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ARTICLE

Effect of general anaesthesia on intraocular pressure in paediatric patients: a systematic review

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Abstract

Objectives Assessment of the impact of general anaesthetic agents on intraocular pressure (IOP) in children via systematic review.

Methods Pubmed, Embase, and CENTRAL databases were systematically searched to identify randomised controlled trials, prospective, and interventional studies. The search included all studies through October 5, 2018 with no date or language restrictions. A linear mixed-effects regression analysis was performed to study the change in IOP after general anaesthesia (GA).

Results The strategy identified 518 studies that met search criteria. Six studies (531 eyes) were included for quantitative synthesis. Seven categories of mixed and non-mixed induction and maintenance agents were compared. When assessing all agents utilising a model of mean IOP as a function of time, IOP decreased after induction phase at a rate of -0.59 ± 0.19 mmHg/min (P value $= 0.006$).

Conclusions This systematic review showed that most anaesthetic agents significantly decrease IOP over time after the induction phase of general anaesthesia in children. An understanding of the effects of GA on IOP is critical for those performing paediatric ophthalmic examinations under anaesthesia.

Introduction

Intraocular pressure (IOP) is an important clinical parameter for the diagnosis, monitoring, and treatment of glaucoma. Obtaining accurate and reliable IOP measurements in awake children is generally more challenging than in adults often due to poor cooperation, eye squeezing, or Valsalva effects related to crying in the former. The availability of an easy to use portable tonometer (Icare USA, Raleigh, NC) has improved the ability to obtain IOP measurements in children, but an examination under anaesthesia (EUA) is often still required, particularly in young children being evaluated or treated for glaucomatous disease [1, 2].

It is well known that general anaesthesia (GA) may affect IOP measurement [3]. Different anaesthetic agents and depth of anaesthesia may have varying effects on IOP, and measurement may be further confounded by methods of airway management. Anaesthetic agents may directly affect IOP through mechanisms such as changes in aqueous humour or intraocular blood volume modulated by changes in blood pressure. The IOP level may also be indirectly impacted by altered vascular tone or central control of IOP in the hypothalamus as well as by local effects such as varying tone of the extraocular muscles with resultant increased or decreased compression of the sclera [4, 5]. Patient positioning, use of an eyelid speculum, tonometer type, and scleral rigidity may also alter IOP measurement under anaesthesia [3, 6, 7].

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Although many studies have evaluated the effect of general anaesthetic agents on IOP in children, conclusions regarding IOP changes during EUA remain controversial. We performed a systematic review to study and compare the rates of change in IOP over time following the administration of GA among different anaesthetic agents in paediatric patients.

Materials and methods

This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, following the PRISMA checklist.

Literature search

A comprehensive literature search of Pubmed, Embase, and CENTRAL databases was performed to identify studies published until October 5, 2018. Searches were conducted using the following terms for Pubmed: (Intraocular pressure [MeSH] OR Intraocular pressures OR IOP OR Ocular Tension OR Ocular Tensions) AND (Paediatric[MeSH] OR Children OR Boys OR Girls OR Infants) AND (General Anaesthesia[MeSH] OR Anaesthesia). The search was run according to Medical Subject Headings (MeSH) with no date or language restrictions. This search was also supplemented by hand searching the bibliographies of all included studies. Abstracts and titles were screened independently by two reviewers (ST and JO) to exclude irrelevant studies. Full-text articles were also carefully and independently assessed by the same reviewers with regards to criteria for inclusion in the systematic review. Any disagreement was resolved through discussion and reached consensus with a third reviewer (YH).

Study selection

Studies were selected based on the following inclusion criteria: (1) randomised controlled trial (RCT), prospective cohort study, or non-randomised controlled clinical study, (2) non-glaucomatous paediatric patients (0–18 years old) undergoing GA, and (3) reporting of specific anaesthetic agents, anaesthesia time points, and IOP measurement. Studies were excluded for one or more of the following criteria: (1) each measured IOP not reported and data limited to IOP range, IOP change or mean IOP over the entire anaesthetic period, (2) anaesthesia performed for surgical procedures that are known to affect IOP including those involving the eye, the cardiovascular system or those performed with the patient in prone position, (3) studies including patients with diagnoses of glaucoma or glaucoma suspect, or (4) studies of older anaesthetic agents not currently used in practice today. In studies that compared IOP measurements with multiple tonometers in the same study population, we only analysed Perkins tonometry data and thus avoided duplication.

Data extraction and quality assessment

Data were extracted from all eligible studies by one reviewer (ST), using a standard data recording sheet to collect the following information: first author, year of publication, study country, study design, age, gender, premedications, general anaesthetic agent(s) used, number of eyes, mean IOP at each time point, and tonometry type. The second reviewer (JO) subsequently verified the extracted data. Authors of the studies included were contacted to request any unpublished data.

Because each study defined time in different ways and most of the data was limited to the first 5 min of anaesthesia, we re-categorised them into five time points: baseline before induction (T0), 30 s after induction (T1), 1 min after induction (T2), 3 min after induction (T3), and 5 min after induction (T4). Data from each anaesthetic agent were extracted separately.

The methodological quality of the included studies was independently assessed by the two reviewers, using the risk of bias assessment tool. Disagreement between the reviewers were resolved through discussion and consensus as above. The Cochrane's collaboration tool [8] was used to assess randomised studies [9, 10] and the Newcastle–Ottawa Scale (NOS) star system was used to assess non-randomised studies based on study selection, comparability, and outcome [11–15].

Statistical analysis

Statistical analysis was conducted using R version 3.3.3 for Mac OS X. Mean IOP was analysed as a continuous variable. A P value < 0.05 was considered as statistically significant. A heterogeneity test was done on enroled studies via χ^2 statistic, in which P value < 0.1 was regarded as significant heterogeneity. A linear mixed-effects regression analysis was performed to determine the IOP change over each period of time for whole and subgroup analysis.

Results

Inclusion of studies

Seven hundred and fifty-eight studies were identified, 392 from Embase, 302 from Pubmed, and 64 from CENTRAL. Among these studies, 240 were duplicates and excluded.

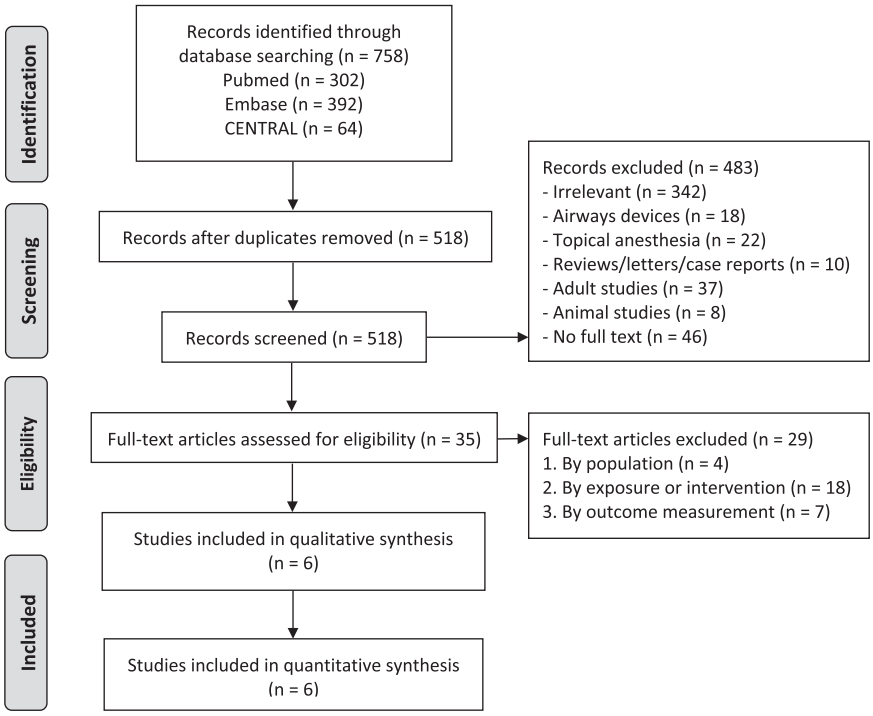

Fig. 1 Flow chart for literature searching. The databases were systematically searched to identify randomised controlled trials, prospective, and interventional studies without date or language restrictions. Six studies were included for analysis.

For the remaining 518 studies, irrelevant studies were identified by screening titles and abstracts. Thirty-five studies were then selected and investigated with a full-text review, of which 29 were further excluded on the basis of including of patients with diagnoses of glaucoma and/or glaucoma suspect ($n = 3$), failing to provide specific anaesthetic agent information ($n = 7$), complicated anaesthetic administration protocol ($n = 2$), use of medications that are no longer in common use ($n = 9$), only reporting IOP ranges with no raw data ($n = 7$), or unmatched age criteria ($n = 1$). After exclusion of these unqualified studies, six studies remained for purposes of data review and analysis (Fig. 1).

Characteristics of studies and quality assessment

A total of 531 eyes from 6 studies were included for analysis. The main characteristics of the included studies are summarised in Table 1. The studies were published between 2005 and 2017, two of which were RCTs with parallel design [9, 10] and the remaining four were prospective cohorts [11–14]. Gender of the included subjects was distributed equally (male:female = 198:210).

Ketamine was evaluated in 2 out of the 6 studies: a double-masked RCT [9] and the a prospective non-inferiority study [12]. Of the 40 children included in the RCT, 26 eyes were in a routine dose of intramuscular ketamine group and 25 eyes were in a low dose of intramuscular ketamine group. IOP was measured in both eyes for children undergoing non-ophthalmic surgery and only in the non-operative eye for those undergoing ophthalmic surgery. IOP was measured by a masked observer before and then 5 min after ketamine administration. In the prospective study of ketamine, all patients underwent non-ophthalmic surgery with intravenous ketamine and IOP was measured.

For the publications studying inhalation agents, one was a single-masked RCT and the remaining three were prospective observational studies. All patients in these studies were undergoing non-intraocular surgery. Propofol with sevoflurane was the most common combination of anaesthetic agents, followed by propofol, sevoflurane, and desflurane, based on number of eyes involved in the included studies. Most of the studies [11, 13, 14] included IOP from both eyes while one included IOP from only one eye [10].

Midazolam was the main premedication used in the 5 out of 6 studies [9–11, 13, 14]. Perkins applanation tonometer was used in four studies [9, 11, 13, 14], and Tono-Pen XL in two [10, 12]. All IOPs were measured in the supine position without an eyelid speculum.

Quality assessment of the Nagdeve et al. [9] RCT showed low risk of bias in all categories. The other RCT from Park et al. [10] showed high risk in the allocation concealment category and unclear risk in the blinding of participants and personnel category (Fig. 2). The remaining four non-randomised studies showed good quality using the NOS (Table 2).

Table 1 Characteristics of studies meeting inclusion criteria.

First author, year of publication	Location	Study type	Age Mean (SD) (years)	Gender M:F	Tonometry	Premedications	Anaesthetic agents	Number of eyes	Intraocular pressure									
									T0		T1		T2		T3		T4	
									Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Nagdeve, 2005 [9]	India	RCT	3.8 (1.6)	34:6	Perkins	Triclofos	Ketamine 3 mg/kg IM	25	11.4	2.0							11.1	2.2
							Ketamine 6 mg/kg IM	26	10.8	2.2							12.6	2.8
Oberacher, 2011 [11]	Germany	Cohort	41.7 (16.1)[a]	24:12	Perkins	Midazolam	Propofol/sevoflurane	36 OD	10.6	0.3							8.1	0.3
							Propofol/sevoflurane	36 OS	10.7	0.3							8.0	0.3
Halstead, 2012 [12]	USA	Cohort	NA	31:49	Tono-Pen XL	None	Ketamine	80	17.5	2.2[b]					18.9	2.0[b]		
Park, 2013 [10]	Korea	RCT	9.1 (1.7)	12:4	Tono-Pen XL	Midazolam, glycopyrolate	Sevoflurane	16	16.0	2.5	11.7	2.0	13.2	2.4	10.8	2.5	10.1	2.1
			9.8 (2.5)	8:8			Desflurane	16	15.0	3.6	12.0	3.6	13.5	3.2	10.8	3.2	9.8	2.5
Termühlen, 2016 [13]	Germany	Cohort	4.5 (2.68)	38:62	Perkins	Midazolam	Propofol	84	7.7	3.3								
							Propofol/sevoflurane	20			4.5	2.0						
							Sevoflurane/propofol	28	6.2	1.9								
Wang, 2017 [14]	China	Cohort	5.1 (2.2)	51:69	Perkins	Midazolam	Propofol	30	7.6	3.1								
							Propofol/sevoflurane	96			4.2	2.2						
							Sevoflurane/propofol	38	5.9	1.6								

RCT randomised controlled trial, *Cohort* prospective cohort, *NA* not available, *OD* right eye, *OS* left eye, *SD* standard deviation.

[a]Months.

[b]Standard error.

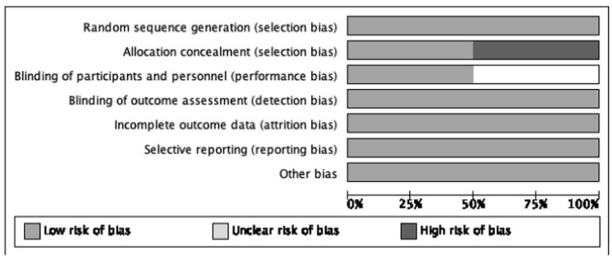

Fig. 2 Risk of bias. One RCT showed low risk of bias in all categories and another RCT showed high risk in the allocation concealment category and unclear risk in the blinding of participants and personnel category.

Table 2 Risk of bias assessment score by Newcastle–Ottawa Scale from Ottawa hospital research institute.

Studies	Selection	Comparability	Outcome	Total
Oberacher	4	2	2	8
Halstead	4	2	2	8
Termühlen	4	2	2	8
Wang	4	2	2	8

IOP change in the six included studies

Table 1 summarises the results of IOP change over time following GA. Nagdeve et al. [9] reported a significant increase in IOP from baseline to 5 min after intravenous administration of induction-dose ketamine ($P < 0.001$) and non-significant change in IOP after intravenous administration of low-dose ketamine. Halstead et al. [12] reported that intramuscular ketamine injection did not significantly increase IOP at 2.5 min post-injection in paediatric patients undergoing procedural sedation and analgesia (PSA) by using a noninferiority margin of 2.6 mmHg (15%). The strength of the study was the age stratification, including younger children, and studying a commonly used ketamine dosage. However, the study was limited by IOP measurements obtained by multiple providers who may be unfamiliar with Tono-Pen XL, potentially resulting in inaccuracy and variability in IOP values.

For the publications studying inhalation agents, Oberacher-Velten et al. [11] found that IOP significantly decreased from baseline to 5 min after propofol injection and sevoflurane inhalation ($P < 0.0001$). The use of oral midazolam as premedication showed no relevant impact on IOP. Park et al. [10] reported a significant decreased in IOP at T1, T2, T3, and T4 when compared to baseline IOP in both sevoflurane and desflurane groups ($P < 0.05$). The sudden increase of IOP at T2 in both groups, 1 min after the intubation, was explained by the secondary increased sympathetic activity due to laryngotracheal stimulation during laryngoscopy and tracheal intubation. Nevertheless,

this increased IOP was still not greater than baseline. There was no difference of IOP between sevoflurane and desflurane groups. The limitation of this study was the use of thiopental sodium for induction, which could potentially lower IOP. Termühlen et al. [13] conducted a prospective cohort study and reported that GA reduced IOP significantly. The patients were grouped into the following groups without randomisation (induction agent/maintenance agent): propofol/propofol, propofol/sevoflurane, sevoflurane/propofol, and sevoflurane/sevoflurane. The results were reported as mean IOP of all children at each time point with a graph demonstrating IOP change for each anaesthetic agent. This study was limited by unequal groups with only a few exact IOP values reported. Lastly, Wang et al. [14] conducted a prospective cohort study similar to the prior study in terms of study groups, premedication, induction agent (remifentanil), and tonometer type, but with a larger sample size (120 versus 100). IOP results were similar to the Termühlen study.

Rate of IOP change after general anaesthesia

After extracting the data from the six included studies, we calculated that the mean IOP at baseline before induction of anaesthesia (T0) was 10.3 mmHg. The change in IOP during GA in each study is shown in Fig. 3. Although not all studies reported IOP at every time point, a trend in IOP following GA was still observed. The use of most agents, including desflurane, sevoflurane, propofol with sevoflurane, and intramuscular ketamine 3 mg/kg (low dose), was associated with decreased IOP over time. In contrast, intramuscular ketamine 6 mg/kg (induction dose) and intravenous ketamine 1.6 mg/kg use resulted in increased IOP [9–12].

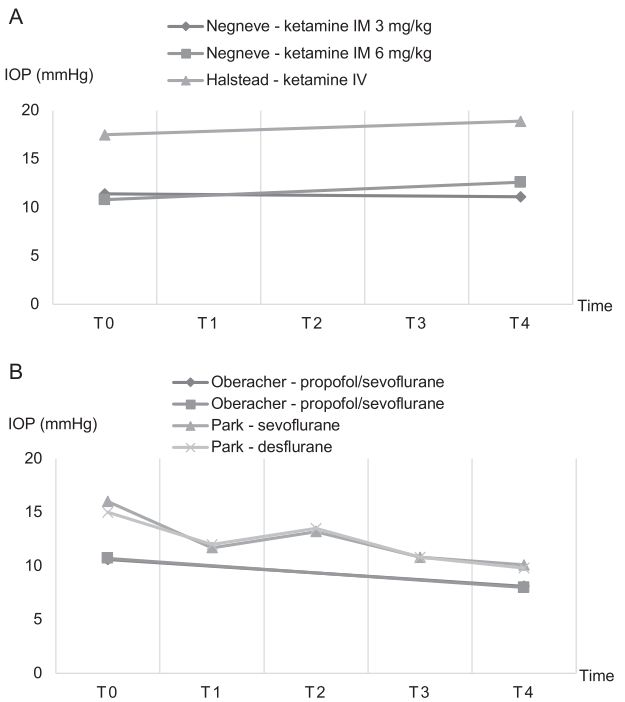

Fig. 3 Graphs demonstrating IOP change over time for each study in ketamine (**a**) and inhalation (**b**) subgroups. IOP increases over time with intravenous and induction-dose intramuscular ketamine and decreases over time with low-dose intramuscular ketamine and inhalation agents.

Statistical heterogeneity was found among the studies (P value < 0.1), thus a linear mixed-effect model was employed to conduct the analysis. By analysis of all agents, the results showed that IOP significantly decreased over time after induction phase at a rate of -0.59 ± 0.19 mmHg/min (mean ± standard error, P value $= 0.006$). This is a model of mean IOP as a function of time and anaesthetic agent, clustered on publications. We attempted to identify the effect of each anaesthetic agent on its impact of IOP, but the data were not sufficient to perform this analysis. Subgroup analysis comparing and contrasting ketamine and inhalation groups showed that IOP significantly increased over time with ketamine at a rate of 0.18 ± 0.10 mmHg/min (P value < 0.05) and significantly decreased over time at a rate of -1.14 ± 0.17 mmHg/min (P value < 0.05) with inhalation agents. The analysis showed a significant effect of time, as a variable, on IOP in both ketamine and inhalation groups.

Adverse events related to anaesthetic agents

Overall, adverse events related to GA were uncommon. Nagdeve et al. [9] reported mild airway obstruction in the 90% of the induction-dose ketamine group (6 mg/kg; 18 patients) compared to 20% in the low-dose ketamine group (3 mg/kg; 4 patients). Significantly more patients in the induction-dose group (19 patients) were sedated immediately after anaesthesia than in the low-dose group (8 patients). Two patients in the induction-dose group had mild postoperative emergence reactions in the form of vocalisation and restlessness: these reactions occurred within 15 min of arrival in the recovery room and subsided without any treatment within 2 h. Laryngospasm was reported in three patients in the induction-dose group and one patient in low-dose group. Another study [12] found no adverse effect of intravenous ketamine injection.

Only one study on inhalation agents reported an adverse event, with one child regurgitating without aspiration during induction of propofol/sevoflurane, 30 min after application of midazolam syrup [11].

Discussion

This study assessed all available evidence in the literature in an effort to determine changes in IOP caused by different

general anaesthetic agents in normal paediatric patients. We found that most anaesthetic agents significantly decrease IOP over time after the induction phase of GA in this patient population. In subgroup analysis, inhalation agents significantly decreased IOP while ketamine significantly increased IOP.

The effect of ketamine, however, was not consistent between the included studies, perhaps due to the fact that dosing of this agent differs depending upon whether the goal is sedation or induction. Intravenous ketamine (mean 1.6 mg/kg) and induction-dose intramuscular ketamine (6 mg/kg) increased the IOP during sedation. Recommended ketamine dosing for induction is 0.5–2 mg/kg for intravenous and 4–6 mg/kg for intramuscular injection, which is higher than the dose used for sedation (0.2–0.8 mg/kg intravenous; 2–4 mg/kg intramuscular) [16]. Our analysis showed variable effects of intramuscular ketamine on IOP. Prior studies have demonstrated that while high doses of ketamine do not have an effect on IOP, one study of lower ketamine dosage showed an increase in IOP [17–19]. Future studies may be needed to further explore the effect of ketamine on IOP during EUA.

Inhalational agents have been postulated to cause IOP reduction through suppression of the diencephalon, reduction of aqueous humour production, increased aqueous humour outflow, and relaxation of the extraocular muscles [3]. Currently, sevoflurane and desflurane are frequently used anaesthetics in the paediatric population due to their fast induction and recovery profiles compared to halothane [20]. Sevoflurane has the advantage of limited cardiorespiratory side effects with more stable heart rate profiles relative to halothane, making it a good choice for children undergoing GA [21]. Desflurane is also used frequently but has been, however, associated with irritation of the upper respiratory system and sympathetic stimulation which can lead to transient hypertension and tachycardia [22].

It is noteworthy that we found baseline IOP to be different between studies, which may be partially explained by the varying use of premedications. For example, baseline IOP in patients who received no premedication (measured under topical anaesthesia) [12], was higher compared to those who received premedication with midazolam [11, 13, 14]. Midazolam itself has no effect on IOP [23], but the presence of eye squeezing and Valsalva manoeuvre in awake children without premedication may contribute to higher baseline IOP measurement. Other factors that may contribute to differences in baseline IOP between studies include patient age and type of tonometer. IOP increases with age due to age-related differences in scleral rigidity, axial length, and central corneal thickness with older children having higher IOP [24, 25]. In addition, two studies used the Tono-Pen XL [10, 12], while the remaining used a Perkins applanation tonometer. Differences in IOP measurement based upon the choice of tonometer may impact intra-study comparisons. Tono-Pen measurements have been reported to be higher than those obtained with the Perkins applanation tonometer [26, 27].

Further consideration should be placed on whether or not IOP measured during EUA represents the "true" IOP. Many factors including body positioning, use of eyelid specula, and use and type of premedication all affect baseline IOP during EUA. This highlights the importance of investigating future approaches of IOP measurement in children that do not rely on anaesthesia. The increasing use of the Icare tonometer has provided an important alternative to reliably check IOP without anaesthesia; however, there remain clinical circumstances where children are unable to cooperate enough to allow the use of this device.

One obvious limitation of this study is the small sample size. Only a small proportion of the many studies conducted on GA in children provided subjects who met eligibility criteria. Most studies were excluded due to the use of older anaesthetic agents, lack of robust outcome reporting, or inclusion of patients with glaucoma. While it would have been fruitful to perform subgroup analyses for patients with glaucoma, there were only two papers meeting the criteria for such inclusion and thus insufficient information draw meaningful conclusions. We chose the path of drawing conclusions only where the data was robust enough to address relevant questions. Another limitation of our analysis was the difference in study design across the included studies. Prospective cohort studies may have selection bias with confounding which could impact the result of our analysis, particularly when combined with RCT data. A further limitation of our analysis was the wide range of baseline IOP measurements observed across studies, adding yet another source of heterogeneity in the result. To solve this problem, a well-design prospective study in normal and glaucomatous paediatric eyes should be conducted.

Conclusion

This systematic review showed that individual studies of most anaesthetic agents indicated a decrease in IOP over time, and regression analysis suggested mean IOP significantly decreased after the induction phase of GA in children when modelled as a function of any anaesthetic agent and time. Moreover, we found that IOP decreased over time following induction with inhalation agents while increased over time after sedation with ketamine. The information obtained from this analysis will undoubtedly be helpful to the clinician who cares for children in whom IOP measurement under anaesthesia will impact decisions pertaining to the diagnosis and treatment of ocular disease. The results of this work may not necessarily be extrapolated to

paediatric glaucoma patients undergoing EUA. It is reasonable to assume, however, that although the magnitude of the effects may differ in the glaucoma population, the direction of the IOP decrease or increase with these agents is likely to be similar to those who do not have glaucoma.

Summary

What was known before

- General anaesthesia affects intraocular pressure (IOP) measurement in children under examination under anaesthesia (EUA) but it remains controversial on how IOP changes during EUA.

What this study adds

- This systematic review indicates that IOP decreases over time following induction with inhalation agents and increases over time after sedation with ketamine.
- This is helpful to the clinicians who care for children in whom IOP measurement under anaesthesia will impact decisions pertaining to the diagnosis and treatment of ocular disease.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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