Acta Anaesth. Bel., 2023, 74 | Suppl. 1: *47-54*

Master thesis | Original study

Evaluation of systemic exposure to intracameral tropicamide 0.02%, phenylephrine 0.31% and lidocaine 1% in pediatric cataract surgery: a pilot study

H. Herbots[1,3], L. Van Os[2,3], W. Aerts[1,3], M.J. Tassignon[2,3], A. Covaci[4], C. Dumitrascu[4], V. Saldien[1,3]

[1]Department of Anesthesiology, Antwerp University Hospital, Edegem, Belgium; [2]Department of Ophthalmology, Antwerp University Hospital, Edegem, Belgium; [3]Faculty of Medicine and Health Science, University of Antwerp, Wilrijk, Belgium; [4]Faculty of Pharmaceutical Sciences, University of Antwerp, Wilrijk, Belgium.

Corresponding author: Herbots Hanne, MD, Department of Anesthesiology, Antwerp University Hospital, Drie Eikenstraat 655, 2650 Edegem, Belgium. E-mail: hanne.herbots@uza.be

Abstract

***Background:* : Pediatric cataract is a rare disease that often requires surgery, for which an adequate and stable mydriasis is necessary. Pupil dilatation is usually achieved by the instillation of mydriatic eye drops. Intracameral Mydrane® (ICM) is a standardized mixture of tropicamide 0.02%, phenylephrine 0.31% and lidocaine 1% and is to be injected into the anterior eye chamber at the beginning of surgery. Its efficacy and safety are already established in adults, but not yet for the pediatric population.**
***Objectives:* The aim of this research was to evaluate the safety profile of ICM in children.**
***Setting:* University Hospital of Antwerp, Belgium, single-centre, tertiary hospital.**
***Methods:* Systemic exposure was assessed by quantification of plasma concentrations of phenylephrine and tropicamide at different time points (2, 10 and 30 minutes after ICM injection) during the procedure. The incidence of hemodynamic side effects was evaluated as an indicator of safety.**
***Results:* The highest plasma concentrations of phenylephrine and tropicamide were detected in the youngest age group A. The increases in plasma concentrations of phenylephrine were statistically significant for the total population (p = 0.019). Clinically important changes in hemodynamic parameters related to phenylephrine or tropicamide were not detected in any age group.**
***Conclusions:* In this pediatric population undergoing cataract surgery under general anesthesia, the administration of ICM was safe and systemic exposure was not clinically significant.**

***Keywords:* Mydriatic, pediatric, cataract, phenylephrine, tropicamide.**

Introduction

Pediatric cataract is a rare condition that often requires surgery to replace the opaque lens. Optimal mydriasis is necessary for successful cataract surgery. In the pediatric population the golden standard to achieve pupil dilatation is the installation of eye drops. However, the instillation of these drops is labor and time intensive, especially with pediatric patients. Many children are uncomfortable and often cry during the instillation, causing the eye drops to be less effective[1]. This can result in a need for repeated instillations of eye drops, which are associated with an increased risk of side effects in addition to the possible traumatic experience for the child.

Topical eye drops must cross the corneal barrier making rapid absorption difficult and bioavailability low. However, absorption by the well perfused conjunctiva is high[2,3]. Furthermore, the volume of these drops often exceeds the capacity of the conjunctival sac. This causes the liquid to drain

The study protocol was approved on 05/10/2020 by the ethical committee of the University Hospital of Antwerp (UZA), Study number: 20/39/504. Chairman: P. Michielsen, MD, PhD, Wilrijkstraat 10, 2650, Edegem, Belgium. E-mail: ethisch.comite@uza.be
An informed consent was acquired from the parents of every participant and from participants older than four years. Patient inclusion took place from November 2020 until May 2021.

through the lacrimal canal, where it is further absorbed. It is estimated that 80% of the volume delivered to the eye enters the lacrimal duct[3,4]. On the other hand, intracameral injection of drugs bypasses the corneal barrier, causing rapid absorption on the target tissue, in this case the dilator muscle of the iris[5].

Mydrane® (Théa Pharma, U.S.) is a mixture of tropicamide 0.02%, phenylephrine 0.31% and lidocaine 1% and is to be injected into the anterior chamber of the eye at the beginning of surgery in a dose of 0.1 mL[6]. Tropicamide is a parasympathetic drug, initiating pupil dilation by inhibiting M4-muscarinic receptors and preventing contraction of the sphincter pupillae, leaving the radial muscles of the eye unaffected[7]. When absorbed systemically, tropicamide can cause systemic anticholinergic effects like tachycardia, dry mucosa and urinary retention. Phenylephrine acts as a pure α1-agonist, causing the iris dilator muscle to contract leading to mydriasis after ophthalmic administration. It can also cause vasoconstriction with a consecutive rise in peripheral vascular resistance and elevation of systolic and diastolic blood pressure. Due to this potent vasoconstriction, a reflex bradycardia may occur through the parasympathetic system[8].

Intracameral injection of Mydrane® (ICM) was proven to be an effective and safe technique to achieve pupil dilatation in adults compared to standard eye drops[9], but its safety and efficacy in children aged 0 to 18 years have not been established. Notwithstanding the possible advantages of a single intracameral injection at the beginning of surgery, the use of intracameral mydriatics itself has not yet been investigated extensively in children. Recently, a pilot study has been published describing the use of an intracameral mixture with the same composition, which demonstrated a successful mydriasis and no side effects[1].

The objective of this pilot study was to evaluate the systemic exposure to ICM and the incidence of adverse events in the pediatric population as solely drug administration to achieve pupil dilatation prior to cataract surgery.

Methods

Study design and sample size

We conducted a single-centre, prospective observational cohort study in the Antwerp University Hospital to investigate the safety of ICM by evaluating the systemic exposure and hemodynamic adverse events in children undergoing cataract surgery under general anesthesia (GA). Approval from the ethical committee of the Antwerp University Hospital was obtained (study number 20/39/504, chairman: P. Michielsen, MD, PhD).

This pilot study, as part of a larger study set up, analyses the results of the first 15 patients included in the study protocol. The first 15 patients aged 8 weeks to 17 years and scheduled for cataract surgery were included from November 2020 to May 2021. When a patient was scheduled immediate sequential bilateral cataract surgery (ISBCS), only the procedure on the first eye was included in this study. Patients younger than 8 weeks or with previous eye surgery or documented allergy to one of the components of Mydrane® were excluded. A written informed consent was obtained from the parents or legal representative and from the child when older than four years.

Study setup

On the day of surgery, no oral or intravenous (IV) premedication, nor local anesthetics such as eutectic mixture of local anesthetics were administered. Standard fasting rules were applied according to the European guidelines[10]. A baseline heart rate, blood pressure and oxygen saturation were measured before induction of GA. Patients were induced by inhalation of 8% sevoflurane. After induction an IV catheter was placed for the administration of fluids and IV medications. Fentanyl (2 µg/kg), propofol (2 mg/kg) and atracurium (0.5 mg/kg) was administered. The airway was secured with a Ring–Adair–Elwyn endotracheal tube. A second peripheral IV catheter was placed to take blood samples during the procedure. A first baseline blood sample was drawn when the second catheter was in place.

After intubation, additional monitoring was established including a temperature probe and capnography. A NeuroSENSE® NS-901 monitor was used to monitor depth of anesthesia (DOA). Anesthesia was maintained with sevoflurane. Insufficient depth of anesthesia was managed by increasing the inhaled concentration of sevoflurane or by administering a bolus of fentanyl or propofol. Plasmalyte® or Kidialyte® (for children under three years old) were used as maintenance fluids according to their weight.

After time-out completion blood pressure and heart rate were recorded, specified as timepoint T(-1). Corneal incision was made and surgery began with the administration of ICM through the incision (T(0)). Hemodynamic parameters were recorded during the procedure and the incidence of adverse events, such as bradycardia and hypertension, were noted on the study form. Blood pressure and heart rate were measured each minute for five minutes after T(0) and subsequently every 5 minutes until 30

minutes after injection. Blood samples were taken at T(-1) and then at 2, 10 and 30 minutes after T(0).

All collected blood samples were labelled with a number, traceable to the patient, to enable linking the results to the clinical data. After centrifugation, the plasma was stored at -70°C until analysis. After liquid-liquid extraction of 200 µL plasma, the concentrations of phenylephrine and tropicamide were quantified by liquid chromatography coupled to tandem mass spectrometry (LC-MSMS) at the Toxicological Centre (University of Antwerp) (see analysis details in the Supporting Information).

To minimize the risk of operator bias all surgeries in this study were performed by the same surgical (MJT and LVO) and anesthetic (HH, WA and VS) team. All data were anonymized to protect the identity of the patients.

Statistical analysis

The statistical analyses in this study were performed using SPSS statistics, version 28.0.0. The total population of patients was subdivided in three categories according to age (group A: 8 weeks to 1 year, group B: 1 year and 1 day to 6 years, group C: 6 years and 1 day to 17 years old). General characteristics of the study population are reported using descriptive statistics. For further statistical analysis of the blood samples all values below the lower limit of quantification (LLOQ) were substituted for the value equal to LLOQ /2, resulting in a substitution value of 0.1 ng/mL and 0.4 ng/mL for phenylephrine and tropicamide respectively. The non-parametric Friedman test was used to analyze whether there were statistically significant differences in plasma concentrations of phenylephrine and tropicamide between the different time points before and after injection of ICM. When the Friedman test was significant ($p < 0.05$), post hoc Wilcoxon tests were performed to identify the moments of sample collection that were significantly different. We defined hemodynamic adverse events as an increase or decrease in heart rate (HR) or mean blood pressure (MBP) of more than 20% after the administration ICM compared with the values at T(-1)[11].

Results

General characteristics of the study population

General characteristics are presented in Table I. The median age of the study population was 4 months, with the youngest patient being 2 months and the oldest 5 years and 9 months. Nine patients were allocated to age group A and six patients to age group B. There were no children older than 6 years (group C) in this study group. Ten patients were male (66.7%), compared to five female patients (33.3%). The mean duration of the surgery was 82 minutes (S.D.: 31.77). In two cases the patient was scheduled for ISBCS (Table I).

Plasma concentrations of phenylephrine and tropicamide after injection of ICM

The plasma concentrations of phenylephrine and tropicamide at each point in time for the total population and for each age group are visually presented in Figure 1 and Figure 2.

Table II represents the results of blood sample analysis after the injection of ICM for each age group. The highest concentration of phenylephrine was detected 2 minutes after injection in group A (1.85 ng/mL) and at T(+10) in group B (0.82 ng/mL). After 30 minutes the plasma concentration decreased to baseline in group B or approaching baseline in group A.

In group A, the highest concentrations of tropicamide were detected, with a maximal value of 0.30 ng/mL at T(+10). The median concentrations of tropicamide were below the LLOQ/2 of 0.04 ng/mL in both groups (Table II).

Table I. — Descriptive statistics of the overall study population and subdivisions of the study population according to age category. Group A: 8 weeks to 1 year, group B: 1 year, 1 day – 6 years, group C: 6 years, 1 day – 17 years. S.D. = Standard Deviation, N/A = Not Applicable.

	Minimum	Maximum	Median	Mean	S.D.
Age (months)	2	69	4	14.1	18.2
Sex	Frequency (N)		Percent (%)		
Male	10		66.7		
Female	5		33.3		
	Minimum	Maximum	Mean	S.D.	
Duration of surgery (minutes)	30	137	82	31.8	
Age categories	Frequency (N)	Percent (%)		Mean weight (kg)	
Group A	9	60		6.3	
Group B	6	40		13.6	
Group C	0	0		N/A	

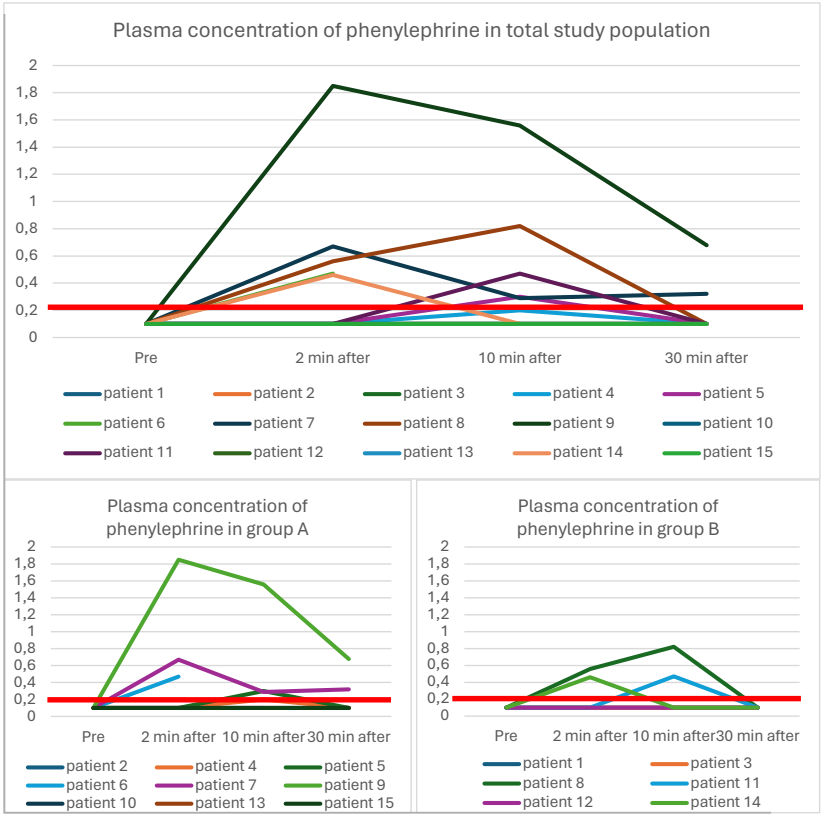

Fig. 1 — Plasma concentrations of phenylephrine in the total population and each age group. Red line: LLOQ, measurements below LLOQ were substituted with the value of LLOQ/2.

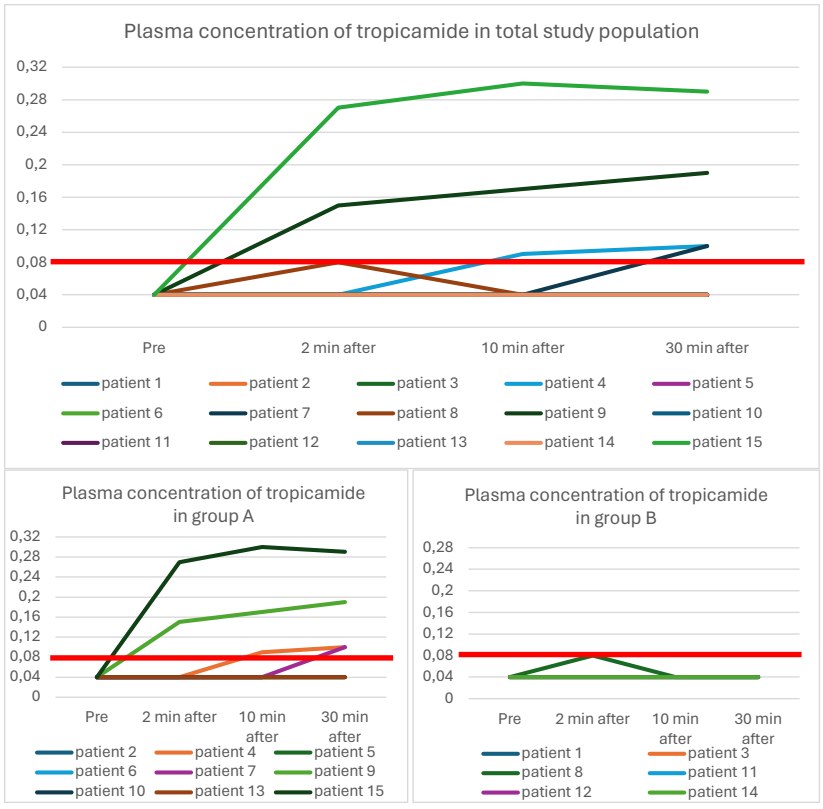

Fig. 2 — Plasma concentrations of tropicamide in the total population and each age group. Red line: LLOQ, measurements below LLOQ were substituted with the value of LLOQ/2.

Table II. — Overview of plasma concentrations of phenylephrine and tropicamide at each point in time for each age category and results of non-parametric Friedman test. N = Number of patients, N < LLOQ = Number of patients below LLOQ, Sig. (p) = Asymptotic significance level of Friedman test.

Plasma concentrations of phenylephrine						Plasma concentrations of tropicamide					
	N	N > LLOQ	Max.	Median	Sig. (p)		N	N > LLOQ	Max.	Median	Sig. (p)
Group A (n=9)						Group A (n=9)					
Baseline	9	0	0.1	0.1	0.131	Baseline	9	0	0.04	0.04	0.023
T(+2)	9	3	1.85	0.1		T(+2)	9	2	0.27	0.04	
T(+10)	8	5	1.56	0.15		T(+10)	8	4	0.30	0.04	
T(+30)	8	3	0.68	0.1		T(+30)	8	5	0.29	0.04	
Group B (n=6)						Group B (n=6)					
Baseline	6	0	0.1	0.1	0.194	Baseline	6	0	0.04	0.04	0.392
T(+2)	6	2	0.56	0.1		T(+2)	6	1	0.08	0.04	
T(+10)	6	2	0.82	0.1		T(+10)	6	0	0.04	0.04	
T(+30)	6	0	0.1	0.1		T(+30)	6	0	0.04	0.04	
Total population (n=15)					0.019	Total population (n=15)					0.069

The results of Friedman tests for the total population and each age group are also shown in Table 2. In the total population, plasma concentration of phenylephrine increased significantly after the administration of ICM (p = 0.019). Additionally, post hoc Wilcoxon tests (Table III) showed a significant increase from baseline to T(+2) and T(+10 (p = 0.043 and p = 0.028, respectively), with a stable concentration between T(+2) and T(+10) (p = 0.735), followed by a significant decrease to T+30 (p = 0.046). When analyzing the plasma levels of phenylephrine for each age group separately, the Friedman test did not show an observable significance. For tropicamide, only group A demonstrated a significant increase in its plasma concentration after ICM (p = 0.023), although subsequent Wilcoxon tests could not confirm significant differences in tropicamide concentration between different time points (Table III).

Incidence of hemodynamic adverse events

The results on hemodynamic side effects are presented in Figure 3 and Figure 4. For group A, we did not observe a relevant rise in mean blood pressure (MBP) after ICM. At each time point there were patients in this group with a significant decrease in MBP compared to the baseline value after induction, with a peak incidence at T(+20) and T(+25) (n = 4, 44.4%). In group B, we documented only once a rise in MBP at T(+1). Subsequent measurements in this patient were normal. In two patients of group B (33.3%) a decrease of MBP was noted across all points in time after ICM.

After the administration of ICM the heart rate (HR) of patients in group A remained stable, with one outlier, who showed a decrease of HR from T(+20) to T(+30). This patient showed at these time points a concomitant decrease in MBP and a phenylephrine concentration below LLOQ. In group B all measurements of HR remained in a stable range with no significant deviating values

At no point in this study, a hemodynamic side effect was reported by the anesthetic team and/or an intervention was necessary to resolve a hemodynamic complication.

Discussion

This study is a pilot study to evaluate the safety profile of ICM in a pediatric population, based on the measurement of phenylephrine and tropicamide in plasma at different time points and the incidence of hemodynamic side effects in the first 15 patients included in the MyKid study. ICM is a standardized preservative-free intracameral combination of

Table III. — Post hoc Wilcoxon test for phenylephrine in the total population and for tropicamide for group A only. Sig. (p) = Asymptotic significance level.

Phenylephrine, total population (p = 0.019)						
	Baseline – T(+2)	Baseline – T(+10)	Baseline – T(+30)	T(+2) – T(+10)	T(+2) – T(+30)	T(+10) – T(+30)
Sig. (p)	0.043	0.028	0.180	0.735	0.043	0.046
Tropicamide, group A (p = 0.023)						
	Baseline – T(+2)	Baseline – T(+10)	Baseline – T(+30)	T(+2) – T(+10)	T(+2) – T(+30)	T(+10) – T(+30)
Sig. (p)	0.180	0.109	0.066	0.109	0.066	0.197

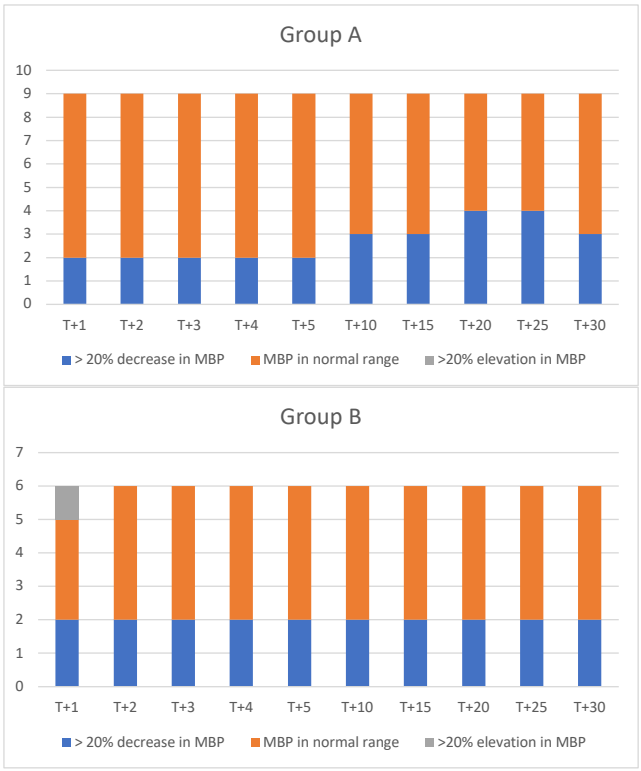

Fig. 3 — Evaluation of mean blood pressure (MBP) after the administration of ICM.

Fig. 4 — Evaluation of heart rate (HR) after the administration of ICM.

mydriatics and a local anesthetic. A Phase-III clinical trial was conducted by Labetoulle et al. in 2016 and demonstrated a safe profile of ICM in adults based on the low incidence of ocular and systemic adverse events[9]. A follow-up study by Guell et al. in 2019 described the systemic exposure of phenylephrine and tropicamide in 271 adult patients receiving ICM compared to 283 patients who received mydriatic eye drops. This study showed a lower systemic exposure in the ICM group and no adverse cardiovascular events. The method of quantification used in the research of Guell et al. produced a LLOQ of 0.1 ng/mL for both phenylephrine and tropicamide[6].

In this pilot research, we observed 15 pediatric patients from 2 months to 5 years and 9 months old, undergoing cataract surgery under GA and receiving ICM at the beginning of surgery. The highest levels of phenylephrine were detected in our youngest patients from group A, aged 8 weeks to 1 year, with a maximum concentration of 1.85 ng/mL in a 2 month old patient. In both groups, the plasma phenylephrine concentrations showed a significant early increase, suggesting a rapid systemic absorption after intracameral injection. The highest concentrations of phenylephrine were measured at two minutes after administration of ICM. Further on, the plasma levels did not change substantially between two and ten minutes and seemed to decrease towards baseline at 30 minutes. Similar to phenylephrine, the highest concentration of tropicamide was detected in in the youngest age group (0.30 ng/mL at T(+10)). Since the changes in plasma concentration of tropicamide were not statistically significant, we were unable to reach solid conclusions about a pharmacokinetic profile in this small study population.

The evaluation of hemodynamic parameters in children under GA brings many challenges, since there are many variables to be considered. When considering possible hemodynamic side effects of ICM, we were especially interested in the occurrence of hypertension, bradycardia or tachycardia, based on the pharmacologic characteristics of phenylephrine and tropicamide. In our study population most important hemodynamic changes were observed in the youngest patient group. In these patients we frequently noted a decrease in MBP when compared to the baseline value after induction of anesthesia. Hypotension or a decrease in blood pressure could not be explained pharmacologically by the administration and absorption of phenylephrine or tropicamide. We hypothesize that these low MBPs may be due to the GA caused by the vasodilatory effects of propofol and sevoflurane. In only two patients, we did observe a notable hemodynamic change which could be triggered by the systemic absorption of phenylephrine or tropicamide. However, other procedural factors could possibly account for these hemodynamic changes.

To our knowledge, there is no previous research on plasma concentrations of phenylephrine and/or tropicamide after topical administration in eye surgery in a pediatric population. There are, on the other hand, many studies available evaluating the effects and side effects of topical administrations of mydriatics in children12 and preterm infants, where mydriatics are used in the screening for retinopathy of prematurity[4]. One study by Christensen et al. evaluated the plasma concentrations of phenylephrine after intranasal administration before intranasal intubation. In their study plasma levels as high as 50 ng/mL were detected. This systemic absorption of phenylephrine led to a significant increase in blood pressure, but this was deemed clinically insignificant[13].

In this study we did not evaluate the effect or measure the plasma concentrations of lidocaine, the third component of ICM. Considering the maximal allowed dose of 4.5 mg/ml for intravenous administration, one dose of 0.1 mL ICM, containing 1 mg of lidocaine, is considered to be safe for intracameral administration in the investigated pediatric population[14].

This pilot study was a preliminary analysis of the safety of ICM in a small study group. A larger research and analysis will follow, considering that pediatric cataract is a rare condition making it difficult to produce large study samples. Our aim was not to prove superiority for the use of intracameral Mydrane® in cataract surgery in children. Therefore, we did not compare the effects, plasma concentrations and the incidence of side effects of ICM with the golden standard of mydriatic eye drops. We recommend this study design for future research because we believe there are many advantages to the use of intracameral mydriatics.

Conclusion

This pilot study on the first 15 patients included in the MyKid study offers a first impression on the systemic exposure to ICM after intracameral injection at the beginning of cataract surgery in a pediatric population. Plasma concentrations of phenylephrine and tropicamide were detected above the thresholds, but we did not observe clinically significant hemodynamic side effects that are directly the result of the systemic absorption of these components of ICM.

Conflicts of interest and funding: The authors declare no conflicts of interest and received no funding for this research.

Acknowledgments : The authors would like to thank C. Smitz and I. De Backer for their supporting role during data collection and C. Christia, T. Garroy and A. van Nuijs for the optimization and validation of the analytic method for quantification of phenylephrine and tropicamide.

References

1. Kaur S, Korla S, Ram J, Gupta PC, Sukhija J. Intracameral anesthetic mydriatic (ICAM) assisted pediatric cataract surgery. Eur J Ophthalmol. 2021:11206721211006575.
2. Lundberg B, Behndig A. Intracameral mydriatics in phacoemulsification cataract surgery. J Cataract Refract Surg. 2003;29(12):2366-71.
3. Farkouh A, Frigo P, Czejka M. Systemic side effects of eye drops: a pharmacokinetic perspective. Clin Ophthalmol. 2016;10:2433-41.
4. Kremer LJ, Reith DM, Medlicott N, Broadbent R. Systematic review of mydriatics used for screening of retinopathy in premature infants. BMJ Paediatr Open. 2019;3(1):e000448.
5. Behndig A, Lundberg B, Bäckström G. Intracameral mydriatics in cataract surgery. Cataract Surgery: IntechOpen; 2013.
6. Guell J, Behndig A, Pleyer U, Jaulerry S, Rozot P, Pisella PJ, et al. Systemic exposure to intracameral vs topical mydriatic agents: in cataract surgery. Clin Ophthalmol. 2019;13:811-9.
7. Caputo AR, Schnitzer RE. Systemic response to mydriatic eyedrops in neonates: mydriatics in neonates. J Pediatr Ophthalmol Strabismus. 1978;15(2):109-22.
8. Kumar V, Schoenwald RD, Chien DS, Packer AJ, Choi WW. Systemic absorption and cardiovascular effects of phenylephrine eyedrops. Am J Ophthalmol. 1985;99(2):180-4.
9. Labetoulle M, Findl O, Malecaze F, Alio J, Cochener B, Lobo C, et al. Evaluation of the efficacy and safety of a standardised intracameral combination of mydriatics and anaesthetics for cataract surgery. Br J Ophthalmol. 2016;100(7):976-85.
10. Frykholm P, Disma N, Andersson H, Beck C, Bouvet L, Cercueil E, et al. Pre-operative fasting in children: A guideline from the European Society of Anaesthesiology and Intensive Care. Eur J Anaesthesiol. 2022;39(1):4-25.
11. Nafiu OO, Voepel-Lewis T, Morris M, Chimbira WT, Malviya S, Reynolds PI, et al. How do pediatric anesthesiologists define intraoperative hypotension? Paediatr Anaesth. 2009;19(11):1048-53.
12. Sbaraglia F, Mores N, Garra R, Giuratrabocchetta G, Lepore D, Molle F, et al. Phenylephrine eye drops in pediatric patients undergoing ophthalmic surgery: incidence, presentation, and management of complications during general anesthesia. Paediatr Anaesth. 2014;24(4):400-5.
13. Christensen LK, Armstead VE, Bilyeu DP, Johnson KE, Friesen RH. Hemodynamic responses and plasma phenylephrine concentrations associated with intranasal phenylephrine in children. Paediatr Anaesth. 2017;27(7):768-73.
14. Bahar E, Yoon H. Lidocaine: A Local Anesthetic, Its Adverse Effects and Management. Medicina (Kaunas). 2021;57(8).

doi.org/10.56126/75.S1.14