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Research Article

Evaluation of Analgesic Nociceptive Index in intraoperative and postoperative pain management in general anesthesia applied with two different methods

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ABSTRACT

Aim: Effectiveness of analgesic nociceptive index (ANI) monitoring in predicting both intraoperative and postoperative early pain in neurosurgery patients undergoing lumbar spinal surgery. The patients were administered general anesthesia using different anesthesia management techniques.

Method: The study included a total of 60 patients with American Society of Anesthesiologist (ASA) I-III. The patients were randomly divided into two groups of 30 each using the closed envelope method. Group T received total intravenous anesthesia (TIVA) with remifentanil-propofol, while Group D with desflurane-remifentanil. Non-invasive ANI monitoring was applied to patients undergoing lumbar spinal surgery, and ANI, heart rate, systolic/diastolic arterial pressure values were recorded before and after induction, skin incision, major muscle incision, laminectomy, right-left fasciectomy, screw fixation, after extubation and during the postoperative period. Postoperative heart rate, ANI value, mean arterial pressure values, and visual analog scale (VAS) values were measured.

Results: No statistically significant difference was found in terms of the demographic data of the patients. According to the groups, no statistically significant difference was found between the ANI and VAS measurements of the cases at the postoperative 5th minute (P=0.261), postop 10th minute (P=0.379), postop 15th minute (P=0.673), postop 30th minute (P=0.784) and postop 60 minute (p =0.750).

Conclusions: In our study on lumbar spine surgery, we could not detect any significant relationship between ANI monitoring and VAS values in the early postoperative period. There was no difference in ANI and VAS with either anaesthetic technique. In light of the results of our study, we believe that more studies are needed on the use of ANI monitoring in the early postoperative period.

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1. Introduction

The role of anesthesia and anesthesiologist in lumbar spinal surgery is very important not only in the intraoperative period but also in the entire perioperative period and postoperative rehabilitation to discharge. In addition to providing appropriate anesthesia during surgery, the anesthesiologist is especially responsible for providing adequate pain control in the postoperative period to maintain the normal respiratory and cardiovascular functions of the patient [1]. Postoperative pain is a type of acute pain that begins with surgical trauma and gradually decreases as tissues heal. Applicable and acceptable pain management after surgery is an important factor that accelerates recovery and shortens hospital stays [2]. Postoperative pain is affected by many factors including the location, type, duration, incision type and size of the surgery, the patient's approach to pain, physical and mental status, preoperative preparation of the patient, type of anesthesia, pain treatment before and after surgery, previous pain experiences, presence of preoperative pain, incidence of surgical complications, quality of postoperative care and environmental factors [3]. While the importance of starting pain management in the preoperative period is emphasized, the anesthesia method used in the intraoperative period and the drugs used are important components of postoperative pain management [4]. For anesthesiologists, adequate suppression of the sympathetic response is considered a requirement for good anesthesia. Since methods that can measure this suppression may serve as a guide for the maintenance of anesthesia, studies on this subject have gained momentum in recent years. Analgesia Nociception Index (ANI), which measures the tone of the parasympathetic autonomic nervous system during anesthesia and shows the nociception-analgesia balance and thus the adequacy of analgesia in the perioperative period, has emerged as a parameter in recent years [8,9]. ANI is a numerical value ranging from 0 to 100. Below 30 indicates severe pain, between 30-50 indicates moderate pain, and between 50-70 indicates adequate analgesia [5].

In this study; we aimed to compare the importance of analgesic nociceptive index (ANI) monitoring in predicting both intraoperative and postoperative early pain in neurosurgery patients who underwent general anesthesia with different anesthesia management and in patients who underwent lumbar spine surgery, where there are almost no similar studies in the literature.

2. Material and Method

Our study was designed as a prospective randomized controlled study and approved by the Harran University Faculty of Medicine Clinical Research Ethics Committee (dated 04.01.2021 and Session no. 01, and Ethics Committee Decision Approval no. 20). We conducted the study in accordance with the Declaration of Helsinki. The study comprised of 60 patients between the ages of 18-65 years, with American Society of Anesthesiologist (ASA) I-III Classification and diagnosed with spinal stenosis. These patients were scheduled to undergo elective L4-5 Lumbar spinal stabilization under general anesthesia, after obtaining written and verbal informed consent.

2.1. Inclusion criteria of patients in the study

Our study included patients between the ages of 18-65 who were evaluated preoperatively and classified in the ASA I, II, III risk group. Pregnant and breastfeeding patients, patients with uncontrolled hypertension and diabetes were not included in the study. Patients with significant cardiac pathology, in sinus rhythm, who had not received intraoperative administration of epinephrine, phenylephrine, atropine, B-blockers, and clonidine, and who had no significant preoperative chronic pain, no autonomic nervous system disorders, and no psychiatric disorders were included. Additionally, patients who were cooperative and oriented, had no intubation difficulties, and agreed to participate in the study were included.

2.2. Study groups

The patients were randomized into 2 groups with equal numbers by closed envelope method before surgery. A total of 60 patients were included in the study. Two different anesthesia management techniques were used; one was total intravenous anesthesia (TIVA) and the other was inhalation anesthesia (desflurane). Patients were divided into two groups of 30 patients each by closed envelope method; group T was total intravenous anesthesia (propofol/remifentanil) and group D was inhaled anesthesia (desflurane/remifentanil).

2.3. Monitoring

The patients included in the study were brought to the operating room without premedication and routine monitoring including Electrocardiography (ECG), heart rate (HR), Noninvasive blood pressure (NIBP), Mean Arterıal Pressure (MAP) peripheral oxygen saturation (SpO_2), End Tidal Carbon dioxide (ETCO2), was performed. In addition to standard anesthesia monitoring, Bispectral index (BIS) monitoring was used in all patients of both groups before induction. In 60 patients undergoing spinal stabilization, an ANI pallet was placed noninvasively 2 cm below the xiphoid process of the sternum and an ECG pallet was placed in the region corresponding to the V5 chest lead. ANI values were recorded before and after induction, skin incision, incision of major muscles, laminectomy, right-left fasciectomy, screw topping, extubation and postoperative period. ANI V1 monitor (Mdoloris Medical Systems) was used for ANI.

2.4. Anesthesia practices and data collection

All patients included in the study underwent standard anesthesia induction. Anesthesia induction was achieved with intravenous (IV) propofol 2-3 mg/kg, IV

fentanyl 2 mcg/kg and IV rocuronium bromide 0.6 mg/kg using the same induction agents. After adequate depth of anesthesia and muscle relaxation were achieved, the patients were intubated by the same anesthesiologist.

Anesthesia maintenance was provided with desflurane with a minimum alveolar concentration (MAC) of 1 in Group D. In Group T, propofol infusion was started at a dose of 12 mg.kg'1 and decreased to 9 mg.kg'1 after 20 minutes, 6 mg.kg'1 after 40 minutes and 4 mg.kg'1 after 60 minutes. Propofol was administered with 0.05-0.3 mcg/kg/min IV remifentanil infusion. The depth of anesthesia was adjusted according to the BIS value after induction. The BIS value was titrated to be in the range of 40-60. During anesthesia maintenance, oxygen-dry air mixture was given to all patients at a rate of 4L.min'1 at a rate of 50% O_2.

Among the parameters we examined, HR, NIBP and ANI values were measured before anesthesia, before induction, after induction and during the operation for 5 minutes in the first 30 minutes and 30 minutes after 30 minutes at 30 minute intervals. HR, NIBP and ANI values were recorded after skin incision, major muscle incision, laminectomy, right-left fasciectomy, screw fixation and discectomy.

In hypotensive anesthesia, a range of 50-65 mmHg was targeted in patients without hypertension and a range of MAP values of up to 30% of the baseline MAP value was targeted in patients with hypertension. Increases in MAP were controlled by increasing the remifentanil dose between 25-100%.

2.5. Surgical procedures

All surgeries were performed by the same surgical team. By making a classical midline incision, anatomical layers were passed and the facet joints were reached. Transpedicular screws were placed under scope guidance, preserving the adjacent facet joints. The screws were joined with the help of rods. Decompression and foraminotomies were performed based on imaging and patients' symptoms.

2.6. Postoperative follow-up

All patients participating in the study were administered analgesia with IV paracetamol 1 g/100 mL and IV tramadol 100 mg 30 minutes before the end of the surgery. HR, NIBP and ANI were measured at 5, 10, 15, 30, 60, 90, and 120 minutes after extubation. In addition, all patients were given detailed information about VAS in the preoperative period and their postoperative pain levels and VAS values were questioned and recorded at the 5th, 10th, 15th, 30th, 60th, 90th, and 120th minutes.

2.7. Statistical method

Statistical analysis and evaluation of the study were conducted using the NCSS (NumberCruncher Statistical System) 2020 statistical software (NCSS LLC, Kaysville, Utah, USA). Quantitative variables were reported using mean, standard deviation, minimum, and maximum, while qualitative variables were reported using descriptive statistical techniques such as frequencies and percentages. To assess data suitability to a normal distribution, the Shapiro-Wilks test and boxplot graphs were applied. Mann Whitney-U test was used to evaluate two quantitative groups with normal distribution. Student t-test (for normal data) was used to compare numerical data between two groups, while the Chi-square test was done to observe the relationship between categorical data. Spearman's correlation analysis was used to identify the relationships between variables. The results were evaluated at 95% confidence interval and significance at a p-value of less than 0.05. Sample size was calculated based on published ANI studies to detect a stimulus-induced difference of 15%, with an alpha-error of 0.05 and 90% power [9,11].

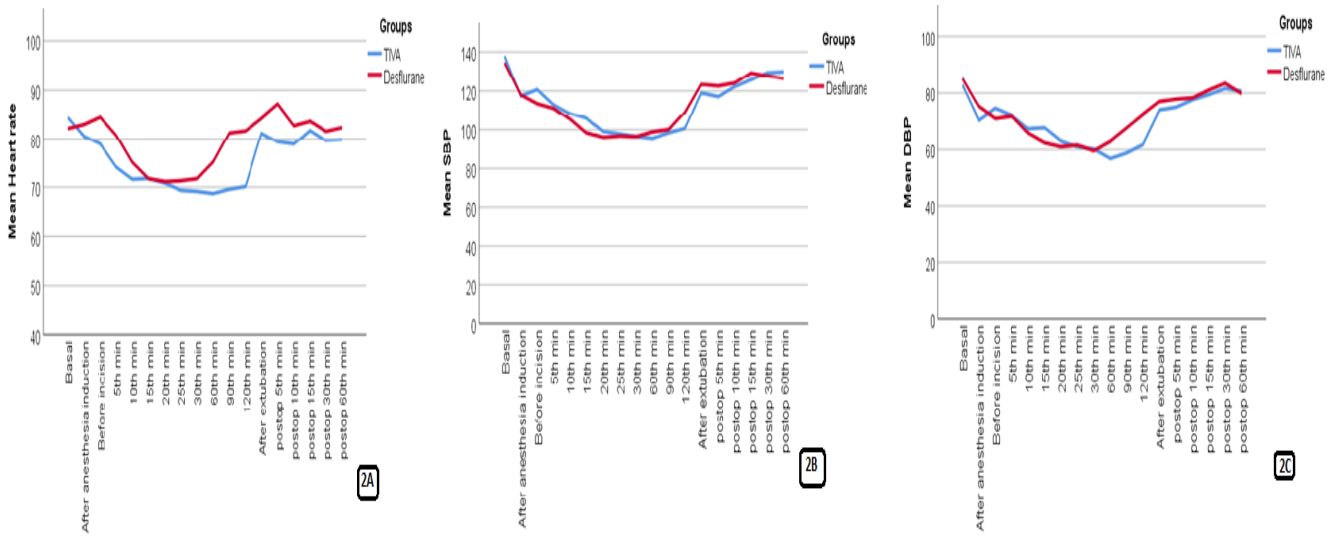
3. Results

A total of 60 patients between the ages of 27 and 64 were included in the study. Demographic data is provided in Table 1 and Fig. 1 shows the Consort Diagram.

Table 1. Distributions of descriptive features.

		Group T	Group D	*p* values
Age (years)		47.23 ± 10.04	46.73 ± 8.78	0.838*
BMI (kg/m^2)		27.73 ± 3.28	28.67 ± 3.76	0.307*
Gender	female	17	19	0.598^0
	male	13	11	
ASA	ASA 1	12	8	0.273^0
	ASA 2	18	22	
Comorbidity	yes	9	14	0.184^0

The data are presented as mean ± standard deviation or number.
BMI: Body Mass Index. ASA: American Society of Anesthesiologists.
^{0}Chi-square test. *Student t test.



SBP: Systolic Blood Pressure DBP: Diastolic Blood Pressure TİVA: Total intravenous anesthesia 2A:Heart Rate Values 2B: SBP Values 2C: DBP Values

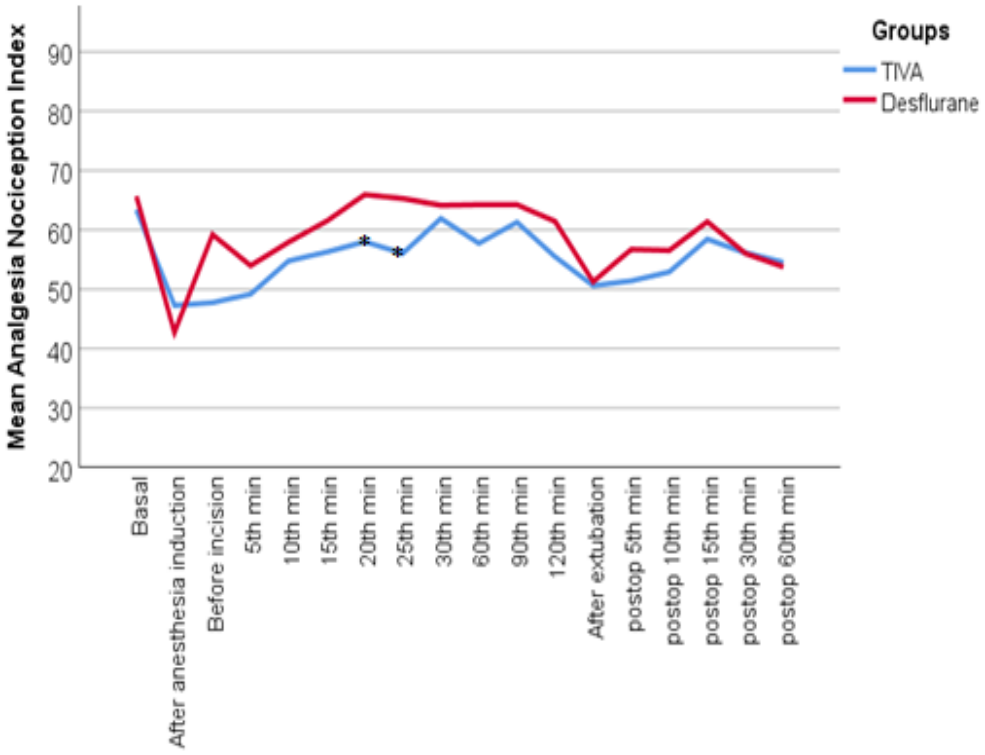
Fig. 1. The mean Heart Rate, SBP and DBP values for perioperative and postoperative period.

Heart rate measurements during surgery were significantly higher in Group D compared to other group at 90th and 120th minutes, during skin incision, and incision of major muscles (p: 0.005, p: 0.005, p: 0.005, p: 0.010, p: 0.008, respectively). However, there was no significant difference in systolic blood pressure measurements between the groups. Diastolic blood pressure measurements were significantly higher in Group D at 60th, 90th, and 120th minutes (p: 0.026, p: 0.010, p: 0.004, respectively).

During surgery, ANI values were significantly higher in Group D than in the TIVA group at 20th minute and 25th minute (p: 0.040, p: 0.025 respectively). No significant differences were found between the groups at other time intervals (Fig. 2).

There was no statistically significant difference (p>0.05) between the ANI measurements of the subjects during extubation, postoperative 5, 10, 15,30 or 60 minutes between the groups (Table 2).

There was no statistically significant difference (p>0.05) between the VAS measurements of the subjects during extubation postoperative 5, 10, 15, 30 or 60 minutes between the groups (Table 3).



ANI: Analgesia Nociception Index TİVA: Total intravenous anesthesia

Fig. 2. The ANI values for perioperative and postoperative period.

Table 2. Comparison of ANI measurements by groups.

ANI		Group T (n=30)	Group D (n=30)	p values
Extubation	Mean±SD	50.6±16.42	51.27±19.58	[a]0.836
Postop 5th min	Mean±SD	51.4±14.89	56.70±19.62	[a]0.261
Postop 10th min	Mean±SD	52.9±18.19	56.53±18.93	[a]0.379
Postop 15th min	Mean±SD	58.43±15.81	61.37±19.73	[a]0.673
Postop 30th min	Mean±SD	56.13±14.28	56.03±16.88	[a]0.784
Postop 60th min	Mean±SD	54.53±14.06	53.77±15.19	[a]0.750

[a]MannWhitney-U Test

Table 3. Comparison of VAS measurements by groups.

VAS		Group T (n=30)	Group D (n=30)	p values
Postop 5th min	Mean±SD	4.00±1.34	3.97±0.96	[a]0.830
Postop 10th min	Mean±SD	4.73±1.36	4.77±0.97	[a]0.700
Postop 15th min	Mean±SD	5.17±1.46	5.23±1.07	[a]0.659
Postop 30th min	Mean±SD	5.93±1.51	5.80±1.19	[a]0.849
Postop 60th min	Mean±SD	6.37±1.25	6.23±1.10	[a]0.721

[a]MannWhitney-U Test

When the postop 5th minute VAS measurements of both groups were classified according to the value of 3, there was no statistically significant difference between the postop 5th minute ANI measurements (p>0.05). In all cases, there was no statistically significant difference between postop 5th minute ANI measurements when classified according to VAS 3 value (p>0.05).

In Group T, there was no statistically significant difference between the postop 5th minute ANI measurements when the postop 5th minute VAS measurements were classified according to the value of 5 (p>0.05). In Group D, there were no cases with a VAS value above 5. In all cases, when classified according to VAS value 5, there was no statistically significant difference between postop 5th minute ANI measurements (p>0.05).

There was no statistically significant correlation between postop 5th min VAS measurements and ANI measurements (p>0.05).

4. Discussion

Our study was designed as a combination of these two studies and compared desflurane/remifentanil with propofol/remifentil anesthesia management in patients undergoing lumbar spinal surgery. Although desflurane initially produced slightly higher ANI data than TIVA, this difference was not statistically significant. We were unable to find a correlation between VAS and ANI values in patients under anesthesia.

The most basic expectation in the administration of anesthesia is to maintain hemodynamic stability, prevent metabolic and endocrine responses, and avoid side effects with low-dose drug use during the administration of anesthesia, maintenance and postoperative period. The anesthetic technique and agent to be selected are of great importance in meeting these expectations. The different effects of general anesthetics on nociceptive pathways may affect the development of postoperative pain. Inhalational and intravenous are the two major methods of administering general anaesthesia. Volatile Induction and Maintain Anesthesia (VIMA) and TIVA are the prominent methods in general anesthesia management. The effects of these anesthesia methods on postoperative pain have always been wondered and studies have been conducted [6].

There have been a limited number of randomized controlled trials comparing inhalation anesthesia with TIVA using propofol, in terms of postoperative acute pain scores or opioid consumption. Overall, there is a relative lack of clinical evidence in this area, partly due to the absence of objective methods of pain assessment. Although postoperative VAS and Numerical Rating Scale (NRS) are mostly used to measure pain, intraoperative measurements are less reliable. Our study is the first to explore VAS and analgesic nociceptive index parameters in the literature.

It is important for anesthesiologists to ensure that the patient's sympathetic response is adequately suppressed during anesthesia. In recent years, a new parameter called ANI has emerged which measures the tone of the parasympathetic autonomic nervous system. This parameter helps to determine the balance between nociception and analgesia during the peroperative period, and can be used to assess the adequacy of analgesia [8]. ANI has been used both intraoperatively and postoperatively in studies involving various surgical cases and different results have been obtained. In bariatric and breast surgery, ANI guidance resulted in a reduction in intraoperative opioid consumption, but no postoperative benefit was proven in these studies [9,10]. In another study, it was reported that during laparoscopic cholecystectomy, intraoperative opioid dose was not reduced with ANI guidance and no postoperative benefit was proven [11]. In our study, we used VAS and ANI parameters for both intraoperative and postoperative analgesia and anesthesia management in patients we received with two different anesthesia methods. We detected a significant difference in the ANİ in Group D compared to Group T at the intraoperative 20th and 25th minutes. However, no significance in this sense could be detected in other time periods. The fact that the significant time intervals coincided especially with the moment of fasciotomy suggests that more extensive research should be conducted on this subject, even though no significant difference was detected in other time intervals.

However, there is no consensus on which anesthetic agent will improve the correlation of the ANI with subjective pain measures, probably because studies compare different types of anesthetics as well as their respective heterogeneity [12]. In a study involving 200 patients anesthetized with a halogenated agent or propofol/remifentanil, Boselli et al. showed that the performance of the ANI in detecting moderate to severe pain was very good for patients anesthetized with a halogenated anesthetic [13]. In contrast, other authors have reported poor performance of the ANI for postoperative pain assessment in patients anesthetized with a halogenated agent [14,15]. In our study, we detected the only significant difference in group D. In this sense, our study is parallel to these studies in the literature.

As with any surgical procedure, there will be severe post-operative pain, especially after lumbar spinal surgery. Many factors are involved in the development of this pain. One of them is the postoperative inflammatory response of the tissue and the long-term use of automatic retractor systems attached to the paravertebral muscles during lumbar spinal surgery. As a result of prolonged paravertebral muscle retraction, edema and inflammation are observed in the paravertebral muscles [16]. In a study conducted in this type of surgery, the effects of anesthesia management on intraoperative and postoperative pain were compared between propofol-remifentanil and sevoflurane-remifentanil anesthesia with the help of ANI in terms of its importance in early postoperative pain prediction. While there was no difference between mean ANI at all measurement times in both groups, ANI measurements after perioperative analgesic drug administration were significantly higher than baseline values in both groups. They found a correlation between ANI and VAS mean values after anesthesia [17]. In another study close to ours, the effect of intraoperative propofol-based total intravenous anesthesia on postoperative pain in lumbar spinal surgery was compared with desflurane anesthesia, but ANI monitoring was not performed in this study. In conclusion, the study showed that patients using TIVA reported significantly less pain than patients receiving desflurane-based inhalation anesthesia; this was reflected in lower mean NRS pain scores on day 1 and less fentanyl consumption on postoperative day 2. They also showed that TIVA-propofol anesthesia provided a more effective effect in relieving pain with a decrease in opioid consumption during the first 2 days after surgery [18]. Our study was designed as a combination of these two studies and compared desflurane/remifentanil with propofol/remifentil anesthesia management in patients undergoing lumbar spinal surgery and performed intraoperative and postoperative follow-up with ANI. As a result of our study, heart rate measurements were significantly higher in the desflurane group at 90th and 120th minutes intraoperatively, during skin incision and incision of major muscles, and diastolic blood pressure measurements were significantly higher in the desflurane group at 60th, 90th, and 120th minutes. Although we say that the patient was in pain at the moments when these values were significantly higher, the ANI value did not parallel this. In the measurements of ANI values between groups, it was found to be significantly higher in the desflurane group than in the TIVA group during intraoperative 20th minute, 25th minute and fasciectomy, but it does not agree with the hemodynamic parameters in this time period. The ANI values drop with Induction of anaesthesia to between 30-50 from a baseline of 70. We attribute this decrease to the pain caused by the anesthesia drugs we use during induction and the response of hemodynamics during intubation. Apart from this, there was no difference in the ANI values at the 5th postoperative minute and the correlation with the VAS when analyzed in detail.

It is important to note several limitations of this study. Firstly, this was a single-center observational study and the results may not be applicable to all types of surgery. Secondly, patients with arrhythmias who were taking medications that affect heart rate variability (such as ephedrine, phenylephrine, atropine, neostigmine or beta-blockers) or chronic analgesics were excluded, and their effects are unknown. Finally, we were unable to perform blood sample analysis of propofol and remifentanil plasma levels in our patients. We adjusted propofol and remifentanil dosing targets based on target BIS and previous doses of propofol.

5. Conclusions

Similar analgesia can be achieved with both remifentanil-propofol and desflurane- remifentanil administration in spinal stabilization surgeries. Based on the data collected in this study, we could not detect a correlation between VAS and ANI values in patients under the influence of anesthetic agents. We recommend that more studies be conducted to contribute to the literature on this subject.

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Conflict of Interest

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Author Contributions

All of the authors made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; were involved in drafting the manuscript or revising it critically for important intellectual content; and gave final approval of the version to be published.

Data Availability

The datasets created and/or analyzed during the current study are not publicly available, but are available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

This study was approved by the ethics committee of Harran University Faculty of Medicine Clinical Research Ethics Committee (dated 04.01.2021 and Session no. 01, and Ethics Committee Decision Approval no. 20). All methods were performed in accordance with relevant guidelines and regulations.

REFERENCES

1. Artukoğlu F, Asenjo JF. Anesthesia in spinal surgery. In AF Özer, editors. Lumbar degenerative disc disease and dynamic stabilization. *American Hospital Publications*. **2010**: 194-199.
2. Lovich-Sapola J, Smith CE, Brandt CP. Postoperative pain control. *Surg Clin North Am.* **2015**; 95(2):301-18
3. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. *Lancet* **2006**; 367(9522):1618–25.
4. Eisenberg E. Post-surgical neuralgia. *Pain* **2004**; 111(1-2):3-7.
5. Köprülü AŞ, Toptaş M, Gül YG, Haspolat A, Yılmaz H, Özenç E. Prediction of hemodynamic reactivity during sevoflurane remifentanyl anesthesia for laparoscopic cholecystectomy using Analgesia Nociception Index. *Med Bull Haseki* **2016**; 54:212-218.
6. Fassoulaki A, Melemeni A, Paraskeva A, Siafaka I, Sarantopoulos C. Postoperative pain and analgesic requirements after anesthesia with sevoflurane, desflurane or propofol. *Anesth Analg*. **2008**; 107(5):1715-9.
7. Wong SSC, Chan WS, Irwin MG, Cheung CW. Total intravenous anesthesia (TIVA) with propofol for acute postoperative pain: A scoping review of randomized controlled trials. *Asian J Anesthesiol*. **2020**; 58(3):79-93.
8. Logier R, Jeanne M, De Jonck heere J, et al. Physio Doloris: a monitoring device for analgesia/nociception balance evaluation using heart rate variability analysis. *Conf Proc IEEE Eng MedBiol Soc* **2010**; 2010:1194-7
9. Dundar N, Kus A, Gurkan Y, Toker K, Solak M. Analgesia nociception index (ani) monitoring in patients with thoracic paravertebral block: A randomized controlled study. *J. Clin. Monit. Comput.* **2018**; 32: 481–486.
10. Le Gall L, David A, Carles P, Leuillet S, Chastel B, Fleureau C, Dewitte A, Ouattara A. Benefits of intraoperative analgesia guided by the Analgesia Nociception Index (ANI) in bariatric surgery: An unmatched case-control study. *Anaesth. Crit. CarePain Med.* **2019**; 38: 35–39.
11. Sabourdin N, Burey J, Tuffet S, Thomin A, Rousseau A, Al-Hawari M, Taconet C, Louvet N, Constant I. Analgesia Nociception Index-guided remifentanil versus standard care during propofol anesthesia: A randomized controlled trial. *J Clin Med.* **2022**; 11(2):333.
12. Baroni DA, Abreu LG, Paiva SM, Costa LR. Comparison between Analgesia Nociception Index (ANI) and self-reported measures for diagnosing pain in conscious individuals: a systematic review and meta-analysis. *Sci Rep.* **2022**; 12(1):2862.
13. Boselli E, Bouvet L, Bégou G. Prediction of immediate postoperative pain using the analgesia/nociception index: a prospective observational study. *Br J Anaesth.* **2014**; 112:715–721.
14. Charier D, Vogler MC, Zantour D, et al. Assessing pain in the postoperative period: Analgesia Nociception Index (TM) versus pupillometry. *Br. J. Anaesth.* **2019**; 123:322–327.
15. Jeanne M, Delecroix M, De Jonckheere J, Keribedj A, Logier R, Tavernier B. Variations of the analgesia nociception index during propofol anesthesia for total knee replacement. *Clin. J. Pain.* **2014**; 30:1084–1088.
16. Linzer P, Filip M, Šámal F, Kremr J, Šálek T, Gajdoš M, Jarkovský J. Comparison of biochemical markers of muscle damage and inflammatory response between the open discectomy, microsurgical discectomy, and microsurgica ldiscectomy using tubular retractor. *J NeurolSurg A CentEurNeurosurg.* **2015**; 76(5):384-91.
17. Turan G, Ar AY, Kuplay YY, Demiroluk O, Gazi M, Akgun N, Celikoglu E. Índice de analgesia/nocicepção para monitorização da analgesia perioperatória na cirurgia da coluna vertebral [Analgesia Nociception Index for perioperative analgesia monitoring in spinal surgery]. *Rev Bras Anestesiol.* 2017; 67(4):370-375.
18. Lin WL, Lee MS, Wong CS, Chan SM, Lai HC, Wu ZF, Lu CH. Effects of intraoperative propofol-based total intravenous anesthesia on postoperative pain in spine surgery: Comparison with desflurane anesthesia - a randomised trial. *Medicine (Baltimore).* **2019**; 98(13):e15074.