MEDASENSE

# PERSONALIZED INTRAOPERATIVE ANALGESIA FOR IMPROVED PATIENT OUTCOMES

## NOL® (Nociception Level) Technology
## Clinical Evidence Guide

CL2U-02-766 01

January 2023 |

NEXT

## CLINICALLY VALIDATED

NOL is clinically validated as a reliable measure of intra-operative nociception.[1,2,3,4,5,6]

## PERSONALIZED ANALGESIA

NOL supports personalized analgesic titration, thereby helping reduce opioid associated complications.[7,8]

## IMPROVED PATIENT OUTCOMES

NOL guided analgesia can reduce postoperative pain, and improve patient recovery.[9,10,11]

## SUPPORTS MULTIPLE ANALGESIA REGIMENS

NOL can be used in different analgesia protocols, including regional analgesia and non-opioid analgesia.[1,12,13]

**Monitoring intra-operative nociception levels can assist clinicians to personalize analgesic administration, reduce postoperative pain and improve patient recovery.**

This guide will illustrate the supporting evidence behind each of these claims.

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# Multiple studies conducted worldwide and key results published in peer reviewed medical journals, have validated that the NOL Index:

- Can differentiate, with high sensitivity and specificity, between noxious and non-noxious stimuli[2,3,4] >>
- Reflects the balance between noxious stimuli and analgesia at different opioid concentrations[2,3]
- Demonstrates superiority over commonly used nociception indicators[2]
- Performs reliably in patients receiving beta-blockers[5]
- Performs consistently in multiple patient cohorts including different anesthetic and analgesic techniques[6]

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NOL is a reliable indicator for the presence and severity of the nociceptive response, and reliably measures the changes in nociceptive response at different remifentanil concentrations.

### ABILITY OF THE NOCICEPTION LEVEL (NOL), A MULTIPARAMETER COMPOSITE OF AUTONOMIC SIGNALS, TO DETECT NOXIOUS STIMULI DURING PROPOFOL-REMIFENTANIL ANESTHESIA.[3]

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|---|---|---|---|---|---|
| **YEAR** | 2015 | **AUTHOR** | Martini et al. | **PUBLICATION** | Anesthesiology 2015; 123:524-34 |
| **PATIENTS** | N=72; ASA I – III; Ages 18-80; BIS target 45+/-5; Elective surgery under general anesthesia | | | | |
| **ANESTHESIA REGIMEN** | Propofol & remifentanil | | | | |
| **KEY FINDINGS** | NOL correctly grades the level of nociceptive reaction: non-noxious stimulus NOL < incision NOL < intubation NOL ($p < 0.05$). | | | | |
| **AUTHORS' CONCLUSIONS** | NOL® is a reliable measure of moderate and intense noxious stimulation and outperforms HR and MAP in differentiating noxious from non-noxious stimuli. In contrast to HR and MAP, the NOL was not affected by hemodynamic effects of remifentanil. | | | | |

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NOL discriminates noxious from non-noxious stimuli with high sensitivity and specificity, and outperforms other parameters and indices.

### PRELIMINARY INTRAOPERATIVE VALIDATION OF THE NOCICEPTION LEVEL INDEX: A NONINVASIVE NOCICEPTION MONITOR.[2]

| YEAR | 2016 | AUTHOR | Edry et al. | PUBLICATION | Anesthesiology 2016; 125:193-203 |
|---|---|---|---|---|---|
| PATIENTS | (N=58; ASA I – III; Ages 18-75; Entropy target <60 ; Elective surgery under general anesthesia) laparoscopic and open abdominal procedures, laparoscopic and open gynaecologic procedures, neurosurgical procedures, and plastic or head and neck procedures. | | | | |
| ANESTHESIA REGIMEN | Remifentanil & sevoflurane | | | | |
| KEY FINDINGS | The NOL index outperforms commonly used parameters HR, PPGA and SPI (GE). | | | | |
| AUTHORS' CONCLUSIONS | The NOL index changes proportionately with patients' response to various clinical and experimental noxious stimuli and discriminates noxious from non-noxious stimuli with high sensitivity and specificity. The NOL index also responds progressively to increasing stimuli intensity and is appropriately blunted by analgesic administration. The NOL index was superior to other compared measures and appears to accurately characterize nociception during general anesthesia. | | | | |

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NOL results are generalizable to different patient cohorts

### NOCICEPTION LEVEL (NOL) AS A MEASURE OF NOCICEPTIVE STIMULI: A RETROSPECTIVE ANALYSIS OF 8 PROSPECTIVE STUDIES[6]

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| **YEAR** | 2021 | **AUTHOR** | Montalvo-Campana et al. | **PUBLICATION** | PGA Conference Dec 2021 (peer reviewed publication pending) |
| **PATIENTS** | N = 447 adult patients from 8 prospective studies. | | | | |
| **ANESTHESIA REGIMEN** | Multiple regimens: propofol, sevoflurane, desflurane with remifentanil and fentanyl | | | | |
| **KEY FINDINGS** | The NOL number is agnostic to different patient demographics (age, sex, BMI, ASA status), and anesthestic approaches (remifentanil/fentanyl, desflurane/sevoflurane/propofol) | | | | |
| **AUTHORS' CONCLUSIONS** | The authors concluded that the NOL number is a constant reliable measure between different populations under various noxious and non-noxious stimuli, independent of patients characteristics and the threshold of 25 is generalizable to different patient cohorts. | | | | |

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NOL-guided opioid administration has a significant effect on opioid consumption and hemodynamic stability in patients undergoing major surgery.

### NOCICEPTION-GUIDED VERSUS STANDARD CARE DURING REMIFENTANIL–PROPOFOL ANESTHESIA: A RANDOMIZED CONTROLLED TRIAL[7]

| YEAR | 2019 | AUTHOR | Meijer et al. | PUBLICATION | Anesthesiology 2019; 130:745-755 |
|---|---|---|---|---|---|
| PATIENTS | (N=80 (40 in each group); ASA I – III; Ages 18-80; major abdominal surgery, urologic or gynaecologic procedures under general anesthesia | | | | |
| ANESTHESIA REGIMEN | Remifentanil-propofol TIVA target controlled infusion without epidural analgesia. | | | | |
| KEY FINDINGS | · NOL - guided opioid administration resulted in 80% less hypotensive events (5% vs 28% (p=0.006))<br>· NOL - guided opioid administration resulted in 30% less intraoperative opioids (0.086 vs 0.119 µg/kg/min (p<0.001)) | | | | |
| AUTHORS' CONCLUSIONS | The authors studied the influence of nociception-guided anesthesia using the nociception level monitor and observed that, compared with standard clinical care, nociception level guidance resulted in about 30% less remifentanil use during anesthesia. Nociception level monitoring had no effect on postoperative pain scores or postoperative opioid requirements. | | | | |

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Intraoperative opioid administration is lower in patients receiving nociception monitor guided analgesia

### NOCICEPTION MONITORS VS. STANDARD PRACTICE FOR TITRATION OF OPIOID ADMINISTRATION IN GENERAL ANESTHESIA: A META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS[8]

| YEAR | 2022 | AUTHOR | Ma et al. | PUBLICATION | Front. Med. 9:963185. doi: 10.3389/fmed.2022.963185 |
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| **PATIENTS** | N=1957 patients from 21 studies, 201 of which were NOL monitored. All under general anesthesia |
| **ANESTHESIA REGIMEN** | Mixed (meta-analysis) including fentanyl, remifentanil and sufentanyl with IV and inhalational anesthesia |
| **KEY FINDINGS** | • Intraoperative opioid administration was significantly lower in patients receiving nociception monitor-guided analgesia than in patients receiving standard management (SMD -0.71 95% CI−1.07 to −0.36 p<0.0001)<br>• Opioid administration was significantly lower with NOL or PPI guidance than with standard anesthesia; however, no significant difference was found with ANI or SPI guidance<br>• Time to extubation and PONV incidence were also reduced in the nociception monitoring guided group. |
| **AUTHORS' CONCLUSIONS** | The authors concluded that intraoperative nociception monitoring guidance may reduce intraoperative opioid administration and appears to be a viable strategy for intraoperative titration of opioids |

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Intraoperative NOL monitoring can reduce postoperative pain by 33% compared to standard of care monitoring

### REDUCED POSTOPERATIVE PAIN USING FENTANYL DOSING DURING SEVOFLURANE ANAESTHESIA: A RANDOMIZED CONTROLLED TRIAL.[9]

| YEAR | 2020 | AUTHOR | Meijer et al. | PUBLICATION | British Journal of Anaesthesia, 125(6):1070-1078. |
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| **PATIENTS** | (N=50 (25 in each group); ASA I – III; Ages 18-80; elective major abdominal surgery under general anesthesia (without epidural) |
| **ANESTHESIA REGIMEN** | Fentanyl-sevoflurane |
| **KEY FINDINGS** | · Postoperative pain scores in the PACU reduced by 33% in NOL-guided patients (3.2 median score; 1.6-point improvement from 4.8 in standard care group p< 0.006)<br>· Stress hormone levels up to 50% lower in NOL-guided group, both during and after surgery. |
| **AUTHORS' CONCLUSIONS** | Despite absence of differences in fentanyl and morphine consumption during and after surgery, a 1.6-point improvement in postoperative pain scores was observed in the NOL-guided group. The authors attribute this to NOL-driven rather than BP- and HR-driven fentanyl dosing during anesthesia. |

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

### REDUCED POSTOPERATIVE PAIN IN PATIENTS RECEIVING NOCICEPTION MONITOR GUIDED ANALGESIA DURING ELECTIVE MAJOR ABDOMINAL SURGERY: A RANDOMIZED, CONTROLLED TRIAL[10]

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|---|---|---|---|---|---|
| **YEAR** | 2022 | **AUTHOR** | Fuica et al. | **PUBLICATION** | J Clin Monit Comput (2022). https://doi.org/10.1007/s10877-022-00906-1 |

| | |
|---|---|
| **PATIENTS** | (N=75 (36 NOL-guided & 39 SOC); ASA I – III; Ages 18-80; major abdominal surgery under general anesthesia (without epidural) |
| **ANESTHESIA REGIMEN** | Fentanyl-sevoflurane |
| **KEY FINDINGS** | · Postoperative pain scores reduced by 30% in NOL-guided patients (Actual difference of 1.5 95% CI 0.4-2.6 in NRS PACU pain scores at 90 min; p=0.06)<br>· Less patients reporting severe pain (8 vs 3) |
| **AUTHORS' CONCLUSIONS** | Postoperative pain scores were significantly improved in nociception level index-guided patients. The authors attribute this to more objective fentanyl dosing when timed to actual nociceptive stimuli during anesthesia, contributing to lower levels of sympathetic activation and surgical stress |

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Intraoperative opioid dosing based on NOL reduces the proportion of patients with severe pain by 70%

## INTRAOPERATIVE USE OF THE MACHINE LEARNING-DERIVED NOCICEPTION LEVEL MONITOR RESULTS IN LESS PAIN IN THE FIRST 90 MIN AFTER SURGERY[11]

| YEAR | 2022 | AUTHOR | Van Der Waal et al. | PUBLICATION | Frontiers in Pain Research 3:1086862 |
|---|---|---|---|---|---|
| PATIENTS | (N=125 (61 NOL guided vs 64 SOC); ASA I – III; Ages 18-80; major abdominal surgery under general anesthesia without epidural | | | | |
| ANESTHESIA REGIMEN | Fentanyl-sevoflurane | | | | |
| KEY FINDINGS | Intraoperative NOL guidance was the only significant factor explaining the difference in the number of patients experiencing severe pain (OR 5.98, p=0.02). Median PACU pain score was 1.5 points (0.8–2.2) lower in the NOL group compared to the standard care; the proportion of patients with severe pain was 70% lower in the NOL group ( p = 0.045). | | | | |
| AUTHORS' CONCLUSIONS | The use of a machine learning-based technology to guide opioid dosing during major abdominal surgery resulted in reduced PACU pain scores with less patients in severe pain. | | | | |

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NOL-guided regional blocks in multimodal anesthetic protocols can help reduce intraoperative opioid administration

### NOCICEPTION LEVEL INDEX-DIRECTED ERECTOR SPINAE PLANE BLOCK IN OPEN HEART SURGERY: A RANDOMIZED CONTROLLED CLINICAL TRIAL.[12]

| | | | | | |
|---|---|---|---|---|---|
| **YEAR** | 2022 | **AUTHOR** | Balan et al. | **PUBLICATION** | Medicina 2022, 58, 1462. |
| **PATIENTS** | 83 patients undergoing on-pump cardiac surgery with (40) or w/o (43) erector spinae plane block (ESPB) | | | | |
| **ANESTHESIA REGIMEN** | Propofol-fentanyl | | | | |
| **KEY FINDINGS** | · NOL index-directed ESPB reduced intraoperative fentanyl by 73.3% and 48 h morphine by 63.5% (p<0.001) | | | | |
| **AUTHORS' CONCLUSIONS** | This prospective randomized study demonstrates that the Nociception Level index directed bilateral single-shot ESPB compared to no block is superior in reducing total intraoperative fentanyl consumption in adult patients undergoing open heart surgery | | | | |

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NOL can be used to monitor the opioid sparing effects of dexmedetomidine

### EFFECT OF DEXMEDETOMIDINE ON NOCICEPTION LEVEL INDEX-GUIDED REMIFENTANIL ANTINOCICEPTION[13]

| | | | | | |
|---|---|---|---|---|---|
| **YEAR** | 2021 | **AUTHOR** | Coeckelenbergh et al. | **PUBLICATION** | European Journal of Anaesthesiology, 38(5), 524–533 |
| **PATIENTS** | N=58 (ASA I-II) undergoing maxillofacial or cervicofacial surgery | | | | |
| **ANESTHESIA REGIMEN** | Propofol-remifentanil TCI | | | | |
| **KEY FINDINGS** | Dexmedetomidine administered immediately before surgery decreases intraoperative remifentanil requirements | | | | |
| **AUTHORS' CONCLUSIONS** | Combined frontal electroencephalogram and Nociception Level Index monitoring can measure dexmedetomidine's hypnotic and opioid-sparing effects during remifentanil-propofol target-controlled infusion anesthesia. | | | | |

NOL is a useful tool to evaluate the efficacy of an intraoperative epidural analgesia.

## THE NOCICEPTION LEVEL INDEX (NOL) RESPONSE TO INTUBATION AND INCISION IN PATIENTS UNDERGOING VIDEO-ASSISTED THORACOSCOPIC SURGERY (VATS) WITH AND WITHOUT THORACIC EPIDURAL ANALGESIA.[1]

| | | | | | |
|---|---|---|---|---|---|
| **YEAR** | 2018 | **AUTHOR** | Bollag et al. | **PUBLICATION** | F1000 Research 2018, 7:875 |
| **PATIENTS** | N=20 (10 in epidural group, 10 non epidural group); ASA I – III; video-assisted thoracoscopic surgery (VATS) | | | | |
| **ANESTHESIA REGIMEN** | Intravenous lidocaine, fentanyl, propofol | | | | |
| **KEY FINDINGS** | Skin incision followed by the first trocar insertion and endoscope placement for the VATS procedure caused a significant NOL index increase in patients without epidurals, despite the standardized fentanyl administration prior to incision. In patients with a prior to incision activated epidural catheter in place, NOL values did not significantly increase after incision, while the HR did not significantly vary in both groups after incision emphasizing the NOL's higher sensitivity and specificity to detect nociceptive stimuli. | | | | |
| **AUTHORS' CONCLUSIONS** | This pilot study suggests that the NOL monitoring may be a useful tool to evaluate the efficacy of an intraoperative thoracic epidural analgesia. | | | | |

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**MORE INFORMATION**

*IMPORTANT: Please refer to the PMD-200 user manual for complete instructions, contraindications, warnings and precautions. NOL® is a registered trademark of Medasense Biometrics Ltd.*

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