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Effects of multimodal analgesia of flurbiprofen axetil, nalbuphine and patient controlled intravenous analgesia on inflammatory factor levels and stress response in patients after laparoscopic radical gynecological malignancy surgery

Bin An[1] and Wenyue Dong[2]*

[1]Department of Anesthesiology, Tangshan Maternal and Child Health Hospital (Tangshan Women and Children's Hospital), Tangshan, Hebei, China

[2]Department of Anesthesiology, Tangshan People's Hospital, Tangshan, Hebei, China

Abstract: To evaluate the efficacy of multimodal analgesia of flurbiprofen axetil, nalbuphine hydrochloride and patient controlled intravenous analgesia (PCIA) on inflammatory factor levels and stress response in patients after laparoscopic radical gynecological malignancy surgery. The data of 100 patients admitted to our hospital from May 2019 to May 2020 for laparoscopic radical gynecological malignancy surgery were retrospectively analyzed and they were assigned (1:1) to either an experimental group or a control group according to the alphabetical order of their initials. The experimental group was given preemptive analgesia with flurbiprofen axetil, postoperative analgesia with nalbuphine hydrochloride, and PCIA and the control group was given conventional analgesic measures. The pain scores at 1h, 6h, 12h, 24h and 48h postoperatively in the experimental group were remarkably lower than those in the control group ($P<0.001$). The experimental group showed significantly lower inflammatory factor levels, pain mediator levels and stress response indexes in the morning before surgery, 1d, and 2d after surgery than the control group ($P<0.001$). The multimodal analgesia of flurbiprofen axetil, nalbuphine hydrochloride and PCIA can effectively alleviate the stress response and inflammatory response in patients after radical gynecologic malignancy surgery and the patients' pain perception is reduced with a high safety profile.

Keywords: Flurbiprofen axetil, nalbuphine hydrochloride, patient controlled intravenous analgesia, laparoscopy, gynecological malignancy.

INTRODUCTION

Gynecologic malignancies refer to malignant tumors in the female reproductive system, in which cervical cancer, endometrial cancer and ovarian cancer are the most common clinical cases. In recent years, with environmental and lifestyle changes, the incidence of gynecologic malignancies in China has shown an increasing trend, among which the incidence of ovarian cancer has increased at an annual rate of 1.83% and the age of onset has presented a marked decline (Balkan *et al*., 2020; Weiniger *et al*., 2020; Wiesmann *et al*., 2018). Currently, laparoscopic radical surgery is the choice of treatment for early gynecologic malignancies due to its less invasiveness to the tissue adjacent to the lesion and lower risks of severe scarring, which satisfies the treatment needs of female patients. However, radical laparoscopy may lead to post-pneumoperitoneal diaphragmatic strain, local peritonitis and hypoxic stress. Tissue trauma with repeated afferents of injurious stimuli enhances the response of patient's central and peripheral nerves to pain, which, coupled with the release of inflammatory mediators that directly cause pain, leads to reduced pain thresholds and peripheral and central sensitization in patients with more significant postoperative pain (Ackroyd *et al*., 2020; Nong *et al*., 2013; Watanabe *et al*., 2020). Postoperative pain can be alleviated by the scientific use of anesthetic drugs. Previous studies have demonstrated that preemptive analgesia can suppress surgery-induced central neuronal excitation. Flurbiprofen axetil is a common non-selective analgesic that efficiently inhibits prostaglandin secretion and mitigates inflammatory response by peripheral and central sensitization (Chen *et al*., 2021). Moreover, postoperative analgesia also reduces postoperative pain, of which nalbuphine hydrochloride is a routine postoperative analgesic drug. Studies have reported a better postoperative analgesic effect of nalbuphine hydrochloride than fentanyl with longer analgesic maintenance (He *et al*., 2021; Liu *et al*., 2021a). Patient controlled intravenous analgesia (PCIA) can effectively meet the demand for on-demand drug delivery to avoid delayed analgesia. To date, no studies have been conducted to evaluate the efficacy of the joint application of the above three analgetic measures in patients after laparoscopic radical gynecological malignancy surgery. Accordingly, this study was designed to examine its treatment efficacy to provide clinical support for analgesia. The report is as follows.

**Corresponding author:* e-mail: yuezhandong36815@126.com

MATERIALS AND METHODS

Study design

The data of 100 patients admitted to our hospital from May 2019 to May 2020 for laparoscopic radical gynecological malignancy surgery were retrospectively analyzed, to investigate the effects of multimodal analgesia of flurbiprofen axetil, nalbuphine hydrochloride and PCIA on inflammatory factor levels and stress response in patients after laparoscopic radical gynecological malignancy surgery.

Inclusion and exclusion criteria

Inclusion criteria: (1) Patients who were diagnosed with ovarian cancer, cervical cancer and endometrial cancer by pathological examination (Schoppmann *et al*., 2021) and treated with laparoscopic radical malignancy surgery; (2) Patients aged between 40-70 years; (3) Patients with American Society of Anesthesiologists (ASA) classification of I-III; (4) Patients without preoperative treatment such as radiotherapy and chemotherapy; (5) Surgery time between 2-5 hours.

Exclusion criteria: (1) Patients with mental illnesses that prevent communication; (2) Patients with other serious organic diseases; (3) Patients with coagulation abnormalities; (4) Patients with contraindications to surgery or a history of major abdominal surgery; (5) Patients with a history of drug, alcohol, or addictive substance abuse; (6) Patients with preoperative medical system diseases such as hypertension, diabetes, or hyperthyroidism without effective control; (7) Patients with preoperative chronic pain; (8) Patients with distant metastases; (9) Patients who refused to participate in this study; (10) Patients with preoperative medical system diseases such as hypertension, diabetes and hyperthyroidism without effective control.

General information

A total of 100 patients were recruited and assigned at a ratio of 1:1 to an experimental group or a control group according to the alphabetical order of their initials. There was no statistical difference between the general information of patients in the two groups (P>0.05), as shown in table 1.

Ethical considerations

This study was conducted as per the principles of the Declaration of Helsinki (2013) (World Medical, 2013) and patients and their families all provided writen informed consent.

Methods

All eligible patients were managed by the same group of surgeons for surgical operations and the same group of anesthesiologists for perioperative anesthesia. Routine postoperative care was performed after surgery. The control group received postoperative PCIA. The experimental group was given a multimodal analgesia protocol with preemptive analgesia, postoperative analgesia and PCIA.

(1) Preemptive analgesia: 2h before surgery, 50mg flurbiprofen axetil (Beijing Tide Pharmaceutical Co., Ltd., State Drug Administration H20041508) was administered intravenously.

Transverse abdominis plane (TAP) block: Bilateral TAP blocks were performed under ultrasound guidance using a 5-12 MHZ linear probe and a short oblique puncture needle. The probe was placed at the midpoint of the iliac crest and rib margin line for scanning and positioning and the ultrasound probe angle was adjusted to obtain a clear ultrasound image of the three muscle structures of the external oblique abdominal muscle, the internal oblique abdominal muscle and the transversus abdominis muscle. After sterilization of the puncture area with iodophor, the tip of the block needle was slowly inserted into the transversus abdominis fascial area between the internal oblique and transversus abdominis muscles using the ultrasound in-plane technique. If no gas or blood was obtained after retraction, 1-2 ml of the drug was injected to separate the fascial layer between the muscles and 20ml 0.25% ropivacaine (Guangdong Jia Bo Pharmaceutical Co., Ltd., State Pharmacopoeia H20173193) was administered. The block was considered successful if a shuttle-shaped dark fluid area was visible on ultrasound. The same method was used on the opposite side.

(2) Postoperative analgesia: 10min before the end of the operation, intravenous slow drip nalbuphine (Yichang Renfu Pharmaceutical Co., Ltd., State Drug Quantifier H20130128) was performed, 0.2 mg/kg.

(3) PCIA: Sufentanil (Yichang Renfu Pharmaceutical Co., Ltd., State Drug Quotient H20054171) 1.5ug/kg + dexmedetomidine (Jiangsu Enhua Pharmaceutical Co., Ltd., State Drug Quotient H20110085) 0.1ug/(kg.h) +0.9% sodium chloride injection, total 100ml, 2ml/h, lockout time 15min.

Patients in both groups drank a small amount of water before surgery and received a medical thermal blanket for intraoperative body temperature maintenance after entering the operating room. Conventional rapid anesthesia induction was performed with intraoral tracheal intubation. Intraoperatively, the same static inhalation compound general anesthesia protocol was used for maintenance. Induction period: Midazolam (Jiangsu Enhua Pharmaceutical Co., Ltd., State Drug Quotient H10980025) 0.05mg/kg, sufentanil 0.3ug/kg, propofol (Jiangsu Enhua Pharmaceutical Co., Ltd., State Drug Quotient H20123137) 2mg/kg, cisatracurium

besilate (Jiangsu Shengdi Pharmaceutical Co., Ltd., State Drug Quotient H20060868) 0.3mg/kg.

Maintenance period: Tidal volume was set at 8-10 ml/kg, frequency at 12-15 times/min, inspiration-to-expiration ratio at 1:2, oxygen flow rate at 1 L/min and end-expiratory carbon dioxide at 35-45 mmHg.

Intraoperatively, propofol 4-8mg/kg/h, remifentanil (Yichang Renfu Pharmaceutical Co., Ltd., State Drug Quantifier H20030199) 6-18ug/kg/h and sevoflurane (Shanghai Hengrui Pharmaceutical Co., Ltd., State Drug Quantifier H20070172) 1%-3% were continuously pumped intravenously to maintain the EEG dual frequency index between 45-55. Intermittent injection of cisatracurium besilate (0.05 mg/kg) was administered to maintain muscle relaxation. Blood pressure and heart rate were maintained at ±20% of the preoperative base and appropriate vasoactive drugs were applied if necessary.

After surgery, an intravenous self-controlled analgesia infusion pump was connected and PCIA was performed once for enhanced analgesia, followed by postoperative resuscitation in the recovery room.

Observation criteria

(1) General information: general information contains patients' age, height, weight, BMI, tumor category, clinical stage, ASA classification, marital status, monthly income and education level.

(2) Pain scores: The pain scores of patients at 2h, 4h, 6h, 12h, and 24h after surgery were evaluated by the numerical rating scale (NRS) (Mercadante *et al*., 2020). On the scale, 0 points refer to no pain, 1-3 points mild pain that does not affect sleep, 4-6 points moderate pain, 7-9 points severe pain that prevents sleep or wakes up in pain during sleep and 10 points intense pain. The higher the score, the more intense the pain.

(3) Inflammatory factor levels: 2 mL of morning venous blood was collected from patients of the operation day, 1d and 2d postoperatively, and centrifuged to obtain the serum. Serum tumor necrosis factor (TNF-α) and interleukin-6 (IL-6) levels were determined using an enzyme-linked immunosorbent assay (Beijing Kewei Clinical Diagnostic Reagent Co.

(4) Pain mediators: 2 mL of venous blood was collected from patients in the morning of the operation day, 1d and 2d postoperatively and centrifuged to isolate the serum. The content of pain mediator substance P (SP) and prostaglandin E2 (PGE2) in serum was determined by radioimmunoassay (Swiss Roche electro-chemiluminescence instrument, original supporting reagents, State Food and Drug Administration Arms Entry No. 3402843, 2011).

(5) Stress response: 3 mL of venous blood was collected from patients in the morning of the operation day, 1d and 2d postoperatively and centrifuged to obtain the serum. Serum cortisol (Cor) and adrenocorticotropic hormone (ACTH) levels were determined using an enzyme-linked immunosorbent assay.

(6) Incidence of adverse reactions: adverse reactions included gastrointestinal reactions, dizziness, drowsiness, pruritus, and hypotension and the number of patients with postoperative adverse reactions was recorded.

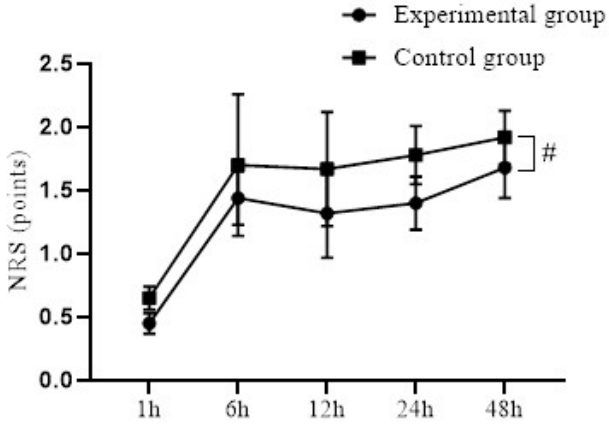
STATISTICAL ANALYSES

SPSS 20.0 was used for data analyses and GraphPad Prism 7 (GraphPad Software, San Diego, USA) was used to visualize the data into matching graphics. Count data were tested using the chi-square test and measurement data were analyzed using the t-test. Differences were considered statistically significant at $P<0.05$.

RESULTS

Comparison of general information

There was no statistical difference between the two groups in terms of general information such as age, body mass, BMI, and tumor stage ($P>0.05$), as shown in table 1.



Note: In fig. 1, the abscissa is 1h, 6h, 12h, 24h and 48h postoperatively from left to right and the ordinate is NRS (score). The dotted line is the experimental group and the square line is the control group; # indicates $P<0.001$.

Fig. 1: Comparison of pain scores of patients ($x \pm s$, points)

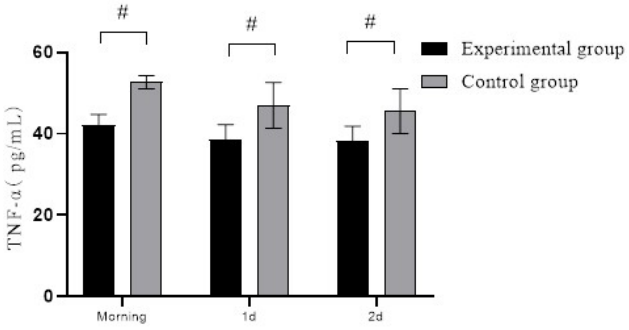
Comparison of pain scores

The pain scores of 1h, 6h, 12h, 24h, and 48h postoperatively in the experimental group were remarkably lower than those of the control group ($P<0.001$). See fig. 1.

Comparison of inflammatory factor levels

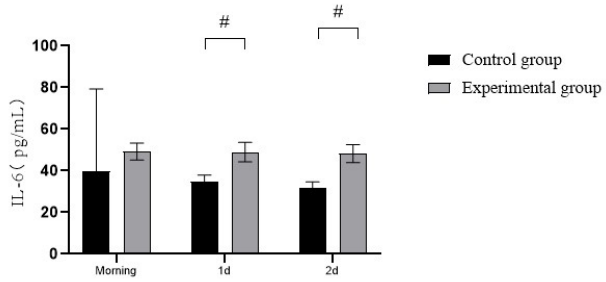
The levels of inflammatory factors in the experimental group were significantly lower than those in the control

group in the morning of the operation day, 1 d and 2 d after the operation (P<0.001), as shown in fig. 2, 3.



Note: In fig. 2, the abscissa from left to right is morning on the operation day, 1d and 2d postoperatively, and the ordinate is TNF-α (pg/mL); the black area in the figure is the experimental group, and the gray area is the control group; # indicates P<0.001.
The TNF-α levels in the control group were significantly higher than those in the experimental group on the morning of the operation day and 1d and 2d postoperatively (42.15±2.65 vs 52.65±1.65, 38.65±3.65 vs 46.98±5.65, 38.22±3.65 vs 45.55±5.47, P<0.001).

Fig. 2: Comparison of TNF-a levels in patients (x±s, pg/mL)



Note: In fig. 3, the abscissa from left to right is morning of the operation day, 1d and 2d postoperatively, and the ordinate is IL-6 (pg/mL); the black area in the figure is the experimental group and the gray area is the control group; # indicates P<0.001.
The IL-6 levels in the experimental group were significantly higher than those in the control group on the morning of the operative day and 1d and 2d postoperatively (39.65±3.20 vs 49.23±4.10, 34.65±3.22 vs 48.98±4.68, 31.98±2.68 vs 48.21±4.30, P<0.001).

Fig. 3: Comparison of IL-6 levels in patients ($\bar{x} \pm s$, pg/mL)

Comparison of pain mediators
The experimental group presented significantly lower pain mediators than the control group in the morning of the operation day, 1d and 2d postoperatively (P<0.001) (table 2).

Comparison of stress response indexes
Markedly lower stress response indicators were observed in the experimental group in the morning of the operation day, 1d and 2d postoperatively than in the control group (P<0.001), as shown in table 3.

Comparison of the incidence of adverse reactions
The two groups showed a similar incidence of adverse reactions (P>0.05) (table 4).

DISCUSSION

Pain is considered the fifth category of vital signs in addition to body temperature, respiration, pulse and blood pressure (Kjolhede *et al*., 2019). Acute postoperative pain may lead to a cascade of physiological and psychological issues that severely compromise postoperative recovery. Pain elicited by gynecologic laparoscopic surgery is considered moderate pain. However, laparoscopic radical surgery pain arises from peripheral sensitization and central sensitization, coupled with a vicious cycle formed by the interaction of inflammatory mediators that amplifies pain receptor sensitivity and aggravates peripheral sensitization in patients (Wang *et al*., 2016; Yu *et al*., 2021). Tissue injury with injurious stimuli persistently acting on the central nervous system, which predisposes patients to abnormal pain in response to normal non-injurious stimuli, with prolonged pain duration and increased pain in the trauma area. Therefore, some cases may experience intense postoperative pain, for which conventional analgesic drugs are insufficient for clinical needs and more effective multimodal analgesic measures are required.

Preemptive analgesia is a new analgesic measure to enhance postoperative analgesia, which mitigates the stress response due to intense intraoperative stimuli and weakens central neuronal excitation, thereby eliminating abnormal postoperative pain and achieving successful analgesia (Ayad *et al*., 2021; Chaudhary *et al*., 2021; Mongan and Wibowo, 2021). Flurbiprofen is a nonsteroidal anti-inflammatory drug, a conventional drug for preemptive analgesia, which can diminish peripheral and central sensitization induced by noxious stimuli, reduce peripheral injurious perception and pain perception, to further minimize pain perception in patients (Inan *et al*., 2021)-(Abdel-Wahab *et al*., 2021). Flurbiprofen axetil is a precursor of flurbiprofen and can selectively act on inflammatory tissues and sites of vascular damage to allow targeting of the drug. Sun Chengcheng *et al*. found that flurbiprofen axetil decreased inflammatory factor levels in patients (Sun *et al*., 2021), which was consistent with the results of the present study.

On top of the preemptive analgesia, PCIA was adopted here, along with nalbuphine hydrochloride used for postoperative analgesia. Nalbuphine hydrochloride is an opioid receptor agonist-antagonist that selectively stimulates κ receptors with a weak antagonistic effect on μ receptors. There are analgesic and sedative effects of κ

Table 1: Comparison of general information of patients

Groups	Experimental group (n=50)	Control group (n=50)	X^2/t	P
Age (year)				
Range	40-70	40-70		
Mean age	54.98±5.65	55.10±5.41	0.108	0.914
Height(cm)				
Range	154-176	155-177		
Mean height	162.55±2.65	162.65±2.01	0.213	0.832
Mean weight(kg)	56.10±2.65	56.21±2.45	2.216	0.830
BMI(kg/m^2)	22.11±1.20	22.13±1.25	0.082	0.935
Tumor types				
Cervical Cancer	20	18	0.170	0.680
Endometrial Cancer	18	19	0.043	0.836
Ovarian Cancer	12	13	0.053	0.817
Clinical stage			0.164	0.685
α	30	28		
β	20	22		
ASA classification			0.361	0.548
α	25	28		
β	25	22		
Marriage			0.191	0.663
Married	36	34		
Unmarried	14	16		
Monthly income (yuan)			0.040	0.841
<4000	28	27		
≥4000	22	23		
Education level			0.361	0.548
High School and below	28	25		
Junior college and above	22	25		

Table 2: Comparison of pain mediators in patients (x±s)

Groups	Experimental group (n=50)	Control group (n=50)	X^2/t	P
SP(μg/mL)				
Morning of the operation day	10.65±2.65	20.22±2.32	19.213	<0.001
1d after surgery	12.65±2.15	22.68±1.32	28.112	<0.001
2d after surgery	13.45±1.22	22.10±1.23	35.306	<0.001
PGE2(pg/mL)				
Morning of the operation day	160.65±12.65	256.98±12.65	30.075	<0.001
1d after surgery	163.65±10.22	289.65±12.54	55.075	<0.001
2d after surgery	165.65±15.65	298.65±15.22	43.080	<0.001

Table 3: Comparison of stress reactions of patients (x±s)

Groups	Experimental group (n=50)	Control group (n=50)	X^2/t	P
Cor(ng/mL)				
Morning of the operation day	120.65±12.65	220.78±12.54	39.750	<0.001
1d after surgery	125.65±12.65	236.98±12.65	44.004	<0.001
2d after surgery	130.65±5.98	238.65±15.55	45.838	<0.001
ACTH(μg/L)				
Morning of the operation day	18.22±1.23	24.65±2.68	15.419	<0.001
1d after surgery	20.12±2.65	25.87±2.22	11.761	<0.001
2d after surgery	22.12±2.60	26.88±2.10	10.071	<0.001

Table 4: Comparison of the incidence of adverse reactions in patients [n(%)]

Groups	Experimental group (n=50)	Control group (n=50)	X^2/t	P
Gastrointestinal reactions	8(16.0)	10(20.0)	0.271	0.603
Dizziness	4(8.0)	3(6.0)	0.154	0.695
Drowsiness	5(10.0)	4(8.0)	0.122	0.727
Pruritus	6(12.0)	4(8.0)	0.444	0.505
Hypotension	3(6.0)	2(4.0)	0.211	0.646

receptors, which are closely related to the occurrence of visceral pain and can alleviate the stress response induced by visceral pain (Chang *et al*., 2021; Liu *et al*., 2021b). Therefore, patients in the experimental group of the present study showed lower postoperative stress response indexes compared with those of the control group. A recent study revealed superior results of nalbuphine hydrochloride application in female patients compared to male patients (Dong *et al*., 2021), the mechanism of which remains poorly understood. This property may indicate a high promotion value of nalbuphine hydrochloride in female patients with gynecological malignancies. The study results showed that the pain scores in the experimental group were significantly lower than those in the control group at 1h, 6h, 12h, 24h and 48h after surgery, and the two groups had a similar incidence of adverse reactions, suggesting the promising efficiency of the joint analgesic protocol employed in the present study, with a high safety profile.

CONCLUSION

To sum up, the multimodal analgesia of flurbiprofen axetil, nalbuphine hydrochloride and PCIA can effectively alleviate the stress response and inflammatory response in patients after radical gynecologic malignancy surgery and the patients' pain perception is reduced, with a high safety profile, which is worthy of clinical promotion.

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