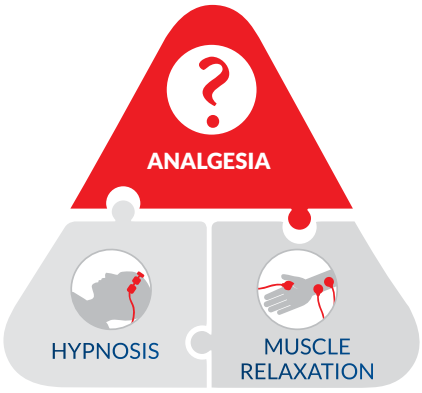
Introducing the NOL® (Nociception Level) Index Algorithm

A Technical Overview

Background

The role of anaesthesia is to provide optimal conditions during surgery to treat patients, whilst ensuring patient safety and comfort. The components required to achieve this goal when using general anaesthesia are hypnosis, analgesia, amnesia, and when indicated, muscle relaxation. There are non-invasive monitors that help anaesthesia providers gauge the adequacy of hypnosis, amnesia, and muscle relaxation. The last remaining component of anaesthesia that has no objective, non-invasive monitor available to anaesthesia providers, is analgesia.

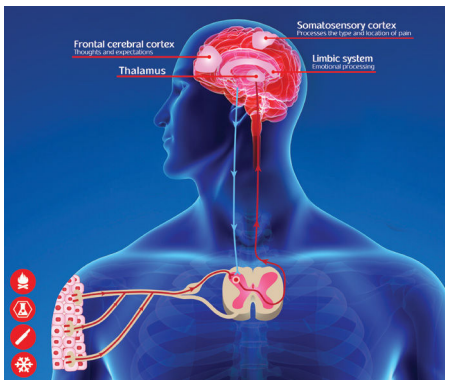


Analgesia is loss of sensation of pain that results from an interruption in the nervous system pathway between sense organ and brain.

Nociception Vs. Pain

The term pain is by definition reserved for a conscious perception of actual or potential tissue damage and cannot be used during an unconscious state of general anaesthesia. Therefore, the term nociception was introduced and describes the neural process of encoding noxious stimuli. Nociception refers to the peripheral (PNS) and central nervous system (CNS) processing of information about the internal or external environment, as generated by activation of nociceptors. Typically, noxious stimuli, including tissue damage, activate nociceptors that are present in peripheral structures and transmit information to the spinal cord dorsal horn. From there, the information continues to the brainstem (nucleus caudalis) and ultimately the thalamus and the somatosensory cortex, where the perception of pain is generated.

Pain is a product of higher brain center processing, whereas nociception can occur in the absence of pain.

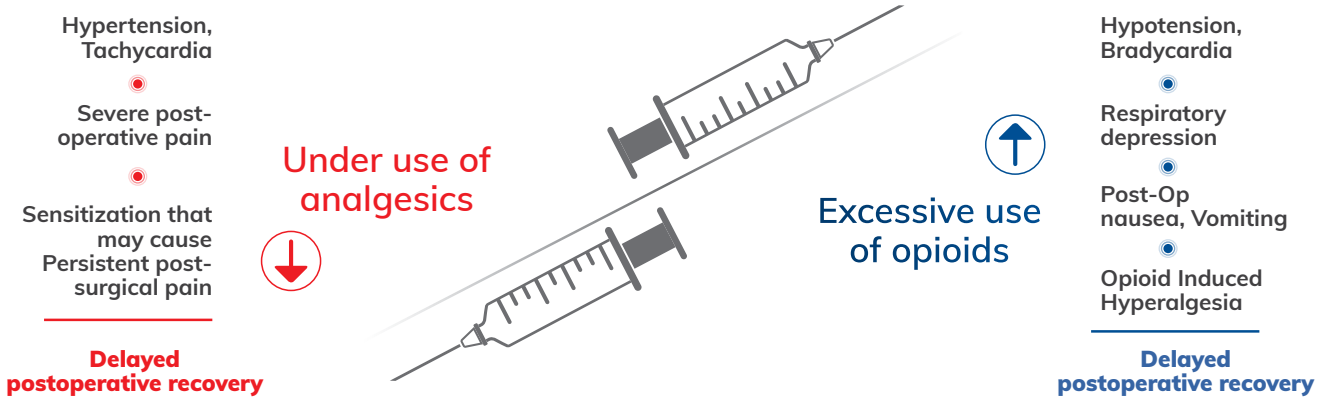


The importance of nociception monitoring

The adequacy of the level of analgesia in an anaesthetized patient is currently assessed using surrogate measures, such as heart rate, blood pressure, tearing, pupillary response, and sweating. These surrogate measures are influenced by factors not related to pain, such as hypoxia, hypercarbia, hyperthermia, and medications. As a result, treatment of analgesia is highly subjective and variable between providers as they interpret these surrogate measures as a sign of insufficient or excessive analgesia. This is reflected in wide ranges of dosing of opioids, the primary drugs used to treat moderate to severe surgical pain during the operation. **Excessive or insufficient doses of opioids carry negative consequences to the patient in terms of symptoms and outcomes.[1]**

The characteristics of individual patients, specific procedures, and various analgesia regimens make the titration of analgesics an even more challenging issue. Any over- or underdosage during anaesthesia carries additional risks.[1]

Underdosage of opioids during anaesthesia may result in sympathetic activation with tachycardia and hypertension or additional neuroendocrine activation with potential effects on acute or chronic postoperative pain,[2,3] and in extreme cases even arousal and initiation of awareness. **Opioid overdose** may cause intraoperative cardiovascular depression, intraoperative hypotension, prolonged time of emergence and, postoperatively, respiratory depression,[4] nausea and vomiting,[5] cognitive disturbances, increased postoperative pain[6] (hyperalgesia), and constipation.



Anaesthesia practice is evolving to address the need for better nociception management, with efforts to spare and/or substitute opioids, as well as using multimodal analgesia regimens. This underscores the need for a reliable and accurate way to assess the nociceptive/non-nociceptive state of the patient, as a basis for optimizing intraoperative analgesia according to each patient's particular sensitivity and needs.

Setting criteria for the perfect nociception monitor

Developing an objective method of nociception assessment requires creating tools that are sensitive and specific to the physiological response to noxious stimuli. They need to be observer-independent, and not reliant on the patient's ability to communicate.

Although there is no direct tool to assess the level of nociception, there is adequate evidence in the scientific literature that the following nociception characteristics are valid and accepted[7]:

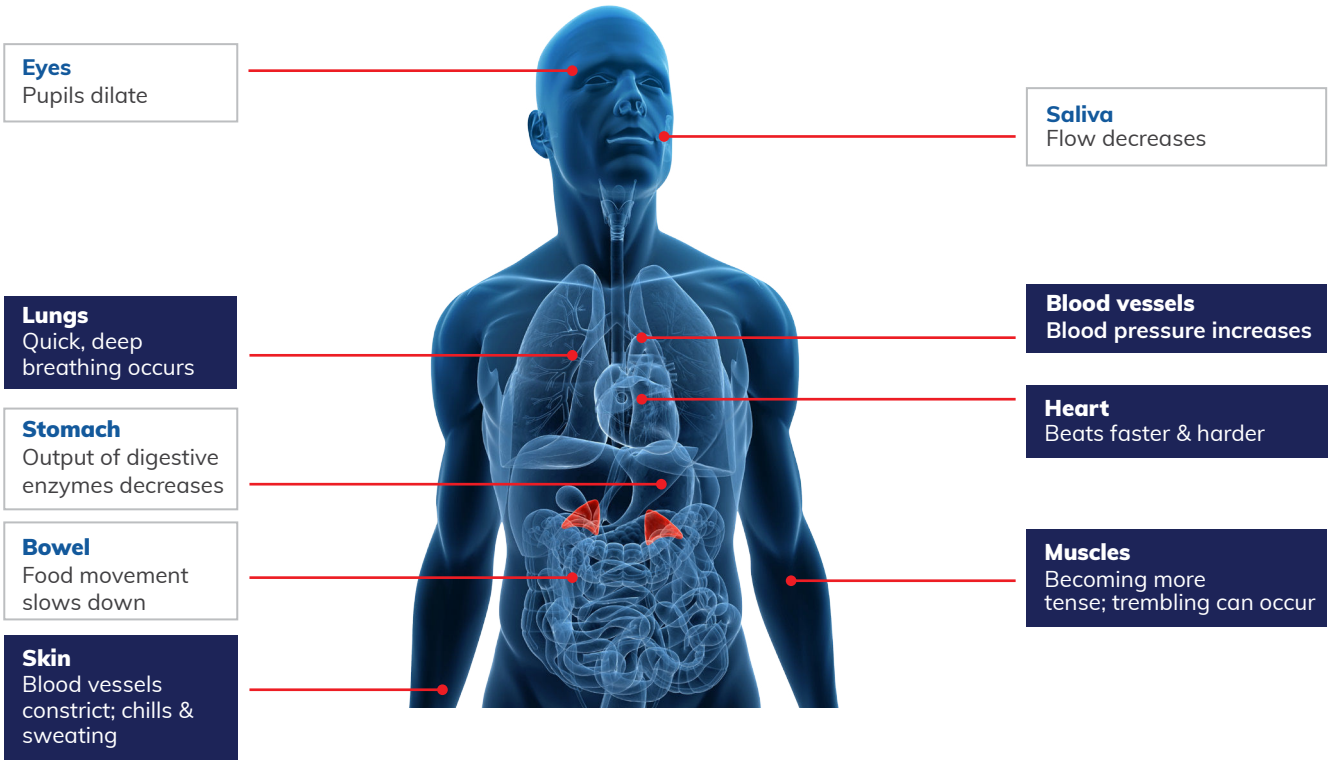
1. The activation of nociceptors increases with increasing levels of noxious stimuli.
2. Analgesia blocks/inhibits the secretion of neurotransmitters after the activation of nociceptors, thereby preventing/attenuating the pain/nociception level.
3. Maintaining the same noxious stimulus while increasing the level of analgesics should result in a decreased level of nociception (and vice versa if decreasing the level of analgesics).

The complexity of the sympathetic nervous system (SNS) response

Activation of the sympathetic nervous system, as a result of multiple stimuli and inputs, leads to a wide range of nociception-related physiological responses.

Different physiological parameters, representing different systems, may exhibit complex inter-associations and variable response profiles. Consequently, the appreciation of intraoperative nociception should integrate multiple physiological parameters in order to reflect the complex nature of pain.[8]

Recognizing the complex nature of this process, the Nociception Level (NOL®) index was developed as a multiparameter composite of autonomic signals, reflecting the integrated physiological response to noxious stimuli.



The proprietary PMD-200™ system and the NOL® index*

The PMD-200 is a physiological monitor that helps to reduce excessive or insufficient analgesia dosing by providing a numeric scale of nociceptive response levels, called NOL – the nociception level index. During surgical stimulation under general anaesthesia, NOL of zero indicates no nociceptive response, and NOL of 100 indicates extreme nociceptive response.

The NOL technology focuses on the integrated physiological response to noxious stimuli, rather than a single indicator or individual pain pathway.

System components

The PMD-200 system consists of a monitoring unit, a reusable non-invasive finger probe and a single-use sensor.

The proprietary signal acquisition sensor platform (the combination of the finger probe and the single-use sensor) acquires physiological signals. Using advanced algorithms, the system processes and analyses multiple nociception-related physiological parameters and their various derivatives, which correspond with the SNS's response to noxious stimuli.

The finger probe and single-use sensor continuously acquire physiological signals through the following four sensors:

1. Photoplethysmograph (PPG)
2. Galvanic Skin Response (GSR)
3. Peripheral Temperature (Temp)
4. Accelerometer (ACC)

From these four signals the NOL algorithm extracts and analyses nociception-related physiological parameters and derivatives: pulse rate, pulse rate variability, pulse wave amplitude, skin conductance level, skin conductance fluctuations, skin temperature, movement, and their various derivatives. Then a patient's personalized nociception signature is established and continuously monitored.

Simplified illustration

* U.S. patent 9,498,138, U.S. patent 8,512,240

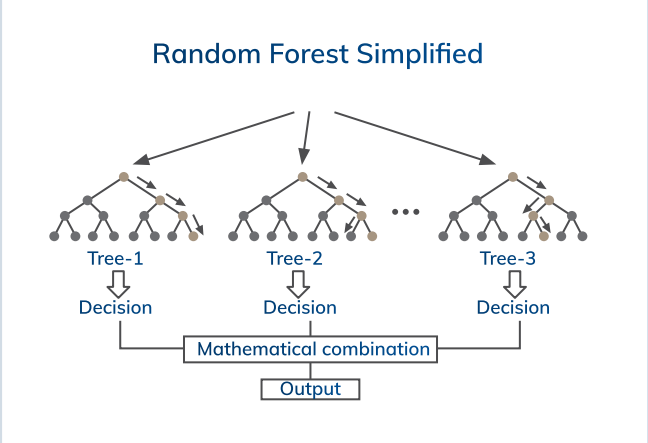
NOL algorithm development phase

The NOL algorithm was developed using a random forest machine-learning model approach.

Random forest, introduced by Breiman in 2001, is a powerful method that makes a prediction by aggregating results from an ensemble of randomized regression trees.

The NOL algorithm was trained on tens of thousands of data points to characterize nociception patterns in terms of physiological response, interactions and correlations between different variables, including multiple mathematical derivatives and various time derivatives of the parameters.

A training database comprising multiple examples of input and output pairs was constructed. The NOL algorithm input values were based on a set of features associated with a noxious response and its output values were based on a reference clinical score of nociception. This clinical score, named the Combined Index of Stimulus and Analgesia (CISA), is a combination of the estimated stimulus level during surgery and the effect of the analgesic drugs.



$$CISA = Stim_{intensity} - ß \cdot ce_{opioids} + Y$$

The stimulus intensity level ($Stim_{intensity}$) was defined as a discrete ordinal number between 0 and 10 that represented the intensity of the surgical event. The effect of analgesic drugs ($- ß \cdot ce_{opioids}$) was defined according to the site concentration of opioids ($c_{eopioids}$) scaled by a normalization factor (ß=0.125). The effect of the site concentration of opioids ($ce_{opioids}$) was calculated as the sum of the effect of site concentration of remifentanil and fentanyl, which were continuously calculated based on annotated infusion rates, boluses, and the pharmacokinetics models of Minto et. al. and Schafer et al. An offset Y of 1.5 was added to ensure that CISA is always positive. The level of analgesia and the type of stimuli were continuously annotated during surgeries and processed following the surgeries to compute the CISA score.

The resulting model captures the pattern that best describes the response of all parameters and derivatives to the different CISA levels.

The NOL index is based on random forest regression fitted to estimate CISA. The regression used the extracted parameters as predictor variables and the CISA score as the observed variable for the regression model.

The resulting NOL algorithm is loaded in the monitor and is not further refined or “taught” during the clinical use of the monitor.

NOL in clinical practice

As detailed above, the NOL index is a multiparameter-based, nonlinear combination of physiological signals and their derivatives, resulting from random forest regression.

During monitoring, the algorithm draws on hundreds of decision trees, each of which is based on large numbers of variables. Each of the decision trees is constantly "polled" by the algorithm and a mathematical combination of the output of all the decision trees delivers a value that is then processed and displayed as the NOL index on a scale of 0-100. During surgical stimulation under general anaesthesia, zero represents the absence of nociceptive response and 100 represents extreme nociceptive response.

NOL is a continuous, relative, personalized measure of nociception. The numerical integer is normalized to the patient's baseline at rest (in the absence of noxious stimuli). The initial NOL values for any given patient are calculated based on comparison to a preloaded population database; while monitoring, a personalized baseline is derived from the patient's own accumulating data and the NOL is continuously calculated.

By following the personalized NOL trend, the clinician holds a powerful tool to assess changes in the patient's nociception state over time.

The design, verification and validation of the NOL algorithm has been further described in a peer-reviewed publication.[9]

Clinical validation

Following the development of the NOL index, validation studies were performed to assess its ability to respond to noxious stimuli and to changes in analgesics dosage.

The results from Martini et al.,[10] Stöckle et al.,[11] and Edry et al.[12] validation trials, demonstrate NOL's performance in the intraoperative care setting during general anaesthesia, using various regimens, e.g., volatile anaesthesia, TIVA, regional anaesthesia etc.

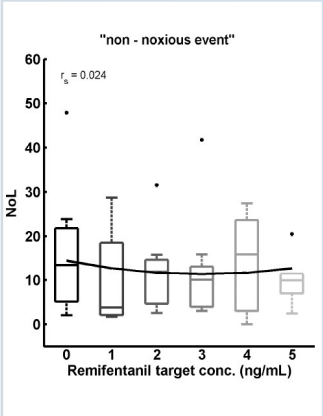
The NOL index reliably measures the changes in the nociceptive response at different remifentanil concentrations (inter-patients)[10]

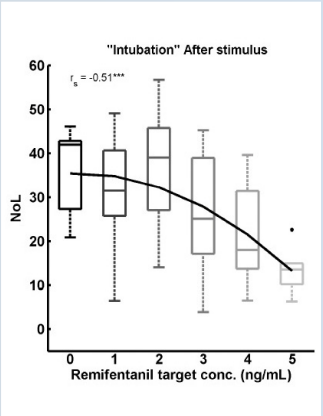
N=71; ASA I – III; Ages 18-80; BIS target 45+/-5 ; Elective surgery under general anaesthesia

NOL demonstrated clinically relevant correlation with the analgesic state of the subject.

The NOL index remains unaffected under non-noxious conditions, regardless of remifentanil concentration, and decreases for the same noxious stimulus with increasing remifentanil concentrations.

This analysis indicates that the NOL is a reliable measure of nociception and is not affected by the hemodynamic effects of remifentanil.



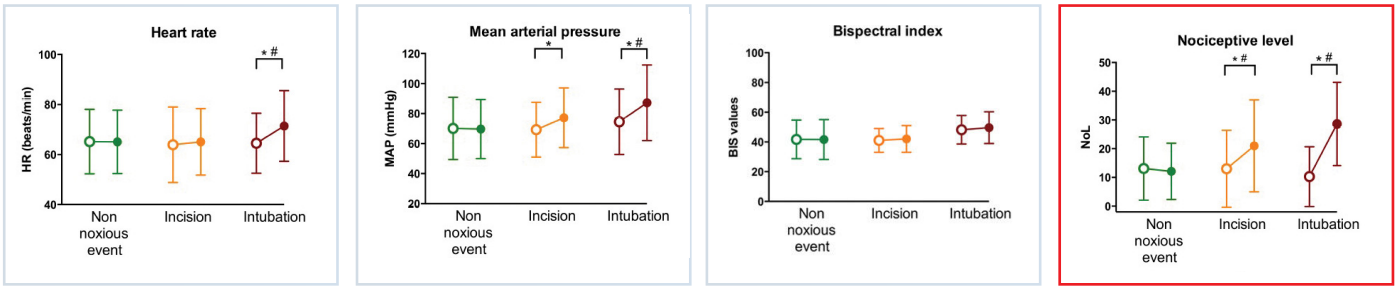


Superiority of the NOL index in detecting and distinguishing between various noxious stimuli, compared to commonly used parameters[10]

N=71; ASA I – III; Ages 18-80; BIS target 45+/-5 ; Elective surgery under general anaesthesia

In the analysis testing the response of NOL, BIS, HR and MAP to different noxious stimuli and non-noxious periods, NOL demonstrated clinically relevant grading of noxious stimuli as expected by the intensity of a stimulus, significantly changing after intubation and incision, while showing no significant change during the non-noxious period.

NOL correctly graded the level of nociceptive reaction:
non-noxious stimulus NOL < incision NOL < intubation NOL ($p < 0.05$).



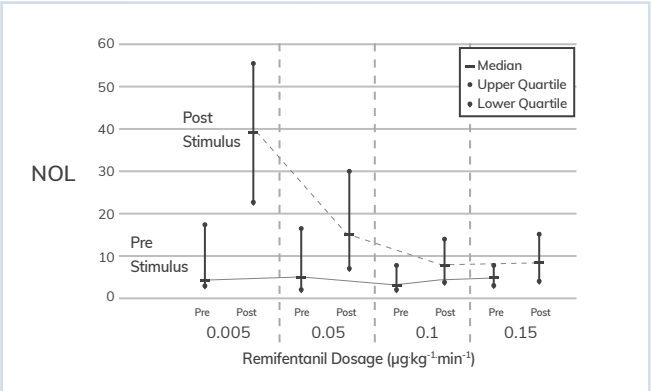
○ Prior to stimulation ● Following stimulation # Unpaired * Paired

The NOL index correlates with increased dosage of analgesics (intra-patient)[11]

N=40; ASA I – III; Age >18; Elective abdominal surgery under general anaesthesia and epidural analgesia

Standardized painful stimuli were applied to patients under general anaesthesia, while each patient received infusion of various doses of remifentanil.

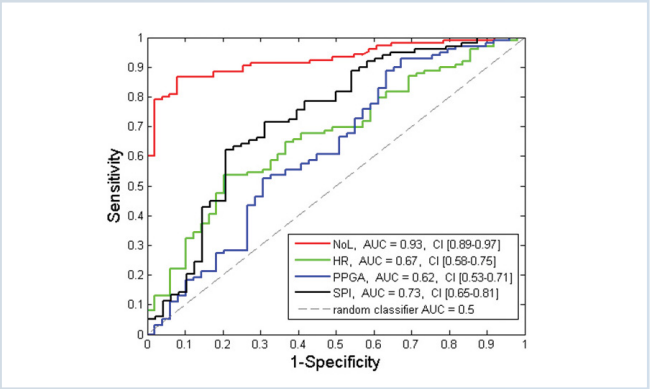
The magnitude of the NOL index response to standardized nociceptive stimulus decreases with higher doses of remifentanil.



The NOL index outperforms commonly used parameters (HR, PPGA) and SPI (GE)[12]

N=58; ASA I – III; Ages 18-75; Entropy target <60 ; Elective surgery under general anaesthesia

In the analysis testing the ability of NOL vs. other parameters and indices to discriminate between noxious stimuli (incision & intubation) and non-noxious periods, NOL reached an AUC of 0.93, outperforming all the other parameters.



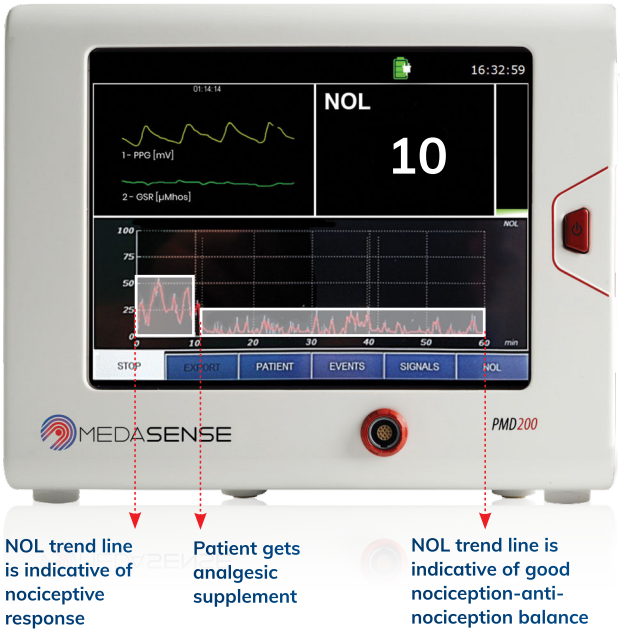
The multiparameter NOL index demonstrated high levels of sensitivity and specificity outperforming single parameters in routine use for nociception assessment in the operating room

Clinical implementation

Latest clinical evidence[13,14] from surgery under general anaesthesia, indicates that maintaining a NOL < 25 during surgical stimulation suggests sufficient analgesia and a good nociception-antinociception (NAN) balance.

A NOL trend line variation > 25, for 1-2 minutes (not as response to sympathomimetic drugs), suggests a high nociceptive response. Supplemental analgesics can be considered.

When using IV analgesia (not combined with regional analgesia/blocks), NOL < 10 under surgical stimulation, for 1-2 minutes, may indicate excessive analgesia.



Patients experience less postoperative pain when intraoperative opioid dosing is guided by NOL monitoring[14]

- Two-center randomized controlled trial, NOL-guided (NOL target range: below 25) vs standard of care (HR/BP)
- Elective abdominal surgery under general fentanyl/sevoflurane anaesthesia, N=50 (25+25)
- Primary end point: **Postoperative pain** score in the postanaesthesia care unit (PACU)

Results:

Postoperative pain scores were significantly improved by 33% in NOL-guided patients (NRS score of 3.2 vs 4.8 in the control group (Figure 1)) *without an increase* in intraoperative fentanyl dosing. This indicates that the reduction in pain score is due to the correct **timing** of medication. There was higher variability of fentanyl administration in the NOL-guided group demonstrating individualized titration. In the NOL-guided group, a larger proportion of patients were NRS < 4, thus did not require rescue opioids in the PACU vs. the standard of care group.

In addition, patients' stress hormone levels, ACTH and cortisol (% of baseline), were up to 50% lower in the NOL-guided group, both during and after surgery, supporting the lower pain scores reported by patients (Figure 2).

This study provides evidence that titrating analgesia using NOL during surgery improves postoperative pain outcomes.

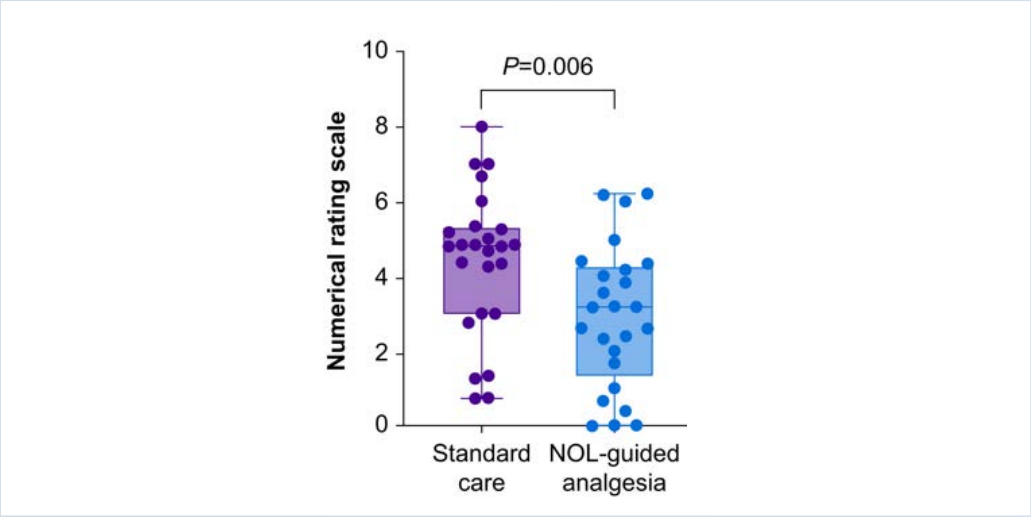


Figure 1: Box plots of the median pain scores observed per subject in the PACU. Each symbol reflects the individual median pain scores during the subject stay in the PACU.

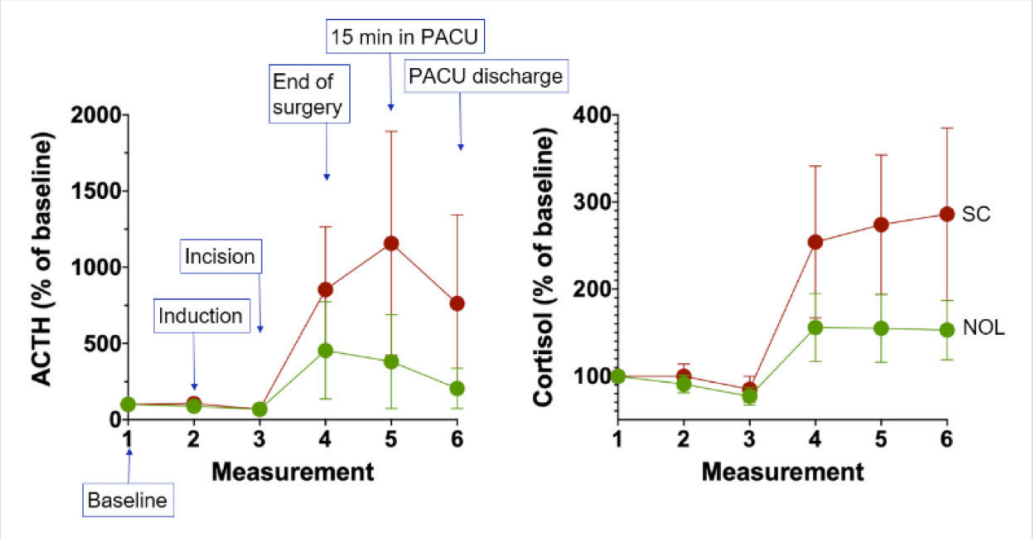
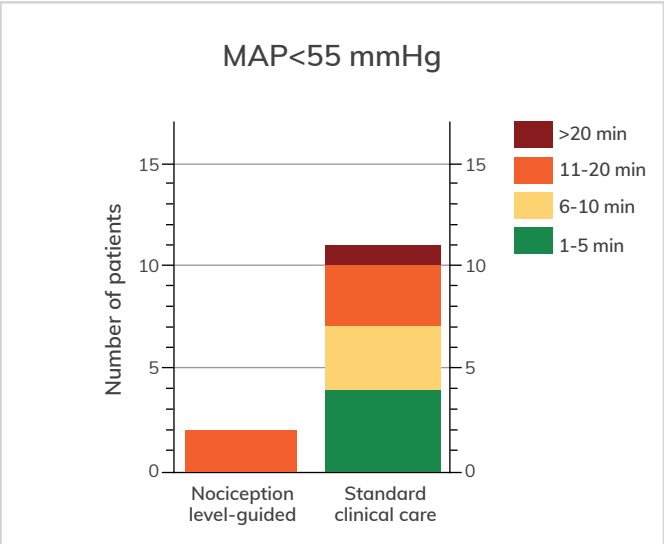


Figure 2: ACTH and cortisol concentrations from induction on until discharge from the PACU

NOL-guided opioid administration reduces opioid consumption and improves hemodynamic stability in patients undergoing major surgery[13]

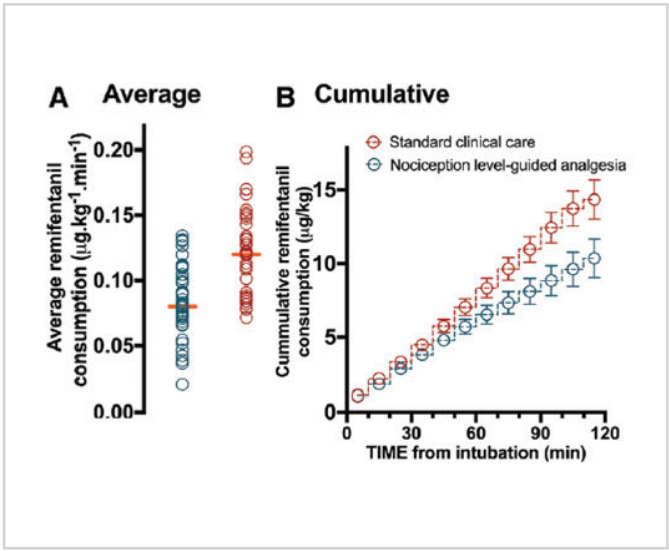
N=80 (40 in each group); ASA I – III; Ages 18-80; major abdominal surgery, urologic or gynecologic procedures under general anaesthesia without epidural analgesia[7]

A study evaluating the influence of nociception-guided analgesia using the NOL monitor, found that compared to standard clinical care, NOL guidance resulted in 30% less remifentanil use during anaesthesia and an 80% reduction of hypotensive events during surgery.



Number of patients and duration of hypotensive events in standard clinical practice and nociception level–guided patients with a mean arterial pressure (MAP) cutoff of 55 mm Hg (P = 0.006).

NOL-guided opioid administration resulted in 80% fewer hypotensive events (5% vs 28%).



(A) Individual remifentanil doses (in µg · kg-1 · min-1) and mean values in the two treatment groups (P < 0.001).

(B) Cumulative remifentanil consumption (µg/kg) during the first 2 h of anaesthesia.

NOL-guided opioid administration resulted in 30% reduction in intraoperative opioids administration.

A growing body of evidence indicates that intraoperative hypotension (sustained MAP < 55 mmHg) increases the risk of myocardial injury, acute kidney injury and mortality.[15]

The study demonstrates the potential of NOL monitoring to reduce the probability of postoperative complications.

By reducing these complications, NOL monitoring can also contribute to cost avoidance for the hospital, with potential ROI achieved in under one year.[16]

Future directions

The clinical utility of NOL in various settings, is continuously evaluated in multiple clinical studies around the world. Medasense anticipates further development and implementation of validated solutions for measuring nociception and pain in both communicating and non-communicating patients to improve patient outcomes throughout the continuum of care.

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