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Analgesic Effect of Nalbuphine Combined with Sufentanil After Laparoscopic Hysterectomy

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ABSTRACT

The objective of this study was to examine the effect of PCIA analgesia after laparoscopic hysterectomy (LH) with Nalbupine combined with Sufentanil on Visual Analogue Scale/Score (VAS), Ramnsay sedation score, serum prostaglandin E2 (PGE2), 5-hydroxytryptamine (5-HT). A convenient sampling method was used to select 86 patients who were scheduled to undergo total LH from March 2020 to April 2022. The patients were divided into control group (CG) and research group (RG), 43 cases each. All patients are treated with PCIA, CG with Sufentanil+Granisetron, RG with Nalbuphine combined with Sufentanil+Granisetron. At 6h and 12h after operation, the scores of VAS and Ramnsay sedation was lower in the RG. The PGE2 and 5-HT water of the RG patients at 6h, 12h and 24h after operation were lower on average. The total adverse reactions incidence in the RG, PCIA press times and tramadol administration times were lower. It was found that Nalbupine combined with Sufentanil can effectively reduce the postoperative pain degree of patients, reduce the release of PGE2 and 5-HT pain factors in serum, and reduce PCIA press number and tramadol administration number.

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ZC and XJ conducted the experiments in this study. XD and PW contributed to the design and interpretation of the current study and wrote the article. All authors read, revised, and approved the final manuscript.

Key words
Nalbuphine, Sufentanil, LH, Patient controlled analgesia, Pain

INTRODUCTION

Patient controlled intravenous analgesia (PCIA) mainly uses sufentanil-based opioid drugs (Park *et al*., 2022). Opioids can cause an increased risk of nausea and vomiting, and reducing the dosage of opioids has become a trend of postoperative analgesia (Rosen *et al*., 2022). Sufentanil is a fentanyl analogue, which has no active metabolite, relatively high therapeutic index and low respiratory inhibition frequency, and is suitable for postoperative pain control stage. Sufentanil has comparable analgesic effect and safety in PCIA after total laparoscopic hysterectomy (LH), and the consumption of analgesics is less. However, 12%-20% of patients still have visceral pain after gynecological surgery (Oh *et al*., 2019). CO_2 pneumoperitoneum is required in LH, which stimulates peritoneum and has a high incidence of postoperative neck and shoulder pain and visceral pain (Aboelela, 2021). Neck-shoulder pain and visceral pain can lead to postoperative emotional problems of patients, leading to cardiovascular and respiratory system dysfunction. The analgesic effect after LH will affect the prognosis of patients (Ji *et al*., 2019). Visual analogue scale/score (VAS) belongs to the subjective pain perception evaluation of patients. Ramnsay sedation score can be used to evaluate the mental state of patients and analyze whether the patients' consciousness is clear. Serum prostaglandin E2 (PGE2) and 5-hydroxytryptamine (5-HT) are the main objective quantitative markers of human pain. Nalbuphine is a new semi-synthetic opioid receptor analgesic with lower malignant vomiting and respiratory inhibition, and can be used in PCIA process.

Operation and high abdominal pressure will stimulate the body, which will be transmitted to the sympathetic-adrenal medulla system, and then activate the stress response of the body. The body's pain perception and pain-related factors will increase (Sollie *et al*., 2022). Postoperative pain stimulation can cause changes in neurosecretion and metabolism, induce a variety of severe complications, and even threaten the life of patients (She *et al*., 2021). Sufentanil, as a commonly used opioid drug in PCIA after hysterectomy, has a good analgesic effect. Sufentanil is generally administered intravenously, and the onset time is about 1~3 min. The efficacy of sufentanil lasts about half an hour. Compared with other opioid drugs, sufentanil can play a better role in potency. However, sufentanil can cause many adverse reactions such as

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drowsiness, nausea and vomiting (Ren and Ning, 2021). In addition, sufentanil can combine with μ receptor in a large amount and can easily pass through the blood-brain barrier, thus achieving better analgesic effect. However, its tolerance is also related to the activation of μ receptor, so the analgesic effect of sufentanil in clinical application is limited. Because women have high sensitivity to pain, their response to analgesics is weak. Therefore, during hysterectomy, female patients have a large demand for sufentanil. In order to improve the clinical effect of sufentanil, it is often used in combination with other drugs in practical application to reduce drug resistance and improve the analgesic effect. The purpose of this study was to examine the effect of nalbuphine combined with sufentanil on the levels of VAS, PGE2 and 5-HT in PCIA analgesia after LH.

MATERIALS AND METHODS

General information

Convenient sampling method is used to select 86 patients with scheduled LH who visited The People's Hospital of Yuhuan from March 2020 to April 2022. Inclusion criteria: Diagnosis of uterine malignant tumor, ovarian or fallopian tube malignant tumor criteria in obstetrics and gynecology, and TLH indication; ASA is graded at grade I and II. Patients with severe dysfunction of heart, liver, lung, immune function, coagulation function defect or endocrine system abnormality, other perioperative infection, and mental or psychological emotion or abnormal perception of pain before operation were excluded from the study. The patients are divided into CG and RG by red and blue ball method, 43 cases each.

Anesthesia method

After the patient enters the operating room, first it was necessary to open the upper limb vein access and use the life monitor to dynamically monitor the patient's ECG, BP, BIS, HR and SpO_2. Then, anesthesia induction work was carried out. 0.3 μg/kg sufentanil, 0.03mg/kg midazolam, 0.15 mg/kg cisatracurium besilate and 0.3mg/kg etomidate were successively injected intravenously. After the patient's BIS was controlled below 60 and maintained for 5s, the patient was intubated and connected to the anesthesia machine for mechanical ventilation. After that, anesthesia was maintained by intravenous infusion of 4~8mg.kg^{-1}.h^{-1} propofol, 0.2~0.3 μg.kg^{-1}.min^{-1} sufentanil and 1~2 μg.kg^{-1}.min^{-1} cisatracurium besilate. During the operation, the patient took a flat recumbent position and established a CO_2 pneumoperitoneum. The head and buttocks were taken low and high, the patient's uterus and appendages were fully reserved, and the uterine lift was placed during the establishment of pneumoperitoneum. Total LH was completed according to the procedure of hysterectomy. The infusion of cisatracurium besilate and sufentanilis terminated 30 min before the end of the operation. Routine electrocoagulation and hemostasis were performed. The front end of the approach was sutured and the peritoneum was reinforced. At the end of the operation, 0.04 mg/kg neostigmine and 0.02 mg/kg atropine were injected intravenously and the tracheal catheter was removed immediately after the patient was naturally awake.

Analgesic methods

PCIA was performed at the end of the operation, and the CG was sufentanil + granisetron. Sufentanilis was 2.0 μg/kg and granisetron was 2mg. They were mixed with 0.9% sodium chloride injection to 120 ml PCIA preparation solution. The RG adopted nalbupine compound sufentanil + granisetron. Nalbupine is 0.2 mg/kg. Sufentanil is 2.0 μg/kg, and granisetron is 2 mg. They were mixed with 0.9% sodium chloride injection to 120ml PCIA preparation solution. The background infusion speed of the analgesia pump was set at 2 ml/h, the infusion volume was 1 mL per press, and the locking time was set at 15 min. After PCIA analgesia, when patients still had a resting VAS score>4 or dynamic VAS score > 6, they were given tramadol tablets 50 mg/time and oral analgesia was taken.

Observation indicators

The pain VAS scores of patients in the two groups were recorded before operation, 6 h after operation, 12 h after operation and 24 h after operation. The scores ranged from 0 to 10, representing painless to severe pain, respectively. The pain degree of patients increased with the increase of the score, which was evaluated and recorded by the full-time medical staff of the hospital.

The ramnsay sedation scores of patients in the two groups were recorded before operation, 6h, 12h and 24h after operation. Ramnsay sedation score was 1~6. Among them, 1 point indicates that the patient's heart rate was fast and could not cooperate with the command sent.

5 ml of elbow vein blood was collected from patients before, 6h, 12h and 24h after operation, and the PGE2 and 5-HT levels of patients were evaluated by automatic biochemical analyzer and ELISA. The number of cases of postoperative nausea, vomiting, dizziness, lethargy and respiratory depression were recorded and the incidence of adverse reactions was calculated. The total number of PCIA compressions and the actual amount of tramadol were collected and compared between the two groups.

Statistical analyses

SPSS 25.0 software is used as the statistical tool. The measurement data that conforms to normal distribution and variance homogeneity is described as $\bar{x}$±s. The inter-group comparison uses independent sample *t* test. The intra-group comparison uses repeated measurement analysis of variance at different time points. The comparison between two groups uses SNK-q test. The count data description uses example (%), and χ^2 test is used (when $1 \leq T < 5$, χ^2_c test is used). Correction level is $\alpha = 0.05$.

RESULTS

From the 92 assigned people, 86 patients took part in the study. The age distribution was between 30 and 51 years, with a M (SD) age of 38.51 (5.43) years in the CG and 39.44 (6.21) in the RG (Table I). Table I shows demographic and clinical-related variables of the patients who participated in the study. The Table I shows that there are no significant differences between the CG and the RG so it can be concluded that they are homogenous groups.

Table I. General data of the patients.

Characteristic	CG (n=43)	RG (n=43)	χ2/t	P
Age (year)	38.51±5.43	39.44±6.21	1.838	0.432
BMI(kg/m²)	21.56±2.05	22.42±2.28	2.357	0.891
ASA I/II(case)	27/21	26/22	0.357	0.131
Cervical carcinoma	12	9		
Endometrial carcinoma	11	11		
Oophoroma	8	11	4.198	0.101
Fallopian tube carcinoma	12	12		

Table II indicate descriptive data for VAS, Ramsay sedation, PGE2 and 5-HT for before and 6h, 12h and 24h after the operation. No significant baseline differences were found between the CG and the RG. The patients reported low symptom scores and levels on the study indicators during perioperative period. The VAS, Ramsay sedation, PGE2 and 5-HT scores of the RG at 6h, 12h and 24h after the operation were significantly lower than those of the CG (Table II). The subjective pain level of the RG patients is lower until 24 h after the operation, at this time, two groups' pain feeling are similar. The sedative effect of the RG patients is lower until 24 h after the operation, at this time, two groups mind states are similar. After the operation, PGE2 level in the RG is lower until 24 h after the operation. 5-HT level in the RG patients is lower after the operation, the highest value appears at 12 h after the operation, and then gradually decreases. Both groups still have difference until 24 h after the operation.

Table III compares postoperative adverse reactions for participants in the CG and the RG groups. The results in the table shows that only one patient with drowsiness occurs in the RG, and the total incidence of adverse reactions is 2.33% lower than the CG (P<0.05). The study results also for main anesthetic dosage shows that in the RG, total presses number is lower than the CG, which is (11.42±1.64) (t=10.034, *P*<0.001). In the RG, tramadol is taken 0 (0,3) times. Compressions number in the CG is (15.7±2.3). Tramadol administration number is 0 (0,4), and both groups are different (χ^2_c=17.480, *P*<0.001).

Table II. Indicators scores (mean±SEM) for the patients at pre- and post-operation.

Indicator	Time	CG (n=43)	RG (n=43)	t	P
VAS ($\bar{x}$±s)	BO	1.65±0.48	1.60±0.50	0.441	0.660
	6h AO	5.40±1.62	4.07±0.96	4.614	<0.001
	12h AO	6.77±1.73	5.19±1.42	4.636	<0.001
	24h AO	3.16±1.09	3.14±0.80	0.113	0.911
Ramsay sedation ($\bar{x}$±s)	BO	3.61±0.47	3.67±0.52	1.352	0.557
	6h AO	3.07±0.43	2.31±0.40	2.919	<0.001
	12h AO	2.36±0.63	1.46±0.32	3.756	<0.001
	24h AO	1.54±0.61	1.51±0.55	0.158	0.876
PGE2 (pg/mL, $\bar{x}$±s)	BO	110.68±18.23	110.78±19.45	-0.026	0.979
	6h AO	217.21±23.74	194.52±24.38	4.373	<0.001
	12h AO	248.88±32.58	221.06±33.95	3.876	<0.001
	24h AO	174.06±22.74	157.37±24.66	3.263	0.002
5-HT (ng/L, $\bar{x}$±s)	BO	162.13±20.42	159.98±25.70	0.429	0.669
	6h AO	218.48±34.42	194.01±30.63	3.483	0.001
	12h AO	249.55±37.50	228.24±29.83	2.915	0.005
	24h AO	192.91±33.50	171.87±36.03	2.805	0.006

BO, before operation; AO, after operation; VAS, visual analogue scale/ score; PGE2, serum prostaglandin E2; 5-HT, 5-hydroxytryptamine; CG, control group; RG, research group.

Table III. Postoperative adverse reactions of the patients (%).

Group	Nausea and vomiting	Dizzy	Drowsiness	Respiratory depression	Total
CG (n=43)	3(6.98)	3(6.98)	1(2.33)	3(6.98)	10(23.26)
RG (n=43)	0	0	1(2.33)	0	1(2.33)
χ^2_c	-	-	-	-	6.672
P	-	-	-	-	0.010

DISCUSSION

In hysterectomy, visceral pain is the main clinical symptom for patients to feel pain. In the recovery of LH patients after surgery, visceral pain can cause negative emotions of patients. At the same time, patients will also have physiological reactions such as nausea and vomiting. Activating the κ receptor is the main inducement of visceral pain in patients, so the antagonist of this receptor can be considered in the clinical application of LH. Nalbuphine is a widely used opioid receptor agonist-antagonist at this stage. It can act on the κ receptor and exert the analgesic effect. Nalbuphine can combine with μ, κ and δ receptors to produce complete activation on κ receptors and antagonism on μ receptors. At the same time, nalbuphine showed extremely weak δ receptor activity and would not bind to δ receptor. After hysterectomy, visceral pain was inhibited by activation of peripheral κ receptor pathway. Research shows that the combination of nalbuphine and sufentanil in surgery can affect more pain receptors and further reduce the severity of visceral pain, shoulder and back pain (Sun *et al*., 2021). Chen *et al*. (2021) applied nalbuphine and sufentanil to the recovery after laparoscopic surgery. By comparing the VAS score of the patients after laparoscopic surgery with the indexes such as flatulence, it is confirmed that nalbuphine and sufentanil have better effects in relieving postoperative pain (Chen *et al*., 2021).

The results showed that the VAS score of RG was lower than that of CG at 6h and 12h after operation ($P<0.05$). Nalbupine combined with sufentanil could reduce the subjective pain degree faster, but the pain degree was similar to sufentanil alone at 24h after operation. A study on postoperative analgesia of induced abortion showed that the effect of nalbuphine on postoperative analgesia of patients with early abortion was better than that of sufentanil (Fang *et al*., 2022). Nalbuphine was a partial μ receptor antagonist/κ receptor agonist analgesic, which could be used for single injection or clinical use of PCIA (He *et al*., 2021). Some scholars studied and observed that the analgesic effect of nalbupine combined with sufentanil was better than that of sufentanil alone, with fewer adverse reactions (Ren and Ning, 2021). At the same time, the levels of PGE2 and 5-HT in RG patients were significantly lower at 6h, 12h and 24h after operation ($P<0.05$). Nalbupine combined with sufentanil could reduce the level of pain-related factors during PCIA after operation. To find out the reason, an animal experiment was conducted. In the rat model of inflammatory visceral pain, Nalbuphine inhibited inflammation and reduced inflammatory pain by down-regulating the NF-κB pathway of the spinal cord (Ruan *et al*., 2022). PGE2 was an important factor of pain signal transduction in the body, which could enhance the excitability of neuron cell membrane and subjective pain perception (Elwakeel *et al*., 2019). PGE2/EP1 receptor-Gq-PKCε was an important signal pathway that regulated the chronic pain of peripheral dorsal root ganglion neurons. And it also played a role in the late stage of hyperalgesia in acute and chronic pain transformation (Sun *et al*., 2019). 5-HT would activate the peripheral nerve receptors, which would enhance the nociceptive signal transmission. Under the stimulation of enhanced pain perception, the production of monoamine 5-HT in the body increased (Turan Yücel *et al*., 2021). The combination of Nalbuphine and Sufentanil could block the opioid peptide negative feedback related pathway, play a stronger analgesic role, and reduce the body's production of more PGE2 and 5-HT pain factors.

At the same time, total adverse reactions incidence in RG, PCIA press times and tramadol administration times were lower ($P<0.05$). Nalbuphine combined with sufentanil was the main drug for postoperative PCIA analgesia. This could reduce the adverse reactions of sufentanil alone, reduce the number of PCIA presses, and reduce the number of tramadol administration. Nalbuphine could stimulate the κ receptor. Its combination with the opioid sufentanil can inhibit the excitability of the trigger area of emetic chemical receptor and effectively reduce nausea and vomiting (Wang *et al*., 1998; Costa *et al*., 2021). At the same time, based on the analgesic effect of Nalbupine and Sufentanil, it could effectively reduce the frequency of PCIA consumption and reduce the ceiling effect of respiratory inhibition. This could effectively reduce the risk of adverse reactions during PCIA after operation, reduce PCIA press frequency and tramadol administration number after operation.

CONCLUSION

Nalbuphine combined with sufentanil can be effectively used in the PCIA analgesia stage after LH. This combination can effectively reduce the postoperative pain degree of patients and reduce the release of PGE2 and 5-HT pain factors in serum. The combination has fewer adverse reactions and can reduce the times of PCIA compression and tramadol administration. This provides a more efficient clinical option for PCIA analgesia after hysterectomy.

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IRB approval

This study was approved by The People's Hospital of Yuhuan, Yuhuan, 317600, China.

Ethical approval

The study was carried out in compliance with guidelines issued by ethical review board committee of The People's Hospital of Yuhuan, China. The official letter would be available on fair request to corresponding author.

Statement of conflict of interest

The authors have declared no conflict of interest.

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