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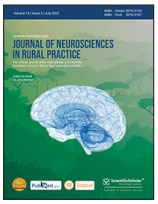

Original Article

Evaluation and correlation of nociceptive response index and spectral entropy indices as monitors of nociception in anesthetized patients

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ABSTRACT

Objectives: During anesthesia, the response to these stimuli depends on the balance between nociception and antinociception. Recently, various monitoring systems based on the variables derived from electroencephalography, plethysmography, autonomic tone, reflex pathways, and composite algorithms have been introduced for monitoring nociception. The main aim of our study was to evaluate and correlate the physiological variables which reflect the autonomic nervous system response to nociception, such as heart rate (HR), systolic blood pressure (SBP), perfusion index (PI), and nociceptive response index (NRI), with the spectral entropy indices response entropy (RE) and RE-state entropy (SE), which reflects electromyographic (EMG) activation as a response to pain.

Materials and Methods: This is a retrospective analysis of the data from a prospective study on the hypnotic and analgesic effects and the recovery profile of sevoflurane-based general anesthesia. Eighty-six patients undergoing single-agent sevoflurane anesthesia were recruited in the study. The study parameters, HR, SBP, SE, RE, RE-SE, PI, and NRI, were recorded at predefined time points before and after a standardized noxious stimulus. Correlation between the variables was carried out by applying the Pearson correlation equation for normal and the Spearman correlation equation for non-normally distributed data. Receiver operating characteristic (ROC) graphs were plotted, and the area under the curve was calculated to assess the diagnostic accuracy of post-stimulus NRI in detecting pain which was defined as RE-SE >10.

Results: There was a significant increase in the SBP, HR, NRI, RE, SE, and RE-SE and a considerable decrease in PI values during the post-noxious period compared to the pre-noxious period. There was no correlation between the absolute values of NRI and entropy indices at T2. However, among the reaction values, there was a weak correlation between the reaction values of NRI and RE (r = 0.30; *P* = 0.05). The area under the ROC curve for NRI to detect pain as defined by RE-SE >10 was 0.56.

Conclusion: During sevoflurane anesthesia, the application of noxious stimulus causes significant changes in variables reflecting sympathetic response and EMG activity. However, NRI failed to detect nociception, and there was only a weak correlation between the reaction values of NRI and RE-SE.

Keywords: Nociceptive response index, Entropy, Intraoperative pain, Neuroanesthesia

INTRODUCTION

The International Association for the Study of Pain defines pain as "An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage."[1,2] While pain is a subjective experience, the neural encoding of the stimulus is referred to as nociception.[3] Noxious stimuli produce autonomic activation, which increases with the intensity of noxious stimuli.[4,5] During anesthesia, the response to these stimuli depends on the balance between nociception and antinociception.[6]

Ironically, estimating this balance and monitoring the "analgesia" component of anesthesia relies on surrogate yet non-specific autonomic reactions such as tachycardia, hypertension, sweating, and lacrimation. Ironically, these responses could be suppressed by anesthetic agents or anesthesia-related drugs such as beta-blockers and muscle relaxants.[4] Recently, various monitoring systems based on the variables derived from electroencephalography (EEG), plethysmography, autonomic tone, reflex pathways, and composite algorithms have been introduced for monitoring nociception.[4,7] The lack of a validated

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measure precludes the extensive use of these monitors in the clinical setting.

The perfusion index (PI) is derived from the photoelectric plethysmographic signal of pulse oximetry. It is calculated as the ratio between the pulsatile component and the non-pulsatile component of the light reaching the detector of the pulse oximeter.[8-10] A change in the pulsatile component accompanies any alteration in the peripheral perfusion. The sympathetic activation in response to nociception is accompanied by peripheral vasoconstriction, which is reflected by the PI.[9] The nociceptive response index (NRI) is a novel index based on a hemodynamic model that uses hemodynamic variables such as heart rate (HR), systolic blood pressure (SBP), and PI.[11] It is currently being evaluated as an index to assess nociception-antinociception balance.[11-13]

Another monitor used to assess nociception is based on frontal electromyographic (EMG) activity from the M-Entropy TM module (GE Healthcare, Helsinki, Finland).[14] The frontal EMG component is created by muscle activity and usually dominates at frequencies higher than 30 Hz. The electroencephalogram (EEG) component reflecting the state of consciousness dominates the lower frequencies and is indicated by state entropy (SE) computed over 0.8–32 Hz. Response entropy (RE) includes EEG and EMG, computed over a frequency range of 0.8–47 Hz. When the EMG power (sum of spectral power between 32 Hz and 47 Hz) equals zero, there would be no difference between RE and SE. An EMG activation during nociception would increase the RE and RE-SE difference.[14-16]

The main aim of our study was to evaluate and correlate the physiological variables which reflect the autonomic nervous system's response to nociception, such as HR, SBP, PI, and NRI, with the spectral entropy indices, that is, RE and RE-SE, which reflects EMG activation as a response to pain.

MATERIALS AND METHODS

This is a retrospective analysis of the data from a prospective study conducted after obtaining institutional ethics committee approval, on the hypnotic and analgesic effects and the recovery profile of sevoflurane-based general anesthesia. Consenting patients aged between 18 and 60 years scheduled for elective lumbar disk surgery were included in the study. Patients with the American Society of Anesthesiologists (ASA) physical status classification of III and higher, neurologic or psychiatric ailments, diabetes mellitus, systemic or peripheral vascular disease, obesity (body mass index [BMI] >30 kg/m^2) and underweight (BMI <18.5 kg/m^2), and history of alcohol or drug abuse were excluded from the study. Moreover, patients receiving any medications affecting the nervous system, that is, sedatives and anxiolytics, medicines that can affect vasomotor tone, that is, vasopressors and anti-hypertensive drugs, medications acting on the autonomic nervous system, that is, beta-blockers and vagolytics, and those who had a history of chronic usage of analgesics were also excluded from the study.

Premedication drugs such as anxiolytics and anticholinergics were avoided in the study population. Standard ASA pre-induction monitors were placed in the operating room, and peripheral intravenous access was established. The entropy electrode was applied to the patient's forehead as per the manufacturer's instructions and connected to the monitor (M-Entropy module for S/5™ Anesthesia Monitor, GE Healthcare). General anesthesia was induced with IV Propofol 2–3 mg/kg, and IV lignocaine 2 mg/kg was administered to blunt the autonomic responses to intubation. The peripheral nerve stimulator electrodes were placed over the ulnar nerve on the volar aspect of the distal forearm, and Inj. Succinylcholine 2 mg/kg was then administered. A train-of-four (TOF) count of 0 was ensured before intubation using a neuromuscular monitor device (M-NMT MechanoSensor, GE Healthcare, Finland). After intubation, mechanical ventilation with Air: O_2 (1:1) mixture was initiated. Temperature monitoring with a nasopharyngeal probe was instituted to ensure normothermia, and end-tidal CO_2 was monitored to ensure normocarbia. A pulse oximeter (Beneview T8, Mindray, China) was placed in the arm contralateral to the side of non-invasive blood pressure monitoring. The room's ambient temperature was constant at approximately 23–25°C throughout the study. In both groups, I.V. fluid administration was standardized to 4 mL/kg^{-1}/h^{-1} of normal saline solution.

With over-pressurization to target an age-corrected MAC of 1.0, sevoflurane was administered. The noxious stimulus was provided after 20 min to ensure the volatile agent's steady-state concentration and to avoid propofol's residual effects. We also confirmed a TOF count of 4 before the stimulus. A tetanic stimulus (square-wave, 70 mA stimulus, 30-s duration at 50 Hz) was applied as the standardized noxious stimuli, after which the post-noxious stimulus study parameters were obtained. Opioids were administered only after the recording of the post-stimulus values.

The study parameters, namely, HR, SBP, SE, RE, RE-SE, and PI, were recorded at predefined time points before and after the noxious stimulus. The NRI was calculated retrospectively using the NRI formula, which includes the intraoperative hemodynamic variables HR, SBP, and PI, as follows:[12,13]

$$NR\ index = -1 + \frac{2}{1 + e^{-(0.01HR + 0.02SBP - 0.17PI)}}$$

The formula of NRI was fed into and computed in the data entry sheet (Microsoft Excel, Microsoft Corporation [2018]). Hence, the values of the variables were recorded as follows:

1. Pre-stimulus or the non-noxious period (T1) parameters: recorded after induction of anesthesia, before providing noxious stimulus as the mean value for 1 min

2. Post-noxious stimulus period (T2) parameters: recorded after application of noxious stimuli recorded as a maximal value within 1 min
3. Reaction values: NRI (normalized index) calculated as the maximal difference between post-stimulus and pre-stimulus values.

For HR, SBP, PI, and entropy indices, reaction (Δ) was normalized as follows:

$$Reaction = \frac{Maximal\ difference\ between\ post\text{-}Stimulus\ and\ pre\text{-}Stimulus\ values}{Pre\text{-}stimulus\ values} \times 100$$

During the study duration, hemodynamic derangements were promptly managed. If the entropy values were >70, additional sedatives/analgesics would be administered, and such patients were excluded from the study. Participants with motion artifacts in the plethysmographic wave were also excluded from the study.

Statistical analysis

Statistical calculations were done using the Statistical Package for the Social Sciences (SPSS) software version 22 for Microsoft Windows (SPSS Inc., Chicago, IL, USA). The normality of the data was checked using Shapiro–Wilk test. Continuous data were described as means ± SD for normally distributed data and medians and interquartile ranges for non-normally distributed data. Categorical data were expressed as frequencies (%). Data analysis was performed using paired *t*-tests for normally distributed data and the Wilcoxon rank test for non-normally distributed data. Correlation between the variables was carried out by applying the Pearson correlation equation for normal and the Spearman correlation equation for non-normally distributed data. For absolute values of r, 0–0.29 is regarded as negligible, 0.3–0.49 as weak, 0.5–0.69 as moderate, 0.7–0.89 as strong, and 0.9–1 as very strong correlation.[17]

Receiver operating characteristic (ROC) graphs were plotted, and the area under the curve was calculated to assess the diagnostic accuracy of post-stimulus NRI in detecting pain was defined as RE-SE >10. $P < 0.05$ is considered statistically significant, and $P < 0.001$ is considered highly significant.

RESULTS

A total of 96 patients presenting for lumbar spine surgery were recruited for the study. Ten patients were ineligible based on the exclusion criterion. Therefore, 86 subjects were included in the study. [Table 1] shows the patient demographic characteristics.

There was a significant increase in the SBP (146.1 ± 7.2 vs. 124.4 ± 10; $P = 0.003$), HR (99.1 ± 13.3 vs. 74.8 ± 11.9; $P = 0.000$), and NRI (0.93 ± 0.02 vs. 0.83 ± 0.05; $P = 0.01$) values during the post noxious period compared to the pre-noxious period [Table 2]. A significant decrease in PI was also observed in the T2 compared to T1 (3.1 [2.3–4.2] vs. 4.9 [4.2–5.5]; $P = 0.01$) [Table 2]. In addition, an increase in RE (55.8 ± 6.3 vs. 34.9 ± 5.8; $P = 0.000$), SE (46.8 ± 5.1 vs. 34.3 ± 5.9; $P = 0.02$), and RE-SE (11 ± 4 vs. 2.4 ± 1.3; $P = 0.01$) was also observed in the post-noxious period (T2) compared to the pre-noxious period (T1) [Table2].

A moderate correlation (r = 0.50, $P = 0.05$) was observed between HR and SBP in the post-noxious period [Table 3]. A weak correlation was observed at T2 between RE and hemodynamic variables of HR (r = 0.31, $P = 0.04$) and MAP (r = 0.32, $P = 0.04$) [Table 3]. There was no correlation between the absolute values of NRI and entropy indices at T2 [Table 3]. However, among the reaction values, there was a weak correlation between the reaction values of NRI and RE (r = 0.30; P 0.05) [Table 4]. The area under the ROC (AUROC) curve for NRI to detect pain as defined by RE-SE >10 was 0.56 [Figure 1].

DISCUSSION

Noxious stimuli, including surgical procedures, induce a stress response by activating the autonomic response system and the hypothalamo-pituitary-adrenal axis, thus generating biochemical reactions throughout the body.[18] Prolonged

Table 1: The demographic details of patients in the study.

Parameters	Results
Age (years)	45±12
Male: female ratio	44:42
Height (cm) (mean±SD)	160±12
Weight (kg) (mean±SD)	69±15
ASA PS (I/II)	38/46

ASA PS: American society of anesthesiologists physical status, SD: Standard deviation

Table 2: Comparing the study parameters at T1 (before noxious stimuli) and T2 (after noxious stimuli).

Study parameters	At T1	At T2	*P*-value
HR (bpm)	74.8±11.9	99.1±13.3	0.000#
SBP (mmHg)	124.4±10	146.1±7.2	0.003*
PI	4.9 (4.2–5.5)	3.1 (2.3–4.2)	0.01*
RE	34.9±5.8	55.8±6.3	0.000#
RE-SE	2.4±1.3	11±4	0.01*
NRI	0.83±0.05	0.93±0.02	0.01*

Data are presented as mean±standard deviation and median (quartiles). *P<0.05 is considered statistically significant. #P<0.001 is considered highly significant. NRI: Nociceptive response index, SBP: Systolic blood pressure, HR: Heart rate, RE: Response entropy, SE: State entropy, PI: Perfusion index

Table 3: Correlation between the study parameters at T2 (after noxious stimuli).

Correlation between study parameters	r-value	*P*-value
HR and SBP	0.5	0.05
HR and RE	0.31	0.04*
HR and RE-SE	0.08	0.27
HR and PI	−0.12	0.2
SBP and PI	−0.005	0.9
SBP and RE	0.32	0.04*
SBP and RE-SE	0.12	0.23
RE and PI	0.18	0.19
RE and NRI	0.23	0.06
RE-SE and PI	−0.12	0.23
RE-SE and NRI	0.13	0.2

*$P<0.05$ is considered statistically significant. #$P<0.001$ is considered highly significant. HR: Heart rate, RE: Response entropy, SE: State entropy PI: Perfusion index, NRI: Nociceptive response index, SBP: Systolic blood pressure

Table 4: Correlation between the reaction values of the study parameters.

Correlation between reaction values	r-value	*P*-value
ΔHR andΔRE-SE	0.28	0.05
ΔHR andΔSBP	0.27	0.05
ΔHR andΔPI	0.16	0.22
ΔHR andΔRE	0.18	0.26
ΔSBP andΔPI	−0.14	0.21
ΔSBP andΔRE	0.34	0.04*
ΔSBP andΔRE-SE	−0.02	0.90
ΔPI andΔRE	−0.23	0.07
ΔPI andΔRE-SE	0.10	0.24
ΔRE andΔNRI	0.30	0.05
ΔRE-SE andΔNRI	0.08	0.86

*$P<0.05$ is considered statistically significant. #$P<0.001$ is considered highly significant. NRI: Nociceptive response index, SBP: Systolic blood pressure, HR: Heart rate, RE: Response entropy, SE: State entropy

surgical stress can lead to increased morbidity and delayed postoperative recovery.[19-21] Thus, it is imperative to optimize perioperative analgesia to improve postoperative outcomes. However, intraoperative assessment of pain with monitors of nociception-antinociception balance has been limited by their caveats, and their use is still not incorporated in standardized intraoperative monitoring. In addition, many modalities of pain monitoring require specific monitoring equipment. Therefore, a new modality that does not require the same would be of benefit in the clinical setting. We evaluated HR, BP, PI, entropy indices, and NRI as markers of nociception, as these variables can be easily obtained from routine perioperative monitors. The variables such as HR, SBP, PI, and NRI reflect the autonomic nervous system response to nociception. HR variability and peripheral vasoconstriction are better indicators of autonomic activation to pain than

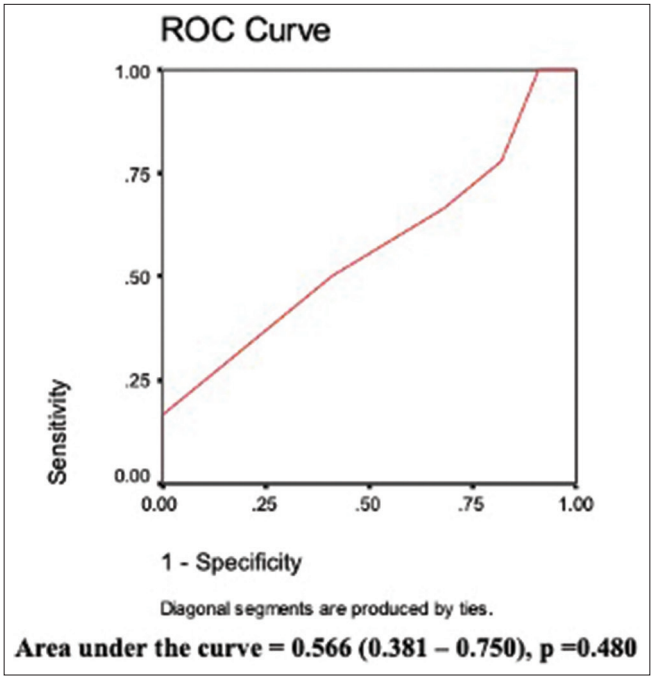

Figure 1: Diagnostic accuracy of post-stimulus nociceptive response index in predicting pain defined as response entropy-state entropy >10.

electrodermal, cardiovascular, and pupillary measures.[5] The latter indices also detect non-specific sympathetic arousal not attributed to noxious stimuli and, hence, are not precise indicators of pain.[5] We used PI as a marker of peripheral vasoconstriction, HR and SBP as hemodynamic parameters, and NRI as the normalized index of autonomic response to the noxious stimuli.

This study found a significant decrease in PI in the post-noxious period. The previous studies have found an association between nociception-associated sympathetic stimulation and a reduction in PI. Chu *et al.* evaluated PI for pain assessment in the post-anesthesia care unit. They found PI values increased when intravenous analgesics were administered and suggested that a percentage change in the PI of more than 12% can be used as an additional discharge criterion for pain assessment in the post-operative period.[22] Hasanin *et al.* observed that the application of a noxious stimulus was associated with a decrease in PI in critical care settings. Although there was no correlation between the absolute values of PI and the behavior pain scale (BPS), there was a good correlation between the change in the PI and the change in BPS values in the post-noxious stimuli period.[8] PI has also been a helpful nociception monitor during labor analgesia.[23] It has also been found to be a sensitive indicator to detect the early onset of caudal block in pediatric patients.[24] Nishimura *et al.* measured PI and HR changes to increase electrical stimulus until the subjects reached the tolerance threshold gradually. They observed

that lesser-intensity stimuli that failed to induce HR changes caused a significant change in PI in healthy volunteers.[25]

NRI, a recently proposed index, is a dimensionless number between 0 and 1; it was developed based on appropriate mathematical models representing autonomic activation responses to noxious stimulation and considering HR, SBP, and PI in calculating the numerical value.[11,13] However, the index has not been widely validated in the intraoperative setting. Hirose *et al*., evaluated its utility to discriminate nociceptive responses to a small and large skin incision in laparoscopy and laparotomy and found that NRI quantitatively discerned the differences.[11] They suggested that NRI could be used to assess either real-time nociceptive responses or averaged nociceptive responses throughout surgery without special equipment. We observed that NRI increased significantly in the post-noxious period along with the hemodynamic variables of HR and MAP and a concurrent decrease in PI.

Many studies have explored the potential of entropy monitors to reflect nociceptive-antinociceptive balance. Entropy indices have the added advantage of monitoring response to noxious stimuli even in patients whose autonomic response is attenuated, for example, patients on alpha- or beta-blockers. We found that all the spectral entropy-based parameters (SE, RE, and RE-SE) increased significantly during post-noxious period. Guerrero *et al*. found that the RE-SE difference increased significantly after a noxious stimulus during sevoflurane anesthesia.[15] Mathews *et al*. integrated the difference between RE and SE into an automated algorithm for opioid administration in an intraoperative setting.[26] Gruenewald *et al*. found that RE-SE <10 was associated with a significant reduction in opioid consumption.[16] However, one of the caveats of using these variables is that it is significantly impaired during the neuromuscular blockade. Prior studies have shown that muscle relaxants suppress entropy changes to noxious stimuli.[27,28] Aho *et al*. observed that both EEG and EMG activation occurred after skin incision, increasing RE–SE values significantly. However, this increase was noted only in patients who were not administered neuromuscular blockers.[29] Weil *et al*. found that the motor response to a noxious stimulation could be detected by an EMG-mediated increase in spectral entropy predominantly in RE. They also observed that the neuromuscular blockade prevents the nociception-induced EMG activation reflected by a rise in RE and RE-SE. To avoid the confounding influence of neuromuscular blockade, we ensured a TOF count of 4 before applying noxious stimuli to ensure no residual effects of neuromuscular blockade.

In our study, though all the parameters responded to nociception, there was only a weak correlation between RE with HR and SBP. There was no correlation between RE-SE and any of the other variables. Furthermore, there was no correlation between NRI and any entropy indices at T2. However, a weak correlation was observed between the reaction values of NRI and RE. These results should be cautiously interpreted considering the limitations of entropy indices as a nociception monitor. It remains to be a well-validated monitor of nociception. One study analyzed the absolute entropy values and the raw EEG data and found that the increase of RE was soon followed by an increase in SE values, thus decreasing the RE-SE difference. They presumed that the cause of the rise in SE was not due to EEG activation but due to the intense EMG activity changing the EEG spectrum at 20 Hz.[30] As all activity below 32 Hz is regarded as EEG, SE can also capture some EMG activity. Although, in our study, there was a concurrent increase of RE-SE and a significant increase in SE and RE after the noxious stimuli, the reason for the lack of correlation is a conundrum. Moreover, NRI could not detect nociception as defined by RE-SE >10 as the AUROC was only 0.56. Further prospective studies are needed to validate NRI as a measure of nociception.

We chose a long-lasting tetanic stimulus (30 s) of the ulnar nerve as the standardized noxious stimulus. It has been shown to provide a better experimental pain model for surgical pain during general anesthesia than shorter stimuli.[6,31] We did not include intubation as a noxious stimulus as the use of neuromuscular blockade would preclude using entropy indices as a measure of nociception. In addition, the study did not use graded stimuli, and response to opioids was not evaluated.

This study also carries the inherent limitations of a retrospective analysis. Assuming a correlation coefficient (r) of 0.3 to detect the presence of any correlation between the study variables, a minimum of 84 patients should be enrolled in a study for a power of 80% and an alpha error of 0.05. Our analysis, though retrospective in nature, is based on data from 86 patients and, hence, is adequately powered for the results to be valid. Nonetheless, prospective studies are necessary to validate the use of NRI as a measure of nociception-antinociception balance. The study was conducted only on ASA 1 and 2 patients presenting for elective lumbar disk surgery. Many of them had sciatica and lower back pain; the influence of preoperative pain on the intraoperative analgesia indices is not vastly studied and could potentially impact the study results. The results are also limited to a single-standardized noxious stimulation 20 min after starting sevoflurane anesthesia (at 1.0 MAC). The values were not recorded at any point after the start of the surgery, and hence, the results need to be interpreted cautiously since NRI values were obtained based on a single non-surgical noxious stimulus. For validation of any monitor, studies on different cohorts of patients presenting for various types of surgeries are required for discriminative and criterion testing. Furthermore, we have not used any other nociception

monitors; studies analyzing correlation with monitors such as surgical plethysmographic index or analgesia nociception index are warranted to assess the utility of NRI as a simple, non-invasive, and objective tool for nociception monitoring.

CONCLUSION

During sevoflurane anesthesia, the application of noxious stimulus causes an increase in HR, MAP, NRI, RE, SE, and RE-SE, along with a decrease in PI. In addition, there was a weak correlation between the reaction values of NRI and RE-SE. However, NRI failed to detect nociception. Therefore, further studies for evaluating the NRI index to discriminate various types of noxious stimuli, and its response to opioid administration, are warranted.

Declaration of patient consent

The Institutional Review Board (IRB) permission obtained for the study.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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