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SCIENTIFIC ARTICLE

Analgesia Nociception Index for perioperative analgesia monitoring in spinal surgery

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Abstract
Background and objectives: The Analgesia Nociception Index is an index used to measure the levels of pain, sympathetic system activity and heart rate variability during general anesthesia. In our study, Analgesia Nociception Index monitoring in two groups who had undergone spinal stabilization surgery and were administered propofol–remifentanil (Total Intravenous Anesthesia) and sevoflurane–remifentanyl anesthesia was compared regarding its significance for prediction of postoperative early pain.
Methods: BIS and Analgesia Nociception Index monitoring were conducted in the patients together with standard monitoring. During induction, fentanyl 2 μg.kg^{-1}, propofol 2.5 mg.kg^{-1} and rocuronium 0.6 mg.kg^{-1} were administered. During maintenance, 1.0 MAC sevoflurane + remifentanil 0.05–0.3 μg.kg^{-1}.min^{-1} and propofol 50–150 μg.kg^{-1}.min^{-1} + remifentanil 0.05–0.3 μg.kg^{-1}.min^{-1} were administered in Group S and Group T, respectively. Hemodynamic parameters, BIS and Analgesia Nociception Index values were recorded during surgery and 30 min postoperatively. Postoperative visual analog scale (VAS) values at 30 minutes were recorded.
Results: While no difference was found between mean Analgesia Nociception Index at all times of measurement in both groups, Analgesia Nociception Index measurements after administration of perioperative analgesic drug were recorded to be significantly higher compared to baseline values in both groups. There was correlation between mean values of Analgesia Nociception Index and VAS after anesthesia.
Conclusion: Analgesia Nociception Index is a valuable parameter for monitoring of perioperative and postoperative analgesia. In spine surgery, similar analgesia can be provided in both Total Intravenous Anesthesia with remifentanil and sevoflurane administration. Analgesia Nociception Index is efficient for prediction of the need for analgesia during the early postoperative period, and therefore is the provision of patient comfort.

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Índice de analgesia/nocicepção para monitorização da analgesia perioperatória na cirurgia da coluna vertebral

Resumo

Justificativa e objetivos: O Índice de analgesia/nocicepção (ANI) é usado para medir os níveis de dor, a atividade do sistema simpático e a variabilidade da frequência cardíaca durante a anestesia geral. Em nosso estudo, a monitoração do ANI em dois grupos que foram submetidos à cirurgia de estabilização da coluna vertebral e receberam propofol-remifentanil (*Total Intravenous Anesthesia* - TIVA) e sevoflurano-remifentanil foram comparados para identificar sua importância na previsão precoce de dor no pós-operatório.

Métodos: Os pacientes foram monitorados com o uso de BIS e ANI juntamente com a monitoração padrão. Durante a indução, fentanil ($2 \mu g.kg^{-1}$), propofol ($2,5 mg.kg^{-1}$) e rocurônio ($0,6 mg.kg^{-1}$) foram administrados. Durante a manutenção, 1 CAM de sevoflurano + remifentanil ($0,05-0,3 \mu g.kg^{-1}.min^{-1}$) e propofol ($50-150 \mu g.kg^{-1}.min^{-1}$) + remifentanil ($0,05-0,3 \mu g.kg^{-1}.min^{-1}$) foram administrados aos grupos S e T, respectivamente. Parâmetros hemodinâmicos, valores de BIS e ANI foram registrados durante a cirurgia e aos 30 minutos de pós-operatório. Os valores Visual Analogue Scale (VAS) aos 30 minutos de pós-operatório foram registrados.

Resultados: Enquanto não observamos diferença entre as médias do ANI em todos os tempos de mensuração de ambos os grupos, as mensurações do ANI após a administração do analgésico no perioperatório foram significativamente maiores que os valores basais de ambos os grupos. Houve correlação entre as médias dos valores de ANI e VAS após a anestesia.

Conclusão: ANI é um parâmetro importante para o monitorização de analgesia nos períodos perioperatório e pós-operatório. Na cirurgia da coluna vertebral, analgesia semelhante pode ser obtida com anestesia intravenosa total com remifentanil e com a administração de sevoflurano. O ANI é eficiente para prever a necessidade de analgesia durante o período pós-operatório imediato e, portanto, para proporcionar conforto ao paciente.

Introduction

Spinal stabilization surgery is a top-level surgery for causing painful stimuli. Perception of pain by the patient during monitoring of anesthesia can be observed as elevated arterial blood pressure and/or heart rate. The analgesia nociception index is calculated by measurement of change in the nociception–antinociception balance reflecting to heart rate simultaneously.[1,2] A patient without pain will have a dominant parasympathetic tone. Normally, Analgesia Nociception Index (ANI) value ranges from 0 to 100, but when parasympathetic activity is dominant, then ANI shows the values over 50 or more. When the pain is perceived, sympathetic system will be dominant and the ANI value will fall below 50. Under general anesthesia, the ANI range of 50–70 shows the adequate level of analgesia. In a conscious patient, while higher values are indicative of analgesia, in lower levels, psychological stress factor may come into play and ANI may lose its reliability.[3,4]

Since ANI yields continuous and a single numerical value, it can be a valuable parameter during the monitoring of the level of analgesia. Additionally, it may play a role in prediction of the level of postoperative early pain. Thus, patient comfort can be provided by enabling to administer additional analgesic drug at the end of the surgery.

In our study, we ensured ANI monitoring during surgery and during the early postoperative period in the following two groups of patients who had undergone spinal stabilization surgery, which was a painful surgery: the first group was administered Total Intravenous Anesthesia (TIVA) with propofol and remifentanyl and the second group was administered sevoflurane–remifentanyl anesthesia. The aim of the study was to investigate if there was a difference or not between the two anesthesia methods regarding prediction of perioperative analgesia level and the level of postoperative early pain.

Materials and methods

Approval was obtained from the hospital's ethics committee (FSMEAH KAEK no 2015/59) and informed contents from each patient for the study.

Thirty patients aged between 18 and 70 years with ASA grade I–II (American Society of Anesthesiologists Group I–II) undergoing spinal stabilization surgery were included in the study. Patients with arrhythmia, receiving beta-receptor blocker drugs, neuromuscular or neurological disease, diabetes *mellitus* and pregnant women were excluded from the study. The patients in whom perioperative or postoperative ANI monitoring was interrupted, perioperative beta-blocker drug infusion was initiated, and the patients who were required to be transferred to the intensive care unit without postoperative arousal were planned to be excluded from the study. The patients not receiving

premedication were randomly divided into two equal-sized groups preoperatively by using simple computer program.

The patient was placed on the operating table and a venous access was established through the dorsum of the hand. After administration of local anesthetic agent, Allen test was performed and then invasive arterial blood pressure was performed with arterial cannulation preferably through right radial artery. Heart rate and peripheral oxygen saturation monitorization were performed (Mindray, China). BIS monitorization (Covidien, Dublin, Ireland) was performed by using 4 electrodes suitably placed on the patient's forehead. Two probes of ANI monitor (MetroDoloris, Lille, France) were suitably placed. According to recommendation of the manufacturer, the front facing electrode of ANI probes was planned to be placed on the middle of the sternum as the first choice. Since the patients would be in prone position due to certain characteristics of the surgery, the probe was placed behind the middle of the sternum as the second choice, and the measurement was obtained. The second ANI probe was placed on the region corresponding to the 8–9th rib at the level of the midaxillary line.

ANI points were considered as the following: 0–30 severe pain, 30–50 moderate pain, 50–70 comfortable and 70–100 no pain, and no need of any analgesic.

After basal measurements, during induction, fentanyl $2 \mu g.kg^{-1}$, propofol $2.5 mg.kg^{-1}$ and rocuronium $0.6 mg.kg^{-1}$ were administered in both groups. During maintenance, according to BIS values between 40 and 60, 1.0 MAC sevoflurane + remifentanil $0.05–0.3 \mu g.kg^{-1}.min^{-1}$ and propofol $50–150 \mu g.kg^{-1}.min^{-1}$ + remifentanil $0.05–0.3 \mu g.kg^{-1}.min^{-1}$ were administered in Group S and Group T. Measurements were recorded as the following: after induction, intubation, surgical incision, at 5–10 min intervals perioperatively, at the end of anesthesia, after extubation and at the postoperative 5th, 15th and 30th minutes. For analgesic purpose, paracetamol $1 g.100 mL^{-1}$ (IV infusion), diclofenac sodium 20 mg (IV) and tramadol 100 mg (IV infusion) were administered in all of the patients approximately 30 min before the end of surgery. Five minutes after the end of 10 min infusion of analgesic drugs, measurements were separately recorded as measurements at the end of analgesic drug. Postoperative 5, 15 and 30 min VAS values were recorded on a score between 0 and 10 (0: no pain, 1–3: mild pain, 4–7: moderate pain, 8–9: severe pain and 10: very severe pain). Atropine and ephedrine administrations, which might influence heart rate variability, were recorded.

Statistical evaluations

When we considered $\Delta = 26$ and SD = 16 at the end of power analysis performed by using power and sample-size program, sample size was determined to be minimum n: 9 for each group detected for Power = 0.80 and $\alpha = 0.05$.

During the evaluation of the data obtained from the study, IBM SPSS Statistics 22.0 program was used for the statistical analysis. During the assessment of the study data, conformity of the parameters to the normal distribution was assessed by the Kolmogorov–Smirnov test. During the evaluation of the study data, regarding the comparisons of descriptive statistical methods (Mean, Standard deviation) as well as quantitative data, Student t test was used for the
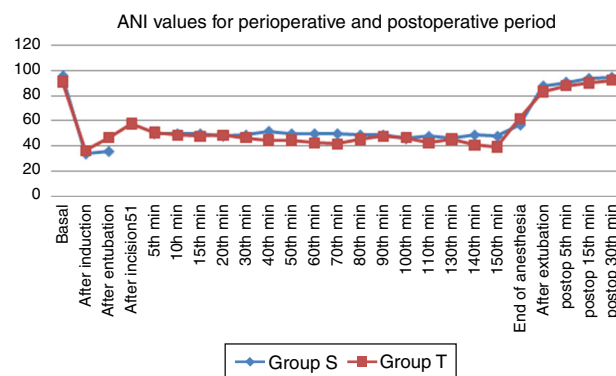

Figure 1 ANI values for perioperative and postoperative period.

intergroup comparisons of parameters with normal distribution and Mann Whitney U test was used for the intergroup comparisons of parameters without normal distribution. Paired Samples t-test was used for the in-group comparisons of parameters with normal distribution. Wilcoxon Signed Ranks test was used for the in-group comparisons of parameters without normal distribution. During the evaluation of correlation between the parameters conforming to a normal distribution, Pearson's correlation analysis was used. Chi-square test was used for the evaluation of qualitative data. Significance was evaluated at a level of $p < 0.05$.

Results

There was no difference between demographic characteristics and durations of anesthesia and surgery of the patients (Table 1).

While there was no difference hemodynamically at all the measurement times in mean arterial pressures between groups, heart rate measurements at the perioperative 20th and 30th minute were found to be higher in TIVA group compared to sevoflurane group ($p = 0.038$, $p = 0.031$).

There was no difference between the two groups regarding mean ANI values at all the measurement times. While mean ANI values at all the measurements after intubation were below 50 in both groups (Group T 44.3 ± 10.9, Group S 39 ± 11.2), ANI value was measured to be 43.7 ± 9.2 in Group S after incision (in Group P 51.33 ± 16.14). Mean values of ANI measurements performed at the 5th minute after incision were found to be below 50 in both groups (Group T 44.7 ± 8.7, Group S 48.8 ± 14). Mean ANI values at all the other measurement times were above 50 or more. Mean ANI values measured after administration of perioperative analgesic drug were recorded at the ideal levels in both groups (Group T 67.6 ± 13.1, Group S 68.1 ± 18.3) (Fig. 1).

There was no difference between groups regarding mean postoperative VAS values. There was correlation between mean ANI values and VAS values at the end of anesthesia (Table 2).

There was no difference between groups regarding mean BIS values.

Since a slow heart rate of less than 50 beats per minute was observed in 2 patients in both groups, a single dose of 0.5 mg atropine was administered intravenously.

Table 1 Demographic characteristics and durations of anesthesia and surgery.

	Group S Mean ± SD	Group T Mean ± SD	p
Age (years)	56.27 ± 8.3	54.27 ± 9.81	0.552
Body mass index (kg.m^{-2})	28.0 ± 3.76	28.8 ± 5.47	0.644
Duration of anesthesia (min)	183.4 ± 54.67	180.93 ± 52.75	0.930
Duration of surgery (min)	159.27 ± 53.2	155.87 ± 57.29	0.898

Student *t*-test.

Table 2 Visual analog score values according to ANI.

Visual analog score	Analgesia Nociception Index			p
	Medium (30–50) n (%)	Normal (50–70) n (%)	No pain, no need of any analgesic (70–100) n (%)	
After extubation				0.066
No pain (0)	1 (33.3)	12 (92.3)	9 (64.3)	
Moderate (4–7)	2 (66.7)	1 (7.7)	5 (35.7)	
VAS 5th min				0.109
No pain (0)	0 (0)	10 (76.9)	7 (50)	
Mild (1–3)	3 (100)	3 (23.1)	6 (42.9)	
Moderate (4–7)	0 (0)	0 (0)	1 (7.1)	
VAS 15th min				0.259
No pain (0)	0 (0)	7 (53.8)	5 (35.7)	
Mild (1–3)	2 (66.7)	6 (46.2)	7 (50)	
Moderate (4–7)	1 (33.3)	0 (0)	2 (14.3)	
VAS 30th min				0.522
No pain (0)	0 (0)	6 (46.2)	4 (38.6)	
Mild (1–3)	2 (66.7)	6 (46.2)	8 (57.1)	
Moderate (4–7)	1 (33.3)	1 (7.7)	2 (14.3)	

Ki-Kare test.

Discussion

Since analgesia nociception index yields continuous and a single numerical value especially in the most painful surgical procedures, it can be a valuable parameter during monitoring of level of analgesia. Additionally, it may play a role in prediction of the level of postoperative early pain. Thus, patient comfort can be provided by enabling to administer additional analgesic drug at the end of the surgery.

Jeanne et al.[5] performed ANI monitoring in 15 adult patients who had undergone laparoscopic appendectomy or cholecystectomy. In the study, propofol and remifentanil infusion was used during maintenance of anesthesia, and while higher ANI values (88 or more) were observed with anesthesia induction, ANI values decreased to 60–50 levels with initiation of surgery. After completion of surgery, an ANI value of 90 was observed. The authors found ANI to be more sensitive than heart rate variability and systolic arterial blood pressure as an indicator of pain.

In thirty patients administered sevoflurane anesthesia, Ledowski et al.[6] observed a decrease in ANI value with intubation and after skin incision and an increase in ANI value with administration of fentanyl. Also, in our study, similar to sevoflurane group, a decrease was observed in ANI value with skin incision.

Szental et al.[7] divided 120 patients who had undergone laparoscopic cholecystectomy into two equal groups and performed analgesia protocol with ANI monitoring. At the end of their study evaluating the postoperative VAS and morphine requirement, they reported that ANI monitoring did not provide an advantage in prediction of postoperative pain.

Jeanne et al.[8] monitored the ANI values in the patients who had undergone total knee replacement with propofol anesthesia and reported that although the data were reliable in the patients under general anesthesia they might not be reliable in awakened patients.

Logier et al.[9] reported that an increase could be observed in heart rate variability and systemic arterial blood pressure due to tourniquet pain in the patients used long-term tourniquet but this increase could occur due to other reasons. They stated that use of ANI monitoring could be efficient in order to make this discrimination.

Boselli et al.[10] investigated the correlation between ANI values immediately before extubation and postoperative VAS values in 100 patients and determined a correlation as

ANI < 50 value and VAS > 3. The authors reported that ANI value immediately before extubation was based on many different factors other than pain commonly encountered in the Post-Anesthesia Care Unit (PACU) that was known to affect sympathetic activity, such as stress and anxiety, and therefore might influence ANI value in awakened patients. They reported that ANI values might be affected depending on whether the anesthetic method selected was inhalation or TIVA and inhalation anesthetics might result in a more marked reduction in heart rate variability.

Again the same investigators stated that the limitations of their study was the use of atropine and neostigmine to prevent residual paralysis after reversal of neuromuscular blockade in case use of cisatracurium and atropine might affect heart rate variability. In our study, we also administered atropine and neostigmine to prevent residual paralysis after reversal of neuromuscular blockade. Considering that standard procedures are applied in all of the patients and the drugs counterbalance their influences on heart rate variability, we think that routine procedures will not cause problem. However, it can be recommended to monitor safe reversal by performing routine TOF monitorization and/or to prefer sugammadex to provide more ideal conditions. Besides that, since ANI values are compared with postoperative VAS values at the end of anesthesia in our study, the influence of atropine/neostigmine administered is not observed at the measurements.

The investigators of the aforementioned study stated that the influence of short-acting remifentanil, used also in our study on heart rate variability, might be different than long-acting fentanyl or sulfentanyl and may act as another limitation of their study. Although long-acting opioids can be preferred, we think that their influences on recovery from anesthesia should also be considered.

In the study performed in 120 patients by Ledowski et al.,[11] the authors evaluated the correlation between ANI values and VAS values in the postoperative care unit and observed a correlation between ANI values and severe pain in limited number of patients. As it was interpreted by Borelli et al.,[10] this might result from other factors influencing ANI values in the postoperative care unit. Therefore, we used ANI value at the end of anesthesia as a base in our study.

Gruenewald et al.[12,13] published two different studies on this subject. The authors compared ANI value and Surgical Pleth Index (SPI) for the measurement of nociception–antinociception balance in both of their studies. The Surgical Pleth Index (SPI) is a value derived from measurement performed with finger photoplethysmographic signal. Twenty-five patients were included in both the studies; BIS value was monitored to be between 30 and 60, and while the authors used sevoflurane and remifentanil in one of their studies, they used propofol and remifentanil in another study. They reported that both of the methods in both of their studies performed with both of the anesthesia methods were found to be significant as indicator of analgesia and they emphasized that it was necessary to perform studies with ANI in different patient groups with large number of patients. Additionally, they stated that larger number of female patients in their study performed with sevoflurane might affect the study results due to higher incidence of chronic diseases involving the regulation mechanisms of autonomic nervous system in male gender.

Bollag et al.[14] performed a study in 20 patients who had undergone hysterectomy to demonstrate the sympathomimetic and also analgesic effect of ketamine on ANI measurements. They administered ketamine as a single i.v. bolus of dose of $0.5\,\mu g.kg^{-1}$ 5 min after intubation and reported that ANI values did not change toward analgesia with administration of ketamine. Here, the sympathomimetic effects of ketamine might affect ANI measurements.

Sabourdin et al.[15] administered desflurane and remifentanyl in 12 pediatric patients with mean age of 8 years and emphasized that ANI measurements were more sensitive as an indicator of perioperative pain and it is necessary to perform studies with large number of patients in the pediatric patient group.

When the limitations of our study are investigated, this can be explained as administration of atropine and neostigmine to prevent residual paralysis after reversal of neuromuscular blockade regarding influencing the heart rate variability. For this purpose, administration of sugammadex can be recommended. However, since we compared ANI values with postoperative VAS value at the end of anesthesia in our study, we did not observe the influence of atropine/neostigmine administered at the measurements. Also, administration of perioperative drugs influencing the heart rate variability such as atropine and ephedrine might influence ANI values. We found no difference between our groups regarding perioperative atropine administration. Therefore we predicted that the mean values were not affected. However, during evaluation of ANI values, we think that the effects of administration of drugs influencing the heart rate variability should be certainly considered.

The second limitation of our study was not being able to place the front face of the electrode of the ANI probes on the middle of the sternum in the surgeries performed in the prone position. Since surgery position of our patient group was prone position, we placed the front face of the electrode of the ANI probes on the back region of the patient according to recommendation of the manufacturer under the necessary conditions. Therefore, we encountered no technical problem associated with measurement in our patients. Additionally, we developed a solution by covering the surface of electrode with transparent surgical drapes to prevent the detachment of ANI electrodes from the skin as a result by getting wet with the sterilization solution and therefore not being able to perform the measurement as we experienced in our previous study of patients during clinical practice.

In conclusion, under the condition that considering the factors which may influence the measurement of perioperative and postoperative monitoring of analgesia (superficial anesthesia, drug administration influencing heart rate variability, etc.), ANI is a valuable parameter. In spinal stabilization surgeries, similar analgesia can be provided in both TIVA with remifentanil and sevoflurane administration. ANI is efficient for prediction of the need for analgesia during the early postoperative period and therefore provision of patient comfort.

Conflicts of interest

The authors declare no conflicts of interest.

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