



A Prospective Study of the Effects of General Anesthesia on Intraocular Pressure in Healthy Children

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Purpose: To determine the effect of general anesthesia on intraocular pressure (IOP) in children with no intraocular pathology and determine which postanesthetic time point is most predictive of preinduction IOP.

Design: Prospective observational study.

Participants: Children with no intraocular pathology ≤ 18 years scheduled for general anesthesia as part of their routine care followed by a pediatric ophthalmologist at Nanjing Medical University.

Methods: Participants underwent a standardized general anesthetic protocol using a mask induction with sevoflurane and propofol maintenance. Intraocular pressure was measured at the following 7 time points: preinduction (taken in the preoperative area), postinduction minutes 1, 3, and 5, and postairway placement minutes 1, 3, and 5 for a total time period of 10 minutes after induction. A generalized estimating equation was used to evaluate the effect of anesthesia on IOP and the effect of patient factors (age, gender, vital signs, and airway type) on preanesthetic and postanesthetic IOP. An IOP prediction model was developed using the postanesthesia IOP measurements for predicting preinduction IOP.

Main Outcome Measures: Intraocular pressure and change in IOP at prespecified time points.

Results: Eighty-five children were enrolled with a mean \pm standard deviation (SD) age of 7.5 ± 2.9 years. Mean \pm SD preinduction IOP was 20.1 ± 3.7 mmHg. Overall, IOP was lowest at 3 minutes postinduction, decreased to a mean of 13.4 ± 3.7 mmHg ($P < 0.001$). After this, IOP rose 5 minutes postinduction to 16.5 ± 4.2 mmHg, which did not reach preinduction IOP levels ($P < 0.001$). The IOP prediction model showed that combining 1 minute postinduction and 3 minutes postairway was most predictive ($R^2 = 0.13$), whereas 1 minute postairway was least predictive of preinduction IOP ($R^2 = 0.01$).

Conclusions: After the induction of general anesthesia in children, IOP temporarily decreases with a trough at 3 minutes postinduction before increasing and remaining stable just below preinduction levels. Intraocular pressure measurements taken 1 minute after induction with 3 minutes after airway placement are most predictive of preinduction IOP, though predictive value is relatively low.

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Supplemental material available at www.ophtalmologyscience.org.

Intraocular pressure (IOP) is considered one of the “vital signs” of the eye and is one of the most important components of a comprehensive ophthalmic examination.¹ Intraocular pressure is elevated in a number of conditions, including glaucoma, which is the second leading cause of blindness in adults in the United States.² Glaucoma in children is less common, but can be visually devastating, responsible for up to 18% of blind children, worse in low-resource communities.³ Measuring IOP is one of the most important aspects in the diagnosis and monitoring of glaucoma in children.⁴ Currently, IOP is measured using a variety of instruments, most of which require direct

contact with the cornea and an extrapolation of the IOP based on the amount of force required to flatten the cornea.

Obtaining reliable and accurate IOP measurements in children is difficult given that it often requires administration of anesthetic eye drops and an instrument held very close to the face. When children are fearful or uncooperative, IOP measurements may be inaccurate or unattainable.⁵ In an uncooperative child where there is a concern for abnormal IOP, an examination under general anesthesia is often required.⁶ Studies in adults have shown that IOP measured under general anesthesia correlates well with in-office measurements, but similar studies in children have

shown varying effects of general anesthesia on IOP. Our group previously published a meta-analysis summarizing the effects of different anesthetic agents on IOP in children, with some agents dramatically lowering IOP and others raising it.⁷ Most studies evaluating the effect of anesthesia on IOP in children are small or contain data from heterogeneous anesthetic protocols, limiting their clinical applicability.

The goal of this project was to determine the effect of general anesthesia on IOP in children using a prospective, standardized anesthetic protocol. Additionally, we aimed to develop a prediction model to determine which time point after anesthesia was most predictive of preinduction IOP. A better understanding of the relationship between IOP and anesthesia will allow clinicians to more accurately diagnose and monitor ocular disease in children who are unable to cooperate with in-clinic IOP measurement.

Methods

Inclusion and Exclusion Criteria

This was a prospective study approved by the institutional review board at the University of California, San Francisco and Nanjing Medical University. The study adhered to the tenets of the Declaration of Helsinki and written informed consent was obtained from parents/guardians. Children aged ≤ 18 years scheduled for general anesthesia as part of their routine care followed by a pediatric ophthalmologist at Nanjing Medical University were included. Patients were excluded if they met any of the following criteria: history of elevated IOP during any prior clinic visit (> 21 mmHg), history of intraocular surgery, corneal opacity or scar, abnormal intraocular examination findings, intracranial or spinal cord disease, history of intracranial surgery, or taking topical or systemic medications known to affect IOP. The study was designed to enroll ≥ 68 patients to provide 90% power for detecting a 2 mmHg IOP change from baseline assuming standard deviation (SD) of 5 mmHg (paired *t* test, 2-sided alpha error 5%).

Standardized General Anesthetic Protocol

General anesthesia was administered in a standardized fashion which included a mask induction with sevoflurane and propofol maintenance. If premedication was clinically indicated, the agent and dose of the premedication were recorded. Sevoflurane concentration was titrated as clinically indicated, starting at 8%. Propofol maintenance was given at 100 mcg/kg/min. Vital signs including blood pressure, heart rate, and oxygen saturation were collected 1, 3, and 5 minutes after induction. We waited 5 minutes between induction and airway placement to measure the effect of

anesthesia before and after airway placement. Intubation was performed with a laryngeal mask airway or endotracheal tube and time of airway placement and type of airway were recorded.

IOP Measurement

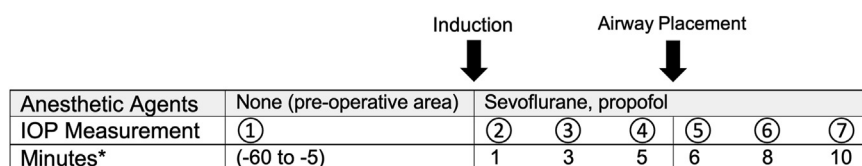
Intraocular pressure was measured at the following 7 time points: preinduction (taken while the child was awake in the preoperative area), postinduction minutes 1, 3, and 5 (induction defined as time of mask induction initiation), and postairway placement minutes 1, 3, and 5. The total time period was 10 minutes after induction (5 minutes before airway placement and 5 minutes after, Fig 1). No eye drops were administered before IOP measurements. Intraocular pressure was measured using the iCare tonometer (IC200; iCare), which can perform supine measurements. This tonometer was chosen given its ability to obtain rapid measurements and not require anesthetic eye drops.⁸ Intraocular pressure was measured in the right eye first at each time point to prevent confounding. The iCare produces a measurement which is the average of 6 IOP readings, which were considered 1 measurement for study purposes and data analysis. Two measurements from each eye were taken at each time point. When the difference between these measurements was ≥ 3 mmHg, a third measurement was taken and the average of all measurements was used for statistical analysis.

Statistical Analysis

Descriptive statistics were performed using mean, SD, median and range for continuous measures, and count and percent for categorical measures. Intraocular pressure change over time before and after anesthesia was visualized using Spaghetti graphs. Generalized linear regression models were performed to evaluate the effect of anesthesia on IOP and to study the association of patient factors (age, gender, vital signs, and airway type) on preanesthetic and postanesthetic IOP. A generalized estimating equation was used to account for the correlations between IOP measurements from 2 eyes of each participant and repeated measurements from the same eye taken at different time points. An IOP prediction model was developed using the postanesthesia IOP measurements as the predictors and preinduction IOP as the outcome. The performance of the prediction model was evaluated using R^2 , and the comparison between predicted IOP and observed IOP. Statistical analysis was performed in SAS version 9.4 (SAS Institute Inc).

Results

Eighty-five children were enrolled with a mean \pm SD age of 7.5 ± 2.9 years and 40.5% were male. Patient demographics are shown in Table 1. Mean height was 128.8 ± 19.9 cm and weight was 30.8 ± 15.2 kg. All patients were undergoing strabismus surgery under general anesthesia. All patients



*Number of minutes measured relative to induction (0), negative values represent prior to induction

Figure 1. Study protocol demonstrating 7 intraocular pressure (IOP) measurement points.

Table 1. Participant Demographics and Baseline Characteristics

	Total (n = 85 Participants, 170 Eyes)
Age (yrs)	
Mean (SD)	7.5 (2.9)
Median (range)	6.5 (2.7–16.7)
Sex: male (%)	34 (40.5)
Height (cm)	
Mean (SD)	128.8 (19.9)
Median (range)	123.0 (90.0–182.0)
Weight (kg)	
Mean (SD)	30.8 (15.2)
Median (range)	25.0 (12.0–98.0)
Central corneal thickness (µm)	
Mean (SD)	544.5 (27.9)
Median (range)	539.5 (481.0–610.0)
Preinduction IOP (mmHg, n = 127 eyes)	
Mean (SD)	20.1 (3.7)
Median (range)	21.4 (10.0–27.5)

IOP = intraocular pressure; SD = standard deviation.

underwent the standardized anesthetic protocol and no patient required premedication before induction. The majority of patients received an endotracheal tube, with only 1 patient receiving a laryngeal mask airway. Preinduction IOP was able to be obtained in 140 eyes of 70 patients (82.4%). The majority of patients (116 eyes of 58 patients, 68%) had IOP measured at 5 time points, with the postairway 5 minute point as the most common missing time points. Data from all 7 time points were available for 10 eyes of 5 patients. Number of eyes at each time point is shown in Table 2.

Mean \pm SD preinduction IOP was 20.1 ± 3.7 mmHg. Mean central corneal thickness was 544.5 ± 27.9 µm. Overall, there was significant IOP change over time ($P < 0.001$, Table 2). Intraocular pressure was lowest at 3 minutes postinduction, decreased to a mean of 13.4 ± 3.7 mmHg from preinduction IOP of 20.1 ± 3.7 mmHg ($P < 0.001$). After this, IOP rose 5 minutes postinduction to 16.5 ± 4.2 mmHg, which did not reach preinduction IOP levels ($P < 0.001$). After airway placement, IOP remained

generally stable and lower than preinduction IOP: 15.4 ± 3.9 mmHg ($P < 0.001$) and 15.6 ± 2.9 mmHg ($P < 0.001$) at 1 and 3 minutes postairway placement, respectively (Table 2). General trends of IOP in the entire cohort as well as the subgroup of 10 eyes with IOP measurements at all time points are shown in Figure 2.

The majority of participants had a decrease in IOP at 1 minute postinduction (109 eyes of 58 participants). In the remaining 13 eyes of 10 participants (11.7%), IOP increased at postinduction 1 minute. In those eyes that had an increase in IOP, the preinduction IOP was generally lower, 16.4 ± 4.17 mmHg compared with 20.4 ± 3.49 mmHg in the group with a decrease in IOP ($P = 0.004$). In the 13 eyes with an increase in IOP, mean IOP increase was 3.7 ± 1.9 mmHg compared with the mean IOP decrease of 5.8 ± 3.9 mmHg seen in the 109 eyes with IOP decrease ($P < 0.001$, Table 3). When stratifying the study population based on IOP 1 minute postinduction into “IOP increase” and “IOP decrease” groups, there are no statistically significant difference between eyes with IOP decrease and eyes with IOP increase in baseline participant and ocular characteristics including age, sex, weight, height, or central corneal thickness (Table S4, available at www.opthalmologyscience.org). Measurements for the “IOP increase” group did not differ significantly from the remainder of the cohort at other time points.

Using R^2 , we assessed various linear regression models of predicting preinduction IOP using singular or multiple postinduction or postairway IOP. R^2 ranged from 0.01 to 0.13. The most predictive was 1 minute postinduction IOP and 3 minutes postairway with or without 3 minutes postinduction (each $R^2 = 0.13$). The least predictive of preinduction IOP was 1 minute postairway (each $R^2 = 0.01$, Table S5 and Fig S3, available at www.opthalmologyscience.org).

Discussion

Understanding the effect of anesthesia on IOP in children is crucial, as many vision-preserving diagnostic and treatment decisions are based on these measurements. In our study using a standardized protocol of sevoflurane and propofol,

Table 2. Change in IOP Over Time

	Preinduction	Postinduction 1 Min	Postinduction 3 Min	Postinduction 5 Min	Postairway 1 Min	Postairway 3 Min	Postairway 5 Min
IOP (mmHg)							
n	127	162	164	34	154	154	30
Mean (SD)	20.1 (3.7)	15.3 (4.0)	13.4 (3.7)	16.5 (4.2)	15.4 (3.9)	15.6 (3.2)	15.6 (2.9)
Median	20.5	15.0	13.5	15.6	15.0	15.0	14.3
Q1, Q3	18.5, 22.7	12.5, 17.5	10.5, 15.0	14.0, 17.0	13.5, 17.0	14.0, 17.5	13.7, 17.0
Range	(9.0–27.7)	(5.5–25.0)	(6.3–29.0)	(9.5–30.0)	(7.0–29.0)	(6.5–23.0)	(11.0–22.7)
P value to preinduction*		< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001

n = 170 eyes.

IOP = intraocular pressure; SD = standard deviation.

*Generalized estimating equation and treating time as a categorical variable.

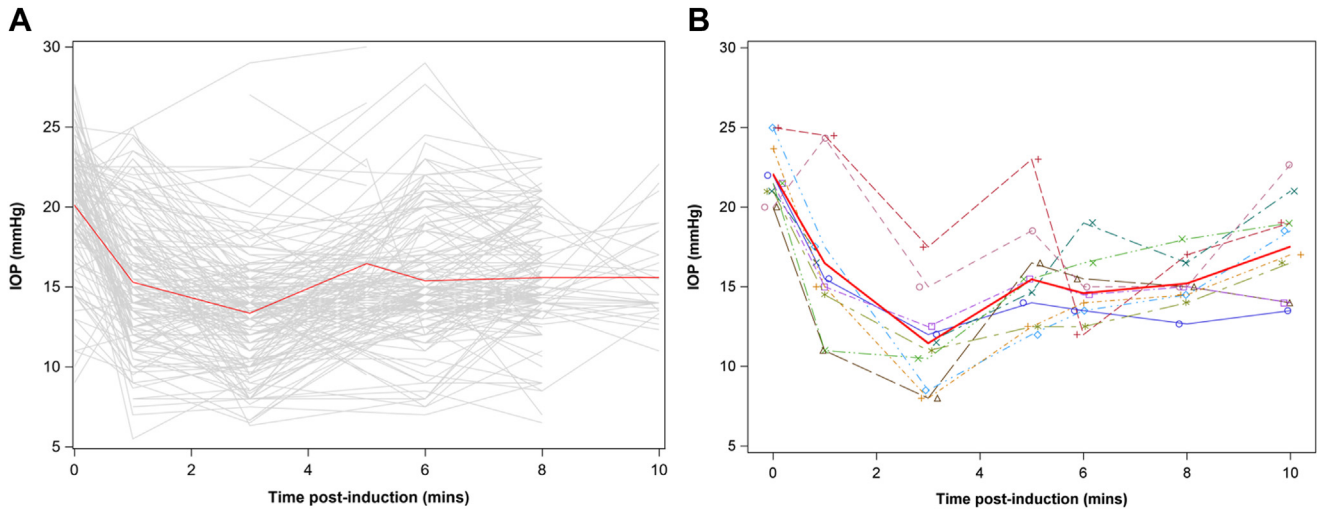


Figure 2. Spaghetti graphs showing change in intraocular pressure (IOP) before and after anesthesia. **A**, All data (n = 170 eyes); **B**, data for only eyes with data at all 7 study time points (n = 10 eyes). The red line represents the mean IOP over time.

we found that general anesthesia in children without intraocular pathology caused a temporary decrease in IOP followed by a slight increase and remaining stable just below preinduction levels.

Intraocular pressure measurement is a key component of pediatric eye care, and the most important parameter in the diagnosis of childhood glaucoma.⁴ For children with glaucoma, IOP reduction is the only proven treatment to prevent permanent vision loss from progressive glaucomatous optic neuropathy.⁹ Often, a target IOP is set based on the patient’s clinical characteristics to dictate a threshold beyond which treatment must be initiated or escalated. Unlike adults with glaucoma, due to their level of cooperation, younger children are often unable to cooperate with other ancillary diagnostics such as visual field testing or OCT imaging of the optic nerve.^{10,11} Although other clinical examination findings such as myopic shift, corneal diameter enlargement, or progressive optic nerve cupping are signs of disease progression, IOP

remains a critical clinical parameter used to monitor disease status and determine disease progression. Thus, accurate IOP measurement is crucial to preventing glaucoma-related blindness.

The general trend we observed in our study was that IOP decreased immediately after the induction of general anesthesia with IOP lowest at 3 minutes postinduction (approximately 7 mmHg lower than preinduction IOP). After this, IOP rose slightly before leveling off to an IOP that did not reach preinduction levels. Although the large majority of participants in our study demonstrated this postinduction decrease in IOP, a small subset (11.7%) had an increase in IOP at that time point. We found no difference in patient demographics to explain the difference between those likely to increase versus decrease at postinduction 1 minute, though in those with an increase in IOP, their preinduction IOP was lower. It is possible that these children are more relaxed (resulting in lower preinduction IOP) or that the effect of anesthesia is dependent

Table 3. Preinduction and 1 Minute Postinduction IOP Stratified by Change in IOP

	Change in IOP at Postinduction 1 Min (mmHg)		P Value*
	IOP Reduction (109 Eyes, 58 Participants)	IOP Elevation (13 Eyes, 10 Participants)	
Preinduction IOP			
Mean (SD)	20.4 (3.49)	16.4 (4.17)	0.004
Median (range)	21.0 (11.0, 27.7)	18.3 (9.0, 22.0)	
Postinduction 1 min IOP			
Mean (SD)	14.6 (3.61)	20.1 (4.42)	< 0.001
Median (range)	14.5 (5.5, 24.5)	22.5 (12.0, 25.0)	
P value†	< 0.001	< 0.001	

IOP = intraocular pressure; SD = standard deviation.

*P value comparing preinduction and postinduction IOP between the group with an IOP reduction at 1 minute postinduction and the group with an IOP elevation at 1 minute postinduction.

†P value comparing preinduction IOP with postinduction 1 minute IOP within the same group.

upon the baseline IOP. Additionally, given that the preinduction IOP was higher than expected, the trend for IOP to decrease postinduction could also be related to non-anesthetic factors such as patient positioning.

Our findings are consistent with prior studies which have shown that most anesthetic agents decrease IOP over time.^{12–14} Ketamine is one anesthetic agent generally thought to raise IOP, though several small studies have shown conflicting results in children.^{15–19} The variable outcomes in these studies is likely attributable to nonstandardized anesthetic protocols and patient populations. General anesthesia likely affects IOP through several mechanisms. First, there is a direct impact from changes in the rate of aqueous humor production and changes in intraocular blood volume.^{20,21} Second, indirect effects on IOP related to decreased vascular tone, decreased extraocular muscle tone, or changes to hypothalamic control of IOP contribute.²² Finally, confounding factors such as airway type and patient positioning may also affect IOP measurements taken under anesthesia.^{23,24} These anesthetic-related changes in IOP may have clinical implications, though better prediction models are needed. Practically, our predictive model found that IOP measured 1 minute postinduction or 3 minutes postairway were most predictive of preinduction IOP, though IOP at these time points may be impractical to obtain given the need for hemodynamic stability and oxygenation. Given this, it might be reasonable for an ophthalmologist to record the times of induction, airway placement, and IOP measurement to allow for future comparison.

Despite its well-powered prospective study design, there are several limitations to this study. First, the study

represents a relatively homogenous patient population, which may limit the generalizability of these findings to other populations. Additionally, several participants were not able to cooperate with preinduction IOP testing or IOP testing at all predefined study time points, preventing the establishment of baseline IOP or complete trend analysis in the entire cohort. Of note, the mean preinduction IOP was higher than expected (20.1 ± 3.7 mmHg), which may suggest nonanesthetic effects contributing to the IOP trends we observed. Additionally, though the anesthetic protocol was standardized, the concentration of sevoflurane was titrated as clinically indicated, which could have affected postinduction IOP and there were likely small variations in the time required to place the airway. Lastly, the standardized general anesthetic protocol used in this study may not reflect clinical practices based on anesthesiologist preference and medication availability. Future studies could consider different anesthetic protocols and evaluation of this study question in children with and without glaucoma or corneal pathology.

In conclusion, we show the effects of general anesthesia on IOP in healthy children, demonstrating that anesthesia decreased IOP most prominently 3 minutes postinduction, then increasing slightly, but not to preoperative levels, after airway placement. Variations in type of anesthetic, timing of induction, and timing of airway placement may also influence these trends. These findings suggest that clinicians should consider that IOP measured under anesthesia may be lower than true IOP and can consider 1 minute postinduction and 3 minutes postairway placement as most predictive of preinduction IOP.

Footnotes and Disclosures

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HUMAN SUBJECTS: Human subjects were included in this study. This was a prospective study approved by the institutional review board at the

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No animal subjects were used in this study.

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Data collection: Oatts, Shen, Zhu, Gong, Liu

Analysis and interpretation: Oatts, Shen, Yu, Ying, Han, Liu

Obtained funding: Oatts

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Abbreviations and Acronyms:

IOP = intraocular pressure; **SD** = standard deviation.

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