Pupillary reflex dilatation and analgesia nociception index monitoring to assess the effectiveness of regional anesthesia in children anesthetised with sevoflurane

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Summary

Background: Pupillary diameter (PD) monitoring and Analgesia Nociception Index (ANI) (Metrodoloris, Lille, France), an online wavelet transform-based heart rate variability index, have been used in the assessment of pain.

Objective: The aim of this study was to evaluate the capacity of pupillary reflex dilatation and ANI to provide early assessment of regional anesthesia (RA) success following skin incision in children anesthetised with sevoflurane.

Methods: A total of 58 children, eligible for RA, were included after sevoflurane induction. The sevoflurane concentration was adjusted to maintain a MAC of 1.3 in oxygen and nitrous oxide, and a RA was performed. Pupillary diameter and ANI were recorded just prior to skin incision and then every 30 s for a period of 2 min. Regional anesthesia failure was defined by an increase in heart rate ≥ 10% occurring during the first 2 mins following incision. 

Results: Thirty-nine and 19 subjects presented RA success and failure, respectively. In the RA failure group, skin incision induced both changes in PD (P < 0.01) and ANI (P < 0.05) within 1 min of incision. Areas under the receiver-operating curves (95% confidence interval) to identify regional anesthesia failure were 0.747 (0.613–0.881) and 0.671 (0.514–0.827) for the minimal value of ANI and the maximal value of PD recorded during the 2-min period from skin incision, respectively.

Conclusion: Both PD and ANI rapidly change after skin incision in case of RA failure. These indices may provide a useful tool alone, or in combination with heart rate changes in the assessment of RA efficacy in children anesthetised with sevoflurane.

Introduction

Regional anesthesia (RA) in children is usually performed after induction of general anesthesia, but prior to skin incision (SI), to reduce the surgical stress response and limit or avoid the use of intravenous opioid analgesia during surgery. Adequacy of RA blockade in children is currently assessed by monitoring hemodynamic changes from the baseline, following exposure to a noxious stimulus. Inadequate regional anesthesia is usually identified by an increase in the heart rate (HR) from the baseline, in response to a surgical stimulus. However, the use of such hemodynamic parameters to assess effectiveness of RA is not standardized and has been shown to be imprecise (1–4).

The nociceptive and autonomic nervous systems are two components of an integrated central network, interacting at multiple levels of the central and peripheral
nervous systems. A noxious stimulus can lead to sym-
pathovagal balance disturbances (5). Autonomic nerv-
ous system monitoring techniques may help clinicians
to identify inadequate analgesia promptly and to adjust
the analgesic strategy during the intraoperative period.

Heart rate variability (HRV) is a noninvasive measure
dergiving cardiac autonomic activity and reflects sympathetic
and parasympathetic activity at the sinoatrial node (6).
Heart rate variability can detect autonomic and hemo-
dynamic responses to noxious stimuli, in patients undergo-
ing general anesthesia (7) HRV analysis has seldom been
studied in children, but has been found to be a reliable
marker of pain sensitivity in awake neonates (8). The
Analgesia Nociception Index (ANI) is an online HRV
analysis that can be used to assess the presence of pain
in individuals undergoing general anesthesia (9–12). To
date, there has been little research in this area, and
therefore, there is not much evidence for the use of ANI
in children undergoing general anesthesia (12). How-
ever, it may be that it is a useful tool in this setting.

A noxious stimulus causes dilatation of the pupil in
anesthetised subjects. Pupillary reflex dilatation (PRD)
response to a noxious stimulus has been demonstrated
as a sensitive indicator of pain in adults and children
(13–18). Previous studies have also demonstrated that,
following the noxious stimulus, opioid administration
results in a rapid decrease in pupil dilatation (13,16,17).
Therefore, pupillary diameter (PD) monitoring could
provide a measure of pain assessment during the in-
traoperative period.

The aim of this study was to investigate the hypothesis
that PRD or ANI monitoring can provide early assess-
ment of adequacy of RA after SI in children undergoing
general anesthesia with sevoflurane.

Methods
After Ethics Committee approval (Comité de Protection
der Personnes Lyon Sud Est II, Ref: 2011-027-2) and
written parental consent, 58 children over 2 years of age
referred for urological, visceral, or orthopedic surgery
under general anesthesia and requiring RA were
recruited. Patients with cardiac arrhythmias, ocular
diseases, neurological disorders, and those treated with
opioids or drugs interfering with autonomic function
were not included.

All children received premedication with midazolam
(0.3 mg·kg\(^{-1}\) orally or rectally, maximum 10 mg) 30 min
before arrival in the operating theater. Anesthesia was
induced with 6.0% inhaled sevoflurane in 50% nitrous
oxide and oxygen. Once intravenous access had been
established, the airway was secured using either a laryn-
geal mask airway or tracheal intubation. Anesthesia was
maintained with sevoflurane in 50% nitrous oxide and
oxygen, to obtain a MAC of 1.3. Ventilation was
adjusted to maintain the ETCO\(_2\) near to 35 mm Hg.
Regional anesthesia (either a central neuraxial or a
peripheral nerve block) was performed, as appropriate
for the planned surgical procedure, to avoid the use of
opioid analgesia. The decision about which type of block
(cenral neuraxial or peripheral nerve block), localization
(ultrasound, landmark technique, or nerve stimulator),
type, and amount of local anesthetic was made by the
anesthetist with overall responsibility for the case. All
RA techniques performed were carried out following
standard operating procedures developed in our depart-
ment, by a physician trained in pediatric RA. Skin inci-
sion was allowed only after a period of 10 min from local
anesthetic injection.

A rise in HR ≥ 10% from baseline occurring within
the 2-min period following SI was considered to be RA
failure (13). In cases where RA failure was identified,
surgery was temporarily stopped until the administra-
tion of an intravenous bolus dose of alfentanil
(10 \(\mu\)g·kg\(^{-1}\)) at two minutes after SI. No further drugs
were administered until completion of the study.

Analgesia Nociception Index was continuously dis-
played on the Physiodoloris-specific monitor (Metrodol-
oris, Lille, France). The algorithm used for ANI
computation has been previously described (9–11). It is
based on the magnitude analysis of the respiratory pat-
terns on the R-wave to R-wave (RR) series automati-
cally detected on the electrocardiogram. RR series are
then filtered, normalized, and high-pass filtered between
0.15 and 0.50 Hz (frequencies corresponding to para-
sympathetic tone), using a wavelet transform-based
numerical filter. The area between the lower and upper
envelopes of the RR series is then automatically mea-
sured over four 16-s subwindows, leading to ANI cal-
culation by dividing this surface by its maximum possible.
This gives a measure of the relative parasympathetic
tone. Analgesia Nociception Index is expressed as a
numerical value between 0 and 100.

Pupillary diameter was monitored using an infrared
digital commercially portable quantitative videopupillo-
meter (IDMed, Marseille, France). Maximal PD was
obtained after illumination of the eye with a set of infra-
red light rays at 850 nm. The spatial and time resolu-
tions of the pupillometer system are 0.01 mm and
50 Hz, respectively. All measurements were taken from
the same eye in each patient. A mask was worn, by each
patient, to prevent ambient light from entering the con-
tralateral eye.

Pupillary diameter and ANI values were recorded after
induction of general anesthesia, just before SI (baseline
value) and then every 30 s up to 2 min following SI.
Heart rate was automatically and continuously displayed, and the maximum percentage change in HR during the first 2 min following SI was calculated and recorded. All relevant patient data, details of type of anesthesia received, and the surgical procedure performed were prospectively recorded.

Subjects were allocated into two groups according to the maximum percentage change in HR during the first 2 min following SI. Regional anesthesia failure was defined as an increase in HR $\geq 10\%$ and RA success as an increase in HR $< 10\%$ from baseline. The data between these groups were compared by Fisher’s exact test or Student’s $t$-test. The PD and ANI following SI were compared with the baseline values by repeated-measures ANOVA with Tukey correction for multiple comparisons. To assess the ability of the parameters to identify failure of RA, receiver-operating characteristic (ROC) curves were generated, varying the discriminating threshold for the maximal value of PD and the minimal value of ANI recorded during the first 2 min after SI. The power calculation assumed an area under ROC of 0.75, with a Type 1 error of 0.05, Type 2 error of 0.20, and null hypothesis of 0.5. As there are no similar data in the literature for comparison, the area of 0.75 was calculated for ANI from a previous pilot study of 20 patients. A minimum of 40 patients needed to be recruited into the study. A $P$-value $< 0.05$ was considered significant. Statistical analysis was performed using GraphPad InStat 3.00 and Prism 6.00 (GraphPad Software, San Diego, CA, USA).

## Results

Data were analyzed from fifty-eight patients aged from 2 to 16 years (mean age, 6 years). Thirty-nine patients presented RA success, and nineteen patients presented RA failure. There were no significant differences between these groups with respect to age, gender, and type of surgery or RA technique (Table 1). Time between performance of block and SI was also similar between the groups.

There was a significant increase in PD within 1 minute of SI ($P < 0.01$), lasting for 30 s ($P < 0.05$) in the RA failure group (Figure 1). The mean maximum increase in PD during the first 2 min following incision was 77% [95% confidence interval (CI) 33%–122%]. Children in the RA success group did not show any increase in PD at any of the observed time intervals following SI. Pupillary diameter increase was significantly higher in the RA failure group, compared with the RA success group, between 1 and 2 min following SI ($P < 0.005$).

Skin incision resulted in a significant decrease in ANI at 1 min, which lasted for 30 s ($P < 0.05$), in the RA failure group. The ANI pre-incision value was restored to baseline 2 min after the noxious stimulus (Figure 2). The mean maximum decrease in ANI during data

### Table 1 Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Regional anesthesia success ($n = 39$)</th>
<th>Regional anesthesia failure ($n = 19$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male/female)</td>
<td>13/26</td>
<td>2/17</td>
</tr>
<tr>
<td>Age (years)</td>
<td>4 [2–16]</td>
<td>7 [2–15]</td>
</tr>
<tr>
<td>Type of regional anesthesia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral nerve block</td>
<td>30 (51)</td>
<td>16 (28)</td>
</tr>
<tr>
<td>Abdominal wall and perineal nerve block</td>
<td>20 (34)</td>
<td>12 (21)</td>
</tr>
<tr>
<td>Upper and lower limb nerve block</td>
<td>10 (17)</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Central neuraxial block</td>
<td>9 (16)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Type of surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urological or visceral surgery</td>
<td>28 (48)</td>
<td>15 (26)</td>
</tr>
<tr>
<td>Orthopedic surgery</td>
<td>11 (19)</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Time regional anesthesia—incision (min)</td>
<td>15.9 ± 8.3</td>
<td>16.8 ± 10.3</td>
</tr>
<tr>
<td>Local anesthetic used</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ropivacaine</td>
<td>16 (28)</td>
<td>9 (16)</td>
</tr>
<tr>
<td>Levobupivacaine</td>
<td>17 (29)</td>
<td>6 (10)</td>
</tr>
<tr>
<td>Mepivacaine</td>
<td>6 (10)</td>
<td>4 (7)</td>
</tr>
</tbody>
</table>

Data are expressed as median [range], number (proportion), or mean ± SD.
collection following SI was 36% [95% CI 17%–55%] in this group. In the RA success group, there were no significant changes in ANI throughout the study period. The ANI value was significantly lower in the RA failure group, compared with the RA success group, at all of the observed time points between 1 and 2 min from surgical stimulus \( (P < 0.005) \).

Results of ROC analysis are shown in Table 2. Both ANI and PD were able to identify failure of RA. The areas under the ROC curves obtained with the minimal value of ANI and the maximal value of PD recorded during the first 2 min after SI were 0.747 (95% CI 0.613–0.881) \( (P = 0.002) \) and 0.671 (95% CI 0.514–0.827) \( (P = 0.04) \), respectively. There was no statistical difference between these two areas (Figure 3).

Table 2 Areas under the receiver-operating characteristic curves and cutoff values for maximal pupillary diameter and minimal Analgesia Nociception Index recorded during the first 2 min following skin incision in the identification of failure of regional anesthesia

<table>
<thead>
<tr>
<th></th>
<th>AUC</th>
<th>Standard error</th>
<th>Lower bound</th>
<th>Upper bound</th>
<th>P-value</th>
<th>Cutoff</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD (mm)</td>
<td>0.671</td>
<td>0.080</td>
<td>0.514</td>
<td>0.827</td>
<td>0.04</td>
<td>&gt;4.2 mm</td>
<td>58</td>
<td>79</td>
</tr>
<tr>
<td>ANI</td>
<td>0.747</td>
<td>0.068</td>
<td>0.613</td>
<td>0.881</td>
<td>0.002</td>
<td>&lt;51</td>
<td>79</td>
<td>62</td>
</tr>
</tbody>
</table>

AUC, area under the curve; PD, pupillary diameter; ANI, Analgesia Nociception Index.

Discussion

This study demonstrates that RA failure is associated with a significant increase in PD and decrease in ANI, in children over 2 years of age, within the first minute of SI. Both ANI and PD have the ability to identify failure of RA in children undergoing general anesthesia.

Currently, it is usual practice for pediatric anesthetists to monitor changes in HR from baseline, following SI, to assess the effectiveness of RA (1–4). However, HR depends not only on the adequacy of analgesia during surgery, but on several other factors such as volume status, age, and depth of anesthesia. Therefore, HR changes do not solely reflect RA success or failure. Additionally, the percentage rise in HR required to identify RA failure in children under general anesthesia is debateable (2–4).

Analgesia Nociception Index represents a measure of the relative parasympathetic tone. If ANI has been used successfully to detect the presence of pain during surgery in adults (7,9–11), there is little evidence available to support its use in children (12). Insufficient analgesia leads to a reduction in parasympathetic tone, in response to an increase in sympathetic activity, and thus a decrease in ANI (10,12). Our study shows that SI induces a significant reduction in ANI in the RA failure group, but not in those with a successful block. The 1-min delay between SI and the decrease in ANI may be explained by the fact that the instantaneous ANI value, continuously displayed by the Physiodoloris monitor, is the result of computations average made over the 64 previous second (9,10).

Several studies have demonstrated that pupillary dilation in response to a noxious stimulus is a very sensitive measure of nociception in adults and children under general anesthesia (13–18). Pupillary reflex dilation can be defined as the difference between the baseline PD, prior to a noxious stimulus, and the PD at the point of maximal dilation following the noxious stimulus (19). Pupillary reflex dilatation is depressed by opioids in a dose-dependent manner (13,16,17) and can be used to estimate a sensory level in children with caudal anesthesia, under general anesthesia, because it is reduced in
blocked dermatomes and preserved cephalad to the sensory level (19). Pupillary reflex dilatation monitoring may become a useful tool in the assessment of intraoperative pain in children. In our study, PD significantly increased in cases of RA failure, from the first minute following SI, but remained unchanged in the RA success group. The mean maximum percentage rise in PD after noxious stimulation in the RA failure group was only 77%, whereas it reached approximately 200% in previous studies (13,15). Also, the 1-minute time delay between SI and significant pupillary dilatation was longer than in previous reports (13,15). These differences may be explained by the presence of partially effective RA blocks among some of the children in the RA failure group. This could be because there was insufficient time between siting the RA block and SI (the minimum time in our study being 10 min), or the surgical incision site may have exceeded the anatomical limits of the sensory block.

Sevoflurane anesthesia itself can have parasympathetic and sympathetic effects on the cardiovascular system in children (20,21). Therefore, we cannot absolutely exclude the potential pharmacological effect of sevoflurane on the observed differences in ANI between the groups. Nor can we comment on differences in depth of anesthesia between the groups, or the effect of this on ANI, as this was not measured in our study. However, we feel that it is unlikely that either would have had any significant effect, as recordings in both the groups were taken at steady state, when end-tidal sevoflurane concentrations had been adjusted to maintain a MAC of 1.3. For the same reason, we feel we can also conclude that any observed differences in PD between the two groups following SI were related to the analgesia effects of the RA. This is supported by the view that halogenated agents, as opposed to opioids, do not inhibit PRD in response to a noxious stimulus, especially at 1.3 MAC (13–15,18,19).

A further limitation of our study is related to the method we used to identify RA failure or success. As mentioned previously, a rise in HR from baseline is currently considered to be the best way to identify RA failure in children undergoing general anesthesia, even if HR may be affected by several factors other than pain. We used this widely accepted method in our protocol, as there is currently no evidence to support the use of another parameter. The percentage rise in HR required to define RA failure is a matter of some debate. Some authors have suggested an increase in HR following SI of 15–25% from baseline (2–4). In our department, we use an increase in HR of 10% from the baseline, after SI, as an indicator of inadequate analgesia following RA. This lower threshold for HR change may partly explain the high RA failure rate we observed in our patients, but is consistent with the findings of another previously published study which reported a mean increase in HR of only 11% following SI in patients not receiving opioid analgesia (13). In fact, it is our opinion that by increasing the threshold for the rise in HR in response to SI, we would have incorrectly identified
References


Conclusion

This study demonstrates that both PD and ANI rapidly change following SI in cases of RA failure in children over 2 years of age anesthetised with sevoflurane without opioid. This would suggest that both PRD and ANI monitoring are useful tools in the assessment of RA failure or success in children under general anesthesia. They can be used in combination with or as an alternative to more traditional methods, such as HR monitoring. However, more research is required to confirm these results and further establish an interest in PD and ANI monitoring as a method to discriminate between RA failure or success in children undergoing surgery.

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Conflict of interest

No conflicts of interest declared.