International Journal of Medical Ophthalmology

E-ISSN: 2663-8274
P-ISSN: 2663-8266
www.ophthalmoljournal.com
IJMO 2020; 2(2): 39-42
Received: 02-06-2020
Accepted: 09-07-2020

Dr. T Sadasiva Rao
Associate Professor, Department of Ophthalmology, Sree Lakshmi Narayana Institute of Medical Sciences, Puducherry, India

Dr. A Ashok Vardhan
Associate Professor, Department of Anaesthesiology, Sree Lakshmi Narayana Institute of Medical Sciences, Puducherry, India

Corresponding Author:
Dr. A Ashok Vardhan
Associate Professor, Department of Anaesthesiology, Sree Lakshmi Narayana Institute of Medical Sciences, Puducherry, India

Children's intraocular pressure during exams under anaesthesia: The impact of ketamine and sevoflurane

Dr. T Sadasiva Rao and Dr. A Ashok Vardhan

DOI: https://doi.org/10.33545/26638266.2020.v2.i2a.184

Abstract
Background and Objective: The impact of anesthesia during examination under anesthesia (EUA) on intraocular pressure (IOP) in children.
Methods: In this randomized trial, children having EUA had their intramuscular ketamine hydrochloride and breathed sevoflurane gas to compare their IOP. As soon as feasible after anesthetic induction (T_1) and at two, four, six, and eight minutes later, the intraocular pressure (IOP) in thirty eyes was measured. We simultaneously monitored heart rate (HR) and systolic and diastolic blood pressure (SBP, DBP).
Result: For every measurement taken between two and eight minutes later, the sevoflurane group's IOP was considerably lower than the mean IOP at T_1 (mean drop in IOP: two minutes = 12%, four minutes = 19%, six minutes = 19%, eight minutes = 17%, all $p<.01$). Mean IOP in the ketamine group was 7% lower (P =.03) at eight minutes, but did not change significantly from T_1 through six minutes. At two minutes onward, sevoflurane significantly lowered SBP and DBP compared to ketamine at all measurements; at two, four, and six minutes, sevoflurane also lowered HR.
Conclusion: Compared to sevoflurane anesthesia, the IOP recorded following ketamine sedation is more likely to reflect the IOP while awake. Sevoflurane's effects on IOP may be due to hemodynamic changes, as seen by changes in SBP, DBP, and HR.

Keywords: Intraocular anesthesia, ketamine, sevoflurane, anesthesia, SBP, DBP, HR

Introduction
Although it can be challenging to get accurate intraocular pressure (IOP) measurements in children, they are crucial for the diagnosis and treatment of pediatric glaucoma. In order to get young patients to cooperate sufficiently for an IOP measurement, examination under anesthesia (EUA) is frequently necessary. However, depending on the degree of anesthesia, anesthetics may raise or lower IOP, and their effects may vary over time [1, 2]. Halothane and other older inhalational anesthetics have been shown to considerably reduce intracranial pressure [1, 2]. Sevoflurane, a different halogenated hydrocarbon, has mainly taken the position of halothane in recent years due to its quick start of action, quicker recovery period, and decreased frequency of reported side effects [3]. The effects of sevoflurane on childhood IOP have not been the subject of any published research. During EUA, ketamine, a dissociative anesthetic, has been used to quantify IOP. Ketamine's potential impact on intraocular pressure has generated debate. While some research indicate that ketamine increases intraocular pressure (IOP), others indicate that the effect is rather small [4-6] No research has been done on the temporal course of any ketamine-induced effects on IOP.
In infants with suspected or confirmed congenital or secondary glau- coma, we created a randomized clinical trial to investigate the effects of ketamine and sevoflurane on intracranial pressure (IOP) eight minutes after anesthetic induction. We wanted to assess this time because there are reports that anesthetics have little effect on measurements taken right after induction. During the course of the same eight minutes, we assessed the effects of ketamine and sevoflurane on heart rate (HR), systolic blood pressure (SBP), and diastolic blood pressure (DBP) [6-9].

Materials and Methods
Institutional Review Board approved the prospective, randomized trial, which was carried out in Department of Anaesthesiology, Sree Lakshmi Narayana Institute of Medical Sciences, Puducherry, India from August 2019 to July 2020 in compliance with the

Declaration of Helsinki. Each subject's age, gender, diagnosis, current drug regimen, and surgery history were taken from their clinical chart. Patients unable to have their IOP measured while wearing a face mask filled with 100% oxygen were omitted. There was no usage of any additional systemic anesthetics. Induction of all patients was successful as long as the protocol was followed.

Because of the documented impact of muscle relaxants and endotracheal intubation on IOP, one participant who was randomly assigned to receive sevoflurane needed to be intubated before to the completion of IOP measurements. This individual was subsequently removed from the trial [10, 11]. It was determined that in three individuals, using a laryngeal mask airway was clinically necessary prior to the completion of IOP measurements. There is no evidence that this airway significantly affects IOP [12]. IOP readings were not possible for the three extra subjects that were randomized (two to the sevoflurane group and one to the ketamine group). As a result, 40 patients were randomized to one of the two groups; however, the findings presented here only pertain to 35 subjects. Prior to the first surgical incision, all IOP measurements were finished [13].

Due to their inability to cooperate sufficiently to provide precise IOP readings while they were awake, the study individuals had EUAs performed in order to monitor their glaucoma. Therefore, it was not possible to measure IOP prior to the induction of anesthesia. The initial measurement of IOP was taken as soon as anesthesia was induced. T_1 was the time of this initial measurement. For ketamine and sevoflurane, the interval between the first administration of study medication and T_1 was three to ten minutes and two to four minutes, respectively. Because ketamine and sevoflurane are administered in different ways, their respective times for reaching anesthesia are longer. A single intramuscular dose of ketamine was administered. The exact position of the injected depot in relation to the muscle belly and the blood flow within the muscle are two factors that influence the drug's absorption and the time it takes for the intended effect to manifest. Conversely, sevoflurane is an anesthetic that is breathed. Very high inspired concentrations are used to start the dosing process, which reliably and quickly induces general anesthesia. The inspired concentrations are lowered to normal maintenance levels once the patient has lost consciousness. The same instrument was used to measure each subject's IOP. Before each use, the tonometer was calibrated. Either D.B. or N.C., one of the two investigators, took the measurements for each IOP. After applying one drop of proparacaine hydrochloride (0.5%), two IOP measurements were obtained, each with a coefficient of variation less than 5%. The mean of the two readings was noted if there was a difference between them of less than 2 mm Hg. The median of the three measurements was utilized if there was a difference between the two readings of ≥3 mm Hg. A third reading with a coefficient of variation <5% was obtained [13, 14].

IOP readings for one eye of each research participant were taken at T_1, as well as two, four, six, and eight minutes later. The nonsurgical eye was selected in cases where one eye required surgery. The choice of eyes was made at random if neither was having surgery. At each IOP measurement, HR, SBP, and DBP were recorded. The odor of sevoflurane made it impractical to mask the researcher who tested the IOP to the anesthetic drug.

Sequential, numbered, sealed envelopes were used to randomly assign subjects to receive intramuscular ketamine or sevoflurane via face mask. Before induction, the anesthesia team received printed copies of the protocol and a random medication assignment to either intramuscular ketamine or inhaled sevoflurane. Premedication with midazolam was most frequently administered to sevoflurane group patients orally (0.5 to 1.0 mg/kg up to 20 mg), intravenously (0.05 to 0.1 mg/kg up to 5 mg), or subrectally (0.5 to 1.0 mg/kg up to 20 mg; Table). Additionally, some patients received atropine intravenously (0.01 mg/kg) or intramuscularly (0.02 mg/kg; Table). Neither atropine nor midazolam have been shown to significantly alter intraocular pressure [14, 15]. Sevoflurane 8% in 100% oxygen carrier gas was used for induction, and maintenance under spontaneous breathing was maintained at one to two millimal alveolar concentrations of sevoflurane (2 to 4%) in 100% oxygen. Ketamine (5-7 mg/kg) was administered intramuscularly to the ketamine group. Every patient was to compare the characteristics of the children in the two study arms, contingency table analysis was employed. Using t-tests, the significance of changes in IOP, heart rate, systolic and diastolic blood pressure, and within-arm variations from T_1 to two, four, six, and eight minutes later was evaluated. The model employed an exchangeable correlation structure and predicted the IOP as a function of the measurement duration and randomization arm.

Results

Table 1: Baseline Characteristics of Children Undergoing Examination under Anesthesia by Treatment Group

Characteristic	Ketamine	Sevoflurane	P value
Male	7	8	.52
Female	8	7	
Mean age, months (±SD)	60.0±55.0	67.9±65.2	.75
Primary glaucoma	5	6	1.0
Secondary glaucoma	12	11	
Prior glaucoma surgery	8	7	1.0
No prior glaucoma surgery	9	10	
No present glaucoma drops	12	9	.45
Taking glaucoma drops	5	7	
Midazolam: Yes	11	9	.42
No	4	7	
Atropine: Yes	13	6	.004
No	2	10	

Of the 35 participants in the study from whom the IOP readings were taken, fifteen were given sevoflurane and the remaining fifteen were given ketamine. The individuals ranged in age from one to 216 months, with a mean of 62±54.0 months. Age, gender, number of glaucoma drugs, percentage of participants with primary vs secondary glaucoma, and history of surgery in the study eye did not substantially differ between the two treatment groups (Table). While only one-third of sevoflurane patients received atropine to suppress salivary secretions, the majority of ketamine group patients did. The amount of midazolam used by each group did not differ significantly.

The sevoflurane group had a lower mean IOP at T_1 (23.6±10.5) than the ketamine group, however the difference was only marginally statistically significant (29.8±12.0; P =.15). At each subsequent measurement after T_1, the mean IOP in the sevoflurane group showed a

significant and prolonged drop (mean difference from T_1 = 11.5%, 19.2%, 18.5%, and 16.7% at two, four, six, and eight minutes, respectively, all P <.01). At two, four, and six minutes, the mean IOP in the ketamine group did not differ significantly from that of T_1, and at eight minutes, it was slightly lower (mean difference = 7.4%, P =.03). For all measurements taken after two minutes, the mean intraocular pressure (IOP) for sevoflurane (20.4±8.6 mm Hg) was considerably lower than that of ketamine (28.7±12.3 mm Hg, P =.04). The generalized estimation approach prediction model revealed that the mean intra-observational pressure (IOP) of subjects treated with sevoflurane was considerably lower than that of individuals treated with ketamine (P <.03). Additionally, the model indicated that the mean IOP decreased from T_1 to eight minutes following sevoflurane; however, this was not the case for the ketamine individuals (P =.03). Only one out of fifteen ketamine patients experienced a 20% or greater drop in IOP from baseline, compared to six out of fourteen sevoflurane patients (P =.07).

For every time point starting at T_1, the sevoflurane group's SBP and DBP were considerably lower than the ketamine group's. At every time point from T_1 to T_8, the sevoflurane group's HR was likewise significantly lower.

Discussion

We often have to use anaesthetics to test children since many of them are uncooperative during tonometry, which may change the intraocular pressure. It is discussed to what extent anesthesia lowers intraocular pressure (IOP). Children sevoflurane-sedated demonstrated a significant reduction in intracranial pressure (IOP) as compared to ketamine sedation. Sevoflurane's ability to lower IOP is most likely the cause of this. This conclusion is supported by a substantial body of previously published research. Initially, a limited amount of observations were made on babies who were assessed both when they were conscious and unconscious. These cases showed that intracranial pressure (IOP) was similar to that following ketamine sedation even though sevoflurane and other gas anesthetics decreased IOP. Moreover, research on nonhuman monkeys that have been trained to allow for applanation tonometry in both conscious and unconscious conditions suggests that ketamine does not change intraocular pressure (IOP) [15-17].

Sevoflurane reduced intraocular pressure. According to the aforementioned evidence on humans and monkeys, the IOP after ketamine is thought to represent awake IOP more accurately than the IOP after sevoflurane anesthesia. The well-known halothane effect on blood pressure and IOP is produced via gas anesthesia. Sevoflurane has numerous advantageous properties, however its mode of action is comparable to that of halothane. It makes sense that it would have the same ability to decrease IOP as other substances in its family. This is supported by the information we have provided. In our young children, we were unable to take their IOP while they were asleep, but following sevoflurane sedation, it was much lower than following ketamine sedation. Moreover, IOP decreased significantly more in individuals who received sevoflurane treatment during the eight minutes of monitoring. However, in the eight minutes that followed induction, there was virtually no reduction in the ketamine readings [17-19].

Estimates of the IOP in both groups at the time of the initial anesthetic delivery can be made with confidence thanks to mathematical modeling of the sevoflurane and ketamine data. The data from T_1 to eight minutes later yielded the greatest fit for both the ketamine and sevoflurane, resulting in a power function for the former and a linear fit for the latter. It's quite possible that the two groups' baseline IOPs were the same because we randomly assigned eyes to each group. By going further back in time to the point at which both groups would have experienced equal IOP, we may ascertain the most likely IOP. By doing this, we find that the intersection point of the two curves is approximately three minutes prior to T_1, which is the median time the anesthesia is administered [20]. This is where the actual ketamine data, which is about 30 mm Hg, determines the "true" IOP. We get the same result if we model this backward extrapolation for the percent IOP decreasing with time (data not shown) or the change in IOP starting at T_1. Even if measurements are taken as soon as tonometry is feasible after sedation, clinically significant measurement errors in IOP may be difficult to prevent given the size and speed of the reported changes in IOP following sevoflurane administration. Since sevoflurane is said to have more subdued effects on HR, SBP, and DBP than its predecessor, halothane, we had thought that its effect on IOP would be less than that of the latter drug.16 However, as was previously shown with halothane, we discovered that individuals treated with sevoflurane had statistically higher lowerings of each vascular parameter than individuals treated with ketamine. IOP decrease may be connected to this sharp decline in blood pressure and heart rate with sevoflurane. Numerous mechanisms have been proposed to explain the lowered intraocular pressure (IOP) linked to inhalational anesthetics [21, 22].

These processes include modifications to the production of aqueous humor, elevations in outflow facility, adjustments to ventilation and metabolic state, and more. The speed at which IOP dropped after sevoflurane raises the possibility that mechanisms other than aqueous production or outflow are at play. Quigley *et al*. have compiled evidence that suggests variations in choroidal volume cause momentary changes in intraocular pressure. An IOP drop would make sense if the sevoflurane-induced reduction in blood pressure and heart rate was linked to a drop in central venous pressure or choroidal volume. Changes in intraocular and systemic vascular tone during gas anesthesia are thought to be caused by variations in the partial pressure of carbon dioxide (pCO2)20-22. This theory is quite fascinating. Sevoflurane may lower IOP via reducing pCO2, as decreased IOP and a decreased choroidal volume have been linked to pCO2 decreases [23].

This research is limited in a number of ways. Because of this, we don't have a perfect gold standard to compare the effects of anesthesia with. Our patients' IOP cannot be properly monitored without anesthesia. More research with a larger sample size is required, even if the results we got from our sample size were statistically significant. There is much dispute over pneumotonomy, and applanation tonometry accuracy during EUA in children. While our data seems free of measurement error, comparing two groups (ketamine and sevoflurane) recorded with the same equipment raises questions. Furthermore, the similarity of results at T_1 and T_8 between the study and contralateral eyes suggests that repeated applanation may not have had a significant effect. It is hypothesized that assessing IOP frequently every two minutes could cause it to decrease.

This theory is contradicted by the predictive model's failure to identify a trend toward lower IOP in the ketamine group during the eight minutes that followed the baseline measurement. Observers were not masked to the anesthetic agent since it would have been difficult to conceal the distinct aroma of sevoflurane; nonetheless, it is unlikely that this had any effect on the digital values that were detected. Although the effects of atropine, propofol, and midazolam have not been demonstrated to decrease intraocular pressure, we cannot completely rule them out.

Sevoflurane appears to have an IOP-lowering effect as soon as cooperation is established, hence it is important to be cautious when interpreting IOP measurements obtained after sevoflurane injection since they can be lower than the IOP of the waking individual. Sevoflurane is a compromise, however in order to get the most accurate pressure reading upon induction, it's critical to evaluate IOP as soon as feasible. Intramuscular ketamine appears to lack this characteristic when evaluating children during EUA; in fact, it may even be better [24].

Conclusion

Compared to sevoflurane anesthesia, the IOP recorded following ketamine sedation is more likely to reflect the IOP while awake. Sevoflurane's effects on IOP may be due to hemodynamic changes, as seen by changes in SBP, DBP, and HR.

Conflict of interest

None.

Funding support

Nil.

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