Postoperative pain assessment in children: a pilot study of the usefulness of the analgesia nociception index†

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Abstract

Background: The ability to perform objective pain assessment is very important in paediatric patients. The goal of this study was to investigate the relationship between the analgesia nociception index (ANI), which is based on the heart rate variability, and objective measurements of pain intensity in young or cognitively impaired children, after surgical or imaging procedures (control group) under general anaesthesia.

Methods: On arrival in the recovery room and subsequently at 5–10 min intervals, the level of pain was rated using the FLACC pain scale (0–10). The ANI values (0–100; 0 indicating the worst pain) were recorded simultaneously. The area under the receiver operating characteristic curve (AUC) and grey zone approach were used to evaluate the performance of the ANI to detect patients with FLACC >4. Instantaneous ANI values were compared with ANI values averaged over 256 s periods of time.

Results: All children in the surgical group (n=32) developed moderate-to-severe pain (FLACC >4). Children in the control group (n=30) exhibited minimal pain. Instantaneous ANI values were lower in children of the surgical group than in the control group \[(52 (±16) vs 69 (16), P<0.001)\]. The AUC for the 256 s ANI recording period \([0.94 (95\% confidence interval 0.85–0.99)\] was significantly higher than for instantaneous ANI \(P<0.05\). When measured for a period of 256 s, an ANI cut-off value of 56 (grey zone \([58–60]\)) was most predictive of a FLACC ≥4.

Conclusions: The ANI may provide an objective measurement of acute postoperative pain, which is correlated with that measured on a FLACC scale in young or cognitively impaired children.

Key words: analgesia, paediatric; children; pain, paediatric; parasympathetic nervous system

Postoperative pain in children needs be managed effectively to avoid postoperative behavioural problems\(^1\) and persistent postsurgical pain.\(^2\) Adequate pain management in children requires adapted pain assessment using tools that must be developmentally appropriate. As recently underlined by Morton, ‘good pain assessment is always linked to appropriate pain control measures’,\(^3\) emphasizing the key role of pain assessment in the provision of optimal pain relief. However, pain assessment in children can be extremely challenging, especially in infants or in children with cognitive impairment.\(^4\) Even in cognitively intact children, the choice of the best pain-assessment tool remains controversial and has been the subject of many debates.\(^5–9\)

Regardless of which tool is used to assess pain, factors such as age, anxiety, language, ethnic background, and the child’s level of cognition need to be taken into account.\(^10–12\) The Association of Paediatric Anaesthetists recognizes that more than one tool is

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necessary, because no individual scoring system will be appropriate for pain assessment for all children and in all contexts. Recently, several monitoring tools have been developed to provide a better evaluation of pain and analgesia in anaesthetized and awake patients. One of them, the analgesia nociception index (ANI, Physiodoloris™; Metrodoloris, Loos, France) is a non-invasive tool based on the analysis of the respiratory fluctuations of heart rate that mainly reflect the variability in the parasympathetic tone. The ANI monitor records the ECG signal continuously, enabling a quantitative assessment of the respiratory variability of heart rate, which decreases during a noxious stimulation. The majority of studies assessing the ANI have been performed in adult patients under general anaesthesia or in the immediate postoperative period and have shown that the measurement of ANI was significantly correlated with pain intensity. To date, very few data are available regarding the usefulness of ANI in children, and those data that are available were obtained in children during surgery under general anaesthesia. The goal of this prospective observational study was to investigate the relationship between ANI measurement and postoperative pain intensity in young or cognitively impaired children during recovery from general anaesthesia.

Methods

After approval by the Institutional Review Board (Comité de Protection des Personnes Ile-de-France VI) and written informed consent, children who had undergone elective surgery associated with moderate-to-severe postoperative pain, and for whom analgesia with morphine titrated i.v. was planned, were included in the experimental group. Patients were recruited if they were aged <7 yr or if they had a communication disability that would prevent self-rating-based pain assessment. Children <7 yr of age or cognitively impaired, who were admitted to the postanaesthesia care unit (PACU) after medical imaging procedures (without any painful stimulus) under sedation or general anaesthesia, were included in the control group.

Exclusion criteria included dysrhythmia, autonomic neuropathy, and administration of atropine, neostigmine, β-blockers, ketamine, or clonidine during the surgery or imaging procedure. Children who received any form of regional anaesthesia were not considered for inclusion; otherwise, the study protocol did not place any other restriction on the anaesthetic technique. During surgery, multimodal analgesia was provided with a combination of paracetamol, ketoprofen, or both, and morphine as required, according to our standard practice.

The study began upon admission to the PACU (Fig. 1). Pain intensity was assessed by the PACU nurse, using the FLACC behavioural observational scale (0–10) at the time of admission and every 5 or 10 min thereafter. The PACU nurses were unable to see the ANI values displayed on the monitor. The FLACC score, which assesses pain based on five criteria (facial expression, leg position, degree of activity, quality of cry, and consolability) is used in children who are unable to report a pain score. The revised FLACC was used in children with significant neurological impairment.

Noxious stimulus can induce sympathovagal imbalance. Heart rate variability measures the cardiac autonomic activity non-invasively and can detect autonomic responses to noxious stimuli in patients. The ANI is based on ECG data and is computed from a frequency domain-based analysis of the high-frequency component of heart rate variability (high frequency, 0.15–0.5 Hz) corresponding to parasympathetic tone, using a wavelet transform-based numerical filter, and also includes the respiratory rate as a potential confounding variable. The algorithm used for ANI computation has been described previously. The ANI, expressed as a numerical value between 0 and 100, is continuously displayed on a specific monitor (PhysioDoloris monitor; MetroDoloris™, Loos, France).

The ANI values were stored on a hard drive in ASCII format. Event markers, such as first pain assessment yielding FLACC ≥4 and administration of morphine, were stored in the same file. Heart rate (HR), mean arterial pressure (MAP), and respiratory rate were collected from the patient PACU monitor at the time of pain assessment.

Data were recorded with the child recumbent; the parent was invited to stay nearby. Attempts were made to minimize noise and disturbance in the PACU, which is a 12 bed open space.

### Flow chart of the study

#### Fig 1 Measuring periods after admission to the PACU. ANI, analgesia nociception index; PACU, postanaesthesia care unit.

#### Fig 2 Flow chart of the study.

<table>
<thead>
<tr>
<th>Children &lt;7 yr of age or with communication disability undergoing a procedure under general anaesthesia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experimental group: surgical patients</td>
</tr>
<tr>
<td>Control group: non-surgical patient</td>
</tr>
<tr>
<td>62 patients screened for eligibility</td>
</tr>
<tr>
<td>35 patients screened for eligibility</td>
</tr>
<tr>
<td>4 excluded: 1 arrhythmia 2 ketamine 1 neostigmine</td>
</tr>
<tr>
<td>3 excluded: 1 arrhythmia 2 autonomic neuropathy</td>
</tr>
<tr>
<td>58 patients studied</td>
</tr>
<tr>
<td>32 patients studied</td>
</tr>
<tr>
<td>28 excluded: 2 recording failure 24 FLACC &lt;4</td>
</tr>
<tr>
<td>30 patients with complete data and analysed</td>
</tr>
<tr>
<td>32 patients with complete data and analysed</td>
</tr>
</tbody>
</table>
Statistical analysis

The ANI data were tested for normal distribution by means of the Kolmogorov–Smirnov test. For the comparison between patients of the surgical and control groups, Student’s t-tests, Mann–Whitney U-tests, and χ² tests were performed where appropriate. Correlations between ANI and FLACC measurements were tested using the non-parametric Spearman rank test.

A sample size of 58 patients was estimated to detect a clinically relevant difference of 15 ANI points between mild pain (FLACC ≤ 3) and moderate-to-severe pain (FLACC ≥ 4) with 80% power and an α error of 5%, based on an estimated ANI standard deviation of 20, as observed in the study by Sabourdin and colleagues.17

To investigate the ability of the ANI to discriminate children with moderate or severe pain (FLACC ≥ 4) from children with mild or no pain (FLACC ≤ 3), receiver operating characteristic (ROC) curves were built with single and serial ANI measurements. Instantaneous (single) ANI measurements were collected at the time of pain assessment. Serial ANI measurements were collected over a 256 s period and averaged over time, in order to account for their fluctuations. Cut-off values were determined as values maximizing Youden’s index (J), where J is the difference between the true-positive rate and the false-positive rate. Maximizing this index enables the optimal cut-off point to be found from the ROC curve.23 Areas under the ROC curves (AUC-ROC) were used to determine which among instantaneous or 256 s period ANI measurement is the most accurate for predicting moderate-to-severe postoperative pain. The AUC-ROC were compared

Table 1 Characteristics of the patients included in the surgical group and the control group. No significant difference was observed between the two groups. Data are mean (range) or n(%).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Surgical group (n=32)</th>
<th>Control group (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [yr; mean (range)]</td>
<td>7.7 (0.4–16)</td>
<td>7.4 (0.8–15)</td>
</tr>
<tr>
<td>Sex ratio (male/female)</td>
<td>68%</td>
<td>71%</td>
</tr>
<tr>
<td>Reliable self-report of pain in PACU</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cognitive impairment*</td>
<td>15 (47)</td>
<td>12 (40)</td>
</tr>
<tr>
<td>Other causes</td>
<td>9 (28)</td>
<td>10 (33)</td>
</tr>
<tr>
<td>Surgical procedure [n (%)]</td>
<td>32 (100)</td>
<td>0</td>
</tr>
<tr>
<td>Major orthopaedics</td>
<td>15 (47)</td>
<td></td>
</tr>
<tr>
<td>General surgery</td>
<td>8 (25)</td>
<td></td>
</tr>
<tr>
<td>Maxillofacial surgery</td>
<td>6 (18)</td>
<td></td>
</tr>
<tr>
<td>Neurosurgery</td>
<td>3 (10)</td>
<td></td>
</tr>
</tbody>
</table>

Table 2 Physiological measurements in the experimental and control group. Data are mean (sd). *P<0.001 (Student’s t-test).

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Surgical group (n=32)</th>
<th>Control group (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Max FLACC (0–10)</td>
<td>6.1 (1.2)</td>
<td>0.2 (0.6)*</td>
</tr>
<tr>
<td>ANI instantaneous</td>
<td>52 (16)</td>
<td>75 (17)*</td>
</tr>
<tr>
<td>ANI 256 s period</td>
<td>49 (9)</td>
<td>76 (15)*</td>
</tr>
<tr>
<td>Heart rate (beats min⁻¹)</td>
<td>117 (25)</td>
<td>115 (22)</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>79 (12)</td>
<td>75 (8)</td>
</tr>
<tr>
<td>Respiratory rate (bpm)</td>
<td>24 (8)</td>
<td>21 (5)</td>
</tr>
</tbody>
</table>

Fig 3 Individual ANI values [256 s period (A) and instantaneous (B)], on arrival in the PACU, in patients with or without FLACC >4. The horizontal lines show the cut-off values of ANI optimizing the area under the receiver operating characteristic curves. These cut-off values are 66 and 56 for instantaneous and 256 s period ANI measurements, respectively.
using a non-parametric approach. The grey zone corresponds to a range of values for which the variable of interest does not provide conclusive information. Inconclusive responses are defined for ANI values with sensitivity lower than 90% or specificity lower than 90% (diagnosis tolerance of 10%). Grey zone limits are expressed as [low limit–high limit].

Results are expressed as mean (sd), median [95% confidence interval (CI)] or number of patients (%), as appropriate. The threshold for statistical significance was set at a $P$-value of 0.05.

Statistical analyses were performed using MedCalc for Windows, version 12.7 (MedCalc Software, Ostend, Belgium).

Results

Thirty-two patients, of whom 15 had cognitive disability, were included in the surgical group and 30 were included in the control group, 12 with cognitive disability (Fig. 2). Patient characteristics are presented in Table 1. All children of the surgical group developed moderate-to-severe pain after admission to the PACU, achieving FLACC ≥4 after a median of 28 min (95% CI 5–100 min). In contrast, children of the control group exhibited no pain or minimal pain throughout the observation period (Table 2). Children in the surgical group had normally distributed ANI recordings, centred at a value of ∼50, and remaining <60 for >75% of the time. In contrast, children in the control group spent most of the time with ANI recordings >60. Cardiorespiratory data collected at the time of pain assessment did not differ between the surgical and control groups (Table 2). The ANI values, both instantaneous and averaged over a 256 s period, were significantly lower in children of the surgical group compared with the control group, being respectively 52 (16) vs 75 (17) ($P<0.001$) and 49 (9) vs 76 (15) ($P<0.001$). Individual ANI values on arrival in the PACU in patients with or without FLACC >4 are shown in Fig. 3. A statistically significant negative linear relationship was observed between ANI 256 s period and FLACC ($-4.3 \times \text{FLACC}+76.1$, $r^2=0.54$, Spearman’s rho coefficient $-0.72$, $P=0.00001$) and between ANI instantaneous and FLACC ($-3.7 \times \text{FLACC}+75.5$, $r^2=0.34$, Spearman’s rho coefficient $-0.54$, $P=0.00001$; Fig. 4).

The AUC-ROC for the 256 s ANI recording period [0.94 (95% CI 0.85–0.99)] was significantly higher than the AUC-ROC for instantaneous ANI [0.83 (95% CI 0.74–0.91); $P=0.00097$; Fig. 5]. When measured for a period of 256 s, an ANI cut-off value of 56 [grey zone [58–60]] was most predictive of a FLACC ≥4 and had a Youden index of 0.77 (95% CI 0.50–0.83; Table 3).
contrast, regular measurement of pain intensity improves pain in infants, because inadequate assessment of pain intensity may increase in response to painful stimuli in adult patients under general anaesthesia. This suggests that ANI may constitute a sensitive and useful indicator of the antinoception–nociception balance in awake paediatric patients.

Self-assessment pain scales express a subjective experience of nociception that cannot be acquired in young children. Children younger than 5–7 yr of age cannot provide meaningful self-reports of pain intensity, because they may have difficulty in focusing on more than one dimension of a target at this stage of their cognitive development. In addition, young children who are not regularly attending school are not used to being asked questions by strangers and have a marked tendency to use only the extremes of scales, treating the scale as dichotomous rather than graded. Furthermore, whatever the age, self-reports of pain intensity are an oversimplification of the complexity of the experience of pain.

Nonetheless, pain scores are central to our ability to evaluate and titrate pain relief; therefore, there is a need for an objective pain-assessment tool that is not influenced by cultural, comprehension, or communication issues in children, especially in infants, because inadequate assessment of pain intensity may lead to analgesia that is delayed or inadequate, or both. In contrast, regular measurement of pain intensity improves pain management.

The ANI is a 0–100 non-invasive index, calculated from heart rate variability analysis, which provides a continuous measurement of the parasympathetic tone as a surrogate for the analgesia–nociception balance, with high values corresponding to maximal parasympathetic activity (analgesia) and low values corresponding to sympathetic activation (nociception). It has been demonstrated that the respiratory variability of heart rate decreases in response to painful stimuli in adult patients under general anaesthesia. More recently, the ANI has also been used to evaluate pain in awake surgical patients or in parturients during labour. The results of these studies showed that the ANI had an inverse linear relationship with pain scores and might be predictive of immediate pain intensity in the recovery room. Adrenoceptor agonists, such as clonidine or dexmedetomidine, can induce changes in ANI independently from pain and nociception, because their sympatholytic properties may be responsible for reductions in the systemic sympathetic tone; therefore, children who had received clonidine were excluded from the study. Dexmedetomidine was not available for use in our hospital at the time of the study.

Very little has been published regarding the usefulness of the ANI in children. The ANI has been found to provide a more sensitive assessment of nociception in anaesthetized children than haemodynamic parameters or skin conductance. In addition, the ANI proved to be useful in assessment of the efficacy of regional anaesthesia in children anaesthetized with sevoflurane. As far as we know, ours are the first data regarding the usefulness of the ANI in the postoperative period in children.

Discussion

The main result of this observational study is that the relative parasympathetic tone, as assessed by ANI monitoring, is consistently related to pain intensity during the recovery phase after procedures under general anaesthesia in children. This suggests that ANI may constitute a sensitive and useful indicator of the antinoception–nociception balance in awake paediatric patients.

<table>
<thead>
<tr>
<th>ANI measurement</th>
<th>Cut-off value</th>
<th>AUC (95% CI)</th>
<th>Specificity (%)</th>
<th>Sensitivity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>Grey zone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Instantaneous</td>
<td>66</td>
<td>0.83 (0.71–0.91)</td>
<td>70</td>
<td>87</td>
<td>74</td>
<td>84</td>
<td>[47–71]</td>
</tr>
<tr>
<td>256 s period</td>
<td>56</td>
<td>0.94* (0.86–0.99)</td>
<td>93</td>
<td>83</td>
<td>93</td>
<td>85</td>
<td>[58–60]</td>
</tr>
</tbody>
</table>

Table 3 Prediction of moderate-to-severe postoperative pain by ANI measurements. Instantaneous ANI measurements were collected at the time of pain assessment. Serial measurements were also collected over a 256 s period and averaged as a means to account for their fluctuation. *P < 0.00007 vs instantaneous. ANI, analgesia nociception index; AUC, area under the ROC curve; 95% CI, 95% confidence interval; grey zone, range of values with a sensitivity <90% or specificity <90%; NPV, negative predictive value; PPV, positive predictive value; ROC, receiver operating characteristic curve. Comparison of the AUC of the ROC curve was performed using the method of DeLong and colleagues.

In summary, single ANI measurements perform poorly in predicting moderate-to-severe postoperative pain, relative to conventional behavioural assessment, because 16% of the time a control patient will have ANI measurement below the threshold. However, with 87% sensitivity and 84% negative predictive value, the single ANI measurement may still constitute a simple non-invasive screening test. Furthermore, serial ANI measurements over a 4 min period are more accurate, with 93% specificity and 93% positive predictive value, in predicting moderate-to-severe postoperative pain in children.

It remains to be determined whether the ANI monitor, with graphic display of measurement trends over time, could be used by PACU nursing staff to guide the administration of morphine i.v. for postoperative pain relief.

Authors’ contributions

Study design: O.G., G.O.
Patient recruitment: O.G., B.C., B.S., T.D.
Data collection: O.G., B.C., B.S., T.D.
Data analysis: O.G., O.M., J.M.V., G.O.
Writing the manuscript: O.G., G.O.
Help with preparation of the final manuscript: O.M., J.M.V.
Archiving of the study files: G.O.

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Declaration of interest

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