Original Article

Effective concentration (EC50) of sevoflurane for intraocular pressure measurement in anaesthetised children with glaucoma: A dose-finding study

Address for correspondence:
Dr. Nitika Goel,
HNO-825, Sector 16D,
Chandigarh, India.
E-mail: nitikagoel7@gmail.com

Submitted: 30-Oct-2023
Revised: 01-Feb-2024
Accepted: 07-Feb-2024
Published: 12-Apr-2024

Access this article online

Website: https://journals.lww.com/ijaweb

DOI: 10.4103/ija.ija_1058_23

Quick response code

Elayavel Ravichandran, Nitika Goel, Babita Ghai, Vikas Saini, Sushmita Kaushik[1]
Departments of Anaesthesia and [1]Ophthalmology, PGIMER, Chandigarh, India

ABSTRACT

Background and Aim: Sevoflurane, a preferred anaesthetic for children, exhibits a dose-dependent reduction in intraocular pressure (IOP). However, consensus is lacking regarding optimal end-tidal sevoflurane concentration for safe IOP measurement. This study aimed to identify the concentration at which IOP measurement could be attempted without inducing movements in paediatric patients after inhalational induction. **Methods:** Two paediatric groups (1–12 months and 12–36 months) with glaucoma undergoing examination under anaesthesia were recruited. After induction with 8% sevoflurane and 100% oxygen, the first child had an end-tidal sevoflurane concentration maintained at 2% for 4 min, followed by IOP measurement. Success was defined as 'no movement', and subsequent concentrations (adjusted in 0.2% steps) were determined using the Dixon and Massey method based on the previous patient's responses. **Results:** The study included 75 children. The effective concentration of sevoflurane causing 'no movement' during IOP measurement in 50% of the study population for successful IOP measurement was 1.98% (95% confidence interval [CI] 1.63, 2.17, $P = 0.017$) for 1–12 months group and 0.55% (95% CI 0.39, 0.66, $P = 0.002$) for 12–36 months group. Probit regression analysis yielded effective concentration of sevoflurane causing 'no movement' during IOP measurement in 95% of the study population values of 2.47% (95% CI 2.24, 4.58, $P = 0.017$) for 1–12 months group and 0.94% (95% CI 0.78, 1.57, $P = 0.002$) for 12–36 months group. **Conclusion:** In paediatric patients, a higher end-tidal sevoflurane concentration of 2% is needed for IOP measurement in 1–12 months age group compared to 0.5% required in 12–36 months age group, achieving success in 50% of the study population.

Keywords: Children, dose-finding study, glaucoma, intraocular pressure, sevoflurane

INTRODUCTION

Reliable and accurate intraocular pressure (IOP) measurements are the most challenging to obtain in a child. Still, they are clinically significant in diagnosing and treating a paediatric glaucoma case.[1,2] Because of the absence of cooperation in paediatric glaucoma cases, IOP measurements are mostly feasible only with sedation or general anaesthesia.[3] Inhalational anaesthetic agents are widely used to maintain general anaesthesia for children undergoing examination under anaesthesia (EUA), given their ease of administration and acceptable intraoperative and recovery characteristics.[4] However, it has been studied that inhalational anaesthetic drugs decrease IOP to variable extents depending on the depth of anaesthesia given.[5,6]

Sevoflurane has become the preferred inhalational anaesthetic in pediatric practice due to its smooth induction, efficient uptake and distribution,

How to cite this article: Ravichandran E, Goel N, Ghai B, Saini V, Kaushik S. Effective concentration (EC50) of sevoflurane for intraocular pressure measurement in anaesthetised children with glaucoma: A dose-finding study. Indian J Anaesth 2024;68:480-5.

diminished systemic side effects and prompt recovery. However, in higher doses, sevoflurane causes a decrease in IOP.[1] Dhillon *et al*. reported reduced IOP with sevoflurane anaesthesia (10% fall at 2% end-tidal concentration of sevoflurane [EtSevo]).[7] Studies show a linear decrease in IOP of 10% as EtSevo increases by 2%.[7] Thus, maintaining a higher concentration of sevoflurane for a longer period is bound to decrease IOP, causing misinterpretation of results and further treatment.

There is no consensus on what effective sevoflurane concentration must be maintained after eyelash reflex loss to result in minimum changes in IOP during EUA. Also, age is an important factor affecting the EtSevo required for IOP measurement. Since infants have lower lung volumes, higher minute ventilation and higher cardiac output than toddlers,[8] they require a higher EtSevo for IOP measurement than older children. Hence, we proposed to estimate the EtSevo required to measure IOP successfully in two different age groups of children. The study hypothesised that the EtSevo required for successful IOP measurement in 1–12 months would be higher than the EtSevo required for IOP measurement in children 12–36 months.

METHODS

The proposed study was a prospective, double-blinded clinical study carried out at a tertiary care centre in 75 children with suspected or congenital glaucoma scheduled for EUA. After obtaining institute ethical clearance (vide approval number: NK/6960/MD/107, dated 5 April 2021), the study was registered in the Clinical Trials Registry-India (vide registration number CTRI/2021/04/032551, accessible at www.ctri.nic.in/). The study procedures follow the guidelines laid down by the World Medical Association. The study was carried out in accordance with the principles of the Declaration of Helsinki, 2013 from 15 April 2021 to 30 November 2021. Written informed consent was obtained from the parent or guardian of all the study children to use the patient data for research and educational purposes.

Children posted for non-glaucoma surgery were excluded. In addition, children with cardiac anomalies, potentially difficult airways, reactive airway malformation, signs of upper respiratory infection or a need for rapid-sequence induction were also excluded. No premedication was given to any study child. To reduce preoperative anxiety, the children were accompanied by their parents/guardians inside the operation theatre.

The children were monitored using electrocardiography, pulse oximetry, capnography and non-invasive blood pressure. Induction of anaesthesia was achieved using a closed circuit and silicone mask with sevoflurane (Tec 7, GE Healthcare, Helsinki, Finland), with the dial concentration set at 8% and 100% oxygen at a flow rate of 6 L/min with preservation of spontaneous breathing using standard anaesthesia workstation (Datex Ohmeda S/5 Avance GE Healthcare, Madison WI, USA). Induction time was defined as the time from the start of anaesthesia to loss of eyelash reflex. Just after the loss of eyelash reflex, local anaesthetic drops (proparacaine HCI USF 0.5% sterile ophthalmic solution) and fluorescein sodium (Fluoro Touch, fluorescein sodium 1 mg strip) dye were instilled, and the baseline IOP was measured, followed by intravenous cannulation. Afterwards, the sevoflurane dial setting was adjusted to achieve an EtSevo at the predetermined level (2% for the first child). In each child, the target EtSevo was maintained for a minimum of 4 min by adjusting the vaporiser dial setting and also by ensuring a tight seal of the face mask throughout the period to maintain the EtSevo at the desired level of range (±0.1%) for the whole period, following which IOP measurement was done. This period was chosen because it has been shown that 4–8 min is required to attain more than 90% cerebral partial pressure equilibrium with the arterial sevoflurane.[9] IOP was recorded in both eyes of the child being examined using a hand-held Perkins application tonometer (Perkins Mk3 Tonometer, Clement Clarke, Columbus, Ohio, USA). The child was observed for 'any movement' or 'no movement'. It was designated as 'unsuccessful' if there was movement in the form of purposeful movement of extremities, coughing and breath holding and 'successful' if the child showed 'no movement' to the above mentioned response.

The unsuccessful IOP measurement due to limb movement was rectified by raising the sevoflurane concentration to 8% or administering drugs like propofol in case of adverse effects like laryngospasm. The IOP was measured once the child was adequately anaesthetised. EtSevo was increased or decreased (step-wise 0.2% for sevoflurane) using Dixon and Massey's up-and-down method in the following patient, depending on the previous patient's response.[10]

The researcher recording the observations in response to IOP measurement was not aware of the EtSevo. This was achieved by applying a screen between the monitor and the anaesthetist recording the observations. The ophthalmologist was also blinded to the EtSevo reading. The endpoint of the study was the response to the IOP measurement.

The primary outcome was the effective concentration (EC50) of sevoflurane causing 'no movement' during IOP measurement in 50% of the study population. The secondary outcomes included effective concentration (EC95) of sevoflurane causing 'no movement' during IOP measurement in 95% of the study population, the difference between the IOP reading measured at the baseline and pre-determined EtSevo concentration and the presence of any adverse effects such as laryngospasm, bradycardia, breath holding, desaturation with SpO_2 <92% at the time of attempting IOP measurement.

Statistical analysis was performed using Excel 2007 (Microsoft, Redmond, WA, USA) and Statistical Package for the Social Sciences statistics software version 15.0 (IBM Corp, Armonk, NY, USA). Data were represented as mean and standard deviation (SD) or numbers with percentages. The categorical values were analysed by the χ^2 test and the continuous variables by the *t*-test. The mean of the midpoint of all unsuccessful/successful pairs was used to determine EC50 using Dixon and Massey's up-and-down method. Dose–response curves for EC50 with 95% confidence intervals (CI) were determined using probit regression analysis (PRA). The sample size was calculated based on the fact that a minimum of eight crossover pairs were required for the analysis using modified Dixon and Massey's up-and-down method.[10] Pearson correlation analysis was used to study the correlation between patient's characteristics and response to IOP measurement.

RESULTS

We assessed 83 children (49 in 12–36 months group and 34 in 1–12 months group, respectively) for eligibility. Of these, 75 children were recruited for the study [Figure 1]. Demographic characteristics of the study population are shown in Table 1.

Using the modified Dixon up-and-down method, the mean of midpoints of all pairs was calculated individually in each group, and it was found to be 0.6% in the 12–36 months age group and 2.0% in the 1–12 months age group. The end-tidal sevoflurane concentration–response data of IOP measurement attempts for each child of both groups obtained by the up-and-down method are represented in Figures 2a and b. This was further analysed using PRA, which confirmed the EC50 of 1.98% (95% CI 1.63, 2.17, P = 0.017) in 1–12 months group and 0.548% (95% CI 0.39, 0.66, P = 0.002) in 12–36 months group. The concentration–response curve of sevoflurane plotted from PRA of individual end-tidal concentrations and the respective response to IOP measurement in both the groups are shown in Figures 3a and b.

Using PRA, the EC95 of sevoflurane was measured to be 2.47% (95% CI 2.24, 4.58, P = 0.017) in 1–12 months group of children and 0.94% (95% CI 0.78, 1.57, P = 0.002) in 12–36 months group of children.

In both the study groups, there was a significant difference between the IOP measured just after induction and at predetermined EtSevo, that is, mean (SD) change in IOP: 1.8 (1.5) mmHg, P = 0.017 in 1–12 months and 1.3 (1) mmHg, P = 0.002 in 12–36 months. Hence, it was found that there was a

Table 1: Demographic data of children

	1–12 months group	12–36 months group
Gender – male/female	15/15	25/20
American Society of Anesthesiologists physical status I/II	28/2	43/2
Age (months)	7.2 (4.8)	23.52 (9)
Weight (kg)	6.3 (1.9)	11 (1.71)
Taking antiglaucoma drops	24	37
Prior glaucoma surgery	16	38

Data are represented as absolute numbers or mean (standard deviation)

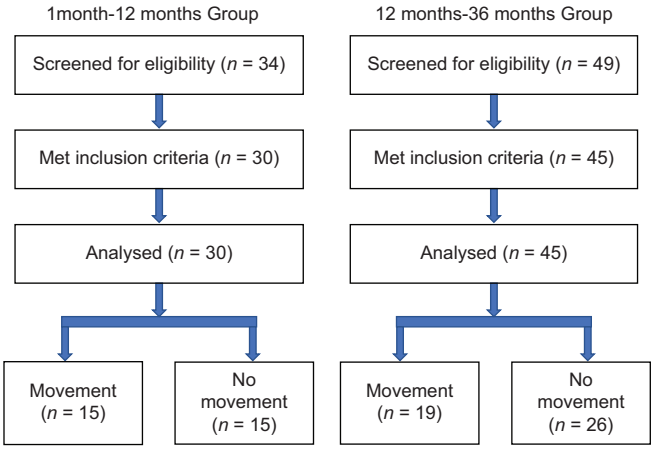

Figure 1: Study flow diagram showing patient recruitment

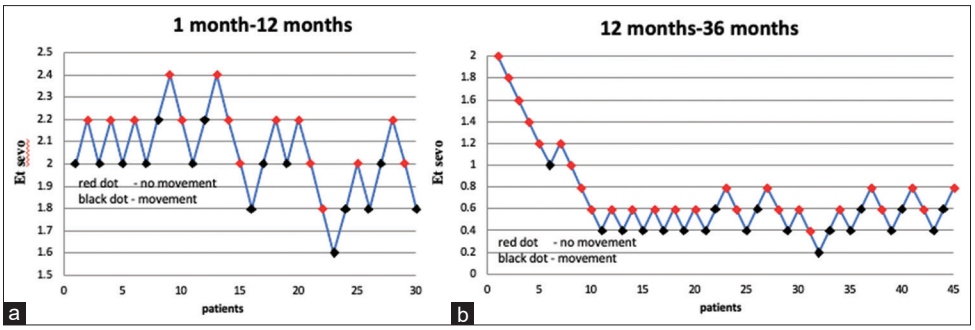

Figure 2: (a) Responses of 30 children (X-axis) in 1–12 months age group and in whom intraocular pressure measurement was attempted and end-tidal concentration of sevoflurane (Y-axis) was determined with Dixon and Massey's up-and-down method. (b) Responses of 45 children (X-axis) in 12–36 months age group in whom intraocular pressure measurement was attempted, and end-tidal concentration of sevoflurane (Y-axis) was determined with Dixon and Massey's up-and-down method

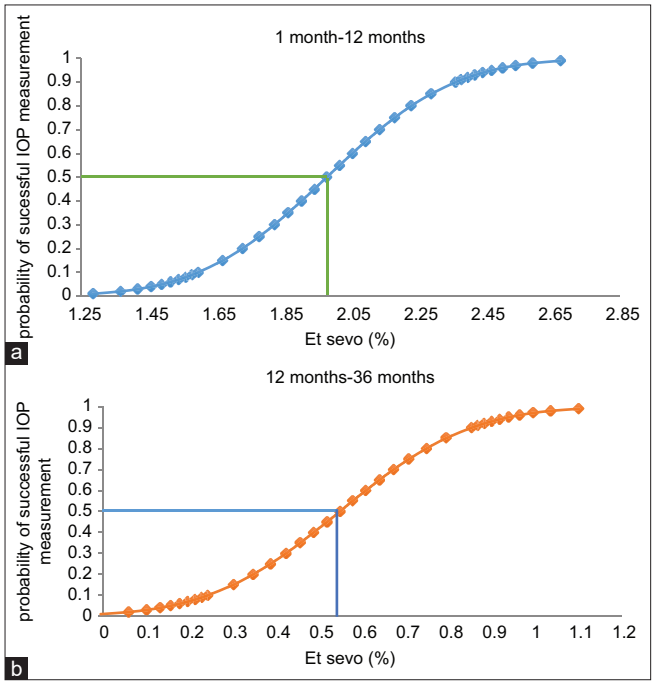

Figure 3: (a) Concentration–response curve of sevoflurane plotted by probit regression analysis of individual end-tidal concentrations (X-axis) and the probability of successful intraocular pressure measurements (Y-axis) in children of age group 1–12 months. b) Sevoflurane's concentration-response curve plotted by probit regression analysis of individual end-tidal concentrations (X-axis) and the probability of successful intraocular pressure measurements (Y-axis) in children of age group 12–36 months. EtSevo = end-tidal sevoflurane, IOP = intraocular pressure

significant difference in the IOP measured at baseline and equilibrium in both groups of children. Figures 4a and b show the mean IOP of both eyes after induction and at predetermined EtSevo in the 1–12 months age group and 12–36 months age group.

DISCUSSION

Our findings revealed an EC50 of 1.98% for the age group spanning 1–12 months and 0.548% for the age group of 12–36 months, both deemed requisite for accomplishing accurate IOP measurements without eliciting any movement.

EC50, denoting the end-tidal sevoflurane concentration, signifies the concentration at which a 50% probability of no movement in response to IOP measurement is achieved using Perkins tonometry. This measure is widely acknowledged as the standard for determining anaesthetic potency in volatile agents, including sevoflurane.[9]

The context of our study arises from the necessity of deep sedation or general anaesthesia in paediatric examinations, which raises concerns about potentially distorted IOP readings due to the influence of anaesthetic agents, particularly inhalational agents. Notably, we emphasise the importance of identifying the optimal timing for IOP measurement during general anaesthesia and establishing the minimum effective concentration of the inhalational agent to prevent any undesired movement in paediatric patients. Samy *et al*., in their study, recommended that IOP be checked during intermediate plane of anaesthesia to obtain near-awake values.[1] However, they did not mention the end-tidal concentration of the anaesthetic agent required for IOP measurement. Therefore, in addition to knowing the timing of IOP measurement during general anaesthesia, it is also pertinent to ascertain the minimum effective concentration of inhalational agent that should be maintained without causing any movement in the child.

Given the current absence of consensus on the minimal anaesthetic concentration for IOP measurement and uncertainties regarding the accuracy of such measurements for subsequent clinical decisions, our study contributes to addressing these gaps in knowledge. Determining near-awake IOP values

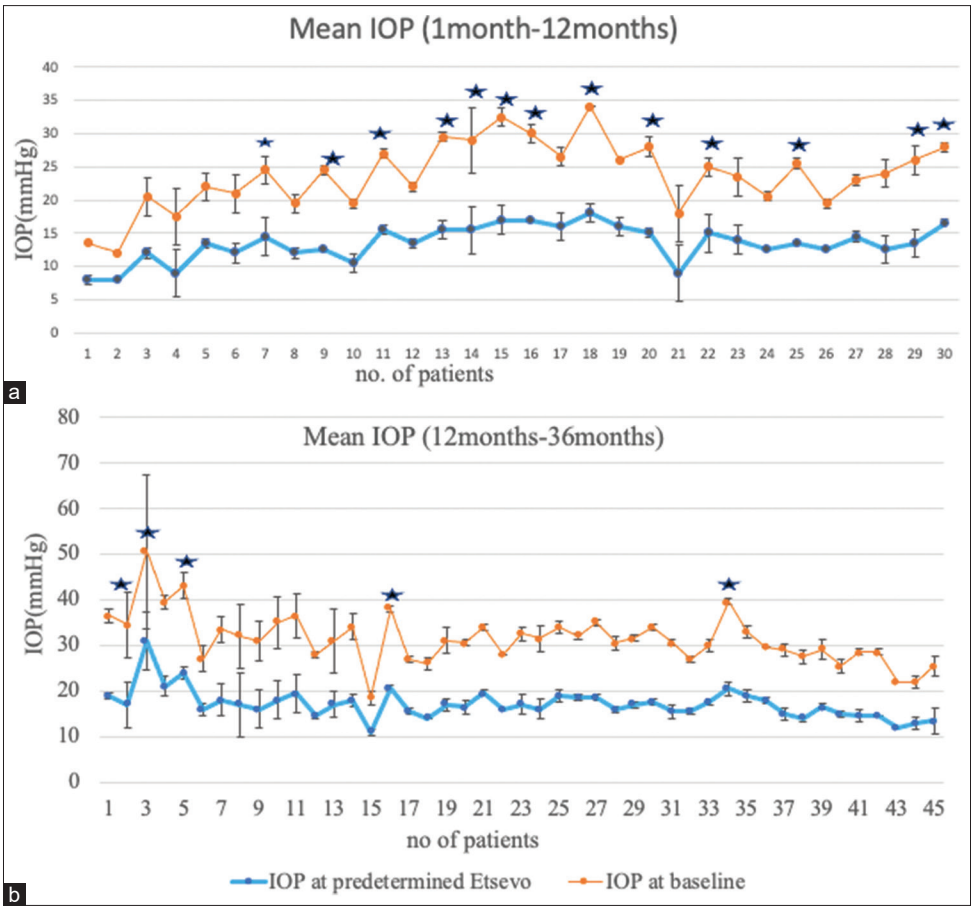

Figure 4: (a) Graph showing the mean intraocular pressure of both eyes just after induction and at a predetermined EtSevo in 1–12 months age group of children. (b) Graph showing the mean intraocular pressure of both eyes just after induction and at predetermined EtSevo in 12–36 months age group of children. *$P < 0.05$. EtSevo = end-tidal sevoflurane, IOP = intraocular pressure, no = number

holds significant implications for managing glaucoma in paediatric patients, influencing decisions regarding surgery or medical interventions based on the obtained IOP values during ophthalmological examinations.

Conventionally, after inhalational induction with 8% sevoflurane, the sevoflurane dial setting is arbitrarily adjusted to maintain the minimum alveolar concentration (MAC) within the 2%–3% range. It has been found that a higher concentration of any inhalational anaesthetic agent given for a longer duration of time not only causes a fall in IOP but also has a potential implication on the child's haemodynamic and respiratory physiology.[11] It also leads to increased theatre pollution, higher anaesthetic costs and many significant health-related problems among anaesthesiologists and surgeons.

Infants require higher MAC for an adequate depth of anaesthesia for any procedure than older children.[11] Acknowledging the physiological differences between infants and older children, our study underscores the need for higher MAC in infants to achieve adequate anaesthesia depth. This, coupled with a fresh gas flow of 6 L/min, contributed to higher end-tidal sevoflurane concentrations in infants (1.98%) compared to older children (0.548%).

IOP is reduced by sedative premedication and use of opiates.[12,13] Since IOP measurement is usually a day-case procedure, these agents are frequently omitted to facilitate early emergence from anaesthesia and timely discharge. Withholding preoperative sedation may contribute to preoperative anxiety, which can lead to higher anaesthetic requirements. These factors result in the inhalational agent often being the sole anaesthetic medication given for EUA eyes, with a higher MAC required to obtain an appropriate depth of anaesthesia than other surgical procedures on eyes.

This study should also be read in terms of some limitations. Firstly, none of the children were

cooperative for an awake IOP measurement. Therefore, we could not ascertain whether the IOP values obtained after induction resembled awake IOP. Secondly, we included all patients with suspected (enlargement of cornea, bulbous) or diagnosed glaucoma. The results may not apply to non-glaucomatous patients. Thirdly, the selected age group was only 1 month to 3 years, so the results are not applicable to neonates and older children. Fourthly, no premedication was used in any of the children. This made most of our study children more anxious and uncooperative during induction, which led to the possibility of the generation of higher minute ventilation during crying and faster induction times than usual so that they attain early equilibrium at the same anaesthetic concentrations. However, this is a transient type of equilibrium and any attempt for IOP measurement at this point can lead to the movement of children, resulting in unsuccessful measurement. Thus, premedicated and un-premedicated children might differ in the EtSevo required for IOP measurement. Our study had a minimum delay period of 4 min before IOP measurement could be performed. We feel that the time at which IOP measurement can be done successfully with these EC50 and EC95 values still needs further exploration. Therefore, future trials evaluating the minimum time for IOP measurement in glaucomatous children can be planned.

Through this study, we endeavoured to postulate the minimum safe and effective concentration of sevoflurane for IOP measurement in children aged 1–36 months. Though the previous studies suggest IOP measurement to be done immediately after induction, the anaesthetic concentration required for IOP measurement has not been documented.

CONCLUSION

We conclude that end-tidal sevoflurane of 2% has a 50% probability for successful IOP measurement in children aged between 1 and 12 months. In comparison, the end-tidal sevoflurane of 0.5% has a 50% probability for successful IOP measurement in children aged between 12 and 36 months.

Data availability statement

De-identified data may be requested with reasonable justification from the author (nitikagoel7@gmail.com) and shall be shared after approval as per the authors' institutional policy.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

ORCID

Elayavel Ravichandran: https://orcid.org/0009-0007-5626-432X
Nitika Goel: https://orcid.org/0000-0002-6572-0311
Babita Ghai: https://orcid.org/0000-0003-1885-332X
Vikas Saini: https://orcid.org/0000-0002-9987-4984
Sushmita Kaushik: https://orcid.org/0000-0002-9175-5497

REFERENCES

1. Samy E, El Sayed Y, Awadein A, Gamil M. Effect of general inhalational anesthesia on intraocular pressure measurements in normal and glaucomatous children. Int Ophthalmol 2021;41:2455-63.
2. Sun Y, Wang J, Wang W, Fan G, Wu S, Zhao F, *et al*. Effect of different surgical positions on intraocular pressure: A cross-sectional study. BMC Ophthalmol 2022;22:318. doi: 10.1186/s12886-022-02547-z
3. Termühlen J, Gottschalk A, Eter N, Hoffmann EM, Van Aken H, Grenzebach U, *et al*. Does general anaesthesia have a clinical impact on intraocular pressure in children? Paediatr Anaesth 2016;26:936-41.
4. Gofman N, Cohen B, Matot I, Cattan A, Dotan G, Stolovitch C, *et al*. Do intraocular pressure measurements under anesthesia reflect the awake condition? J Glaucoma 2017;26:299–302.
5. Mikhail M, Sabri K, Levin AV. Effect of anesthesia on intraocular pressure measurement in children. Surv Ophthalmol 2017;62:648–58.
6. Ding C, Wang P, Tian N. Effect of general anesthetics on IOP in elevated IOP mouse model. Exp Eye Res 2011;92:512-20.
7. Dhillon HK, Agarkar S, Vijaya L, Bhende M, Baskaran M, Jaichandran VV. Examination under anesthesia: Preferred practice. Indian J Ophthalmol 2023;71:3438-45.
8. Sethi S, Goel N, Ghai B, Sharma MN, Ram J. EC_{50} of sevoflurane for classic laryngeal mask airway insertion in children at different time points: A randomized blind trial. J Anaesthesiol Clin Pharmacol 2020;36:489-93.
9. Goel N, Jain D, Ghai B. Sevoflurane EC50 for intravenous cannulation attempt and movement in children. Acta Anaesthesiol Scand 2019;63:842–6.
10. Oron AP, Souter MJ, Flournoy N. Understanding research methods: Up-and-down designs for dose-finding. Anesthesiology 2022;137:137-50.
11. Cao Y, Zhang L, Peng X, Wu Y, Zhang Q, Gu E, *et al*. Increased minimum alveolar concentration-awake of Sevoflurane in women of breast surgery with sleep disorders. BMC Anesthesiol 2020;20:17. doi: 10.1186/s12871-020-0931-3.
12. Oberacher-Velten I, Prasser C, Rochon J, Ittner KP, Helbig H, Lorenz B. The effects of midazolam on intraocular pressure in children during examination under sedation. Br J Ophthalmol 2011;95:1102-5.
13. Pal CK, Ray M, Sen A, Hajra B, Mukherjee D, Ghanta AK. Changes in intraocular pressure following administration of suxamethonium and endotracheal intubation: Influence of dexmedetomidine premedication. Indian J Anaesth 2011;55:573-7.