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Role of the pupillometer in the assessment of pain in the sedation of pediatric patients

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Abstract. – OBJECTIVE: Pupillometry has been used to assess pain intensity and response to analgesic drugs in adults. The aim of this study was to verify the usefulness and effectiveness of the pupillometer to assess pain and depth of sedation in pediatric patients undergoing painful procedures and to optimize pain management by observing pupillary variations induced by opioids.

PATIENTS AND METHODS: This is a prospective, monocentric study conducted in the sedation room of the Pediatric Intensive Care Unit of Fondazione Policlinico A. Gemelli in Rome. A population of 22 pediatric patients who underwent painful procedures was enrolled. Eleven children were sedated by opioid drugs. Heart rate, systolic blood pressure, diastolic blood pressure, bispectral index, maximum pupil size (Size), pupil change (CH), Neurological Pupil Index (NPi) were collected over four times: before starting the procedure; before the painful stimulus (when the patient was sedated); when the painful stimulus was applied; at the end of the procedure. A NeurOptics NPi-200 pupillometer was used for the study.

RESULTS: Statistical significance in the variation of haemodynamic parameters was less significant than the variation obtained by analyzing the pupillary parameters: a significant change in NPi and CH in the transition from wakefulness to sedation and from the application of the painful stimulus to awakening was found in both study populations, patients who have received opioids and patients who have not received opioids. Changes in the mean CH of the pupil diameter correlate with the depth of sedation and the size values vary in relation to the administration of opioids.

CONCLUSIONS: Our findings highlight the potential role of pupillometry as a non-invasive method to objectively quantitate pain response in children to reach an efficient analgesic approach.

Key Words:
Pain monitor, Children, Pupillometer, Quantitative pupillometry.

Introduction

For the past few decades many studies have improved the recognition and management of pain in children[1,2]. However, despite important advances in understanding the mechanisms of pain, children interpretation ad expression of pain remains a quite unexplored field.

Self-assessment scales are the main method used to quantify pain because they are easy to use and based on the perception that children have of pain[3-7]. But self-assessment tools are not useful in preverbal infants or children. Furthermore, self-assessment measures in school-age children can be influenced by psychological and social factors, thus pain assessment and analgesic response may be less reliable[8]. Pain assessment is fundamental in Pediatric Intensive Care Unit (PICU), because of the severity of the diseases, the multiple invasive procedures and the difficult patient pain expression. PICU hospitalization is an unpleasant experience for the newborn and the child, which can be exposed to stress and painful stimuli. Therefore, the control of pain and the management of fear, agitation and stress represent an essential aim in the management of the critically ill pediatric patient[9].

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Thus, an accurate assessment of pain is critical, in order to satisfactory manage it. It is also important to use a tool based on scientifically validated and universally recognized evidence, to avoid errors and ensure uniformity of treatment among the different operators[10,11].

Monitoring of nociception is currently one of the major challenges of anesthesiology. Insufficient analgesia can lead to potentially deleterious hemodynamic changes. Conversely, the number of opioids administered correlates with the incidence of general side effects, such as respiratory depression, nausea, itching or urinary retention. Thus, it is important to determine the minimum effective opioid dose for each patient. Clinical parameters such as heart rate or blood pressure changes are currently used to assess intraoperative analgesia. Since these parameters could not be reliable and specific in many circumstances, other physiological indices may be useful to provide more accurate clinical feedback of analgesia level. Among them, the pupillometer method can be an excellent choice. The pupillometer is a non-invasive tool that allows to monitor the intraoperative balance between nociception and analgesia. Its aim is to personalize the opioid dose for each patient, avoiding both underdose and overdose[12-17].

However, most of the studies available in literature involve adult patients and there is still poor evidence on the use of the pupillometer in children. Encouraging results were obtained by Connelly and Brown[18], who studied the pupillary response in 30 pediatric patients undergoing surgery to correct pectus excavatum, comparing the pupillometry measurements with the pain intensity expressed by the VAS scale. Each point change on a 10 cm Visual Analogic Scale (VAS) was associated with a 0.11 m/s change in maximum pupillary constriction rate and with an approximately 0.39% pupil diameter change. Furthermore, all measurements of pupillary response were inversely associated with opioid dose, considering the effects of opioids on pupillary function[18]. Thus, the pupillometer represents a valid opportunity to detect and treat pain even in children, which need of special care and attention.

The aim of our study is to verify usefulness and effectiveness of the pupillometer in order to assess the pain and depth of sedation in pediatric patients undergoing painful procedures under NORA (Non-Operating Room Anesthesia) and to optimize pain management observing pupillary variations induced by opioids.

Patients and Methods

This is a prospective, non-randomized and monocentric study conducted in the sedation room of the Pediatric Intensive Care Unit of Fondazione Policlinico A. Gemelli in Rome, Italy. Written informed consent was obtained from caregivers of all subjects involved in the study.

Before starting the invasive procedure, all patients underwent standard multi-parametric monitoring according to the Italian Society of Anesthesia, Analgesia, Resuscitation and Intensive Care (SIAARTI) guidelines. The anesthetic technique was based on the administration of an inhalation mixture of Sevoflurane and Oxygen, initially with a MAC of 6% (induction) and subsequently reduced to 2% for maintenance. Then, a peripheral venous access was placed for as needed administration of Midazolam 0.1 mg/kg and Fentanyl 2 mcg/kg. Patients maintained spontaneous breath in face masks.

For each patient, the following data were recorded: heart rate (HR, bpm), systolic blood pressure (SBP, mmHg), diastolic blood pressure (DBP, mmHg), BIS (bispectral) index, maximum left and right pupil size (Size, mm), left and right pupil change (CH, %), right eye and left eye Neurological Pupil Index (NPi). These data were collected in four different times: before starting the procedure, with the patient awake (Basic); before the painful stimulus, when the patient was sedated (Pre-stimulus); when the painful stimulus was applied to a sedated patient (Stimulus); at the end of the procedure, upon awakening the patient (Awakening).

A NeurOptics NPi-200 pupillometer was used for the study. In each of the four moments, the operator centered the pupil by pressing the button corresponding to the right or left eye. Afterwards, the button was released, thus generating a 0.8 second light burst which activated the photomotor reflex. The device then recorded the pupillary responses, providing the results on its display. The values of NPi, size and CH were recorded, both for the right eye and for the left eye. If the pupillometer was unable to track the pupil for a significant portion of the measurement due to eye blinks, closures, or eye movements, the measurement was discarded and repeated. In addition, the Medtronic BIS™ system was used for the evaluation of the BIS index.

Statistical Analysis

The data obtained were processed using Microsoft Excel calculation software version 16.24

for Mac and Prism statistical software version 8.0 for Mac.

HR, SBP, DBP, BIS index, mean NPi (calculated as the average between right and left NPi), mean Size (calculated as the average between the right size and the left size) and the average CH (calculated as the average between the right and left CH), obtained in the four different moments, were analyzed, using the Student's *t*-test for paired data, in order to evaluate any significant variations.

The study population was divided into two groups: patients who have received opioids and patients who have not received opioids.

The opioid-treated and non-opioid-treated patient groups were first assessed separately, using the Paired Student's *t*-test according to the following scheme: – Base *vs.* Pre-stimulus; – Pre-stimulus *vs.* Stimulus; – Stimulus *vs.* Awakenings.

Subsequently the two groups were compared using the *t*-test for unpaired data by examining the four moments: Base, Pre-stimulus, Stimulus, Awakening. A value of $p<0.05$ was required for statistical significance.

Results

A population of 22 pediatric patients who underwent painful procedures between July 2018 June 2019 was enrolled. The only exclusion criteria were eye injuries and ocular pathologies. The study included 10 females and 12 males: Eleven children were sedated by opioid drugs. The clinical characteristics of these patients are summarized in Table I.

Values of the recorded parameters are expressed as mean ± SD and are summarized in Tables II, III, IV.

Student's *t*-test for paired data used for the opioid-treated patient group showed statistically significant changes in hemodynamic parameters in the Base *vs.* Pre-stimulus comparison. The HR went from an initial mean value of 98.27±21.68 at the Base moment, to a value of 89.09±24.29 at the Pre-stimulus (*p*:0.02); the SBP at the Base time recorded an average value of 113.64±16.94, while at the Pre-stimulus it showed a value of 94.36±10.98 (*p:*0.0007); finally, the DBP went from an average value of 76.73±18.68 to a value of 57.09±14.82 (*p:0.0028*). The hemodynamic parameters analyzed, however, did not show significance in the transition from Pre-stimulus to Stimulus and from Stimulus to awakening.

As regards value recorded with the BIS, a high significance was found, i.e., $p<0.0001$, both in the comparison Base (91.91±6.19) *vs.* Pre-stimulus (48.00±15.27) and Stimulus (47.73±12.17) *vs* Awakening (87.09±6.61). Finally, the values ob-

Table I. Clinical characteristics of the study population.

Patient	Age (y)	Sex	Weight (kg)	Disease	Procedure	Opioid
1	26	M	70	Sarcoma	Lumbar puncture	YES
2	15	F	65	Cerebral space occupying lesion	PICC placement	YES
3	12	F	28	Spinal muscular atrophy	Lumbar puncture	NO
4	11	F	20	Spinal muscular atrophy	Lumbar puncture	NO
5	4	M	18	Burkitt Lymphoma	Lumbar puncture	YES
6	13	M	59	Cerebral space occupying lesion	PICC placement	YES
7	0.66	M	8	Megacolon	PICC placement	NO
8	4	M	18	Linfoma di Burkitt	Lumbar puncture	NO
9	5	M	20	Acute lymphoblastic leukemia	Lumbar puncture	NO
10	0.7	M	9	Bowel obstruction	PICC placement	NO
11	8	M	33	Acute lymphoblastic leukemia	Bone marrow aspirate	YES
12	7	F	26	Acute lymphoblastic leukemia	Lumbar puncture	YES
13	7	F	26	Acute lymphoblastic leukemia	Bone marrow aspirate	YES
14	3	F	13.8	Acute lymphoblastic leukemia	Lumbar puncture	NO
15	8	M	33	Acute lymphoblastic leukemia	Bone marrow aspirate	YES
16	8	M	33	Acute lymphoblastic leukemia	Bone marrow aspirate	NO
17	7	F	26	Acute lymphoblastic leukemia	Lumbar puncture	YES
18	2	M	12	Thrombocitopenia	Bone marrow aspirate	NO
19	7	F	26	Acute lymphoblastic leukemia	Bone marrow aspirate	YES
20	3	F	14	Acute lymphoblastic leukemia	Lumbar puncture	NO
21	19	F	57	Acute myeloid leukemia	Bone marrow aspirate	YES
22	8	M	33	Acute lymphoblastic leukemia	Lumbar puncture	NO

Peripherally Inserted Central Catheter (PICC).

Table II. Clinical characteristics of the study population.

Parameter	Base	Pre-Stimulus	*p*	Pre-Stimulus	Stimulus	*p*	Stimulus	Awakening	*p*
FC	98.27±21.68	89.09±24.29	**0.02**	89.09±24.29	89.27±19.15	0.9541	89.27±19.15	91.45±22.01	0.4702
SBP	113.64±16.94	94.36±10.98	**0.0007**	94.36±10.98	95.09±11.09	0.7103	95.09±11.09	109.09±14.92	0.1023
DBP	76.73±18.68	57.09±14.82	**0.0028**	57.09±14.82	58.09±9.33	0.8094	58.09±9.33	64.18±14.76	0.1258
BIS	91.91±6.19	48.00±15.27	**<0.0001**	48.00±15.27	47.73±12.17	0.9487	47.73±12.17	87.09±6.61	**<0.0001**
NPi	4.15±0.63	3.79±0.57	**0.0461**	3.79±0.57	3.83±0.48	0.7928	3.83±0.48	4.23±0.48	**0.0044**
CH	0.32±0.09	0.19±0.18	**0.0139**	0.19±0.18	0.14±0.11	0.2251	0.14±0.11	0.24±0.07	**0.0133**
SIZE	4.30±0.55	2.82±0.91	**0.0002**	2.82±0.91	2.72±1.15	0.7389	2.72±1.15	3.19±0.87	0.0630

Table III. Comparison in non-opioid-treated group.

Parameter	Base	Pre-Stimulus	*p*	Pre-Stimulus	Stimulus	*p*	Stimulus	Awakening	*p*
FC	105±22.10	109.18±23.54	0.7071	109.18±23.54	9.64±27.81	0.2712	9.64±27.81	106.73±17.37	0.1876
SBP	95.91±9.95	87.82±11.54	0.0911	87.82±11.54	86±7.92	0.3039	86±7.92	98.27±12.38	**0.0008**
DBP	56.18±9.17	49.09±12.68	0.0831	49.09±12.68	50±10.95	0.6137	50±10.95	56.64±9.04	**0.0164**
BIS	93.27±9.56	43±7.17	**<0.0001**	43±7.17	45±12.97	0.4694	45±12.97	89.91±6.85	**<0.0001**
NPi	4.05±0.44	3.35±0.70	**0.0104**	3.35±0.70	3.42±0.65	0.6415	3.42±0.65	3.89±0.51	**0.0294**
CH	0.34±0.09	0.17±0.10	**0.0069**	0.17±0.10	0.14±0.09	0.4539	0.14±0.09	0.28±0.14	**0.0123**
SIZE	4.76±0.69	4.88±1.67	0.8052	4.88±1.67	3.62±1.54	**0.0306**	3.62±1.54	3.47±0.92	0.7251

tained by pupillometer showed significant variations of the NPi med in comparison of the following times: Base (4.15±0.63) *vs.* Pre-stimulus (3.79±0.57) (*p*:0.0461); Stimulus (3.83±0.48) *vs.* Awakening (4.23±0.48) (*p*:0.0044).

The CH recordings revealed significance with a *p*-value: 0.01 both in the Base (0.32±0.09) *vs* Pre-stimulus (0.19±0.18) and in the Stimulus (0.14±0.11) *vs.* Awakening (0.24±0.07). The Size measurements showed a variation from an average value of 4.30±0.55 at the time of the Base, to an average value of 2.82±0.91 at the time of the Pre-Stimulus, with high significance (*p:*0.0002). It is possible to compare these data with Table II.

By analyzing the pediatric population not treated with opioids, the statistical analysis does not reveal significant changes in HR, but significance is found for the other two hemodynamic parameters, SBP and DBP. SBP varied in the transition from Stimulus (86±7.92) to Awakening (98.27±12.38) (*p*=0.0008); the DBP gives an average value of 50±10.95 on the Stimulus to a value of 56.64±9.04 on Awakening (*p:* 0.0164). The BIS values showed a *p*-value <0.0001 in the comparison Base (93.27±9.56) *vs.* Pre-stimulus (43±7.17) and Stimulus (45±12.97) *vs.* Arousal (89.91±6.85).

The measurements with the pupillometer showed significance of the NPi in: Base (4.05±0.44) *vs.* Pre-stimulus (3.35±0.70) and Stimulus (3.42±0.65) *vs.* Awakening (3.89±0.51), with significance of *p:*0.0104 and *p:*0.0294, respectively. The CH values were also significant in the comparison between Base (0.34±0.09) *vs.* Pre-stimulus (0.17±0.10) (*p*: 0.0069) and Stimulus (0.14±0.09) *vs.* Base (0.28±0.14) (*p*: 0.0123). The significance of the Size results with a *p: 0.0306*, even for the non-opioid group in the transition from Pre-stim-

Table IV. Comparison between Opioid-treated *vs.* non-opioid-treated group.

Parameter	Base	Pre-Stimulus	*p*
FCb	9.64±27.81	105±22.10	0.4794
SBP b	86±7.92	95.91±9.95	0.0072
DBP b	50±10.95	56.18±9.17	0.0038
BISb	45±12.97	93.27±9.56	0.6955
NPib	3.42±0.65	4.05±0.44	0.6576
CHb	0.14±0.09	0.34±0.09	0.6507
SIZEb	3.62±1.54	4.76±0.69	0.0999
FCp	89.09±24.29	109.18±23.54	0.0629
SBP p	94.36±10.98	87.82±11.54	0.1880
DBP p	57.09±14.82	49.09±12.68	0.1888
BISp	48.00±15.27	43±7.17	0.3374
NPip	3.79±0.57	3.35±0.70	0.1239
CHp	0.19±0.18	0.17±0.10	0.7190
SIZEp	56.18±9.17	4.88±1.67	0.0018
FCs	89.27±19.15	9.64±27.81	0.4210
SBP s	95.09±11.09	86±7.92	0.0388
DBP s	58.09±9.33	50±10.95	0.0770
BISs	47.73±12.17	45±12.97	0.6166
NPis	3.83±0.48	3.42±0.65	0.1087
CHs	0.14±0.11	0.14±0.09	0.9145
SIZEs	2.72±1.15	3.62±1.54	0.1355
FCr	91.45±22.01	106.73±17.37	0.0859
SBP r	109.09±14.92	98.27±12.38	0.5210
DBP r	64.18±14.76	56.64±9.04	0.1636
BISr	87.09±6.61	89.91±6.85	0.3378
NPir	4.23±0.48	3.89±0.51	0.1232
CHr	0.24±0.07	0.28±0.14	0.3600
SIZEr	3.19±0.87	3.47±0.92	0.4593

ulus (4.88±1.67) to Stimulus (3.62±1.54). The data listed above for the non-opioid-treated population are summarized in Table III.

Ultimately, the comparison between the opioid-treated and non-opioid treated children group using Student's unpaired *t*-test showed significant changes in the SBP at baseline of opioid-treated patients (86 ±7.92) *vs.* non-opioids (95.91±9.95) (*p:*0.0072) and at the moment of Stimulation in patients who received opioids (50±10.95) *vs.* non-opioids (56.18±9.17) (*p:*0.0038). DBP showed significance in the awake patient *p:*0.0038, with a mean value of 50±10.95 in the population that received opioids and 56.18±9.17 in the population that did not. There were no significant results for the BIS values and for the parameters Npimed and CH evaluated with the pupilometer in the four moments (Base, Pre-stimulus, Stimulus and Awakening), while a high statistical significance (p=0.0018) emerged from the Size value at the Pre-stimulus with an average value of 56.18±9.17 in children treated with opioids and 4.88±1.67 in children not treated with opioids. These data are highlighted in Table IV.

Discussion

Differently from the adult patients in children it is more difficult to assess and treat efficaciously the pain and often this symptom is undertreated. Recent evidence has documented the deleterious physiologic effects of pain and the beneficial results of efficacious analgesia both in adult patients and in children. In 2001, the American Academy of Paediatrics issued a statement to ensure human and competent treatment of pain in all children and adolescents in order to focus the attention on an interdisciplinary therapeutic approach, including pharmacologic, cognitive-behavioural, psychologic and physical treatments. Due to the increasing prevalence of both acute and chronic pain in the paediatric age new techniques and tools for pain management have been developed. The diagnosis and treatment of the cause of acute pain must always have high priority. Improved understanding of the pharmacology of the analgesics and the development of new techniques for analgesic administration and pain management have greatly enhanced the ability of doctors to control efficaciously pain. Even for children and adolescent with the most severe pain early evidence shows that it may be possible to reduce the impact of pain on the lives of the patients and their families. However, more action is necessary. Firstly, more paediatric centres are needed, to develop specific post-operative and intra-operative pain programmes. Moreover, cooperation and communication between the anaesthesiologist, surgeon, and paediatrician are essential for successful anaesthesia and pain management, with the support of new techniques to evaluate and control pain symptoms, such as pupillometer. The analysis of the data obtained in our study allows us to make some considerations, not only to evaluate the effectiveness and usefulness of pupillometry in assessing pain and the depth of sedation, but also with regard to pain management during procedures in general. Statistical significance in the variation of hemodynamic parameters, normally recorded during a painful procedure and historically a guide in the management of pain, was null or in any case less significant than the variation obtained by analyzing the pupillary parameters. The parameters of HR, SBP and DBP, in the transition from the waking phase (Base) to that of sedation (Pre-stimulus) in the population that received opioids, and the values of SBP and DBP from the application of the painful stimulus to awakening in the population that did not received opioids, showed significant changes probably related to the effect of sedative drugs in the initial phase and to the activation of the sympathetic-mediated response in the awakening phase. About the pupillometry data, there was a significant change in NPi and CH in the transition from the wakefulness to sedation and from the application of the painful stimulus to awakening, in both study populations. In particular, the changes in the mean CH of the pupil diameter correlate with the depth of sedation and with the response to the painful stimulus, as reported in other studies. In the literature, a recent study[19] evaluated that, in adult patients undergoing surgical treatments, a CH greater than 19% was related to a greater perception of the painful stimulus. The most relevant data, however, refers to the Size values. Consistent with other studies, it emerged that it varies in relation to the administration of opioids[20-23]. Therefore, analyzing children who received opioids and children who did not receive opioids, there was a variation in Size in the pre-stimulus phase. While precise pupil measurements and subjective pain assessment have not been previously compared in children, Aissou et al[24] performed a study in 100 adults comparing changes in the pupil dilatation reflex and self-reported pain scores *via* a 5 points verbal rating scale.

The value of the BIS index, in agreement with what is already found in the literature, significantly reflects the depth of sedation and its variation was significant in the Base *vs.* Pre-stimulus and Stimulus *vs* Awakening comparison in both populations[25-27].

Limitations

The limitation of our study is related to the small size and heterogeneity of the sample relatively to weight, age and type of procedures performed. Further studies are needed to evaluate the role of pupillometer in a wider population with homogeneous auxological data and procedures performed in evaluating pain and depth of sedation in pediatric patients undergoing Non-Operating Room Anesthesia.

Conclusions

Our study highlights the utility of pupillometer as an important tool that plays a key role in the assessment of pain in children. The innovations of our study are the better correlation of pupillometry's measurement with the perception of painful stimulus in the sedated patients than the hemodynamic values nowadays used as reference parameters of pain evaluation. This instrument could be a valid support not only to detect pain in sedated children, but also to optimize the analgesic approach in the pediatric population.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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