Nociception level monitoring for personalized analgesic treatment. Response to Br J Anaesth 2020; 125: 1070-8

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intraoperative doses, as clearly shown in their figure 3. This was associated with increased postoperative comfort (i.e. better pain scores) in the NOL-guided group, for a similar opioid request in PACU. We congratulate the authors for their outstanding work and thank them for addressing what we consider to be key points of interest. Hopefully, future investigations will elaborate upon the foundations that Meijer and colleagues have established by focusing on the long-term effects of guiding anti-nociception with the NOL (e.g. from the first 24 h up to beyond patient discharge) and the influence of multimodal analgesia on a goal-directed anti-nociceptive strategy.

Declarations of interest

All authors have received honoraria from Medasense for consultation or presentation fees.

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Nociception level monitoring for personalized analgesic treatment. Response to *Br J Anaesth* 2020; 125: 1070-8

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Editor—We thank Coeckelenbergh and colleagues[1] for their interest in our work, particularly in our study on the influence of Nociception Level (NOL) index-guided fentanyl dosing during sevoflurane anaesthesia on postoperative pain and stress hormone levels during and after surgery (with acronym SOLAR trial).[2] In summary, we observed that although NOL index-guided fentanyl dosing during anaesthesia did not result in differences in total fentanyl dosing between groups, differences in timing of dosing, based on the value of the NOL index, resulted in less postoperative pain (difference in pain of 1.6 points) and 50% lower stress hormone (adrenocorticotropic hormone [ACTH] and cortisol) levels during and after surgery.

Coeckelenbergh and colleagues[1] raise several questions regarding our study. The first question is 'whether dexamethasone, nonsteroidal anti-inflammatory drugs or any other components of multimodal analgesia were administered?' Our analgesic protocol was aimed at discovering if a stringently applied regimen consisting of NOL index-guided fentanyl dosing during anaesthesia combined with perioperative morphine or piritramide dosing would result in less postoperative pain. Apart from pre-emptive paracetamol, no additional analgesics were given. After study completion, which was after 90 min in the PACU, any other analgesic modality could be administered. We are convinced that this approach allows a well-defined study of NOL index-guided opioid administration during anaesthesia and nociception or pain relief, respectively during or after surgery, with as few confounders as possible. Additional analgesic modalities given during surgery will further reduce the pain score and, indeed, stress hormone levels in both groups.

Our colleagues next ask whether 'we could confirm absence of differences between groups if multimodal pain relief was used'. We agree that differences in groups will be diminished but not lost when treatment of nociception during

surgery, such as trocar port infiltration, is not based on measured nociception values in either group. As this is one of the first studies on this topic, there is room for further clinical investigations exploring the impact of nociception monitoring on postoperative pain using different analgesic regimens.

Their last question is whether 'we believe there were false positive NOL index values, i.e. NOL index values above 25 despite adequate antinociception'. We have no indication that any of the NOL index values were falsely positive. The NOL is a validated parameter that is able to distinguish between no, mild, moderate, and intense noxious stimuli.[2,3] We did observe in three (6%) patients that high NOL index values were not reduced by fentanyl. Reviewing the data, we noted that in these patients high NOL index values coincided with high blood pressure values (and *vice versa*, depending on the study group), an indication that the NOL index correctly tracked high nociception. We previously showed that fentanyl potency varies considerably among humans.[4] In addition, we observed that low fentanyl analgesic potency does not coincide with low potency for side-effects.[4] Hence, we advise not to continue dosing when the opioid effect is small or absent but to rotate to another opioid or another analgesic regimen (e.g. ketamine). In our study, we rotated our patients from fentanyl to remifentanil when high NOL index values or high arterial pressures did not change in response to high doses of fentanyl. Remifentanil controlled nociception in these patients well, and there was no indication of hypercapnia or fluid imbalance.

Finally, it of interest to briefly discuss two differences in outcome between the SOLAR trial and our earlier published paper on NOL-guided during remifentanil and propofol anesthesia (with acronym NOLA), both randomised controlled trials.[1,5] The current SOLAR trial studied NOL-guided fentanyl dosing during sevoflurane anaesthesia,[1] whereas earlier we studied NOL-guided remifentanil dosing during propofol anaesthesia.[5] The SOLAR trial showed no effect of NOL guidance on haemodynamics (there were very few haemodynamic events) but a large beneficial effect on postoperative pain scores, whereas the NOLA trial showed that NOL-guided remifentanil dosing had a remarkable positive effect on the number of haemodynamic events, but did not influence postoperative pain scores.[1,5] We relate this to the differences in pharmacokinetics and pharmacodynamics between the two opioids under investigation. In the NOLA trial, subjects experienced no residual analgesic effect of remifentanil during stay in the PACU, whereas some residual effect from fentanyl may have occurred in the SOLAR trial. Consequently, the fentanyl dosing strategy aimed at reducing nociceptive effects during surgery may have caused the difference in pain scores between the two study groups in the SOLAR trial. Finally, it is our clinical experience that fentanyl causes less vasodilation than remifentanil during anaesthesia. Fewer haemodynamic events were observed in the SOLAR trial compared with the NOLA trial. More importantly, NOL guidance in the NOLA trial resulted in less remifentanil administration and consequently less haemodynamic instability. We agree that further studies are warranted to corroborate our observations, but our data do show different outcomes depending on anaesthesia technique. This explains the sometimes-large differences in findings between different research groups that test the effect of nociception monitors on patient outcome but that use very different protocols.

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Declarations of interest

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Doing more and doing better: improving racial and ethnic disparities research in anaesthesiology

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