Targeted interventions in mechanically ventilated patients

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Evaluating opioid dosing in the ICU using Nociception level Monitoring:

comparing COVID-19 and non-COVID-19 patients

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Submitted

Supplemental digital content of this article is available upon request

ABSTRACT

Background

During the COVID-19 pandemic, concerns grew about excessive opioid dosing in COVID-19 ICU patients. This study aimed to evaluate opioid dosing in the ICU by comparing objective (Nociception Level Monitor (NOL)) and subjective (Behavioral Pain Score (BPS)) pain measurement tools in COVID-19 and non-COVID-19 ICU patients.

Methods

This observational study included 40 sedated, mechanically ventilated ICU patients, of whom half were confirmed COVID-19. Measurements included NOL, BPS, Richmond Agitation Sedation Scale (RASS), Bispectral Index (BIS) and nurse questionnaires. NOL was categorized as <10 (possible excessive analgesia), 10-25 (adequate analgesia), and >25 (possible need for more analgesia). The Time Weighted Average (TWA) assessed duration of NOL >25 ($TWA_{NOL>25}$). Primary outcomes were NOL and BIS over time.

Results

COVID-19 patients received higher sufentanil (18 $\pm$ 9 µg/h versus 9 $\pm$ 6 µg/h) and propofol (307 $\pm$ 127 mg/h versus 277 $\pm$ 137 mg/h) doses (P<0.001). No significant differences were found in $TWA_{NOL>25}$ (P=0.78) or BPS (P=0.1). NOL values were <10 for 63% and 57% of the time in COVID-19 and non-COVID-19 patients. BIS (P<0.001) and RASS (P=0.02) were lower in COVID-19 patients.

Conclusions

While COVID-19 patients received significantly higher opioid doses, low NOL and BPS were seen in all patients, suggesting high analgesia in all patients. Therefore, based on our data, we cannot determine if COVID-19 patients required more opioids.

INTRODUCTION

Optimal pain management is crucial for ICU patients. Insufficient pain management can trigger a series of physiological responses, including elevated stress hormones, hypercoagulability and immune system dysfunction (1, 2). While sufficient analgesia is beneficial, excessive doses of opioids and sedatives negatively impact long term outcomes such as duration of ventilation and survival (3-5).

During the COVID-19 pandemic, concern grew regarding excessive opioid dosing in ICU COVID-19 patients (6). In some instances, COVID-19 patients required three times the opioid dose compared to a historical cohort of ICU patients (7). This raised questions on whether higher doses of opioids were required to achieve comparable levels of analgesia or if clinicians for some reason aimed at a higher level of analgesia in these patients.

Adequate dosing of analgesics in sedated ICU patients is challenging due to their inability to self-report on pain (8, 9). Current methods use vital signs or subjective tools such as the Behavioral Pain Score (BPS) or the Critical Care Pain Observation Tool (CPOT) (10, 11). Vital signs, however, can be affected by many physiological conditions (12), and the BPS and CPOT remain subjective measurements that can vary among health care professionals. Consequently, objective measures are needed to quantify pain in the ICU population.

In recent years, monitors like the Nociception Level (NOL) monitor (Medasense Biometrics Ltd. Ramat Gan, Israel) have been developed to objectively track nociception in sedated patients. Nociception is defined as the neural process of detection, transduction and transmission of noxious stimuli (13). It is assessed by the NOL monitor by combining heart rate, heart rate variability, peripheral vasoconstriction and skin conductance (14). Several studies in the operating room (OR) (14-21) demonstrate that NOL-guided analgesia reduces stress hormones and postoperative pain, and improves hemodynamics. Limited research on NOL in the ICU showed that NOL can identify nociceptive stimuli in ICU patients able to self-report (22, 23). However, further research is needed to assess efficacy of NOL in anesthetized ICU patients.

The aim of this exploratory observational study was to determine whether COVID-19 patients needed higher opioid doses by comparing subjective and objective measures to asses pain in sedated COVID-19 and non-COVID-19 ICU patients.

METHODS

This exploratory observational study was performed in the Leiden University Medical Center (LUMC) between October 6, 2020, and November 11, 2021. This two-phase study initially included 20 patients from October 6 to October 22, 2020. In order to also assess the depth of sedation, 20 additional patients with Bispectral Index (BIS) measurements were included from September 9 to November 11, 2021.

The first phase was registered on the Dutch Trial Register (NTR) (NL9159) (registration approval date: 17-12-2020). Because the NTR and the Central Committee on Research Involving Human Subjects (CCMO) register were merged, temporarily no protocol modifications were possible, leading to registration of the second phase on ClinicalTrials.gov (NCT05579106) (registration approval date:12-10-2022) . Both protocols received Institutional Review Board approval (Title: "Nociception Level Monitoring in the Intensive Care (NEMO)", approval number: A020-001, approval date: 04-09-2020; Title: "Nociception Level Monitoring in COVID-19 patients in the Intensive Care Unit", approval number: CoCo 2021-017, approval date: 08-06-2021. Principle investigator: A. Dahan). The requirement for informed consent was waived by the medical ethics committee. This study was conducted in accordance with the Declaration of Helsinki.

Patients

The study included 20 ICU patients with proven COVID-19 disease by PCR of nose- or airway sample, and 20 non-COVID-19 ICU patients. All patients aged 18 or older receiving mechanical ventilation were eligible. Exclusion criteria included aged 17 or younger. In the second phase the following exclusion criteria were added: severe peripheral edema, heart rate <35, veno-arterial (VA) and veno-venous (VV) extracorporeal membrane oxygenation (ECMO), and abdominal position. Non-COVID-19 ICU patients were randomly selected and were admitted to the ICU in the same period as the COVID-19 patients. The same exclusion criteria applied to this group.

The NOL Monitor

The NOL monitor by Medasense Biometrics Ltd. uses a finger probe to measure skin conductance, vasoconstriction, heart rate, heart rate variability and their time derivatives. These parameters are analyzed using a nonlinear Random Forest regression technique, calculating the NOL index which ranges from 0-100 (14). In the OR, NOL values between 10-25 suggests adequate analgesia, values <10 in the presence of noxious stimuli may suggest excessive analgesia, and >25 may indicate need for additional analgesia (15-17, 24). Only a NOL value above 25 for > 60 seconds during a

medical intervention is deemed indicative of pain. The NOL monitor received EU and health Canada certification, and U.S. Food and Drug Administration de novo grant.

Trial procedures

NOL was measured for 8 hours in all 40 patients. The finger probe was moved every 4 hours to prevent possible skin damage. In 20 patients, additional BIS measurements were done for 8 hours to assess sedation levels. Behavioral Pain Score (BPS) and the Richmond Agitation Sedation Scale (RASS) were documented at least once within the study period. There were no restrictions on types or doses of sedatives and analgesics used.

Nurses annotated clinical interventions such as change in patient position, airway management (e.g. endotracheal suctioning), and patient care (e.g. wound care, bathing) in the electronic medical record database. Subsequently, the type of event was matched with the corresponding NOL and BIS values at the same date and time. Standard care procedures were performed as usual, therefore if the patient needed to be transported for a scan or intervention, measurements were temporarily stopped and resumed as soon as possible.

For the 20 patients where both BIS and NOL were monitored (Supplemental digital content, appendix 1), an evaluation questionnaire was completed. This questionnaire included 7 closed-ended questions and three options to provide a textual response to the choice "other". The questionnaire included questions on the nurses' perception of patients' pain, moments when they believed the patient was in pain, signals that led them to suspect pain, actions taken based on the pain, and communication about their concerns with the attending physician. Results of pain-related questions were compared to the corresponding NOL values.

Data collection

Data was derived from three sources: 1. The NOL index monitor, 2. The BIS monitor, 3. The electronic medical record database (MetaVision). All monitors were time aligned before the start of the measurement. Hemodynamic parameters (heart rate, blood pressure) were extracted from MetaVision. Demographic data, medication, answers from the questionnaires, and annotation data were entered manually in an electronic case report form (eCRF) designed with Castor EDC (25).

Outcome measures

Primary outcomes were BIS and NOL values over time. Secondary outcomes were propofol and sufentanil dose, RASS and BPS, and feasibility of using NOL in the ICU. Feasibility of NOL was assessed in three ways, namely, the quality of the NOL signal, NOL's ability to identify a nociceptive event, and the alignment of nurses' responses to

pain-related questions and the corresponding NOL values.

Statistical analysis

NOL values over time were analyzed by calculating the Time Weighted Average when NOL exceeds 25 ($TWA_{NOL>25}$). The $TWA_{NOL>25}$ was calculated by dividing the accumulated area (AUC) of NOL values above 25 by the total time period ($TWA_{NOL>25}$ = (Area of NOL values above threshold)/(Total time (end-start)). A low $TWA_{NOL>25}$ shows minimal excursions above 25, while a higher $TWA_{NOL>25}$ shows more excursions above 25, which may indicate untreated nociceptive events. $TWA_{NOL>25}$ is presented as medians with interquartile ranges (IQR), and compared using the Mann-Whitney U test. BIS values over time were presented as mean with standard deviation (SD), and compared using an unpaired t-test.

For the secondary endpoints, continuous variables with a normal distribution were reported as means with SDs, whereas variables with a non-normal distribution were reported as medians with IQRs. Differences between groups were assessed using an unpaired t-test or a Mann-Whitney U test. Categorical variables were presented as frequencies and percentages, and differences were analyzed using a chi-squared test.

NOL signal quality was categorized based on the percentage of occurrences where NOL indicated NaN. Signal quality categories were as follows: <10% = very good, 10-30% = good, 30-50% = moderate, 50-70% = poor, 70-90% = very poor. When NaN values exceeded 90% the patients were excluded from the analysis.

NOL responses before and after painful stimuli were calculated in a systemic approach. NOL before a painful stimulus was calculated as the average of NOL values in a 20 second window, which started 30 seconds before the stimulus annotation and lasted until 10 seconds before stimulus annotation. NOL post a painful stimulus was calculated as the average of NOL values in a 20 second window, which were calculated around the maximum NOL value between stimulus annotation and up to 90 seconds afterwards.

Statistical analyses were performed using MATLAB software (MathWorks, Natick, MA, USA) and R language and environment (R Foundation for Statistical Computing, Vienna, Austria, version 4.0.3). Statistical significance was defined as a P-value of <0.05 in a two-sided test.

Table 1. Baseline characteristics of patients.

Variables	COVID-19 ICU (N=20)	non-COVID-19 (N=20)
Age (median [IQR])	67 [61, 71]	65 [51, 71]
Sex = female (%)	16 (80)	13 (65)
BMI (mean (SD))	29 (5)	28 (5)
Day of ICU submission measurement took place (median [IQR])	3.5 [2, 7.25]	3.5 [2, 6.75]
Factors potentially influencing the NOL measurements		
Vasopressive/inotropic medication	14 (70)	15 (75)
Arrythmia	6 (30)	6 (30)
Hypertension	2 (10)	1 (5)
Hypotension	1 (5)	1 (5)
Hypothermia	4 (20)	1 (5)
Bradycardia	6 (30)	1 (5)
Tachycardia	2 (10)	8 (40)
Peripheral edema	3 (15)	9 (45)
VV-ECMO[a]	2 (10)	0 (0)
No influential circumstances	2 (10)	0 (0)
RASS (%)		
-5	9 (45)	8 (40)
-4	10 (50)	8 (40)
-3	1 (5)	4 (20)
BPS (%)		
3	16 (80)	15 (75)
4	3 (15)	4 (20)
5	1 (5)	1 (5)
Ventilation mode (%)		
PCMV	14 (70)	9 (45)
ASV	2 (10)	11 (55)
PSV	4 (20)	0 (0)
Rocuronium	3 (15)	0 (0)

BMI = Body Mass Index, VV-ECMO = Veno-Venous Extracorporeal Membrane Oxygenation, PCMV = Pressure control Continuous Mandatory
Ventilation, ASV = Adaptive Support Ventilation, PSV = Pressure Support Ventilation.
[a] These patients were included in the first phase of the study. VV-ECMO was added as an exclusion criteria in the second phase of the study.

RESULTS

Baseline characteristics can be observed in Table 1 and were similar between the two groups. Two patients were excluded from the analysis because in 98% and 100% NOL indicated NaN.

Primary outcomes

The total $TWA_{NOL>25}$ was 0.39 (IQR 0.09-0.82). No significant differences were observed

between the $TWA_{NOL>25}$ in the COVID-19 (0.33) and the non-COVID-19 group (0.46) (P=0.78) (Table 2). NOL was below 10 for 63% and 57% of the time, and between 10-25 for 22% and 33% of the time in the COVID-19 and non-COVID-19 group, respectively (Figure 1, Table 2). BIS values were 34±15 versus 47±17 in the COVID-19 and non-COVID-19 group (P<0.001) (Table 2).

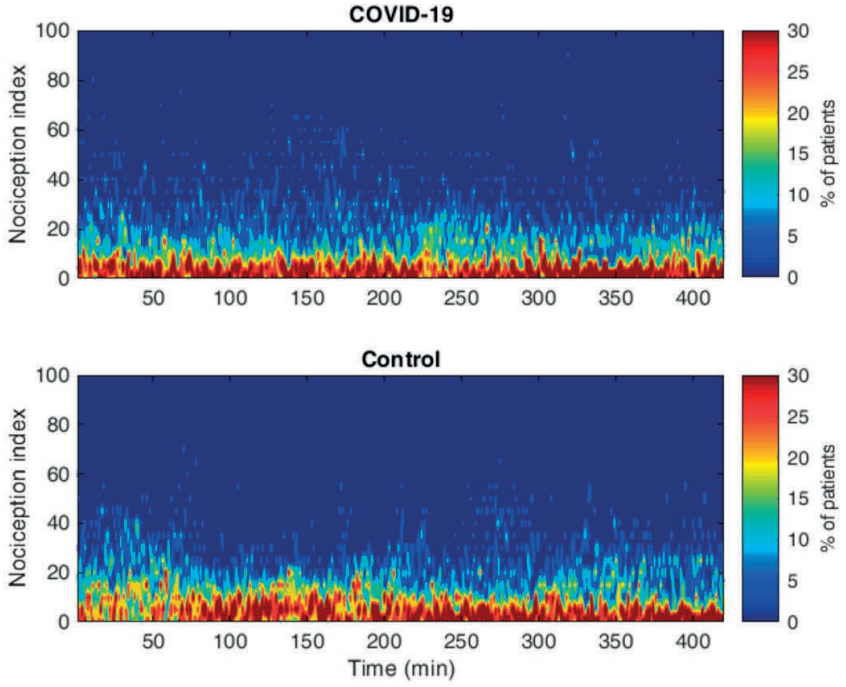

Figure 1. Fire plots of Nociception Level (NOL) index. Values are shown during 8 hours in COVID-19 and Control (non-COVID-19) patients. The colors reflect the percentage of subjects at any time point and range from 0% (dark blue) to 30% (dark red).

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Secondary outcomes

COVID-19 patients received higher doses of sufentanil compared to non-COVID-19 patients (18 ± 9 µg/h versus 9 ± 6 µg/h, P <0.001). Propofol was also dosed higher in COVID-19 patients (307 ± 127 mg/h) compared to non-COVID-19 patients (178 ± 140 mg/h) (P<0.001) (Table 2). Details on additional medication can be found in supplemental Table 1.

Table 2. Patient outcomes.

Variables	COVID-19 ICU	non-COVID-19	Total
NOL and BIS[a]	N=20	N=18	N=38
$TWA_{NOL>25}$ (median [IQR])	0.33 [0.12-0.83]	0.46 [0.06-0.81]	0.39 [0.09, 0.82]
NOL < 10 (%)	63	57	60
NOL 10-25 (%)	22	33	28
BIS (mean ± SD)	34±15	47±17	40±17
Medication[a]	N=20	N=18	N=38
Propofol (mg/h) (mean ± SD)	307 ± 127	178 ± 137	245±147
Sufentanil (µg/h) (mean ± SD)	18 ± 9	9 ± 6	13±9
Quality NOL signal	N=20	N=20	N=40
Very good, No. (%)	11 (55)	8 (40)	19 (48)
Good, No. (%)	6 (30)	5 (25)	11 (28)
Moderate, No. (%)	3 (15)	4 (20)	7 (18)
Poor, No. (%)	0 (0)	0 (0)	0 (0)
Very poor, No. (%)	0 (0)	1 (5)	1 (3)
Unusable , No. (%)	0 (0)	2 (1)	2 (5)
Annotations clinical intervention[a]			
All annotations [b]	N=39	N=39	N=78
Before (median [IQR])	3 [2-7]	4 [2-7]	4 [3-16]
After (median [IQR])	23 [16-32]	25 [14-34]	25 [13-41]
P-value	P<0.001	P<0.001	P<0.001
Airway management	N=20	N=21	N=41
Before (median [IQR])	4 [3-16]	3 [2-7]	4 [3-9]
After (median [IQR])	39[23-47]	26 [17-34]	32 [17-39]
P-value	P<0.001	P<0.001	P<0.001
Change of position	N=15	N=13	N=28
Before (median [IQR])	7 [4-15]	3 [2-5]	7 [4-15]
After (median [IQR])	22 [13-28]	18[12-26]	22 [13-28]
P-value	P=0.02	P<0.001	P<0.001
Patient care	N=3	N=4	N=7
NOL Before (median [IQR])	1 [1-8]	8 [4-14]	7 [1-19]
NOL After (median [IQR])	13 [13-18]	28 [22-31]	19 [15-29]
P-value	P=0.1	P=0.05	P=0.007

[a] Two patients were excluded from the analysis because the NOL signal was categorized as unusable. [b] More than one annotation of a clinical intervention could occur in the same patient.

BPS values were similar for both COVID-19 and non-COVID-19 patients, with scores of 3 (IQR 3-3.2) and 3 (IQR 3-3.5), respectively (p=0.1). RASS scores differed, with a median score of -4.5 (IQR -5 to -4) for COVID-19 and -4 (IQR -4.74 to -3.83) for non-COVID-19 patients (p=0.02). Table 3 shows BPS, BIS, RASS, sufentanil and propofol doses, categorized by mean NOL. Sufentanil levels were higher in COVID-19 patients across all categories, with higher propofol doses in COVID-19 patients when NOL was <10. Furthermore, BPS and RASS were lower in COVID-19 patients when NOL was 10-25.

NOL signal quality was mostly rated very good (48%), good (28%) or moderate (18%) (Table 2). Combining all NOL measurements, a significant difference was observed in the NOL measurement before (4, IQR 3-16) and after (25, IQR 13-41) interventions (P<0.001). During airway management, a median NOL of 4 (IQR 3-9) before and 32 (IQR 17-39) after was observed (P<0.001). When changing patients' position a median NOL value of 7 (IQR 4-15) before and 22 (IQR 13-28) after the intervention was observed (P<0.001). When receiving patient care a median NOL of 6.8 (IQR 1.0-19.3) before and 19 (IQR 15-29) after the intervention was observed (P=0.007). Comparing NOL values before and after interventions in COVID-19 and non-COVID-19 patients yielded similar results (Table 2).

Table 3. Categories based on mean NOL value.

Variables	COVID-19	non-COVID-19	p-value
NOL <10			
BPS (median [IQR])	3 [3, 3.5]	3 [3, 4]	0.5
BIS (median [IQR])	33 [18, 41]	46 [40, 52]	0.1
RASS (median [IQR])	-4.5 [-5, -4]	-4 [-4, -3.5]	0.2
Sufentanil µg/h (mean (SD))	16.4 (10)	10.5 (6)	0.08
Propofol mg/h (mean (SD))	334 (94)	233 (143)	0.08
NOL 10-25			
BPS (median [IQR])	3 [3, 3]	3.3 [3, 4]	0.08
BIS (median [IQR])	42 [36, 44]	48 [39, 62]	0.6
RASS (median [IQR])	-4.8 [-5, -4.5]	-3.8 [-4.6, -3]	0.03
Sufentanil µg/h (mean (SD))	20 (6.3)	8.8 (3.3)	0.005
Propofol mg/h (mean (SD))	311 (139)	233 (61)	0.3
NOL >25			
BPS (median [IQR])	3.5 [3.5, 3.5]	NA	NA
BIS (median [IQR])[a]	NA	NA	NA
RASS (median [IQR])	-4 [-4, -4]	NA	NA
Sufentanil µg/h (mean (SD))	20 (NA)[b]	NA	NA
Propofol mg/h (mean (SD))	250 (NA)[b]	NA	NA

BPS, BIS, and RASS values, and propofol and sufentanil doses when patients are categorized based on their mean NOL value. Two patients were excluded from this table because the NOL signal was categorized as unusable. [a]No BIS measurements were done in this patient. [b]A standard deviation could not be calculated because only one patient with a single measurement was assigned to this group.

Questionnaire

Table 4 shows details of responses to the questions. Most nurses (90%) found the pain medication the patient received "sufficient". Half (50%) of the nurses reported there were no signs of pain, 35% reported signs of pain "during interventions". When comparing NOL values in patients for whom nurses reported no pain (n=10), a median NOL value of 4 (IQR 2-8) before and 19 (IQR 14-27) after an intervention was observed. For those

thought to be in pain (n=10) a median NOL value of 5 (IQR 3-17) before and 30 (IQR 21-30) after an intervention was observed. Change in hemodynamics (60%) was the most frequently reported indicator of pain. In 66% additional actions were taken when patients showed signs of pain, and a bolus of pain medication was given in all cases. Concerns regarding the patients' pain were discussed with the attending physician in 3 out of 9 cases (33%), resulting in changes in the treatment plan in all cases. Questionnaire outcomes were similar between COVID-19 and non-COVID-19 groups (Table 4).

Table 4. Results evaluation questionnaire. It was possible to provide multiple answers for questions 2 and 5. Textual responses to "other" in question 2 were: "difficulty in assessment due to muscle relaxants" and "pain started after stopping/lowering the sedation/remifentanil". Textual responses to "other" in question 3 were: "breathing frequency", "desaturation in combination with drop in heart rate", and "coughing".

Questions		COVID-19 (N=10)	non-COVID-19 (N=10)	Total (N=20)
1.	**What is your general impression of the pain medication the patient has received today? (%)**			
	Sufficient	9 (90)	9 (90)	18 (90)
	Reasonable	1 (10)	1 (10)	2 (10)
	Insufficient	0 (0)	0 (0)	0 (0)
	Too much	0 (0)	0 (0)	0 (0)
2.	**What were moments when the patient gave the impression of experiencing pain?**			
	During interventions	3 (30)	4 (40)	7 (35)
	Throughout the whole day	0 (0)	0 (0)	0 (0)
	In intermittent episodes throughout the day	0 (0)	0 (0)	0 (0)
	Other	2 (20)	2 (20)	4 (20)
	The patient was comfortable and did not experience any pain	5 (50)	5 (50)	10 (50)
3.	**What signals gave you the impression that the patient was in pain? (%)**			
	Facial grimaces	0/5 (0)	1/5 (20)	1/10 (10)
	Higher blood pressure/heart rate	3/5 (60)	3/5 (60)	6/10 (60)
	Motor restlessness	1/5 (20)	0/5 (0)	1/10 (10)
	Other	1/5 (10)	1/5 (20)	2/10 (20)
4.	**Was any action taken when the patient gave the impression of being in pain? (%)**			
	Yes	3/4 (75)	3/5 (60)	6/9 (67)
	No	1/4 (25)	2/5 (40)	3/9 (33)
5.	**If yes, What actions were taken? (%)**			
	Bolus of pain medication	3/3 (100)	3/3 (100)	6/6 (100)
	Maintenance dose was increased	1/3 (25)	0/3 (0)	1/6 (17)
	Initiated new pain medication	0/3 (0)	0/3 (0)	0/6 (0)
	Other	0/3 (20)	0/3 (20)	0/6 (0)
6.	**Were concerns regarding the patients' pain communicated with the treating physician? (%)**			
	Yes	1/4 (25)	2/5 (40)	3/9 (33)
	No	3/4 (75)	3/5 (60)	6/9 (67)
7.	**Has this led to any changes in the treatment plan?**			
	Yes	1/1 (100)	2/2 (100)	3/3 (100)
	No	0/1 (0)	0/2 (0)	0/3 (0)

DISCUSSION

In this observational study, including 40 mechanically ventilated and sedated adult ICU patients, COVID-19 received higher sufentanil and propofol doses compared to non-COVID-19 patients. Both groups had low NOL and BPS values with lower BIS and RASS values in the COVID-19 group, suggesting high analgesia in both groups and deeper sedation in the COVID-19 group.

Most previous studies evaluated the use of NOL in the OR, showing potential benefits in reduced postoperative stress hormones, opioid use, and postoperative pain scores (15-21). Within an ICU setting, only two previous studies have been conducted (22, 23). These studies, including 15 and 54 patients, aimed to assess the ability of NOL to identify nociceptive stimuli in patients able to self-report. While both studies found that NOL could identify nociceptive stimuli, it is important to note that NOL is primarily validated in sedated patients. Therefore, an important added value of the current study is the focus on sedated ICU patients, offering new insights in using NOL in unresponsive ICU patients.

Our results show low NOL, BPS, RASS and BIS values in both groups. COVID-19 patients received higher doses of analgesia and sedation, however, NOL values were below 10 in more than 50% of the time in both groups, suggesting that in both groups greater amounts of analgesics were administered than required. However, before drawing this conclusion, several points should be considered. Firstly, it is important to note that the validation of NOL reference values was conducted in the OR (14, 17). Therefore, different reference values could be more appropriate for the ICU population, potentially misclassifying them as either under- or overdosed. Additionally, comparing NOL with subjective pain indicators like BPS and CPOT, is difficult as these measures are often biased by the feeling that the dosing of opioids is appropriate. Secondly, little is known about the influence of sedation on NOL. A previous study suggested that propofol had minimal effect on NOL, however, due to a small sample size this effect could not be properly investigated (17, 26). If the effect is present, this could be more pronounced in ICU patients due to longer periods of sedation compared to OR patients. Lastly, in the ICU, several indications, besides pain or discomfort, warrant higher doses of analgesics and sedatives. In COVID-19 patients, for example, higher doses of analgesics and sedatives were often required due to difficult mechanical ventilation and to subdue excitation (27, 28). All the above mentioned aspects require further investigation before ICU patients can be categorized as either under- or overdosed based on NOL values.

Our findings suggest that NOL has a good signal quality, has the ability to identify nociceptive stimuli, and has a reasonably well alignment with nurses' observations.

This suggests that the NOL monitor offers a valuable representation of pain levels. However, some observations need to be considered in the interpretation of the data. We observed that the NOL measurements may be impacted in the presence of factors such as tachycardia, peripheral edema and arrhythmias. Previous studies in the OR, where NOL showed to be of added value, mainly excluded patients under these conditions (14-21). The higher prevalence of these conditions in the ICU compared to the OR may reduce the added value of NOL. However, in our data we mostly observed a "good" or "very good" signal quality. Interestingly, COVID-19 patients seemed to have better signal quality, likely due to mono-organ dysfunction, compared to the non-COVID-19 group that had a higher incidence of conditions that could interfere with the NOL signal quality (e.g. tachycardia, peripheral edema). Hence, for a more conclusive statement on NOL reliability, further testing in a larger and more diverse ICU patient cohort is needed.

Since NOL measurements align reasonably well with nurses' observation, one may speculate whether we need a specific objective device to assess pain. In favor of the NOL is a previous study showing limited benefit of subjective pain assessment methods (CPOT and BPS) (29). In our data, we see a low BPS in both groups. A limitation of the BPS is when it is at its lowest (a value of 3), it is difficult to determine whether this low value is acceptable or if too much analgesics were administered. NOL might offer added value here, being a continuous monitor with a larger scale (between 0 and 100) and therefore could be better at making this distinction. Additionally, studies on NOL in the OR demonstrated a reduction in stress hormone levels when analgesia is guided by NOL (16). If NOL can effectively regulate pain and minimize stress hormone release in the ICU, it could have significant impact on both short- and long-term outcomes (3-5). Large-scale randomized controlled trials are needed to confirm these advantages.

Some limitations must be considered. Firstly, the small sample size limits robust statistical analysis. Nonetheless, it still remains one of the largest observational studies in this field. Secondly, half of the patients had COVID-19, allowing us to explore opioid administration in this subgroup, but impacting generalizability. Thirdly, in only half of the patients all measurements (BIS, NOL and evaluation questionnaire) were done. Replicating these findings in a larger patient cohort is therefore imperative. Also, the time gap between inclusion of the first and second 20 patients can influence outcomes due to changing COVID-19 protocols. However, when analyzing primary and secondary endpoints of both datasets separately, we obtained similar results.

In conclusion, COVID-19 patients received higher opioid doses compared to non-COVID-19 patients. Both groups had low NOL and BPS values with lower BIS and RASS values in the COVID-19 group, suggesting high analgesia in both groups and deeper

sedation in the COVID-19 group. Since all patients had low BPS and NOL values, we cannot determine whether COVID-19 patients needed more opioids. NOL shows promise for ICU use, however, further investigation is needed regarding reference values, medication effects, and specific ICU conditions on NOL measurements. Once these aspects are better understood, a randomized controlled trial is warranted to assess the impact of NOL-guided pain management on short- and long-term outcomes.