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Research Article

A feasibility study of the Pupillary Pain Index measurement in Anesthetized Children

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Abstract

What we already know

a) Pain assessment in anesthetized children is challenging and currently used methods are not specific.

b) Pupillometry has already shown to be interesting and the pupillary pain index (PPI) in anesthetized adults shows promising results. What new information this study ads.

c) PPI can be a useful tool for non-invasive nociceptive assessments, in anesthetized, pediatric patients.

Background: Inadequate treatment of pain has numerous negative consequences. However, treatment with opioids can also be detrimental, with potential harmful effects after overdosing. Intraoperative hemodynamic parameters used today are non-specific nociceptive surrogate markers and insufficient to provide an objective nociceptive

assessment. Furthermore, those variables have a wide variety depending on age.

Aim: This study aims to evaluate whether pupillary pain index (PPI), via pupillary dilation reflex (PDR), can be used as a feasible nociceptive monitoring tool in the pediatric surgical population. Furthermore, pupil characteristics in two age classes (A = 28 days to 23 months, B = 24 months to 11 years) are identified.

Methods: Twenty pediatric patients scheduled for elective surgery under general anesthesia at the Antwerp University Hospital (UZA, Edegem, Belgium) were included. PDR was determined by an automatic stimulation pattern whereby intensity was increased (1s stimulation, 10-60mA, steps of 10mA). Pupil measurements were executed at two standardized times during a steady state sevoflurane T0 and T1, respectively without and with opioids. Vital signs were registered during measurement.

Results: PPI score decreased after opioid administration (group A: 2 vs 1, P<0.05; group B: 2 vs 1 P<0.05). Vital signs did not change significantly during noxious stimulation. In both groups the PDR amplitude and pupil variation decreased when opioids were administered (amplitude A: 0.24mm vs 0.06mm, B: 0.24mm vs 0.07mm; variation A: 12.1% vs 2.9%; B: 10.3% vs 2.5%, respectively). At T1, miosis was only observed in group B (group A: 1.87mm vs 1.84mm, P=0.7; group B: 2.27mm vs 2.51mm, P<0.05).

Conclusions: These preliminary results clearly confirm earlier novel research. The PPI via PDR evaluation provides a fast and easy approach to assist in the evaluation of the nociceptive- anti-nociceptive balance in anesthetized children. The pupil differs in size depending on age and opioid dosage. Further research is essential to evaluate opioid dosing effects on PDR.

Keywords: Pupillary pain index; Pupillometry; Children; Nociception; Opioids; Perioperative

Background

Pain is a complex concept, as it combines multiple features of psychology, while it also encompasses behavioral aspects and physiology. Nociception is the sensory nervous system's process of encoding noxious stimuli. Monitoring nociception remains a challenge in patients. Non-specific parameters such as elevated heart rate (HR), systolic blood pressure (SBP) or movement, used as surrogate nociceptive indicators, have already shown to be inaccurate to assess this nociceptive- anti-nociceptive balance [1-4].

Opioids are mainly used for perioperative analgesia despite our knowledge of its consequences, such as more opioid dependency, constipation, urine retention and respiratory depression, even in children [5]. This re-enforces the need for adequate pain management and prevention of excess use of opioids,

avoiding under-or overdosage contributing to discomfort.

Moreover, nociceptive neural activation augments a stress response. Minimizing this response has obvious beneficial effects on outcome, namely decreased morbidity and mortality in surgical patients [6]. In addition, excessive nociceptive activity could initiate chronic (postoperative) pain [7]. To adequately manage anti-nociceptive therapies, optimal monitoring tools should ideally be available. Therefore, there is a need for more objective nociceptive evaluation in order to accommodate patient-specific analgesia by using adequate titration of opioids.

Pupil size is determined by the opposing action of smooth muscles in the iris innervated by the sympathetic and parasympathetic divisions of the autonomic nervous system [8]. During general anesthesia, sedative drugs are depressing the sympathetic activity whereby the parasympathetic system gains influence through the Edinger-Westphal (EW) nucleus, resulting in miosis. In awake subjects, pupillary reflex dilation (PRD) occurs after sympathetic pathway stimulation with a dilatation response. In anaesthetized subjects, a nociceptive stimulus will inhibit the EW nucleus leading to a passive sphincter relaxation, thus PRD [9]. Opioids block the inhibitory influence on the EW nucleus whereby miosis is induced. Further, they depress PRD in a dose-dependent fashion [9].

Pupillometers are widely available to allow accurate quantification of the pupil diameters [9,10]. PRD is a physiological response to noxious stimuli. We can describe PRD as (1) the maximal increase in the pupil diameter after noxious stimulation, the amplitude (PRDA) or as (2) a percentage of initial pupil diameters, the variation (PRDV). Studies in both children and adults have shown that it is a particularly sensitive noxious stimulation measurement, which is moreover well correlated with opioid concentrations [1-3,11]. However, without a standard pupillary measurement technique, there can be no meaningful comparison of PRD for nociception. Hence, the pupillary pain index (PPI) was created. PRD measurements derived from titrated noxious stimulation will allow to determine a score from 1 (high electrical stimulus, no PRD) to 9 (low electrical stimulus, high PRD). In adults, PPI have been shown to be a reliable indicator [12,13]. To date, no data regarding the accurateness of PPI in the pediatric population is available. Therefore, this study investigates pupil reactivity, after standardized noxious stimulation in anesthetized children before and after opioid administration.

The primary objective of the study was to determine the electrical intensity of the PPI protocol necessary to have a pupil dilation of >13% with and without opioids, as defined by the in-built stimulation protocol. In other words, to determine the PPI score with and without opioids in different age classes.

Secondary objectives were to differentiate the obtained information from commonly used variables for nociception: HR, SBP and movement of a limb (e.g. withdrawal or extension of arm). An additional

secondary objective was to identify age-specific pupil characteristics.

Methods

This prospective, observational, and open study was approved by the local ethics committee of the Antwerp University Hospital, Belgium (study identifier: 17/46/519) and registered at Clinicaltrials.gov (NCT03449732). After obtaining informed written consent of parents and children, 20 subjects of two age classes (A= 28 days-23 months, B= 24 months-11 years) were included, with physical status I-II of the American Society of Anesthesiologists (ASA). All patients were scheduled for elective surgery with general anesthesia.

Exclusion criteria were; history of eye disease or current eye disease, current treatment with drug interacting with the autonomic or central nervous system, expected difficult airway and preoperative opioid use.

Anesthesia Protocol

Patients received no premedication. Standard monitoring was used throughout the pupil measurements, including heart rate (HR), pulse oximetry, electrocardiogram (ECG) monitoring, non-invasive blood pressure (NIBP) and gas analysis (sevoflurane, CO_2 and O_2). Anesthetic induction was performed either intravenously (propofol) or by inhalation (8% sevoflurane in 100% oxygen), as chosen by the attending anesthesiologist. If not yet present, an IV line was placed before tracheal intubation.

After tracheal intubation, mechanical ventilation was initiated and adapted to maintain end-tidal (ET) carbon dioxide (CO_2) between 35 and 40 mmHg. A steady-state end-tidal concentration of sevoflurane minimum alveolar concentration (MAC) of 1.5 was obtained during pupil measurements.

Pupillometric measurements

Pupil measurements were assessed through Algiscan (IDMed, Marseille, France), a non-invasive portable infrared pupillometer. The upper eyelid was opened and the rubber cup of the infrared camera was placed on the orbit, so it surrounded the eye, excluding the contralateral light reflex. The same eye was used for every measurement, the contralateral eye remained closed. Two electrodes with low impedance were placed on the skin area innervated by the median nerve. This pupillometer has an inbuilt standardized algorithm of automated increase in stimulus intensity, with the end of the stimulation being determined by a threshold of pupillary dilation. The protocol was created to provide a uniform nociceptive stimulus, the pupillary pain index (PPI). It consists of measuring the changes in pupillary dilation in response to an automatic increase of noxious stimulus, which is the intensity of electrical stimulation through the electrodes. The protocol starts at 10mA and raises to 60mA by incremental steps of 10mA. If a pupillary dilation of >13% compared to baseline pupil size is met, electrical stimulation automatically stops,

reducing unnecessary noxious stimulation. A PPI score is generated based on the maximum intensity value to provoke a pupil dilation of >13% and pupil reflex amplitude. The score ranges from 1, PRD <5% for 60mA stimulation, to 9, PRD of >13% for 10mA stimulation. In addition, the baseline (minimum) and maximum amplitude were recorded. Total duration of PRD using PPI is maximum 30 seconds including eye opening and placement of the pupillometer. Stimulation of a complete PPI protocol lasts maximum 8 seconds, followed by an standard post-stimulation observation period of 15 seconds and eyelid closing.

Data analysis including HR, systolic blood pressure (SBP), patient movements and pupil measurements was performed in two different ways. First, at baseline steady-state without opioids (T0), one before and one after PPI measurement. Second, one after injection of fentanyl 2µg/kg (T1), also one measurement before and after PPI. Measurement was at least 3 minutes after the opioid injection to obtain a pharmacological effect. A study design flowchart is presented in figure 1.

Figure 1: Flowchart of the study design. Twenty children, planned for elective surgery, were included. During measurement, a steady-state sevoflurane MAC of 1.5 was achieved and vital signs were monitored. Pupil measurements were taken at two standardized times, without (T0) and with opioids (T1). PRD, pupillary reflex dilation.

Statistical analysis

In this pilot study, no previously published data were available to make assumptions for the sample size calculation. Pupil characteristics, HR and SBP variables are given as mean ± standard deviation (SD). Non-parametric analyzation methods were used for pupil size variation. Mean stimulation, pupil diameter, HR, SBP and movement pre- and post-stimulus were compared using the unpaired Wilcoxon signed rank test. Statistical analyses were performed with SPSS Statistics software, version 26.0 for Windows (IBM Corp., Armonk, NY, USA). P-values less than 0.05 were considered as statistically significant.

Results

Data were collected in 20 children, 10 from each age class. Table 1 shows the demographics of the participants, including the anesthetic induction method and the use of muscle relaxants. Most subjects were male since the study took place predominantly in urological procedures.

	Group A (n=10)	Group B (n=10)
Male / Female	09-Jan	09-Jan
Age (months)	15 ± 3	(57 ± 34)
Age (years)	(1 ± 0)	4 ± 3
Length (cm)	78 ± 5	100 ± 19
Weight (kg)	11 ± 2	20 ± 10
BMI (kg/m2)	17 ± 1	17 ± 3
ASA		
1	7	6
2	3	4
Induction		
sevoflurane	9	7
intravenous	1	3
Muscle relaxant	9	9

Table 1: Demographics of the participants

After the administration of opioids, there was a significant decrease in PPI scores and reduction of the pupil dilation amplitude (PRDA) and variation (PRDV).

In group A no difference in pupil baseline diameter was found (p=0.731), whereas in group B there was a difference in baseline diameter of the pupil before and after fentanyl use (p = 0.026).

The electrical intensity necessary to dilate the pupil >13% was maximum (60mA) in group A for all participants. In group B less electrical stimulation was needed in one patient to obtain a dilation of >13%. A summary of these findings is displayed in table 2.

Data are presented as mean ± SD. T0 describes time at baseline without opioids, whereas T1 describes time after injection of fentanyl. Data are presented as mean ± SD. There were no significant differences in HR or SBP before and after pupil measurements, with or without opioid. Hemodynamic variables are shown in table 3. None of the patients moved, curare were administered in 90% (n=18) of the cases.

Group A	**T0**	**T1**	**P NPAR**
Baseline (mm)	1.87 ± 2.50	1.84 ± 0.32	0.731
Stimulation intensity (mA)	60 ± 0	60 ± 0	1
PDRA (mm)	0.24 ± 0.14	0.06 ± 0.04	0.007
Variation (%)	12.1 ± 6.62	2.9 ± 2.42	0.007
PPI	2.3 ± 1.05	1.1 ± 0.32	0.01
Group B	**T0**	**T1**	**P NPAR**
Baseline (mm)	2.27 ± 0.46	2.51 ± 0.68	0.026
Stimulation intensity (mA)	58 ± 6.32	60 ± 0	0.317
PDRA (mm)	0.24 ± 0.11	0.07 ± 0.06	0.005
Variation (%)	10.3 ± 5.19	2.50 ± 2.17	0.005
PPI	2.4 ± 1.65	1.1 ± 0.32	0.007

Table 2: Changes in pupil characteristics before and after fentanyl administration for both groups.

Group A	**Pre**	**Post**	**P**	**P wilcoxon**
HRT0	142.8 ± 12.59	146.80 ± 14.91	0.231	0.074
HRT1	141.70 ± 16.23	141.70 ± 15.23	0.231	0.863
SBPT0	84.4 ± 4.20	83.20 ± 4.96	0.316	0.396
SBPT1	80.5 ± 10.10	78.70 ± 8.22	0.254	0.095
Group B	**Pre**	**Post**	**P**	**P wilcoxon**
HRT0	114.60 ± 17.73	116.2 ± 16.36	0.283	0.258
HRT1	111.80 ± 16.01	112.8 ± 15.88	0.231	0.473
SBPT0	85.10 ± 8.63	80.4 ± 7.56	0.283	0.03
SBPT1	77.00 ± 6.99	78.40 ± 7.41	0.333	0.257

Table 3: Vital signs before and after fentanyl administration for both groups. HRT0 (heart rate at T0), HRT1 (heart rate at T1), SBPT0 (systolic blood pressure at T0), SBPT1 (systolic blood pressure at T1). Pre and post describe the vital signs at, before, and after stimulation.

Data are presented as mean ± SD.

Discussion

Our study demonstrates that opioids have a markable influence on the PRD and PPI scores in anesthetized children, with a significant result in both age classes. This suggests that PPI may be useful as an objective parameter of nociception.

In our study, miosis after opioid administration only occurred in children older than 2 years. One explanation is that the dose of fentanyl is too little to elicit miosis in children younger than 2. As demonstrated in a study of Barvais et al., basal pupil size in adults decreased from a target effect

compartment concentration of remifentanil upward of 2 ng/ml, (but not at a concentration of 1 ng/ml) [3]. On the contrary, Larson et al. describes a stable resting pupil size in adults at isoflurane end-tidal concentrations of 0.8%. Even at incrementing doses of alfentanil, they did not observe increasing miosis [2]. A recent study of Sabourdin et al. also found these unexpected results [14].

Another explanation could be that at this depth of anesthesia, high concentrations of sevoflurane blunts the sympathetic tone of the pupil so that the maximum miotic state of the pupil is already met before administrating opioids in children younger than 2 years.

In our work, almost everyone could be maximally electrically stimulated with a stimulation of 60mA before developing a pupil dilatation of >13%. This is in line with earlier research of Bourgeois et al. They observed a markedly higher MACpup of sevoflurane (MAC to inhibit the PRD in 50% of the subjects in response to skin incision) in prepubertal children (2-12 years). PRD remained because a MAC of 1.5 is still lower than the MAC of 1.9 necessary to abolish PDR in MACpup [4].

Emery et al. investigated the use of PRD in children aged 10 months to 5 years during combined general/caudal epidural anesthesia. They observed a significantly greater maximum pupillary dilation in response to tetanic stimulation in children over 2 years of age (1.3 ± 0.8 mm SD) compared with children less than two years of age (0.6 ± 0.3 mm SD) [15]. In our study we could not confirm these findings, given the fact that we did not observe a significant difference of PRDA or PRDV between both age classes. They related these data to an incomplete optic nerve myelination and maturation of the cells of the lateral geniculate body until approximately the age of 2 years. [15] In our data, we did detect a difference in basal diameters between children younger or older than 2 years old, independent of opioid use. Indeed, this can be linked to the maturation of distinct neural pathways. Our findings of the basal diameter in children >2 years old can be well correlated to those in other studies. [1,2,14]

Our findings are consistent with earlier research which shows that commonly used variables for analgesia as HR, SBP and movement are less sensitive than PRD. As confirmed in adults [3,16], as well as in children. [1,17] These surrogates depend on many more factors than analgesia alone, such as volume status, age and depth of anesthesia. Further, it is interesting that PPI can be used without eliciting hemodynamic changes or inappropriate high noxious stimulation.

By using PPI, we can measure the reactivity of the autonomous system to noxious stimuli on a scale from 1 to 9. Recently, Sabourdin et al. concluded that PPI indeed reflects the level of analgesia in children older than 2 years [14]. Other research of Vinclair et al. has demonstrated that the PPI score could accurately predict the nociceptive response in sedated critically ill adults [12]. Additionally, it is proven that the PPI score is reduced after remifentanil administration [13]. Our results of reduced PPI scores after fentanyl are in line with these earlier findings. A

preliminary study even showed a correlation between the PPI score and an observational pain scale [18]. Indeed, pupil measurements have been shown to correlate with pain intensity [17] Further investigations are necessary to examine the clinical implications of our findings.

Undeniably, pupillometry does have certain shortcomings. It only provides discontinuous information in contrast to other systems. Additionally, no information is provided regarding the patient's ascending and descending pain pathways. This pilot study has several limitations. First, unequal gender distribution is present in the study population. This can be explained by the fact that most of the included children were scheduled to undergo a urological surgical procedure. Second, different induction methods were used.

However, theoretically, propofol would have little effect at time of measurement considering the half-life of propofol. Further, no significant difference of basal pupil size was found regarding the induction method and earlier studies have been used successfully in patients receiving sevoflurane and propofol [16]. The third limitation is the lack of accurate measurement of depth of hypnosis because MAC brain does not equal MAC lungs. However, we waited until a steady state was reached. Fourth, opioid administration with estimated effect site concentrations would define analgesic plasma concentrations in a better way. Finally, there is little specificity of PPI to different noxious stimulations or clinical situations.

Conclusion

In conclusion, this pilot study shows a significant reduction in PPI scores following fentanyl administration in anesthetized children. It suggests that this technique may have a value for objective nociceptive assessment in the pediatric surgical population. More clinical research is necessary to confirm this hypothesis and to assess the clinical implications.

Declarations

Ethics approval and consent to participate

This study was approved by the ethics committee of the Antwerp University Hospital, Belgium (study identifier: 17/46/519) and registered at Clinicaltrials.gov (NCT03449732). We obtained an informed consent of all participants before inclusion.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests related to the present study.

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Authors' contribution

NK collected, analyzed and interpreted data, and was a major contributor in writing the manuscript. DW designed the study, contributed to the literature research and was a contributor in writing the

manuscript. VS contributed to study design, data analysis and manuscript preparation. GH revised critically the manuscript for important intellectual content.

All authors read and approved the final manuscript.

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Availability of data and materials

The dataset analyzed in the current study are available from the corresponding author on reasonable request.

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