Randomized Controlled Trial

Pre-incisional Preventive Precise Multimodal Analgesia May Enhance the Rehabilitation Process of Acute Postoperative Pain Following Total Laparoscopic Hysterectomy: A Randomized Controlled Trial

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Background: There has been limited research regarding the effect of preventive precise multimodal analgesia (PPMA) on the duration of acute postoperative pain after total laparoscopic hysterectomy (TLH). This randomized controlled trial aimed to evaluate how PPMA affects pain rehabilitation.

Objectives: Our primary objective was to reduce the duration of acute postoperative pain after TLH, including incisional and visceral pain.

Study Design: A double blind randomized controlled clinical trial.

Setting: Department of Anesthesiology, Xuanwu Hospital, Capital Medical University, Beijing, People's Republic of China.

Methods: Seventy patients undergoing TLH were randomized to Group PPMA or Group Control (Group C) in a 1:1 ratio. Patients in Group PPMA were given PPMA through the pre-incisional administration of parecoxib sodium 40 mg (parecoxib is not approved for use in the US) and oxycodone 0.1 mg/kg as well as local anesthetic infiltration at the incision sites. In Group C, similar doses of parecoxib sodium and oxycodone were injected during uterine removal, and a local anesthetic infiltration procedure was performed immediately before skin closure. The index of consciousness 2 was utilized to titrate the remifentanil dosage in all patients to ensure sufficient analgesia.

Results: Compared with the Control, PPMA shortened the durations of incisional and visceral pain at rest (median, interquartile range [IQR]: 0, 0.0– 2.5) vs 2.0, 0.0–48.0 hours, $P = 0.045$; 24.0, 6.0–24.0 vs 48.0, 24.0–48.0 hours, $P < 0.001$; and during coughing 1.0, 0.0–3.0 vs 24.0, 0.3–48.0 hours, $P = 0.001$; 24.0, 24.0–48.0] vs 48.0, 48.0–72.0] hours, $P < 0.001$). The Visual Analog Scale (VAS) scores for incisional pain within 24 hours and visceral pain within 48 hours in Group PPMA were lower than those in Group C ($P < 0.05$). PPMA evidently decreased the VAS scores for incisional pain during coughing at 48 hours ($P < 0.05$). Pre-incisional PPMA significantly reduced postoperative opioid consumption (median, IQR: 3.0 [0.0–3.0] vs 3.0 [0.8–6.0] mg, $P = 0.041$) and the incidence of postoperative nausea and vomiting (25.0% vs 50.0%, $P = 0.039$). Postoperative recovery and hospital stay were similar between the 2 groups.

Limitations: This research had some limitations, including that it was a single-center research with a limited sample size. Our study cohort did not represent the overall patient population in the People's Republic of China; therefore, the external validity of our findings remains limited. Furthermore, the prevalence of chronic pain was not tracked.

Conclusion: Pre-incisional PPMA may enhance the rehabilitation process of acute postoperative pain after TLH.

Key words: Total laparoscopic hysterectomy, preventive precise multimodal analgesia, incisional pain, visceral pain, rehabilitation process

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Total laparoscopic hysterectomy (TLH) is a well-known gynecological treatment. Although TLH has been demonstrated to be minimally invasive, it may cause moderate to severe postoperative pain. Visceral pain, in particular, can remain for up to 72 hours postoperation (1). Inadequate management of postoperative pain may result in greater opioid consumption, more adverse events, and possibly an increased risk of chronic postoperative pain.

Multimodal analgesia is a key component of preventive analgesia. It is described as a combination of 2 or more analgesic regimens or procedures that exert their effects through distinct pathways. Multimodal analgesia has been shown to benefit postoperative pain management and reduce opioid-related side effects in all types of gynecological operations (2). Preventive analgesia, which includes the administration of pre-incisional analgesia to avert pain sensitization, has demonstrated great potential to help control postoperative pain (3). However, few studies have reported the effect of preventive precise multimodal analgesia (PPMA) on the rehabilitation process of acute postoperative pain, particularly focusing on the PPMA protocol, which is based on the characteristics and origins of intraoperative pain, such as incisional pain, visceral pain, and pain sensitization.

Our research team discovered that pre-incisional injection of parecoxib can significantly shorten the duration of acute postoperative pain after laparoscopic-assisted vaginal hysterectomy (4). Based on the findings (4), we developed an enhanced PPMA protocol that included the pre-incisional administration of parecoxib (parecoxib is not approved for use in the US) and oxycodone along with local anesthetic infiltration at the incision site to accurately regulate pain sensitization, visceral pain, and incisional pain. We hypothesized that this PPMA protocol can enhance the rehabilitation process during acute postoperative pain. This randomized controlled trial aimed to examine the effect of pre-incisional PPMA on the duration of acute postoperative pain after TLH. Further, this study aimed to evaluate the effect of pre-incisional PPMA on postoperative pain severity, intraoperative and postoperative opioid consumption, postoperative recovery, hospital length of stay (LOS), and postoperative adverse events.

Methods

Ethics Approval

The ethical committee of Xuanwu Hospital Capital Medical University approved this trial, which was conducted from July 2021 through December 2021. The study was conducted in accordance with the Declaration of Helsinki. This trial was registered in the Chinese Clinical Trial Registry (ChiCTR2100048632). Before participating in this trial, all patients were informed regarding the study and signed informed consent was obtained.

Study Design

This study was a prospective, randomized controlled trial with patient and outcome assessor blinding.

During the pre-anesthesia evaluation, patients scheduled for TLH who met the inclusion criteria were informed regarding the study via a patient information sheet. Those patients who were willing to sign and did sign the written informed consent were enrolled in this study.

Randomization was performed in a 1:1 ratio using a random digit table generated via computer software (https://tools.medsci.cn/rand). An investigator who was unaware of this study prepacked the grouping information according to the random digit table in sequentially numbered and concealed envelopes and attached these envelopes to case report forms. When a patient who met the inclusion criteria was enrolled, the anesthesiologist opened the attached envelope and administered the appropriate therapy to the patient. The group assignment was concealed from the patients and outcome assessor.

Patients

This study included adult patients aged between 18 and 65 years who were undergoing elective TLH under general anesthesia at our institute. Patients with an American Society of Anesthesiologists physical status classification of I or II were eligible for the research.

The exclusion criteria were as follows: contraindicated or allergy to study medication; body mass index (BMI) of $\geq$ 35 kg/m^2; drug or alcohol abuse; vertigo; long-term constipation; esophageal reflux; chronic pain or frequent opioid use; and cognitive or mental disorders. Patients who scheduled a change in operation technique and perioperative use of unexpected medicines, which may alter outcomes or result in loss to follow-up, were dropped out of the study.

Interventions

Patients were randomized to either Group PPMA or Group Control (Group C). Patients in Group PPMA

received parecoxib sodium 40 mg and oxycodone 0.1 mg/kg 30 minutes before skin incision. For local anesthetic infiltration, 0.5% ropivacaine (5 mL/keyhole) was administered 5 minutes before skin incision for each laparoscopic keyhole.

At the time of uterine removal, the patients in Group C were intravenously injected with parecoxib sodium 40 mg and oxycodone 0.1 mg/kg. For local anesthetic infiltration, 0.5% ropivacaine (5 mL/keyhole) was administrated immediately before skin closure.

Outcomes

The primary outcome of our study was the duration of acute postoperative pain, including incisional and visceral pain.

The secondary outcomes were as follows: 1) comparison of postoperative Visual Analog Scale (VAS) pain scores at surgery end, and at 30 minutes, one hour, 3 hours, 6 hours, 24 hours, 48 hours, and 72 hours postsurgery; 2) comparison between intraoperative remifentanil consumption and postoperative oxycodone consumption; 3) assessment of postoperative recovery, including postoperative LOS, time to first ambulation, first drinking, first semiliquid food intake, and first exhaustion after surgery; and 4) comparison of postoperative adverse events.

Anesthesia Management

The patients fasted according to the enhanced recovery after surgery (ERAS) guidelines. Heart rate, electrocardiogram, noninvasive blood pressure, pulse oxygen saturation, body temperature, partial pressure of end-tidal carbon dioxide, and indexes of consciousness (IoC 1 and IoC 2) were continuously recorded in both groups during general anesthesia. An Angel-6000A Multi-parameter Anesthesia Monitor (Shenzhen Weihaokang Medical Technology Co.) provided IoC 1 and IoC 2. IoC 1 and IoC 2 are also known as qCON and qNOX, respectively, in the European market. Moreover, IoC 1 is a hypnosis index, whereas IoC 2 is designed to evaluate the probability of a patient's response to noxious stimuli (5).

Dexamethasone 5 mg and ondansetron 4 mg were intravenously administered at 5 minutes before induction. Then, the patients received a standard anesthesia induction with propofol (1.5–3 mg/kg), remifentanil (1–2 μg/kg), and rocuronium (0.6 mg/kg). When the adequate depth of sedation (IoC 1 at 40–60) and analgesia (IoC 2 at 30–50) was achieved, endotracheal intubation was performed. The propofol infusion rate (4–6 mg/kg/h) was modified based on IoC 1 readings (40–60). IoC 2, which was used to adjust remifentanil infusion (0.2–0.4 μg/kg/min), was maintained between 30 and 50 during surgery. If the mean arterial pressure was < 80% of the baseline value or the systolic blood pressure was < 90 mmHg, the patient's heart rate was used to determine whether ephedrine 3 mg or phenylephrine 25 μg should be administered. If the heart rate was < 60 beats/min, ephedrine was injected, whereas phenylephrine was given in other cases. At the time of uterine removal, all patients were intravenously injected with metoclopramide 10 mg.

Patients in both groups did not use a postoperative analgesia pump. If the VAS score during coughing was ≥ 4, oxycodone (0.05 mg/kg) was given; the same dose of oxycodone was repeated at an interval of 5 minutes until the VAS score was < 3. Ondansetron (4 mg) was administered in cases of postoperative nausea and vomiting (PONV).

After surgery, all patients were admitted to the postanesthesia care unit for follow-up observation and treatment. During this period, the treatment of hemodynamics and postoperative pain were the same as described above.

Data Collection

The demographic characteristics of the patients, including age, height, weight, and BMI were recorded. Further, surgical data, including blood loss, urine output, time to awakening, and operation and anesthesia duration, were collected.

Patients were trained to assess the intensity of acute postoperative pain via VAS scores on the day before surgery. Incisional pain was defined as pain in the abdominal wall at a distinct location, whereas visceral pain was classified as dull/heavy interior pain at an indeterminate location (1). During immobility (rest pain) and coughing (motor pain), the VAS scores for postoperative incisional and visceral pain (1) were evaluated. The time points of assessment were at surgery end, and at 30 minutes, one hour, 3 hours, 6 hours, 24 hours, 48 hours, and 72 hours after surgery.

The occurrence of adverse events, such as respiratory depression, PONV, pruritus, constipation, hypoxemia, hypotension, pneumonia, wound infection, arrhythmia, and postoperative fever (defined as postoperative body temperature of ≥ 38.0°C [6]), was documented. All adverse events were defined according to standard definitions.

According to prior studies (4), the duration of acute

postoperative pain is defined as the time between the end of surgery and the time when the postoperative VAS score decreased to 0. First, the duration of acute postoperative pain was measured as the duration of incisional and visceral pain. Second, the durations of both types of acute postoperative pain were measured independently at rest and during coughing. If a patient's VAS score was > 0 at the time of discharge, the duration of acute postoperative pain was calculated from the end of surgery to the time of discharge. Intraoperative remifentanil and postoperative oxycodone consumptions were recorded. Further, the IoCs were recorded at the time points of anesthesia induction (T1), endotracheal intubation (T2), carbon dioxide pneumoperitoneum establishment (T3), trocar insertion (T4), hysterectomy (T5), and postoperative recovery (T6).

Sample Size Calculation

The sample size was determined using recent literature (1) in which the pain duration following TLH was assumed to be 72 hours. We expected that preincision PPMA can shorten the duration of acute postoperative pain by 30%. Assuming a 10% dropout rate, a total sample size of 70 (35 in each group) would be required ($\alpha = 0.05$, $\beta = 0.2$), as computed using PASS software.

Statistical Analysis

SPSS 25.0 statistical software (IBM Corp.) was used for statistical analyses. Data are presented as mean ± standard deviation, median and interquartile range (IQR), or frequency. The Kolmogorov–Smirnov test was used to determine the normality of a continuous variable distribution. Independent sample t test was used to analyze consistent data with a normal distribution (demographics, duration of operation and anesthesia, time to first exhaustion). The Kruskal–Wallis test was used to analyze the data that did not follow a normal distribution (time to awakening; blood loss; urine output; incisional and visceral pain duration; intraoperative remifentanil consumption; postoperative oxycodone consumption; postoperative VAS scores; IoCs; postoperative LOS; and duration to first ambulation, first drinking, and first semi-liquid food intake after surgery). Pearson χ^2 test or Fisher's exact test was used to compare the frequency of adverse events. A *P* value of < 0.05 was considered statistically significant.

Results

This study included 160 patients who were undergoing elective TLH. Seventy patients were included and were randomly assigned to one of 2 groups (Fig. 1). Three patients were dropped from Group PPMA due to a modification in the surgical technique. Three patients were dropped from Group C due to a change in surgical strategy (n = 1) and unanticipated postoperative medication (n = 2). Finally, 64 patients were included in the study with 32 patients in each group. The patients were assessed for all outcomes.

Demographic Characteristics and Surgical Data

There were no significant differences in demographic characteristics and surgical data between the 2 groups (Table 1).

Duration of Acute Postoperative Pain

Table 2 shows the duration of acute postoperative pain in both groups. In Group PPMA, the durations of incisional and visceral pain at rest were shorter than those in Group C (median [IQR]: 0 [0.0–2.5] vs 2.0 [0.0–48.0] hours, *P* = 0.045; 24.0 [6.0–24.0] vs 48.0 [24.0–48.0] hours, *P* < 0.001). Moreover, PPMA reduced the durations of incisional and visceral pain during coughing (median [IQR]: 1.0 [0.0–3.0] vs 24.0 [0.3–48.0] hours, *P* = 0.001; 24.0 [24.0–48.0] vs 48.0 [48.0–72.0] hours, *P* < 0.001).

Intensity of Acute Postoperative Pain

Figure 2 depicts the intensity of acute postoperative pain in the two groups. Pain intensities (VAS scores) were recorded at surgery end, 30 minutes, one hour, 3 hours, 6 hours, 24 hours, 48 hours, and 72 hours postsurgery. The visceral pain in the 2 groups (both at rest and during coughing) peaked at 30 minutes and dropped to 0 at 72 hours postsurgery. Within 48 hours postsurgery, the VAS scores for visceral pain in Group PPMA at rest and during coughing were statistically lower than those in Group C at all other time points (Figs. 2A and 2B; Supplemental Tables 1 and 2). The incisional pain (both at rest and during coughing) peaked at 30 minutes and gradually dropped to 0 at 72 hours postsurgery Group C. The incisional pain (both at rest and during coughing) peaked at 30 minutes and gradually dropped to 0 at 24 hours postsurgery in Group PPMA. Within 24 hours postsurgery, the VAS scores for incisional pain in Group PPMA at rest and during coughing were statistically lower than those in Group C at all other time points. The VAS scores for incisional pain in Group PPMA during coughing at 48 hours postsurgery were significantly decreased compared with those in Group C (*P* < 0.05) (Figs. 2C and 2D; Supplemental Tables 3 and 4).

Opioid Consumption

Table 3 shows the intraoperative and postoperative opioid usage. The consumption of intraoperative remifentanil in Group PPMA appeared to be lower than that in Group C (median [IQR]: 1.8 [1.6–2.2] vs 1.9 [1.7–2.4] mg; P = 0.059). Further, the consumption of postoperative oxycodone in Group PPMA was considerably reduced than that in Group C (median [IQR]: 3.0 [0.0–3.0] vs 3.0 [0.8–6.0] mg; P = 0.041).

IoC

Tables 4 and 5 demonstrate that there were no significant differences in IoC 1 and IoC 2 between the 2 groups.

Patients' Postoperative Recovery

Table 6 presents patients' postoperative recovery, including recovery durations for postoperative gastrointestinal function, postoperative LOS, and duration to first ambulation after surgery. There were no statistically significant differences between the 2 groups (P > 0.05).

Postoperative Adverse Events

Only PONV, arrhythmia, and postoperative fever were observed in this study; no other postoperative adverse events were noted (Table 7).

The incidence of PONV in Group PPMA was evidently decreased compared with that in Group C (P < 0.05). However, there were no statistically significant differences in postoperative fever or arrhythmia between the 2 groups (P > 0.05).

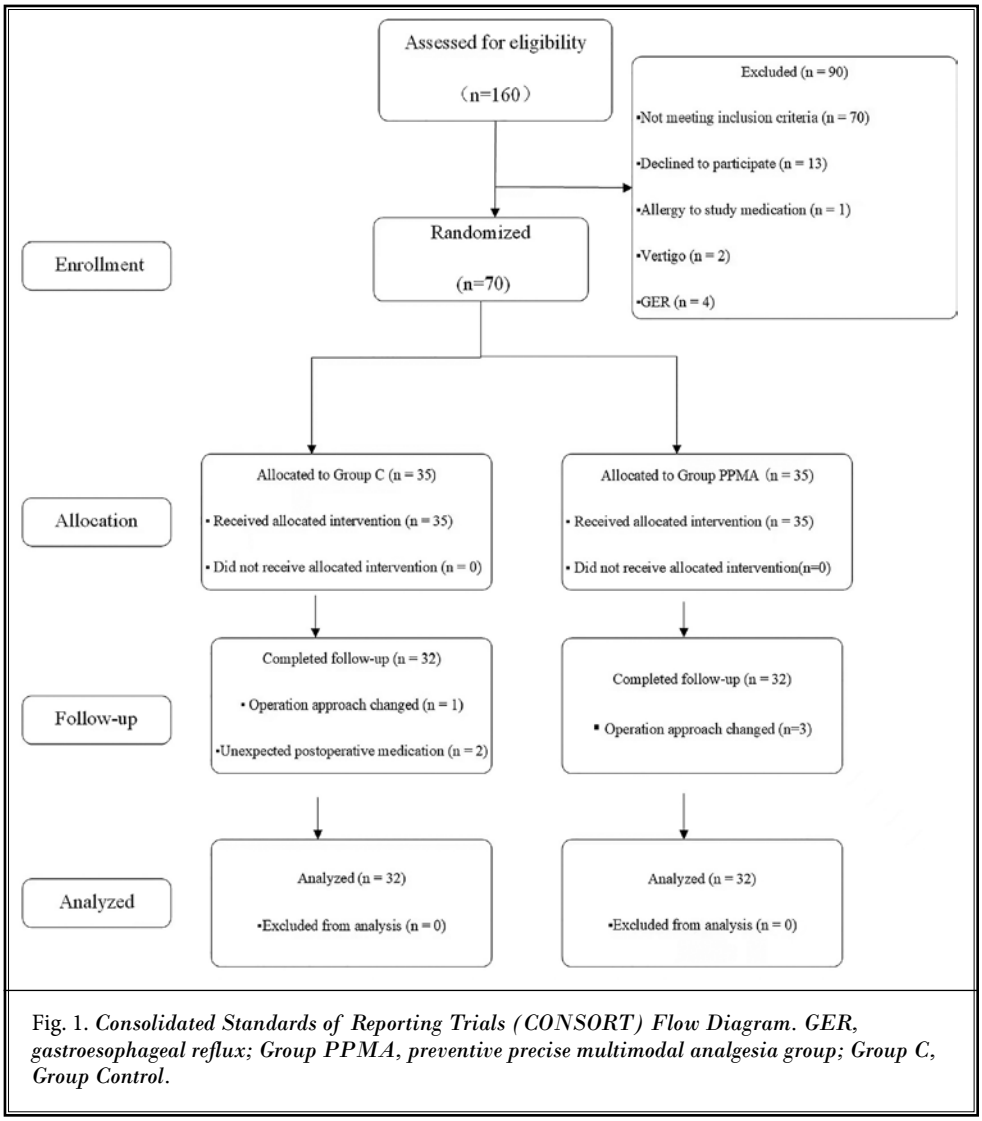

Fig. 1. *Consolidated Standards of Reporting Trials (CONSORT) Flow Diagram. GER, gastroesophageal reflux; Group PPMA, preventive precise multimodal analgesia group; Group C, Group Control.*

Discussion

The present study revealed that the pre-incisional administration of parecoxib and oxycodone, along with local anesthetic infiltration, significantly reduced the durations of incisional and visceral pain (both at rest and during coughing) after TLH. Because of this pre-incisional PPMA, the intensity of incisional and visceral pain was reduced, thereby lowering postoperative oxycodone consumption and PONV incidence.

TLH is a minimally invasive gynecological surgery. Compared with abdominal hysterectomy, TLH can shorten hospitalization and accelerate patient recovery. TLH can induce incisional and visceral pain caused by surgical incisions and visceral manipulations, respec-

Table 1. *Comparison of demographic characteristics and surgical data.*

	Group PPMA (n = 32)	Group C (n = 32)	*P* Value
Age (years)	52.5 ± 7.5	50.6 ± 9.7	0.375
Height (cm)	159.8 ± 4.5	161.0 ± 4.3	0.301
Weight (kg)	63.8 ± 10.4	62.5 ± 8.0	0.564
BMI (kg/m^2)	24.8 ± 3.4	24.1 ± 2.9	0.408
Blood loss (mL)	15.0 (10.0–20.0)	10.0 (10.0–27.5)	0.883
Urine output (mL)	300.0 (200.0–500.0)	200.0 (125.0–400.0)	0.113
Duration of operation (min)	76.8 ± 13.4	79.8 ± 12.3	0.355
Duration of anesthesia (min)	100.8 ± 14.1	102.1 ± 13.0	0.687
Time to awakening (min)	8.0 (8.0–10.0)	9.0 (7.0–9.0)	0.556

Data are presented as mean ± standard deviation or median and interquartile range; Group PPMA: preventive precise multimodal analgesia group; Group C: Group Control; BMI, body mass index

tively; moreover, inflammation caused by surgery can induce potential sensitization (1,7). TLH may not only lead to acute postoperative pain (8) but may also increase the risk of chronic pain. Therefore, it is necessary to improve postoperative pain management following TLH.

Table 2. *Comparison of acute postoperative pain duration.*

	Group PPMA (n = 32)	Group C (n = 32)	*P* Value
Incisional pain at rest (h)	0.0 (0.0–2.5)	2.0 (0.0–48.0)	0.045
Incisional pain during coughing (h)	1.0 (0.0–3.0)	24.0 (0.3–48.0)	0.001
Visceral pain at rest (h)	24.0 (6.0–24.0)	48.0 (24.0–48.0)	< 0.001
Visceral pain during coughing (h)	24.0 (24.0–48.0)	48.0 (48.0–72.0)	< 0.001

Data are presented as median and interquartile range. Group PPMA: preventive precise multimodal analgesia group; Group C: Group Control

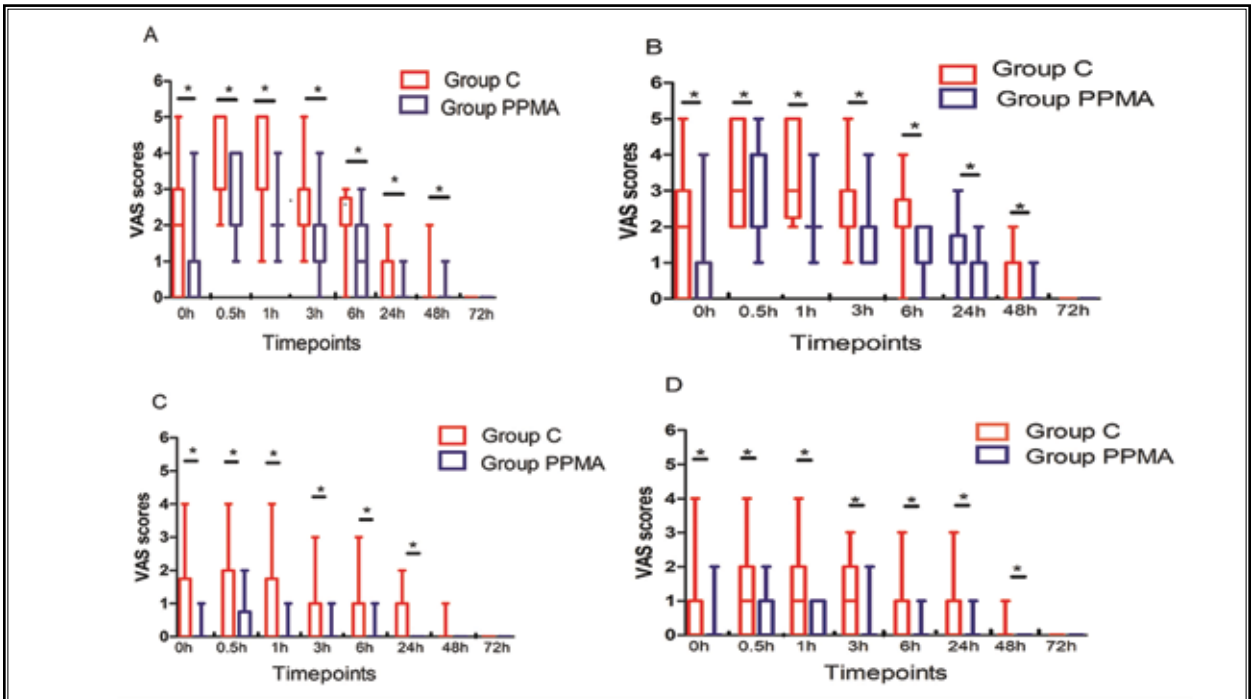

Fig. 2. *Visual Analog Scale (VAS) scores following surgery. (A) VAS scores of visceral pain at rest in the 2 groups: Group PPMA and Group C. (B) VAS scores of visceral pain during coughing in the 2 groups. (C) VAS scores of incisional pain at rest in the 2 groups. (D) VAS scores of incisional pain during coughing in the 2 groups. Group PPMA: preventive precise multimodal analgesia group; Group C: Group Control. Red box represents VAS scores in Group C, and blue box indicates VAS scores in Group PPMA. Vertical lines over boxes represent minimum and maximum values. Asterisks indicate a statistically significant difference between the groups: *P < 0.05.*

Table 3. *Comparison of intraoperative and postoperative opioid consumption.*

	Group PPMA (n = 32)	Group C (n = 32)	*P* Value
Intraoperative remifentanil consumption (mg)	1.8 (1.6–2.2)	1.9 (1.7–2.4)	0.059
Postoperative oxycodone consumption (mg)	3.0 (0.0–3.0)	3.0 (0.8–6.0)	0.041

Data are presented as median and interquartile range. Group PPMA: preventive precise multimodal analgesia group; Group C: Group Control

Table 4. *Comparison of the indexes of consciousness (IoC 1).*

	Group PPMA (n = 32)	Group C (n = 32)	*P* Value
T1	99.0 (99.0–99.0)	99.0 (99.0–99.0)	0.608
T2	44.5 (42.0–47.0)	43.5 (40.0–46.0)	0.160
T3	46.5 ± 4.2	45.4 ± 2.7	0.219
T4	47.0 (44.0–50.0)	45.0 (41.0–48.8)	0.058
T5	44.0 (40.3–47.0)	46.0 (43.0–48.8)	0.138
T6	98.0 (90.3–99.0)	98.0 (93.0–99.0)	0.668

Data are presented as mean ± standard deviation or median and interquartile range. Group PPMA: preventive precise multimodal analgesia group; Group C: Group Control; T1: the time point of anesthesia induction, T2: the time point of endotracheal intubation, T3: the time point of carbon dioxide pneumoperitoneum establishment, T4: the time point of trocar insertion, T5: the time point of hysterectomy, T6: the time point of postoperative recovery.

Preemptive analgesia refers to the administration of analgesia before a noxious stimulus (9). Preemptive analgesia has a contradictory effect on acute postoperative pain. Ong et al (10) reviewed 66 studies (total n = 3,261) and reported that pre-incisional local anesthetic infiltration and systemic nonsteroidal anti-inflammatory drugs (NSAIDs) improved opioid analgesic intake and time to first rescue analgesic requirement, but did not improve postoperative pain scores. Sun et al (7) showed that pre-incisional oxycodone administration can provide effective postoperative pain control in gynecological laparoscopic surgery. However, other systematic reviews reported that preemptive analgesia given before incision showed no superior results compared with that given after incision or postoperatively (11). Preemptive analgesia regimens used in a few studies may be insufficient to cover the types or duration of pain in relevant surgeries, resulting in these controversial results.

The initial activation of primary afferent fibers via surgical incision can result in a shorter duration of

Table 5. *Comparison of the indexes of consciousness (IoC 2).*

	Group PPMA (n = 32)	Group C (n = 32)	*P* Value
T1	99.0 (98.0–99.0)	99.0 (97.3–99.0)	0.974
T2	43.0 ± 5.1	43.8 ± 5.0	0.521
T3	46.5 (44.0–50.0)	44.5 (42.0–47.8)	0.084
T4	47.5 (43.5–49.0)	47.0 (42.0–50.0)	0.962
T5	44.8 ± 5.5	44.8 ± 3.7	0.979
T6	99.0 (99.0–99.0)	99.0 (98.0–99.0)	0.050

Data are presented as mean ± standard deviation or median and interquartile range. Group PPMA: preventive precise multimodal analgesia group; Group C: Group Control; T1: the time point of anesthesia induction, T2: the time point of endotracheal intubation, T3: the time point of carbon dioxide pneumoperitoneum establishment, T4: the time point of trocar implantation, T5: the time point of hysterectomy, T6: the time point of postoperative recovery.

Table 6. *Comparison of postoperative recovery.*

	Group PPMA (n = 32)	Group C (n = 32)	*P* Value
Time to first drinking (h)	2.0 (1.9–2.3)	2.0 (2.0–2.7)	0.525
Time to first semi-liquid food intake (h)	4.1 (4.0–5.8)	4.0 (4.0–4.8)	0.605
Time to first exhaustion (h)	18.6 ± 4.9	19.7 ± 4.9	0.346
Time to first ambulation (h)	10.0 (6.0–18.5)	15.0 (6.1–19.4)	0.424
Postoperative LOS (d)	3.0 (3.0–3.0)	3.0 (3.0–3.0)	0.400

Data are mean ± standard deviation or median and IQR (interquartile range). Group PPMA: preventive precise multimodal analgesia group; Group C: Group Control; LOS: hospital length of stay.

Table 7. *Comparison of postoperative adverse events.*

	Group PPMA (n = 32)	Group C (n = 32)	*P* Value
PONV (n, %)	8 (25.0%)	16 (50.0%)	0.039
Postoperative fever (n, %)	0	2 (6.3%)	0.492
Arrhythmia (n, %)	0	1 (3.1%)	> 0.999
Pruritus (n, %)	0	0	—
Respiratory depression (n, %)	0	0	—
Constipation (n, %)	0	0	—
Hypoxemia (n, %)	0	0	—
Hypotension (n, %)	0	0	—
Pneumonia (n, %)	0	0	—
Wound Infection (n, %)	0	0	—

Group PPMA: preventive precise multimodal analgesia group; Group C: Group Control; PONV: postoperative nausea and vomiting; —: no statistical data.

peripheral sensitization and evident central sensitization. The surgical incision lasts for a shorter duration than the nerve injury and inflammation, both of which can cause peripheral and central sensitization. Therefore, the duration and efficacy of analgesic therapies are as important as their timing. An effective analgesia protocol should not only emphasize the importance of performing analgesia before noxious stimuli but should also be capable of covering the types and duration of acute postoperative pain. Currently, preemptive analgesia is transformed into preventive analgesia. Preventive analgesia is defined as preemptive analgesia to control sensitization as well as an analgesic treatment that covers the duration of pain (12). Multimodal analgesia, an important component of preventive analgesia, aims to simultaneously improve various pain controls via different mechanisms, thus working synergistically to promote analgesia and minimize adverse effects (13).

In this study, we optimized the administration time of drugs, and a pre-incisional PPMA protocol for TLH was designed. According to their pharmacologic properties, all analgesic interventions used in the PPMA protocol showed their effects before skin incision, which continued via repeated doses of oxycodone during the postoperative period. The analgesic effects of oxycodone, an opioid μ and κ double receptor agonist, can last for approximately 3.5 hours. Moreover, the analgesic effects of parecoxib and local anesthetic infiltration with ropivacaine can last for 8 and 2–6 hours, respectively. According to Choi et al (1), incisional pain showed the highest intensity on the day of surgery, whereas visceral pain peaked at 24 hours postsurgery. Finally, the PPMA protocol used in our research was designed to match the pain characteristics post-TLH.

Few studies have investigated the mechanism by which pre-incisional PPMA affects the duration of acute postoperative pain. Local anesthetic infiltration at incisional sites was used in our PPMA protocol to block peripheral nerve fibers before incision. This may avoid sensitization in the dorsal horn of the spinal cord, thus reducing eventual hypersensitivity (14). Parecoxib, which is an intravenous injectable preparation with a long duration of action, was used to inhibit the prostaglandin E2-prolonged sensitization of the nociceptive dorsal root ganglion (4). Further, Yang et al (4) revealed that pre-incisional parecoxib reduced the duration of acute postoperative pain after laparoscopic-assisted vaginal hysterectomy (4). Oxycodone was used to block the afferent route of painful visceral stimuli via κ receptors (15). As our research indicated that pre-incisional PPMA reduced pain duration, we believe that our PPMA protocol can aid in pain processing.

Indeed, our pre-incisional PPMA improved the severity of acute postoperative pain, thus improving postoperative oxycodone intake. Several studies have explored the effect of pre-incisional analgesia or multimodal analgesia on the intensity of acute postoperative pain. Pre-incisional oxycodone has been shown to have a superior inhibitory impact to post-incisional administration on visceral pain (16,17). Pre-incisional local anesthetic infiltration reduced postoperative wound pain for up to 10 hours and opioid analgesic use for up to 24 hours after laparoscopic gynecologic examination (18). Several studies have found that some preventive multimodal analgesia protocols can reduce postoperative pain scores and lower opioid requirements (2,19).

IoC is derived from recorded electroencephalogram signals. IoC 1 is developed using an adaptive neuro-fuzzy inference system based on β ratio and burst suppression rate (20). IoC 1 should be maintained at 40–60 during surgery. IoC 2 is derived from IoC 1, and the score for IoC 2 ranges from 0 to 99. It is recommended that IoC 2 should be maintained between 30 and 50 throughout surgery. An IoC 2 score of ≥ 50 suggests insufficient analgesia, whereas that of ≤ 30 indicates excessive analgesia. In our research, IoC 2 monitoring was used to titrate an intraoperative remifentanil infusion to avoid hyperalgesia or insufficient analgesia. Higher remifentanil doses can surpass the patient's needs, potentially resulting in postoperative hyperalgesia, which might increase postoperative pain and opioid consumption (21). Inadequate analgesia can cause noticeable hemodynamic changes, worsen systemic inflammation, and increase pain sensitization. With a comparable level of intraoperative analgesia between the 2 groups, our pre-incisional PPMA protocol also tended to spare intraoperative opioid administration.

PONV increases patient dissatisfaction. Patients undergoing gynecological laparoscopic surgery are considered to be at a high-risk of PONV (22). Other risk variables for PONV reported by Gan et al (22) were comparable between the 2 groups, except for postoperative opioid usage. Thus, we believe that the lower incidence of PONV in Group PPMA was attributed to the sparing effect of postoperative opioids and the reduced side effects of opioids.

In patients undergoing abdominal surgeries, multimodal preventive analgesia with intravenous parecoxib and ropivacaine for regional anesthesia has been demonstrated to enhance early ambulation and

gastrointestinal function recovery (23). However, as the patients in our research were already managed according to the ERAS guidelines, no variations in patients' recoveries were detected between the 2 groups.

Limitations

This research has some limitations, including that it was conducted at a single-center with a limited sample size. Our study cohort does not represent the overall patient population in the People's Republic of China; therefore, the external validity of our findings remains limited. Furthermore, the prevalence of chronic pain was not assessed.

Conclusion

In patients undergoing TLH, PPMA with the pre-incisional administration of parecoxib sodium and oxycodone, along with local anesthetic infiltration at the incisional site, may considerably shorten the duration of acute postoperative pain. Pre-incisional PPMA may also significantly lower the intensity of postoperative incisional and visceral pain, reduce the postoperative consumption of opioids, and decrease the incidence of PONV. Further research on the relationship between pre-incisional PPMA and chronic pain is required.

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Supplemental Table 1. *Visceral pain at rest between the 2 groups*.

	Group PPMA (n = 32)	Group C (n = 32)	*P* Value
VAS @ 0h	0.0 (0.0–1.0)	2.0 (0.0–3.0)	0.015
VAS @ 30 min	2.0 (2.0–4.0)	3.0 (3.0–5.0)	0.002
VAS @ 1 h	2.0 (2.0–2.0)	3.0 (3.0–5.0)	< 0.001
VAS @ 3 h	2.0 (1.0–2.0)	2.0 (2.0–3.0)	< 0.001
VAS @ 6 h	1.0 (0.0–2.0)	2.0 (2.0–2.8)	< 0.001
VAS @ 24 h	0.0 (0.0–0.0)	1.0 (0.0–1.0)	< 0.001
VAS @ 48 h	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.042
VAS @ 72 h	0.0 (0.0–0.0)	0.0 (0.0–0.0)	—

Data are median and IQR (interquartile range); VAS: Visual Analog Scale; Group PPMA: preventive precise multimodal analgesia group; Group C: Group Control. *P* value represents comparison between the groups. —: no statistical data.

Supplemental Table 2. *Visceral pain during coughing between the 2 groups*.

	Group PPMA (n = 32)	Group C (n = 32)	*P* Value
VAS @ 0 h	0.0 (0.0–1.0)	2.0 (0.0–3.0)	0.015
VAS@ 30 min	2.0 (2.0–4.0)	3.0 (2.0–5.0)	0.010
VAS @ 1 h	2.0 (2.0–2.0)	3.0 (2.3–5.0)	< 0.001
VAS @ 3 h	2.0 (1.0–2.0)	2.0 (2.0–3.0)	< 0.001
VAS @ 6 h	1.0 (1.0–2.0)	2.0 (2.0–2.8)	0.001
VAS @ 24 h	0.0 (0.0–1.0)	1.0 (1.0–1.8)	< 0.001
VAS @ 48 h	0.0 (0.0–0.0)	0.0 (0.0–1.0)	< 0.001
VAS @72 h	0.0 (0.0–0.0)	0.0 (0.0–0.0)	—

Data are median and IQR (interquartile range); VAS: Visual Analog Scale; Group PPMA: preventive precise multimodal analgesia group; Group C: Group Control. *P* value represents comparison between the groups.—: no statistical data.

Supplemental Table 3. *Incisional pain at rest between the 2 groups*.

	Group PPMA (n = 32)	Group C (n = 32)	*P* Value
VAS @ 0 h	0.0 (0.0–0.0)	0.0 (0.0–1.8)	0.004
VAS @ 30 min	0.0 (0.0–0.8)	0.0 (0.0–2.0)	0.045
VAS @ 1 h	0.0 (0.0–0.0)	0.0 (0.0–1.8)	0.042
VAS @ 3 h	0.0 (0.0–0.0)	0.0 (0.0–1.0)	0.022
VAS @ 6 h	0.0 (0.0–0.0)	0.0 (0.0–1.0)	0.001
VAS @ 24 h	0.0 (0.0–0.0)	0.0 (0.0–1.0)	0.001
VAS @ 48 h	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.317
VAS @ 72 h	0.0 (0.0–0.0)	0.0 (0.0–0.0)	—

Data are median and IQR (interquartile range); VAS: Visual Analog Scale; Group PPMA: preventive precise multimodal analgesia group; Group C: Group Control. *P* value represents comparison between the groups.—: no statistical data.

Supplemental Table 4. ***Incisional pain during coughing between the 2 groups***.

	Group PPMA (n = 32)	**Group C (n = 32)**	***P* Value**
VAS @ 0h	0.0 (0.0–0.0)	0.0 (0.0–1.0)	0.023
VAS @ 30 min	0.0 (0.0–1.0)	1.0 (0.0–2.0)	0.039
VAS @ 1 h	0.0 (0.0–1.0)	1.0 (0.0–2.0)	0.006
VAS @ 3 h	0.0 (0.0–0.0)	1.0 (0.0–2.0)	< 0.001
VAS @ 6 h	0.0 (0.0–0.0)	1.0 (0.0–1.0)	< 0.001
VAS @ 24 h	0.0 (0.0–0.0)	0.0 (0.0–1.0)	< 0.001
VAS @ 48 h	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.021
VAS @ 72 h	0.0 (0.0–0.0)	0.0 (0–0,0.0)	—

Data are median and IQR (interquartile range); VAS: Visual Analog Scale; Group PPMA: preventive precise multimodal analgesia group; Group C: Group Control. *P* value represents comparison between the groups. —: no statistical data.