Hemodynamic Changes Associated with Mydriatic Eye Drop Administration in Anesthetized Pediatric Patients

Vittoria Arslan-Carlon^a Maria C. Walline^b Kenneth Seier^c Kay See Tan^c
David H. Abramson^d

^aDepartment of Anesthesiology and Critical Care Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA; ^bDepartment of Anesthesiology, Montefiore Medical Center, New York, NY, USA; ^cDepartment of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY, USA; ^dDepartment of Surgery, Ophthalmic Oncology Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Keywords

Mydriatics · Phenylephrine · Tropicamide · Retinoblastoma · Pediatric anesthesia

Abstract

Background: Dilating eye drops are routinely used in pediatric retinoblastoma patients during anesthetized ophthalmologic exams. Information on the systemic effects of ocular mydriatics, especially in anesthetized pediatric patients, is limited. **Objective:** The primary aim of this study was to analyze hemodynamic changes during mydriatic eye drop administration in anesthetized pediatric patients. **Methods:** A retrospective chart review was performed for pediatric retinoblastoma patients who underwent MRI with anesthesia. Baseline blood pressure (BP) and heart rate (HR) were charted for each patient at induction. HR and mean arterial pressure (MAP) measurements were recorded at 5, 10, 15, 30, and 45 min after eye drop administration. Secondly, we included data from 15 patients who received dilating eye drops while under sevoflurane general anesthetic. All patients were dilated with phenylephrine 2.5 or 10% (depending on age) and tropicamide 1%. **Results:** The final analysis included 176 anesthesia encounters. The results demonstrate no

statistically significant deviation of more than 20% from baseline for either HR or MAP. Additionally, we did not detect any difference between patients who were anesthetized with propofol versus sevoflurane. **Conclusions:** We did not observe significant hemodynamic instability with administration of dilating eye drops during propofol anesthesia.

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Introduction

The use of dilating eye drops is imperative for performing thorough ophthalmologic exams. Despite their topical mode of administration, there has been much debate about the systemic effect of dilating eye drops, especially with regards to phenylephrine. While tropicamide causes vasoconstriction through its anticholinergic effect, phenylephrine is a direct alpha agonist known to cause local and systemic vasoconstriction. Both of these mydriatic agents have been associated with ocular and systemic adverse effects [1, 2], with hemodynamic changes a particular concern when phenylephrine is used [3]. Pediatric patients with retinoblastoma undergo frequent dilation for ophthalmologic exams and localized treatment, often

when anesthetized. Understanding the systemic effects of mydriatic agents is imperative to minimize risks and separate the direct effect of eye drops from intrinsic pediatric hemodynamic variability.

Most studies to date include only adults and focus on systemic effects associated with phenylephrine eye drops. In a systematic review and meta-analysis, Stavert et al. [4] found minimal systemic cardiovascular changes (i.e., variation in blood pressure [BP]) with administration of phenylephrine 2.5% eye drops. However, phenylephrine 10% led to a transient increase in BP that returned to baseline as early as 10 min after administration [4]. In other studies, a significant transient effect on hypertension has not been seen [5, 6]. Furthermore, certain studies indicate the absence of hemodynamic changes with administration of either 2.5 or 10% phenylephrine drops [7].

Children are at increased chance of systemic side effects – eye drop dosing is not weight-adjusted, eye membranes in young children are thin, and tear volume is lower – all characteristics that could enhance systemic absorption [1]. Furthermore, the lack of lacrimation due to the anesthesia could increase the concentration of single drops at the time of administration. Though there are few studies in pediatric patients examining hemodynamic changes associated with mydriatics, it has been demonstrated that the size of dilating drops used can impact hemodynamics, particularly in infants. In one study, infants receiving standard mydriatic drops showed a significant increase in mean arterial pressure (MAP), while in those given microdrops, MAP was stable [8]. Prior studies have largely looked at hemodynamic changes in awake patients. Especially in children, crying during administration is common and complicates the study of hemodynamic changes as lacrimation can dilute eye drops.

To more thoroughly assess the hemodynamic effects of mydriatic eye drops in children, we performed a retrospective study in pediatric patients who underwent anesthesia for MRI with dilating eye drops administered at the start of the procedure. We hypothesized that mydriatic drops administered under anesthesia would have pronounced hemodynamic effects due to the higher concentration of medication in the eye in the absence of lacrimation. We investigated anesthesia with both propofol infusion and sevoflurane, with the prediction that patients undergoing a sevoflurane general anesthetic would have greater hemodynamic variability after mydriatic eye drop administration, due to the known effects of sevoflurane anesthetic on heart rate (HR) variability [9]. This work

serves as a foundation for determining the safest and least distressing manner to administer mydriatic eye drops to pediatric patients.

Materials and Methods

After institutional review board (IRB) approval (IRB protocol #16-228), an exploratory retrospective chart review was performed. Pediatric patients aged 10 years and younger diagnosed with retinoblastoma (2016 ICD-10 code C69.2 or equivalent) who underwent pediatric MRI with anesthesia (CPT 01922 “under anesthesia for radiological procedures” or equivalent) from January 1, 2010, to December 31, 2015, were included.

Standard American Society of Anesthesiologists (ASA) monitors and airway management with nasal cannula were used for all patients. Baseline BP and HR were charted for each patient prior to eye drop administration but after anesthetic induction. Patients received a propofol bolus (2 mg/kg), and propofol infusion (200 µg/kg/min) began simultaneously with eye drop administration (according to institutional guidelines – 1% tropicamide for all ages, and 2.5% phenylephrine for patients less than 1 year and 10% phenylephrine for patients over the age of 1). The propofol infusion start time was considered the time of eye drop administration. BP and HR were documented at this time as well as at 5-, 10-, 15-, 30-, and 45-min time points during the procedure. Patients were maintained on propofol infusions at 200–300 µg/kg/h for the duration of the procedure; no additional boluses were given. The MRI was completed at 45 min, and subsequently, an eye exam under anesthesia was performed. Patients were only excluded if there was not complete data recorded during the case.

To further investigate the possible confounding effects of the anesthetic, we included data from 15 consecutive patients who underwent ophthalmologic exam in an outpatient clinical setting from August 1, 2017, to August 31, 2017, and received dilating eye drops while under a sevoflurane general anesthetic. For all patients, sevoflurane was administered starting at 8% and decreasing to 4.5% once the patient was asleep. BP and HR were recorded at baseline (after induction but prior to eye drop administration) as well as at 5-, 10-, and 15-min time points after eye drop administration and prior to any stimulation by the ophthalmologic exam.

Data Analysis

The final analysis included 176 anesthesia encounters from 131 patients, as some patients underwent more than one procedure during the study’s timespan. The primary outcome was differences in HR and MAP. Sensitivity analysis was performed using the first encounter for each patient; there was no difference in using all available data compared to using only the first encounter for each patient. As such, we report the analysis of all available data.

Descriptive statistics are shown as median and interquartile range for continuous variables, and totals and percentages were used for categorical variables. The Fisher exact test was used to compare MAP and HR in groups receiving different phenylephrine concentrations and receiving different anesthetic agents. A 20% change from baseline was selected as clinically meaningful and not traceable back to the normal variability on induction. SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) was used for all analyses. All tests were two-sided, and $p < 0.05$ was considered significant.

Table 1. Patient data

	Propofol (<i>n</i> = 161)	Sevoflurane (<i>n</i> = 15)
Median age (IQR), years	3 (2–5)	3 (2–4)
Patients receiving tropicamide 1%	161 (100)	15 (100)
Patients receiving phenylephrine 2.5%	9 (5.6)	0 (0)
Patients receiving phenylephrine 10%	152 (94.4)	15 (100)
Patients with at least one HR $\geq 20\%$ from baseline ¹	12 (7.5)	1 (6.7)
Patients with at least one MAP $\geq 20\%$ from baseline ¹	24 (14.9)	0 (0)

Data are presented as *n* (%) unless otherwise indicated.

¹ For propofol, any change at 5, 10, 15, 30, or 45 min after eye drop administration; for sevoflurane, any change at 5, 10, or 15 min after eye drop administration.

Results

For propofol procedures, all cases (*n* = 161) received tropicamide 1% per institutional guidelines, while 94.4% (*n* = 152) of patients received phenylephrine 10% drops and 5.6% (*n* = 9) received 2.5% drops (Table 1). Percent change from baseline was calculated for HR and MAP at each time point. For all propofol time points (*n* = 966), there were 33 instances (3.4%) of an HR change $\geq 20\%$ from baseline and 40 instances (4.1%) of a MAP change $\geq 20\%$ from baseline (Fig. 1a). At the patient level (*n* = 161), 7.5% of patients (*n* = 12) had at least one recorded HR measurement that was $\geq 20\%$ from baseline, and 14.9% of patients (*n* = 24) had at least one recorded MAP measurement that was $\geq 20\%$ from baseline. To further examine the overall stability of HR and MAP throughout the procedure, we used box and whisker plots of all values at each time point (Fig. 1b). There was more variability and a slight downward trend in MAP, but HR was fairly consistent over time. There were no statistically significant differences between a 20% increase in HR or MAP when comparing the phenylephrine 2.5% and phenylephrine 10% groups (Table 2).

We also investigated a cohort of pediatric patients (*n* = 15) who received sevoflurane general anesthetic. Only 1 patient had two instances where the HR exceeded a 20% change from baseline, and MAP was unaffected in all patients (Fig. 2a). The box and whisker plots in Figure 2b illustrate the data for all patients at each time point. We note that the decrease in baseline HR and MAP is expected at the 5-min time point with this anesthetic. There was no statistically significant difference in patients experiencing a 20% increase in HR or MAP between the propofol and sevoflurane groups (Table 3).

Table 2. Comparison of phenylephrine 2.5% and phenylephrine 10%

	Phenylephrine 2.5%	Phenylephrine 10%	<i>p</i> value
HR $\geq 20\%$ from baseline	1 (11.1)	11 (7.2)	0.51
MAP $\geq 20\%$ from baseline	1 (11.1)	23 (15.1)	>0.95

Data are presented as *n* (%). HR, heart rate; MAP, mean arterial pressure.

Discussion

We performed a retrospective study of the hemodynamic changes associated with mydriatic eye drop administration in anesthetized pediatric patients undergoing an MRI. A higher volume of eye drop is expected to remain in contact with the conjunctiva in an anesthetized population, potentially leading to higher systemic absorption [1] as compared with awake administration where tearing of the eye dilutes the medication. Moreover, in our patient population, eye drops were administered at the start of the procedure, when hemodynamic effects of anesthesia are also possible. We found no significant changes in HR or MAP over the span of 45 min after administration of ophthalmic mydriatic agents in patients who received propofol anesthetic. Additionally, our results show that deviation $>20\%$ from baseline was not frequent, and the majority of the patients were hemodynamically stable during anesthetized eye dilatation. An additional comparison was made with a smaller pediatric

Fig. 1. Hemodynamics in pediatric patients receiving propofol anesthetic. **a** Percent change from baseline for all data points for heart rate (HR, left) and mean arterial pressure (MAP, right) in pediatric patients who received propofol anesthetic. The horizontal line indicates a 20% change from baseline. **b** Box and whisker plots of heart rate (HR, left) and mean arterial pressure (MAP, right) values for all patients receiving propofol anesthetic.

patient set receiving sevoflurane anesthetic, an agent with known effects on HR variability [9]. As with propofol, we found no statistically significant hemodynamic changes with sevoflurane, and there was no difference in the number of significant hemodynamic changes ($\geq 20\%$ from baseline) with the use of these different anesthetic agents.

In order to have an adequate ophthalmic exam, pediatric retinoblastoma patients must be anesthetized and undergo the concurrent hemodynamic changes associated with anesthesia in addition to the potential influence

of vasoactive mydriatic agents. Because propofol is known to cause arterial and venous vasodilation while blunting the typically associated baroreceptor response, the resultant hypotension is more significant than with any other induction agent [9]. Conversely, ophthalmic phenylephrine, while shown to have minimal systemic absorption [5], is a potent alpha-adrenergic agonist that causes local vasoconstriction and is used regularly intravenously during anesthetic inductions to counteract the vasodilating effects of propofol and other induction agents. Tropi-

Fig. 2. Hemodynamics in pediatric patients receiving sevoflurane anesthetic. **a** Percent change from baseline for all data points for heart rate (HR, left) and mean arterial pressure (MAP, right) in pediatric patients who received sevoflurane anesthetic. The horizontal line indicates a 20% change from baseline. **b** Box and whisker plots of heart rate (HR, left) and mean arterial pressure (MAP, right) values for all patients receiving sevoflurane anesthetic.

Table 3. Comparison of propofol and sevoflurane anesthetics

	Total	Propofol ¹	Sevoflurane ¹	<i>p</i> value
HR $\geq$ 20% from baseline	6 (3.6)	5 (3.3)	1 (6.7)	0.44
MAP $\geq$ 20% from baseline	20 (12)	20 (13.2)	0 (0)	0.22

Data are presented as *n* (%). HR, heart rate; MAP, mean arterial pressure.

¹ Patients with a change at the 5-, 10-, or 15-min time point.

camide is an anticholinergic agent and therefore could cause tachycardia if systemically absorbed. Because these agents are all initiated at the same time, it is premature to say the eye drops do not cause any hemodynamic change, when in fact they may contribute to counterbalancing the effect of a propofol induction. Conversely, hemodynamic changes are likely during administration of eye drops to awake children, but these have not been well assessed in prior studies and are complicated by the natural reaction to the stress of the drop administration with tachycardia and hypertension in pediatric patients. Our results show that the hemodynamic effect of mydriatic eye drops is likely insignificant when it comes to the overall hemodynamic stability of the patient and the effects of the anesthetic.

There are few studies examining the hemodynamic effects of mydriatic agents in pediatric patients. A study by Elibol et al. [8] suggested that dilating eye drop size could have a significant effect on MAP in infants and showed that awake patients dilated with microdrops were hemodynamically more stable over 60 min in comparison to standard drop size. The data obtained for the microdrops indicated there was no significant change in MAP, suggesting children were not particularly distressed during the administration, a potential confounding factor for increased MAP. At our institution, we only use standard-sized eye drops, and our data show that even in small children standard-sized drops do not have a significant impact on hemodynamic stability.

Recovery time from mydriasis is 3–8 h for phenylephrine and 6–7 h for tropicamide. Because systemic absorption is considered minimal, hemodynamic changes would most likely occur close to the time of administration. In the most extensive systemic review and meta-analysis to date, Stavert et al. [4] found that a hemodynamic effect was associated with 10% phenylephrine, but not 2.5%. Moreover, this review found evidence of statistically significant hypertension 5 and 10 min after phenylephrine administration with resolution at 20 min and tachycardia at 20 and 30 min with resolution to baseline at 60 min. Although this analysis only included studies in unanesthetized adults, the findings support that, despite the prolonged mydriatic effect of the drops used, our patients were monitored long enough to detect hemodynamic changes.

Limitations of this study include the small sample size and the single institutional nature. These features limit statistical power and generalizability of our findings. In addition, data on preoperative HR and BP were not available for all patients. We used HR and BP measurements

obtained after induction with propofol as the baseline measurement; as the bolus dose of propofol can decrease systolic BP and MAP and have a variable effect on HR, using this as the baseline may introduce variability. Finally, in the sevoflurane group, the latest time point (15 min after induction) was limited by the length of the procedure. It is possible that potential hemodynamic effects that potentially occur 30–60 min after induction were missed in this group.

In summary, our results indicate that anesthetized pediatric patients are hemodynamically stable after administration of ophthalmic mydriatic agents. To further understand the systemic effects of mydriatic agents, ideally, hemodynamic effects would be measured in awake children. However, most children will not tolerate eye drop administration without behavior-associated hemodynamic changes, and controlling for these changes would be challenging at best. A potential solution would be to allow children to reach a steady anesthetic state and administer eye drops at a predetermined time thereafter in an effort to minimize the potential mitigating effect of the induction of anesthesia. Such future studies will be necessary to obtain a complete understanding of the systemic effects of mydriatic agents, and thereby inform strategies to minimize the risk of their use in pediatric patients.

Statement of Ethics

The study protocol was approved by the Institutional Review Board.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

V.A.-C. and D.H.A. conceived and designed the study, performed data interpretation, and drafted the manuscript. M.C.W. collected the data. K.S. and K.S.T. performed data analysis. All authors critically reviewed and approved the final version of the paper.

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