23. Lund I, Lundeberg T, Kowalski J, et al. Evaluation of variations in sensory and pain threshold assessments by electrocutaneous stimulation. *Physiother Theory Pract* 2005; **21**: 81–92

24. McCracken LM, Morley S. The psychological flexibility model: a basis for integration and progress in psychological approaches to chronic pain management. *J Pain* 2014; **15**: 221–34

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Nociception level-guided fentanyl titration: potential impact of multimodal anaesthesia and false positives. Comment on *Br J Anaesth* 2020; 125: 1070–8

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Editor—Meijer and colleagues[1] recently reported in the *British Journal of Anaesthesia* a two-centre RCT investigating the capacity of the nociception level (NOL) index to guide fentanyl administration during laparoscopic/robotic abdominal surgery. They reported that this strategy significantly decreased postoperative pain scores during the first 90 min of recovery in the PACU. In accordance to the work of Funcke and colleagues,[2] the stress response, which Meijer and colleagues measured through serial analyses of serum cortisol and adrenocorticotropic hormone levels, decreased significantly in the NOL index group. This study shows potential advantages of guiding intraoperative fentanyl dosing based on the NOL index. However, we think certain factors may have had an impact on the studied outcomes and that they should be clarified.

(i) It is unclear if dexamethasone, NSAIDs, or any other components of multimodal analgesia were administered. The authors explicitly state that patients were scheduled for surgery 'without epidural anaesthesia, local blocks, or infiltration', removing useful adjuvants to control postoperative pain. With the exception of paracetamol, their anti-nociception protocol seems to be exclusively opioid based (i.e. fentanyl-boluses-maintained NOL index or haemodynamic targets, remifentanil infusion if fentanyl was insufficient, and a transition dose for all patients of either piritramide or morphine at the end of surgery). Despite such a strong opioid strategy, rather high pain scores were observed in the control group. Dexamethasone, an NSAID, and trocar site infiltration are in many centres standard care, and could have possibly improved the immediate postoperative baseline conditions in both groups and led to lower initial pain scores, less nausea, and a modified stress response. Dexamethasone, for example, has become an essential perioperative drug, as its prophylactic administration is linked to decreased postoperative pain, nausea, and vomiting.[3] The majority of patients in this study were women, and all patients were expected to require postoperative opioids. Yet, the incidence of nausea were 28% and 36% of the patients in the NOL-guided and standard care groups, respectively, which suggests that dexamethasone was not administered. Furthermore, dexamethasone could have had an impact on the outcome of stress hormone release, one of their statistically significant findings.

(ii) Another point of discussion is the possibility of false-positive NOL index values (i.e. NOL index values >25 despite adequate anti-nociception). Three patients required remifentanil in addition to fentanyl because either blood pressure (standard care group) or NOL index (NOL-guided group) remained above target. Perhaps targets were not reached in the NOL-guided group because factors other than nociception caused the index to increase. High arterial CO_2, which can occur during laparoscopic surgery, leads to increased sympathetic tone and may cause arrhythmias.[4] In addition, plethysmographic variation has been used to predict fluid responsiveness,[5] and such variations could perhaps influence another parameter of the NOL index: photoplethysmogram amplitude. Non-nociceptive-related changes in the NOL index are possible, for example, after a bolus of phenylephrine,[6] and clinicians should be aware of potential cofounders.

Meijer and colleagues[1] showed several benefits of personalising intraoperative anti-nociception. Most notably, they were able to target outliers who required higher or lower

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.

References

1. Meijer F, Honing M, Roor T, et al. Reduced postoperative pain using nociception level-guided fentanyl dosing during sevoflurane anaesthesia: a randomised controlled trial. *Br J Anaesth* 2020; **125**: 1070–8
2. Funcke S, Pinnschmidt HO, Wesseler S, et al. Guiding opioid administration by 3 different analgesia nociception monitoring indices during general anesthesia alters intraoperative sufentanil consumption and stress hormone release. *Anesth Analg* 2019; **130**: 1264–73
3. De Oliveira GS, Almeida MD, Benzon HT, McCarthy RJ. Perioperative single dose systemic dexamethasone for postoperative pain. *Anesthesiology* 2011; **115**: 575–88
4. Atkinson TM, Giraud GD, Togioka BM, Jones DB, Cigarroa JE. Cardiovascular and ventilatory consequences of laparoscopic surgery. *Circulation* 2017; **14**: 700–10
5. Cannesson M, Desebbe O, Rosamel P, et al. Pleth variability index to monitor the respiratory variations in the pulse oximeter plethysmographic waveform amplitude and predict fluid responsiveness in the operating theatre. *Br J Anaesth* 2008; **101**: 200–6
6. Raft J, Coulombe MA, Renaud-Roy E, et al. Impact of intravenous phenylephrine bolus administration on the nociceptive level index (NOL). *J Clin Monit Comput* 2020; **34**: 1079–86

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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