped significantly in Badrinath et al's study (35) but not in Peuler et al's study (34), where changes although of a similar trend were smaller.

In a study by Ausinsch et al (36), despite 8mg/kg doses of ketamine intramuscularly, intraocular pressure under ketamine anaesthesia was found to be lower than measurements taken prior to induction. Importantly, it was felt that ketamine did not lower intraocular pressure but rather eliminated the anxiety and lack of cooperation experienced in all but three of their awake patients. In phase II of this study the patients were given a further 1mg/kg bolus of ketamine intravenously 20 minutes after the initial intramuscular ketamine bolus. This had no significant effect on the intraocular pressure compared to the values obtained at 20 minutes, confirming their hypothesis that ketamine reduced intraocular pressure through relief of anxiety rather than directly affecting intraocular pressure.

In a trial by Halstead et al (37), baseline pressures were taken after drug administration, reducing the chance of finding a change in intraocular pressure. A study published by Drayna et al (38) observed a small, not clinically significant, elevation in intraocular pressure after administration of low doses of ketamine.

Wadia et al (39) found only mild elevations in intraocular pressure with clinically significant elevations being transient. Since it has been shown that transient increases in intraocular pressure above 5mmHg in previously damaged eyes reduces ocular fundus pulsations and choroidal blood flow, it was felt that a clinically significant increase would need to be in this region. Of note, the patients who experienced higher increases in intraocular pressure were found to have lower baseline pain scores. This highlights a problem with using this population for studying the effect of ketamine on intraocular pressure, patients requiring procedural sedation are often anxious and in pain and thus any effect of ketamine could be masked by already elevated sympathetic stimulation during baseline intraocular pressure measurements. These studies have limitations which include the variety of procedures for which sedation is required, lack of control over the drugs given prior to sedation for analgesia and anxiolysis and lack of standardisation of other drugs administered.

Nagdeve et al (40) suggested that the effect of ketamine was dose dependant. They found an increase in intraocular pressure when 6mg/kg of ketamine was administered but not when a lower dose was given.

Blumberg et al (23) randomised 30 uncooperative paediatric patients with diagnosed or suspected glaucoma to undergo intraocular pressure measurement under either ketamine or sevoflurane anaesthesia. They found the mean intraocular

pressure at the first possible measurement to be significantly lower in those who received sevoflurane than that in the ketamine group. There was also a significant sustained decline in intraocular pressure at each subsequent reading in the sevoflurane group. After mathematical modelling was applied to both groups' data it was shown that the true intraocular pressure was likely to have been the same as that measured in the ketamine group. They concluded that intramuscular ketamine may provide more accurate readings of intraocular pressure than inhalational anaesthetics but that if sevoflurane is used intraocular pressure should be measured as soon as possible after induction in order to reduce the pressure lowering effects of sevoflurane on the measurements taken. As with many of the studies included here, limitations included a lack of awake measurements, a small sample size, the reliability of the readings taken using a TonoPen and that the investigators were not blinded.

Jones et al (41) retrospectively looked at the effects of ketamine and sevoflurane in the same patients. Sixteen uncooperative children with glaucoma had intraocular pressure measured under ketamine anaesthesia and then again after sevoflurane had been administered. A 28.5% reduction in intraocular pressure was found after sevoflurane administration compared with initial ketamine readings. They felt that ketamine did not have a clinically meaningful effect on intraocular pressure and may be a better surrogate for awake intraocular pressure readings than sevoflurane.

Studies evaluating the effects of sevoflurane or ketamine on intraocular pressure are summarized in Table C.

Table C: Summary of Trials on the Effect of General Anaesthetic Agents, Ketamine and Sevoflurane, on Intraocular Pressure

Study	Year	Population	Number of patients	Ocular pathology	Method	Timing of measurements	Results	Airway Manipulation	Carbon Dioxide manipulation	Surgical Procedure	Additional drugs used	Topical anaesthesia	IOP assessment tool	Number of IOP investigators	Conclusion
Corssen (31)	1967	Both; age range 6months-77yrs	46	Normal	Intravenous ketamine 1mg/lb	Control IOP measurements taken the evening prior to surgery; then 45 min after premedication , immediately after onset of anaesthesia and then 3 minutes after onset of anaesthesia	The preoperative IOP values were lower than control readings and those recorded under the influence of ketamine were higher than controls (p=0,005)			Various	Barbiturate (seconal or nembutal) or Narcotic(morphine or demerol) and an Anticholinergic(atropine or scopolamine)		Schiotz tonometer with 5,5g and 7,5g weight	1	Ketamine increases intraocular pressure
Yoshikawa (32)	1971	Children; Age Range 4-7 years	15	Normal	IM (gluteal) ketamine 5mg/kg injected to induce and maintain anaesthesia	Pre-anaesthetic readings were taken after training patients for 3 days preoperatively to reduce anxiety. IOP measured every 5 minutes for 30 minutes	IOP increased after ketamine injection to a peak pressure at 15 minutes(37% increase); (p<0,001) thereafter returning to pre-anaesthetic level by 30 minutes			IOP measurement	None	Benoxinate hydrochloride	Schiotz tonometer with 5,5g weight	1	IM Ketamine transiently increases IOP

Study	Year	Population	Number of patients	Ocular pathology	Method	Timing of measurements	Results	Airway Manipulation	Carbon Dioxide manipulation	Surgical Procedure	Additional drugs used	Topical anaesthesia	IOP assessment tool	Number of IOP investigators	Conclusion
Adams (33)	1973	Children; Age range 3 months-6 years	15	Both normal(6/15) and glaucomatous (9/15) eyes	Induction with nitrous oxide/ halothane; then ketamine 10mg/kg IM	IOP measured at the lightest plane of halothane anaesthesia when eyes were central; IOP repeated 3-6 minutes after IM ketamine	IOP rose from 11mmHg after induction to 15,5mmHg after ketamine and falling to 14mmHg after 5-8 minutes			IOP measurement			Applanation tonometry		IOP was elevated after ketamine administration relative to IOP after halothane induction
Peuler (34)	1975	Adults; aged 16-61 years	20	Normal	IV induction of anaesthesia with ketamine 2mg/kg	Control IOP measurements taken the evening prior to surgery; then after premedication , and 1,2,3,4,5 and 10 minutes after ketamine administration	After premed IOP dropped from 18mmHg to 17,3mmHg; further decrease after ketamine - lowest value @ 2 minutes (15,9mmHg) gradually rising thereafter - not statistically significant	Patent airway maintained at all times		Elective surgical procedures	Pethidine; Diazepam and Atropine (20/20)	Proparacaine hydrochloride	Schiotz tonometer with 5,5g weight	1	In clinically used doses ketamine has no effect on IOP in premedicated patients
Ausinsch (25)	1975	Children; aged 1-17 years	28	No glaucoma	Induction and maintenance of anaesthesia with halothane (13/28) or isofluran e (15/28)	IOP measured after premedication and then after induction with nitrous oxide and sevoflurane or halothane during spontaneous and controlled ventilation	Significant decrease in IOP after induction in those premedicated with chloral hydrate ($p<0,01$)	All intubated	IOP measured over a range of different $PaCO_2$ - little difference in IOP noted	Extraocular muscle procedures	Chloral hydrate(15/28)/Pethidine+/- Pentobarbital(13/28); Atropine(28/28)	0,5% Proparacaine hydrochloride	MacKay-Marg electronic applanation tonometer		IOP taken under halothane or sevo anaesthesia does not differ from that taken in sedated, cooperative paediatric patients

Study	Year	Population	Number of patients	Ocular pathology	Method	Timing of measurements	Results	Airway Manipulation	Carbon Dioxide manipulation	Surgical Procedure	Additional drugs used	Topical anaesthesia	IOP assessment tool	Number of IOP investigators	Conclusion
Ausinsch (36)	1976	Children; aged 2-10 years	10	Normal	Induction and maintenance of anaesthesia with 8mg/kg IM ketamine followed by 1mg/kg IV ketamine after 20 minutes	IOP measured prior to induction and at 5, 10, 15 and 20 minutes after administration of IM ketamine and then again 5, 10, 15 and 20 minutes after IV ketamine	Mean IOP reduced from 22,2 torr to 16,7 torr after IM ketamine ($p< 0,001$) but was significantly lower prior to induction in 3 premedicated children who were relaxed during measurement; further administration of IV ketamine did not influence IOP	All breathed room air for IM ketamine phase of trial then 5/10 intubated 5 minutes after IV ketamine and ventilated for last 10 minutes of trial		IOP measurement	Atropine(10/10) and Pentobarbital/Pethidine(5/10); d-Tubocurarine (5/10); N_2O(5/10)	Proparacaine hydrochloride 0,5%	MacKay-Marg electronic applanation tonometer		Ketamine did not significantly increase IOP
Ausinsch (26)	1977	Children aged 0,1-15 years	15 studies on 10 children	Glaucoma(22/30); Normal (7/30)	Induction and maintenance of anaesthesia with halothane in 50% N_2O	IOP measured after premedication and then 12-15 minutes after induction	In the presence of glaucoma IOP decreased by 30% but with wide variation	All intubated, spontaneous ventilation		Ophthalmological surgical procedures	Pentobarbital, Meperidine and Atropine used as premed in all patients	Proparacaine hydrochloride 0,5%	MacKay-Marg electronic applanation tonometer		IOP in children with glaucoma under halothane anaesthesia is not similar to that in healthy children

Study	Year	Population	Number of patients	Ocular pathology	Method	Timing of measurements	Results	Airway Manipulation	Carbon Dioxide manipulation	Surgical Procedure	Additional drugs used	Topical anaesthesia	IOP assessment tool	Number of IOP investigators	Conclusion
Badrinath (35)	1986	Adult; aged 15-76 years	70	Normal	Comparison of IOP changes during RSI using atracurium with various combinations of IV anaesthetics;10 patients received ketamine 2mg/kg	IOP measured before and 15s after anaesthetic induction, 90s after atracurium and 30,60 and 120s after intubation	IOP decreased significantly after induction, IOP increased during intubation and remained above pre intubation value but not above preinduction value	All intubated - RSI (vocal cords sprayed with lignocaine)		Elective non-ocular surgery	Pethidine/ Morphine/ Diazepam and Atropine/Glycopyrrolate	Proparacaine hydrochloride 0,5%	Mueller electronic tonometer with 5,5g weight	1	IV ketamine reduced IOP
Yoshitake (42) (Abstract only)	1992	Adult	40		Maintenance of anaesthesia with either sevoflurane or isoflurane 1-3% with N2O after induction of anaesthesia	IOP measured prior to induction and then 5, 10, 15, 30, 45, 60 and 120 min after intubation	40% reduction in IOP 10 minutes after intubation with both agents	Intubation	Controlled		Thiamylal (40/40); Vecuronium (40/40)				Both sevoflurane and isoflurane significantly reduce intraocular pressure

Study	Year	Population	Number of patients	Ocular pathology	Method	Timing of measurements	Results	Airway Manipulation	Carbon Dioxide manipulation	Surgical Procedure	Additional drugs used	Topical anaesthesia	IOP assessment tool	Number of IOP investigators	Conclusion
Yoshitake (27) (Abstract only)	1993	Children	20		Induction and maintenance of anaesthesia with sevoflurane	IOP measured immediately after induction and then after vecuronium administration, after intubation and then 5,10,15 and 30 min after intubation	No significant change in IOP	Intubation			Vecuronium(40/40)				No significant change in intraocular pressure noted after induction of anaesthesia; peak IOP measurements were taken 5 and 10 minutes after intubation
Schafer (43)	2002	Adult; aged over 50 years	40	Cataracts	Induction and maintenance of anaesthesia with sevoflurane (20/40) or propofol (20/40)	Serial IOP measurements at key points during anaesthetic: prior to premedication; prior to induction;1min after start of continuous remifentanil infusion;1min after induction;1 min after muscle relaxation; after intubation and before and after extubation of trachea	65% reduction in IOP from baseline with remi/propofol and 52% reduction from baseline with remi/sevo (p<0,05)	All intubated	End tidal CO2 maintained @ 4,3-4,6kPa	Cataract Surgery	Remifentanil infusion(40/40); Midazolam (40/40); Mivacurium (40/40)		Draeger hand held applanation tonometer	1	Reduction in IOP from baseline with both remifentanil/propofol and remifentanil/sevoflurane anaesthesia

Study	Year	Population	Number of patients	Ocular pathology	Method	Timing of measurements	Results	Airway Manipulation	Carbon Dioxide manipulation	Surgical Procedure	Additional drugs used	Topical anaesthesia	IOP assessment tool	Number of IOP investigators	Conclusion
Sator-Katzenschlager (44)	2002	Adult; 16 - 60 years	33	Normal	Induction with propofol 2mg/kg, fentanyl 2mcg/kg and vecuronium 0,1mg/m aintenance Group S(n=17)sevofluran e 1,5-2,5% vs Group P(n=16) propofol 4-8mg/kg/hr	IOP measured before induction, after induction, 1min after intubation, 5min after intubation, 2 min after skin incision, then every 15 min during maintenance, after skin closure, after extubation and 30 min after recovery	Significant decrease in IOP after induction and during maintenance in both groups. IOP returned to baseline 30 minutes after anaesthesia (p<0,05)	All intubated	End tidal CO2 partial pressure maintained @ 4,3-4,6kPa	Elective gynaecological or urological procedure	Midazolam (33/33)		Perkins Applanation Tonometer	1	Both sevoflurane and propofol maintain IOP at an equally reduced level

Study	Year	Population	Number of patients	Ocular pathology	Method	Timing of measurements	Results	Airway Manipulation	Carbon Dioxide manipulation	Surgical Procedure	Additional drugs used	Topical anaesthesia	IOP assessment tool	Number of IOP investigators	Conclusion
Blumberg (23)	2006	Children; Age range 1-216 months	30	Glaucoma	15 Patients induced with sevoflurane 8% in 100% O2 followed by maintenance with 2-4% sevoflurane ; 15 patients induced with 5-7mg/kg ketamine IM and 100% O2 via face mask	IOP measured asap after induction and then 2,4,6 and 8 minutes thereafter	Lower IOP @T1 in sevoflurane group - borderline statistical significance(p =0,15) ; Significant decline in IOP with each subsequent reading in sevoflurane group (p<0,01)but no significant decline in IOP in ketamine group(p=0,03)	Face mask oxygen; 1 excluded due to intubation; 3 LMA	None	IOP measurement	Midazolam (18/30); Atropine(17/30)	0,5% Proparacaine hydrochloride	TonoPen XL	2	IOP measured after ketamine sedation more likely to represent awake IOP than that after sevoflurane

Study	Year	Population	Number of patients	Ocular pathology	Method	Timing of measurements	Results	Airway Manipulation	Carbon Dioxide manipulation	Surgical Procedure	Additional drugs used	Topical anaesthesia	IOP assessment tool	Number of IOP investigators	Conclusion
Nagdeve (40)	2006	Children; aged 1-6 years	40	Normal	Induction and maintenance of anaesthesia with halothane followed 10 minutes later with IM (deltoid) injection of an induction dose (6mg/kg) or low dose (3mg/kg) ketamine (20 patients in each group)	IOP measured before ketamine administration and then every 5 minutes thereafter for 20 minutes	No significant change in IOP after administration of low dose ketamine but significantly higher IOP(2mmHg) after induction dose of ketamine administered lasting for 10 minutes, peaking @ 5minutes			Surgery lasting 30-90 minutes requiring general anaesthesia			Perkins applanation tonometer	1, blinded to ketamine dose	Ketamine had a dose dependant effect on IOP -a small increase in IOP noted after 6mg/kg ketamine administered
Dominguez (28)	2009	Children; Age range 3-10 years	30	Normal	Induction with sevo 8% in 100% O2; maintenance with sevo in 40% N2O titrated to keep BIS at or below 50	IOP measured after induction and then after procedure (Botox injection); sevoflurane was stopped and IOP was measured at 1 minute intervals until arousal	IOP correlated negatively and significantly with end tidal sevoflurane concentration with a linear regression coefficient of 0,4 ($p<0,001$) reaching maximum values just prior to arousal	Face mask and spontaneous/ assisted ventilation	End tidal CO2 partial pressure maintained @ 30-35mmHg	Botulinum toxin injection for strabismus	None	Lignocaine 4%	Perkins applanation tonometer	1	Sevoflurane affects IOP but leads to a small decrease in IOP (10% decrease @ sevo 2%)

Study	Year	Population	Number of patients	Ocular pathology	Method	Timing of measurements	Results	Airway Manipulation	Carbon Dioxide manipulation	Surgical Procedure	Additional drugs used	Topical anaesthesia	IOP assessment tool	Number of IOP investigators	Conclusion
Jones (41)	2010	Children; age range 26-89 months	8	Glaucoma	IM ketamine 5mg/kg or IV ketamine 2mg/kg to induce anaesthesia, maintenance of anaesthesia with sevoflurane 1,2% in 60% N_2O	IOP measured 3 times after ketamine induction and rechecked after sevoflurane	28,5% reduction in IOP after sevoflurane administration; Mean IOP after ketamine was 24,4mmHg, mean IOP after sevoflurane was 17mmHg, statistically lower than ketamine (p<0,001)	LMA		IOP measurement		0,5% Proxymethacaine hydrochloride	Perkins Applanation Tonometer		Sevoflurane lowers IOP significantly when compared to IOP measured under ketamine anaesthesia
Drayna (38)	2011	Children; aged 7-17 years	25	Normal	IV ketamine (mean dose 1,88mg/kg, range 0,96-4mg/kg) for procedural sedation	IOP measured before and 1, 3, 5,15 and 30 minutes after IV ketamine	Largest difference in IOP from baseline@ 15 minutes -1,09mmHg(95 % CI -0,37 to 2,55mmHg)			Procedural sedation for non-periorbital injuries	Glycopyrrolate (11/25); Ondansetron(25/25); Midazolam (19/25)	Proparacine hydrochloride	TonoPen XL	2	No clinically significant increases in IOP measured

Study	Year	Population	Number of patients	Ocular pathology	Method	Timing of measurements	Results	Airway Manipulation	Carbon Dioxide manipulation	Surgical Procedure	Additional drugs used	Topical anaesthesia	IOP assessment tool	Number of IOP investigators	Conclusion
Halstead (37)	2012	Children; aged 1-15 years	80	Normal	Procedural sedation; Mean total dose of ketamine administered was 1,6mg/kg	IOP measured asap after IV ketamine administration and then 2,5, 5 and 10 minutes after administration	Mean increase in IOP was 1,4mmHg - less than 15% increase from baseline (statistically but not clinically significant) (p<0,01)			Procedural sedation for non-periorbital injuries	Glycopyrrolate(9/80)/Ondansetron (1/80)/Midazolam(1/80); Lignocaine cream(1/80); Methylene blue(1/80)	Proparacaine hydrochloride 0,5%	TonoPen XL	Paediatric emergency medicine attending physicians	Ketamine did not significantly increase IOP

Study	Year	Population	Number of patients	Ocular pathology	Method	Timing of measurements	Results	Airway Manipulation	Carbon Dioxide manipulation	Surgical Procedure	Additional drugs used	Topical anaesthesia	IOP assessment tool	Number of IOP investigators	Conclusion
Wadia(39)	2014	Children; 8-18years	60	Normal	Procedural sedation with IV ketamine 0,5mg/kg/minute; Average total dose 1,48mg/kg (range 0,62-3,77mg/kg)	IOP measured before sedation and then after initial dose ketamine , 2 min post infusion, every 5 minutes until 30 minutes	Maximal IOP within first 5 minutes after ketamine these increases were mild (0-8mmHg, average 3mmHg) and transient	Spontaneous ventilation		Procedural sedation for non-periorbital injuries	Ondansetron(39/60); Morphine (29/60); Oxycodone (22/60); Midazolam (2/60); Fentanyl (2/60); Ibuprofen (2/60); Diphenhydramine (1/60); Ropivicaine(1/60); Diazepam (1/60); Cefazolin (1/60)	Tetracaine	TonoPen XL	Study investigators trained by ophthalmologist	Mild increase in IOP after ketamine - not clinically important

Some of the common additional drugs that are administered include glycopyrrolate or atropine, ondansetron, nitrous oxide, and opioids.

Anticholinergic agents inhibit the muscarinic cholinergic receptors. In the eye, the sphincter muscle of the iris and the ciliary body are both innervated by the parasympathetic nervous system via the oculomotor nerve. When this parasympathetic innervation is blocked, the sphincter muscle relaxes and the sympathetic innervation of the dilator papillae muscle is unopposed leading to dilatation of the pupil and potential obstruction of the drainage of aqueous humour leading to raised intraocular pressure. Fortunately, in clinically used premedication doses these effects are not seen. In a study by Cozanitis neither glycopyrrolate nor atropine in clinically used doses were shown to increase intraocular pressure in healthy adult eyes.(45)

Ondansetron, an antiemetic, has been shown not to increase intraocular pressure in adult patients requiring cataract surgery under general anaesthesia.(46)

In 1985 Murphy (47) noted that the effect of nitrous oxide on intraocular pressure had received little attention despite its widespread use in anaesthetic techniques and its use in several of the studies documented above. This opinion still holds true. Besides its elevation of intraocular pressure when intravitreal gas is injected, little else is noted on nitrous oxide's effect on intraocular pressure.

Murphy (47) also concluded that intramuscular morphine reduces intraocular pressure in both those with and those without glaucoma. While it has been established that opioids would blunt a sympathetic surge to intubation which may increase intraocular pressure(48) as well as blunt sympathetic stimulation as a result of its analgesic properties, some studies have found intraocular opioid receptors which can directly reduce intraocular pressure. In rabbits, intraocular injection of morphine resulted in an acute reduction in intraocular pressure – an effect which was prevented when conjunctival naloxone was administered. Also, it has been found that conjunctival instillation of morphine in patients with chronic closed angle glaucoma reduces their intraocular pressure(49). Studies on fentanyl and alfentanil show significant reductions in intraocular pressure(50)

The variability of the anaesthetic technique between these studies challenge interpretation. This was highlighted by Al-Abrak et al (51) when they studied the effect of halothane on intraocular pressure. They highlighted standardisation of all

aspects of the anaesthetic in order to achieve reliable results. This included the avoidance of premedications and depolarizing muscle relaxants, maintenance of constant intrathoracic pressure and central venous pressure through ventilator settings, a constant inspired oxygen concentration, maintenance of arterial pressure and supine positioning.

It is well established that airway manipulation particularly endotracheal intubation influences intraocular pressure(52). Whether or not a premedication is given, the dose given and the timing of the dose in relation to measurements can also influence outcomes. Position of patient (53) and whether ventilation is controlled could also influence intraocular pressure (53, 54). Lastly, outcomes of studies can be influenced by the technique used for measurement of intraocular pressure – the gold standard instrument would be a Goldman tonometer, this requires a sitting position and is thus unsuitable for use in theatre. The technical experience of the person taking measurements as well as the number of investigators measuring pressures and whether they are blinded to the anaesthetic technique could influence the outcome.

Deficits in current literature

No single study evaluated the use of sevoflurane induction followed by intravenous ketamine infusion. The literature highlights the need for a standardised anaesthetic technique which includes guidelines on anaesthetic agents to be used, additional drugs to be given, the timing of intraocular pressure measurements, position of patient as well as guidelines for airway manipulation and ventilation control.

It would appear that there are several confounding factors that make the literature difficult to interpret and the variability of the anaesthetic technique between the studies will also challenge interpretation.

Few studies have looked at the particular population in which these findings are significant – those too young to cooperate with awake readings. Also, it is not clear whether results from a population without glaucoma can be extrapolated to those who do have glaucoma. The type of surgery that the study population is undergoing may influence results as well. For instance, patients in an emergency department requiring procedural sedation may have high levels of sympathetic stimulation due to recent injury which could influence the awake readings.

Particularly with regard to paediatric data we are often unable to obtain awake intraocular pressure measurements, precisely why an examination under anaesthesia is indicated. Recently, the trials where awake paediatric pressures have been taken have used older children, not the population which we need to study. Some older studies took awake pressure readings, Corssen et al (31) omitted awake readings if the child was uncooperative, Yoshikawa et al (32) obtained readings after training patients prior to data collection and Ausinsch et al (25, 26, 36) used a heavy premedication regime, which may have interfered with intraocular pressure, in order to obtain awake measurements. Most trials simply took baseline intraocular pressure readings as soon as possible after induction of anaesthesia. While this may have impacted on the outcome of some trials, Adams (33) found that intraocular pressure increased after administration of ketamine but baseline pressures were measured under halothane anaesthesia. Other trials have attempted to eliminate this impact. Dominguez et al (28) repeated pressure measurements at 1 minute intervals until arousal and suggested measuring intraocular pressure just prior to arousal when Bispectral Index (BIS) indicates light anaesthesia. The interpretation of BIS in a paediatric context is not discussed here. In Blumberg et al's trial (23) best fit regression lines for actual data were extrapolated backward in time to before induction.

Contributions of this study

Aileen Adams (33) said, 'It would seem wise that any individual child should always be examined under the same anaesthetic agent if truly comparable readings are to be obtained'. We share goals in common with other authors on this subject. Dominguez et al (28) hoped to establish a general anaesthetic standard that would allow for repeated determinations of intraocular pressure in a quiet child. They felt that such a protocol should be safe and reliable, and use drugs with little or no effect on intraocular pressure or at least with known effect on intraocular pressure.

We aim to standardize the anaesthetic technique for intraocular pressure measurements in children with glaucoma presenting for examinations under anaesthesia at Red Cross War Memorial Children's Hospital, to validate our clinical practice and determine the optimal timing for intraocular pressure measurement.

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Part C: Publication Ready Manuscript

How does sevoflurane induction, followed by a ketamine maintenance infusion affect intraocular pressure?

Establishment of a protocol for paediatric glaucoma examinations under anaesthesia.

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Abstract

How does sevoflurane induction, followed by a ketamine maintenance infusion affect intraocular pressure?

Establishment of a protocol for paediatric glaucoma examinations under anaesthesia.

Purpose: 1.To determine the effect of sevoflurane induction, followed by intravenous (IV) ketamine infusion on intraocular pressure (IOP) in the paediatric glaucoma population. 2. To establish the earliest time point at which IOP measurement most closely resembles awake values.

Methods: A prospective, descriptive study of the IOP changes occurring in 25 children requiring IOP measurements at our institution. A standardised anaesthetic technique was employed; sevoflurane induction, intravenous cannulation, ketamine bolus (2mg/kg) and maintenance (4mg/kg/hr) for 15 minutes. IOP measurements and physiological variables were recorded after sevoflurane induction, then every 2 minutes for a period of 10 minutes, one at 15 minutes as well as 5 minutes after ketamine discontinuation.

Results: IOP was measured in 25 patients (50 eyes). Twenty-six eyes (52%) had glaucoma. The mean patient age was 29 months (range 2-88 months). The mean IOP after sevoflurane induction was 3,68mmHg lower than that with ketamine maintenance (sevoflurane eliminated) (95% CI 1,35 to 6,02mmHg) (p=0,002)).

Physiological variables return to baseline at 8 minutes, which correlates with the time taken for sevoflurane to be eliminated from exhaled gas. The difference in IOP between ketamine anaesthesia (time 15 minutes) and near wakefulness was only 0,28 mmHg (95% CI -2,23 to 2,79mmHg) (p=0,826). Mixed effects models showed similar trends but a higher baseline (7,85mmHg (6,19 to 9,51mmHg) (p<0,001)) in those with glaucoma when compared to those without.

Conclusion: Sevoflurane lowers IOP significantly when compared to ketamine anaesthesia. While eyes with glaucoma had a higher baseline than those which did not have glaucoma, both groups followed similar trends in response to the anaesthetic agents. This standardised anaesthetic protocol allows reliable IOP measurement 15 minutes after termination of sevoflurane and commencement of ketamine infusion, with no reported adverse events.

Key Words: Intraocular Pressure, Paediatric, Glaucoma, Sevoflurane, Ketamine

Introduction

Accurate measurement of intraocular pressure (IOP) is central to the management of paediatric glaucoma. Despite newer rebound technology techniques, many young children are uncooperative when attempting awake IOP measurements. Squeezing of the eyelids as well as sympathetic surges from anxiety falsely raise intraocular pressure (1). Thus, young patients often require examination under anaesthesia (EUA) or sedation in order to obtain reliable readings.

Most general anaesthetic agents appear to reduce intraocular pressure. These changes may be due to indirect mechanisms, reduction of arterial pressure, improved venous drainage and/or alteration of arterial blood chemistry (1). Anaesthetic agents can also interfere with central nervous system control of intraocular pressure (2). More directly, anaesthetic agents can facilitate the production or drainage of aqueous humour or cause contraction or relaxation of the extraocular and orbicularis oculi muscles (2). Opioid receptors present within the eye influence intraocular pressure (3). In addition, practical aspects of anaesthesia such as endotracheal intubation and patient position can alter intraocular pressure (4).

Sevoflurane progressively reduces intraocular pressure with prolonged duration of administration and increasing alveolar concentration (5). Reduction of intraocular pressure has also been seen with intravenous maintenance of anaesthesia using propofol (6). The effect of ketamine on intraocular pressure appears to be controversial. Early trials indicated that ketamine elevated intraocular pressure (7-9). These trials were criticised for measuring baseline pressures after drug administration and using larger doses of ketamine than usually used in clinical practice. Recent trials conclude that intraocular pressure measurements under ketamine anaesthesia are more likely to represent awake values than those measured under other forms of anaesthesia (10-13).

At our institution, a quaternary paediatric hospital, the standard of care is an inhalational induction with sevoflurane, followed by intravenous cannulation. Intravenous cannulation can be challenging in young children, topical anaesthetic cream is not freely available and requires time to achieve good effect. Furthermore, the sympathetic stimulation caused by a difficult IV cannulation in an awake,

uncooperative child may itself elevate intraocular pressure. Even under the ideal conditions created by anaesthesia IV cannulation can be difficult. An ideal sedative for ophthalmic examinations, chloral hydrate (14), is not available at our institution. Concerns regarding midazolam sedation and intramuscular or oral ketamine are: the variability of systemic absorption, inability to titrate to clinical effect and the delay in onset of clinical effect. Prior to this study there was no standardised anaesthetic technique for glaucoma EUA's and IOP measurement times were random at best.

The primary aim of this prospective, observational study was to standardise the anaesthetic technique for the measurement of intraocular pressure, in order to obtain consistent effects with serial investigations. The second aim was to establish the earliest time at which measurements could be made, that most closely reflect awake values. No other studies that the authors are currently aware of, have looked at the effects on intraocular pressure with the sequential use of sevoflurane induction followed by intravenous ketamine.

Method

The study was approved by the Human Research Ethics Committee (HREC ref 459/2015). The study was conducted in accordance with the Declaration of Helsinki. Written informed consent was taken from each child's parents or caregivers prior to commencement of the anaesthetic.

Inclusion criteria were ASA 1-2 children under 36 months of age or those unable to cooperate for awake measurements, who required intraocular pressure measurement under anaesthesia. Exclusions included ASA 3 or 4 patients, patients with cardiac comorbidities, known difficult airways or any patient with a contraindication to the drugs used in the protocol.

A standardised anaesthetic technique was introduced, with normal fasting guidelines and no premedication given. Pre-operative demographic data was recorded, including age (months), weight (kg), heart rate (beats per minute) and blood pressure (mmHg). Each patient's ocular pathology was noted as well as any previous ophthalmic surgery that they had undergone. Anaesthesia was performed with two anaesthetists present, routine intraoperative monitoring and anaesthetic record keeping.

A graded inhalational induction was performed, with sevoflurane increased to 6% in 100% oxygen. This was done with a carefully applied facemask, avoiding pressure

on the eyes, and an Ayre's T-piece. Parents were present at induction. Once adequate depth of anaesthesia had been reached, assessed by the central position of patient's eyes, an initial intraocular pressure measurement was obtained in each eye after instillation of lignocaine local anaesthetic eye drops. All readings were taken by a single ophthalmologist using a Perkins applanation tonometer. Blood pressure, heart rate, end-tidal carbon dioxide concentration and sevoflurane were recorded at each measurement.

Intravenous access was obtained, followed by a 2mg/kg bolus of ketamine and maintenance of a 4mg/kg/hr ketamine infusion (Alaris PK (CareFusion, South Africa) syringe driver by means of a 20ml BD plastic syringe (BD Medical-Pharmaceutical Systems, South Africa)). Sevoflurane was discontinued at the time of the initial ketamine bolus (time 0). Intraocular pressure and other vitals were then recorded every 2 minutes up until 10 minutes (times 2,4,6,8 and 10 minutes). Another measurement was taken at 15 minutes, at which point the ketamine infusion was discontinued and a final measurement was taken at 20 minutes, or earlier if the patient showed signs of emergence.

Spontaneous ventilation was maintained throughout the procedure and supplementary oxygen supplied via nasal prongs, with end-tidal carbon dioxide and sevoflurane analysis.

The administration of additional drugs or need for rescue airway management was documented. Where additional sedation was required an intravenous bolus of 1 mg/kg ketamine was delivered. In the presence of excessive secretions, 10mcg/kg intravenous glycopyrrolate was administered at the anaesthetist's discretion.

Post-operative recovery and monitoring was performed according to the normal theatre recovery protocol and clinical practice. Recovery time and complications were documented.

Statistical Methods: A sample size of up to 30 patients (60 eye evaluations) in this prospective observational study was regarded as likely to provide adequate statistical power, based on similar studies in literature. Data was captured in Microsoft Excel® and analysed using Statistica® (version 12.5). Normally distributed demographic data was reported as mean, range and standard deviation. Categorical data was reported as counts and proportions.

Generalized estimating equations described changes in IOP, heart rate and blood pressure and end tidal sevoflurane. Paired Student's t-test was used if data was

normally distributed and a p-value of <0.05 was considered significant, as well as a Wilcoxon signed-rank test in the event of non-normal distribution.

Results

Demographics

Data of 25 discrete examinations (50 eyes) was collected over a 25 month period from December 2013 to January 2015. Twenty-two patients were enrolled in the study. Three children required repeat examinations 5, 16 and 18 months apart. During this time 50 patients were scheduled for EUA, with 14% (7/50) not arriving and another 10% (5/50) cancelled on the day of surgery (Figure 1).

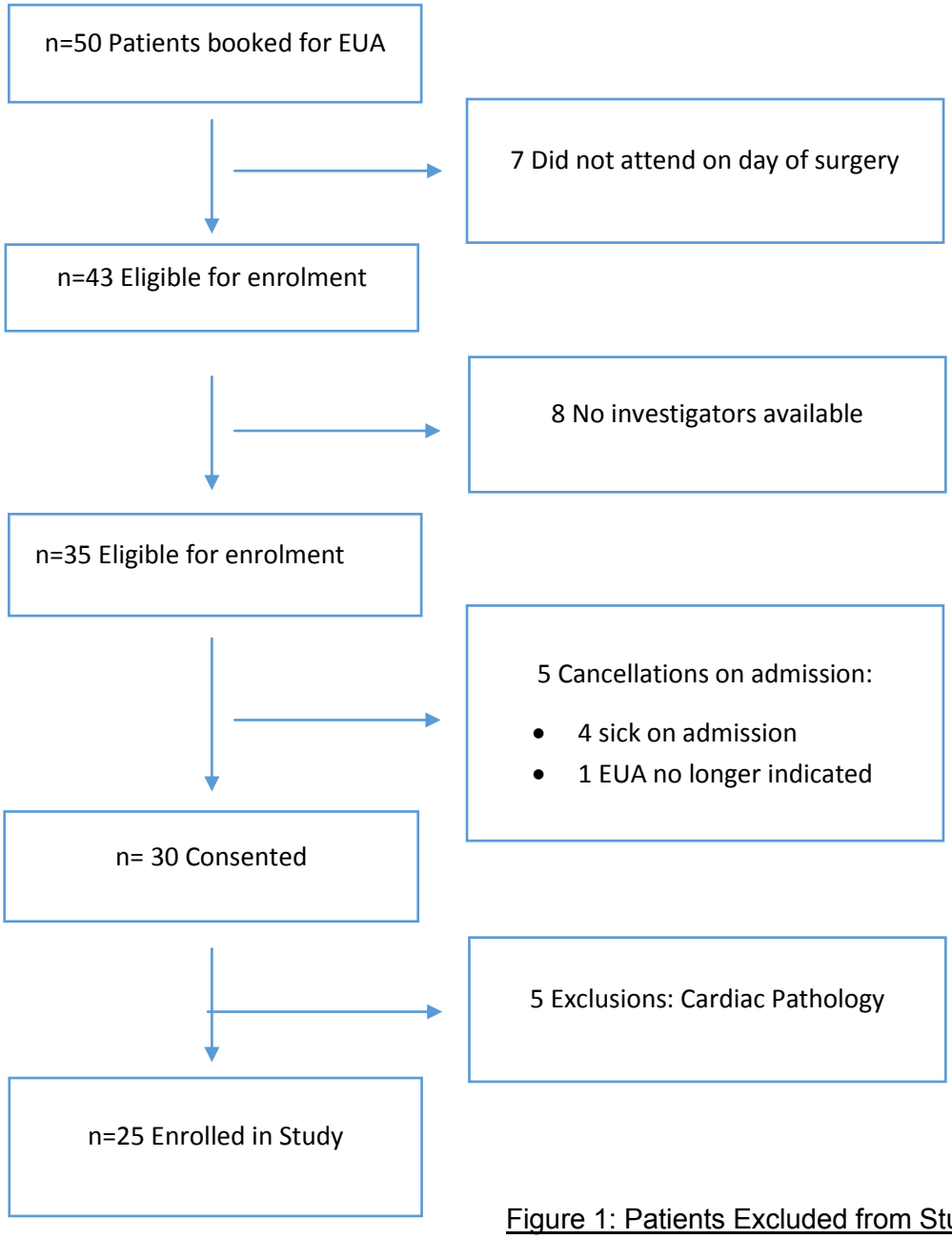

Figure 1: Patients Excluded from Study

Combination of data from left and right eyes was avoided as the physiological influences of one patient may have impacted on both eyes' pressures.

Table 1: Demographics of children included in study (n=25)

Characteristics	Count	SD	Range
Male: Female	14:11		
Age (months)	29	±20	2-88
Weight (kg)	12	±4	5,8-21,5

Table 2: Presenting Pathology

	Both eyes	Right eye	Left eye	Neither eye	Total
Glaucoma	9	6	2	8	25
Glaucoma Surgery	6	3	3	13	25
Cataract Surgery	11			14	25

Table 3: Anaesthetic characteristics

Characteristics	Count	SD	Range
Time to 1st IOPM (s)	319	±110	150-525
Time to achieve IV access(s)	192	±93	50-432
Time to sevo washout(s)	420	±120	240-600

Legend: IOPM: Intraocular pressure measurement; IV: Intravenous; Sevo: Sevoflurane

The average time to achieve adequate depth of anaesthesia and first IOP measurement was 6 minutes. Fourteen patients (56%) received low dose ketamine (<4mg/kg) and 2 patients (8%) had a total ketamine dose > 6mg/kg. With the exception of one child, all additional ketamine boluses were required after 8 minutes (2 patients prior to 10 minute measurements, 5 patients (20%) after 10 minute measurements, and a further 2 patients at 15 minutes).

A single patient required glycopyrrolate and airway intervention for increased secretions due to a recent upper respiratory tract infection.

Physiological Variables

Physiological variables, heart rate (HR), systolic blood pressure(SBP) and mean blood pressure (MBP) were plotted along with intraocular pressure.(Figure 2) Blood pressure tends to drop after induction with sevoflurane (time 0) from preoperative values and then returns to preoperative levels 6 minutes after the sevoflurane has been discontinued. Similarly, heart rate increases after induction, and returns to preoperative values at 6 minutes. Heart rate values were not statistically different from preoperative values at 8 minutes (p=0,165). Similarly for systolic and mean blood pressure no statistical difference from preoperative pressures were found at 8 minutes (p_{SBP}=0,109 & p_{MBP}=0,079 respectively).

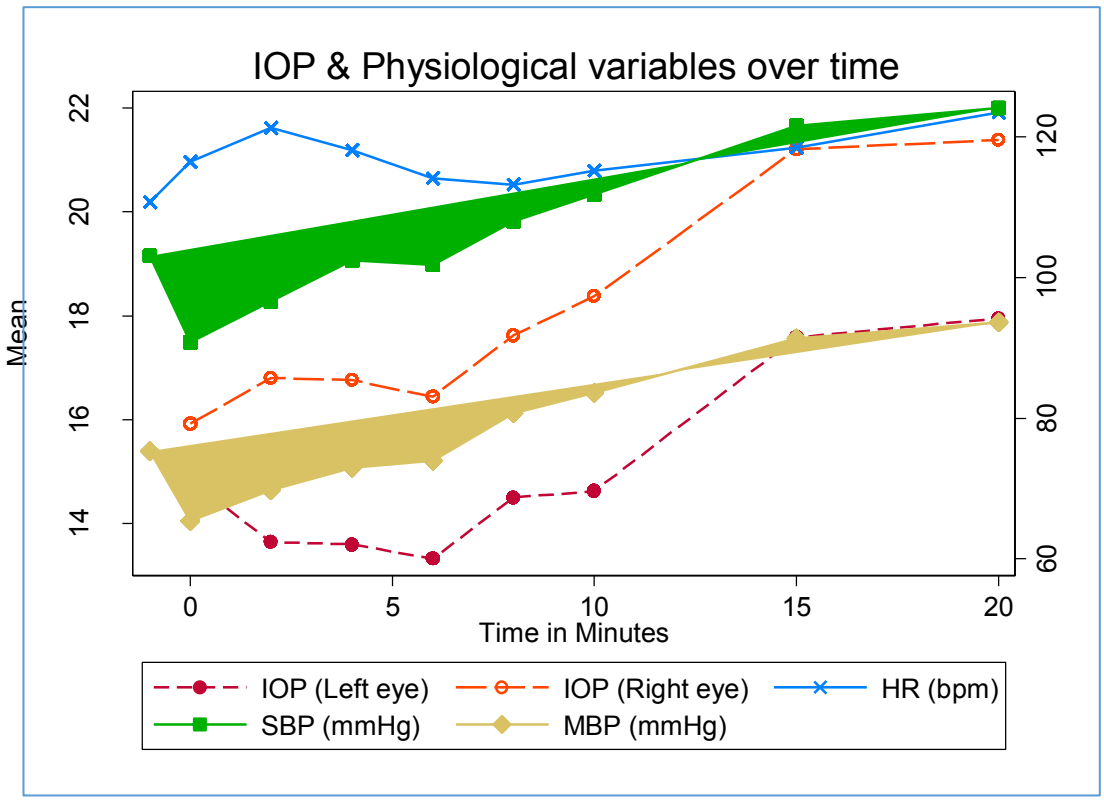

Figure 2: Physiological Variables and IOP over Time

End-tidal CO_2 measurement with nasal cannula was achieved in 92% (23/25) of patients with a reading greater than 2 kPa. Sixty-eight percent (17/25) of patients consistently maintained an end-tidal CO_2 >4 kPa throughout the 20 minute observation period. No statistically significant difference was found between preoperative physiological values and sevoflurane 'washout time' (7 ± 2 minutes). (Students' paired t tests (p_{HR}=0,2362; p_{SBP}=0,0793; p_{MBP}=1,0) (Wilcoxon – Rank tests p_{HR}=0,2402; p_{SBP}=0,1027; p_{MBP}=0,8527)).

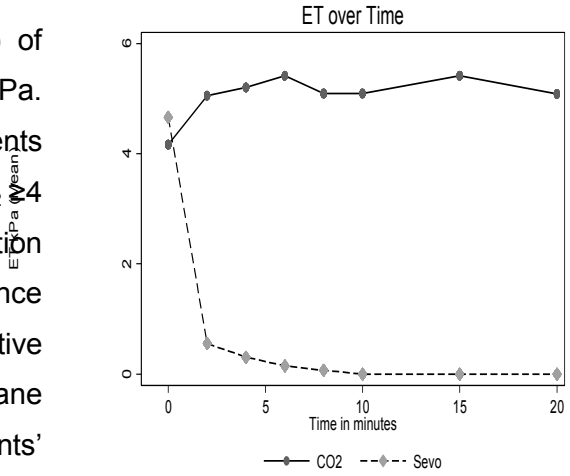

Figure 3: End-Tidal Sevoflurane and Carbon Dioxide over Time

Length of recovery period did not correlate with ketamine dose. Less than a third of the patients had a recovery room stay longer than 10 minutes (including those with >6mg/kg dose.) No child required overnight admission or had any side effects as a consequence of this anaesthetic technique.

Intraocular Pressure Measurements

Intraocular pressure measurements were performed in 50 eyes at stipulated time points (Figure 4). More right eye measurements were affected by glaucoma (15/25) than left eyes (11/25) and the same number of left and right eyes had undergone glaucoma surgery. The mean intraocular pressures of eyes with glaucoma was higher than non-glaucomatous eyes, by 7,85 mmHg (95% CI 6.19 to 9.51)(p<0,001). Despite this, they seemed to follow similar pressure trends to non-glaucomatous eyes. The confidence interval for the glaucoma group was wider than the non-glaucoma group implying more variability in intraocular pressure values within this group.

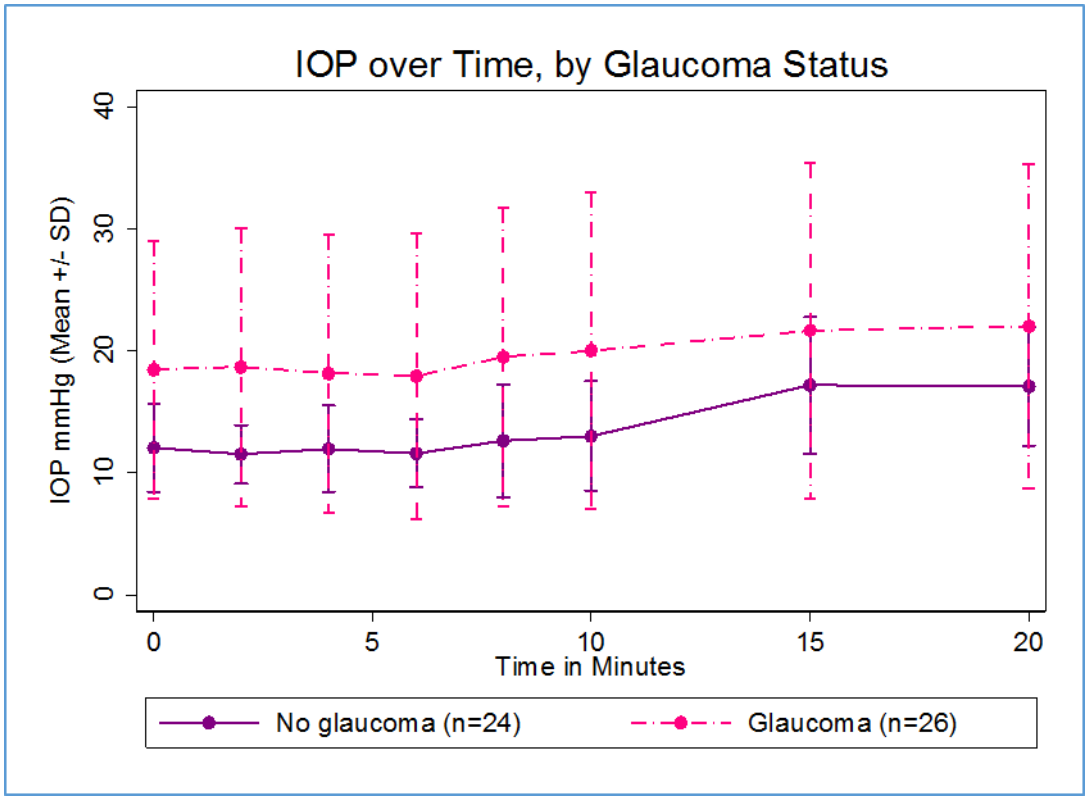

Figure 4: IOP over time by glaucoma status

Both the glaucoma and non-glaucoma mean intraocular pressures in the low dose ketamine group (<4 mg/kg) follow similar trends, with an elevation in baseline pressures in the glaucoma group.

Comparing the intraocular pressure at time 0 (sevoflurane only) and time 15 minutes (ketamine alone, sevoflurane eliminated) showed a 3,68mmHg increase in average intraocular pressure. (95% Confidence Interval 1,35 to 6,02mmHg) (p=0,002) Comparing time 15 minutes (ketamine only) and time 20 minutes (near wakefulness) there was a 0,28 mmHg difference between the average measured intraocular pressures (95% Confidence Interval -2.23mmHg to 2.79mmHg) (p=0,826)

Discussion

Paediatric glaucoma patients often require serial IOP measurements for optimal management. Al-Abrak et al (15) emphasised standardisation of all aspects of the anaesthetic in order to achieve reliable results.

Awake IOP measurements are usually performed in older, cooperative children (11, 12). Success rates with awake IOP measurements in young children are variable. Sihota et al (17) had a 50-60% success rate in determining awake IOP measurements in the 1-3 year age group (IOP measurements were taken in 405 cooperative, unsedated children). A study by Oberacher-Velten et al (18) had only a 14% success rate with awake IOP measurements in children aged 6 months to 2 years. Ausinsch et al(19) used a heavy premedication regime in order to obtain awake measurements, while Corssen et al (9) omitted awake readings if the child was uncooperative. Shah et al (20) warn against measurement of intraocular pressure in awake paediatric patients even if they are cooperative. They attribute elevated intraocular pressure in cooperative paediatric patients to some unavoidable squeezing of the eyelids.

Sedation would appear a feasible alternative but most general anaesthetic agents reduce intraocular pressure (2).

Chloral hydrate sedation has been shown not to influence intraocular pressure(14) and has a sedation success rate of 93,7%(21). It was a feasible alternative for ophthalmologists in South Africa but has recently been withdrawn from the commercial market.

Dexmedetomidine has been shown to reduce IOP (22-24).

Midazolam's effects on IOP have not been conclusively determined (18, 24-27). Most recently Shah et al (20) showed a significant reduction in intraocular pressure in cooperative patients after titration of midazolam to clinical effect. All opioids reduce intraocular pressure (2, 3, 28, 29).

Young patients often require examination under anaesthesia (EUA) in order to obtain IOP measurements. Due to lack of uniformity between various trials and different population groups, interpretation of the available literature is challenging (Table 4).

Dominguez et al (5) showed a small but significant decrease in intraocular pressure when measured under the influence of sevoflurane (10% decrease at 2% sevoflurane concentration). Blumberg et al (13) showed that intraocular pressure was unchanged under ketamine anaesthesia while intraocular pressure showed significant decline with each subsequent pressure measurement taken under sevoflurane anaesthesia when they administered sevoflurane anaesthesia to half of the study population and ketamine anaesthesia to the other half. Jones et al's results (16) were more substantial with a 28,5% reduction in intraocular pressure after administration of sevoflurane to children whose original pressure measurements were taken under ketamine anaesthesia. The children were induced with ketamine and sevoflurane was then added to maintain anaesthesia. No clinically significant changes in intraocular pressure have been found in recent paediatric trials where intravenous ketamine has been used for procedural sedation (10-12).

The timing of IOP measurements may play a role. Most studies simply took baseline intraocular pressure readings as soon as possible after induction of anaesthesia. While this may have impacted on the outcome of some studies, Adams (8) found that intraocular pressure increased after administration of ketamine but baseline pressures were measured under halothane anaesthesia, other trials have attempted to eliminate this impact. Dominguez et al (5) repeated pressure measurements at 1 minute intervals until emergence and suggested measuring intraocular pressure just prior to arousal when Bispectral Index (BIS) indicates light anaesthesia. The interpretation of BIS in a paediatric context is not discussed here. In a study by Blumberg et al (13), best fit regression lines for actual data was extrapolated backward in time to before induction.

Our findings are in keeping with the pressure changes described in recent paediatric studies investigating the effects of ketamine and sevoflurane on intraocular pressure (13, 16). Our data showed a 3.68mmHg (95% CI 1,35 to 6,02mmHg) (p=0,002) increase in mean intraocular pressure when measured under the influence of ketamine alone, compared to intraocular pressure influenced by sevoflurane alone. This difference is greater than that attributed to diurnal variation. It emphasises the importance of taking intraocular pressure measurements under standardised anaesthetic regimes which include specification of the timing of such measurements. The much smaller difference in mean intraocular pressure when taken in patients under the influence of ketamine anaesthesia when compared to

near awake values (0,28mmHg; 95% CI -2.23mmHg to 2.79mmHg) (p=0,826) suggests that measurements taken under the influence of ketamine anaesthesia are similar to those taken in awake patients. Overall, as expected, the readings appear lower when intraocular pressure is influenced by sevoflurane alone and gradually return to “awake’’ values as the sevoflurane is eliminated and ketamine is used to maintain anaesthesia.

Drayna et al (11) suggested that intraocular pressure was not significantly influenced by ketamine if the dose was kept below 4mg/kg. Nagdeve et al (32) suggested that the effect of ketamine was dose dependant. They found an increase in intraocular pressure when 6mg/kg of ketamine was administered but not when a lower dose was given. Ninety-two percent of our patients had <6mg/kg total ketamine dose. In the 44% that required higher dose ketamine (>4mg/kg) we noted an elevated baseline IOP measurement prior to the administration of additional ketamine boluses. Therefore, the elevated intraocular pressures in this group cannot be explained by the higher ketamine dose alone.

Eyes with glaucoma have higher baseline mean intraocular pressures than those without glaucoma but both groups followed similar trends in their response to the anaesthetic agents. In keeping with our findings, several authors noted inconsistent changes in intraocular pressure in patients with glaucoma(8, 30).

The timing of the readings remains important in obtaining results that reflect the awake state irrespective of whether the examined eye is diseased or not. Sevoflurane could no longer be detected in exhaled gas at 7,4 (SD +/-2,1) minutes, and the physiological variables, heart rate and blood pressure were not statistically different from preoperative values at 8 minutes. However, IOP still appears low at this point which suggests that it may still be under the influence of sevoflurane anaesthesia. In contrast, IOP at time 15 minutes closely resembles the near awake values (IOP difference 0,28mmHg; CI -2.23mmHg to 2.79mmHg) (p=0,826). We would thus recommend reading IOP 15 minutes after sevoflurane has been discontinued.

Aileen Adams (8) said, ‘it would seem wise that any individual child should always be examined under the same anaesthetic agent if truly comparable readings are to be obtained.’

This ideal was in keeping with Al-Abrak et al’s recommendations (15) to avoid premedications and depolarizing muscle relaxants, maintain constant intrathoracic

pressure and central venous pressure through ventilator settings and standardise patient positioning.

The absence of awake IOP reference measurements and the small number of patients recruited are potential limitations of this study. Our sample size is larger than similar studies where statistically significant results were found (11, 13, 16).

Our study reinforces the standardisation of anaesthetic technique, the measurement of intraocular pressure at predetermined time intervals by one ophthalmologist and the limited use of additional drugs which may have confounded the outcome. It adds to the current understanding of the effects of the anaesthetic agents on intraocular pressure.

Conclusion

Sevoflurane lowers IOP significantly when compared to ketamine anaesthesia. While eyes with glaucoma had a higher baseline than those which did not, both groups followed similar trends in response to the anaesthetic agents. This standardised anaesthetic protocol allows reliable IOP measurement 15 minutes after termination of sevoflurane and commencement of ketamine infusion with no reported adverse events.

Table 4: Summary of Paediatric Trials on the Effects of Anaesthetic Agents on Intraocular Pressure

Study	Year	Age	Patients	Pathology	Method	Conclusion
Corssen	1967	6 mths-77yrs	46	Normal	IV Ketamine 1mg/lb	Increase IOP
Yoshikawa	1971	4-7 yrs	15	Normal	IM ketamine 5mg/kg	Transient increase IOP
Adams	1973	3 mths-6 yrs	15	Normal vs Glaucoma	IM Ketamine 10mg/kg	Increase IOP
Ausinsch	1975	1-17 yrs	28	No Glaucoma	Halothane 1% / Isoflurane 1,5%	Volitalie IOP similar to sedated
Ausinsch	1976	2-10 yrs	10	Normal	8mg/kg IM Ketamine, then 1mg/kg IV Ketamine/20 min	Not increase IOP
Ausinsch	1977	0,1-15 yrs	10 (15 studies)	Glaucoma vs Normal	Halothane 1,5-3% in 50% N2O	30% Reduction in IOP
Jaafar	1993	0-5 yrs	60	Normal vs Glaucoma	Chloral hydrate 100mg/kg (10kg), then 50mg/kg	No change in IOP
Blumberg	2006	1-216 mths	30	Glaucoma	O_2 + Sevo 8% induction; Maintenance:Sevo(2-4%)**vs**Ketamine IM(5-7mg/kg)	IOP measured after ketamine represent awake IOP
Nagdeve	2006	1-6 yrs	40	Normal	IM Ketamine 6mg/kg vs 3 mg/kg	Dose dependant effect on IOP, increased after 6mg/kg
Dominguez	2009	3-10 yrs	30	Normal	O_2 + Sevoflurane 8% induction; 40% N_2O + Sevoflurane maintenance, titrated to BIS ≤ 50	2% Sevo decrease IOP by 10%; Measurement of IOP: light anaesthesia(BIS),Sevo eliminated
Jones	2010	26-89 mths	8	Glaucoma	Induction: Ketamine IM(5mg/kg) vs IV(2mg/kg) Maintenance: 60% N2O + Sevoflurane 1,2%	Sevoflurane lowers IOP (28,5%) vs Ketamine anaesthesia
Oberacher-Velten	2011	15-72 mths	36	No effect	Midazolam (1mg/kg) premed. prior to GA	Sedation doesn't reduce IOP
Drayna	2011	7-17 yrs	25	Normal	Procedural sedation: IV Ketamine~1,88mg/kg	No increases in IOP
Xu Lili	2012	3-7 yrs	60	Vitreoretinal	Dexmedetomidine (0,5mcg/kg)IV infusion over 10 min vs placebo after Sevoflurane induction	No reduction in IOP
Halstead	2012	1-15 ys	80	Normal	Procedural sedation: IV Ketamine~1,6mg/kg	No increase in IOP
Wadia	2014	8 -18 yrs	60	Normal	Procedural sedation:IV Ketamine 0,5mg/kg/minute; Ave total dose 1,48mg/kg	Mild increase in IOP (not clinically significant)
Shah	2015	2-15 yrs	40	Strabismus	IV Midazolam 0,1mg/kg bolus; 0,05mg/kg midazolam/3 min. until spontaneous eyelid drooping (max 2,5mg/kg)	Reduction in IOP (eyelid squeeze eliminated)

Author Contributions

All investigators participated actively in the planning and execution of this study. This included patient recruitment and consent, performance of anaesthesia and study technique, data capture and assessment. FR principal investigator, CT all IOP measurements, JvW wrote this manuscript and literature review.

Acknowledgement for Statistical Contribution

Katya Mauff and Ushma Galal, University of Cape Town, Department of Statistics

Declaration of Interest and Funding

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None of the authors have conflicts of interest to declare.

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Part D: Appendices

Original Protocol

Proposed protocol for Intraocular Pressure Measurement in children with glaucoma for examination under anaesthesia.

Aim:

To study the changes in intraocular pressure (IOP) and the correlation of the IOP curve over time, in patients with glaucoma who require examination under anaesthesia as a means to validate current practice at Red Cross Hospital.

Inclusion criteria:

Children with glaucoma

Age 0-3 years

Requiring EUA

Day case surgery

Exclusion criteria:

Contra indication to Sevoflurane / Ketamine anaesthesia

Difficult airway

ASA 3-4

Method:

Prospective observational study over 6 months or 30 patients.

Children with glaucoma aged 0-3 years, who require intraocular pressure measurement under anaesthesia.

Preoperative Demographic data [age (months), weight (kg), pulse, blood pressure]

Standardised anaesthetic technique:

normal fasting guidelines, clear fluids up to 2 hrs before surgery, milk/breastmilk >6hrs
no premedication,
routine intra operative monitoring & anaesthetic record keeping

gas induction with Ayers T-piece, 100% oxygen @ 5 l/min and Sevoflurane, gradual increase & limited to 6% until placement of intravenous cannula
no topical local anaesthetics to eyes

maintenance of anaesthesia with :
IV Ketamine bolus: 2 mg/kg followed by an infusion for 15 minutes
IV Ketamine infusion: 4mg/kg/hr infusion
(Alaris PK syringe driver with a 20ml BD plastic syringe)

should additional sedation be required a further bolus of iv ketamine 1 mg/kg
Maintain spontaneous ventilation with nasal prong oxygen @ 4 l/min, and end tidal CO_2 & Sevoflurane measurement.

Alternative & rescue airway management on anaesthetist's discretion
Glycopyrrolate 10 mcg/kg for excessive secretion (on anaesthetist's discretion)

Should ongoing surgery be required, the anaesthetic technique employed should be at the discretion of the attending anaesthetist.

Post-operative recovery and monitoring as per normal practice.

Intra ocular pressure (IOP) measurements:

Single operator

IOP measurement both eyes, every time, irrespective of diseased/normal – 10 sec/eye

Perkins applanation tonometer is gold standard, calibrated prior to each measurement

Anaesthetic data capture –

- time to IV cannulation and first IOP measurement,
- total Sevoflurane administered, (total dose, dose/kg ,dose/kg/min)
- total Ketamine administered, (total dose at each measurement time interval, initial bolus, repeat boluses, total infused dose, total dose/kg)
- heart rate and Blood pressure (systolic, mean, diastolic) at every IOP measurement intervals to compare with and see at which point it returns preoperative heart rate and blood pressure baseline
- ? time interval to return of baseline heart rate and blood pressure
- Assessment postoperatively for any postoperative complications
-

IOP measurement intervals and data capture:

- just prior to placing the intravenous (16) cannula with only sevoflurane on board, no possible sympathetic effect of siting cannula or ketamine (time 0)
- 1 minute after IVI cannulation with start of Ketamine anaesthesia and discontinuation of Sevoflurane anaesthetic.
- every 2 minutes thereafter
- At 15 minutes after IV cannulation the Ketamine infusion is stopped and final measurement is taken at 20 minutes.

Thus IOPM @ 0, 1,3,5,7,9,11,13,15,20 min

Consent

Informed consent of parent / guardian of child with glaucoma presenting for IOPM EUA to be included into the study and to perform IOPM.

No conflict of interests to declare, no sponsorship from trade.

Background:

Integral to the management of glaucoma is the accurate measurement of intraocular pressure. For accurate IOP measurement in very young children less than 3 years of age examination under general anaesthesia (EUA) is required because they don't tolerate awake IOP measurements.

There are studies reflecting the effects of ketamine induction (intramuscular) followed by sevoflurane, sevoflurane vs ketamine, ketamine alone and halothane with ketamine but no studies have looked at the effects on IOP of sevoflurane induction followed by ketamine sedation.

It is well known that most anaesthetics agents used for EUA may affect the IOP. Sevoflurane may decrease the IOP, and ketamine may increase the IOP. It is claimed that IOP is unaffected directly after induction of anaesthesia and that Ketamine less than 4 mg/kg doesn't have a clinical meaningful elevation in IOP.

At Red Cross Children's Hospital it is currently our practice to induce anaesthesia with a sevoflurane gas induction followed by Ketamine sedation, but there are several variations to this technique and IOP measurements have been at random time intervals.

We would like to validate our current practice and follow the changes of the intraocular pressure with a standardised anaesthetic technique and evaluate the correlation of the IOP curve over time to aid clinical practice, optimal measurements

Dr F Roodt – Anaesthetic consultant

Dr C Tinley – Paediatric Ophthalmologist

Dr Jessica van der Walt – Anaesthetic registrar

Synopsis

Synopsis of the proposed study of:

Intraocular Pressure Measurement in children with glaucoma for examination under anaesthesia

Introduction:

Integral to the management of glaucoma is the accurate measurement of intraocular pressure (IOP). For accurate IOP measurement in very young children less than 3 years of age examination under general anaesthesia (EUA) is required because they don't cooperate nor tolerate awake IOP measurements.

There are studies reflecting the effects of intramuscular ketamine induction followed by sevoflurane, sevoflurane vs ketamine, ketamine alone and halothane with ketamine for EUA's. Propofol sedation is another possibility, but would also potentially decrease IOP, may suppresses airway reflexes and is not widely used in very small children. Dexmedetomidine is an attractive alternative, but its use in paediatric anaesthesia is currently off licence and may be a consideration for a future study.

It is well known that most anaesthetic agents used for EUA may affect the IOP. Sevoflurane may decrease the IOP, and ketamine may increase the IOP. The intraocular effects of ketamine have recently been contested. It is claimed that IOP is unaffected directly after induction of anaesthesia and that Ketamine less than 4 mg/kg doesn't have a clinical meaningful elevation in IOP.

Review of recent literature:

1. 2010 Jones et al – studied 8 patients (16 eyes) to show a statistically significant difference in intraocular pressure when ketamine was used for induction followed sevoflurane for maintenance of anaesthesia, with remeasurement of intraocular pressure.

2. 2011 Drayna et al - measured intraocular pressures in 25 older children with normal eye pressures before and after ketamine - and found no statistical difference in the eye pressures before and after ketamine, concluding that low dose ketamine does not affect intraocular pressure.

3. 2006 Blumberg et al - divided 30 eyes into 2 groups and administered ketamine to one group and sevoflurane to the other and showed that ketamine was more representative of awake intraocular pressures than sevoflurane.

No studies have looked at the effects on IOP of sevoflurane induction followed by ketamine sedation as is currently our practice at Red Cross Children's Hospital and the dilemma at which point the IOP during the EUA best reflect the awake IOP.

Aims:

To study the changes in intraocular pressure (IOP) and the correlation of the IOP curve over time, in patients with glaucoma who require examination under

anaesthesia(EUA) as a means to validate current practice at Red Cross Hospital, with a standardized anaesthetic technique

Methods:

We propose a prospective observational study over 6 months or 30 patients, in children with glaucoma aged 0-36 months, who require intraocular pressure measurement under anaesthesia. We have derived at 30 patients (60 eye evaluations) as guided by literature review and in consultation with a statistician. We do approximately 5 such cases/ month and as such the study should take 6 month to be completed.

At Red Cross Children's Hospital it is currently our practice to induce anaesthesia with a Sevoflurane gas induction followed by Ketamine sedation, but there are several variations to this technique and IOP measurements have been at random time intervals.

To determine the optimal time to measure IOP in paediatric glaucoma patients during EUA, we would like to audit and validate our current practice, with a standardized anaesthetic technique with frequent measurement of the intraocular pressure to best determine when these measurements should be made in daily practice.

The proposed study will lengthen the EUA anaesthetic time by 5-10 minutes compared to standard practice and would allow for 8 intraocular measurements per eye. Standard practice is 2-3 subsequent measurements per eye.

The standardized anaesthetic technique and measurements of intraocular pressure are set out in the proposed protocol.

Data to be collected include preoperative demographical data (age, weight, pulse and blood pressure), ophthalmic data (normal/affected eyes, intraocular pressure) and anaesthetic data (total ketamine and sevoflurane used, end tidal gasses- CO_2 & sevoflurane, blood pressure, pulse, variations in anaesthetic technique, recovery time and any complications).

Patient's safety is paramount and as such there will be two anaesthetists dedicated to the list. The attending anaesthetist performs the anaesthesia with routine anaesthetic care, intra-operative monitoring and record keeping. The ophthalmologist performs the intraocular pressure measurements while the second anaesthetist is the investigator to record the study data.

In the event that further on going surgery are required at the end of the EUA period, the anaesthetic technique to be employed is left up to the discretion of the attending anaesthetist.

Post-operative recovery and monitoring will be as per normal standard of care and practice.

Inclusion criteria:

Children with glaucoma
Age 0-3 years
Requiring EUA
Day case surgery

Exclusion criteria:

Contra indication to Sevoflurane / Ketamine anaesthesia

Difficult airway

ASA 3-4

Most of the proposed Protocol/Study conforms to standard practice of care.

Patient consent

Consent for this study should be no different than normal informed consent obtained preoperatively by the surgeon from the parent/ guardian of the patient who presents with glaucoma for EUA.

The difference of the protocol from standard practice are as follows; implementation of a standardized anaesthetic technique and a more frequent IOP measurements – both of which will be explained at time of consent for the procedure.

Additionally verbal and written information about the audit of current clinical practice will be given to the parent/ guardian with written consent to use the ophthalmic and anaesthetic data collected for possible research, presentation and publication purposes. This is available in Afrikaans, English and Xhosa. The written information sheet is given to the parent and the consent is attached to normal procedural consent form.

Cost and consumables

No special equipment or consumables are required. All equipment stipulated in the protocol is available in theatre and is used on a daily basis as part of routine anaesthetic practice.

No conflict of interests to declare, and no sponsorship from trade.

Attached are the following:

Proposed Protocol and application form FSHO13

Appendices A: patient information sheet and consent to use the data (A1-A3)

Appendices B: Patient data sheet

To be kept in the anaesthetic consultant's office in the Anaesthetic department. No patient information will be disclosed and no data will be linked to the patient details or will be included in any presentations of the audit material.

Appendices C: Anaesthetic and ophthalmic Audit data sheet,

Used for data collection and analysis.

Regards

The investigators:

Dr F Roodt – Anaesthetic consultant, email: francois.roodt@gmail.com

Dr C Tinley – Paediatric Ophthalmologist, email: Christopher.Tinley@uct.ac.za

Dr Jessica van der Walt – Anaesthetic registrar, email: jessicagwendoline@hotmail.com

Form FHS013: New protocol application form – section A

Researchers must ensure that they use the current version of the application form on the Administrative Forms web page

1. General information

Protocol number (if applicable) & Protocol title	To study the changes in intraocular pressure (IOP) and the correlation of the IOP curve over time, in patients with glaucoma who require examination under anaesthesia as a means to validate current practice at Red Cross Hospital

2. Investigator(s) profile

UCT's principal investigator (PI)				
Title, first name, surname	Dr Fancois Roodt			
Department/Division	Department of Anaesthesia			
Phone	0214045001			
Email address	francois.roodt@gmail.com			
Office Internal Mail Address	D23 Department of Anaesthesia			
Registration with HPCSA (tick √)	x Yes	☐ No	Registration #	Mp0533823

Note:

- If a non-medically trained PI is overseeing research which involves medical procedures, the application must include a medical doctor registered with the HPCSA as a co-investigator.
- The research must have a UCT-based principal investigator, co-investigator or supervisor.

2.2 Co-investigator(s)		
Title, first name, surname	Department/Division	E-mail
Dr Christopher Tinley	Peadiatric	Christopher.Tinley@uct.ac.za
Dr Jessica van der Walt	Anaesthetic Registrar	jessicagwendoline@hotmail.com

2.3 How many of the following does the PI currently oversee?

(Total number for all research projects)

Open research studies	0	Sites (excluding this application)	0
Co-investigators	0	Number of participants	0

2.4 What is the PI's role in authoring this protocol? (tick √)	
Primary author	x
Collaborator	
None (developed by sponsors)	

2.5 Are there any publication restrictions on the research?	
x No	☐ Yes
If yes, please describe and justify:	
-	

3. Protocol profile

3.1 Has this protocol been submitted to another Human Research Ethics Committee?		
x No	☐ Yes	
If yes, please complete:	Name of Institution	Outcome

3.2 To your knowledge, has this protocol been rejected by another HREC? (tick √)		
x No	☐ Don't know	☐ Yes
If yes, please provide the reasons:		
-		

3.3 Is this application similar or related to research previously approved by this Committee? (e.g. a sub-study, follow-up study, earlier phase trial)? (tick √)		
x No	☐ Yes	
If yes, please complete:	REC REF	Project title

3.4 Is this protocol for degree purposes? (tick √)	
☐ No	x Yes
If yes, please specify:	

Type of degree	MMed
Student's name and e-mail	Dr Jessica van der Walt, jessicagwendoline@hotmail.com
Supervisor's name and e-mail	Dr Francois Roodt, francois.roodt@gmail.com
Department and University	Department of Anaesthesia - UCT

3.5 Does this protocol comply with the Helsinki Declaration of 2008? (tick √)	
☐ No	x Yes
If no, please explain with full justification	

3.6 Does the protocol provide insurance for research-related adverse events (tick √)		
☐ NA (e.g. minimal risk research, medical record review)	x	☐ Yes
If yes, please describe:		
ABPI-compliant corporate insurance policy		
UCT's no-fault insurance policy		
Other. Please specify		

3.7 Does the protocol comply with UCT's intellectual property rights policy? (tick √)	
x Yes	☐ No
If no, please justify	

4. Funding and grant information **(No funding/sponsor → skip to Q. 5)**

4.1 Funding source	**(tick √ at least one)**	**Ethics Review Levy – cost including vat**
UCT (e.g. departmental funding)		R0
Grant Funding Organizations (e.g. MRC, NRF, CANSA,)		R0
Federally funded / Foundation sponsored / Private Institutions (**BELOW R1m**)		R5 700
Federally funded / Foundation sponsored / Private Institutions (**ABOVE R1m**)		R11 400

Pharmaceutical / Industry Driven company sponsors an investigator to conduct a new research project		R22 800
Pharmaceutical / Industry Driven Additional Clinical Site / Extension study		R11 400

Note: the HREC does not have the authority to waiver the ethics review levy. If a waiver is required, please contact Mr Salie Nassiep, the Research Management Accountant in the Faculty of Health Sciences (021 406 6409) email: salie.nassiep@uct.ac.za

4.2 What is the total sponsorship/funding for this	

4.3 Into what entity will the funding be paid?	

4.4 Ethics review levy (Clinical & Industry-sponsored research only)	
For invoicing purposes, please provide:	
Sponsor's name	
Contact person	
Address	
Telephone number	

4.5 Where applicable, has the PI negotiated an agreement with the hospital or other health or laboratory services to cover the costs of interventions/ procedures/ investigations performed solely for research purposes? (e.g. extra MRIs, CT scans, diagnostic tests, prolonged hospitalisation, use of non-research staff to collect research-related data or perform research-related procedures) **(tick √)**		
☐ NA	☐ Yes	☐ No
If no, please explain how research costs will be recovered		

Note: a summary budget must be attached in the appendices.

5. Characteristics of the protocol

5.1 Category of research Please select an appropriate category for your protocol. If the protocol falls in more than one category, please designate a primary and secondary category by entering a '1' and a '2'.	
Medical intervention/ clinical trial (e.g. drugs, devices, innovations)	
Behavioural/ psychosocial interventions (e.g. comparison of counselling	
Epidemiology/ observational study (e.g. survey, prevalence, case control, cohort	1
Quality improvement	2
Testing new technologies	
Medical record review, audit	
Establishment of a specimen repository, medical data base/ registry	
Clinical laboratory studies	

Clinical laboratory studies (DNA related)	
Qualitative research (e.g. focus groups, in-depth interviewing, ethnography)	
Pilot study	
Other. Please describe:	

5.2 Category of	☐	x Minors (<18 years). Please specify age range: 0-3

5.3 Estimated number of	30

5.4 Estimated duration of the	6 months

5.5 Location(s) of the study:
Red Cross Children's Hospital – ophthalmic theatre

5.6 Will non-English speaking participants be enrolled in the study? (tick √)		
☐ NA	☐ No	x Yes

If yes, please tick √ what measures will be used to promote participants' and families' understanding:

Written translation of consent/ assent forms into Afrikaans	
Written translation of consent/ assent forms into Xhosa	
Use of trained translator(s)/ interpreter(s)	
Other. Please specify below and describe how the investigators intend to explain the study	

5.7 What measures will be taken to protect confidentiality (tick √)	
Paper-based records will be kept in a secure location and only accessible to personnel involved in the study	x
Computer-based records will only be available to personnel involved in the study through the use of access privileges and passwords	x
Personnel will be required to sign statements agreeing to protect the security and confidentiality of identifiable information	
Personal identifiers will be removed from research-related information	x
Encryption	
Audio and/ or video recordings will be transcribed and then destroyed to eliminate identification of participants	
Use of pseudonyms	
Participants in focus groups will be advised that confidentiality cannot be assured	

Other. Please specify:	

6. Clinical trials

This section must be completed only if the research involves a clinical trial of drugs/ medicines, herbal, complementary or indigenous therapies; therapeutic devices; an innovative therapy or intervention; off-label use or a departure from standard treatment or care. The SA GCP Guidelines (2006) define a clinical trial as any investigation in human participants intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s) and/or to study absorption, distribution, metabolism and excretion of an investigational product(s) with the objective of ascertaining its safety and/or efficacy		
Is this protocol a clinical trial (tick √):	☐ Yes	x No (If no, please go to

6.1 Is the product registered with the Medicines Control Council (MCC)? (tick √)	☐ Yes	☐ No
If yes, please provide the registration number		
If no, is the MCC's letter for use of an unregistered medicine attached?	☐ Yes ☐ No ☐ Application submitted	

If registered, will the product be studied for an **indication** different to that approved in the SA package insert?	☐ Yes	☐ No
If registered, will the product be studied using a **dose** different to that approved in the SA package insert?	☐ Yes	☐ No
If registered, will the product be studied using a **formulation** different to that approved in the SA package insert?	☐ Yes	☐ No
If registered, will the product be studied using **a route of administration** different to that approved in the SA package insert?	☐ Yes	☐ No

Note: If yes to any of the above, MCC approval is required.

6.2 Does the study involve an FDA-monitored product (drug, device or biological)? (tick √)	☐ Yes	☐ No

6.3 Is this trial registered with the South African Clinical Trial Register?	☐ Yes	☐ No
If yes, please provide the registration number		
If no	☐ Application submitted	

6.4 Does this trial comply with the Guidelines for Good Practice in the Conduct of Clinical Trials with Human Participants in South Africa, 2nd Edition, 2006? (tick √):	☐ Yes	☐ No
If no, please justify		

6.5 Is the PI covered by professional liability insurance? (tick √):	☐ Yes	☐ No
If yes, please provide Medical Protection number		

6.6 Trial design (tick √ all that apply)	
☐ Placebo-control	Please justify use of a placebo:

☐ Phase I ☐ Phase II ☐ Phase III ☐ Phase IV

☐ Single centre ☐ National multi-centre ☐ International multi-centre

☐ Open label/ roll-over/ extension study. (If yes, a summary of the main findings, including safety and efficacy data, from the previous study must be included in the appendices. This is a requirement for HREC review.)

6.7 Is the PI free to publish the findings of this trial? (tick √)	☐ Yes	☐ No
If no, please describe the conditions of publication.		

7. Statement of conflict of interest

The PI is expected to declare any existing or potential conflict of interest that may affect the scientific integrity and ethical conduct of this research. For purposes of this section, 'immediate family' means the PI's spouse or domestic partner and dependent children. Please tick √ all that apply:	
I, or any member of my immediate family, do not have any interest related to this research (e.g. financial interest in the sponsor of the research or intervention being tested.)	x
I, or any member of my immediate family, do not have a proprietary interest in the product being tested in this research (e.g. patent, trademark, copyright, licensing agreement).	x

I, or any member of my immediate family, do not have any relationships related to this research (e.g. board membership, consultative, executive, employment) or any entity with an ownership interest in the research other than the relationship of sponsor-investigator.	x
As Principal Investigator of this research I am aware of a potential conflict of interest. Please describe and provide a plan to manage the conflict of interest in the space below:	
none	

8. Declarations and Signatures

This application will not be processed unless all the required declarations and signatures are completed according to the Committee's Standard Operating Procedures.

8.1 Head of Department or Division

My signature confirms that:

i. The researcher(s)/student(s)/supervisor(s) have the skills, training, experience and time to undertake this research.
ii. There are adequate resources (e.g. equipment, space, support services) to perform this research

Signature of Head		Date	
Print name			

Note: Where the PI is also Head of Department, confirmation must be obtained from an authorised designee. PIs may not approve their own research.

8.2 Chairperson of the Departmental Research Committee (DRC)

My signature confirms that:

i. This research has undergone peer review by a person(s) experienced in the field of study.
ii. This research is well-designed and scientifically sound.
iii. Where relevant, all methodological issues have been resolved to the satisfaction of the peer reviewer(s).
iv. If conducted according to the protocol, this research is expected to yield valid and

Signature of Chairperson		Date:	
Print name			

Note: Where the PI is also the Chairperson of the DRC, confirmation must be obtained from an authorised designee. PIs may not approve their own research.

8.3 Student supervisor (if research is for a degree)
My signature confirms that:

i. The student researcher has adequate training and resources to complete the research in the allocated timeframe.
ii. The research has scholarly merit.
iii. The level of risk inherent in the study is commensurate with the student researcher's experience and the extent of oversight that I will provide.
iv. I will meet the student on a regular basis to monitor progress and address any problems that may arise during the study.
v. If applicable, I will ensure that the research undergoes continuing review as required by the HREC.
vi. If applicable, I will ensure that the student researcher reports unanticipated problems or serious adverse events to the HREC.
vii. I will arrange for an alternative faculty supervisor to take responsibility for this research

Signature of Supervisor		Date:	1/7/2012
Print name	Francois Roodt		

Note: The supervisor and student researcher are jointly responsible for the ethical conduct of this research from inception to dissemination of findings.

8.4 Principal investigator
My signature confirms that:

i. Information in this application is true and accurate.
ii. I will begin the research only after HREC approval is obtained.
iii. I accept full responsibility for the conduct of this research and the protection of participants' rights and welfare.
iv. I will conduct the research according to all ethical, regulatory and legal requirements laid down in the HREC's Standard Operating Procedures.
v. I will provide progress reports to the HREC as requested, including a final closing report at the end of the research.
vi. I will notify the HREC in writing if any change to the research is proposed and await approval before proceeding with the proposed change except when urgently necessary to protect participants' safety.
vii. I will notify the HREC in writing immediately if any adverse event or unanticipated problem occurs during the research.
viii. I will allow an audit of my research if requested by the HREC.

Signature of PI		Date:	1/7/2012
Print name	Francois Roodt		

New protocol submission checklist

Please ensure that all the applicable sections are fully completed and included in the submission. Missing information will delay the review process as the application will be returned to the PI. Sections A-C must be included. Instructions for submission of new applications are posted on the HREC website

Have you included?

Number of Copies	Full Committee Review
x Section A: New Protocol Application Form	3
x Section B: Synopsis	35
x Section C: Research Protocol	3
□ Appendices (as applicable):	3
□ Sponsor's protocol	3
□ NIH or other US federal grant application (if PI is primary awardee)	3
□ Investigator's brochure and package inserts	3
□ Surveys, questionnaires, interview schedules	3
□ Recruitment materials: advertisements, flyers, posters	3
□ Materials for participants: diaries, patient identification cards	3
□ Consent and assent forms (English versions)	35
□ Letters of authorisation from institutions such as hospitals, clinics and schools	3
□ A summary of Phase III efficacy and safety data if this is an application for an open label or extension study	3
□ Budget summary	3
□ MCC letter of approval, if available	3
□ If an application has been submitted to the MCC, a copy of Section 13 (Ethical Issues) extracted from the CTF1 application form	3
□ In the case of clinical trials, PI's declaration, CVs and GCP certificates for PI and co-investigators	
□ Other relevant documentation	

Please submit the completed protocol together with an electronic copy to:	**Mrs Lamees Emjedi** Research Ethics Committee E 52 Room 24, Old Main Building, Groote Schuur Hospital, Observatory Telephone: 27 21 406 6338 Fax: 27 21 406 6411 Email: nosi.tsama@uct.ac.za and shuretta.thomas@uct.ac.za

Human Research Ethics Committee – Study Approval

UNIVERSITY OF CAPE TOWN

Faculty of Health Sciences
Faculty of Health Sciences Human Research Ethics Committee
Room E52-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Telephone [021] 406 6338 • Facsimile [021] 406 6411
e-mail: sumayah.ariefdien@uct.ac.za

30 October 2012

HREC REF: 459/2012

Dr F Roodt
Department of Anaesthesia
D-23
NGSH

Dear Dr Roodt

PROJECT TITLE: TO STUDY THE CHANGES IN INTRAOCULAR PRESSURE (IOP) AND THE CORRELATION OF THE IOP CURVE OVER TIME, IN PATIENTS WITH GLAUCOMA WHO REQUIRE EXAMINATION UNDER ANAESTHESIA AS A MEANS TO VALIDATE CURRENT PRACTICE AT RED CROSS HOSPITAL.

Thank you for addressing the issues raised by the committee.

It is a pleasure to inform you that the Ethics Committee has **formally approved** the above-mentioned study.

Approval is granted for one year till the 28 October 2013.

Please submit a progress form, using the standardised Annual Report Form, if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the HREC. REF in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, HSF HUMAN ETHICS

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

sAriefdien

UNIVERSITY OF CAPE TOWN

Human Research Ethics Committee
FACULTY OF HEALTH SCIENCES

FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001938) This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	22.3.2015
☐ Not approved	See attached comments		
Signature Chairperson of the HREC		Date Signed	19/6/2014
Comments to PI from the HREC: Amendment Approval to include patients 736 months.			

Principal Investigator to complete the following:

1. Protocol information

Date form submitted	1 June 2014		
HREC REF Number	459/2012	Current Ethics Approval was granted until	28/6/2013
Protocol title	To Study the change in intraocular pressure and the correlation of the intraocular pressure curve over time, in patients with glaucoma who require examination under anaesthesia as a means to validate current practice at Red Cross Children's Hopsital		
Protocol number (if applicable)			
Are there any sub-studies linked to this study?	**No**		
If yes, could you please provide the HREC Ref's for all sub-studies? Note: A separate FHS016 must be submitted for each sub-study.			
Principal Investigator	Francois Roodt		
Department / Office Internal Mail Address	D 23 Department of Anaesthesia f.roodt@uct.ac.za		

1.1 Does this protocol receive US Federal funding?	☐ Yes	X **No**
1.2 If the study receives US Federal Funding, does the annual report require full committee approval?	☐ Yes	X **No**

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

4. Detailed description of the change(s)

Please attach, for each amendment, a summary of all changes which clearly indicates:

i. Old wording (e.g ~~strikethrough~~ text, CHANGED FROM and CHANGED TO)

ii. New wording (e.g *italicized*, **bold**, tracked)

iii. Detailed rationale/ justification/ explanation for each change

5. Documents for approval

Please itemise on the following page all amendments, with revised version numbers and dates, which need approval. This page will be detached, signed and returned to the PI as notification of approval. Please add extra pages if necessary

Signature of PI		Date	3/3/2015
Signature of Supervisor (if PI is a student)		Date	

Amendment Form

Date	3/3/2015
HREC REF Number	459/2015
Protocol number (if applicable) & Protocol title	
Principal Investigator	Dr Francois Roodt
Department / Office Internal Mail Address	D23 Department of Anaesthesia, Groote Shuur Hospital. e-mail: f.roodt@uct.ac.za

List of Proposed Amendments with Revised Version Numbers and Dates

New wording – adding a paragraph to include statistical analysis and methods for the study.
Statistical methodes to follow after protocol methods.

See attached paragraph

List of Proposed Amendments with Revised Version Numbers and Dates

Statistical methods

This is a prospective observational study, and analysis will be descriptive in nature. The aim is to assess the change in intraocular pressure over time, using a standardised anaesthesia technique. In 3 previous studies, sample sizes were 8, 25 and 30 respectively. In the last study, 2 groups of 15 patients were randomised to two anaesthesia interventions. In that study, there was no basis for a formal sample size calculation, but the investigators demonstrated significant differences in intraocular pressure at specified time points. Based upon these investigations, a sample size of 30 patients (60 eye evaluations) in the current observational study was regarded as likely to provide adequate statistical power. The aim is to plot the physiological variables against time, and obtain an estimate of the effects of the anaesthesia agents on intraocular pressure.

Generalised estimating equations will be used to describe changes in heart rate, blood pressure, end-tidal $PaCO_2$, end-tidal concentration of inhalational agent, and total ketamine dose at each time point (0, 2, 4, 6, 8, 10, 15 and 20 minutes, see Methods, above). Intraocular pressure will also be measured at these time points. During anaesthesia, the time at which heart rate and blood pressure returned to levels measured pre-induction of anaesthesia, will be considered appropriate to estimate a surrogate value for preoperative intraocular pressure.

Comparisons will be made between all parameters at each time point, using the Student's t-test should data be normally distributed, and the Wilcoxon signed-rank test in the event of non-normal distribution. These tests will be used to estimate the time point at which heart rate and blood pressure do not differ significantly from baseline values. The intraocular pressure at this time point will be assumed to approximate preoperative intraocular pressure. The intraocular pressure at the time point when end-tidal sevoflurane concentration returns to zero, will also be noted.

HREC office use only (FWA00001637; IRB00001938)

☐ Approved	☑ Type of review: Expedited	☐ Full committee

This serves as notification that all changes and documentation described above are approved

Signature Chairperson of the HREC	Date	5/3/2015

HUMAN RESEARCH
ETHICS COMMITTEE
- 4 MAR 2015
HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

Consent Form

Dear Parent / Guardian

Your child with glaucoma is scheduled for an examination under anaesthesia with regard to his medical condition. In order to improve services at Red Cross Hospital, we are auditing current anaesthetic practise for children who have glaucoma.

At present, we put these patients to sleep using Sevoflurane anaesthetic gas, we insert an intravenous line (drip) into the child when he or she is asleep and then turn the anaesthetic gas off, keeping the child asleep with an intravenous drug called Ketamine. We then take three intraocular pressure measurements on the patient and then wake him or her up again. We know that both the anaesthetic gasses and our intravenous drugs can have an effect on the pressure within the patient's eyes and thus would like to take a few more readings in order to establish more clearly how much effect these drugs are having on our measurements and at what stage we are achieving the most accurate results. We will thus take eight measurements of intraocular pressure as opposed to the usual three readings. This will mean that your child's anaesthetic will last five to ten minutes longer than a routine examination.

As always we will strive to deliver a safe anaesthetic to your child with no deviation from our standard care.

We request your permission to use the data we collect in our research and possibly in publications at a later stage. No personal information will be used in this research that would allow your child to be personally identified.

We thank you for your cooperation in allowing us to improve our standard of care to children with glaucoma.

Should you have any queries please feel free to contact one of our researchers.

Regards

Chris Tinley

Francois Roodt 079 679 1030

Jessica van der Walt 082 348 6566

Human Research Ethics Committee

Reference number 459/2012

Contact number 021 406 6338

I ---------- give permission for my child's data to be used as part of an audit of anaesthetic management during intraocular pressure measurements.

Signature of parent / guardian ---------- Date----------

Patient's Sticker

Data Capture Form

Anaesthetic Data Sheet - Intraoccular Pressure Study

Patient Details	
Study Number	
Age (months)	
Weight (kg)	

Opthalmic data			
Left eye	glaucoma	normal	surgery
Right eye	glaucoma	normal	surgery
Previous Surgery:			

Measurements

Time	Preop	0 min	2 min	4 min	6 min	8 min	10 min	15 min	20 min
IOP - Left									
IOP - Right									
HR (bpm)									
SBP(mmHg)									
DBP(mmHg)									
MBP (mmHg)									
ET CO2 (kPa)									
ET Sevo (kPa)									
Total Sevo (ml)									
Total Ketamine (mg)									
Ketamine (mg/kg)									
Variation									

Anaesthetic Details	
Time to 1st IOP measurement	
Time to Ketamine Bolus	

Post Op	
Arrival in Recovery	
Discharge from recovery	
Complications:	

Key	
A	Airway intervention
B	Bolus
G	Glycopyrolate
O	Other

Other Observations

Patient Data Form

Study no.	Date	Patient Sticker	Diagnosis
1			
2			
3			
4			
5			
6			
7			
8			
9			

Journal of Glaucoma – Author Instructions

Journal of Glaucoma

Online Submission and Review System

SCOPE

The *Journal of Glaucoma* is a peer reviewed journal addressing the spectrum of issues affecting definition, diagnosis, and management of glaucoma and providing a forum for lively and stimulating discussion of clinical, scientific, and socioeconomic factors affecting care of glaucoma patients.

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Ethical/Legal Considerations. A submitted manuscript must be an original contribution not previously published (except as an abstract or preliminary report), must not be under consideration for publication elsewhere, and if accepted, it must not be published elsewhere in similar form, in any language, without the consent of Lippincott Williams & Wilkins. Each person
listed as an author is expected to have participated in the study to a significant extent. Although
the editors and referees make every effort to ensure the validity of published manuscripts, the final responsibility rests with the authors, not with the Journal, its editors, or the publisher. All manuscripts must be submitted online through the journal's electronic submission
site www.editorialmanager.com/jog See submission instructions under "Online manuscript submission."
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Work and on the Copyright/Financial Disclosure form that is requested upon acceptance.

Patient Anonymity and Informed Consent

It is the author's responsibility to ensure that a patient's anonymity be carefully protected and to
verify that any experimental investigation with human subjects reported in the manuscript was performed with informed consent and following all the guidelines for experimental investigation with human subjects required by the institution(s) with which all the authors are affiliated. Authors should mask patients' eyes and remove patients' names from figures unless they obtain
written consent from the patients and submit written consent with the manuscript.

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will automatically receive an Email with instructions on
completing the form upon submission.

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Journal article

1. Budenz DL, Chen PP, Weaver YK. Conjunctival advancement for lateonset filtering bleb leaks:
indications and outcomes. *Arch Ophthalmol* 1999;117:10141019.

Book chapter

2. Skuta GL, Morgan RK. Corticosteroidinduced glaucoma. In: Ritch R, Shields MB, Krupin T, eds.
The Glaucomas. St. Louis: Mosby; 1996:11771188.

Entire book

3. Gelatt KN, ed. Veterinary Ophthalmology. Philadelphia: Lippincott Williams & Wilkins; 1999.

Software

4. *Epi Info* [computer program]. Version 6. Atlanta: Centers for Disease Control and Prevention;
1994.

Online journals

5. Friedman SA. Preeclampsia: a review of the role of prostaglandins. *Obstet Gynecol* [serial online]. January 1988;71:2237.
Available from: BRS Information Technologies, McLean, VA.
Accessed December 15, 1990.

Database

6. CANCERNETPDQ
[database online]. Bethesda, MD: National Cancer Institute; 1996. Updated March 29, 1996.

World Wide Web

7. Gostin LO. Drug use and HIV/AIDS [*JAMA* HIV/AIDS web site]. June 1, 1996. Available at: http://www.amaassn.
org/special/hiv/ethics. Accessed June 26, 1997.

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