Intraoperative "Analgesia Nociception Index"– Guided Fentanyl Administration During Sevoflurane Anesthesia in Lumbar Discectomy and Laminectomy: A Randomized Clinical Trial

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BACKGROUND: The "Analgesia Nociception Index" (ANI; MetroDoloris Medical Systems, Lille, France) is a proposed noninvasive guide to analgesia derived from an electrocardiogram trace. ANI is scaled from 0 to 100; with previous studies suggesting that values ≥50 can indicate adequate analgesia. This clinical trial was designed to investigate the effect of intraoperative ANI-guided fentanyl administration on postoperative pain, under anesthetic conditions optimized for ANI functioning.

METHODS: Fifty patients aged 18 to 75 years undergoing lumbar discectomy or laminectomy were studied. Participants were randomly allocated to receive intraoperative fentanyl guided either by the anesthesiologist's standard clinical practice (control group) or by maintaining ANI ≥50 with boluses of fentanyl at 5-minute intervals (ANI group). A standardized anesthetic regimen (sevoflurane, rocuronium, and nonopioid analgesia) was utilized for both groups. The primary outcome was Numerical Rating Scale pain scores recorded from 0 to 90 minutes of recovery room stay. Secondary outcomes included those in the recovery room period (total fentanyl administration, nausea, vomiting, shivering, airway obstruction, respiratory depression, sedation, emergence time, and time spent in the recovery room) and in the intraoperative period (total fentanyl administration, intraoperative-predicted fentanyl effect-site concentrations over time [CeFent], the correlation between ANI and predicted CeFent and the incidence of movement). Statistical analysis was performed with 2-tailed Student t tests, χ^2 tests, ordinal logistic generalized estimating equation models, and linear mixed-effects models. Bonferroni corrections for multiple comparisons were made for primary and secondary outcomes.

RESULTS: Over the recovery room period (0–90 minutes) Numerical Rating Scale pain scores were on average 1.3 units lower in ANI group compared to the control group (95% confidence interval [CI], −0.4 to 2.4; $P = .01$). Patients in the ANI group additionally had 64% lower recovery room total fentanyl administration (95% CI, −12% to 85%; $P = .44$, unadjusted $P = .026$), 82% lower nausea scores (95% CI, −19% to 96%; $P = .43$, unadjusted $P = .03$), and a reduced incidence of shivering (ANI 4%, control 27%, $P = .80$, unadjusted $P = .047$) compared to the control group. Intraoperatively, ANI group patients had on average 27% higher predicted CeFent levels during the highly nociceptive periods of intubation and first incision (5–30 minutes) compared with control group patients (95% CI, 3%–57%; $P = .51$, unadjusted $P = .03$). For a 1-unit decrease in ANI scores, predicted CeFent on average increased by an estimated 1.98% in the ANI group (95% CI, 1.7%–2.26%; $P < .0001$) and 1.08% in the control group (95% CI, 0.76%–1.39%; $P < .0001$). This correlation was significantly different between groups (0.9%, 95% CI, 0.5%–1.3%; $P < .0001$). Recovery room vomiting, airway obstruction, respiratory depression, sedation, emergence time, time spent in the recovery room as well as total intraoperative fentanyl administration, hypnotic parameters, and incidence of intraoperative movement were not different between groups.

CONCLUSIONS: Patients receiving intraoperative ANI-guided fentanyl administration during sevoflurane anesthesia for lumbar discectomy and laminectomy demonstrated decreased pain in the recovery room, likely as a result of more objective intraoperative fentanyl administration. (Anesth Analg 2017;125:00–00)

The administration of analgesia in conscious patients is traditionally guided by the self-reporting of pain, often using formal scales such as the Numerical Rating Scale (NRS) from 0 = "no pain" to 10 = "the worst pain imaginable."[1] The neurological processing of noxious stimuli is defined as nociception.[2] To guide the administration

of analgesia in anesthetized patients, the anesthesiologist must rely on indirect parameters that reflect the patient's physiological reaction to nociception like sweating, movement, heart rate (HR), and blood pressure (BP). The low specificity of these signs means that under-dosage or over-dosage of intraoperative analgesia can occur,[3,4] resulting in intraoperative movement, postoperative pain, nausea, vomiting, and respiratory depression.[5–7]

The "Analgesia Nociception Index" (ANI; MetroDoloris Medical Systems, Lille, France), derived from an electrocardiogram (ECG) trace, has been proposed as a noninvasive guide to analgesia.[8] The ANI monitor calculates HR variation with respiration, a response mediated primarily by changes in the parasympathetic nervous system (PNS) stimulation to the sinoatrial node of the heart.[9] A painful stimulus will cause a relative decrease in parasympathetic tone and therefore result in a decrease in ANI scores. A score of 100 indicates maximum parasympathetic tone and low nociceptive levels, while a score of 0 indicates minimum parasympathetic tone and high nociceptive levels. Factors that may make ANI scores unreliable include significant variations in hypnosis, nonregular sinus cardiac rhythm, implanted pacemakers, prescribed antimuscarinic agents, α2-adrenergic agonists, β1-adrenergic antagonists, and antiarrhythmic agents.[9,10]

In both volatile and intravenous anesthesia, ANI scores reflect changes in the nociceptive level with more sensitivity than traditional parameters like HR and BP.[11–13] In adult patients undergoing propofol anesthesia, remifentanil effect-site concentrations of 0, 2, and 4 ng/mL corresponded to median ANI values of 61, 71, and 88, respectively, with a median decrease of 24, 30, and 13 points after standardized nociceptive stimulation.[12] This nonlinear reduction in ANI to nociceptive stimulation is consistent with other trials.[13] In conscious patients, studies have found ANI scores ≥50 correspond with a tolerable level of pain, defined as NRS pain scores ≤3.[14–16] It is therefore plausible that maintenance of an ANI value ≥50 in anesthetized patients may ensure effective intraoperative obtundation of nociceptive stimuli, providing more appropriate analgesia on emergence from anesthesia than clinical judgment alone.

A recent randomized trial where scaled intraoperative morphine doses were guided by ANI monitoring failed to demonstrate a benefit over standard care.[17] The current randomized clinical study aimed to determine the effect of intraoperative ANI-guided fentanyl administration under anesthetic conditions optimized for ANI functioning. The primary hypothesis was that intraoperative ANI-guided fentanyl administration would reduce pain in the recovery room when compared to standard practice. Secondary hypotheses were that the ANI group would show reduced postoperative analgesic requirement, would show reduced incidence of adverse perioperative events, and would receive more objective administration of intraoperative fentanyl.

METHODS

This single-blinded, parallel-group, randomized clinical trial was conducted from February 2014 to April 2015 at the Royal Adelaide Hospital (R.A.H.), Adelaide, Australia, after approval from the R.A.H. Human Research Ethics Committee (Ref: HREC/130714). The trial was registered before enrolment on February 11, 2014 with the Australian New Zealand Clinical Trials Registry (ACTRN12614000169640). Written informed consent was obtained from all patients before participation, and the trial was conducted in accordance with the Declaration of Helsinki.

Baseline population characteristics and NRS pain scores were obtained from all patients preoperatively. Only elective lumbar discectomy or laminectomy cases were enrolled. Patients were 18 to 75 years old, with an American Society of Anesthesiologists Physical Status score of 1 to 2 and a body mass index range of 18.5 to 35 kg/m². Patients with nonregular sinus cardiac rhythm, implanted pacemakers, prescribed antimuscarinic agents, α2-adrenergic agonists, β1-adrenergic antagonists, and antiarrhythmic agents were excluded, as these factors may make ANI scores unreliable. Patients with preoperative opioid use equivalent to >20 mg oxycodone daily for >6 weeks, intolerance to trial medication, intraoperative cardiac arrhythmia, and surgery lasting >3 hours were also excluded. Patients were recruited by the principle investigator.

This trial was designed to establish if there was a clinical benefit in ANI-guided analgesia. The primary outcome was NRS pain scores recorded from 0 to 90 minutes of recovery room stay. Secondary outcomes included those in the recovery room period (total fentanyl administration, nausea, vomiting, shivering, airway obstruction, respiratory depression, sedation, emergence time, and time spent in the recovery room) and in the intraoperative period (total fentanyl administration, intraoperative-predicted fentanyl effect-site concentrations [CeFent] over time, the correlation between ANI and predicted CeFent, and the incidence of movement). Variables that may influence the primary and secondary outcomes were also recorded (intraoperative end-tidal sevoflurane minimum alveolar concentration [MAC] multiples, intraoperative and recovery room fentanyl bolus size and frequency of administration, intraoperative time with good-quality ANI readings [%], time ANI <50 [%], mean bispectral index [BIS], mean ANI, and total operative time).

Intraoperatively

Nine experienced anesthesiologists took part in the trial and were allocated at random. ECG, 5-minute BP, and end-tidal sevoflurane MAC multiples adjusted for age, temperature, and ambient pressure ($MAC_{multiple}$) were monitored intraoperatively (Intellivue MX8000/Intellivue X2/AGM G5, J.10.50, Philips Healthcare, Amsterdam, the Netherlands). $MAC_{multiple}$ was calculated from end-tidal sevoflurane concentrations and predefined sevoflurane $MAC_{movement}$ values[18] as follows: $MAC_{multiple} = ((\text{end-tidal sevoflurane concentration}) / (1 - ((0.05) \times (37 - \text{temperature } °C))) \times (\text{sevoflurane } MAC_{movement}) \times 1.32 \times 10^{-(0.00303 \times age)}) \times (\text{ambient pressure}/760 \text{ mm Hg})$. The ANI lead was attached to the patient's chest according to manufacturer's recommendations and connected to a commercially available stand-alone ANI monitor (MetroDoloris, ANI-V1-041). A BIS monitor was used to assess the degree of hypnosis. A BIS-XP Sensor was positioned on the patient's forehead according to manufacturer's recommendations and connected with an M-BIS module (M1034A,

J.10.50, Philips Healthcare, Amsterdam, the Netherlands). A peripheral venous cannula was inserted. After adequate preoxygenation with 100% oxygen, a bolus of fentanyl 1 to 2 µg/kg intravenously (IV) and propofol 1 to 2 mg/kg IV were administered for anesthetic induction, followed by rocuronium 0.6 mg/kg IV for muscle relaxation. The patient's trachea was intubated and positive-pressure ventilation applied. Sevoflurane in an air/oxygen mixture was administered to maintain a BIS level between 40 and 60 in all patients.

After anesthetic induction, patients were randomly allocated by the principle investigator to the ANI or control groups, with computer-generated random numbers produced by a research assistant. Fentanyl administration was the only analgesic variable between the groups:

- For control group patients, the administration of intraoperative fentanyl IV was by standard clinical practice. ANI monitor readings were not visible to the anesthesiologist.
- For ANI group patients, the administration of intraoperative fentanyl IV was guided by maintaining the 4-minute moving average of ANI ≥50 from intubation to extubation. Boluses of fentanyl 50 µg IV (patients <50 years old) or fentanyl 25 µg IV (patients ≥50 years old) were administered only if ANI scores decreased below 50, and repeated every 5 minutes until ANI scores increased above 50. This bolus regimen was conservative as a precaution but consistent with clinical practice at our institution. Anesthesiologists traditionally administer fentanyl boluses as multiples of 25 µg with reduced dosing beyond 50 years of age. Five-minute assessment periods coincided with automatic BP measurements and allowed for the 80- to 120-second delay in ANI to maximally reflect nociceptive stimulation.[12] Fentanyl was only administered if ANI scores were <50, given that no ANI threshold for excessive analgesic effect has been identified.

Both groups received parecoxib 40 mg IV following induction. Before wound closure paracetamol 1000 mg IV was given and local anesthetic (20 mL 0.5% bupivacaine with epinephrine) was infiltrated by the surgeon into the wound. All other analgesic adjuvants were prohibited. Antiemetic prophylaxis (dexamethasone 4 mg IV and ondansetron 4 mg IV) was administered intraoperatively in all patients. BP was managed using Hartmann solution, metaraminol, and phenylephrine administered IV according to anesthesiologist's preference. Intraoperative movement of the head or limbs prompted administration of rocuronium 0.1 mg/kg IV as per anesthesiologist's clinical acumen. Sugammadex was used for reversal of muscle relaxation. In both groups, ANI, BIS, HR, MAC$_{multiple}$, and fentanyl dosing were manually recorded at 2-minute intervals by a research assistant. The ANI monitor displayed readings that were not affected by artifact including high ECG impendence or electrical interference like diathermy. These were recorded as good-quality ANI readings.

Postoperatively
All patients were transferred to the recovery room and received analgesia by nursing staff as per standard institutional pain protocol: fentanyl 20 µg IV for patients ≥70 years or 40 µg IV for patients <70 years, administered in 3-minute intervals when NRS pain scores were >6 (provided the patient was easily roused, stayed awake, and had systolic BP >90). No other analgesics were administered until recovery room discharge.

Every 5 minutes, nursing staff recorded NRS pain scores (0–10), accumulated fentanyl dose, respiratory rate, and Ramsay Sedation Score (1–6).[19] Nursing staff also recorded the incidence of vomiting, requirement for antiemetic medication or naloxone, episodes of airway obstruction (requiring manual support with jaw-thrust or devices including oro-pharyngeal airway), and shivering (gross movement of the upper extremities, neck, and thorax for >2 minutes).[20] The patient's worst sensation of nausea while in the recovery room was self-reported using an NRS (0–10).[21,22] Patients were ready for discharge when the Modified Aldrete Score recorded by nursing staff reached 10, and data recording was then ceased.[23]

In this single-blinded trial, the treating anesthesiologist had to be aware of group allocation when administering fentanyl. A double-blind design was not possible. The anesthesiologist was not involved in enrolment, randomization, or data collection and was not present postoperatively. No researchers were involved in data collection during the recovery period. The patient, surgical staff, and recovery room nursing staff were unaware of group assignment.

Statistical Analysis
Demographic balance of the groups was analyzed with 2-tailed Student t tests and χ^2 tests. We did not intend to adjust for group imbalances. The effect of treatment allocation on the primary outcome (NRS pain scores recorded from 0 to 90 minutes of recovery room stay) was assessed using a linear mixed-effects model and presented as estimated ratio of means. A logarithmic transformation of NRS pain score was used as the outcome, such that assumptions of a linear model (including normal distribution of residuals) were upheld. The predictor or fixed effect was treatment group and a random effect for subject was added to account for repeated measurements over time. A compound symmetry covariance structure was used because it provided the best model fit (lowest Akaike Information Criterion value). An additional linear mixed-effects model test was conducted for NRS pain scores in the recovery room from 15 to 55 minutes.

Secondary outcomes were assessed as follows: To compare the timing of intraoperative fentanyl administration between groups, the predicted CeFent over time was calculated with a 2-compartment mammillary model, using the Matlab programming environment (Matlab R2013a, Mathworks, Natick, MA). This model was modified from previously published population-based estimates of pharmacokinetic parameters for the central and slow peripheral compartments[24] with the addition of an effect-site lag (assuming a Keo of 0.147/min). The effect of treatment allocation on intraoperative-predicted CeFent (0–125 minutes) was assessed using a linear mixed-effects model, as per the previously described model for the primary outcome. An additional linear mixed-effects model test was conducted for intraoperative-predicted CeFent from 5 to 30 minutes.

The effect of treatment allocation on recovery room sedation scores and respiratory rate was assessed with ordinal logistic generalized estimating equation models to adjust for repeated measurements. The effect of treatment allocation on recovery room total fentanyl administration, nausea (log normal), vomiting, airway obstruction, emergence time, shivering, time spent in the recovery room as well as the incidence of intraoperative movement, and total intraoperative fentanyl administration were assessed with linear regression models with logarithmic transformation, presented as estimated ratios of geometric means, and χ^2 tests.

Additional variables were assessed as follows: The effect of treatment allocation on intraoperative sevoflurane MAC$_{multiple}$ (0–125 minutes) was assessed using a linear mixed-effects model presented as difference in means. The predictor or fixed effect was treatment group, and a random effect for subject was added to account for repeated measurements over time. A compound symmetry covariance structure was used because it provided the best model fit (lowest Akaike Information Criterion value). Intraoperative and recovery room fentanyl bolus size and frequency of administration, intraoperative time with good-quality ANI readings (%), time with ANI < 50 (%), mean BIS, mean ANI, and total operative time were assessed with 2-tailed Student t tests. To illustrate differences in recovery room fentanyl administration, the accumulated weight-adjusted fentanyl dose over time was recorded. This was descriptive and not statistically assessed. To illustrate the variation in intraoperative ANI values and their response to surgery over time, the probability distribution of ANI scores was calculated using the "histc.m" function, set with 11 bins from 0 to 100. The time evolution of probability was captured using a sequential 5-minute moving window with 4-minute overlap. This was descriptive and not statistically assessed.

Bonferroni correction for multiple comparisons was conducted for the primary outcome (2 tests) and secondary outcomes (17 tests). Unadjusted P < .05 was considered statistically significant. We have chosen to present both the adjusted and unadjusted P values for the outcome variables where Bonferroni correction increased P > .05. Statistical analysis was performed using commercially available statistics software (SAS 9.3 [2010] SAS Institute Inc, Cary, NC).

Sample size estimation was conducted to demonstrate a significant difference in recovery room pain with intraoperative ANI-guided analgesia. A clinically significant pain reduction was considered to be a mean decrease in the NRS scores by 2 over 0 to 90 minutes of recovery room stay.[25] An average reduction in pain score from 5 to 3 (assuming a standard deviation = 2 and a uniform distribution)[26] would require 25 patients in each group to achieve a power of 0.94 (Mann-Whitney function of Power Analysis/Sample Size, PASS v 08.0.8, NCSS, Kaysville, UT).

RESULTS

In total, 79 patients were consented to the trial, with 25 patients excluded as a result of scheduling (n = 20) and surgery cancellation (n = 5). After randomization, 4 patients were excluded intraoperatively for arrhythmia or surgical duration >3 hours (n = 2$_{ANI}$; 2$_{control}$) (Figure 1). Data from 50 patients were included in this analysis (n = 24$_{ANI}$; 26$_{control}$). Patient characteristics preoperatively were well balanced between groups (Table 1). The patients treated by each individual anesthesiologist were: (4$_{ANI}$; 3$_{control}$), (3$_{ANI}$; 4$_{control}$), (3$_{ANI}$; 3$_{control}$), (3$_{ANI}$; 3$_{control}$), (2$_{ANI}$; 4$_{control}$), (3$_{ANI}$; 2$_{control}$), (2$_{ANI}$; 3$_{control}$), (2$_{ANI}$; 2$_{control}$), (2$_{ANI}$; 2$_{control}$).

Figure 2 shows differences between groups in recovery room NRS pain scores. Over the recovery room period (0–90 minutes), NRS pain scores were on average 1.3 units lower in ANI group compared to the control group (95% confidence interval (CI), −0.4 to 2.4; P = .01). From 15 to 55 minutes, NRS pain scores were on average 1.8 units lower in the ANI
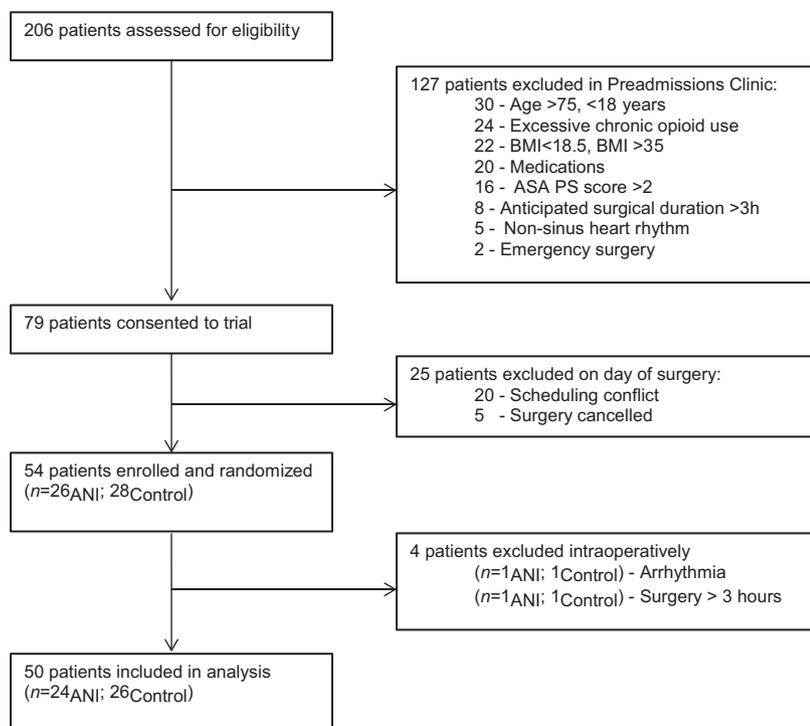
Figure 1. Participant flowchart. ANI indicates Analgesia Nociception Index; ASA PS, American Society of Anesthesiologists Physical Status; BMI, body mass index.

group than the control group (95% CI, −0.8 to 2.7; P = .007). Figure 3 illustrates weight-adjusted accumulated recovery room fentanyl administration over time and was not statistically assessed. In the recovery room, ANI group patients on average received 64% less total fentanyl (µg) (95% CI, −12% to 85%; P = .44, unadjusted P = .026) administered at a lower rate (boluses per hour: ANI 1.3 ± 1.4, control 2.6 ± 1.6, P = .004) compared to control group patients (Table 2). ANI group patients showed lower incidence of postoperative shivering (ANI 4%, control 27%, P = .80, unadjusted P = .047) and 82% lower nausea scores (95% CI, −19% to 96%; P = .43, unadjusted P = .03) compared to the control group. No difference was found between groups in time spent in the recovery room (estimated ratio of means ANI:control = 0.93, 95% CI, 0.78–1.11; P > .99), emetic episodes (ANI 0 [0%], control 2 [8%], P > .99), antiemetic requirements (ANI 4 [17%], control 9 [35%], P > .99), naloxone requirements (ANI 0 [0%], control 1 [4%], P > .99), Ramsay Sedation Score (odds ratio ANI group higher = 0.61, 95% CI, 0.32–1.17; P > .99) or respiratory rate (odds ratio ANI group higher = 1.76, 95% CI, 0.83–3.72; P > .99).

Intraoperatively, predicted CeFent levels from 5 to 30 minutes were 27% higher in the ANI group than in the control group (95% CI, 3%–57%; P = .51, unadjusted P = .03) (Figure 4). Predicted CeFent levels from 0 to 125 minutes were not different between ANI and control groups (estimated ratio of means ANI:control = 0.92, 95% CI, 0.7–1.27; P > .99). For a 1-unit decrease in ANI scores, predicted CeFent on average increased by an estimated 1.98% in the ANI group (95% CI, 1.7%–2.26%; P < .0001) and 1.08% in the control group (95% CI, 0.76%–1.39%; P < .0001). This correlation was significantly different between groups (0.9%, 95% CI, 0.5%–1.3%; P < .0001). Intraoperative fentanyl boluses in the ANI group were administered at twice the frequency (bolus per hour: ANI 5.1 ± 3, control 2.4 ± 1.2, P = .0001) and half the size (bolus size [µg]: ANI 41 ± 12, control 82 ± 49, P = .0002) when compared with the control group. Intraoperatively, the total fentanyl administration (estimated ratio of means ANI:control = 1, 95% CI, 0.78–1.27; P > .99), emergence times (estimated ratio of means ANI:control = 0.91, 95% CI, 0.72–1.14; P > .99), and the incidence of movement (ANI 4 [17%], control 5 [19%], P > .99) were not different between groups (Table 3). Total operative time (minutes) (ANI 85 ± 28, control 100 ± 51, P = .21), average BIS (ANI 40 ± 6, control 40 ± 5, P > .99), average ANI (ANI 68 ± 11, control 64 ± 12, P = .23), time with ANI < 50 (ANI 20 ± 15%, control 25 ± 23%, P = .39), and time with good-quality ANI readings (ANI 97 ± 2%, control 98 ± 2%, P = .25) were not different between groups (Table 3).

Figure 5 illustrates the probability distribution of intraoperative ANI scores and was not statistically assessed. During the course of surgery, the ANI score did not fall below 50 in 2 patients (n = 1$_{ANI}$; 1$_{control}$). Both patients received standardized weight-based induction doses of fentanyl and intraoperative analgesia was administered as per group allocation. Figure 6 shows intraoperative sevoflurane MAC$_{multiple}$ with no significant difference between groups from 0 to 125 minutes (difference in means ANI-control = 0.02, 95% CI, −0.05 to 0.08; P > .99)

Table 1. Baseline Patient Characteristics		
	ANI Group (n = 24)	Control Group (n = 26)
Sex (m/f)	11/13	12/14
Age (y)	47 (21–75)[a]	51 (20–75)[a]
Weight (kg)	85 ± 25	82 ± 15
BMI (weight/height^2)	29 ± 5	28 ± 3
ASA PS score (I/II)	4/20	7/19
Heart rate (beats/min)	84 ± 12	86 ± 18
MAP (mm Hg)	98 ± 10	96 ± 9
ANI baseline	68 ± 14	63 ± 12
BIS baseline	92 ± 9	94 ± 7
NRS scores at rest	4 ± 2	4 ± 3

Values are given as mean ± SD, mean (range)[a] or absolute numbers.
There were no significant differences between the groups.
Abbreviations: ANI, Analgesia Nociception Index; ASA PS, American Society of Anesthesiologists Physical Status; BIS, bispectral index; BMI, body mass index; MAP, mean arterial pressure; NRS, numerical rating scale.
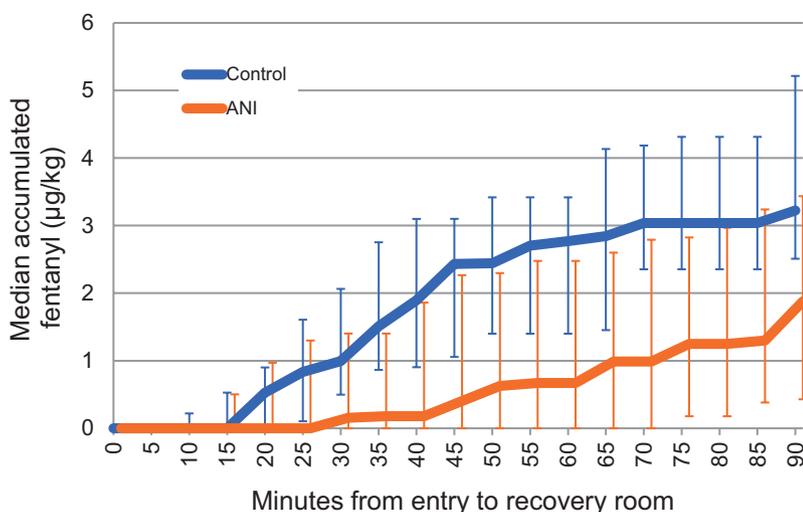

Figure 2. Graph showing mean NRS pain scores (0–10) in the recovery room between ANI group (n = 24, orange) and control group (n = 26, blue). Tabulated data includes number of conscious patients in recovery (N) and difference in mean NRS pain scores (control group minus ANI group) at each 5-minute time period. ANI indicates Analgesia Nociception Index; NRS, numerical rating scale.
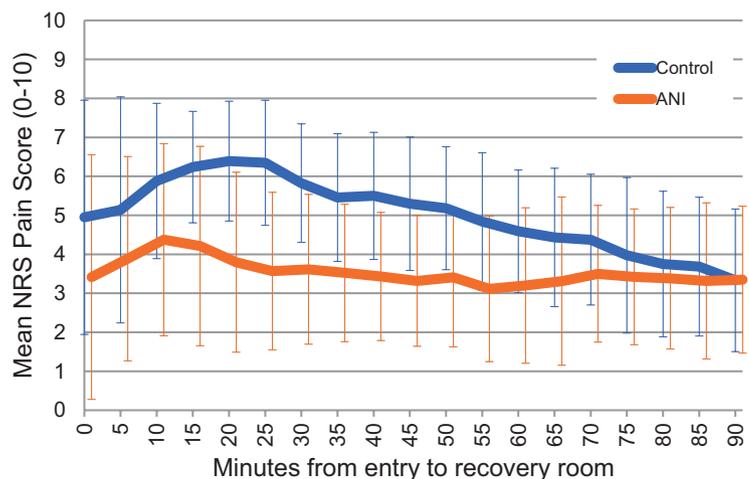
N	24	41	47	50	50	50	50	50	50	50	49	49	49	43	39	37	37	36	30
Difference in mean NRS pain scores	−0.86	−0.88	−0.96	−1.45	−2.04	−2.24	−1.66	−1.50	−1.66	−1.62	−1.59	−1.57	−1.22	−1.09	−0.98	−0.48	−0.28	−0.10	−0.03

Figure 3. Graph showing median accumulated fentanyl administration (weight-adjusted μg/kg) in the recovery room between ANI group (n = 24, orange) and control group (n = 26, blue). Bar represents interquartile range (Q1–Q3). This was not statistically assessed. ANI indicates Analgesia Nociception Index.

Table 2. Comparison of Recovery Room Outcomes			
	ANI Group (n = 24)	**Control Group (n = 26)**	**P**
Time spent in the recovery room (min)	97 ± 36[a]	100 ± 22[a]	>.99[b]
Shortest recovery room stay (min)	65	50	–
Total recovery room fentanyl administration (μg)	135 ± 180[a]	248 ± 200[a]	.44[b]
Fentanyl bolus per hour	1.3 ± 1.4	2.6 ± 1.6	.004
Naloxone required	0 (0%)	1 (4%)	>.99[b]
Worst nausea NRS (0–10)	1 ± 2[a]	2 ± 3[a]	.43[b]
Emetic episodes	0 (0%)	2 (8%)	>.99[b]
Antiemetics required	4 (17%)	9 (35%)	>.99[b]
Shivering	1 (4%)	7 (27%)	.80[b]
Airway intervention	3 (13%)	1 (4%)	>.99[b]

Values are given as mean ± SD or absolute number (%).
Significance calculated with Student t tests and χ^2 tests.
Abbreviations: ANI, "Analgesia Nociception Index"; NRS, numerical rating scale.
[a]Descriptive mean ± SD with difference and significance calculated from linear regression models with logarithmic transformation.
[b]Bonferroni corrected P value for secondary outcome.
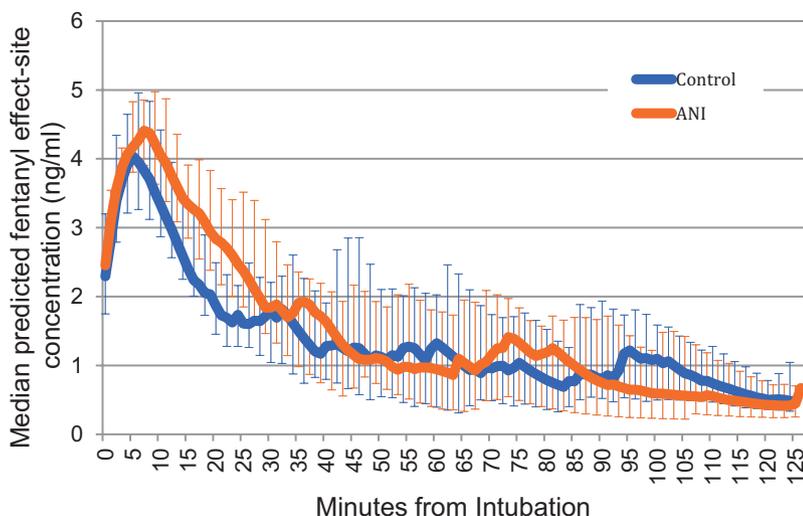
Figure 4. Graph showing median predicted fentanyl effect-site concentration (ng/mL) over the course of surgery between ANI group (n = 24, orange) and control group (n = 26, blue) according to time. Bar represents interquartile range (Q1–Q3). ANI indicates Analgesia Nociception Index.

DISCUSSION

Postoperative pain is the most common concern of patients undergoing surgery.[27] Up to 40% will experience severe pain in the recovery period, with a subsequent increase in the risk of developing chronic pain.[4,26] Our trial found that

pain scores in the first 10 minutes of recovery room stay were relatively low in both ANI and control groups, likely due to the residual effect of anesthesia on pain perception (Figure 2).[28] From 15 to 55 minutes postoperatively, a period when patients had regained consciousness and fentanyl

Table 3. Comparison of Intraoperative Measurements

	ANI Group (n = 24)	Control Group (n = 26)	P
Intubation to first incision (min)	23 ± 7	25 ± 8	–
Total operative time: first incision to final suture (min)	85 ± 28[a]	100 ± 51[a]	>.99[b]
Emergence time: final suture to awake time (min)	14 ± 6[a]	15 ± 6[a]	>.99[b]
Total intraoperative fentanyl administration (μg)	416 ± 191[a]	426 ± 247[a]	>.99[b]
Fentanyl bolus per hour	5.1 ± 3	2.4 ± 1.2	.0001
Fentanyl bolus size (μg)[c]	41 ± 12	82 ± 49	.0002
Fentanyl bolus size for <50 yo (μg)[c]	50 ± 0	93 ± 53	–
Fentanyl bolus size for ≥50 yo (μg)[c]	25 ± 0	64 ± 42	–
Intraoperative movement	4 (17%)	5 (19%)	>.99[b]
BIS[c]	40 ± 6	40 ± 5	>.99
ANI[c]	68 ± 11	64 ± 12	.23
Time (%) good-quality ANI readings	97 ± 2	98 ± 2	.25
Time (%) ANI <50	20 ± 15	25 ± 23	.39

Values are given as mean ± SD or absolute number (%).
Significance calculated with Student t tests and χ^2 tests.
Abbreviations: ANI, Analgesia Nociception Index; BIS, bispectral index; MAC, minimum alveolar concentration; yo, years old.
[a]Descriptive mean ± SD with difference and significance calculated from linear regression models with logarithmic transformation.
[b]Bonferroni corrected P value for secondary outcome.
[c]Mean of patient means.
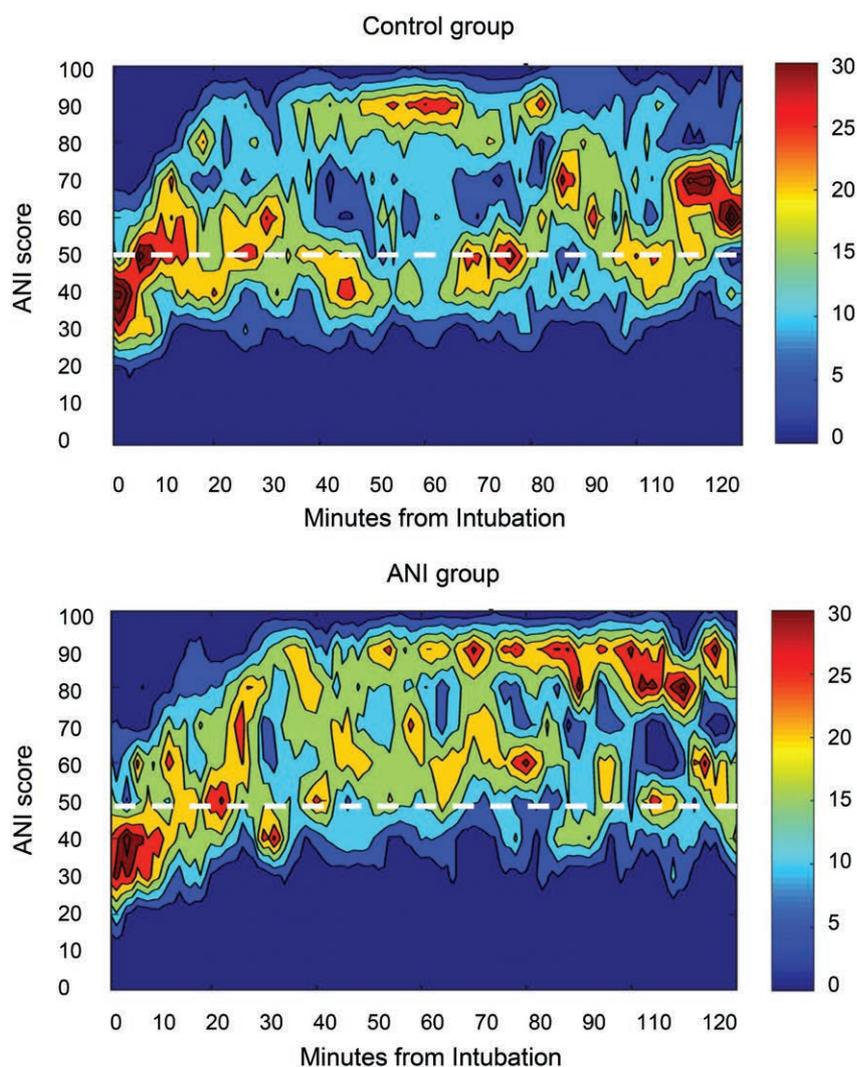
Figure 5. Change in the probability distribution of the ANI scores over the course of surgery in control group (n = 26) and ANI group (n = 24). Color bars are scaled as the percentage of patients within each 5-minute window. White-interrupted line marks ANI = 50. This was not statistically assessed. ANI indicates Analgesia Nociception Index.

pain protocol was used intensively, NRS pain scores were on average 1.8 units lower in the ANI group. This reduction is clinically discernable by patients.[25] Throughout all the recovery room period there was on average a 1.3-unit reduction in NRS pain scores in the ANI group. ANI group patients required less intensive management by nursing staff, receiving half as many fentanyl boluses as the control group and, overall, 64% less total fentanyl (Table 2, Figure
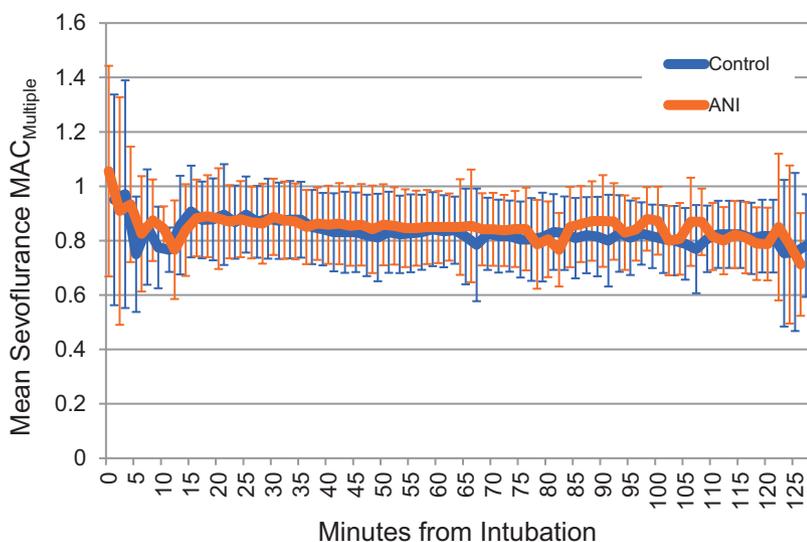
Figure 6. Graph showing mean intraoperative sevoflurane MAC$_{Multiple}$ over the course of surgery between ANI group (n = 24, orange) and control group (n = 26, blue) according to time. Bar represents the width of 2 standard deviations. ANI indicates Analgesia Nociception Index; MAC, minimum alveolar concentration.

3). This was associated with lower nausea scores in the ANI group (Table 2). ANI patients also showed a reduction in postoperative shivering, a potential consequence of postoperative pain. Shivering is associated with increased oxygen consumption and interference with postoperative monitoring.[29] The reduction in pain and analgesic requirement in the recovery room period is comparable to the effect of intraoperative ibuprofen 800 mg IV.[30] This is without the additional risk of renal, gastrointestinal, or hemorrhagic side effects. We consider these results to be clinically significant, but may not yet validate widespread application of the ANI monitor.

Our results suggest that intraoperative fentanyl was more objectively administered in the ANI group than the control group. For a 1-unit decrease in ANI scores, predicted CeFent on average increased by an estimated 1.98% in the ANI group and 1.08% in the control group. This correlation was significantly different between groups. This suggests that, throughout the procedure, higher fentanyl administration occurred in the ANI group during periods of greater nociception, when ANI scores were low. It is probable that the stimulation of laryngoscopy and intubation lowered ANI scores (Figure 5) and prompted more fentanyl administration in the ANI group than the control group before first surgical incision. ANI group patients maintained higher intraoperative-predicted CeFent levels from 5 to 30 minutes when compared with control group patients (Figure 4). During this period, a trough in predicted CeFent levels in the control group coincided with the average time of first surgical incision (25 minutes) (Table 3). Adequate analgesia at the time of first incision may have led to reduced postoperative pain in the ANI group.[31–34] The transmission of nociceptive input from the periphery to the spinal cord on incision can induce a prolonged state of central hyperexcitability, whereby subsequent stimuli in the postoperative period are amplified.[35,36]

Alternative explanations for the improved postoperative outcomes in the ANI group are unlikely. No difference was found between groups in average predicted CeFent levels on extubation or total intraoperative fentanyl dose, indicating that the results were not a direct effect of analgesic loading (Figure 4, Table 3). We specified age-adjusted fentanyl dosing in our ANI group protocol; however, dosing reductions for increasing age were similar between groups (Table 3). The smaller fentanyl boluses in the ANI group were likely a result of the precautionary dose range in our protocol. Small boluses may improve opioid titration akin to an analgesic infusion,[37] although postoperative outcomes have been similar in trials comparing bolus analgesia versus infusion analgesia.[38–40] There was no difference between the groups in other factors affecting postoperative pain, including age, preoperative pain levels, surgical type, or operative time (Tables 1 and 3).[41]

Our findings are in contrast to a similar trial of 120 patients undergoing laparoscopic cholecystectomy, where intraoperative ANI-guided and scaled morphine administration did not demonstrate an advantage over standard care in postoperative pain and analgesic requirement.[17] The use of a variety of opioids in this trial with the reliance on equivalence ratios may have made comparison of patient's analgesic requirement difficult. ANI-guided analgesia may also function better using faster-acting opioids like fentanyl and remifentanil.[7,11,12] Our trial utilized fentanyl only, which, in comparison to morphine, provides more accurate titration of analgesia given its rapid onset of action and shorter half-life.[42] Our trial did not use analgesic doses scaled to ANI values. Studies suggest that the relationship between ANI and analgesic requirement may not be linear, and the ideal scaling of analgesic doses for extreme values of ANI requires further investigation.[43]

A focus of our study was to control factors influencing the PNS, to ensure optimal anesthetic conditions for ANI monitoring. We excluded patients taking preoperative antimuscarinic/antiarrhythmic agents, α2-adrenergic agonists, or β1-adrenergic antagonists.[10,15] Furthermore, we used sugammadex for muscle relaxant reversal, which does not have PNS activity, hence avoiding interference with ANI scores before extubation.[44] Although we demonstrated improved outcomes for ANI-guided analgesia with these exclusions, we did not limit the use of autonomically active agents metaraminol and phenylephrine for the safe management of BP. The extent to which individual

autonomic factors influence ANI function requires further investigation.

Limitations

We appreciate that the use of Bonferroni correction may be conservative, increasing type 2 error due to a lack of intervariable independence. Outcome variables where Bonferroni correction increased the $P > .05$ were recovery room total fentanyl administration (μg) (unadjusted $P = .026$), shivering (unadjusted $P = .047$), nausea score (unadjusted $P = .03$), and intraoperative-predicted CeFent from 5 to 30 minutes (unadjusted $P = .03$). Additionally, it is acknowledged that predicted CeFent is a population-based estimate of concentrations. It is subject to significant variation when compared to actual measured drug levels for individual patients.

There is a potential that single blinding may have influenced the clinical practice of the anesthesiologists in our trial. We enforced predefined criteria for the administration of fentanyl, as well as for sevoflurane and adjuvant analgesic agents that may alter fentanyl consumption. There was no significant difference in intraoperative sevoflurane MAC$_{multiple}$ (Figure 6), while paracetamol, parecoxib, and local anesthetic were administered equally between groups. Regular exposure to intraoperative ANI monitoring may result in learning contamination bias, whereby anesthesiologists adjust their standard practice based upon results seen in the ANI group.[45] To address this, anesthesiologists in our protocol were not present in the postoperative setting and were not made aware of trial results. Ultimately, we found a significant difference between ANI and control group outcomes.

In conclusion, intraoperative ANI-guided fentanyl administration during sevoflurane anesthesia resulted in a decrease in recovery room pain, likely as a result of more objective intraoperative fentanyl administration. These findings apply to a specific group of patients undergoing lumbar discectomy or laminectomy, in the setting where potential influences on the PNS were minimized. ⬛

DISCLOSURES

Name: Henry D. Upton, MBBS, BMedSc (Hons).
Contribution: This author helped recruit patients, enter and assess data, and prepare the manuscript.
Name: Guy L. Ludbrook, MBBS, FANZCA, PhD.
Contribution: This author helped design the trial, review the literature, advise, with the ethics application, and prepare the manuscript.
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Contribution: This author helped design the trial, review the literature, advise with the ethics application, and prepare the manuscript.
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