

The effect on hemodynamic parameters and incidence of systemic side-effects following intracameral injection of a mixture of tropicamide 0,02%, phenylephrine 0,31% and lidocaine 1% in children: a pilot study

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Abstract

Background: intracameral injection with a mixture of tropicamide 0,02%, phenylephrine 0,31% and lidocaine 1% (ICM), has been proven a safe and efficacious alternative to eye drops in adult patients undergoing cataract surgery. It provides a reliable and long-lasting mydriasis and could therefore be used as an alternative in pediatric patients undergoing cataract surgery. A safety profile has been established in adult, but not yet in pediatric populations.

Objective: to evaluate whether ICM is a safe alternative to preoperative eye drops in pediatric populations, with minimal effects on hemodynamic parameters and a low incidence of adverse events.

Materials & Methods: patients aged 8 weeks to 17 years scheduled for cataract surgery under general anesthesia, either unilaterally or bilaterally, were included from November 2020 until October 2021. All subjects received ICM. Perioperative blood pressure, heart rate and any adverse events (e.g. bradycardia, hypertension, etc.) were recorded.

Results: 40 patients were included in this study. A mixed effects model analysis showed that, after a first dose of ICM, the Z-score for systolic blood pressure (zSBP) would increase by a 0,036 (sig=0,617), the Z-score for diastolic blood pressure (zDBP) would decrease by 0,042 (sig=0,151) and the Z-score for heart rate (zHR) would increase by 0,034 (sig=0,250). A second dose of ICM would increase zSBP by 0,021 (sig=0,694), decrease zDBP by 0,006 (sig=0,907) and would decrease HR by 0,038 (sig=0,273). No event of hemodynamic instability requiring stabilization was reported. Five events of inadequate depth of anesthesia were reported.

Conclusion: based on these preliminary findings, ICM has a negligible effect on hemodynamic parameters and can be safely used in a pediatric population. Further research is warranted to confirm the efficacy and safety profile of ICM.

Keywords: Phenylephrine, tropicamide, mydriasis, pediatrics, cataract extraction.

Introduction

Pediatric cataract is one of the leading causes of treatable childhood blindness worldwide^{1,2}, with a reported incidence of 4,24 per 10,000³. Despite

this relatively low incidence, early detection and management remain important.

Most unilateral and a significant number of bilateral cataracts are idiopathic in nature. Identifiable causes include trauma, uveitis,

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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 October 2021.

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intraocular tumors, chronic retinal detachment and maternal infection during pregnancy⁴.

Visually significant cataract in children calls for prompt surgical intervention to clear the ocular media and provide a focused retinal image⁵.

The first step in achieving the best circumstances for surgery and lens implantation is to obtain a stable mydriasis⁶. This allows the surgeon to remove the affected lens and replace it by implanting an artificial intra-ocular lens device. The current worldwide gold standard for achieving mydriasis is the use of tropicamide and phenylephrine eye drops.

Phenylephrine is a pure alpha agonist which mainly acts on the smooth muscles within the walls of the arterioles⁷. This vasoconstriction results in an increased peripheral vascular resistance and elevation of systolic and diastolic blood pressure. This usually results in reflex slowing of the heart rate via the parasympathetic system. When the drug reaches the eye, it relaxes the sphincter muscle of the iris and strongly contracts the radial muscle fibers, leading to mydriasis.

Tropicamide is an anticholinergic mydriatic cycloplegic agent⁷. It blocks the parasympathetic innervation of the eye and causes dilation of the sphincter pupillae muscle. If absorbed systemically, it leads to anticholinergic signs including redness and dryness of the skin, dry mouth, increased heart rate and body temperature, and disorientation with visual hallucinations.

Drugs applied in the conjunctival sac may be absorbed in various amounts and may have clinically evident systemic reactions⁸. Possible mechanisms for rapid systemic absorption would be via the capillaries within the conjunctiva. As the drug passes over the surface of the eye and through the lacrimal drainage system, it may be absorbed via the nasal mucosa⁷.

A multitude of case reports show that the use of phenylephrine and/or anticholinergic mydriatic eye drops in children, especially those of low birth-weight or premature babies undergoing screening for retinopathy of prematurity, can have systemic effects such as tachycardia, bradycardia, increase or decrease in systolic and diastolic blood pressure^{7,9-12}. Ventricular overload, increase in pulmonary artery systolic pressure and pulmonary edema have also been described¹⁰.

Instillation with conventional tropicamide and phenylephrine eye drops is associated with multiple disadvantages^{6,13}. There is a risk of local or systemic toxicity as discussed in the previous section. Another drawback is the need to start administration 30 minutes before surgery and the need for prolonged supervision by nursing staff to instill the eye drops and monitor the mydriasis. Successive doses frequently need to be given to obtain satisfactory

mydriasis and changes in surgical scheduling may require additional administrations. Exposure to higher than anticipated levels of mydriatics may increase the risk for topical and systemic side effects. A mydriatic insert ensures better control of the delivered dose of mydriatics, but a longer time is required to obtain optimal mydriasis, and the risk of toxicity remains¹⁴.

As an alternative to eye drops, intracameral injections with a mixture of tropicamide 0,02%, phenylephrine 0,31%, and lidocaine 1% (ICM), at the beginning of surgery has been proposed^{6,15,16}. In adults, it is generally well tolerated, provides rapid and sustained mydriasis without the use of additional mydriatics and has no serious side effects^{15,17-21}. A particular benefit of ICM is the excellent bioavailability directly in the target tissues and the lower systemic absorption and therefore lower incidence of unwanted systemic effects. Another benefit is that excellent mydriasis can be achieved without the need of multiple instillations and prolonged patient monitoring. A recent phase III study found ICM an effective and safe alternative to standard eye drops for initiating and maintaining intraoperative mydriasis and analgesia in adults¹⁵.

Objective

The efficacy and safety profile of ICM has been established in the adult population undergoing cataract surgery, but has not yet been confirmed in a pediatric population. This study is set up to analyze the efficacy and incidence of systemic effects of ICM in a pediatric population undergoing cataract surgery. In this prospective study, we evaluate the effect of ICM on hemodynamic parameters in children aged 8 weeks to 17 years under general anesthesia (GA).

The objective of this study is to prove ICM shows a safe profile in the pediatric population. Two mechanisms may render ICM safer for use as compared to preoperative ED:

- 1) Less systemic absorption of drugs injected in the anterior eye chamber as there is no contact with the capillaries of the conjunctiva or nasal mucosa.
- 2) A predictable and stable mydriasis produced by ICM reduces the need for subsequent administration of mydriatics and results in a lower cumulative dose administered.

Methodology

This manuscript adheres to the applicable STROBE guidelines for observational studies as provided by the EQUATOR network.

Study design and setting

A single-center, prospective interventional study evaluating the efficacy and systemic side effects of ICM in children undergoing cataract surgery under GA was set up, after approval by the ethical committee of the University Hospital of Antwerp (study number 20/39/504). The study was registered in the EudraCT database with reference number 2020-003422-24. Patients were recruited in the University Hospital between November 2020 and October 2021. Patients eligible for this study were children aged 8 weeks to 17 years, scheduled for unilateral or bilateral surgical cataract repair. Inclusion and exclusion criteria are summarized in Table I. A written informed consent was acquired from parents as well as children older than four years. Study data was collected perioperatively with no long-term follow up of participants (Table I).

Pediatric cataract is a rare condition and the University Hospital is a reference center for cases in small children or for complex cases in older children. An inclusion period of 1 year was used, as choosing a longer period could lead to bias because surgical technique or equipment changed. Within the timespan of one year, number of cases remain very limited, thus reducing the number of recruitable patients.

Study setup

On the day of surgery, patients received no mydriatic eye drops preoperatively, nor any oral or intravenous sedatives. Patients were fasted according to preoperative fasting rules (six hours for solid foods, four hours for breast milk, two hours for clear fluids). Heart rate, blood oxygen saturation and blood pressure were measured before induction of GA. Patients received an inhalational induction of anesthesia with 8% of inspired sevoflurane. After administration of 2 µg kg⁻¹ of fentanyl, 2 mg kg⁻¹ of propofol and 0,5 mg kg⁻¹ of atracurium, the patient was intubated with either a cuffed or uncuffed endotracheal tube. Additional monitoring was established including capnography and continuous temperature measurement. A NeuroSENSE® NS-901 monitor was used monitor depth of anesthesia

(DOA) in all patients. To eliminate for variations in DOA which might influence hemodynamic parameters, we used a target WAVCNS of 40, by either adjusting the minimum alveolar concentration (MAC) of sevoflurane, or by additional administration of propofol or fentanyl boluses. The authors are aware that the use of a NeuroSENSE® monitor is not a reliable tool for use in neonates and young children, so the risk of differences in DOA between study patients could never be completely eliminated²²⁻²⁴. A balanced salt solution was used as perioperative maintenance fluid using to the 4-2-1 rule for fluid management in children. A dose of 0,1 ml of ICM was administered intracamerally. After administration of ICM, surgery was initiated. In bilateral eye surgery, a second dose of 0,1 ml of ICM was administered after completion of surgery on the first eye. At the conclusion of surgery, a dose of 20 mg kg⁻¹ of paracetamol was given intravenously. To compensate for potential variations in surgical technique and different preferences in conduction of anesthesia, which might have influence on hemodynamic parameters, all surgeries were performed by the same two ophthalmologists, and anesthesia was provided by the same two anesthesiologists.

Data collection

Patient demographic data including sex, age, weight and length were recorded. A baseline heart rate (HR), non-invasive blood pressure (NIBP) measurement and blood oxygen saturation were measured before induction of GA. After induction of GA and one minute before administration of ICM, the HR and NIBP were recorded. After the ophthalmologist announced the administration of ICM, the HR and NIBP were noted every minute for five minutes. After the first five minutes, parameters were registered every five minutes until the conclusion of surgery.

The incidence of any adverse effects reflecting systemic absorption of active components of ICM such as blanching or flushing of the skin, changes in body temperature, changes in blood oxygen saturation or abrupt changes in peak inspiratory

Table I. — Inclusion and exclusion criteria used during patient recruitment.

Inclusion and exclusion criteria	
Inclusion criteria	Exclusion criteria
Children aged 3 weeks to 17 years old	Reported allergies for one of the components of TPL
Children undergoing unilateral cataract repair	Children with previous cataract surgery of one eye within this study presenting for surgery of the contralateral eye on a different day
Children undergoing bilateral cataract repair in one surgery ('immediate sequential bilateral cataract surgery')	Pregnancy

pressure or end-tidal carbon dioxide (CO₂) was recorded.

For patients receiving surgery on the contralateral eye during the same GA after having had surgery on one eye, we created a separate new data entry. Baseline parameters were copied from before induction of GA.

Statistical methods

In this study, hemodynamic parameters are analyzed as a substitute of systemic absorption of phenylephrine and/or tropicamide after ICM. SBP, DBP and HR were selected as the main parameters. A significant degree of systemic absorption of phenylephrine would lead to an observable increase in SBP and DBP primarily and a reflex decrease in HR secondarily. A significant degree of systemic absorption of tropicamide would lead to an observable increase in HR. The percentage change and duration of the change in hemodynamic parameters would depend on the amount and rate of systemic absorption of the mixture.

To correct for age-, gender- and height-bound differences in mean or expected SBP, DBP and HR, these values were transformed into Z-Scores, which represent the degree of standard deviations an observed value differs from the mean or expected value at a given age, gender and height. By using Z-scores, gender- age- and height-related variations in hemodynamic parameters were corrected, thus making these observations comparable in statistical analyses.

Z-Scores for SBP and DBP were calculated using the formula provided in the fourth report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents²⁵. The Z-scores for height-for-age and weight-for-age for children aged 0 to 5 years were acquired using the WHO charts on height-for age and weight-for-age which were provided on the WHO website²⁶. For children older than 5 years, Z-score data files from height-for-age and weight-for-age charts available on the CDC website²⁷ were used. Z-Scores for HR were calculated by the age- and gender-corrected mean HR and Standard Deviation provided by Bratincsák et al. in the Electrocardiogram Standards for Children and Young Adults²⁸. Demographic data on mean age-adjusted mean blood pressure and associated standard deviations could not be found and were consequently not used in further analyses.

Descriptive statistics for demographic data were analyzed using IBM SPSS Statistics® v. 28. The same program was used for the Kolmogorov-Smirnov and Shapiro-Wilk tests, which showed a normal distribution of Z-Score data for SBP, DBP and HR (zSBP, zDBP and zHR, respectively) at all points in time.

Hemodynamic parameter measurements were divided in two groups: 'group 1' was defined as all measurements taken in patients during surgery on the first eye. 'Group 2' was defined as all measurements taken in patients during surgery on the second eye, thus after surgery on the first eye was concluded and a second dose of ICM was administered. In these two groups, data was further stratified per age, from 2 – 12 months, 1-6 years and 6-17 years.

Mean values for zSBP, zDBP and zHR were calculated at each time point and were plotted chronologically. Separate plots were generated for patients in group 1 and 2, stratified for age and for total patients in each group.

To account for repeated measurements, a mixed effect model linear regression analysis was used to evaluate the differences in mean zSBP, zDBP and zHR before and after ICM. The presence of ICM was defined as a fixed effect. In group 2, the presence of a second dose of ICM was defined as a fixed effects. Patients and intercept for each patient were defined as a random effect. The autoregressive (AR)1: heterogeneous covariance structure was used. The Akaike's information Criterion (AIC) test showed this to be the best goodness of fit test for our data structure.

The mean difference in Z-scores before and after ICM and significance level were used to evaluate whether hemodynamic parameters differed significantly before and after the administration of ICM.

Data analysis was performed on patients stratified for age, as well as total patients in group 1. A separate analysis was performed on stratified and total patients in group 2.

Sample size

We defined an effect size of 0,5 as a clinically relevant change in blood pressure or heart rate. An effect size of 0,5 would reflect a Z-score or effectively, standard deviation, difference of 0,5 before and after the administration of ICM. The study would require a sample size of 34 to achieve a power of 80% and a level of significance of 5% for detecting an effect size of 0,5 between pairs²⁹. To compensate for possible drop-out of the study, the target study population was increased to 40 participants.

Results

Participants

All patients presenting for cataract surgery and meeting the inclusion criteria were invited to participate in the study. Recruitment started in November 2020 and ended in October 2021. None

of the patients met any of the exclusion criteria and none of the eligible patients or their parents refused to participate in the study.

Patient demographics

Patient demographic data is summarized in Table II. 13 of the participants received bilateral eye cataract surgery and 27 received unilateral surgery. 52% of the unilateral surgery was performed on the left eye and 48% was performed on the right eye. The youngest patient was 8 weeks old, the oldest 15 years. 42,5% of patients was between the age of 0 and 6 months. 27,5% of patients was between the age of 2 and 6 years. Both genders were equally represented in our patient population with a ratio of 50/50 male/female. The mean length was 0,09 standard deviation less (z-score -0,09) than predicted age-corrected length. The mean weight was 0,008 standard deviation less (z-score -0,008) than predicted age-corrected weight. Average duration of surgery was 78 minutes.

The total number of patients group 1 and 2 as well as in each stratified subgroup within group 1 and 2 is summarized in Table III.

Visual presentation of mean Z-Scores over time

In group 1, mean zSBP, zDBP and zHR were plotted over time in patients stratified for age as well as in total patients. These plots are presented in figure 1.

The time points are presented on the X-axis. ‘Baseline’ was defined as measurements taken before induction of general anesthesia. ‘T-1’ was defined as measurements taken after induction of general anesthesia but before surgical incision. ‘T0’

Table II. — Demographic data of study participants. The number of participants and percentages for each age category, sex and surgery side are presented. Mean Z-scores for length and height and duration of surgery with standard deviations are presented.

Patient demographic data			
		Percentage	N
Age categories	2-6 Months	42,5	17
	6-12 Months	2,5	1
	1 – 2 Years	12,5	5
	2-6 years	27,5	11
	6 – 12 years	10	4
	12- 17 years	5	2
Sex	Male	50	20
	Female	50	20
Side of surgery	Left	35	14
	Right	32,5	13
	Bilateral	32,5	13
Z-score length		-0,09 ± 1,61	
Z-score height		-0,008 ± 1,29	
Duration of surgery		78 ± 33,77 min	

Table III. — Total number of patients in group 1 and 2, as well as the number of patients in each subgroup stratified for age.

Group 1 was defined as all measurements taken in patients during surgery on the first eye. Group 2 was defined as all measurements taken in patients during surgery on the second eye, thus after surgery on the first eye was concluded and a second dose of ICM was administered.

Number of patients in each group		
	Group 1	Group 2
2 – 12 months	18	4
1 – 6 years	16	7
6 – 17 years	6	2
Total	40	13

was defined as measurements taken at the time of injection of ICM. ‘T1’ was defined as measurements taken 1 minute after ICM, T2 was 2 minutes after ICM, etc.

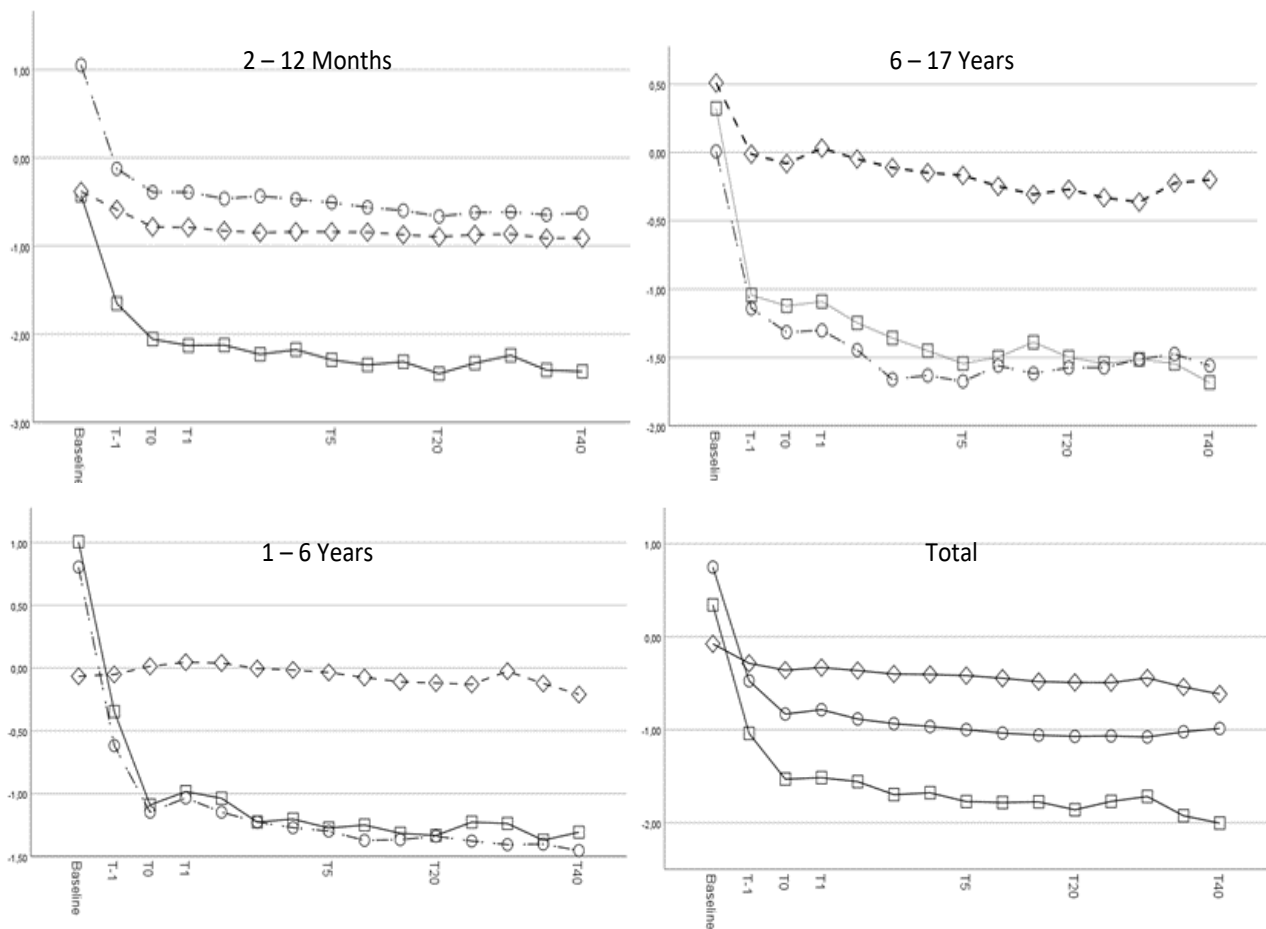
In group 2, mean zSBP, zDBP and zHR were plotted over time in patients stratified for age as well as in total patients. These plots are presented in figure 2.

In group 2, T-1 was defined as measurements taken after surgery of the first eye was concluded, but the second dose of ICM was not yet administered. T0 was defined as measurements taken at the time of the second injection of ICM. T1 was defined as measurements taken 1 minute after the second dose of ICM, T2 was 2 minutes after the second dose of ICM, etc.

Mixed effects model linear regression analysis

In group 1, a mixed effects linear regression analysis was performed on zSBP in each age subgroup as well as in all patients within the group. Mean differences in zSBP before and after ICM and significance levels are summarized in Table IV. After administration of ICM, mean zSBP was 0,055 decreased in patients aged 2-12 months, 0,019 decreased in patients aged 1-6 years, 0,217 decreased in patients aged 6-17 years and 0,036 increased in all patients pooled together. Only in age group 6-17 years, this difference was statistically significant ($p < 0,05$).

An analogous analysis was performed on zDBP and zHR measurements. Mean Z-scores for diastolic blood pressure after administration of ICM were increased by 0,035 in patients aged 2-12 months, decreased by 0,078 in patients aged 1-6 years, decreased by 0,060 in patients aged 6-17 years and 0,042 decreased in all patients. Only in the 1 – 6 year age group, this difference was statistically significant ($p < 0,05$). After administration of ICM, mean Z-Scores for heart rate were 0,091 increased in patients aged 2-12 months, 0,013 decreased in



Legend
 □ zSBP ○ zDBP ◇ zHR / X-Axis: Time Points / Y-Axis: Mean Z-Scores

Fig. 1 — Mean Z-Scores of zSBP, zDBP and zHR over time in group 1.

Average Z-scores for systolic blood pressure (zSBP), diastolic blood pressure (zDBP) and heart rate (zHR) over time in group 1.

Group 1 was defined as all measurements taken in patients during surgery on the first eye.

The X-axis represents the different time points. In group 1, 'baseline' represents measurements taken before induction of general anesthesia. T-1 was defined as measurements taken after induction of general anesthesia but before incision. T0 was defined as measurements taken at the time of injection of an intracameral injection with a mixture of tropicamide 0,02%, phenylephrine 0,31% and lidocaine 1% (ICM). T1 was defined as measurements taken 1 minute after ICM, T2 was 2 minutes after ICM and so on until T40.

The Y-axis represents zSBP, zDBP and zHR values.

patients aged 1-6 years, 0,105 decreased in patients aged 6-17 years and 0,034 increased in all patients. Only in age category 6-17 years, this decrease was statistically significant ($p < 0,05$).

A similar approach was used for measurements in group 2. After administration of ICM, mean Z-scores for systolic blood pressure were 0,039 decreased in patients aged 2-12 months, 0,035 decreased in patients aged 1-6 years, 0,097 decreased in patients aged 6-17 years and 0,021 increased in all patients pooled together. None of these mean differences were considered statistically significant ($p > 0,05$) in this analysis.

In group 2, mean Z-score for diastolic blood pressure decreased with 0,081 after administration of ICM in patients aged 2-12 months, increased with 0,010 in patients aged 1-6 years, decreased with 0,025 in patients aged 6-17 years and decreased with

0,006 in all patients. None of these mean differences were considered statistically significant ($p > 0,05$). After administration of ICM, mean Z-score for heart rate was expected to decrease with 0,026 in patients aged 2-12 months, increase with 0,067 in patients aged 1-6 years, increase with 0,180 in patients aged 6-17 years and decrease with 0,038 in all patients. None of these estimated fixed were considered statistically significant ($p > 0,05$).

Adverse events

During unilateral as well as bilateral surgical procedures, there were no reports of clinically evident bradycardia, tachycardia, hypertension or hypotension. In none of the procedures had any vasoactive substance such as atropine or urapidil to be given. In five cases, additional doses of propofol and/or fentanyl had to be given because inadequate

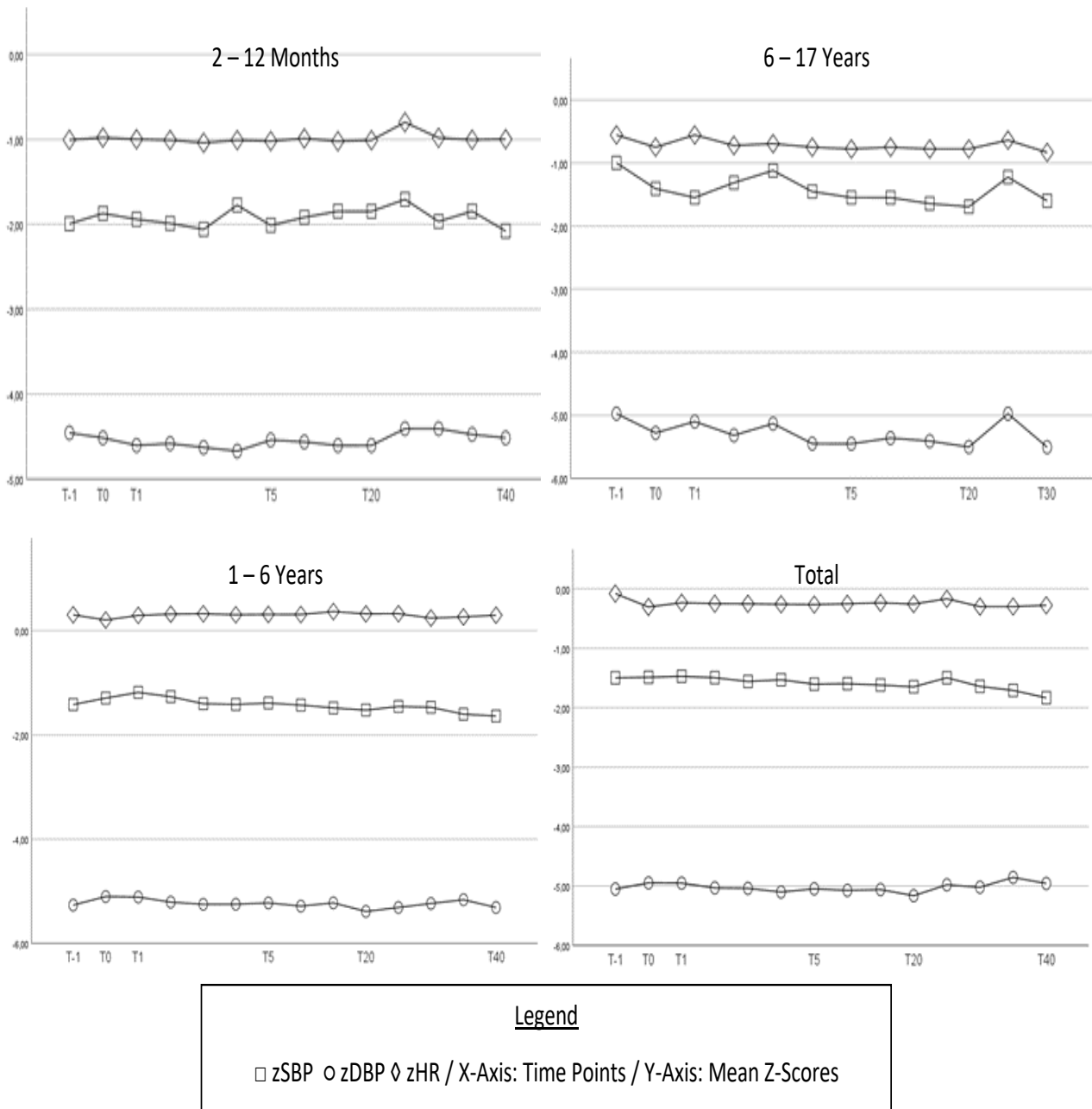


Fig. 2 — Mean Z-Scores of zSBP, zDBP and zHR over time in group 2.

Average Z-scores for systolic blood pressure (zSBP), diastolic blood pressure (zDBP) and heart rate (zHR) over time in group 2.

Group 2 was defined as all measurements taken in patients during surgery on the second eye, thus after surgery on the first eye was concluded and a second dose of an intracameral injection with a mixture of tropicamide 0,02%, phenylephrine 0,31% and lidocaine 1% (ICM) was administered.

The X-axis represents the different time points.

T-1 was defined as measurements taken after surgery of the first eye was concluded, but the second dose of ICM was not yet administered. T0 was defined as measurements taken at the time of the second injection of ICM. T1 was defined as measurements taken 1 minute after the second dose of ICM, T2 was 2 minutes after the second dose of ICM and so on until T40.

The Y-axis represents zSBP, zDBP and zHR values.

depth of anesthesia resulted in eye movement, despite having a sufficient DOA on NeuroSENSE® monitoring.

Discussion

Our results show that the greatest decline in hemodynamic parameters occurs between baseline, T-1 and T0 in all age categories in group 1, as can be observed in figure 1. These are the time points before and immediately after induction of general

anesthesia. After T0, all parameters show further decline but at a slower rate. In general, systolic and diastolic blood pressure show a steeper decline than heart rate. Parameters in group 2, presented in figure 2, stay more stable and visually show little to no decline over time.

Using a mixed effects model linear regression analysis, a significant effect of the presence of ICM on hemodynamic parameters was observed in three subgroups. In patients aged 6-17 years, a first dose of ICM would lead to a significant decrease in systolic

Table IV. — Mean differences in zSBP, zDBP and zHR before and after administration of ICM.

Group 1						
	zSBP		zDBP		zHR	
Age category	ΔMean	Significance	ΔMean	Significance	ΔMean	Significance
2 – 12 mo	- 0,055	0,702	0,035	0,509	0,091	0,071
1 – 6 y	-0,019	0,676	-0,078	0,022	-0,013	0,795
6 – 17 y	-0,217	0,006	-0,060	0,435	-0,105	0,008
All	0,036	0,617	-0,042	0,151	0,034	0,250
Group 2						
	zSBP		zDBP		zHR	
Age category	ΔMean	Significance	ΔMean	Significance	ΔMean	Significance
2 – 12 mo	-0,039	0,762	-0,081	0,351	-0,026	0,269
1 – 6 y	-0,035	0,267	0,010	0,900	0,067	0,191
6 – 17 y	-0,097	0,164	-0,025	0,784	0,180	0,385
All	0,021	0,694	-0,006	0,907	-0,038	0,273

Using a mixed effects model linear regression analysis, mean differences (ΔMean) in Z-scores for systolic blood pressure (zSBP), diastolic blood pressure (zDBP) and heart rate (zHR) before and after an intracameral injection with a mixture of tropicamide 0,02%, phenylephrine 0,31% and lidocaine 1% (ICM) were calculated. A positive ΔMean represents a higher Z-score after administration of ICM, a negative ΔMean represents a lower Z-score after administration of ICM.

Group 1 was defined as all measurements taken in patients during surgery on the first eye. Group 2 was defined as all measurements taken in patients during surgery on the second eye, thus after surgery on the first eye was concluded and a second dose of ICM was administered. ΔMean in this group represents Z-scores before and after administration of a second dose of ICM.

ΔMean values were calculated in stratified age groups of patients aged 2 – 12 months, 1 – 6 years and 6 – 17 years. They were also calculated for all patients.

blood pressure. In patients aged 1- 6 years, a first dose of ICM would lead to a significant decrease in diastolic blood pressure. In patients aged 6-17 years, a first dose of ICM would lead to a significant decrease in heart rate.

In all other groups stratified for age, no significant effect of the administration of ICM on hemodynamic parameters was observed. In all age groups pooled together, no significant effect of administration of a first dose of ICM on either systolic blood pressure, diastolic blood pressure or heart rate was observed. A second dose of ICM did not cause any change in hemodynamic parameters in any of the subgroups.

An important caveat in the interpretation of these results is that, when stratifying data within each group, this reduces the number of observations to a point where a mixed effects model analysis becomes unreliable. For example, only two participants in group 2 were in the 6-17 year age category. Subgroups with a low number of patients produce unreliable results and these should be interpreted accordingly.

In patients aged 6-17 years, a first dose of ICM would lead to a significant decrease in systolic blood pressure and in heart rate. This result was reached by performing a mixed model analysis on observations of 6 patients. In contrast, ICM would

not lead to an increase or decrease in systolic blood pressure or heart rate in patients aged 2-12 months and 1-6 years. The number of patients was higher in these two subgroups (18 and 16, respectively). When performing a mixed model analysis on all age groups pooled, no effect of ICM on systolic blood pressure and heart rate was observed. The decrease in systolic blood pressure after administration of ICM is unexpected, as systemic absorption of phenylephrine would rather lead to an increase in systolic blood pressure. A decrease in heart rate may be due to reflex bradycardia after systemic absorption of phenylephrine. A decrease of a Z-score of 0,105 may be statistically significant, however, the clinical significance of this number is questionable.

In patients aged 1- 6 years, a first dose of ICM would lead to a significant decrease in diastolic blood pressure. This result was reached by performing a mixed model analysis on observations of 7 patients. In contrast, ICM would not lead to an increase or decrease in diastolic blood pressure in patients aged 2-12 months. When performing a mixed model analysis on all age groups pooled, no effect of ICM on diastolic blood pressure was observed. A decrease in diastolic blood pressure does not reflect a systemic absorption of phenylephrine and/or tropicamide.

Globally, administration of ICM changed zSBP, zDBP and zHR minimally. Important to note is the high variability of observed parameters at T-1, and the relative stability of hemodynamic parameters at T0 with only gradual decrease of observed values at later time points. These findings may influence the results of this mixed model analysis. To provide definitive proof that ICM has influence on hemodynamic parameters is not possible in this analysis. Still, it can be used to observe general trends, in conjunction with figure 1 and 2.

More relevant is the observation that, in no cases, stabilizing drugs had to be given after a clinically significant bradycardia or hypertension was observed. None of the other side-effects associated with phenylephrine and/or tropicamide eye drops were observed perioperatively.

This absence of clinically relevant hemodynamic repercussion after ICM is in contrast with previously reported observations that mydriatic eye drops in children may produce systolic hypertension and/or bradycardia^{10,11,13,30}, especially if high concentrations (e.g. 10% or 2,5%) are used^{9,30}.

The perioperative hemodynamic parameters such as blood pressure and HR are subject to a majority of different factors such as fasting status, depth of anesthesia, age differences and interindividual differences. This is a major cause of bias in this study. To compensate for these factors, a standardized DOA by maintaining a WAVCNS of 40 and a predetermined dose of induction agents was provided. However, the use of NeuroSENSE® monitoring is not validated in neonates and young children^{22,31,32}. Furthermore, administration of predetermined doses of anesthetics does not guarantee equipotent doses as there is a large age-related and interindividual pharmacokinetic and pharmacodynamic variance in anesthetic dosing requirements. In five cases, additional anesthetics had to be administered. Despite various strategies to ensure a uniform DOA, the risk of variations herein influencing hemodynamic parameters remains an important risk of bias in this study. To compensate for age-related differences in hemodynamic parameters we performed our analyses on Z-scores. Still, to completely compensate for this broad range of potential bias remains difficult to nearly impossible. For example, a preoperative fasting rule of clear fluids two hours before surgery does not define the amount of fluid intake is permitted and fasting time differed greatly between individual patients. Thus the interpretation of the results as described earlier should be done cautiously.

There remains the question if the third component of ICM, lidocaine, would pose a risk of local anesthetic toxicity. A dose of 1 mg of lidocaine was

administered intracamerally in unilateral cataract surgery and in bilateral surgery, a total dose of 2 mg of lidocaine was administered. If we consider a maximum dose of lidocaine of 5 mg per kg body weight³³, in none of our test subjects maximum dosing was exceeded. In 40 participants, no clinical signs of local anesthetic toxicity were observed perioperatively.

This study was designed as a short-term cohort follow up study in a patient population who were all exposed to an intervention (ICM). We did not set up a control group. Additional studies in which a control group is set up are warranted for producing higher quality of evidence.

Conclusion

The results of this pilot study suggest that a single dose or two doses of an intracameral mixture of 0,1 ml of tropicamide 0,02%, phenylephrine 0,31% and lidocaine 1% does not cause any significant systemic side-effects in children aged 8 weeks to 15 years. In three age groups, a statistically significant effect of ICM on heart rate and systolic blood pressure was observed after administration of a first dose of ICM. The clinical relevance of these findings remains a point of discussion. No major adverse events or need for administration of stabilizing agents were reported in 40 pediatric cataract surgeries using ICM. The data in this pilot study are subject to different sources of bias and should be interpreted accordingly. Further research is warranted to confirm or deny these findings.

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List of abbreviations:

ICM: IntraCameral injection with a Mixture of tropicamide 0,02%, phenylephrine 0,31% and lidocaine 1%

DOA: depth of anesthesia

GA: general anesthesia

NIBP: non-invasive blood pressure

MAC: minimum alveolar concentration

SBP: systolic blood pressure

DBP: diastolic blood pressure

HR: heart rate

zSBP: z-scores for systolic blood pressure

zDBP: z-scores for diastolic blood pressure

zHR: z-scores for heart rate

AIC: Akaike Information Criterion

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