Anaesthesia 2023 doi:10.1111/anae.16008

Original Article

A randomised controlled trial of the analgesia nociception index for intra-operative remifentanil dose and pain after gynaecological laparotomy

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Summary

We aimed to investigate the effect of the analgesia nociception index on postoperative pain. We randomly allocated 170 women scheduled for gynaecological laparotomy and analysed results from 159: in 80 women, remifentanil was infused to maintain analgesia nociception indices 50–70; and in 79 women, remifentanil was infused to maintain systolic blood pressure < 120% of baseline values. The primary outcome was the proportion of women with pain scores ≥ 5 (scale 0–10) within 40 min of admission to recovery. The proportion of women with pain scores ≥ 5 was 62/80 (78%) vs. 64/79 (81%), p = 0.73. Mean (SD) doses of fentanyl in recovery were 53.6 (26.9) μg vs. 54.8 (20.8) μg, p = 0.74. Intra-operative remifentanil doses were 0.124 (0.050) $\mu g.kg^{-1}.min^{-1}$ vs. 0.129 (0.044) $\mu g.kg^{-1}.min^{-1}$, p = 0.55.

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Accepted: 25 February 2023
Keywords: analgesia; nociception; postoperative pain; remifentanil

Introduction

Intra-operative nociception is related to postoperative pain [1, 2]. Inadequate intra-operative analgesia may contribute to accidental awareness of pain and postoperative complications [3, 4]. Excessive analgesia may increase the rate of postoperative hyperalgesia [5, 6]. Various devices intended to monitor nociception and guide analgesic dosing have been developed [7]. These devices may help dosing of intra-operative opioids by discriminating between nociceptive and non-nociceptive stimuli [8–10].

The analgesia nociception index (MetroDoloris Medical Systems, Lille, France) is based on heart rate variability, in particular the variability of higher frequencies [11, 12]. The effects of the analgesia nociception index on postoperative pain and postoperative opioid consumption are varied and studies have included few participants [13–19]. We aimed to investigate the effects of intra-operative analgesia nociception index on remifentanil infusion and acute postoperative pain.

Methods

The Institutional Review Board of the Seoul National University Hospital approved this preregistered trial. We studied women scheduled for gynaecological laparotomy between July 2021 and July 2022. We did not study the following: girls (<18 y); pregnant women; women scheduled for laparoscopic or robotic surgery; women who took regular analgesics, beta-blockers, anticonvulsants or anti-epileptic drugs; women allergic to trial drugs; women with cardiac arrhythmia; and emergency surgery. We excluded from analysis participants discharged to the intensive care

unit after surgery. Participants provided written informed consent. We admitted participants to hospital the day before surgery, whom we educated about using intravenous patient-controlled analgesia (AutoMed 3200, ACE Medical, Seoul, Korea) and the 11-point numeric rating scale. Participants completed the Korean version of the Quality of Recovery-15 questionnaire (QoR-15 K) under the direct supervision of the investigator [20].

Using R software (Version 3.6.1, R Development Core Team, Vienna, Austria), an investigator who was not involved in this study generated a sequence that allocated two participants each to the control group and the

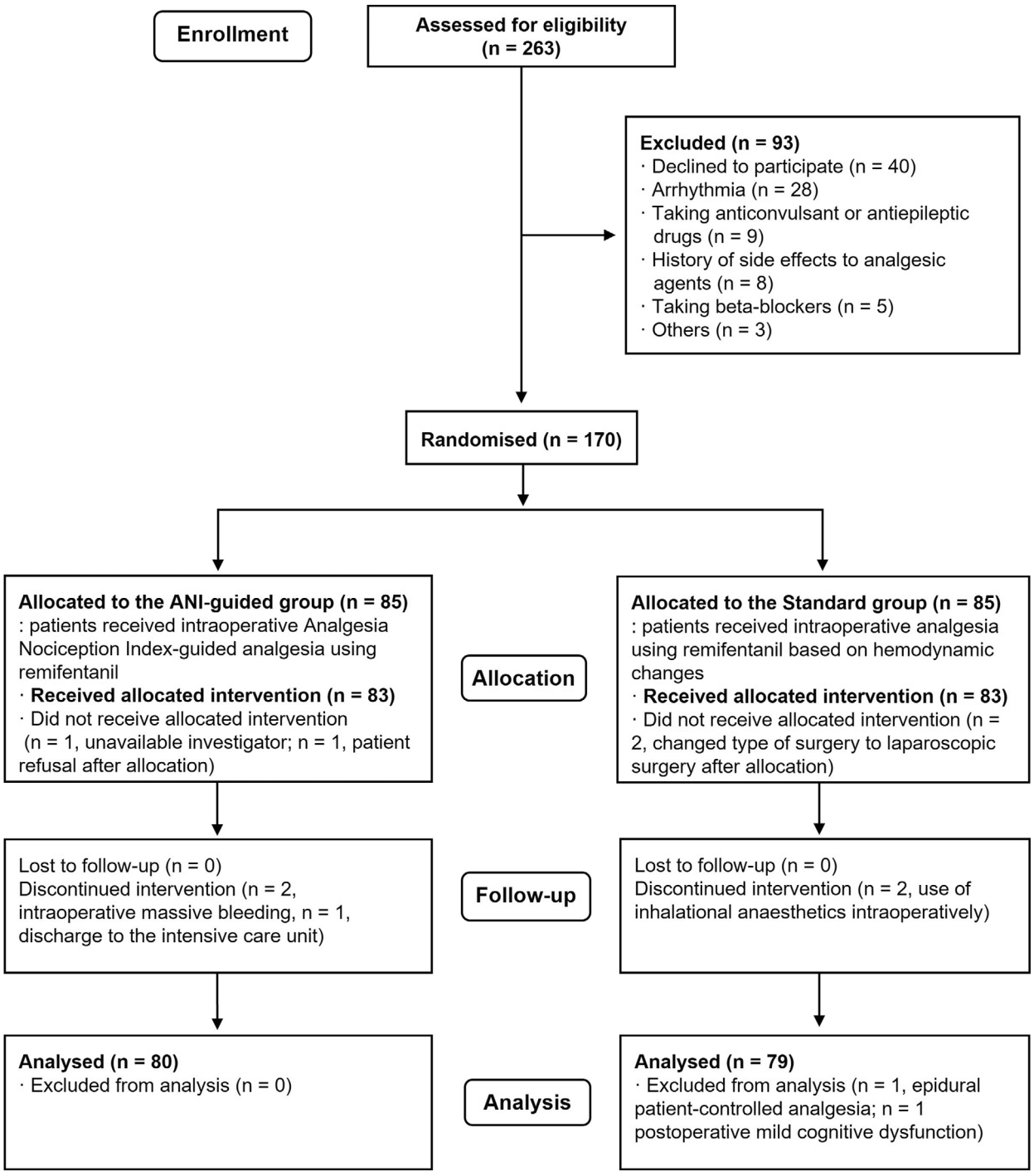

Figure 1 Study flow diagram. ANI, analgesia nociception index.

intervention group in random order in each consecutive block of two to four allocations. The information about the allocation sequence was concealed in serially numbered, opaque sealed envelopes as printed documents by the investigator and handed to an attending anaesthetist on the day of surgery. An anaesthetist opened the envelope immediately before induction of anaesthesia, monitoring with non-invasive blood pressure, ECG and peripheral pulse oximetry. We attached the two leads for the analgesia nociception index to ECG positions V1 and V5. We used intravenous propofol 2% (Fresofol MCT 2%, Fresenius Kabi Korea Ltd., Seoul, South Korea) to induce anaesthesia, targeted to an effect-site concentration of 4.0 $mg.ml^{-1}$ using the Schnider pharmacokinetic model, with remifentanil (Remiva, Hanharm Co., Ltd., Seoul, Korea) targeted to an effect-site concentration using 4.0 $ng.ml^{-1}$ of the Minto pharmacokinetic model. After induction of anaesthesia, propofol infusion was titrated to maintain a processed EEG of 25–50 (PSI; Sedline®, Irvine, CA, USA). Tracheal intubation was facilitated with intravenous rocuronium 0.6–0.8 $mg.kg^{-1}$. We ventilated lungs with 40% oxygen-enriched air at 8 $ml.kg^{-1}$ predicted body weight, adjusted to end-tidal carbon dioxide 4 −5.3 kPa, with a positive end-expiratory pressure of 5 cmH_2O. We used ephedrine for systolic blood pressures ≤ 90 mmHg. We gave intravenous dexamethasone 5 mg, palonosetron 0.075 mg, paracetamol 1 g and fentanyl 50 μg when the Jackson–Pratt drains were inserted. We used acceleromyography to determine the dose of intravenous sugammadex at the end of the operation. We extubated participants' tracheas before transfer to the PACU, where participants controlled a bolus of intravenous fentanyl 20 μg up to every 10 min, which was encouraged by staff for pain scores ≥ 3. Staff supplemented analgesia with intravenous fentanyl 50 μg for pain scores ≥ 7. We treated moderate or severe nausea or vomiting with intravenous metoclopramide 10 mg. We discharged participants from recovery when their modified Aldrete score was 9. On the ward, participants continued to control their analgesia, supplemented by intravenous dexketoprofen 50 mg or ketorolac 30 mg for pain scores ≥ 4, or paracetamol 1 g or tramadol 50 mg for participants with impaired renal function.

The analgesia nociception index was hidden throughout the surgery from anaesthetists looking after women in the control group by covering the screen of the monitoring device with an opaque shield. The remifentanil target

Table 1 Patient characteristics for those whom the intra-operative remifentanil infusion rate was determined by the analgesic nociceptive index or systolic blood pressure. Values are median (IQR [range]), mean (SD) or number (proportion).

Variables	Analgesia nociception index n = 80	Systolic blood pressure n = 79
Age; y	44.5 (38.0–51.0 [22.0–65.0])	46.0 (36.5–51.5 [20.0–75.0])
Height; cm	159.3 (5.5)	159.4 (5.6)
Weight; kg	62.0 (55.7–67.3 [41.5–103.0])	59.6 (55.0–67.2 [43.7–90.4])
BMI; $kg.m^{-2}$	24.3 (21.8–26.7 [16.7–35.0])	23.6 (21.5–27.3 [18.2–37.9])
Current smoker	4 (5%)	1 (1%)
ASA physical status 1/2	19/61	11/68
Comorbidity		
Hypertension	12 (15%)	10 (13%)
Diabetes mellitus	3 (4%)	4 (5%)
Cardiac disease	3 (4%)	1 (1%)
Respiratory disease	4 (5%)	7 (9%)
Chronic liver disease	5 (6%)	2 (3%)
Thyroid disease	13 (16%)	14 (18%)
Chronic kidney disease	2 (3%)	0
Dyslipidaemia	7 (9%)	4 (5%)
Anaemia	9 (11%)	15 (19%)
Previous abdominal surgery	35 (44%)	32 (41%)
Previous PONV	2 (3%)	3 (4%)
Pre-operative haemoglobin; $g.dl^{-1}$	12.6 (11.9–13.6 [9.3–14.8])	13.3 (11.9–14.1 [6.6–15.6])
Pre-operative QoR-15K	136.4 (13.6)	138.0 (13.5)

PONV, postoperative nausea or vomiting; QoR-15K, the Korean version of the Quality of Recovery-15 questionnaire.

effect-site concentration was changed by 0.5 ng.ml^{-1} in control participants to maintain systolic blood pressure 80%-120% of the mean systolic pressure during the first 5 min of anaesthesia. The minimum target effect-site concentration of remifentanil was 1.0 ng.ml^{-1}. In the intervention group, the anaesthetist adjusted the remifentanil infusion every 5 min by 0.5 ng.ml^{-1} as necessary to maintain 4-min average analgesia nociception indices of 50–70.

The primary outcome was pain scores ≥ 5 recorded by an investigator who was blinded to group allocation at 10, 20, 30 and 40 min after arrival in PACU. Secondary outcomes were: intra-operative doses of remifentanil and propofol and time-weighted average intra-operative systolic blood pressure ≤ 90 mmHg [21]; rescue analgesic dose and nausea or vomiting in PACU; analgesic doses, pain scores at rest and on movement and nausea or vomiting on the first postoperative day; the quality of recovery scores at 24 postoperative hours; analgesic dose and anti-emetic drugs on the day of ambulation; and length of hospital stay.

We calculated that we needed 77 participants in each group to have 90% power to detect a 30% relative reduction (26% absolute reduction) in the proportion of pain scores ≥5 from a control proportion of 80% (unpublished local observations) at an α threshold of 0.05. We decided to recruit 85 participants to each group due to dropouts. We used R and SPSS software (version 25.0, IBM Corp., Armonk, NY, USA) to analyse the data. We used the chi-squared test, Fisher's exact test, Student's t-test or Mann–Whitney U-test as appropriate.

Results

We analysed data from 159 participants. Pre-operative characteristics and intra-operative variables were similar for participants whose intra-operative remifentanil infusion rate had been determined by the analgesic nociceptive index vs. systolic blood pressure (Fig. 1, Tables 1 and 2 and online Supporting Information Figure S1).

The proportions of participants with pain scores ≥ 5 during the first 40 min in postoperative recovery were 62/80

Table 2 Intra-operative variables for participants in whom remifentanil infusion rate was determined by the analgesic nociceptive index or systolic blood pressure. Values are median (IQR [range]), mean (SD) or number (proportion).

Variables	Analgesia nociception index n = 80	Systolic blood pressure n = 79	Difference (95%CI)	p value
Operation time; min	118 (88–163 [40–325])	110 (85–135 [45–255])	8 (−10 to 25)	0.09
Anaesthesia time; min	148 (120–193 [65–370])	135 (105–165 [67–282])	13 (−10 to 26)	0.07
Time to extubate; min	7 (5–11 [1–34])	6 (5–11 [1–21])	1 (−2 to 3)	0.96
Incision				
Pfannenstiel/low/middle	57/17/6	49/26/4		0.21
Fluid; ml.h^{-1}	450 (338–600 [114–1513])	394 (281–527 [157–1114])	56 (−12 to 107)	0.09
Blood loss; ml	300 (200–560 [50–2100])	300 (150–500 [50–1750])	0 (−50 to 150)	0.37
Urine output; ml	105 (50–300 [10–2200])	100 (50–250 [10–750])	5 (−50 to 105)	0.37
Transfusion	12 (15%)	4 (5%)	0.10 (0.01–0.19)	0.07
Mean SBP; mmHg	123 (117–132 [100–156])	122 (113–129 [102–147])	1 (−3 to 5)	0.35
Mean heart rate; min^{-1}	65 (61–71 [50–93])	65 (61–72 [50–102])	1 (−2 to 5)	0.80
Time-weighted average SBP < 90 mmHg; mmHg	0.0 (0.0–0.3 [0.0–1.5])	0.0 (0.0–0.2 [0.0–1.9])	0.0 (0.0–0.1)	0.50
Medications				
Propofol; mg.kg^{-1}.min^{-1}	0.128 (0.022)	0.130 (0.026)	−0.002 (−0.010 to 0.005)	0.53
Rocuronium; mg	90 (70–100 [40–170])	80 (70–100 [40–140])	10 (−10 to 10)	0.25
Remifentanil; µg.kg^{-1}.min^{-1}	0.124 (0.05)	0.129 (0.04)	−0.01 (−0.02 to 0.01)	0.55
Ephedrine	38 (48%)	30 (38%)	0.1 (−0.1 to 0.3)	0.29
Ephedrine; mg	10 (5–15 [5–30])	5 (5–15 [5–25])	5 (−5 to 5)	0.81
Analgesic nociceptive index*				
Mean	61.8 (8.1)	60.9 (8.7)	0.9 (−1.9 to 3.7)	0.51
Time under 50; min	4.7 (2.5–7.6 [0.0–37.4])	5.5 (2.9–10.5 [1.1–45.6])	−0.8 (−2.2 to 0.5)	0.22
Patient state index; mean	39.0 (6.0)	37.6 (5.0)	1.4 (−0.6 to 3.3)	0.17

SBP, systolic blood pressure.
*17 values missing (7 in the analgesic nociceptive group and 10 in the systolic blood pressure group).

Table 3 Postoperative variables comparing the two groups. Values are mean (SD), median (IQR [range]) or number (proportion).

Variables	Remifentanil infusion determined by		Difference (95% CI)	p value
	Analgesia nociception index n = 80	Systolic blood pressure n = 79		
Post-anaesthesia care unit				
Pain score	5.4 (1.5)	5.6 (1.5)	−0.2 (−0.3 to 0.6)	0.47
Fentanyl; μg	53.6 (26.9)	54.8 (20.8)	−1.2 (−8.8 to 6.3)	0.74
Nausea	9 (11%)	3 (4%)	0.04 (−0.03 to 0.11)	0.14
Antiemetics	3 (4%)	2 (3%)	0.0 (0.0–0.1)	0.99
Time to discharge; min	39 (35–42 [28–80])	38 (33–40 [28–70])	0 (−1 to 3)	0.18
Postoperative day 0				
Pain on ward admission	4.3 (1.2)	4.1 (1.5)	0.1 (−0.3 to 0.6)	0.57
Rescue analgesics	34 (43%)	31 (39%)	0.0 (−0.1 to 0.2)	0.80
Rescue antiemetics	10 (13%)	7 (9%)	0.0 (−0.1 to 0.1)	0.63
Postoperative day 1				
Fentanyl; μg	450 (300–600 [50–1500])	450 (300–650 [0–1500])	0 (−150 to 180)	0.62
Pain				
At rest	3.3 (1.9)	2.8 (1.7)	0.5 (−0.1 to 1.1)	0.09
On movement	5.9 (1.6)	5.9 (1.9)	0.0 (−0.5 to 0.6)	0.88
Rescue analgesics	35 (44%)	33 (42%)	0.0 (−0.1 to 0.2)	0.93
Nausea*; 0/1/2	39/25/16	41/29/9		0.33
Vomiting*; 0/1/2	73/1/6	72/0/7		0.58
Antiemetics	13 (16%)	14 (18%)	0.0 (−0.1 to 0.1)	0.97
Total score of QoR-15K	95.2 (21.7)	93.3 (23.4)	1.9 (−5.6 to 9.4)	0.62
Time to first flatus; days	1.5 (1.1–2.0 [0.4–3.1])	1.3 (1.0–1.9 [0.5–3.5])	0.2 (−0.2 to 0.4)	0.36
Ambulation; day 0/1/2	1/79/0	0/77/2		0.22
Liquid diet; day 1/2/3/4	66/7/6/1	67/6/4/2		0.85
Hospital stay; days	5 (4–6 [3–13])	5 (4–6 [3–13])	0 (0–0)	0.97

QoR-15K, the Korean version of Quality of Recovery-15 questionnaire.
*0 - no symptom, 1 - untreated symptoms, 2 - treated symptoms.

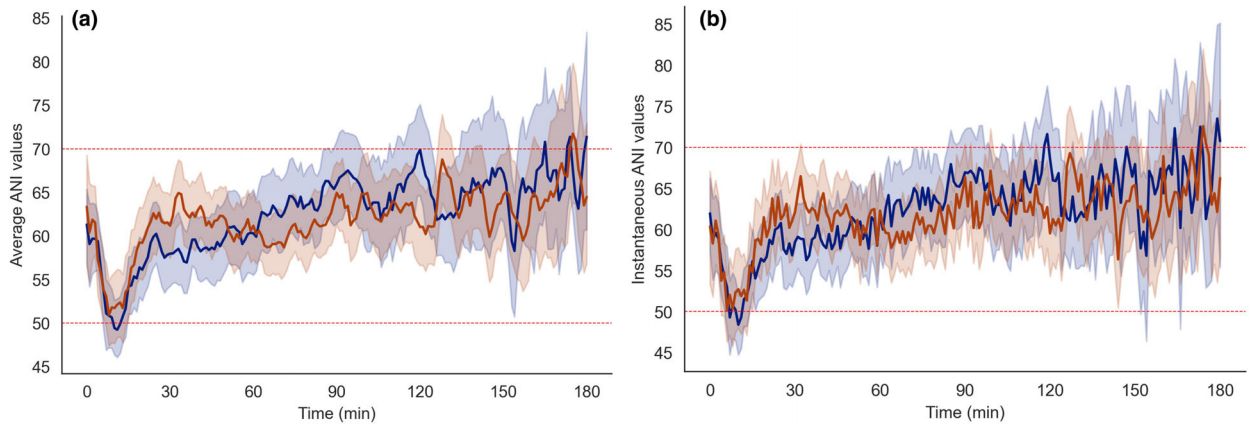

Figure 2 Mean (95%CI) intra-operative analgesia nociception indices when targeted to values of 50–70 (red line and shaded area) or systolic blood pressure < 120% of baseline values (blue line and shaded area): (a) averaged over 4 min; (b) unaveraged.

(78%) vs. 64/79 (81%) after the intra-operative remifentanil infusion rate had been determined by the analgesic nociceptive index vs. systolic blood pressure, respectively, risk difference (95%CI) −0.04 (−0.16 to 0.09), p = 0.73. Secondary outcomes were similar for the two groups (Table 3 and online Supporting Information Tables S1 and S2).

Discussion

We found that intra-operative titrations of remifentanil infusions to analgesic nociceptive indices 50–70 or systolic blood pressure 80%-120% of initial intra-operative measurements resulted in similar rates of pain scores ≥ 5 during the first 40 min in recovery after gynaecological laparotomy. Other outcomes to two postoperative days were also similar.

Some studies have reported that the analgesic nociceptive index can differentiate nociceptive from non-nociceptive sympathetic autonomic activation, whilst others have not [22–27]. Similarly, some trials have reported that the analgesic nociceptive index reduced intra-operative or postoperative opioid consumption, whilst others have not [16–19, 28]. Autonomic signs other than heart rate variability might be used to guide analgesic administration, for instance skin conductance, pupillary diameter and surgical plethysmographic index, but all have elicited contradictory results [29–34].

We had incorrectly assumed that analgesic nociceptive indices < 50 would occur more frequently when blood pressure rather than the index was used to titrate remifentanil infusion (Fig. 2). We used analgesic nociceptive indices averaged over 4 min to determine remifentanil infusion rates; instantaneous indices might have reduced remifentanil infusion. We used the 4-min average values to prevent remifentanil overdose as the instantaneous values can be highly variable. Analgesic nociceptive indices might have an effect on postoperative pain if they are used to determine the administration of drugs other than remifentanil, which is rapidly eliminated [35]. Our single-centre trial might be more vulnerable to biases than a multicentre trial. If the interventions or outcome interact with sex, our results might not apply to men, although relative effects are usually insensitive to variables that interact with absolute effect. Similarly, our results might not be applicable to patients taking drugs that affect the autonomic nervous system, such as beta-blockers, who are more likely to be given drugs to treat hypotension – such as ephedrine – which make autonomic measurements unstable [36]. We did not use regional analgesic techniques or give paracetamol regularly postoperatively [37, 38].

In conclusion, intra-operative control of remifentanil infusion with analgesic nociceptive indices did not reduce postoperative pain scores ≥ 5 immediately after gynaecological laparotomy or change other outcomes compared with changing remifentanil infusion in response to systolic blood pressure. Our results could be used to plan multicentre studies.

Acknowledgements

This trial was registered at Clinicaltrials.gov in May 2021 before we recruited participants (NCT04877574). This work was supported by the Korea Medical Device Development Fund grant funded by the Korea government (the Ministry of Science and ICT, the Ministry of Trade, Industry and Energy, the Ministry of Health and Welfare, the Ministry of Food and Drug Safety). No competing interests declared.

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Supporting Information

Additional supporting information may be found online via the journal website.

Figure S1. Intra-operative anaesthesia depth and haemodynamic variables.

Table S1. Comparison between the Korean version of the Quality of Recovery-15 questionnaire score of the analgesia nociception index and systolic blood pressure groups a day before surgery.

Table S2. Comparison between the Korean version of the Quality of Recovery-15 questionnaire score of the analgesia nociception index and systolic blood pressure groups 24 h after surgery.