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EEG-derived pain threshold index-guided versus standard care during propofol-remifentanil anesthesia: A randomized controlled trial

Yu Jiang, Jian-ming Ding, Xi-xi Hao, Pan-pan Fang *, Xue-Sheng Liu **

Department of Anesthesiology, The First Affiliated Hospital of Anhui Medical University, Hefei, Anhui Province, PR China

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ABSTRACT

Purpose: The pain threshold index (PTI), a novel index of nociception based on spontaneous EEG wavelet analysis, has been reported to provide reliable accuracy for predicting postoperative pain and hemodynamic reactivity. The present study is aimed to investigate whether PTI-guided analgesia reduces the pain intensity and rate of remedial analgesia in the post-anesthesia care unit (PACU).

Methods: A total of 122 females undergoing elective gynecologic surgeries had been randomized to receive either PTI-guided analgesia (PTI group) or standard clinical care (control group). Remifentanil administration in the PTI group was guided by PTI to maintain the value between 40 and 65, while that in the control group was guided by hemodynamic changes. The primary outcome was remedial analgesia rate in the PACU. The postoperative pain scores, intraoperative remifentanil requirements, opioid-related adverse events and perioperative serum stress hormone concentrations between the two groups were also compared.

Findings: It was found that 23 of 58 patients (40%) in the control group and 8 of 58 patients (14%) in the PTI group needed remedial analgesia. The relative risk of receiving remedial analgesia was 2.88 (95% CI, 1.40–5.89, $P = 0.002$) in the control group. Sufentanil consumption in the PACU (μg) was lower in the PTI group ($P = 0.002$) than in the control group. Remifentanil and propofol consumption, opioid-related adverse events between these two groups were comparable.

Implications: PTI-guided analgesia during gynaecologic operations resulted in 25.87% less remedial analgesia. However, studies with different PTI thresholds and larger, more diverse populations should be conducted to further demonstrate the clinical effectiveness of PTI.

1. Introduction

In spite of considerable advancements in perioperative medicine, postoperative pain remains a difficult matter [1]. It is associated with transition to chronic postoperative pain, increased medical costs, and prolonged opioid use [2,3]. Moreover, reasonable opioid consumption during general anesthesia is crucial. Indeed, underdosing of opioids leads to high pain and stress response, whereas overdosing of opioids causes postoperative hyperalgesia, hemodynamic instability or postoperative nausea and vomiting (PONV) [4,

* Corresponding author.
** Corresponding author.
E-mail addresses: fangpanpan1995@163.com (P.-p. Fang), liuxuesheng@ahmu.edu.cn (X.-S. Liu).

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5]. Therefore, nociception monitoring is urgently needed to guide the correct use of opioids and to relieve postoperative pain.

Recently, several monitoring devices for estimating the nociception-antinociception balance during general anesthesia have become commercially available [6,7]. For example, three kinds of nociception monitors including the analgesia nociception index (ANI) monitor [8], the surgical pleth index (SPI) monitor [9] and the nociception level (NOL) index [10] are all based on autonomic responses to noxious stimulation, which may be susceptible to vasoactive drugs and cardiovascular disease.

Basically, subcortical areas are in charge of integrating nociception [11]. As confirmed by a series of studies, pain can cause significant changes in electroencephalogram (EEG) signals and EEG monitoring may be an effective indicator of pain [11–14]. Recently, the pain threshold index (PTI) has been developed by Beijing Easymonitor Technology Co., Ltd. (Beijing, China). It is a novel nociception monitoring index that uses a whole frequency band EEG wavelet algorithm. PTI values (ranging from 0 to 100) are derived to objectively reflect the antinociceptive state.

As shown by previous observational studies, PTI demonstrates good accuracy for predicting postoperative pain [15] and PTI can predict hemodynamic reactivity [16]. However, there are currently no studies to assess whether PTI could guide general anesthesia care. Therefore, we designed a randomized controlled trial to evaluate the ability of PTI to modify general anesthesia care. We also hypothesized that PTI monitoring could improve the acute pain and reduce remedial analgesia in the post-anesthesia care unit (PACU).

2. Materials and methods

The Investigational Review Board of the First Affiliated Hospital of Anhui Medical University approved the study in March 2021 (PJ2021-04-06). The protocol was registered at the Chinese Clinical Trial Registry (identifier ChiCTR2100045011) in April 2021. Then, participants were recruited from April 2021 to September 2021. Prior to their participation, all the patients provided written informed consent. We reported the present study according to the CONSORT statement for reporting of randomized controlled trials. The trial was implemented according to the Declaration of Helsinki.

2.1. Patients

The 18-65-year-old patients scheduled for elective gynecologic surgeries under general anesthesia with the American Society of Anesthesiologists class I–III and body mass indices 18–30 were enrolled in this study. The exclusion criteria were refusal to participate, use of chronic opioids or other analgesic drugs, history of chronic pain, the presence of acute pain, central nervous system disease, severe hepatic or kidney dysfunction, preoperative use of anticholinergic or cholinergic drugs, planned nerve block anesthesia, planned epidural or spinal anesthesia, and all forms of regional anesthesia.

2.2. Randomization and allocation

Eligible patients were randomized to receive PTI-guided analgesia (PTI group) or standard clinical care (control group) with a 1:1 ratio using SPSS software, version 23.0 (IBM SPSS) by a study statistician. The attending anesthesiologists in charge of anesthesia management were informed of the patient's assignment just prior to anesthesia induction. The recovery room nursing staff and specific investigators assessed the outcomes in the PACU and postoperative outcomes without knowledge of group assignments. Surgeons and patients were also blind to the group assignments.

2.3. Anesthesia protocol

Standard monitoring including pulse oxygen saturation, electrocardiography, heart rate (HR), and blood pressure (BP) was established. In order to obtain PTI and wavelet index (WLI), both groups were connected to the HXD-I multifunction combination monitor (Heilongjiang Huaxiang Technology Co., Ltd., Heilongjiang, China). WLI is a parameter (ranging from 0 to 100) for monitoring the depth of sedation. PTI and WLI values were calculated in real time based on frontal raw EEG data (see detailed algorithm in Appendix 1). According to instructions of the manufacturer and our preliminary experimental results, the suitable range of PTI was set to 40–65 and the suitable range of WLI was set to 35–70 [17]. A PTI >65 indicates insufficient analgesia, while a PTI <40 indicates deep analgesia. Similarly, a WLI >70 indicates insufficient depth of sedation, while a WLI<35 reveals deep depth of sedation.

Intravenous anesthesia induction was performed using 2 mg kg^{-1} of propofol, 0.02–0.04 mg kg^{-1} of midazolam, 0.3–0.5ug kg^{-1} of sufentanil and 0.3–0.4 mg kg^{-1} cisatracurium. Furthermore, volume-controlled ventilation with tidal volume 6–8 ml kg^{-1} and respiratory rates at 10–14 times per minute were used to maintain the end-tidal carbon dioxide concentrations between 35 and 45 mmHg. Anesthesia maintenance was performed using continuous intravenous infusion of propofol and remifentanil. Cisatracurium was given intermittently to keep neuromuscular blockade. After the surgery for postoperative analgesia, a postoperative intravenous analgesia pump with a cocktail including 100 mg of flurbiprofen axetil and 2.5ug kg^{-1} of sufentanil in 100 mL of normal saline was used immediately. The constant infusion rate of the intravenous pump was 2 ml/h without a lock-out period. After the surgery, patients were transferred into PACU. Thereinto, the 11-point numeric rating scales (NRS) ranging from 0 (no pain) to 10 (maximal pain) were adopted to assess the pain intensity at rest by PACU nurses. Sufentanil (5 μg) was given intravenously as the remedial analgesic if an NRS ≥ 4. Sufentanil could be administered at 10-min intervals until NRS <4.

2.4. Remifentanil administration in the PTI-guided group

First, WLI was maintained between 35 and 70 through adjustment of propofol infusion. When WLI >70 was maintained for 1 min, 0.4–0.6 mg kg^{-1} of propofol was intravenously injected. When WLI <35 was maintained for 1 min, the propofol infusion rate was reduced by 0.4 mg $kg^{-1}h^{-1}$. Then, patients were evaluated after 3 min until WLI was maintained within the appropriate range. In cases where the PTI was greater than 65 for 1 min, 25–75 μg of remifentanil was intravenously injected. Conversely, the remifentanil infusion rate was reduced by 50 μg h^{-1} when PTI <40 was maintained for 1 min. Again, patients were evaluated 3 min later and until the PTI was maintained within the appropriate range. BP and HR were also monitored and should be maintained within the normal range. Vasoactive medication and/or crystalloids were administered in cases of hypertension (mean arterial pressure [MAP] > 20% increase from baseline or > 110 mmHg) or hypotension (MAP >20% decrease from baseline or < 60 mmHg), or tachycardia (HR > 90 bpm) or bradycardia (HR < 45 bpm) and a PTI within the appropriate range. If the abnormal hemodynamics and an inappropriate range of PTI were present, remifentanil was adjusted to maintain the PTI between 40 and 65 at first. If the target hemodynamic range could not be reached after three adjustments, vasoactive medication and/or crystalloids were also administered despite the PTI value.

2.5. Remifentanil administration in the standard care group

As with the PTI group, the WLI was initially maintained between 35 and 70 through adjustment of propofol infusion. The PTI value was blinded to the anesthesiologist in the standard care group, and remifentanil dosing was solely depended on hemodynamics. In case of hypertension, or tachycardia (defined as above), 20–60 μg of remifentanil was administered at the discretion of the attending anesthesiologist. Conversely, in case of hypotension or bradycardia, the remifentanil infusion rate was reduced at the discretion of the attending anesthesiologist. If the hemodynamics still did not return to normal after 3 adjustments of remifentanil, vasoactive medication and/or crystalloids were given.

2.6. Data collection

When patients were conscious, the first NRS score was evaluated by PACU nurses. Afterwards, the NRS scores were continuously recorded at 10-min intervals until they were discharged from the PACU. The post-surgical pain intensity was evaluated with the NRS during the first 3 days after surgery by an investigator who was blind to group assignment. Inadequate anesthesia events including the use of vasoactive medication, hypertension, hypotension, tachycardia or bradycardia during the surgery were recorded [18]. Perioperative serum adrenocorticotropic hormone (ACTH) and cortisol concentrations were detected at three time points: 5 min before anesthesia induction (t1), at skin closure (t2) and 10 min after extubation in the PACU (t3). Besides, a 4-point rating scale was used to measure PONV, where 0 indicated no nausea, 1 indicated slight nausea, 2 indicated moderate nausea, and 3 indicated vomiting [19]. Emergence delirium in the PACU was evaluated by the confusion assessment method for the intensive care unit (CAM-ICU). In addition, the modified Brice interview was used for assessing indications of awareness during postoperative day 1. Serum ACTH levels were detected by enzyme-linked immunosorbent assay (ELISA) kits from Cusabio (Wuhan, China). ELISA kits from TECAN (Germany) were adopted for enzyme-linked immunosorbent assays of perioperative cortisol.

2.7. Statistical analyses

To our knowledge, this is the first trial that assesses PTI-guided analgesia. According to our pilot data, we estimated that the remedial analgesia rate was 36% in the control group. Meanwhile, the remedial analgesia rate was 13% in the PTI group. A minimum sample of 102 participants was required to detect the differences between the two groups with an α value of 0.05 and a power of 0.8. In view of the 10% dropout rate, at least 114 patient needed to be enrolled.

The continuous normal distribution data were presented as means ± SDs and the continuous skewed distribution data were reported as medians (interquartile ranges, IQRs). Categorical variables were presented as numbers with percentages. Remedial analgesia rates were analyzed through χ^2 test and the relative risks were calculated. Independent two-tailed t-tests were performed to compare intraoperative propofol and remifentanil consumption. The maximum pain score in the PACU, sufentanil consumption in the PACU, PONV scores and time to the first flatus were analyzed by Mann-Whitney U tests. The repeated measurement data over time (NRS score, PTI value, WLI value, MAP and HR) were assessed using the interaction of group and time in a repeated-measures analysis of variance. NRS scores were transformed into normal distribution by taking the rank. If the data violated the assumption of sphericity (determined by the Mauchly test), the Greenhouse-Geisser correction was used. For outcomes showing significant group by time interaction effects, independent t-tests with post hoc Bonferroni correction were performed to examine the differences between the control group and the PTI group. The data was analyzed by SPSS software, version 23.0 (IBM SPSS). Two-sided $P < 0.05$ was considered to be statistically significant.

3. Results

A total of 151 patients had been assessed for eligibility, but 29 patients were excluded. Therefore, 122 patients were randomly assigned to either the PTI group or control group. Three types of gynecologic procedures, including ovarian surgery (excision of ovarian tumor or oophorectomy), uterine surgery (hysterectomy or hysteromyoma enucleation), uterine + ovarian surgery (uterus + bilateral oophorectomy or uterus + bilateral oophorectomy + pelviclymphnode dissection) were included. The proportions of surgery

types between these two groups were similar. Moreover, the surgery methods included laparoscopic and open surgery. The proportion of each between the two groups was comparable. In the PTI group, two patients did not receive the allocated intervention for technical reasons and one patient refused to accept the postoperative analgesia plan. In the control group, one patient was lost to follow-up with incomplete data and two patients refused to accept the postoperative analgesia plan. Overall, 58 patients in each group had been included in the final analysis (Fig. 1). Baseline characteristics including age, body mass index, preoperative MAP and preoperative HR between these two groups were similar. Methods of surgery, anesthesia time and surgery time were comparable (Table 1). No patients had any indications of awareness.

4. Primary outcome

In this study, 23 of 58 patients (40%) in the control group and 8 of 58 patients (14%) in the PTI group needed remedial analgesia. The relative risk of receiving remedial analgesia was 2.88 (95% CI, 1.40–5.89, P = 0.002) in the control group (Table 2).

5. Secondary outcomes

Fig. 2 shows the means and SDs of PTI, MAP, HR, and WLI values during anesthesia. No difference between the two groups was observed in either HR or MAP at any time point. PTI values were lower in the PTI group at T3 (immediately before incision), T4 (1 min after incision), T5 (at skin closure) and T6 (the end of surgery). WLI values were lower in the PTI group at T3, T4, and T6. In comparison to the control group, Sufentanil consumption in the PACU (μg) was lower in the PTI group (P = 0.002). There was no difference in intraoperative remifentanil administration between the two groups: 8.15 ± 1.40 μg $kg^{-1}h^{-1}$ in the PTI group versus 7.82 ± 1.40 μg $kg^{-1}h^{-1}$ in the control group (mean difference −0.33 μg $kg^{-1}h^{-1}$, 95% CI, −0.84–0.18, P = 0.206). Likewise, the intraoperative propofol administration between the two groups was comparable: 3.82 ± 0.83 mg $kg^{-1}h^{-1}$ in the PTI group versus 3.69 ± 0.51 mg $kg^{-1}h^{-1}$ in the control group (mean difference −0.13 mg $kg^{-1}h^{-1}$, 95%CI, −0.38–0.12, P = 0.307). Crystalloid solution, colloidal solution, blood transfusion volume, blood loss and urine output were also similar between the two groups (Table 1).

PACU pain scores and pain scores in the first 3 postoperative days are presented in Fig. 3. It could be observed that pain scores were higher in the control group than in the PTI group at each time point (Fig. 3). The median of maximum PACU pain scores was 3 (IQR,

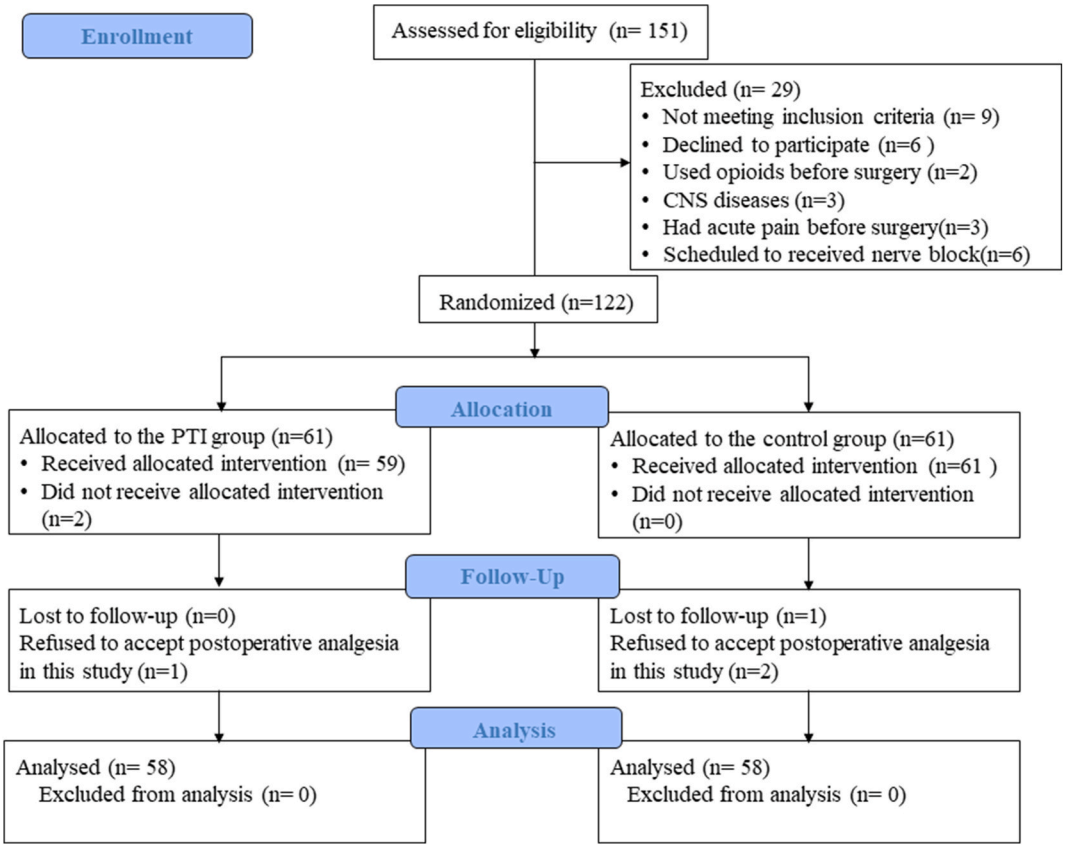

Fig. 1. CONSORT flowchart. Control group: patients received standard clinical care; PTI group: patients received PTI-guided analgesia. CNS, central nervous system; PTI, pain threshold index.

Table 1
Baseline characteristics and intraoperative data between the two groups.

Variables	Control group (n = 58)	PTI group (n = 58)	P-value
Age, yr	46.31 ± 11.09	46.22 ± 11.17	0.967
Hight, cm	159.62 ± 5.66	159.16 ± 4.62	0.628
Weight, kg	60.79 ± 8.50	59.47 ± 7.91	0.386
BMI	23.78 ± 2.86	23.50 ± 3.16	0.623
ASA class (1/2/3)	0/49/9	2/50/6	0.271
Preoperative MAP, mmHg	83.95 ± 7.72	84.59 ± 8.64	0.676
Preoperative HR, beat/min	74.50 ± 8.48	75.74 ± 9.69	0.464
Types of surgery (a/b/c)	14/5/39	14/8/36	0.666
Method of surgery, (laparoscopic/open)	41/17	40/18	0.840
Anesthesia time (min)	126 (99.25–157.5)	127.5 (99–183.25)	0.611
Surgery time (min)	115 (80–145.25)	110 (84–166.25)	0.562
Remifentanil consumption (μg $kg^{-1}h^{-1}$)	7.82 ± 1.40	8.15 ± 1.40	0.206
Propofol consumption (mg $kg^{-1}h^{-1}$)	3.69 ± 0.51	3.82 ± 0.83	0.307
Sufentanil (μg)	28.10 ± 5.12	28.02 ± 3.97	0.919
Crystalloid solution (mL)	1000 (600–1100)	1000 (600–1100)	0.622
Colloidal solution (mL)	500 (500–500)	500 (500–500)	0.500
Blood transfusion volume (mL)	0 (0–0)	0 (0–0)	0.914
Blood loss (mL)	100 (72.5–150)	100 (72.5–150)	0.548
Urine output (mL)	175 (100–200)	150 (100–200)	0.795
No. of patients received at least one vasoactive drug n (%)	34 (59%)	33 (57%)	0.851
No. of patients received at least two vasoactive drugs n (%)	13 (22%)	4 (7%)	0.018
No. of movements	0 (0,0)	0 (0,0)	0.404
No. of hypotension	1 (0–2.25)	1 (0–1)	0.064
No. of hypertension	0 (0–1)	0 (0–0)	0.224
No. of tachycardia	0 (0–0)	0 (0–0)	>0.999
No. of bradycardia	0 (0–1)	0 (0–1)	0.373

All values are represented as mean ± SD, median (interquartile range), or numbers (percentage). Control group: patients received standard clinical care; PTI group: patients received PTI-guided analgesia.
a: ovarian surgery (excision of ovarian tumor or oophorectomy); b: uterine surgery (hysterectomy or hysteromyoma enucleation); c: uterine + ovarian surgery (uterus + bilateral oophorectomy or uterus + bilateral oophorectomy + pelvic lymph node dissection).
BMI, body mass index; ASA, American Society of Anesthesiologists; MAP, mean arterial pressure; HR, heart rate; PTI, pain threshold index.

Table 2
Outcomes collected after surgery.

Variables	Control group (n = 58)	PTI group (n = 58)	P-value
Primary outcome			
Remedial analgesia in the PACU n (%)	23 (39.66)	8 (13.79)	0.002
Secondary outcomes			
Sufentanil consumption in the PACU (μg)	0 (0–5)	0 (0–0)	0.002
Recovery time (min)	23.5 (19–27)	22 (19–26.25)	0.722
Extubation time (min)	24 (20–28)	23.5 (20–28)	0.646
Time spent in the PACU (min)	40 (35–47)	40 (35–50)	0.868
Maximum pain score in the PACU	3 (2–4)	2 (2–3)	<0.001
PONV in the PACU	1 (1–2)	1 (1–1)	0.261
Delirium in the PACU, n (%)	12 (20.69)	7 (12.07)	0.210
PONV in postoperative day 1	1 (1–2)	1 (1–1.25)	0.014
PONV in postoperative day 2	1 (1–2)	1 (1–1)	0.025
PONV in postoperative day 3	1 (1–1)	1 (1–1)	0.319
Time to first flatus (h)	29 (26.25–30)	28 (26.5–30)	0.581

All values are represented as mean ± SD, median (interquartile range), or numbers (percentage). Control group: patients received standard clinical care; PTI group: patients received PTI-guided analgesia.
PACU, post-anesthesia care unit; PONV, postoperative nausea and vomiting; PTI, pain threshold index.

2–4) in the control group and 2 (IQR, 2–3) in the PTI group ($P < 0.001$, actual difference 1 with 95% CI, 1.00–1.00). There was no statistical difference between the two groups in the recovery time, extubation time and the PACU standing time. Incidence of emergence delirium in the PACU, PONV scores in the first 3 postoperative days and time to first flatus were similar (Table 2).

In the PTI group, 57% (33/58) of patients received at least one vasoactive drug and 7% (4/58) of them received at least two vasoactive drugs. In the control group, 59% (34/58) of patients received at least one vasoactive drug and 22% (13/58) of them received at least two vasoactive drugs. The relative risk of receiving at least two vasoactive drugs was 3.25 (95% CI, 1.13–9.38, $P = 0.018$) in comparison to the PTI group. The body movement number and the number of hypotension, hypertension, tachycardia and bradycardia between these two groups were similar (Table 1).

The means and SDs of serum ACTH and cortisol concentrations at t1, t2 and t3 are shown in Fig. 4. Baseline ACTH concentrations

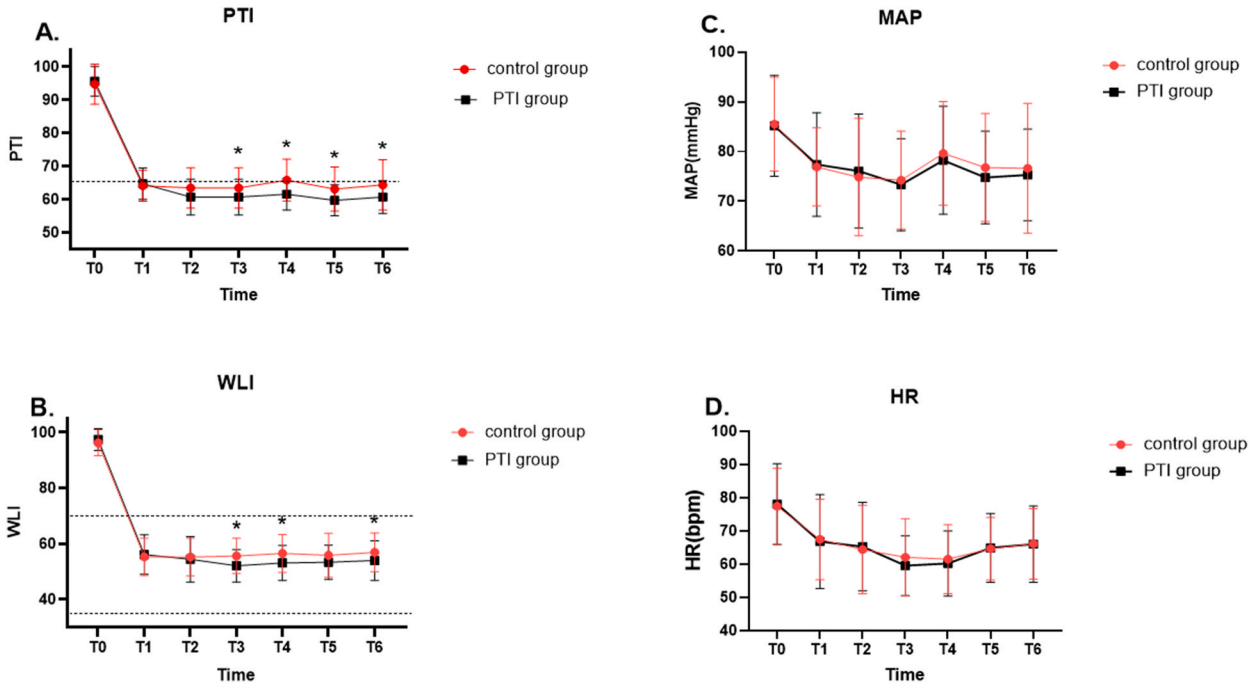

Fig. 2. PTI, WLI, MAP and HR values. The means and SDs of PTI (panel A), WLI (panel B), MAP (panel C), and HR (panel D) values observed at T0 (5 min before induction), T1 (immediately before intubation), T2 (1 min after intubation), T3 (immediately before incision), T4 (1 min after incision), T5 (at skin closure), and T6 (the end of surgery). *: $P < 0.05$, compared with the PTI group. Control group: patients received standard clinical care; PTI group: patients received PTI-guided analgesia. PTI, pain threshold index; WLI, wavelet index; MAP, mean arterial pressure; HR, heart rate.

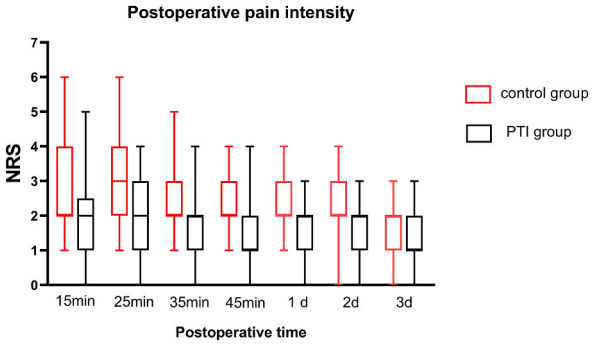

Fig. 3. Postoperative pain intensity. Control group: patients received standard clinical care; PTI group: patients received PTI-guided analgesia. NRS, numeric rating scales; PTI, pain threshold index.

were 86.86 ± 9.85 pg ml^{-1} in the control group and 83.20 ± 12.41 pg ml^{-1} in the PTI group. Baseline cortisol concentrations were 240.58 ± 77.45 ng ml^{-1} and 213.78 ± 68.24 ng ml^{-1} in the control and PTI groups, respectively. Both ACTH and cortisol concentration were lower in the PTI group at t2 ($P = 0.036$, $P = 0.030$). At t3, only the ACTH concentration was lower in the PTI group ($P = 0.009$).

6. Discussion

In this study, we observed that PTI-guided analgesia reduced the rate of remedial analgesia, NRS scores in the PACU and the relative risk of receiving at least two vasoactive drugs. However, we did not find any differences in remifentanil consumption, propofol consumption, or opioid-related adverse events such as PONV or time to first flatus.

By definition, 'nociception' refers to the neural processes of encoding and processing noxious stimuli [20]. Nociception is difficult to quantify in anesthetized or unconscious patients. Despite availability of several commercial nociception monitors, data about the effects of nociception monitoring on opioid consumption and postoperative pain scores are inconclusive. In our study, a statistically

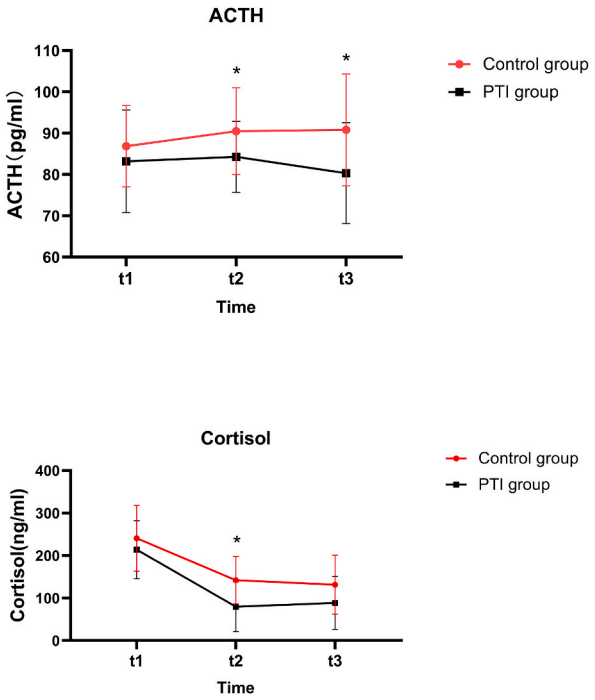

Fig. 4. Perioperative serum stress hormone. The means and SDs of ACTH (panel A), cortisol (panel B) values observed at t1 (5 min before anesthesia induction), t2 (at skin closure), t3 (10 min after extubation in the PACU). *: $P < 0.05$, compared with the PTI group. Control group: patients received standard clinical care; PTI group: patients received PTI-guided analgesia. ACTH, adrenocorticotropic hormone; PTI, pain threshold index.

significant influence of PTI-guided analgesia on postoperative analgesic requirements was observed when there was no difference in intraoperative remifentanil use. It could be explained that the transmission of nociceptive input from the periphery to the spinal cord can induce a prolonged state of central hyperexcitability, whereby subsequent stimuli in the postoperative period are amplified [21, 22]. Intraoperative remifentanil was more objectively administered under PTI guide, and adequate analgesia was acquired at the time of great nociception (e.g. the first incision, exploration the peritoneum), meaning that the direction of PTI values could effectively avoid overdosing and underdosing remifentanil during anesthesia maintenance, and always match the remifentanil dose to the noxious stimulus. This may be supported by lower PTI value and lower stress hormone in the PTI group. Thus, better nociception control during the surgery may lead to reduced postoperative pain in the PTI group. A randomized controlled trial found that NOL-guided anesthesia reduced the postoperative pain scores by 1.6 points, while the intraoperative fentanyl dosing and postoperative morphine consumption were not different [23], which is in line with our study. Another similar randomized clinical trial demonstrated that ANI-guided fentanyl administration decreased 1.3 units of NRS pain scores in the PACU, despite similar administration of intraoperative fentanyl [24].

The lower serum ACTH concentrations at skin closure and 10 min after extubation, with the lower serum cortisol concentrations at skin closure further validated that nociception was more effectively treated in the PTI group. Unlike the aforementioned studies [23, 24], we also found reduced pain intensity after surgery and a decreased the degree of PONV in the first 2 postoperative days in the PTI group. As suggested by these findings, the benefits of effective controlled nociception may persist into the postoperative stage. Similarly, a study revealed that pupillometry-guided intraoperative remifentanil administration reduced the proportion of patients experiencing procedure-related pain 3 months after surgery in comparison to the standard practice [25].

However, the contradictory results were also reported in other studies. In a study comparing SPI-guided analgesia with conventional analgesia, intraoperative fentanyl requirements were decreased, whereas the postoperative pain scores and remedial analgesic consumption were comparable [26]. As indicated by another study, NOL monitoring resulted in 30% less remifentanil consumption, while no difference in postoperative pain was observed [27]. One study also showed that pupillary reflex dilation-guide intraoperative analgesia reduced intraoperative remifentanil consumption with no significant difference in pain scores in the PACU [28]. Three recent systematic reviews reiterated that there were no definitive conclusions regarding the effects of nociception monitoring on intraoperative opioid consumption or other outcomes [7,29,30]. There are several possible explanations that may illustrate the contradictory findings. First, there is a lack of a consensus on meaningful clinical outcomes. Second, the different study protocols and different standard practices may account for the inconsistent data. In our study, sufentanil (a kind of longer-acting opioids) was used as the induction drug. The hyperalgesia induced by short-acting opioids may be reduced. Intraoperative remifentanil was more objectively administered under PTI guide, and adequate analgesia was acquired at the time of great nociception (first incision, exploration the peritoneum). Better nociception control during the surgery with similar doses of opioids may trigger reduced postoperative pain in the PTI group. Third, the high heterogeneities in both surgery type and participants hamper the consistent conclusion.

This study has several limitations. First, the anesthesia depth titration was guided by WLI, rather than a widely-used sedation monitoring index such as the bispectral index (BIS). However, previous studies have confirmed that WLI exerts similar monitoring effects on anesthesia depth to BIS [17]. Second, same with all studies that investigated the effects of nociception monitors, blinding of attending anesthesiologists was difficult to achieve due to impracticality in our trail, which may bring about bias that influences outcomes. With regard to this, a detailed pre-specified dosage regimen was strictly followed by our attending anesthesiologists who have undergone rigorous and professional training prior to the experiments. In addition, the participants and all investigators in charge of postoperative evaluation, including the postanesthesia care unit (PACU) nurses and surgeons, were blind to group assignment. Third, ACTH levels fluctuate in a single person throughout the day, controlling for circadian rhythms that may change the present results of ACTH. Fourth, only the female patients undergoing gynecological operations were enrolled. It remains unclear whether these results in the present study can be extended to the general population. Further studies are needed to investigate the effects of PTI-guided analgesia in both males and females. Fifth, the thresholds of PTI in our study were determined by the instruction of manufacturer and our preliminary experimental results. We argue that some of our results may change when different thresholds with smaller range are applied. Sixth, the sample size of this preliminary trial was small. Larger multicenter, randomized, controlled studies could refine the interpretation of this research. Seventh, the results in the present study were obtained only in specific equilibrium between hypnotic and opioid. It may be different with higher propofol consumption (guided by BIS) or with volatile for hypnosis. Lastly, our intraoperative drugs were not given in target control infusion (TCI) mode. Thus, difference in effect-site concentration of remifentanil at the time of great nociception (such as first incision, exploration the peritoneum) couldn't be calculated, which might contribute to explanation of mechanism of PTI. In fact, however, this could be reflected from the side by lower PTI value at above timing in the PTI group, because concentration of remifentanil is regulated according to PTI.

7. Conclusions

Through this randomized, controlled trial, we observed that participants undergoing elective gynecologic surgery experience lower rates of remedial analgesia, less postoperative pain, and a lower relative risk of receiving at least two vasoactive drugs when opioid dosing is guided by the PTI rather than standard practice. However, future studies with different PTI thresholds and larger, more diverse populations need to be implemented to further demonstrate the clinical effectiveness of PTI.

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Authors' contributions

YJ, PF, XL: Conceptualization, analyzed and interpreted the data, revised the manuscript.
YJ, JD, PF, XH: Acquisition of data and Project administration.
YJ, JD: Writing-Original Draft.
All authors approved the final version and agree to be accountable for all aspects of the work.

Data availability statement

Data will be made available on request.

Additional information

Supplementary content related to this article has been publish online at [URL].

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e18604.

Abbreviation

pain threshold index (PTI)
post-anesthesia care unit (PACU)
postoperative nausea and vomiting (PONV)
analgesia nociception index (ANI)
surgical pleth index (SPI)
nociception level (NL)
electroencephalogram (EEG)
Heart rate (HR)
blood pressure (BP)
wavelet index (WLI)
Numeric rating scales (NRS)
mean arterial pressure (MAP)
confusion assessment method for the intensive care unit (CAM-ICU)
Enzyme-linked immunosorbent assay (ELISA)
adrenocorticotropic hormone (ACTH)
bispectral index (BIS)

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