

The Effects of Ketamine on Intraocular Pressure

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1.0 Background

Children frequently present to Emergency Rooms with lacerations, fractures or other injuries that require repairs that are both painful and scary. In order to ameliorate both the pain and anxiety involved with these procedures, we often elect to perform procedural sedation on children. Ketamine is an anesthetic agent that is widely used to sedate children for painful procedures as it produces an adequate level of anesthesia and analgesia without respiratory depression. The drug has been around since the late 1960's but has become standard procedure in many settings over the past decade.

2.0 Rationale and Specific Aims

Due to conflicting literature pertaining to the effect of ketamine on intraocular pressure, this medication is not used in patients who have a suspected eye injury. Emergency physicians must therefore choose another agent in order to sedate these children, and other agents, such as narcotics, hold other risks as well. Several studies looking at the effects of ketamine on intraocular pressure were done on only a few patients, one study showing finding an increase in pressure and the others showing either a decrease or no change at all. The purpose of this study is to clarify the effects that this drug has on the pressure of the eye in normal children so that we may determine if the drug can be used in an appropriate and safe manner in children with eye injuries.

3.0 Animal Studies and Previous Human Studies

The initial work on ketamine and its effects on intraocular pressure was done by Corsen and Hoy in 1967 and showed an increase of intraocular pressure but only looked at a few patients of various ages. The premedications and doses of Ketamine in this study were not standardized and the investigators only studied the patients for three minutes after drug administration. This is not fitting with the pharmacokinetics of this drug. Yoshikawa and Murai did a further study in 1971 looking at 15 children for a longer duration and also found an increase in pressure but used a much larger dose than is used in clinical practice. Another adult study (Peuler and Glass, 1975) showed both increased values and decreased values and concluded there was no significant effect. In 1973, British physician Aileen Adams, presented correspondence depicting an increase in IOP seen in 15 children and yet in 1976, Ausinsch and Rayburn studied 10 children and found no effects of Ketamine on IOP. More recently, three studies were done which showed a decrease in IOP following the administration of Ketamine and yet review literature in both Pediatric and Emergency Medicine journals give conflicting descriptions of the effect Ketamine has on intraocular pressure. However, this and previous studies were not adequately powered to promote change in clinical practice. We hypothesize that there is no significant change in IOP with administration of Ketamine and wish to perform an adequately powered study that could inform appropriate clinical practice.

References:

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4. Corsen G, Hoy JE: A New Parenteral Anesthetic CI-581: its effect on intraocular pressure. *J Pediat Ophthal* 4:20-23, 1967.
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6. Frey K, et al. Propofol versus propofol-ketamine sedation for retrobulbar nerve block: Comparison of sedation quality, intraocular pressure changes, and recovery profiles. *Anest Analg*. 1999;89:317-21.
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4.0 Inclusion/Exclusion Criteria

A convenience sample of children, ages 7-17 yo, presenting to the Pediatric Emergency Department with lacerations, fractures, or other injuries requiring sedation for repair will be considered for the study. These are the patients for whom Ketamine is routinely used, all belonging to ASA Class I or II. Patients will be excluded if they have a current injury to or around either eye, if they have a current eye disease (strabismus, etc) or if they have a history of eye surgery, eye injury, or other ocular abnormality. Patients will also be excluded if they are unable to cooperate with the measurement of intraocular pressure prior to the administration of ketamine. Patients who are ASA Class III or IV will not be eligible for the study.

5.0 Enrollment/Randomization

Physicians in the Pediatric Emergency Department who have been trained to measure intraocular pressure will identify patients whose clinical course mandates procedural sedation with Ketamine, Glycopyrolate, and Midazolam. Once they have consented the family for the sedation, they will consider the patient for inclusion in the study. The investigators will recruit all patients who fit the inclusion criteria and present for care when one of the study personnel is present in the Emergency Room. Informed consent will be obtained from the patient and parents. All enrolled patients will have their intraocular pressures measured.

6.0 Study Procedures

Once a patient has been determined to require procedural sedation for a therapeutic procedure, the physician caring for the patient will determine if the patient meets inclusion criteria for this study. A brief questionnaire will be filled out by the examiner regarding past medical history, demographic information, and current medications. The study will be explained to both the patient and his or her family. The patient will then be asked to sign the assent and the family asked to sign consent. After this is obtained, the patient will be administered Glycopyrolate (a medicine to decrease the saliva so one does not choke on this while sedated), and then Midazolam. Midazolam is a sedative and anxiety reducing medication. Once the Midazolam is administered, the first intraocular

pressure will be determined. The patient will be asked to lie very still, and look straight ahead.

A bottle of Proparacaine eye drops will be purchased by the investigators and will be labelled and stored in the medication refrigerator in the medication room of the pediatric emergency department. Once opened, this bottle will be replaced every 30 days during the study period. Proparacaine drops will be placed in the right eye to numb the eye. This may result in a “stinging” sensation for a few seconds. Once the eye is numb, the tonopen, with proper sterile cover in place, will be applied to the sclera, using proper technique, three times to obtain accurate measurement of intraocular pressure. The patient will then be administered Ketamine by intravenous route. The dose of Ketamine will be determined by the physician supervising the sedation using a starting dose of 1mg/kg – 2mg/kg, and redosing as necessary to provide adequate sedation and analgesia for the given procedure. The dose of Ketamine will be recorded by the study personnel. Measurements of intraocular pressure will be repeated at the time of Ketamine administration and again at 1, 3, 5, 15, and 30 minutes after administration. Proparacaine drops will be readministered before the 15minute evaluation of intraocular pressure to insure anesthesia for the last two measurements. This study will not impede nor prolong the procedure for which the patient is being sedated. The family will be told the patient’s pressures and provided appropriate referral information if needed. Their involvement will be concluded once the measurements are completed.

Data will be stored on one data sheet per patient. It will be entered twice by the study team into a database, and patient data will be recorded only by a non-identifying number, and then the data sheet will be locked away until completion of the study. All measures to ensure confidentiality of data will be made.

7.0 Risks

Proparacaine drops will be used for anesthetic purposes. These drops are safe, but do cause some stinging sensation as they are applied. This resolves rapidly.

A Tonopen will be used to measure the pressure of the eye and its contents. This device is used in routine eye exams on both adults and children. Its tip is covered with a new latex cover for each patient, so the risk of infection is minimal. There is a risk of allergic reaction to latex. With proper anesthesia, the patient will be unaware of the contact with the eye. Theoretically, there is a risk of damage to this layer of the eye resulting in a scleral abrasion. This happens very rarely. The treatment for a scleral abrasion is antibiotic drops. These abrasions resolve without further intervention or sequelae in 24 hours.

8.0 Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants or Others

A committee of the investigators and other professionals (Pediatric EM faculty, Pediatric Ophthalmologists) will be assembled monthly to review the data that has been collected and any adverse events or problems encountered through the study. At each monthly meeting, the progress of the study will be discussed. A special meeting will be called immediately in the event of any adverse event, and the study altered or terminated

accordingly. Said committee will review AE data and ensure this has been reported appropriately to the IRB committee.

9.0 Study Withdrawal/Discontinuation

Patients may withdraw from the study at any point during the acquisition of intraocular pressure measurements without penalty or alteration in sedation plans or the provision of appropriate medical care. Patients will be withdrawn from the study in the event that they are unable to cooperate, as this will falsely elevate their readings.

10.0 Statistical Considerations

The sample size on this study was calculated based on previous studies. Sample size calculations, using a paired t-test with alpha of 0.05 and standard deviation of 2.7, show that a sample size of 26 is needed to detect a mean difference of 2 with 95% power. A mean difference of 2 is a conservative figure of the mean change in intraocular pressure that would be clinically significant. A standard deviation of 2.7 was based on Peuler et al (citation above). We seek to enroll 30 patients to allow for attrition.

11.0 Privacy/Confidentiality Issues

The patients will each be assigned a sequential number for identification on the data sheet, which will be linked to the medical record number and initial questionnaire. After the patient completes the study, this data will be transferred to a computerized database by two investigators to ensure accuracy of data entry. These two individuals will be the only people with access to this database. The paper data sheet will be destroyed once the information is in the secure database.

No identifying information will ultimately be stored on the patient. This will be used for database entry only. All patient data will remain confidential throughout the study.

12.0 Follow-up and Record Retention

This study will end once at least 50 patients have completed the study. The records will be held on the database for 3 years after completion of the study. This will be a secure database, only accessible by the two lead investigators. This database will be deleted once the three years have expired.

Appendix A

	Phase 1						Phase 2					
Month	1	2	3	4	5	6	7	8	9	10	11	12
Equipment acquisition	→											
Enroll subjects			→									
Data acquisition			→									
Data analysis							→					
Manuscript preparation										→		
Present findings											→	

Principal Investigator: Donald H Arnold, MD Version Date: 3.15.06
Study Title: What Effect Does Ketamine Have on Intraocular Pressure?
Institution/Hospital: Vanderbilt University Medical Center

Appendix B

Ketamine Study Questionnaire

Patient Name:

MR#:

Study #:

This page with confidential information will be destroyed once the data on the following sheet has been entered in the password-guarded study database.

Ketamine Study Questionnaire

Version 3.0
March 15, 2006

Study #:
 Age:
 ED Diagnosis:
 Reason for sedation:

Any previous visits to eye doctor?
 If yes, reason:

Any previous eye surgery?
 If yes, reason:

Any previous injury to either eye?
 If yes, details:

Does the patient wear glasses?

Current Medications:

Other Medical Problems:

Study Data:

Include all medications given along with doses and the route and time of administration
 Only list data with 95% CI on Tonopen

Glycopyrolate	Dose _____
	Time _____
Midazolam	Dose _____
	Time _____
Ketamine	Dose _____
	Time _____
Other drugs/doses:	

Intraocular Pressures +/- SD			
Time0			
1min			
3min			
5min			
15min			
30min			

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Institution/Hospital: Vanderbilt University Medical Center