Master thesis | Original study

Can nociception monitors be used to titrate remifentanil with a stable low noxious stimulation response index (NSRI)?

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Abstract

Purpose: **Opioids blunt autonomic nervous system (ANS) responses to noxious stimuli. Nociception monitors analyze the same ANS responses and thus might prove useful to guide opioid dosing. However, concomitantly administered hypnotics also blunt ANS responses and may thus jeopardize the usefulness of nociception monitors to guide intra-operative opioid dosing. We therefore studied the PK (prediction probability) of 3 nociception monitors (NOL index, qNOX and SPI) for the prevailing opioid concentration while maintaining the NSRI (noxious stimulus response index) at a low constant value with a range of opioids and inhaled agent combinations.**

Methods: **In 24 consenting ASA I-II patients undergoing robotic assisted radical prostatectomy, anesthesia was maintained with desflurane in O2/air and remifentanil (target controlled infusion). During the dissection phase, the remifentanil effect site concentration (Ce) in each patient was maintained at 1, 3, or 5 ng/mL for 20 min while the end-expired desflurane concentration (FET) was adjusted to keep the noxious stimulus response index (NSRI) at 5; the sequence in which each patient received each of the three remifentanil Ce was randomized. After stabilization, during each 20 min study period, the following data were collected: NSRI, NOL Index, SPI, qNOX, and FETdes. For each parameter, the prediction probability (PK) for Ce remifentanil was calculated.**

Results: **All patients remained hemodynamically stable. Surgery was finished before the last data collection period in 5 patients with a remifentanil Ce = 5 ng/mL, and in 1 patient with a remifentanil Ce = 1 ng/mL. All other data have been included in the data analysis. The prediction probability (PK) calculated for NOL Index, qNOX and SPI for Ce remifentanil was 0.519, 0.470, and 0.477, respectively.**

Conclusion: **Nociception monitoring becomes useless to titrate opioids when the concomitantly administered hypnotic is adjusted to maintain a low NSRI, presumably because suppression of movement to laryngoscopy also ensures suppression of the sympathetic nervous system response to the noxious stimulus present during intra-abdominal resection of the prostate. Both the hypnotic/opioid ratio and stimulus intensity of the stimulus/response pair need to be considered when attempting to use nociception to guide opioid administration.**

Keywords: **Nociception monitors, NOL index, NSRI, drug interactions, pharmacokinetics, pharmacodynamics.**

Introduction

General anesthesia is most often attained by the administration of a hypnotic and a noxious stimulus response suppressing drug. If these two drugs could selectively attain these clinical endpoints, it might become possible to monitor their individual desired effects and titrate the drugs accordingly: the hypnotic monitor could be used to titrate the hypnotic drug, and the nociception monitor could be used to titrate the noxious stimulus response suppressing drug. Unfortunately, there is as of yet no drug with such a one-to-one receptor-clinical effect relationship. In real life, a "hypnotic" (most often a GABA receptor acting agent or an inhaled agent with a still enigmatic mode of action) is combined with an opioid (mu receptor agonist). Rather than having separate actions, both clinical endpoints

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(unconsciousness and ANS control) are mediated by the combination of both drugs. Still, attempts are being made to distill out the effect of these drugs on each of the different neural systems that mediate the individual clinical endpoints, with EEG derived parameters focusing on hypnotic drug titration, and nociception monitors focusing on opioid titration.

But not surprisingly, these monitors so far have not succeeded to separately monitor hypnosis or suppression of noxious stimuli. The BIS value (Bispectral index) that is likely to ensure hypnosis is influenced by the amount of opioid present[1], and the value of a noxious stimulus suppression parameter (almost invariably based on some measure of autonomic nervous system activity) is influenced by the amount of hypnotic present [2]. The NOL index (Nociception Level Index; Medasense Biometrics Ltd, Ramat Gan, Israel) on the other hand is a nociception monitor that measures several autonomic responses in the individual patients which are then converted into an index[3-6]. Clinical validation of the NOL index is ongoing We predict that the NOL index and other monitors like qNOX (Quantium Medical, Mataró, Spain)[7] and Surgical Pleth Index (SPI; Anandic Medical Systems, Feuerthalen, Switzerland)[8] are not useful to titrate opioids if the relative contribution of hypnotics on the hypnotic/opioid mix is high: if the opioid concentration is low, but the NSRI is kept at a stable low value by increasing the hypnotic component of the anesthetic, then the nociceptive monitors do not contribute much to the titration of the opioid. Different combinations of hypnotics and opioids were therefore titrated to the same NSRI, a population based calculated index of how likely it is that a patient does not display movement after laryngoscopy[9]. The likelihood of absence of movement in response to laryngoscopy or "probability of tolerance to laryngoscopy, PTOL" is used to help titrate drug dosing. It can be considered analogous to the MAC (median alveolar concentration). The NSRI is a "numerical depth of anaesthesia indicator", derived from and interchangeable with PTOL, merely differing in scale[10]. Movement is a response that is distinctively different from the ANS response to a noxious stimulus. We hypothesize that when the NSRI is maintained at a low constant value with a range of combinations of opioids and inhaled agent, the NOL index, qNOX and SPI are not predictive of the opioid concentration present.

Methods

After obtaining IRB approval (OLV hospital, Aalst, Belgium, study number 2019/016, B126201938844, approved 14/11/2019) and individual patient consent, 24 patients ASA I-II with regular sinus rhythm scheduled to undergo robotic assisted radical prostatectomy were enrolled.

In addition to routine monitoring, several nociception monitors were used. A finger probe was applied to derive the NOL index. A qCON/qNOX electrode was applied on the forehead. The SPI was obtained from a photoplethysmographic pulse oximetry finger sensor. The Noxious Stimulus Response Index (NSRI) was calculated by the SmartPilot View software and displayed on the Zeus anesthesia workstation (Dräger, Lübeck, Germany).

After preoxygenation (8L/min100% O_2 by face mask), anesthesia was induced with propofol (2-3 mg/kg IV) and remifentanil (target controlled infusion (TCI), 3 ng/mL effect site concentration (C_e), Minto model). After tracheal intubation (facilitated with rocuronium, 1 mg/kg IV), anesthesia was maintained with desflurane in 40% O_2/air and remifentanil using a Zeus anesthesia workstation. Prior to the start of the study, desflurane and remifentanil dosing were left at the discretion of the attending anesthesiologist. Ventilation was adjusted to maintain the end-expired CO_2 fraction ($FETCO_2$) between 4.5 and 5%, and PEEP was titrated to individual patient's needs. Additional rocuronium was administered to keep the train-of-four count at zero.

The study started after the patient had been installed in the Trendelenburg position with a capnopneumoperitoneum applied and surgical conditions were stable. During the study period, each patient received a remifentanil infusion with a C_e of 1, 3, and 5 ng/mL for 20 min, the sequence of which was randomized by closed envelope. Prior to the start of data collection during each 20 min time interval, the end-expired desflurane concentration (FETdes) was adjusted to keep the NSRI stable at 5. During each period the following data were collected: NSRI, NOL Index, SPI, qNOX, and FETdes. If atropine, ephedrine or phenylephrine had to be administered (left at the discretion of the attending anesthesiologist), data collection was stopped.

Data were downloaded every 5 sec into a PC and converted into Excel files using RUGloop® (Demed, Temse, Belgium). For each parameter, data were organized per 20 min interval, and the prediction probability (PK) calculated for the NOL Index, qNOX and SPI for C_e remifentanil[11]. A PK value of 1.0 means an exact prediction on every occasion, while a PK of 0.5 is no better than a 50:50 chance of being correct.

Results

Patient age, height, and weight were 63 ± 7 years, 178 ± 6 cm, 87 ± 12 kg (mean ± standard deviation), respectively. None of the patients received atropine, ephedrine or phenylephrine. Surgery was finished before the last data collection period in 5 patients with a remifentanil C_e = 5 ng/mL and in 1 patient with a remifentanil C_e = 1 ng/mL. All other data have been included in the data analysis. Data collection was only started after stabilization of FETdes, C_e Remi and NSRI, which typically took several minutes.

Raw data (FETdes, NOL index, qNOX, and SPI) are presented in Figure 1. The prediction probability (PK) calculated for NOL Index, qNOX and SPI for C_e remifentanil were 0.519, 0.470, and 0.477, respectively (Figure 2); by design there was an inverse relationship between C_e remifentanil and FETdes.

Discussion

The results confirmed our hypothesis: when the NSRI is maintained at a low constant value with a range of combinations of opioids and inhaled agent, the NOL index, qNOX and SPI are not predictive of the opioid concentration present.

These results can be explained by considering the hypnotic and opioid effect site concentration pairs that ensure the same probability of absence of sympathetic response to stimuli of varying intensity, so called isoboles[12]. Katoh determined the isoboles describing the 50 and 90 % probabilities of no sympathetic response to a noxious stimulus with different combinations of sevoflurane and fentanyl. A wide range of hypnotic-opioid pairs can result in the same degree of suppression of the sympathetic response – for example the combination of 3 % FET sevoflurane and 1 ng/mL Ce fentanyl and the combination of ~0.8% s FET sevoflurane and 5 ng/mL Ce fentanyl are points on the same isobole and result in an equal 90% probability of sympathetic response suppression. Because nociception monitors measure the degree of the sympathetic nervous system suppression, it can be expected that they display the same response with either 3% s FET sevoflurane and 1 ng/mL C_e fentanyl or ~ 0.8% sevoflurane FET and 5 ng/mL C_e fentanyl.

Based on those findings, in our current study, nociception monitors cannot be expected to differentiate the C_e of remifentanil of the different desflurane/remifentanil drug. Nociception monitors

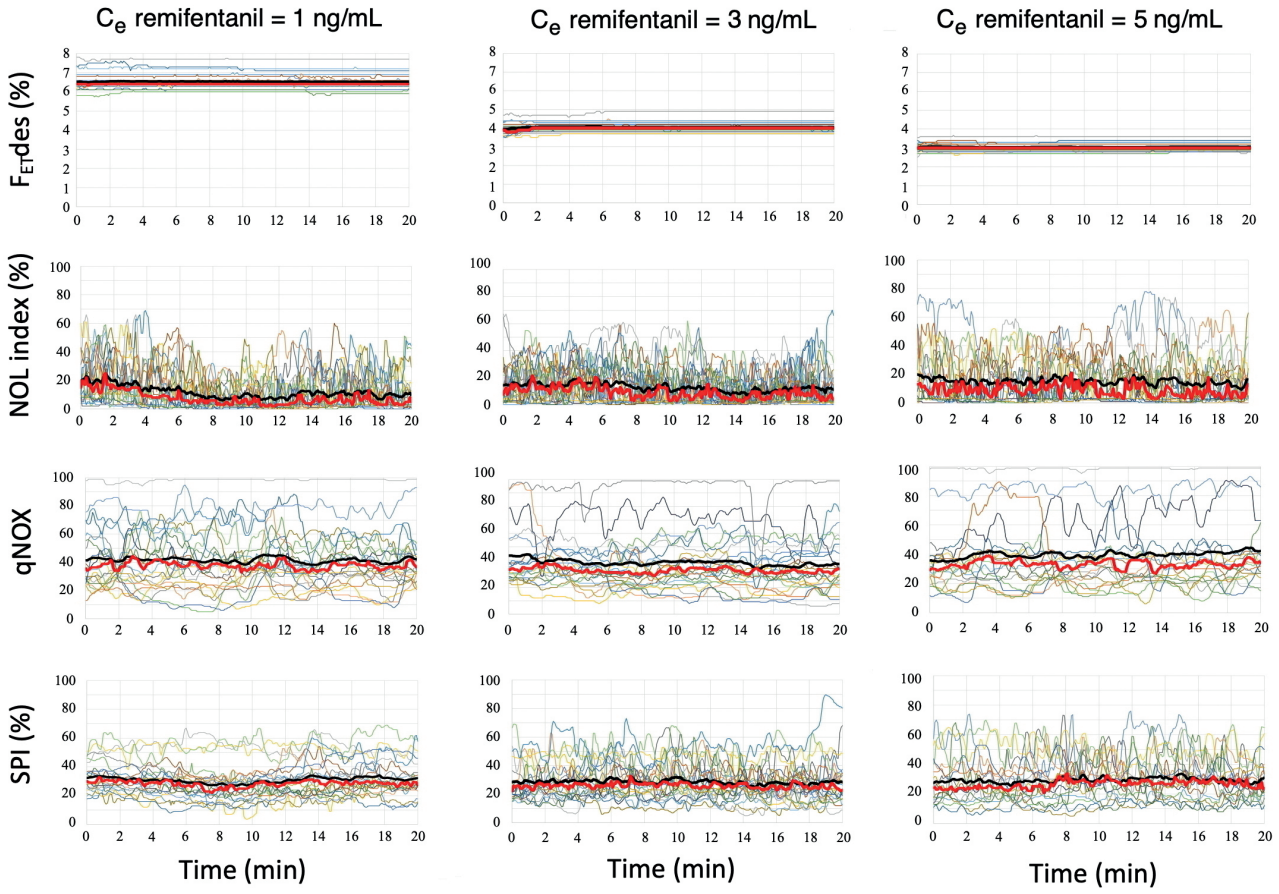

Fig. 1 — Nociception parameters and end-expired desflurane concentration.
Course of end-expired desflurane concentration (%), NOL index, qNOX, and SPI (top to bottom) over 20 min periods with three different effect site concentrations of remifentanil (1, 3, and 5 ng/mL from left to right).

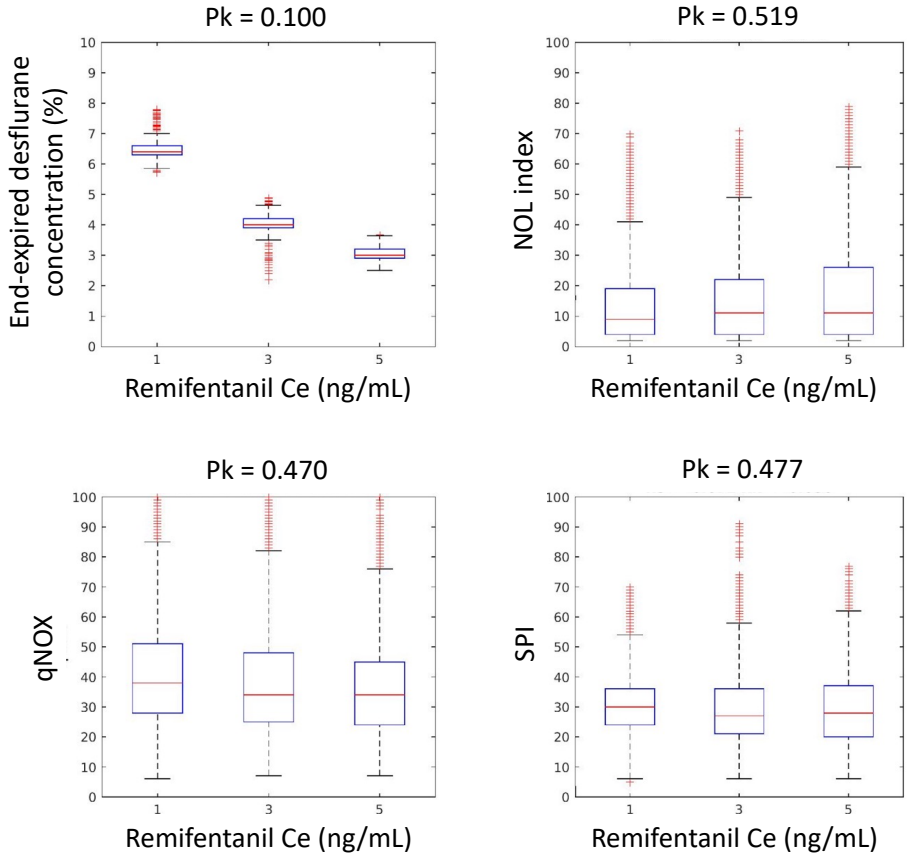

Fig. 2 — Prediction probabilities
SPI = Surgical Pleth Index; NOL index = Nociception Level index. See text for details.

can therefore only be expected to be useful to titrate opioids if the hypnotic concentration is sufficiently low to allow "a window" for the nociception monitor to detect and measure autonomic system responses, which becomes less and less possible as the concentration of the hypnotic in the hypnotic/opioid mixture increases. But in the 3 and 5 ng/mL C_e remifentanil groups in the current study the FETdes was well below 1 age adjusted MAC for the study population, a hypnotic concentration some clinicians might not consider to be high enough to ensure unconsciousness. However, the Katoh drug interaction studies should be very reassuring: at 0.5 MAC and Ce remifentanil of 5 ng/mL the incidence of intraoperative awareness is exceedingly low. Determining for which hypnotic-opioids ratios nociception monitors might prove useful to titrate the opioids requires further work. Future studies could reveal a possible (or absent) relationship between a predicted NSRI and a measured value of nociception. Our work solves one piece of this puzzle: at an NSRI of 5, all desflurane/remifentanil drug pairs that were used in this study suppress sympathetic response to the extent that nociception monitoring becomes useless for opioid titration. This was not entirely expected because the NSRI is a parameter based on movement during laryngoscopy[10], not on sympathetic nervous responses. The current study results therefore suggests that over the range of hypnotic/opioid drug pairs used to maintain NSRI at 5 with the stimulus intensity provided by intra-abdominal dissection during robotic assisted radical prostatectomy sympathetic response suppression is pronounced.

The importance of considering the hypnotic/opioid ratio of a mixture when interpreting monitoring parameters has also been noticed with BIS monitoring 1. Remifentanil has a mild additive effect on the hypnotic effect of sevoflurane (and therefore also the mild effect on BIS), but there is a synergistic or potentiating effect on the effect of sevoflurane for movement and ANS response 1. Therefore targeting a BIS less than 60 may result in an unnecessarily deep anesthetic state during "opioid-heavy" sevoflurane-remifentanil anesthetics. The opposite is true also: the BIS can be 65 or higher yet suppression of movement and autonomic nervous system to noxious stimulation may be adequate in the presence of 1% FET sevoflurane and 5 ng/mL C_e remifentanil.

The study limited itself to examining the value of nociception/antinociception monitors for a specific drug combination relative to the NSRI. In addition, it was tested in one specific patient population undergoing a specific procedure,

therefor more widely applicable conclusions remain limited. The study only addresses a limited aspect of nociception/antinociception monitors: the lack of detection of nociception at low NSRI of the NOL/SPI/qNOX and other monitors confirms the NSRI's capacity to predict intense sympathetic nervous system inhibition.

We conclude that nociception monitoring is useless to titrate opioids when the concomitantly administered hypnotic is adjusted to maintain a low NSRI, presumably because suppression of movement to laryngoscopy also ensures suppression of the sympathetic nervous system response to the noxious stimulus present during intrabdominal resection of the prostate. Both the hypnotic/opioid ratio and stimulus intensity of the stimulus/response pair need to be considered when attempting to use nociception to guide opioid administration.

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Ethics approval: This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of the OLV hospital, Aalst, Belgium (study number 2019/016, B126201938844, approved 14/11/2019).

Consent to participate: written informed consent was obtained from all patient

Consent to publish: written informed consent obtained from all patient also included consent to publish

References

1. Manyam SC , Gupta DK, Johnson KB , White JL, Nathan LP, Westenskow DR, Egan TD. When is a bispectral index of 60 too low?: Rational processed electroencephalographic targets are dependent on the sedative-opioid ratio. Anesthesiology 2007; 106:472-83. https://doi.org/10.1097/00000542-200703000-00011
2. Katoh T , Kobayashi S, Suzuki A, Iwamoto T, Bito H, Ikeda K. The effect of fentanyl on sevoflurane requirements for somatic and sympathetic responses to surgical incision. Anesthesiology 1999; 90:398-405. https://doi.org/10.1097/00000542-199902000-00012
3. Edry R, Recea V, Dikust Y, Sessler DI. Preliminary Intraoperative Validation of the Nociception Level Index: A Noninvasive Nociception Monitor. Anesthesiology 2016; 125:193-203. https://doi.org/10.1097/ALN.0000000000001130
4. Stökle PA, Julien M, Issa R, Décary E, Brulotte V, Drolet P, Henri M, Poirier M, Latulippe JF, Dorais M, Verdonck O, Fortier LP, Richebé P. Validation of the PMD100 and its NOL Index to detect nociception at different infusion regimen of remifentanil in patients under general anesthesia. Minerva Anestesiol 2018; 84:1160-1168. https://doi.org/10.23736/S0375-9393.18.12720-9
5. Martini C, Boon M, Broens, S, Hekkelman E, Oudhoff L, Buddeke A, Dahan A. Ability of the nociception level, a multiparameter composite of autonomic signals, to detect noxious stimuli during propofol-remifentanil anesthesia. Anesthesiology 2015; 123:524-534.https://doi.org/10.1097/ALN.0000000000000757
6. Renaud-Roy E, Stöckle PA, Maximos S, Brulotte V, Sideris L, Dubé P, Drolet P, Tanoubi I, Issa R, Vedonck O, Fortier P, Richebé P.Correlation between incremental remifentanil doses and the Nociception Level (NOL) index response after intraoperative noxious stimuli. Can J Anesth 2019; 66:1049-1061.https://doi.org/10.1007/s12630-019-01372-1
7. Jensen E, Valencia J, Lopez A, Anglada T, Agusti M, Ramos Y, Serra R, Jospin M, Pineda P, Gambus P. Monitoring hypnotic effect and nociception with two EEG-derived indices, qCON and qNOX, during general anaesthesia. Acta Anaesthesiol Scand 2014; 58: 933-941.https://doi.org/10.1111/aas.12359
8. Young W, Byung L, Young K, Mido L, Heezoo K. Usefulness of surgical pleth index-guided analgesia during general anesthesia: a systematic review and meta-analysis of randomized controlled trials. J Int Med Res 2018; 46: 4386-4398. https://doi.org/ 10.1177/0300060518796749
9. Luginbühl M, Schumacher PM, Vuilleumier P, Vereecke H, Heyse B, Bouillon TW, Struys MM. Noxious stimulation response index: a novel anesthetic state index based on hypnotic-opioid interaction. Anesthesiology 2021; 112:872-80.https://doi.org/10.1097/ALN.0b013e3181d40368
10. Hannivoort LN, Vereecke HE, Proost JH, Heyse BE, Eleveld DJ, Bouillon TW, Struys MM, Luginbühl M. Probability to tolerate laryngoscopy and noxious stimulation response index as general indicators of the anaesthetic potency of sevoflurane, propofol, and remifentanil. Br J Anaesth 2016; 116:624-31. https://doi.org/10.1093/bja/aew060
11. Jordan D, Steiner M, Kochs EF, Schneider G. A program for computing the prediction probability and the related receiver operating characteristic graph. Anesth Analg 2021; 111:1416-21.https://doi.org/10.1213/ANE.0b013e3181fb919e
12. Katoh T, Kobayashi S, Suzuki A, Iwamoto T, Bito H, Ikeda K. The Effect of Fentanyl on Sevoflurane Requirements for Somatic and Sympathetic Responses to Surgical Incision. Anesthesiology 1999; 90:398-405.doi: 10.1097/00000542-199902000-00012

doi.org/10.56126/73.S1.32