Monitoring Nociception using NOL® Technology during Anesthesia

A Pocket-Guide for Clinicians

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Learning Objectives

After reading this guide, the anesthesia provider will be able to:

- Describe nociception and the nociception /anti-nociception (NAN) balance during general anesthesia.
- Describe the interactions between hypnotics and analgesic drugs (mainly but not exclusively opioids) in the presence and absence of nociceptive stimulation.
- Describe the NOL monitor algorithm and technology platform.
- Describe the limitations of the NOL technology.
- Integrate NOL-monitoring information into clinical decision-making during induction, maintenance and emergence
- Recommend a role for NOL monitoring in clinical practice.

The content presented in this pocket guide is based on clinical studies, evaluations and practical experience in the implementation of the NOL technology in multiple clinical settings in Europe, Canada and Israel. The NOL tracings depicted in this guide represent actual clinical cases.

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To ensure proper use, handling and care of the patient monitors with NOL technology, the clinician should consult the product specific literature, instruction manual, and/or labeling included with the product or otherwise available including the indications for use currently provided by the manufacturer. Care has been taken to ensure the accuracy of the information in this guide, however, no guarantee is given to the correctness or accuracy of the contents. Neither the publisher, author, nor Medasense Biometrics Ltd. assumes any responsibility, including without limitation, for any injury and or damage to persons or property resulting from information provided in this guide or reliance thereon.

The PMD-200 monitor is commercially available in the United Sates, Europe, Canada, Brazil, South Africa, United Arab Emirates and Israel.

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1. Components of General Anesthesia

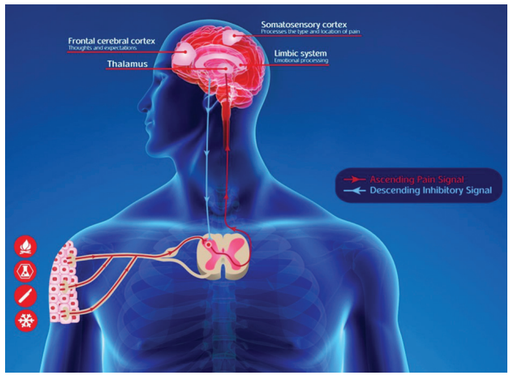
Balanced anesthesia combines drugs to minimize the side effects of individual anesthetic drugs: Operationally, (a) hypnosis is evoked by hypnotics/ anesthetics (midazolam, propofol, halogenated agents, ketamine etc.); (b) anti-nociception is induced by analgesics (opioids, non-opioids, regional analgesics, opioid-free techniques), and (c) muscle relaxation is induced by neuromuscular blockers.

2. Defining the Problem – "Pain" During General Anesthesia

Pain is a descriptor of a conscious, emotional, subjective experience generated by a wide variety of events. Tissue damage-associated acute pain consists of both physiological and psychological elements. During general anesthesia, the conscious experience of pain is blocked. Hence, in an anesthetized patient, it is not appropriate to call the physiological reaction to tissue aggression by surgery 'pain' (Yaksh TL. 1998).

Instead, a surgical stimulus, with its immediate consequences on system function and without the higher order processing that is defined as consciousness, is referred to as 'nociception'. This term covers the integrated response caused by tissue damage, from the peripheral sensory afferent pathway to the brainstem and cortical levels, where nociception may manifest as cardiovascular, hormonal and neurological changes (Eric L. Garland. 2012).

Perioperative nociception management refers to actions prior (preemptive), at the beginning (induction), during surgery (maintenance), and post-surgical procedure that attenuate or eliminate the nociceptive response to expected surgical nociceptive stimuli.



A surgical stimulus, with its immediate consequences on system function and without the higher order processing that is defined as consciousness, is referred to as 'nociception'.

3. Perioperative Nociception Monitoring: Why is it Needed?

The role of anesthesia is to provide optimal conditions for surgeons/interventionists to treat patients whilst ensuring patient safety and comfort. The components required to achieve this goal when using general anesthesia are hypnosis, "analgesia" (best termed anti-nociception during general anesthesia, see below) and when indicated, muscle relaxation. Non-invasive monitors that help anesthesia providers gauge the adequacy of hypnosis and muscle relaxation are commercially available.

The adequacy of the level of anti-nociception provided preemptively or in response to a nociceptive stimulus in an anesthetized patient is currently assessed using surrogate measures, such as heart rate (HR), increased mean arterial pressure (MAP), tearing, and sweating. These surrogate measures are influenced by other factors not related to nociception, such as hyper or hypovolemia, hypoxia, hypercarbia, hypo-or hyperthermia, and medications (e.g., sympathomimetic or anti-cholinergic drugs). Currently, there is no objective, non-invasive monitor available to anesthesia providers that measures the adequacy of preventing/treating the reactions to nociception, hereafter referred to as the "nociceptive anti-nociceptive balance" (NANB). As a result, the administration of potent analgesics, specifically opioids during general anesthesia is highly subjective and variable among providers as they interpret these surrogate measures (HR/MAP changes) as signs of NAN imbalance. This variability in practice is reflected in wide ranges of dosing of opioids during surgery, the primary drugs used to provide anti-nociception during surgery.

Both excessive or insufficient doses of antinociceptive drugs are dangerous. An insufficient dose leads to inadequately suppressed nociception, which results in an excessive and/or prolonged stress response and possible physiological damage. Some patient populations are particularly vulnerable to such damage, including the very elderly and those with compromised cardiovascular systems. In contrast, an excessive dose of antinociceptive drugs (i.e. opioids) can induce apnea, can lead to post-operative nausea and importantly, contribute to intraoperative arterial hypotension, associated with post operative complications such as myocardial injury and acute kidney injury (Barash G. 2017).

Studies have shown large interpatient variability in the response to opioids (Sadhasivam S. 2012), (Searle R. 2009). Personalizing anti-nociception and analgesia during the perioperative period attempts to maximize pain relief while minimizing adverse events from under-dosing or over-dosing of therapy. While various factors influence response to treatment among surgical patients, age, sex, race and pharmacogenetic differences appear to play major roles in predicting post-operative pain (Sadhasivam S. 2012). These variables change from patient to patient leading to different responses to a given drug. Genetic factors include a subset of genes that modulate the proteins involved in pain perception, pain pathway, analgesic metabolism (pharmacokinetics), transport and receptor signaling (pharmacodynamics).

A direct, real time nociception monitor could assist clinicians in tailoring analgesia to specific patient needs.

4. The Relationship Between Anesthesia and Post-Operative Outcomes

The 'triple low' condition, defined as the combination of deep anesthesia, arterial hypotension [low mean arterial pressure (MAP)], and low consumption of hypnotic agent [low minimum alveolar concentration (MAC) of inhaled anesthetic], reflects a fragile state and is associated with increased 30- or 90-days major morbidity (acute kidney and myocardial injury) and mortality, even after adjustment for pre-operative risk factors and patient comorbidities (Maheshwari A. 2017). A 'double low', defined as the combination of deep anesthesia and hypotension has also been associated with an increased risk of post-operative adverse outcomes after non-cardiac surgery (Willingham M. D. 2017). However, in a prospective randomized study, an alert sent to anesthesiologists informing them of the "low status" of their patients (but without an algorithm on how the "low-status" should be corrected) did not change outcome thus revealing the complexity of the situation (Maheshwari A. 2017).

These studies findings indicate that: (i) excessive depth of anesthesia and arterial hypotension are associated with postoperative mortality; (ii) "simple correction" of too deep anesthesia/arterial hypotension does not correct their deleterious effects. Therefore, there is a strong incentive to investigate the role of monitoring in optimizing "adequacy of anesthesia" and reducing excessive depth of anesthesia (Willingham M. D. 2017).

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5. Hypnotics-Opioids Interactions Upon Nociceptive Stimulation

The interaction between the concentrations of hypnotics and opioids upon the application of a nociceptive stimulus is illustrated below:

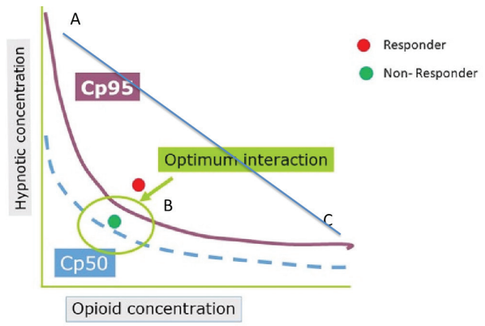

Figure 1: Isobolograms for opioids and hypnotic interaction for an endpoint of no movement to surgical stimuli.
Cp95, plasma concentration at which a drug exerts its function in 95% of cases;
Cp50, Plasma concentration at which a drug exerts its function in 50% of the cases.

A patient's response to a nociceptive stimulus whilst receiving varying concentrations of hypnotic agents and opioids can be qualified as a "Responder" (e.g., movement or increased HR/MAP values) or a "Non-Responder". The interaction between the hypnotics and opioids is synergistic (1 + 1 > 2) as opposed to additive (1+1 = 2).

As a result of this interaction, we know that:

1. It is possible to avoid responses to nociceptive stimuli with high concentrations of hypnotics without opioids (point A).
2. Appropriate concentrations of opioids, even at clinically low concentrations, greatly decrease the requirement for hypnotics (point B) and provide an optimal (> 50 %) reduction in hypnotic requirement.
3. There is a plateau level of opioid concentrations (corresponding to approximately 80 % reduction of hypnotic requirements) beyond which more opioids will not further decrease hypnotic requirements (point C).
4. A minimum concentration of hypnotic is always necessary, even with very high doses/concentrations of opioids to avoid explicit awareness (Mertens MJ. 2003).

Hypnotics and Opioids - the Optimum Doses

The optimum combination of opioids and hypnotics is defined by the smallest doses of hypnotics/ opioids that result in 'non-responsiveness'.

Since clinicians are aware of the fluctuations in opioid concentrations when administered by boluses (and hence the displacement along the hypnotics-opioids interactions graph); and because hypnotics concentrations are usually maintained at fairly constant levels either with inhalation or intravenous administration, there is a tendency to overdose the opioids at the beginning of surgery in order to achieve a "safer" concentration for a longer period of time and thus avoid "responsiveness".

Given the fact that high doses/concentrations of opioids prevent/delay the return of spontaneous ventilation and of consciousness, there is a tendency to underdose patients in preparation for emergence from anesthesia during the last stages of surgery. It is reasonable to consider NANB difficult to uphold because of the lack of objective estimation of a complex process. Intraoperative opioids overdose has recognized clinical consequences: (i) delayed recovery of spontaneous ventilation upon emergence from general anesthesia; (ii) delayed return of consciousness upon emergence from general anesthesia (iii) increased risk of arterial hypotension in the absence (or upon low intensity) nociceptive stimulation related to a lower sympathetic tone; (v) risk of post-operative opioid-induced hyperalgesia resulting in increased pain levels and increased analgesic requirements, both in the acute and long term post-operative periods (Santonocito C. 2018).

Intraoperative opioids underdosing has been associated with undesirable intra-operative effects (movement, hemodynamic instability) and long-term effects of excessive activation of the sympathetic nervous system (Chen A. 2015) .

Given the limitations of using clinical (movement) or hemodynamic monitoring-derived information (HR/MAP) to estimate NANB, it is highly desirable to have objective, sensitive and specific monitors to better estimate NANB and correct NAN imbalance.

6. The PMD-200 Monitor - A Physiological Monitor Device based on Physiological Parameters

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

The device utilizes the following four non-invasive sensors obtained from a finger probe and single-use sensor placed on the patient's finger:

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

From the PPG & GSR signals, the system's proprietary NOL algorithm extracts and analyses nociception-related physiological features and derivatives: heart rate, heart rate variability, PPG amplitude, skin conductance level, and their various derivatives. The Temp & ACC signals are used as guardrails for signal acquisition.

A NOL index value between 0-100 is displayed after 30 seconds of calibration. The index value is derived from the algorithm learning the patient's unique features and initially is normalized to large population preloaded data.

As the patient's own data accumulates during the monitoring session, the calculation of the NOL value is normalized more to the patient's data and less to the large population statistics. After the first 10 minutes of monitoring, the patient data is constantly normalized to a combination of the patient's earlier data (previous 10 minutes) and the large population preloaded data.

The PMD-200 screen display includes a NOL numeric, a trend and a smoothed trendline minimizing the impact of instantaneous fluctuations.

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7. NOL Index Range & Suggested Thresholds

The NOL index is a relative measure with a range of 0–100, where 0 represents no pain/nociceptive response and 100 represents extreme pain/nociceptive response.

The NOL index and trend are intended to support clinical decisions concerning the administration of analgesic medications.

Clinical evidence suggests the following guidelines for surgical procedures under general anesthesia:

- NOL above 25 for more than one minute may indicate the patient requires additional analgesic therapy. Higher values indicate a stronger response to nociception.
- NOL between 0–25 represents an appropriately suppressed physiological response to noxious stimuli and suggests adequate analgesia.
- NOL below 10 for more than one minute, during a painful stimulation, may indicate excessive anti-nociception and reduction of analgesics may be considered.
- The NOL index cannot anticipate noxious stimuli and thus a minimal level of analgesics should always be maintained.

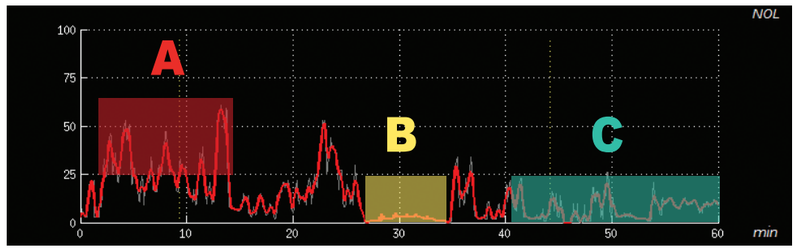
Note:

- The PMD-200 should be used as an adjunct to clinical judgment. Clinical judgment should always be used when interpreting the NOL index and trend line in conjunction with other available clinical and vital signs.
- The magnitude above the NOL threshold of 25 does not provide guidance on the magnitude of the dose of analgesic, but rather indicates timing as to when additional analgesic dosing may be necessary, following a nociceptive response.

7.1 The NOL Index Threshold

The NOL threshold was determined through the analysis of thousands of data points of adult patients receiving general anesthesia with remifentanil or fentanyl in controlled studies (Bollag L. 2018) (Edry R. 2016) (Martini CH 2015). An ROC curve was constructed and a cut-off calculation was performed to identify the optimal threshold to discriminate between noxious and non-noxious events.

A NOL value of 25 was identified as the `best-fit` cut-off score in an analysis performed by the manufacturer based on data from 9 separate clinical studies. The sensitivity and specificity of a NOL score of 25 to discriminate between noxious and non-noxious events were 95% and 92%, respectively.



A. NOL trend above 25 for more than one minute (whether constant or fluctuating) may indicate the patient requires additional analgesic therapy. Higher values indicate a stronger nociceptive response.

B. NOL below 10 for more than one minute during a painful stimulation may indicate excessive anti-nociception and reduction of analgesics may be considered. If regional analgesia is used, a low NOL is expected.

C. NOL between 0-25 represents an appropriately suppressed physiological response to noxious stimuli and indicates adequate analgesia.

A continuum of clinical state and NOL trends (not shown to scale). This chart reflects an established association between clinical state and NOL values. Ranges are based on results from clinical studies of the NOL-index guiding the administration of analgesic agents. Recommended NOL values and ranges assume that the NOL is not temporarily influenced by artifacts that may affect its performance. Titration of analgesics to the NOL-index value should be dependent on the individual goals established for each patient. The goals and associated NOL-index values may vary over time and in the context of patient status and treatment plan.

7.2 The Clinical Relevance of the NOL Trend

The NOL trend represents NOL values calculated every 5 seconds.

Two parameters should be taken into consideration for a clinically relevant interpretation of the NOL index:

1. The NOL value in relation to the NOL threshold, above 25 (or below 10 with remifentanil TIVA/TCI)
2. The time spent above the NOL threshold.

Fluctuations of the NOL trendline above the threshold for a few seconds should not generally be considered as suggesting the need of analgesics.

A 10 minute window or more (set as default in the PMD-200 device) is typically clinically useful. The monitor displays a graphic trend- the NOL trend (see the figure below) – which represents the ongoing calculation of the NOL index during the case.

Common trends suggesting a clinically significant stimulation are:

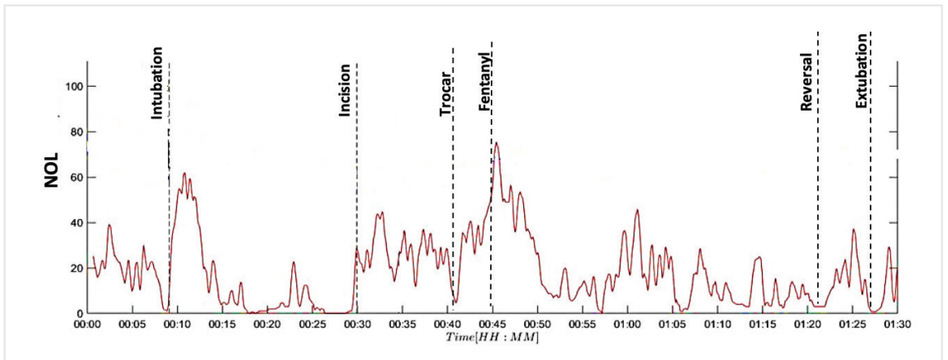
1. NOL values above threshold (>25) for a consecutive period of more than one minute; 2. Recurrent significant fluctuations of the NOL value around the threshold (>25) for a duration of at least one minute.

8. What Information does the NOL Index Provide?

The NOL index provides potentially useful information throughout the surgical session whilst the patient is under general anesthesia. It traces the patient's physiological response to surgical nociceptive stimuli and to analgesics administration, continuously translating the physiological state of nociception to a numerical value.

For didactic purposes, the session is divided into three phases of a "typical" general anesthetic case:

- Induction period (including the intubation phase)
- Maintenance period (from start of surgery to end of sutures)
- Emergence period



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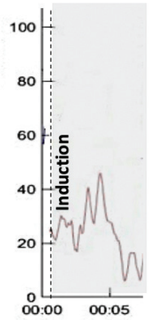
9. NOL Guided Analgesia for Medium or Long-Acting Opioids (Fentanyl, Sufentanil).

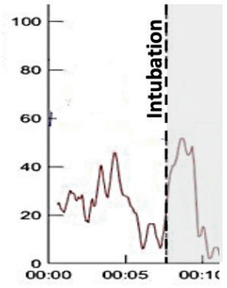
9.1 NOL During Induction

- After placing the finger probe on the patient's finger, a short calibration period of 30 seconds takes place after which the NOL value is displayed. The first NOL values displayed in an awake patient reflect the basic sympathetic tone of an awake person which is characterized by higher physiological parameter values compared to an anaesthetized patient (HR, BP, skin conductance, etc.). Therefore, a NOL value of above 25 is to be expected until start of induction, depending on the patient's stress level.
- After induction, the NOL values will drop, reflecting the NAN balance at that period: no noxious stimulation with reduction of sympathetic tone due to loss of consciousness and administration of an analgesic. A NOL value below 25 should usually be expected.



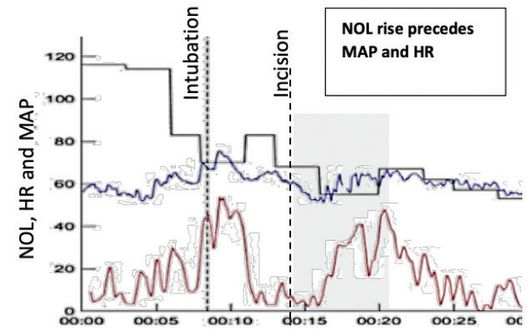
9.11 Intubation

- Intubation is recognized as an intense noxious stimulus and normally prompts an increase in NOL values. Unexpectedly high NOL values during intubation may indicate that onboard analgesia administered during induction is not yet fully effective or is insufficient for the patient or that adjustment to technique may be required during prolonged intubation attempts.
- NOL has been shown to reflect different level of nociceptive response using different intubation techniques (Sbeghen V. 2018).



9.2 NOL During Maintenance

The following figure presents the NOL-index response to nociception events such as intubation and incision and rises beyond 25.



A randomized controlled study showed that NOL-guided opioid dosing under a sevoflurane/fentanyl regimen without the use of regional blocks or epidurals resulted in a reduction in PACU pain score (Meijer F. 2020). A confirmatory study replicating a similar clinical protocol with similar results has been published (Fuica R. 2022). The key points of the clinical guidance are described in the following paragraphs.

Fentanyl dosing was dependent on the NOL index, but MAP and HR were additionally monitored and considered. In cases where the NOL index was >25 for at least 60 seconds, fentanyl 50-100 mcg was administered in a patient >70 kg, and 25-50 mcg in a patient of 70 kg or less. Higher or lower fentanyl doses could be given or opioids could be given below the NOL threshold if estimated required by the attending anesthesiologist.

After fentanyl was given, 5-10 min were allowed before the next evaluation took place. In cases where the index decreased below 25, no more fentanyl was administered. If the index was <25 and the MAP was <60 mm Hg, vasoactive medication (ephedrine, phenylephrine, norepinephrine), crystalloids, or both could be given. Irrespective of the NOL index value, when MAP was >100 mm Hg and not responsive to fentanyl, despite adequate and repeated dosing, and BIS values were <55, a vasodilator (nitroglycerine or sodium nitroprusside) or a continuous infusion of remifentanil could be given. If BIS values were >55, the inspired sevoflurane concentration was increased such that BIS decreased below 55, and the patient condition was reassessed. The authors in both studies reported a reduction in post-operative pain scores that was not accompanied by an increase in intraoperative fentanyl consumption.

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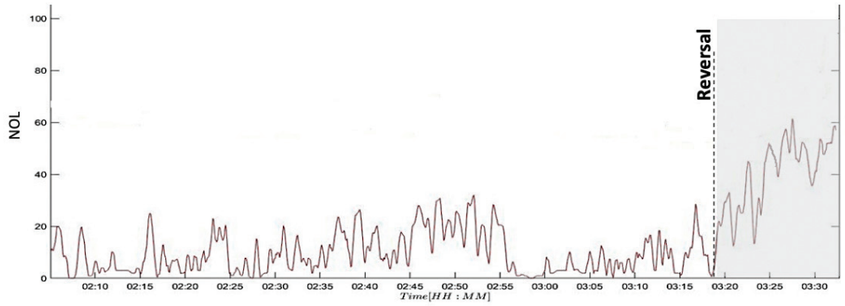
9.3 NOL During Emergence and Extubation

During emergence and extubation, NOL trend will reflect the rising sympathetic tone as the concentrations of hypnotics and opioids are diminishing at the end of surgery in preparation of emergence from anesthesia. Even in a patient with no pain upon emergence, NOL values above the threshold (>25) should be expected.

NOL index values during emergence from anesthesia will increase gradually in response to a reduction in analgesic/ anesthetic doses/ concentrations.

At tracheal extubation NOL values will typically increase immediately to above 25.



10. NOL Guided Analgesia for Short-Acting Opioids (Remifentanil)

Remifentanil is one of the most commonly used analgesics in current anesthesia practice due to its rapid onset and offset. Due to the short duration of action, the analgesic effect of remifentanil rapidly disappears with the termination of infusion, and this must be taken into account when using NOL to manage analgesia as the monitor cannot anticipate noxious stimuli.

Total intravenous anesthesia (TIVA) has become popular in recent years and usage of remifentanil has substantially increased more compared to previous decades in which it was used mostly as an adjuvant in inhalation anesthesia. With the widespread use of processed EEG monitors enabling the titration of the hypnotic component, NOL has a complementary role, enabling titration of opioids. Meijer et al. developed a protocol for NOL implementation in a propofol/remifentanil TIVA TCI regimen without regional blocks (Meijer FS. 2019).

11.1 NOL During Induction & Intubation

NOL behavior is expected to be similar to the fentanyl description above during induction and intubation except that the time to peak effect for remifentanil is shorter (less than 2 minutes).

11.2 NOL During Maintenance

In the Meijer study, the remifentanil target was adjusted to maintain a target nociception level value between 10 to 25 (Meijer FS. 2019).

When the nociception level decreased below 10 for at least 1 min, remifentanil TCI targets were lowered in steps of 0.5 ng/ml, with a minimal target of remifentanil of 1ng/ml maintained as the monitor cannot predict surgical noxious stimuli. If NOL values remained below 10 and patient was hypotensive, vasoactive drugs could be administered.

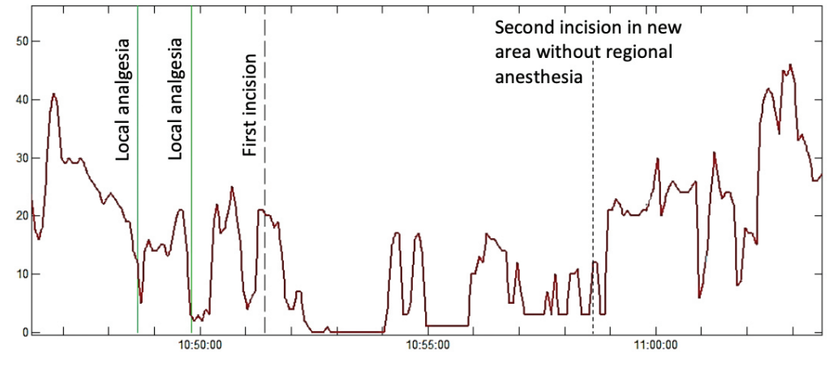
In case of values greater than 25 for at least 1 min, remifentanil TCI targets were increased in steps of 0.5 (when NOL index remained less than 45) or 1.0 ng/mL (when NOL index was above 45). The study authors reported that intraoperative remifentanil consumption and intraoperative arterial hypotension were reduced in the NOL guided group in comparison to a standard of care group.

11.3 NOL During Emergence and Extubation

During emergence the remifentanil is tapered off typically after administration of a long-acting opioid (mostly morphine or hydromorphone) or other means to prevent postoperative pain. During extubation and patient arousal, NOL values will sharply increase, exceeding 25.

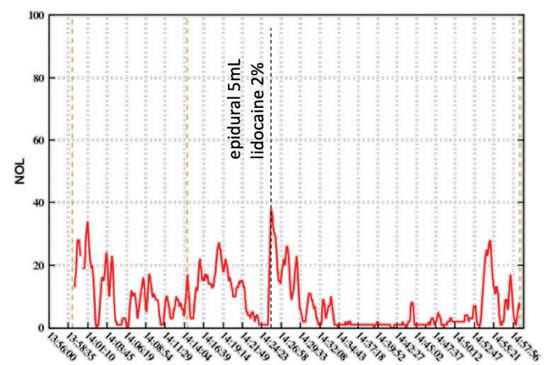
11. NOL Monitoring During Regional Anesthesia & Opioid Sparing Techniques

Regional anesthesia using peripheral nerve blocks is gaining increased popularity. When successful, it promotes efficacious intraoperative anti-nociception and contributes to effective postoperative analgesia. However, the technique may have limitations related to the block efficacy. Sometimes the block fails completely, and conversion to general anesthesia is necessary for surgery to proceed. Once anesthetized, a patient cannot report on the efficacy of the block, which may be working partially or covering only part of the surgical area. Several case reports have shown that the NOL index may help the clinician assess the adequacy of local anesthetic infiltration or peripheral nerve blocks in patients under general anesthesia. Further clinical studies are planned in the field of regional anesthesia.



The NOL index behavior under different anesthesia techniques other than general anesthesia with a systemic opioid, including all types of regional analgesia (neuraxial, peripheral nerve blocks and local analgesia infiltration) as well as under sedation has been less studied to date. However, several validation studies and case reports have demonstrated that reliable NOL index values can be obtained in multiple types of anesthesia regimens. Generally, NOL values will decrease after an anti-nociceptive intervention.

- The following figure demonstrates a typical NOL decrease after epidural and lidocaine administration.



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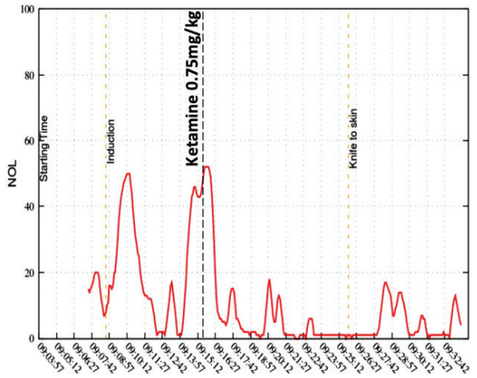
- Ketamine is also increasingly used as an adjuvant anti-nociceptive drug in regimens of opioid-free or opioid-sparing anesthesia. The NOL index could be helpful in assessing the efficacy of ketamine injection. The following figure illustrates a typical NOL decrease a few minutes (~2-3 min.) after intravenous ketamine administration.



- Dexmedetomidine, a potent central alpha-2 agonist, has been shown to have anesthetic and opioid-sparing effects (Bielka K 2018), (Le Guen M 2014), (Ding DF 2017). For example, it reduced fentanyl requirements during cholecystectomy (Bielka K 2018) and remifentanil requirements during abdominal surgery (Le Guen M 2014). A recent randomized control trial (Coeckelenbergh S. 2021) in which both arms were NOL guided, demonstrated that an infusion of dexmedetomidine given prior to surgery reduced intra-operative remifentanil requirements. The study's conclusion was that NOL-index monitoring can measure dexmedetomidine's hypnotic and opioid-sparing effects during remifentanil-propofol target-controlled infusion anesthesia.

12. Exploring the relationship between objective monitoring of intraoperative nociception, hemodynamic indices, and post operative pain

Severe pain after surgery remains a major problem, reported in 20–40% of patients (Gerbershagen HJ. 2013). Despite numerous published studies, the degree of pain following many types of surgery in everyday clinical practice is unknown. Severe pain is associated with decreased patient satisfaction, delayed postoperative ambulation, the development of chronic postoperative pain, an increased incidence of pulmonary and cardiac complications, and increased morbidity and mortality (Kehlet H. 2006). A number of risk factors are known to increase postoperative pain intensity including younger age, female sex, and the presence of preoperative pain (Kalkman CJ. 2003). Gerbershagen et al assessed pain intensity on the first day post surgery in a large dataset of surgical procedures and reported that several common minor- to medium-level surgical procedures, including some with laparoscopic approaches, resulted in unexpectedly high levels of postoperative pain.

However, the relationship between intraoperative nociception management and post operative pain in the first hours after surgery is not well understood. As discussed in previous sections, clinicians traditionally titrate intraoperative analgesia according to surrogate hemodynamic parameters - blood pressure and heart rate (HD), in addition to their own clinical judgement which is based on the level of stimulation, the medical comorbidities of the patient, the patient's prior response to analgesia, and the clinician's experience. This is referred to as the Standard of Care (SOC). By looking at how both NOL and hemodynamic parameters are used to guide analgesia dosing, and evaluating the patients pain scores in the Post Anesthesia Care Unit (PACU), we can better understand the possible benefits of NOL in personalizing analgesia dosing in clinical practice.

The graphs below show the NOL and HD values over the time course of a sevoflurane/fentanyl balanced anesthetic during elective major abdominal surgery. The patient's fentanyl plasma concentration over time is superimposed as the blue line and calculated from the Shafer Pk/Pd model (Shafer L.1991).

NOL provides an objective measure of nociception, which can be used by the clinician in conjunction with other available information to evaluate the need for additional analgesia (fentanyl dose). As mentioned earlier in section 9, on using NOL to guide fentanyl dosing, additional dosing should be considered when NOL is above 25 for at least one minute.

In the following case examples we will evaluate whether the clinician would have changed their analgesia dosing (given more or fewer boluses of fentanyl) had they received objective guidance from NOL in real time during the case. Thus, the examples below were taken from the SOC arm of a controlled clinical study, where the clinician was blinded to the NOL values and opioid dosing was therefore based on HD indices and experience. PACU pain is reported as the median NRS pain score at 90 minutes.

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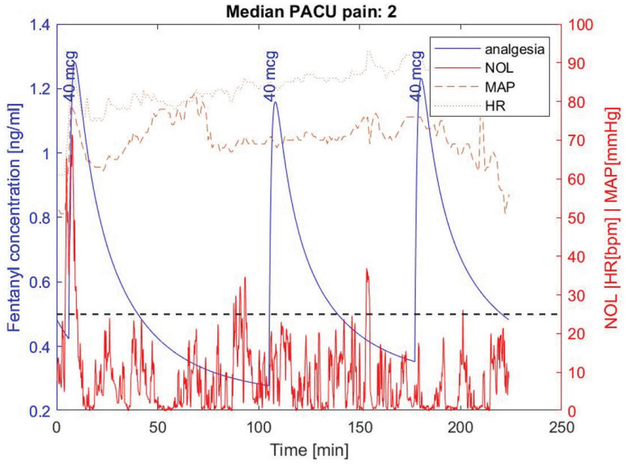
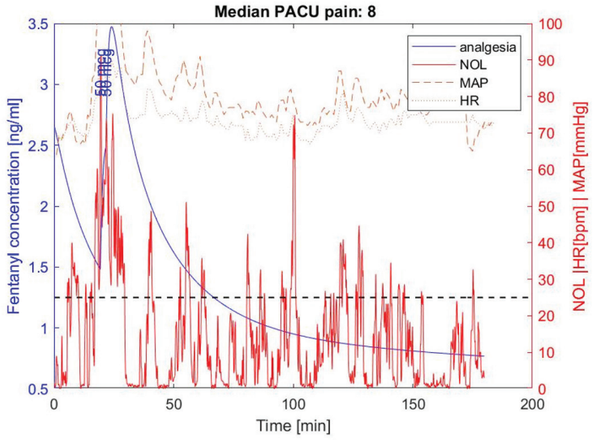
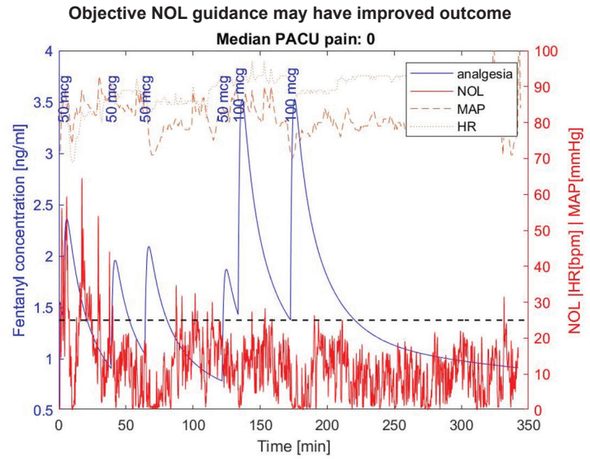


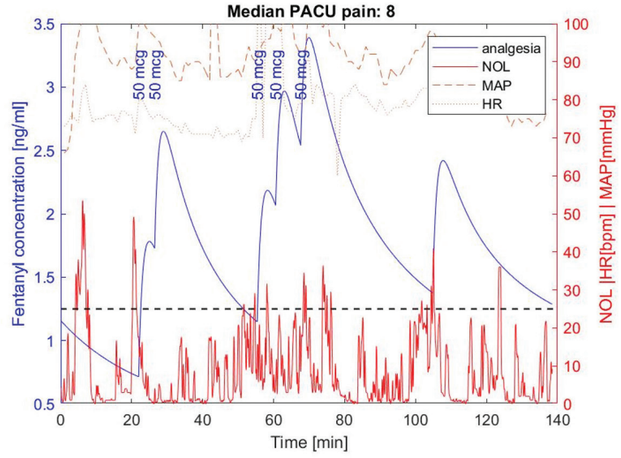
A. In this case, the clinician appears to dose the fentanyl at regular intervals, a typical clinical practice. The patient's PACU pain score was 2, reflecting mild PACU pain. Had this clinician used NOL guidance, they may have given the second and third boluses of fentanyl earlier, in response to the NOL spikes at 90 and 160 minutes.
Conclusion: NOL guidance would not have meaningfully changed the analgesia management. NOL 'confirms' the SOC management of the clinician, based on HD indices and experience.



B. In this case, the clinician chose not to dose any additional fentanyl after a couple of 50 mcg boluses early in the case, although small spikes in HR/BP were present. The NOL tracing has multiple spikes above 25 suggesting the patient was responding to stimuli and could have benefited from additional fentanyl. The patient's PACU pain score was 8 on the NRS scale (range 0-10) reflecting severe pain.
Conclusion: NOL guidance may have prompted the clinician to give additional fentanyl in response to the HD spikes and the pain scores would likely have been lower. Objective NOL guidance may have improved outcome.



C. In this case, the clinician administered frequent doses of fentanyl, apparently in response to spikes in HR/BP. However, the predominant NOL values below 25 suggest this may have been unnecessary since the patient did not have a sustained nociceptive response to the stimuli. A median PACU pain score of zero suggests the patient may have been overly sedated and narcotized and received too much fentanyl during the case.
Conclusion: NOL guidance may have prompted the clinician to withhold fentanyl in response to the HD spikes and prevented over administration of fentanyl. Objective NOL guidance may have improved outcome.



D. Careful analysis of these tracings suggest that the clinician's timing of additional fentanyl doses based on HD indices and experience alone are supported by the NOL index (the last NOL spike was probably close to emergence and would not have been treated in either scenario).
Conclusion: NOL guidance would not have meaningfully changed the management or the outcome. NOL 'confirms' the SOC management of the clinician, based on HD indices and experience. Yet, the patient had a high pain score, which may be due to other factors unrelated to intraoperative nociception.

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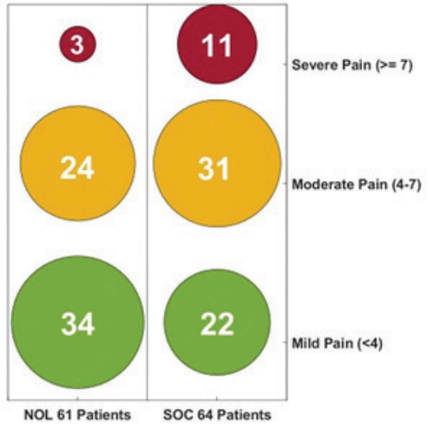
Analyzing such cases shows that although NOL can contribute to improved pain scores, it should not be assumed that NOL guided dosing will provide additional value to traditional HD based opioid dosing in every patient. There are times when HD guided management is adequate, and times when NOL guided analgesia will not result in low pain scores. However, NOL monitoring does not present any additional risk and the importance of improving PACU pain control should not be understated. Not only does inadequate analgesia lead to the negative clinical consequences discussed in section 3, but, high pain scores correlate with low patient satisfaction scores, which are now a quality metric that adversely affects hospital certification, reimbursement, and provider recredentialing. A monitor is not expected to provide benefit for every case, but the extra information NOL gives and for the cases where it does lead to reduced pain or prevents unnecessary opioid use, makes the monitor valuable in clinical practice.

13. Benefits of NOL guided fentanyl administration

The Meijer study (Meijer FS. 2020) and an additional confirmatory study (Fuica et al. 2022) in adult patients undergoing major elective abdominal surgery under general anesthesia demonstrate the benefits of NOL guided fentanyl administration. Patients with non-sinus heart rate, CNS disorders, abuse of alcohol or illicit drugs, chronic use of psychoactive drugs, chronic pain conditions and opioid tolerance were excluded.

In the Meijer study, a reduction of 1.6 in the median pain score (NRS) was reported throughout the 90 minutes. In the Fuica study, a reduction of 1.5 in the median pain score was reported with NOL guided analgesia. These reductions represent a 30-33% improvement in pain scores in comparison to the standard of care control groups and were attributed to more personalized analgesia dosing in the NOL guided group. The number of patients reporting severe pain in the PACU was significantly reduced in NOL monitored groups in both studies. The data from the Meijer study data (n=50) was pooled with the data from the Fuica study (n=75) and a multivariate analysis was conducted to identify the factors that were statistically related to severe pain. Factors included were age, sex, BMI, ASA classification, surgery type, study & group randomization (NOL guided vs. SOC). The odds ratio of experiencing severe PACU pain was 5.98 higher (p=0.017), in the SOC group without NOL guidance (the control group). This was the only factor found to be significantly related to the difference in the odds of severe pain. In the NOL guided group, only 4.9% of patients experienced severe pain versus 17% in the control group (see image to the right).

Most of the patients reporting severe pain were females (12 out of 14) and most of these females underwent gynecological surgeries (9 out of 12). Severe PACU pain indicates a failure of anesthetic management, and is associated with negative clinical outcomes. In addition, patients experiencing mild pain will typically not receive further opioid treatment and thus avoid the opioid-induced negative side effects. These studies demonstrate the potential benefit of NOL-guided fentanyl administration during maintenance of anesthesia.



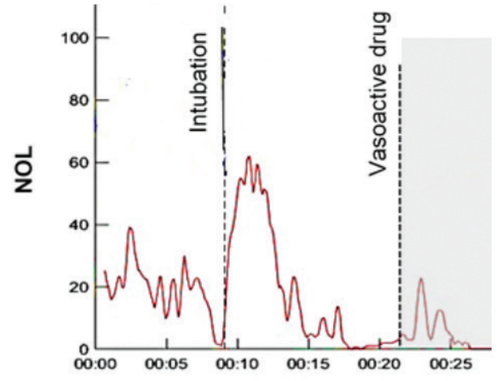
Pooled data from the Meijer study and Fuica study

14. Clinical Limitations of the NOL Technology

The PMD-200 monitor cannot anticipate or predict the application of nociceptive stimuli during surgery. The clinician is the only person that can anticipate the application of such nociceptive stimuli. If the patient's requirements for opioid doses/concentrations upon tracheal intubation were used in order to calibrate the individual patient's requirements, that information can be used subsequently to guide the NANB. Furthermore, NOL should not be used to guide pre-emptive analgesia prior to emergence, since it cannot predict the Pk/Pd effects of the drugs post surgery. During emergence, NOL values may be high due to sympathetic arousal unrelated to nociception and therefore should not be used to guide the analgesia dosing. The NOL monitor must be used by anesthesia personnel trained in administering general anesthesia, with all the best practices and procedures implicit therein, including dosing analgesics in anticipation of noxious stimuli. Limiting the intended users, and providing education, and training mitigates this risk.

Conditions interfering with the correct acquisition of the photoplethysmography signal or skin conductance and various artifacts may temporarily lead to difficult to interpret NOL values. These include some cardiac arrhythmias, electrocautery, severe hypothermia, excessive motion, and impediments to blood flow, such as arterial catheters, blood pressure cuffs, infusion lines, as well as some vasoactive drugs. This is mitigated by alerts presented on the screen and not displaying a NOL value if signal quality is inadequate. Evidence suggests that the clinical performance of NOL in patients receiving chronic beta blockers as part of their care was equivalent to that of normally normotensive patients (Bergeron C. 2021).

Conditions affecting the autonomic nervous system and the volemic state of the patient may temporarily lead to difficulty in interpreting NOL values. These conditions include administration of vasoactive drugs, extremes of patient positioning (i.e., steep Trendelenburg) and hypovolemia. However, the algorithm recognizes Trendelenburg positioning and adjusts for it using the accelerometer. In addition, the NOL is constantly normalized to patient's earlier data. The influence of a bolus of short acting vasoactive drugs such as phenylephrine and ephedrine on NOL values (moderate increase) has been shown to be short lived (Raft J. 2020), and should be expected to fade within 2-3 minutes (see image below).



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A NOL Pocket-Guide for Clinicians

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