Analgesia/nociception index for the assessment of acute postoperative pain

Editor—We have read with interest the study by Ledowski and colleagues concerning the evaluation of analgesia/nociception index (ANI) for the assessment of immediate postoperative pain.

The ANI is a 0–100 index derived from heart rate variability (HRV), which provides a continuous measurement of the parasympathetic tone as a surrogate for the analgesia/nociception balance: high values correspond to maximum parasympathetic activity (analgesia) and low values correspond to sympathetic activation (nociception). In this study, the authors compared the ANI values measured on arrival in the post-anaesthesia care unit (PACU) and subsequently at 5 min intervals to pain intensity measured simultaneously with a 0–10 numeric rating scale (NRS) after elective surgery under general anaesthesia using sevoflurane and fentanyl. In the 114 patients included in analysis, the authors found a small but significant negative correlation between ANI and NRS ($r = -0.075; P<0.05$). A small but significant difference in ANI (63 vs 59, $P<0.05$) was also found when comparing the extremes of pain (NRS 0 and NRS 6–10, respectively). The performance of ANI to distinguish between NRS 0 and NRS 6–10 was poor with an area under the receiver-operating characteristic (ROC) curve (AUC) of 0.434, which explains the low sensitivity and specificity (50%) obtained in this setting. Ledowski and colleagues concluded that ANI did not reflect different states of immediate postoperative pain measured on an NRS scale after sevoflurane–fentanyl anaesthesia.

Boselli and colleagues have recently performed a study very similar to that of Ledowski and colleagues, in which ANI and NRS scores were measured upon arrival in and at departure from PACU in 200 patients undergoing general anaesthesia for ear–nose–throat surgery or endoscopy. Patients undergoing surgery received desflurane or sevoflurane while those undergoing endoscopy received propofol for hypnosis. All patients received remifentanil for analgesia. A negative linear relationship was observed between ANI and NRS ($r^2=0.41, P<0.05$) at arrival in PACU, and a good performance for ANI (ROC curve AUC=0.86) to detect moderate-to-severe pain, defined by NRS $\geq 3$. It should be noted that ANI performed significantly better in patients who had received propofol than in those who had received a halogenated agent (ROC curve AUC=0.93 vs 0.82, respectively, $P<0.05$). The conclusions were thus different from those by Ledowski and colleagues, with ANI measurements during the immediate postoperative period significantly correlated to pain intensity after balanced general anaesthesia using remifentanil.

One may wonder how such different results occurred, despite apparently very similar clinical settings. It has been shown that propofol and halogenated agents have different effects on HRV and on the baroreflex control of heart rate, so that the hypnotic drug chosen for maintenance of general anaesthesia may play a major role in HRV measurements made during and after surgery. The main difference between opioids used during general anaesthesia comes probably from their contextual elimination half-time, but their effect on HRV is more or less the same: they inhibit sympathetic activity but preserve and/or enhance parasympathetic activity.

Jeanne and colleagues have already recorded HRV during PACU stays of conscious adult patients after major orthopaedic surgery made under propofol or sevoflurane anaesthesia with sufentanil (unpublished data). Patients were asked to rate their pain in PACU before and 30 min after regional analgesia. Haemodynamic data were non-invasively collected and ANI was recorded. A clear difference was observed between ANI readings during pain (NRS $>4$) and without pain (NRS $\leq 3$) only in the propofol group, while ANI readings remained constant independent of the perceived pain in the sevoflurane group. There was no difference in the total amount of opioids patients had received between the two groups.

These results may help understand the contradictory results presented by Ledowski and colleagues and Boselli and colleagues:

(i) Since sufentanil was used in Jeanne and colleagues’ study and fentanyl in Ledowski and colleagues’ study, it is probable that the long opioid half-life did not play a role in the negative results by Ledowski and colleagues. Whether the short half-life of remifentanil in Boselli and colleagues’ study played a role remains unclear, but as each patient was compared with his own assessment of pain and his own HRV readings, the effect of the opioid half-life played probably only a minor role in the discrepancies observed between the studies.

(ii) In both Jeanne and colleagues’ and in Boselli and colleagues’ studies, patients who received propofol during surgery presented a good correlation between ANI and their rating of postoperative pain, so that halogenated agents and sevoflurane in particular may be the reason why autonomous reactions are blunted in these conditions, even after awakening.

(iii) Patients in Jeanne and colleagues’ study were exposed to sevoflurane for at least 120 min, probably at least 60 min in Ledowski and colleagues’ study even if these data were not collected by the authors, and 30–60 min in Boselli and colleagues’ study. It appears therefore that the duration of exposure to halogenated agents may be key to understanding the results of these clinical trials: the longer the duration of exposure, the more the autonomic nervous system (ANS) is...
In conclusion, additional clinical evidence is clearly needed to assess further the relationship between opioids, inhalation anaesthesia, duration of exposure to halogenated agents, and their lasting effects on the ANS and therefore on ANI.

Declaration of interest
M.J. owns shares of and is consultant for MDoloris Medical Systems. No other conflict of interest is declared.

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doi:10.1093/bja/aeu116

Analgesia–nociception index

Reply from the author
Editor—I would like to thank Dr Boselli for his detailed letter discussing the outcome differences between our papers! I fully agree with many of the reasons mentioned by Dr Boselli and follow his conclusion that more work is necessary in order to fully understand the many factors potentially influencing the analgesia–nociception index (ANI). In order to contribute a new view on the matter, I may also point out the following: in Boselli and colleagues’1 study, many patients had no postoperative pain at all. This was largely due to the inclusion of, for example, post-endoscopy patients. The prevalence of pain in their cohort was hence relatively low. In the discussion of their paper, the authors point out that ANI showed a low positive predictive value for states of severe pain and that, due to the high negative predictive value (NPV), the monitor might be better suited to exclude states of severe pain. Although this may certainly still be of clinical relevance, it is worth remembering that the NPV for a monitor will always be high whenever the state to be excluded has a low prevalence. In extremis, this means that in the complete absence of severe pain, one would not have to switch the monitor on in order to achieve an NPV for severe pain of 100%. The fact that in our cohort, >40% of subjects had moderate-to-severe postoperative pain2 may hence also help to explain the different conclusions drawn in both studies.

This, and the reasons given by Dr Boselli, shows that although on first sight, both studies looked alike, they may not have been so similar after all. It also reminds us of the reason why validation studies of preliminary findings always require the utmost attention to detail in order to produce meaningful results.

Declaration of interest
None declared.

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doi:10.1093/bja/aeu113