ORIGINAL RESEARCH ARTICLE

Effect of pain sensitivity on the efficacy of opioid-free anesthesia in laparoscopic cholecystectomy

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Abstract

This study explored the effect of pain sensitivity on the application of opioid-free anesthesia (OFA) in laparoscopic cholecystectomy (LC). Fifty-nine patients who accepted LC in the First People's Hospital of Huai'an City from May 2023 to October 2023 were included. Pain sensitivity questionnaire (PSQ) was used for evaluating patients' pain sensitivity before surgery. The results suggested that preoperative PSQ score was positively linked to postoperative VAS pain score at each time point, among which patients with high pain sensitivity had more intraoperative blood pressure fluctuations, higher incidence of postoperative acute pain, more times of remedial analgesia, significantly decreased satisfaction with pain management, and higher VAS score at all time points following surgery than patients with low pain sensitivity. We conclude that pain sensitivity can affect the effectiveness of OFA in LC. Patients with high pain sensitivity have a higher risk of postoperative acute pain and are not suitable for OFA. *(Afr J Reprod Health 2025; 29 [5s]: 35-42).*

Keywords: Opioid-free anesthesia; pain sensitivity; enhanced recovery after surgery; postoperative acute pain; multimodal analgesia

Résumé

Cette étude a exploré l'effet de la sensibilité à la douleur sur l'application d'une anesthésie sans opioïdes (AFO) lors d'une cholécystectomie laparoscopique (CL). Cinquante-neuf patients ayant accepté une CL à l'hôpital First People's Hospital de Huai'an City entre mai et octobre 2023 ont été inclus. Un questionnaire de sensibilité à la douleur (QSP) a été utilisé pour évaluer la sensibilité à la douleur des patients avant l'intervention. Les résultats ont suggéré que le score du QSP préopératoire était positivement corrélé au score EVA de la douleur postopératoire à chaque point temporel. Parmi ces patients, les fluctuations de la pression artérielle peropératoire étaient plus importantes, l'incidence de douleurs aiguës postopératoires plus élevée, le recours à une analgésie corrective plus fréquent, une satisfaction significativement diminuée quant à la prise en charge de la douleur et un score EVA plus élevé à tous les points temporels après l'intervention que les patients présentant une faible sensibilité à la douleur. Nous concluons que la sensibilité à la douleur peut affecter l'efficacité de l'AFO lors d'une CL. Les patients présentant une sensibilité à la douleur élevée présentent un risque plus élevé de douleurs aiguës postopératoires et ne sont pas éligibles à l'AFO. *(Afr J Reprod Health 2025; 29 [5s]: 35-42).*

Mots-clés: Anesthésie sans opioïdes, sensibilité à la douleur, récupération améliorée après une intervention chirurgicale, douleur aiguë postopératoire, analgésie multimodale

Introduction

Enhanced recovery after surgery (ERAS) recommends reducing the use of intraoperative opioid to prevent postoperative opioid-related complications.[1] With the development of multimodal analgesia techniques,[2] some researchers have begun to explore the possibility of opioid-free anesthesia (OFA). OFA refers to the perioperative use of non-opioid related drugs combined with regional nerve block to relieve patients' pain and avoid the application of opioids.[3] Currently, studies have shown that OFA can reduce adverse reactions related to opioid drugs, accelerate postoperative recovery, and shorten the length of hospital stay.[4] However, some scholars have expressed doubts about OFA. Due to the lack of effective nociceptive monitoring, the analgesic

effect of OFA is not clear, the perioperative analgesia is insufficient, and there is a risk of hemodynamic fluctuations.[5,6]

These controversies indicate that OFA is not for everyone. Previous studies discussed the application of OFA in different types of surgery, and did not consider the influence of individual differences on OFA. As a subjective feeling, pain has obvious individual differences, which is mainly linked to the different sensitivity of individuals to pain.[7] Studies have shown that preoperative pain sensitivity assessment can predict postoperative pain and its severity.[8] The objective of this study is to explore the impact of pain sensitivity on the application of OFA in laparoscopic cholecystectomy (LC), and to analyze the risk and benefit groups of OFA, so as to provide a basis for individualized anesthesia program.

Methods

The study was a cross-sectional design, and carried out at the Huai'an First People's Hospital. Fifty-nine patients who accepted LC in the Hospital between May 2023 to October 2023 were included. The inclusion criteria were: (1) patients met the diagnosis of gallbladder disorders, and transcholangiopancreatic ultrasound and magnetic resonance imaging confirmed the diagnosis; (2) patients met the indications for LC surgery; (3) age ranged from 18 to 70 years old; (4) Patients with ASA grade I-II; (5) were literate; (6) BMI ranging from 18.5 kg/m^2-30.0 kg/m^2. The exclusion criteria were patients with: (1) with severe cardiovascular disease, liver or kidney dysfunction; (2) chronic pain; (3) history of abuse of analgesic drugs and long-term use of analgesic drugs or alcohol intake; (4) allergies or contraindications to drugs that may be used in the test; (5) chronic hypertension, diabetes and other effects on pain perception; (6) history of central nervous system and/or mental illness; (7) unable to complete the scale evaluation; (8) intraoperative blood loss > 400 ml or operation time > 3 h; (9) intraoperative change of operation mode or postoperative need for a second operation; (10) postoperative admission to the intensive care unit; and (11) dropout or incomplete follow-up data collection.

All patients were guided to evaluate their pain sensitivity with pain sensitivity questionnaire (PSQ) before surgery.[9] The PSQ consisted of 17 items that assess patients' pain perception, pain response, and pain impact. Each item was evaluated on a scale of 0 to 10, and the average score of all evaluable items was used as the total score of the PSQ. The higher the score, the more sensitive they were to pain stimuli.

After ensuring preoperative abstinence from drinking and fasting, the venous access was opened after entry. VAS scores were performed for venous catheterization pain (VCP) during venous catheterization. Blood pressure, pulse, respiratory rate, oxygen saturation (SpO_2), along with end-expiratory carbon dioxide was routinely monitored. Before anesthesia induction, ultrasound guided bilateral transversus abdominis plane (TAP) block was performed (0.25% ropivacaine 20 ml on each side),[10] dexmedetomidine 0.4 ug/kg was intravenously pumped for 10 min, dexamethasone 0.1 mg/kg was intravenously injected, and flurbiprofen 50 mg pre-analgesia was performed.

Anesthesia induction: Was with lidocaine 1 mg/kg, midazolam 0.04 mg/kg, esketamine 0.5 mg/kg, propofol 1 mg/kg, and rocuronium 0.6 mg/kg. All patients accepted mechanical ventilation after endotracheal intubation.

Maintenance of anesthesia: Was with propofol 3 mg/kg.h with inhalation of sevoflurane. During the operation, the concentration of sevoflurane (1.5% to 3%) was adjusted to maintain the blood pressure at ±20%, and vasoactive drugs were utilized if necessary. Sevoflurane was stopped before suture, propofol was stopped after surgery, and ropivacaine was given for wound infiltration anesthesia. After operation, the patient was sent to postanesthesia care unit (PACU). The pain degree of the patient was assessed within 24 h after surgery. When the VAS was > 3, sufentanil 5 ug, was administered intravenously for relief analgesia.

Method of LC: All patients underwent general anesthesia with tracheal intubation to assist them to maintain supine position. Cut the skin at the top of the umbilicus to help the patient establish artificial pneumoperitoneum and control the pneumoperitoneum pressure to 12 mm Hg (1 mm Hg=0.133 kPa). The umbilical incision and the

subxiphoid incision were made respectively, and 12.5 mm Trocar was added. 5 mm Trocar was routinely placed on the midclavicular line and anterior axillary line under the right costal margin, followed by laparoscopy and corresponding instruments. With the magnification of laparoscope, the exploration of abdominal liver, gastrointestinal and gallbladder tissues was completed. The base of the patient's gallbladder was lifted, the anatomical gallbladder triangle was fully revealed, and the relatively intact gallbladder was peeled off. The removed gallbladder tissue and stones were placed in a specimen bag and removed from the subxiphoid puncture hole. After the completion of electrocoagulation, the pneumoperitoneum was terminated, the instrument was removed, and the surgical wound was sutured.

Observed indicators

Heart rate (HR) and mean arterial pressure (MAP) of the patient at normal time (T_0), after entering the room (T_1), after induction of anesthesia (T_2), 1 min after tracheal intubation (T_3), and 1 min after pneumoperitoneum (T_4) were recorded. The number of hemodynamic fluctuations, postoperative recovery time, intestinal peristalsis recovery time (tracheal catheter extraction to the first anal discharge), postoperative nausea and vomiting incidence, and VAS pain scores immediately following waking up, 30 min, 1 h, 2 h, 6 h, 12 h as well as 24 h after surgery were recorded. Satisfaction with pain management within 24 h after surgery was also recorded.

Statistical analysis

SPSS 26.0 statistical software was implemented for data analysis. Normal distribution measurement data were exhibited as mean ± standard deviation (x±s). Non-normal distribution measurement data were exhibited as median (interquartile). Independent sample t test was employed for comparison between groups. Counting data were tested by chi-square test. Paired sample t test was implemented for intra-group comparison. Correlation analysis was performed by Pearson analysis. $P<0.05$ meant the difference was significant.

Ethical Clearance

This study was consistent with the ethical standards of the 1964 Declaration of Helsinki and its later amendments, and was approved by the Ethics Committee of The Affiliated Huai'an No.1 People's Hospital of Nanjing Medical University. All patients and their families signed informed consent forms.

Results

General information in both groups

Fifty-nine patients participated in the trial (71 cases were enrolled, 5 cases were not able to complete the scale assessment, 5 cases were lost to follow-up, and 2 cases were changed). There were 25 in the high sensitivity group and 34 in the low sensitivity group. Patients with high sensitivity presented higher body mass index (BMI), higher preoperative PSQ score and VCP score, and higher basal blood pressure ($P<0.05$). Women accounted for a higher proportion of patients with high sensitivity, but no statistical differences were seen in gender, age, operation time, and basal heart rate (Table 1).

Correlation between preoperative PSQ and VCP

Pearson correlation analysis was used to carry out correlation analysis between preoperative PSQ score and VCP score, which showed a positive correlation between preoperative PSQ score and VCP score ($r=0.601$, $P<0.001$, Figure 1).

ROC curve

The preoperative PSQ score was adopted as the independent variable, and the occurrence of postoperative acute pain was employed as the dependent variable. The area under the curve was 0.863, suggesting that PSQ could significantly predict the occurrence of postoperative acute pain. The dividing line was calculated by the Youden index (a method of evaluating the authenticity of screening tests)[11] as PSQ=5.45. The patients were separated into high sensitivity and low sensitivity groups with PSQ=5.45 as the dividing line (Figure 2).

Table 1: General data in both groups

Items	Low sensitivity group (n=34)	High sensitivity group (n=25)	*P* value
Gender (male/female)	18/16	7/18	0.1
Age (years)	46.2±12.9	48.6±13.0	0.5
Body mass index (BMI)	24.4±3.1	26.3±3.5	0.0
PSQ score (points)	4.0±0.8	6.3±0.8	0.0
VCP score (points)	2.8±1.2	4.5±1.7	0.0
Operation time (min)	42.0±20.4	47.0±25.0	0.4
Basal blood pressure (mmHg)	90.2±9.1	98.7±13.7	0.0
Basal heart rate (times/min)	73.3±9.5	73.4±7.6	1.0

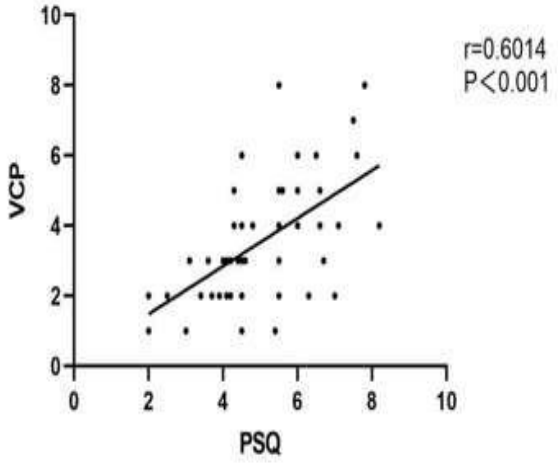

Figure 1: Correlation between preoperative PSQ and VCP

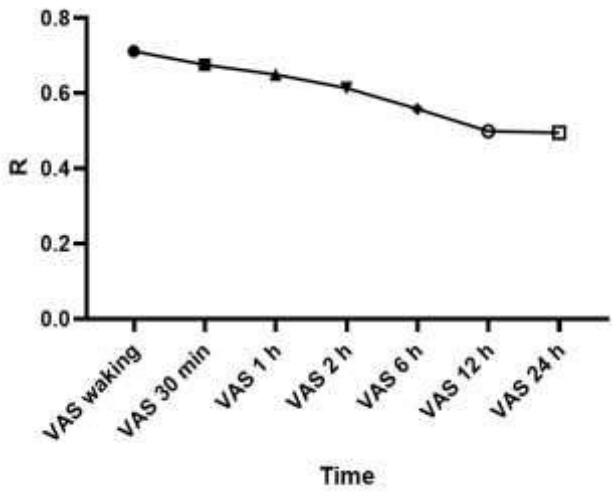

Figure 3: Correlation coefficient between PSQ score and VAS pain score at each time point following surgery

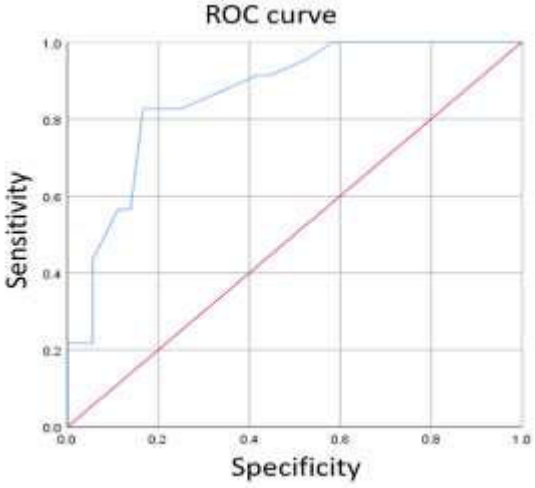

Figure 2: ROC curve

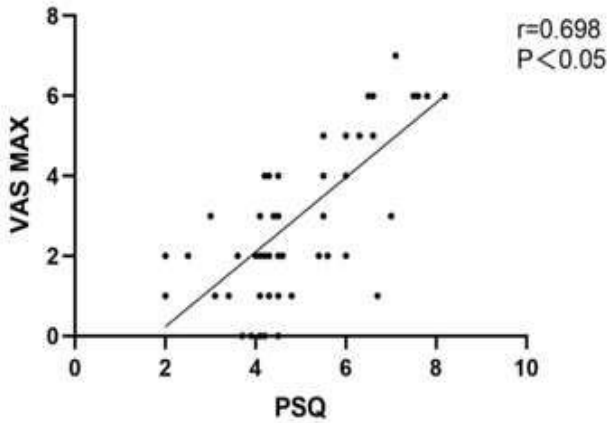

Figure 4: Correlation between PSQ and maximum VAS pain score

Table 2: Blood pressure and heart rate of two groups at each time point

Items	Low sensitivity group	High sensitivity group	*P*
Number of intraoperative blood pressure fluctuations	0.6±0.8	1.2±1.4	0.0
Intraoperative sevoflurane concentration (%)	2.1±0.5	2.1±0.7	0.6

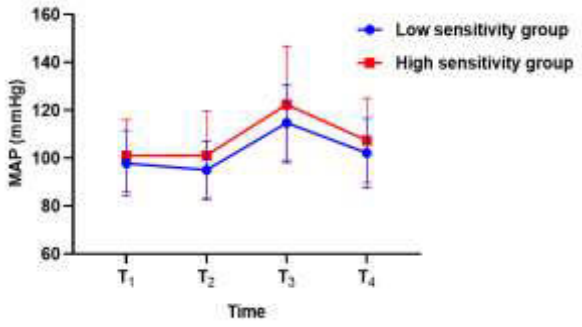

Figure 5: Comparison of blood pressure between 2 groups at different time points

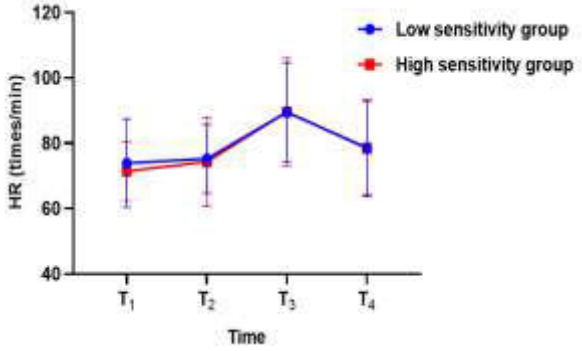

Figure 6: Comparison of heart rate between 2 groups at different time points

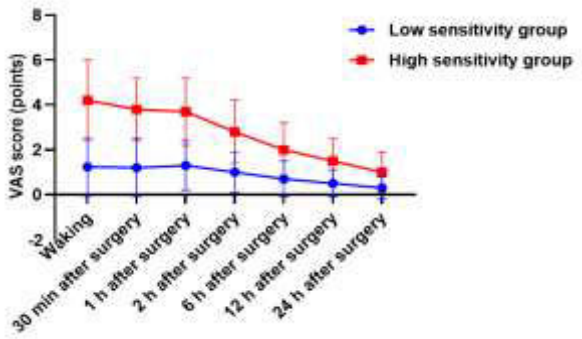

Figure 7: Comparison of VAS at each time point between the two groups

Correlation between PSQ and VAS pain score at each time point following surgery

The outcomes showed that preoperative PSQ score was positively correlated with postoperative VAS pain score at each time point (Figure 3). The correlation coefficient between PSQ score and the maximum postoperative VAS pain score was 0.698 (P<0.05, Figure 4).

Intraoperative indices of patients in 2 groups

Compared with the time of entry, the blood pressure as well as heart rate of 2 groups were significantly increased 1 min followed by endotracheal intubation (P<0.05). Relative to the low sensitivity group, no statistical differences were seen in blood pressure as well as heart rate of the high sensitivity group at each time point (P>0.05). Patients with high sensitivity presented more intraoperative blood pressure fluctuation (P<0.05). No significant difference was exhibited in sevoflurane concentration between 2 groups (P>0.05), as displayed in Table 2 and Figure 5-6.

Postoperative pain degree between 2 groups

Relative to the low sensitivity group, the pain degree of the high sensitivity group presented higher at different time points following surgery (P<0.05, Figure 7).

Postoperative rehabilitation indexes between 2 groups

The incidence of postoperative nausea and vomiting presented higher in the highly sensitive group (P<0.05). No significant difference was seen in postoperative recovery time and intestinal peristalsis between 2 groups (P>0.05, Table 3).

Patients' satisfaction with postoperative analgesia and pain management

Relative to the low sensitivity group, the high sensitivity group had more postoperative remedial

Table 3: Postoperative rehabilitation indexes between the two groups

	Postoperative recovery time (min)	Nausea (cases/rate)	Vomiting (cases/rate)	Intestinal motility recovery time (h)
Low sensitivity group (n=34)	28.2±10.6	1 (3.0)	0 (0.0)	12.8±2.3
High sensitivity group (n=25)	25.7±12.0	5 (20.0)	5 (20.0)	14.2±3.6
P	0.4	0.0	0.0	0.1

Table 4: Patients' satisfaction with postoperative analgesia and pain management

	Number of postoperative remedial analgesia	Satisfaction with pain management			
		Dissatisfied	Generally satisfied	Satisfied	Very satisfied
Low sensitivity group (n=34)	0.3±0.4	0 (0.0)	1 (2.9)	11 (32.4)	22 (64.7)
High sensitivity group (n=25)	1.8±1.1	2 (8.0)	6 (24.0)	7 (28.0)	10 (40.0)
P	0.0	X^2=9.8 P=0.0			

analgesia as well as lower pain management satisfaction scores (P<0.05, Table 4).

Discussion

Opioids play a dominant role in perioperative analgesia, but their adverse effects have received increasing attention. Therefore, the concept of OFA came into being and has been gradually practiced and verified in clinical practice. Many studies have made clear that OFA may have risks of insufficient perioperative analgesia and inability to maintain hemodynamic stability during operation, and it is necessary to explore its benefit/risk balance.[12] This study evaluated the individual differences of patients' sensitivity to pain, observed the impact of pain sensitivity on OFA, and analyzed the risk groups and benefit groups of OFA, so as to provide a basis for individualized implementation of anesthesia strategies.

The main pain sensitivity assessment tools included quantitative sensory testing (QST), VCP and PSQ. Previous studies mostly used QST, which has been verified to be linked to the occurrence of postoperative acute and chronic pain, and may predict the occurrence of postoperative acute pain.[13] However, due to its disadvantages such as time consuming and invasive, its clinical application and promotion are limited. The PSQ used in this study is a tool developed by Ruscheweyh in 2009 to evaluate patients' pain sensitivity, which has the advantages of time-saving, cost-saving and non-invasive.[14] Consistently, the results manifested that PSQ was correlated with VCP, indicating that the evaluation of PSQ for pain sensitivity was reliable.

Besides, we observed a significant correlation between preoperative PSQ score and postoperative pain VAS score, suggesting that the pain sensitivity measured by PSQ score could predict the occurrence of postoperative acute pain. The reasom is that patients with higher pain sensitivity are more prone to central sensitization, more sensitive to postoperative inflammatory stimulation of surgical incisions,[15] and more intense pain perception. However, there is no agreement on the threshold to distinguish between high and low pain sensitivity. Yaari Lee's study discovered that in patients undergoing arthroscopic partial meniscectomy, those with PSQ score ≥5.0 presented a higher incidence of postoperative pain.[8] By drawing the ROC curve, we calculated that the PSQ score cut-off for predicting acute pain following LC was 5.45 points. In this study, patients with PSQ scores higher than 5.45 were considered highly sensitive, suggesting that patients with PSQ scores greater than 5.45 may have an increased risk of acute pain after LC, an increased need for perioperative analgesia, and early intervention by anesthesiologists.

The results of this study indicated that patients with high sensitivity had higher BMI. Similarly, the study of Fan et al. also indicated that patients with BMI > 25 kg/m^2 possessed a higher incidence of postoperative acute pain.[16] This may

be due to the hyperplasia and hypertrophy of adipose tissue in obese patients and the increased concentration of pro-inflammatory cytokines, leading to a long-term pre-inflammatory state, thus enhancing the pain sensitivity of obese patients.[17, 18] Meanwhile, we also observed that patients with high sensitivity had higher basal blood pressure. Although previous reports have shown that individuals at risk of hypertension in healthy people often have the possibility of hypoalgesia,[19] patients in this study who had gallbladder surgery were likely to have chronic abdominal pain before surgery and had more anxiety than healthy people, which may be the reason for their higher basal blood pressure. Additionally, our study indicated a higher proportion of patients with high pain sensitivity were women. Consistently, E. J. Bartley's study also showed that the interaction between endogenous opioid receptors and sex hormones may be a determinant of gender differences in pain sensitivity. Meanwhile, women's pain distress degree and higher pain expression ability of social psychological factors also lead to their higher pain sensitivity.[20]

We also found that relative to the low sensitivity group, the VAS scores of the high sensitivity group were higher at all time points after surgery. Nevertheless, no difference was exhibited in blood pressure along with heart rate between 2 groups. The reason may be that pain, as a subjective feeling, varies from individual to individual due to differences in pain sensitivity. On the other hand, nociceptive stimuli, unlike pain, are not affected by the corresponding feelings and emotions. Patients were exposed to similar injury stimuli during surgery, so were autonomic responses such as hemodynamic fluctuations.[21]

The results showed that the high sensitivity group had more postoperative remedial analgesia and lower pain management satisfaction scores. In addition, the occurrence of postoperative nausea and vomiting was higher in the highly sensitive group, which may be due to the adverse reactions of opioids caused by more postoperative remedial analgesia in the highly sensitive group, or the nausea and vomiting induced by acute postoperative pain. These findings imply that patients with hypersensitivity may not be suitable for OFA. Jenna Goff once pointed out that in the 21st century, the concept of "individualized anesthesia" began to emerge, and the individual differences of patients required that we should a patient-centered anesthesia program, which involved both the choice of drugs and the dose of drugs.[22] By observing the effect of pain sensitivity on OFA, this study explored the risk groups and benefit groups of OFA, so as to provide a basis for the implementation of individualized anesthesia programs.

Strengths and limitations

Study strengths include a feasible and safe of OFA strategy in LC that clinicians can provide to patients, providing a drug reference for patients' postoperative analgesia. The study also has some limitations. The postoperative follow-up only lasted until 24 hours after surgery, without considering the change of patients' condition in the longer postoperative period, and only the patients' resting VAS pain score was recorded, and the VAS pain score during activity was not observed. We did not measure inflammatory mediators and catecholamines in patients, which can objectively reflect the stress level of patients to a certain extent, and thus reflect the effect of different anesthesia strategies on inhibiting nociceptive stimuli during the operation.

Conclusion

This research clarifies that the application of OFA strategy in LC is feasible and safe. However, it is not suitable for everyone, and the application of OFA in people with high pain sensitivity presents the risk of postoperative analgesia insufficiency, which can seriously affect the quality of postoperative recovery. At this stage, due to the imperfect monitoring of intraoperative injurious stimuli, it is too radical to hastily adopt OFA without considering individual differences of patients, and perhaps low-opioid anesthesia is a better choice.[23] In addition, patients with PSQ scores greater than 5.45 have an elevated risk of postoperative acute pain during LC and may need more analgesic drugs, which should be of concern to anesthesiologists.

Competing interests

The authors report no actual or potential conflicts of interest.

Acknowledgements

Xinhua Hong and Haowen Zhu are contributed equally to this work, Zhen Su and Wei Cai are considered co-corresponding authors.

Contribution of authors

Hong XH and Zhu HW: conception and design. Ding LR and Liu HL: analysis and interpretation of data. Su Z and Cai W: drafting the article or revising it critically for important intellectual content. All authors: final approval of the version to be published.

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