

Reliability of analgesia nociception index (ANI) and surgical pleth index (SPI) during episodes of bleeding - A pilot study

Address for correspondence:

Dr. Sonia Bansal,
National Institute of
Mental Health and
Neurosciences (NIMHANS),
Bengaluru - 560 029,
Karnataka, India.
E-mail: itz.sonia77@gmail.com

Submitted: 07-Jan-2022
Revised: 03-Feb-2022
Accepted: 05-Jul-2022
Published: 22-Jul-2022

Sindhupriya Muthukalai, Sonia Bansal, Dhritiman Chakrabarti, GS Umamaheswara Rao

Department of Neuroanaesthesia and Neurocritical Care, National Institute of Mental Health and Neurosciences (NIMHANS), Bengaluru, Karnataka, India

ABSTRACT

Background and Aims: Analgesia Nociception Index (ANI) and Surgical Pleth Index (SPI) are measures of nociception-antinociception balance during general anaesthesia. The validity of these two monitors during autonomic changes brought about by intraoperative blood loss and noradrenaline infusion has not been studied earlier. The primary objective of the study was to determine the effect of bleeding on ANI and SPI. The secondary objective was to observe the effect of noradrenaline infusion on ANI and SPI and the correlation between ANI and SPI. **Methods:** In this prospective observational study, 43 patients undergoing surgery for excision of a meningioma or for traumatic brain injury were included. Heart rate, mean arterial pressure, ANI, SPI, response and state entropy were recorded every 5 min from anaesthetic induction till skin closure. ANI and SPI values before bleeding were compared with the values following bleeding. The effect of bleeding and noradrenaline on ANI and SPI were studied using linear mixed effect model. **Results:** Bleeding increased the values of ANI and the increase was higher in the presence of noradrenaline and it was statistically significant ($P = 0.028$ and 0.023). SPI was not affected by bleeding or with noradrenaline infusion. ANI and SPI had a poor negative correlation ($r = -0.01$). **Conclusion:** Values of ANI increased significantly during episodes of intraoperative acute blood loss and with co-administration of noradrenaline. SPI seems to be more dependable when compared to ANI under such conditions.

Key words: Analgesia nociception, blood loss, neurosurgical procedures, norepinephrine, pain measurement, plethysmography, surgical

Access this article online

Website: www.ijaweb.org

DOI: [10.4103/ija.ija_20_22](https://doi.org/10.4103/ija.ija_20_22)

Quick response code



INTRODUCTION

Assessment of perioperative pain is challenging as pain is a subjective phenomenon. Intra-operatively, autonomic responses are commonly used as surrogate markers for pain but are non-specific and inaccurate. In recent years, a few objective monitors of pain have been developed. Two commonly used indices for intraoperative pain assessment are the Analgesia Nociception Index (ANI) and Surgical Pleth Index (SPI). These indices measure the nociception-antinociception balance and help guide intra-operative analgesic administration.^[1,2] Other methods of intraoperative pain monitoring include perfusion index, difference between response entropy (RE) and state entropy (SE), pupillometry, heart rate (HR) variability.^[3,4]

ANI is a HR variability-based index and analyses the influence of respiratory sinus arrhythmia on the HR derived from electrocardiography (ECG). ANI values range from 0 to 100 where 0 reflects maximal stress response and nociception (minimal parasympathetic tone) and 100 represents minimal stress response (maximal parasympathetic

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

How to cite this article: Muthukalai S, Bansal S, Chakrabarti D, Rao GS. Reliability of analgesia nociception index (ANI) and surgical pleth index (SPI) during episodes of bleeding - A pilot study. *Indian J Anaesth* 2022;66:505-10.

tone).^[5] SPI is based on sympathetic activity of the autonomic nervous system. The signal is obtained from a photoplethysmographic sensor placed on a digit. SPI is derived from normalised heartbeat interval (HBI) (HBI_{norm}) and plethysmographic pulse wave amplitude (PPGAnorm)^[4] An SPI value close to 100 indicates maximum pain and SPI near 0 suggests minimal pain, while a number ranging from 20 to 50 indicates balanced state of nociception-antinociception.^[6]

Thus, the two indices are designed to measure pain. However, in the process of measuring pain, if the HR changes due to any cause other than pain, one would expect an alteration in the values of ANI or SPI, which would clearly be undesirable and make pain assessment inaccurate. The changes in these two indices of pain during tachycardia not caused by noxious stimuli, such as during blood loss, and with administration of inotropes under anaesthesia have not been studied earlier. Intraoperative blood loss is commonly encountered in patients undergoing surgery for traumatic brain injury (TBI) and meningioma. Hence, patients belonging to these groups were chosen for the study.

The main objective of the study was to evaluate changes in ANI and SPI that occur during an episode of bleeding, significant enough to cause tachycardia. During the episode of bleeding, hypotension may demand infusion of noradrenaline to maintain the blood pressure (BP). The secondary objective of the study was to observe the effect of noradrenaline (administered in the event of hypotension) on ANI and SPI and to find the correlation between ANI and SPI.

Since ANI and SPI are expected to measure pain, we hypothesised that the values displayed by these monitors should not be affected by episodes of bleeding or by administration of noradrenaline.

METHODS

This prospective observational study was conducted in a tertiary care hospital for neurological disorders, after obtaining clearance from the Institutional Ethics Committee [NIMH/DO/IEC (BS & NS DIV)/2017-18] in accordance with the declaration of Helsinki. A written informed consent was obtained from the patient/relative before recruiting them into the study. The study was conducted over a period of 16 months (June 2018-October 2019).

The study was registered with Clinical Trials Registry (India) [CTRI/2018/05/014265].

All patients aged 18-60 years undergoing craniotomy for evacuation of subdural haematoma, extradural haematoma, or contusion (after TBI) or patients undergoing resection of a supratentorial meningioma were recruited into the study. Patients of TBI with polytrauma, patients whose HR continued to be elevated (>100 beats/min) even after 15 min of intubation and despite fluid resuscitation, patients on chronic beta blocker therapy and patients with history of cardiac arrhythmias were excluded from the study as it would affect the ANI/SPI monitoring. In addition, pregnant patients, patients with drug allergy to local anaesthetics (as scalp block would be administered for all patients) and patients undergoing surgeries of short duration (<1 hour) were excluded from the study.

In the operation theatre, all patients underwent ECG, non-invasive blood pressure (NIBP), pulse oximetry (SpO₂), ANI (MetroDoloris, @Lille, France), SPI and entropy (General Electric Health Care, Helsinki, Finland, 2003) monitoring. At baseline, HR, mean arterial pressure (MAP), SpO₂, SPI, RE, SE and ANI were recorded. Anaesthesia was induced with injection fentanyl 2 µg/kg followed by thiopentone 3-5 mg/kg titrated to loss of consciousness. Muscle relaxant rocuronium and lignocaine 1.5 mg/kg were administered followed by tracheal intubation. Bilateral scalp block was performed with 10 ml of 0.25% bupivacaine and 10 ml of 2% lignocaine and adrenaline. Infusion of injection fentanyl was started and maintained at the rate of 1 µg/kg/h throughout the surgery.

Anaesthesia was maintained using oxygen and air, sevoflurane and rocuronium top-up doses. Entropy was used to determine the depth of anaesthesia which was maintained between 40 and 50. HR, NIBP, SpO₂, ANI, SPI and entropy values were recorded prior to induction, just prior to intubation, 5 and 15 min post-intubation and every 5 min thereafter till the start of skin closure.

The values recorded 15 min after intubation were taken as a new baseline. One litre of balanced salt solution was administered before skin incision to ensure normovolaemia. Haemoglobin was recorded by a point of care equipment (HemocueHb 201- Hemocue AB, Angelholm Sweden) prior to incision. The time interval between 15 min post-intubation (i.e., the new

baseline) and the onset of blood loss was taken as the control time period. ANI/SPI and other data recorded during this time were compared with the data collected during the period of blood loss.

An episode of significant blood loss was defined as a period of increase in HR and a decrease in MAP by more than 20% of baseline, associated with a blood loss of more than 10 ml/kg. Clinically, the amount of blood loss was quantified from the suction bottle (actual blood loss = total volume of blood and saline in suction bottle – normal saline used for irrigation of surgical field) and from that in the basin placed on the floor underneath the surgical field where the blood gets collected. Haemoglobin estimation was repeated once there was significant blood loss and every 30 min thereafter. Fluid, blood and blood products were administered as required. Values of HR, MAP, ANI, SPI, RE and SE were recorded every 5 min during the period of blood loss.

In spite of treatment with fluids/blood products, if the MAP continued to be < 80 mmHg, noradrenaline infusion was initiated and titrated (at a dose of 5-10 µg/min) according to the MAP. HR, MAP, SpO₂, ANI, SPI, SE, RE data were recorded and compared before and after starting of noradrenaline.

Data was collated offline in a Microsoft Excel version 2007 spreadsheet and analysis was done using R software version 3.5.2. Interval scale data was presented as means ± standard deviation and nominal data as frequencies and proportions. Data were analysed for the effect of bleeding and administration of noradrenaline on study variables. The analysis was conducted separately in the context of absence and presence of noradrenaline infusion. Due to variable length of repeated measures data among the study population, linear mixed effect modelling was used to observe the effect of bleeding and noradrenaline infusion on the study variables. Unstructured covariance matrix structure was assumed and random intercept models were fit, with *P* values calculated using Satterthwaite's degrees of freedom method. Package "lmerTest" was used for the modelling procedure.^[7,8] *P* < 0.05 was considered statistically significant.

The current study was considered as an exploratory study or a pilot study as there are no similar earlier studies in literature. A total of 50 patients were recruited, out of which seven were excluded, resulting in a sample size of 43.

RESULTS

Out of 50 patients enrolled into the study, seven were excluded because of technical difficulty in recording ANI data and lack of significant bleeding. The demographics of the patient population are given in Table 1. The number of subjects included for the analysis was 43, with 1334 cumulative data points. ANI instantaneous was found to increase with the presence of bleeding in both scenarios of absence and presence of noradrenaline infusion and the changes were significant (*P* = 0.028 and 0.023) [Table 2] [Figure 1]. In the absence of noradrenaline, the onset of bleeding increased ANI by 4 units. However, in the presence of noradrenaline infusion, bleeding led to a much higher increase in ANI, with a mean difference of 12 units [Table 2]. However, calculating statistical significance of the same would require introduction of an interaction term in the regression model, which was not done due to small sample size.

Table 1: Demographic characteristics of the study population

Variable	Value
Age (in years)	40±9
Gender (male: female)	3.3:1
PT (in seconds)	17.7±3.7
INR	1.2±0.2
APTT in seconds	31.3±4.7
Number of patients in meningioma group (<i>n</i>)	13
Number of patients in TBI group (<i>n</i>)	30
Mean duration of surgery in minutes (meningioma group)	296 (34.2)
Mean duration of surgery in minutes (TBI group)	169 (22.7)
Number of patients who required noradrenaline infusion	39
Average blood loss in meningioma group in ml	1362±355
Average blood loss in TBI group in ml	989±313
Mean Hb before blood loss in g/dl	12±1.1
Mean Hb after blood loss in g/dl	10.5±1.1

Data is represented as mean±SD or numbers. SD – standard deviation, PT – prothrombin time, INR – International normalised ratio, APTT – activated partial thromboplastin time, TBI – traumatic brain injury, Hb – haemoglobin

Table 2: Descriptive data of study variables under study conditions of bleeding and noradrenaline infusion

Noradrenaline Bleeding	Absent		Present	
	Absent	Present	Absent	Present
ANI	67±14	71±15	67±13	79±13
SPI	46±17	50±16	41±12	47±15
HR in beats/min	86±11	100±7	90±12	101±8
MAP in mmHg	85±9	82±7	75±6	80±9
RE	44±7	43±6	44±7	45±8
SE	39±5	40±5	41±5	40±4

Data displayed as mean±standard deviation. ANI – Analgesia Nociception Index, SPI – Surgical Pleth Index, HR – Heart rate, MAP – Mean arterial pressure, RE – Response entropy, SE – State entropy

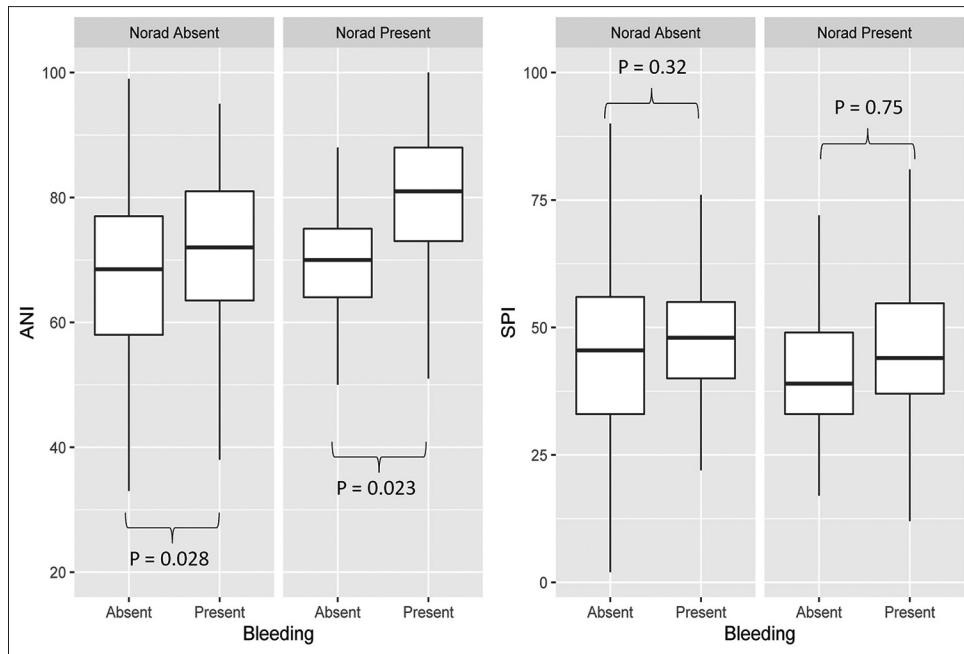


Figure 1: (boxplot) Trend of change of Surgical Pleth Index and Analgesia Nociception Index vis a vis bleeding status (x-axis) and presence of noradrenaline (facets). The box consists of median (middle hinge), first quartile (lower hinge) and third quartile (upper hinge). The upper whisker extends from the hinge to the largest value $\leq 1.5 * IQR$ from the hinge (where IQR is the inter-quartile range). The lower whisker extends from the hinge to the smallest value $\leq 1.5 * IQR$ of the hinge. Statistical significance of hypothesis tests for the same provided in the figure ($P < 0.05$ is level of statistical significance). Norad- noradrenaline

SPI registered a statistically non-significant reduction in both scenarios, with a mean reduction of 0.415 ($P = 1.301$) with bleeding in presence of noradrenaline infusion and reduction of 1.69 ($P = 0.32$) in the absence of noradrenaline [Table 3]. There was no influence of bleeding or noradrenaline infusion on RE and SE [Table 2]. HR was found to increase with bleeding and the rise was statistically significant [Table 3]. The mean increase was higher in the presence of noradrenaline infusion. MAP was found to be unchanged in the presence of bleeding with noradrenaline infusion, but was marginally reduced (statistically significant, but clinically insignificant) in the absence of noradrenaline infusion [Table 3]. There was an inverse correlation between ANI and SPI but the correlation coefficient was low and not significant ($r = -0.01, P = 0.726$).

DISCUSSION

In the current study, a significant increase was observed in ANI with the onset of bleeding. The increase in ANI was higher in the presence of noradrenaline infusion. This signifies that ANI may not be accurate for measuring pain during episodes of bleeding/noradrenaline administration.

Haemorrhage is usually accompanied by sympathetic activation to compensate for the decrease in blood

Table 3: Parameter estimates of regression model of influence of bleeding in the presence and absence of noradrenaline infusion on study variables

Variable	Noradrenaline Present		Noradrenaline Absent	
	Coefficient (standard error)	P	Coefficient (standard error)	P
ANI	2.197 (0.963)	0.023	3.359 (1.527)	0.028
SPI	-0.415 (1.301)	0.75	-1.691 (1.698)	0.32
HR in beats/min	15.05 (0.69)	<0.001	13.442 (0.956)	<0.001
MAP in mmHg	-0.791 (0.893)	0.376	-4.26 (1.265)	0.001
RE	-0.35 (0.581)	0.547	-1.423 (0.977)	0.146
SE	-0.671 (0.552)	0.225	-0.208 (0.837)	0.804

$P < 0.05$ is statistically significant. ANI – Analgesia Nociception Index, SPI – Surgical Pleth Index, HR – Heart rate, MAP – Mean arterial pressure, RE – Response entropy, SE – State entropy

volume. Release of vasoconstrictor substances leads to peripheral vasoconstriction. Administration of painful stimulus also leads to sympathetic activation. It has been observed that with pain, there occurs a decrease in ANI (usually to < 50) and an increase in HR and BP. Although, both these situations, that is, acute blood loss and pain involve sympathetic activation, the ANI changes were in the opposite direction.

Jendoubi A *et al.*^[9] observed that hypotension caused by spinal anaesthesia led to a significant decrease in values of ANI. The authors concluded that a decrease in ANI by 4.5 points could predict the occurrence of

hypotension. Spinal anaesthesia causes arterial and veno-dilatation due to sympathetic block. Another factor which needs consideration is the influence of volume loading and vasopressor use, which was not assessed in Jendoubi's research.

We observed that initiation of noradrenaline infusion resulted in significant increases in ANI (both in the absence and presence of bleeding). To study the association between ANI and noradrenaline, Broucqsaault-Dédrie *et al.*^[10] monitored HR and ANI in 41 sedated patients admitted to the intensive care unit at 3 time points – during 5 min of rest, during the painful stimulus, and 5 min after painful stimulus. The values of ANI were lower during painful stimulus compared to the values at rest and after the stimulus ended. The values of ANI were higher in patients in whom noradrenaline was being administered when compared to patients who were not receiving noradrenaline. ANI decreased with pain and increased 5 min after the painful stimulus even in patients on noradrenaline infusion. The study concluded that ANI could detect pain in the presence of noradrenaline infusion. Similar results have been reported in deeply sedated patients with TBI who were on norepinephrine infusion.^[11]

Chanques *et al.*^[12] studied two groups of critically ill patients, those who were receiving and those who were not receiving noradrenaline infusion. ANI and behavioural pain scales (BPSs) were compared during and after regular procedures such as dressing change, positioning of the patient and tracheal suctioning. ANI was found to be better than BPS for detecting pain. ANI values were again higher in patients receiving norepinephrine infusion.

ANI and SPI are objective indices of nociception and provide measures of analgesia based on changes in autonomic function. Both these indices find applicability in the operation theatre where bleeding episodes are common. In the present study, changes in these indices for measurement of pain during episodes of intraoperative acute blood loss and with administration of inotropic agents were examined. In the present study, SPI was not affected by bleeding or with noradrenaline infusion. There is no literature evaluating the effect of noradrenaline on SPI. Ducrocq *et al.*^[13] observed that in patients with severe heart failure, ephedrine administration corrected the hypotension but did not lead to changes in SPI values before or after the application of pain stimuli.

This finding confirms that SPI is not influenced by vasoactive drugs and continues to be an authentic monitor under these circumstances.

ANI and SPI had a poor negative correlation in our study. This could be because of the effect of blood loss and also noradrenaline infusion, both of which affected only ANI and not SPI. Also, although the scores of both SPI and ANI range from 0 to 100, a value of 100 with SPI indicates pain whereas an ANI of 100 denotes high levels of analgesia. Although both the indices are purported indicators of noxious stimulus, the differing mechanisms behind their derivation belie association under dynamic circumstances such as bleeding and vasopressor infusion. SPI is derived from sympathetic nervous system while ANI is based on parasympathetic activity, hence possibly the poor correlation.

There are a few limitations in our study. We did not monitor cardiac output, pulse pressure variation or stroke volume variation during the period of blood loss. We did not measure the plasma fentanyl during blood loss. Also, the sample size of our study was small. A more detailed measurement of HR variability indices would have helped in better explanation of the study findings.

CONCLUSION

ANI increased during episodes of acute blood loss especially when noradrenaline infusion was co-administered. SPI values on the other hand, were unaffected and therefore SPI appeared to be more reliable when compared to ANI in these situations.

Acknowledgements

We thank Dr Rajeev Dayananda for helping with the study.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

- Gruenewald M, Ilies C, Herz J, Schoenherr T, Fudickar A, Hocker J, *et al.* Influence of nociceptive stimulation on analgesia nociception index (ANI) during propofol-remifentanyl anaesthesia. *Br J Anaesth* 2013;110:1024-30.
- Daccache G, Caspersen E, Pegoix M, Monthé-Sagan K, Berger L, Fletcher D, *et al.* A targeted remifentanyl administration protocol based on the analgesia nociception index during vascular surgery. *Anaesth Crit Care Pain Med* 2017;36:229-32.
- Surekha C, Eadara VS, Satish Kumar MN. Evaluation of perfusion index as an objective tool to assess analgesia during laparoscopic surgeries under general anaesthesia. *Indian J Anaesth* 2022;66:260-5.
- Kommula LK, Bansal S, Umamaheswara Rao GS. Analgesia nociception index monitoring during supratentorial craniotomy. *J Neurosurg Anesthesiol* 2019;31:57-61.
- Sriganesh K, Theerth KA, Reddy M, Chakrabarti D, Rao GSU. Analgesia nociception index and systemic haemodynamics during anaesthetic induction and tracheal intubation: A secondary analysis of a randomised controlled trial. *Indian J Anaesth* 2019;63:100-5.
- Dostalova V, Schreiberova J, Bartos M, Kukralova L, Dostal P. Surgical Pleth index and analgesia nociception index for intraoperative analgesia in patients undergoing neurosurgical spinal procedures: A comparative randomized study. *Minerva Anesthesiol* 2019;85:1265-72.
- Kuznetsova A, Brockhoff PB, Christensen RHB. lmer test package: Tests in linear mixed effects models. *J Stat Softw* 2017;82:1-26.
- Bakdash JZ, Marusich LR. Repeated measures correlation. R package version 0.3.0. 2018 <https://CRAN.R-project.org/package=rmtcorr>.
- Jendoubi A, Khalloufi A, Nasri O, Abbes A, Ghedira S, Houissa M. Analgesia nociception index as a tool to predict hypotension after spinal anaesthesia for elective caesarean section. *J Obstet Gynaecol* 2021;41:193-9.
- Broucqsaault-Dédrie C, De Jonckheere J, Jeanne M, Nseir S. Measurement of heart rate variability to assess pain in sedated critically ill patients: A prospective observational study. *PLoS One* 2016;11:e0147720.
- Jendoubi A, Abbes A, Ghedira S, Houissa M. Pain measurement in mechanically ventilated patients with traumatic brain injury: Behavioral pain tools versus analgesia nociception index. *Indian J Crit Care Med* 2017;21:585-8.
- Chanques G, Tarri T, Ride A, Prades A, De Jong A, Carr J, *et al.* Analgesia nociception index for the assessment of pain in critically ill patients: A diagnostic accuracy study. *Br J Anaesth* 2017;119:812-20.
- Ducrocq N, Hoff T, Huiku M, Junke E, Longrois D. Effect of ephedrine on surgical stress index values during anaesthesia. *Eur J Anaesthesiol* 2008;25(Suppl 44):47.