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Postoperative pain after laparoscopic cholecystectomy is not reduced by intraoperative analgesia guided by analgesia nociception index (ANI®) monitoring: a randomized clinical trial

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Editor's key points

- Immediate postoperative pain is common after laparoscopic cholecystectomy, often requiring rescue analgesia.
- This study used intraoperative heart rate variability as a pain surrogate, to direct analgesia.
- The use of the analgesia nociception index (ANI) to direct intraoperative morphine did not improve postoperative analgesia.
- Further clinical investigation is required to establish the role of the ANI in pain management.

Background. Laparoscopic cholecystectomy frequently results in significant immediate postoperative pain. A new pain monitor, analgesic nociception index (ANI®), based on heart rate variability, has recently been approved for intraoperative nociception monitoring. We designed a single-blind, parallel-group, randomized control trial to test the hypothesis that protocol-driven intraoperative analgesia guided by ANI during laparoscopic cholecystectomy would improve titration of intraoperative analgesics leading to decreased postoperative pain.

Methods. One hundred and twenty consecutive adult participants presenting for elective laparoscopic cholecystectomy were recruited. Participants were randomly allocated by sealed envelope to receive intraoperative morphine either guided by ANI via a protocol (intervention group) or guided by the anaesthetist with ANI concealed (control group). All participants received paracetamol, parecoxib, fentanyl at induction, and local anaesthetic to port sites. The primary endpoint was the presence of moderate/severe pain (visual analogue scale $\geq$50 mm) at any of the four time points in the first postoperative hour. Secondary endpoints included postoperative rescue morphine.

Results. Sixty participants were randomized to each group, and all but one drop-out from the intervention group were analysed. The usage of ANI guidance did not result in a decrease in the rate of moderate/severe pain (50.8% *vs* 45.0%: difference of −5.8%, 95% confidence interval, −23.7% to 12.1%, P=0.58), or the use of postoperative rescue analgesia.

Conclusions. This randomized control trial of intraoperative ANI-guided morphine administration in elective laparoscopic cholecystectomy failed to show any advantage over the current standard of care, and demonstrated a high level of postoperative pain, despite the use of multimodal analgesia.

Clinical trial registration. ANZCTR Reference ACTRN12612000953831 (URL: http://www.anzctr.org.au/trial_view.aspx?ID=362949).

Keywords: analgesics, opioid/therapeutic use; cholecystectomy, laparoscopic; heart rate; pain measurement/methods; pain, postoperative/drug therapy

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Immediate postoperative pain and analgesia requirements in the post-anaesthesia care unit (PACU) varies according to type of surgery, patient characteristics, and the timing and amount of intraoperative analgesia.[1] Laparoscopic cholecystectomy is a surgical procedure that frequently results in significant immediate postoperative pain and the need for rescue analgesia in the PACU.[2 3]

Intraoperative titration of opioids may result in improved immediate postoperative pain management,[4] but there is currently no gold standard for nociception monitoring in unconscious patients. Clinical signs of sympathetic stimulation such as hypertension, tachycardia, and sweating may indicate intraoperative nociception, but these are non-specific and their absence does not rule it out. A variety of analgesia monitors have been

developed based on physiological principles, including skin vasomotor reflexes, plethysomography, pulse transit time, pupillometry, electroencephalography, and heart rate variability (HRV), but all have limitations in intraoperative settings.[5]

A new nociception monitor based on HRV, the analgesia nociception index (ANI) monitor (MetroDoloris, Lille, France), has been approved for use in many countries worldwide, predominantly in Europe and the Asia Pacific. Although HRV is influenced by the sympathetic nervous system, thermoregulatory state, baroreflex, and endocrine systems, high-frequency modulations (0.15–0.4 Hz) of HRV are a highly specific measure of parasympathetic tone.[6] The ANI monitor uses three electrocardiographic leads to measure parasympathetic tone on a scale of 0–100, giving a continuous ANI reading and a continuous moving 4 min average. An ANI over 50 is said to predict adequate analgesia, while an ANI below 30 predicts autonomic reactivity to nociceptive stimuli.[7] There are currently no trials in the literature that have investigated whether intraoperative ANI monitoring can be used to reduce postoperative pain.

Titration of analgesics against haemodynamic parameters with surgical stimulation is common practice, and it follows that a more sensitive measure of autonomic reactivity, such as ANI monitoring, might lead to decreased postoperative pain. In the current study, we tested the hypothesis that protocol-driven intraoperative analgesia guided by ANI monitoring during laparoscopic cholecystectomy would improve titration of intraoperative analgesics leading to decreased immediate postoperative pain.

Methods

This single-blind, parallel-group, randomized controlled trial was conducted across two hospitals of a single health service in outer metropolitan Melbourne, Australia. This study was conducted in accordance with the Declaration of Helsinki and ethics approval was obtained from the Peninsula Health Human Research Ethics Committee (Ref: HREC/12/PH/65). The study was registered with the Australian New Zealand Clinical Trials Registry (Ref: ACTRN12612000953831). All participants provided written informed consent before participation. The ANI device was provided by an unencumbered loan for the duration of the trial by its Australian distributor, Becor Medical Solutions.

One hundred and twenty adult patients having elective laparoscopic cholecystectomy were recruited. Eligible participants were adults aged 18–75, capable of giving consent, and in sinus rhythm. Exclusion criteria were pregnancy, chronic pain (or regular preoperative opioid use), or conditions affecting the autonomic nervous system such as diabetic autonomic neuropathy.

On arrival to the operating theatre, participants were randomly allocated to one of two treatment groups using pre-prepared sealed, opaque, and tamper-proof envelopes with group allocation according to printed tables of random numbers. Participants and PACU nurses performing pain assessments were blinded to group allocation. Participants were managed by a variety of surgeons and senior anaesthetists.

In the intervention group (Group I), the ANI monitor was used to titrate intraoperative morphine using the 4 min moving average of ANI displayed on the ANI monitor. After surgery commenced, morphine 3 mg was given when 4 min average ANI decreased below 50, or 5 mg when below 30, unless a parasympatholytic agent had just been given (e.g. atropine). The ANI was reassessed at 5 min intervals until the end of surgery with further boluses as needed. For participants intolerant of morphine, fentanyl was given in equi-analgesic doses (30 or 50 μg) and fentanyl dosage was converted to morphine equivalents for analysis in a ratio of 100:1.[8] In the control group (Group C), the ANI monitor was connected to the participant but concealed from the anaesthetist, and morphine (fentanyl if intolerant) was administered based on clinical signs and the anaesthetist's usual practice. Morphine was selected for this trial as it is frequently used during surgery in Australia and clinical observation during familiarization with the ANI monitor demonstrated that its intraoperative use resulted in a rapid increase in ANI in a variety of surgical settings.

In all cases, general anaesthesia was induced with propofol (1–3 mg kg^{-1}), an induction dose of fentanyl (1 μg kg^{-1}), and neuromuscular blocking agent (anaesthetists' choice) to facilitate orotracheal intubation. Anaesthesia was maintained with air/oxygen and sevoflurane/desflurane or propofol (one patient) with bispectral index (BIS) monitoring to ensure adequate depth of anaesthesia. Unless contraindicated, all participants received i.v. paracetamol 1 g and parecoxib 40 mg plus local anaesthetic infiltration to port sites. Pneumoperitoneum was actively deflated before wound closure.

On emergence from anaesthesia, our institutional morphine pain protocol was used (if required) in PACU as follows: pain score of 4–6 on the 11-point (0–10) verbal rating scale (VRS) received 2–4 mg morphine and pain score 7–10 received 3–5 mg, with reassessment and treatment every 5 min. Pain scores on the visual analogue scale (VAS) were measured by PACU staff using a VAS ruler at 15, 30, 45, and 60 min after arrival in PACU and participants were familiarized with this before operation during measurement of any pre-existing abdominal pain. Other rescue analgesia including tramadol or ketamine could be used in PACU for opioid-resistant pain after discussion with the anaesthetist and its use was recorded. Nausea was recorded at 30 and 60 min on a three-point scale (none/mild/severe) as were anti-emetic requirements.

The primary endpoint of the study was the presence of moderate/severe pain, defined as a VAS $\geq$ 50 mm, at any of the four time points in the first postoperative hour. Secondary endpoints were cumulative VAS measurements at the four time points, amount of rescue postoperative opioid and other analgesics in PACU, total intraoperative opioid, and postoperative nausea, vomiting, or antiemetic administration within the first hour in PACU. In addition, ANI parameters, intraoperative haemodynamic and BIS data, time from surgical dressings to extubation, and time until readiness for discharge from PACU were collected.

The sample size was calculated based on an initial pilot study of 20 participants. We considered that a 30% decrease in the

rate of severe pain would be a clinically significant benefit. A study of 56 participants per group provided 80% power with a two-sided type I error of 0.05 to find this difference.

Two-sided Student's *t*-tests were used for all numerical data, and Fisher's exact test was used for categorical data. Analysis was undertaken using Stata V13.0 (StataCorp, College Station, TX, USA) and was according to intention to treat.

Results

Between October 2012 and November 2013, 120 patients were assessed for study eligibility and all were recruited and randomized, with equal numbers to the intervention (Group I) and control groups (Group C) (Fig. 1).

One participant (Group I) was withdrawn during surgery due to persistent loss of signal on the ANI monitor, which made intraoperative opioid titration impossible. This participant did not have data collected. Two consecutive participants, one from each group, were accidentally not treated according to the group they were allocated. An intention-to-treat analysis was performed. Occasional interference from the use of diathermy caused the ANI monitor to be momentarily unable to display the ANI reading. The percentage of time with good quality readings was 96.2% in Group I and 96.8% in Group C: a difference of 0.6% (95% confidence interval, −6% to 7%).

The groups were similar at baseline (Table 1). The proportion of participants with moderate/severe pain (VAS≥50 mm at any time) in PACU was high overall and not decreased in Group I. Such pain scores in the first hour in PACU occurred in 50.8% of Group I, and 45.0% of Group C: a difference of −5.8% (95% confidence interval, −23.7% to 12.1%, P=0.58). This corresponds to a −12.9% relative reduction in the rate of moderate/severe pain (95% confidence interval, −52.7% to 26.9%), which does not include the pre-specified reduction of 30% that we deemed clinically significant. Severe pain (VAS≥70 mm) occurred in 39.0% of Group I and 30% of Group C: a difference of −9.0% (95% confidence interval, −26.0% to 8.0%, P=0.34), relative reduction of −30.0% (95% confidence interval, −86.7% to 26.7%). A secondary analysis was done excluding a small number of participants (9% of all participants) that received post-induction intraoperative fentanyl which did not affect the results, with 50.1% of Group I, and 41.2% of Group C experiencing moderate/severe postoperative pain: a

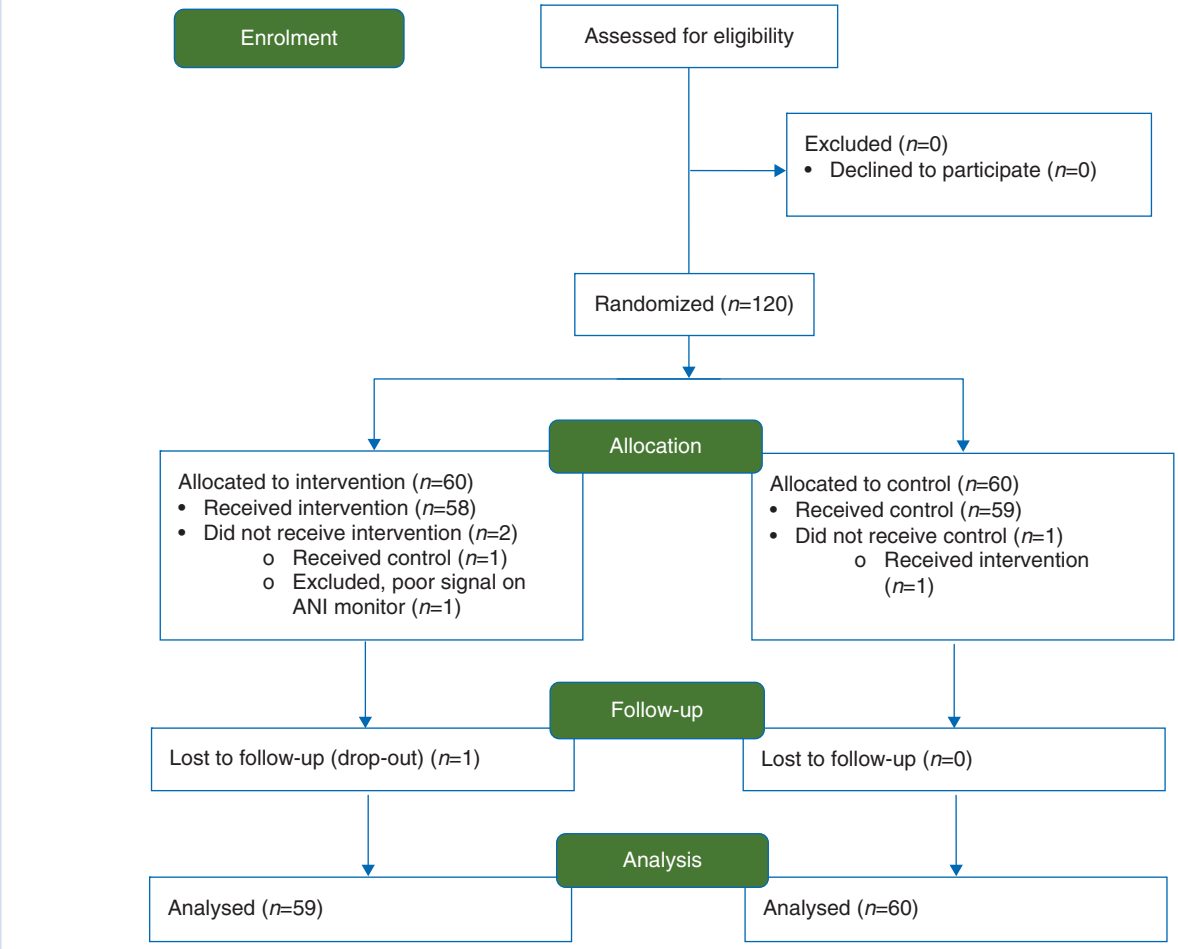

Fig 1 Participant flow chart.

difference of −9.7% (95% confidence interval, −27.5% to 8.1%, P=0.34).

There were also no significant differences in cumulative pain scores, PACU rescue opioid, amount of intraoperative opioid, proportion requiring other rescue analgesia in PACU, postoperative nausea and vomiting, and time for readiness to discharge from PACU. Intraoperative measurements including haemodynamic parameters, BIS, mean ANI energy (a measure of signal quality), and time to extubation were also similar (Table 2).

Of note, the percentage of time each participant spent with an ANI <50 (i.e. in the range said to predict inadequate antinociception) was similar in the intervention group 30.2% (SD 15.1%) and control group 31.0% (SD 13.5%) (P=0.77).

There was no association between moderate/severe postoperative pain and mean ANI or time spent with an ANI <50 in the final 5 min of the case before neuromuscular reversal was given. Participants who developed moderate/severe postoperative pain compared with those who did not had a mean ANI in the last 5 min of 67 and 63, respectively (P=0.19), and time spent with ANI <50 in the last 5 min was 1.1 and 1.5 min, respectively (P=0.21).

Table 1 Baseline characteristics in Group I (intervention) and Group C (control). Presented as mean (range), mean (SD), or number (%). VAS, visual analogue scale

	Group I (n=60)	Group C (n=60)
Age (yr)	43.3 (20–72)	44.4 (23–73)
Gender (female)	45 (75%)	50 (83%)
Weight (kg)	84.0 (20.5)	82.3 (21.2)
Baseline pain (VAS in mm)	4.7 (12.8)	4.5 (10.2)
Intolerant to morphine	2 (3.3%)	5 (8.3%)

A small number of minor protocol violations occurred. BIS was not recorded in 10 participants (three intervention group, seven control group). Parecoxib was omitted in three controls with one receiving ketorolac instead. Time to extubation and PACU discharge was not recorded for 12 participants (four intervention group, eight control group) and three participants left PACU before the specified 60 min (two intervention group, one control group). Missing data were not imputed.

Discussion

Our results suggest that protocol-driven intraoperative analgesia guided by 5 minutely assessment of averaged ANI does not reduce postoperative pain or analgesic requirements in adults undergoing elective laparoscopic cholecystectomy. Of note, the 95% confidence interval upper limit for moderate/severe pain was less than our proposed important difference of a 30% reduction. Therefore, this study indicates that ANI monitoring, using our protocol, does not result in decreased postoperative pain compared with using clinical signs and usual practice.

Moderate/severe pain in the immediate postoperative period was common overall, despite the regimen of fentanyl/morphine, paracetamol, non-steroidal anti-inflammatory drugs, and local anaesthetic to port sites. Such findings are consistent with other studies of laparoscopic surgery[2 3] and may result from the interaction of pain from incisions to skin, liver bed, and peritoneum and also diaphragm irritation from retained gas. Our patient population was predominantly young and female, and both gender and age have been shown to be determinants of postoperative pain and opioid requirements.[9 10] Analgesic techniques such as intraperitoneal local anaesthesia[11] or adjuvants such as ketamine[12] may be useful in reducing pain after laparoscopic cholecystectomy.

We expected that participants in the intervention group would have a smaller proportion of intraoperative time with

Table 2 Comparison of primary and secondary outcomes between Group I (intervention) and Group C (control). Presented as mean (SD) or number (%). VAS, visual analogue scale; PONV, postoperative nausea or vomiting; ANI, analgesia nociception index; HR, heart rate; SAP, systolic arterial pressure; BIS, bispectral index; PACU, post-anaesthesia care unit

	Group I (n=59)	Group C (n=60)	Difference (95% CI)	P-value
Moderate/severe pain at any time	30 (50.8%)	27 (45.0%)	−5.8% (−23.7%, 12.1%)	0.58
Cumulative VAS scores (mm)	152 (100)	138 (79)	−14 (−47, +20)	0.42
Rescue morphine equivalent (mg)	8.8 (7.2)	8.0 (6.5)	−0.8 (−3.3, +1.7)	0.52
Other rescue analgesia needed	17 (29%)	12 (20%)	−9% (−24%, +7%)	0.29
PONV or any rescue antiemetics	19 (33%)	25 (42%)	+9% (−8%, +27%)	0.34
Intraoperative morphine equivalent (mg)	12.4 (6.5)	12.0 (5.0)	−0.4 (−2.5, +1.7)	0.72
Percentage of time spent with ANI® <50	30.2 (15.1)	31.0 (13.5)	−0.8 (−4.4, +6.0)	0.77
Mean ANI®	62.5 (10)	61.0 (8.4)	−1.5 (−4.8, +1.9)	0.38
Mean ANI® energy	0.547 (0.201)	0.523 (0.156)	−0.023 (−0.089, +0.042)	0.48
Mean HR	73 (12)	75 (12)	+2 (−2, +7)	0.30
Mean SAP	113 (13)	117 (18)	+4 (−2, +10)	0.17
Mean BIS®	35 (6)	37 (7)	+2 (−0.6, +4.4)	0.13
Surgical time (min)	74.4 (21)	74.5 (22)	−0.1 (−8, +8)	0.99
Time to extubation (min)	9.3 (4.4)	8.1 (4.2)	−1.1 (−2.7, +0.5)	0.17
Time to readiness for discharge from PACU (min)	55 (23)	55 (20)	0 (−8, +8)	0.93

an ANI of <50 than the control group, but this did not occur. There are a number of possible reasons for this unexpected finding. First, while our protocol seemed reasonable, *a priori*, it may not have been ideal in choice of opioid, bolus dose, or timing. Morphine was selected, as it is a common intraoperative opioid for laparoscopic surgery in Australia. We chose the trigger for analgesia as a decrease in the 4 min average ANI below 50, which was reassessed at 5 min intervals. Although instantaneous ANI could have been used as the trigger for analgesia, it can be highly labile where the nociception–antinociception balance is changing rapidly, and we wanted to avoid the potential for overadministration of analgesia. Shorter dosing intervals or using the instantaneous ANI may have permitted the intervention group to have an ANI value >50 for a greater proportion of time. For example, anaesthetists often saw the instantaneous ANI decrease rapidly with a noxious stimulus for intervention group patients, but were constrained from giving opiates immediately until the 4 min average was below 50. Secondly, control participants were often 'front-loaded' with morphine (a large bolus before the first incision), which may have had a pre-emptive analgesic effect and effectively maintained the ANI in the optimal range in many cases. A future study might avoid this problem by designing a protocol with a loading dose of morphine followed by further titration against ANI, perhaps with higher bolus doses, particularly for quick surgical times. Finally, ANI may not be well correlated with nociception during laparoscopic cholecystectomy, although this is not supported by other studies.[13]

An underpinning assumption of this study is that better intraoperative analgesia will lead to reduced postoperative pain. While this does seem intuitive, and may be true for some surgery,[4] this has not been established in laparoscopic cholecystectomy. Surgeries with periods of intense nociception may not necessarily require significant postoperative analgesia, and as such, the relationship between intraoperative analgesia based on nociception and postoperative pain is not clear. We looked at ANI values in the final 5 min of surgery, but did not find that this was predictive of moderate/severe postoperative pain. This suggests that nociception at the end of laparoscopic cholecystectomy is not well correlated with postoperative pain.

An ideal intraoperative nociception monitor would be easy to use, permit intraoperative titration of analgesia to reduce haemodynamic change with noxious stimuli, reduce postoperative pain, and accurately measure pain in conscious subjects where this is otherwise difficult, for example, in dementia or young children. We found that the ANI monitor was easy to set up and use. Lower values of the ANI have been shown to occur with increased intraoperative nociceptive stimuli and higher values with opioid administration, suggesting effectiveness at measuring nociception/antinociception balance.[13 14] There are conflicting studies on its use as an objective postoperative pain monitor.[15 16] We have conducted the first study examining its effectiveness to reduce postoperative pain but found little benefit using our protocol.

There are several limitations to our study. First, laparoscopic surgery may not be ideal to examine parasympathetic tone due to the effects of pneumoperitoneum on vagal tone and ANI.[13] This may be reflected in the low proportion of time that both groups spent with an ANI<50. Secondly, the control group was not given protocolized care. This was done to mimic real-world anaesthesia and increase the generalizability of the study. However, this introduces a potential treatment bias whereby control participants may have been given more analgesia than a regular laparoscopic cholecystectomy participant due to their participation in the study. Thirdly, pain is influenced by several factors including patient anxiety and expectations, which may have been increased by with recruitment to the trial.

This is the first study, to our knowledge, that has investigated the use of intraoperative ANI monitoring in altering postoperative outcomes. We found that the use of protocol-driven intraoperative analgesia guided by ANI monitoring did not reduce postoperative pain and conclude that this monitor is not useful in altering clinically significant outcomes after elective laparoscopic cholecystectomy.

Authors' contributions

J.S.: idea and protocol development, literature review, ethics application, recruitment of participants, data collection and entry, data analysis, and write-up. A.W.: idea and protocol development, recruitment of participants, data collection, write-up, and supervisor. C.W.: recruitment of participants, data collection and entry, and write-up. A.C.: recruitment of participants, data collection and entry, and write-up. H.S.: recruitment of participants, data collection, and write-up. S.L.: idea and protocol development, recruitment of participants, data analysis, and write-up.

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Declaration of interest

None declared.

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