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Original Article

The analgesic effect and inflammatory mechanism of nonsteroidal analgesics combined with nerve block in post-gynecologic surgery patients

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Abstract: Objective: To investigate the analgesic effect and inflammatory mechanism of nonsteroidal analgesics combined with nerve block in post-gynecologic surgery patients. Methods: Sixty patients who underwent gynecological laparotomies in our hospital were enrolled in this retrospective cohort study, with 30 patients administered nonsteroidal analgesics combined with nerve block (the observation group) and 30 patients administered nonsteroidal analgesics alone (the control group). The patients in the observation group were administered an intravenous injection of flurbiprofen axetil 1 mg/kg before the end of the operation, and 0.375% ropivacaine was used for bilateral transversus abdominis plane block after the operation. The patients in the control group were administered only an intravenous injection of flurbiprofen axetil 1 mg/kg before the end of the operation. The blood pressure (BP), heart rate (HR), visual analogue scale (VAS) scores, and the numerical rating scale (NRS) scores were recorded before the operation (T0) and at 1 h (T1), 6 h (T2), 12 h (T3), and 24 h (T4) after the recovery from the anesthesia. The incidences of emergence agitation, and the operation and recovery times in the two groups were recorded. Blood samples were collected before and at one day after the operations to measure the inflammatory factor levels such as IL-6, IL-1β, and TNF-α. Results: The BP, HR, and the VAS and NRS scores in the observation group at T1, T2, T3, and T4 were lower than they were in the control group ($P<0.01$). The inflammatory factor levels after the operation in the observation group were lower than they were in the control group ($P<0.01$). There was no significant difference in the incidences of complications between the two groups ($P>0.05$). Conclusion: Flurbiprofen axetil combined with ropivacaine for bilateral transversus abdominis plane block has a significant analgesic effect on patients after gynecologic surgery. The mechanism may be due to the fact that nonsteroidal analgesics combined with nerve block further reduce the inflammatory factors in the body, which proves the superiority of multimodal analgesia.

Keywords: Flurbiprofen axetil, bilateral transversus abdominis plane block, multimodal combined analgesia

Introduction

Many gynecological diseases can be treated with laparoscopy [1, 2]. Laparoscopic surgery has significant advantages, such as significantly reducing patients' postoperative pain. However, not all gynecological diseases can be treated using laparoscopy. If there is abdominal adhesion or complex intraoperative conditions, open surgery is still needed. Open surgery results in a large wound and severe postoperative pain, so adequate postoperative analgesia is of great importance. Nonsteroidal anti-inflammatory drugs have antipyretic, anti-inflammatory, and analgesic effects [3, 4]. In recent years, they are increasingly used in intraoperative and postoperative analgesia, and bring in a good analgesic effect.

Flurbiprofen axetil is a targeted nonsteroidal analgesic that can inhibit the reduction of cyclooxygenase and prostaglandin production, thus reducing postoperative pain [5]. Nerve block is a new analgesic mode in recent years [6, 7]. It is used locally, so it has little effect on the whole body. Nerve block can be accurately used for regional analgesia, especially under B-ultrasound. The nerve course can be clearly

observed under ultrasound, so only the nerve that needs to be blocked is blocked, reducing the complications caused by blind nerve block. The most commonly used block method of abdominal incision is the transversus abdominis plane (TAP) block [8, 9]. Under the guidance of B-ultrasound, the transversus abdominis muscle can be seen, and drugs can be accurately injected into the transversus abdominis plane for the nerve block. Previous studies have confirmed that flurbiprofen axetil and TAP block both have an analgesic effect [10, 11]. However, no research has confirmed the combined analgesic effect of flurbiprofen axetil and TAP block in open surgery and its possible analgesic mechanism. This study provides a clinical basis for combining the two analgesic methods in open surgery and also provides a theoretical basis for the future study of the underlying mechanism.

Materials and methods

General information

Sixty patients undergoing gynecological open surgery with an abdominal vertical incision in our hospital from March 1, 2020 to September 30, 2020 were recruited as the research cohort in this retrospective study.

Inclusion criteria: patients ranging in age from 18 to 70 years old, patients in classes I-II according to the American Society of Anesthesiologists (ASA) classification, and patients who underwent gynecological open surgery for gynecological diseases such as ovarian cancer, cervical cancer and huge uterine fibroids.

Exclusion criteria: patients with severe heart, lung, liver, kidney, or other important organ dysfunctions, patients with peptic ulcers, patients with aspirin asthma or previous bronchial asthma, patients allergic to the drugs used in the study, patients who used analgesics within three days before the operation.

This study was approved by the ethics committee of our hospital. The patients were informed of the possible risks and other treatment options if the therapeutic effect was not good. All the patients signed the informed consent form.

Research cohort

Sixty patients eligible for surgery were divided into two groups according to the postoperative analgesia method each underwent, with thirty patients in the nonsteroidal analgesics combined with nerve block group (the observation group) and thirty patients in the nonsteroidal analgesics group (the control group). There were no significant difference in their clinical data, such as body mass index and age, between the two groups.

Anesthesia methods

The patients were fasted for eight hours before the operations. After they entered the operating room, each patient's blood pressure (BP), heart rate (HR), finger pulse oxygen saturation (SpO_2), and electrocardiogram (ECG) were monitored. Both groups were given 0.03 mg/kg of midazolam (Jiangsu Enhua Pharmaceutical Co., Ltd., China), 2-2.5 mg/kg of propofol (Xi'an Libang Pharmaceutical Co., Ltd., China), 0.1-5 μg/kg of sufentanil (Yichang Renfu Pharmaceutical Co., Ltd., China) and 0.8 mg/kg of rocuronium (Merck Sharp & Dohme Ltd.) for the intravenous anesthesia induction. Sevoflurane (Shanghai Hengrui Pharmaceutical Co., Ltd., China), propofol, and remifentanil (Yichang Renfu Pharmaceutical Co., Ltd., China) were used to maintain analgesia during the operations, and the dosages were adjusted according to each patient's intraoperative heart rate, blood pressure and BIS value. Both groups were administered an intravenous injection of 1 mg/kg of flurbiprofen axetil (Beijing Taide Pharmaceutical Co., Ltd., China) 30 minutes before the end of the operation. After the operation, the observation group was administered 0.375% ropivacaine (AstraZeneca Pharmaceutical Co., Ltd., China) 0.6 mL/kg/side for a bilateral transversus abdominis plane block under the guidance of B-ultrasound, but the control group was not administered a nerve block, without a blind test. Then the patients were sent to the recovery room. All the patients were treated with an analgesia pump after the operation, containing 5 mg/kg of flurbiprofen axetil and 1 μg/kg of sufentanil in normal saline (total volume, 100 mL). The parameters of the analgesia pump were set at the background dose of 2 mL/h, along with a patient-con-

trolled analgesia (PCA) dose of 1 mL, with a locking time of 15 min, and a loading dose of 6 mL.

Outcome measures

Primary outcome measures: The visual analogue scale (VAS) scores and the numerical rating scale (NRS) scores were recorded and evaluated before the operations (T0) and at 1 h (T1), 6 h (T2), 12 h (T3), and 24 h (T4) after the recovery from the anesthesia. Blood samples were collected before and at one day after the operations, and the IL-6, IL-1β, and TNF-α levels were measured using ELISA kits (Shanghai Ruiqi Biological Reagent Co., Ltd., China). After the blood was centrifuged, the supernatant serum was separated and added to the ELISA kit. The lysozyme marker was then added to the serum. After incubation and washing, a chromogenic agent was added to develop the color. The absorbance value was measured using a microplate reader (Meigu Molecular Instrument Co., Ltd., China), and the corresponding concentration of the inflammatory factors was calculated according to the absorbance value. Concentration (μg/μL) = (OD260-OD280) * dilution ratio *0.04 μg/μL.

Secondary outcome measures: The mean arterial pressure (MAP) and the heart rate (HR) before the operation (T0), and at 1 h (T1), 6 h (T2), 12 h (T3), and 24 h (T4) after recovery from the anesthesia were recorded and evaluated. The incidences of emergence agitation was observed. The operation and anesthesia recovery times in the two groups were recorded. The incidences of nausea, vomiting, dizziness. and other adverse reactions in the two groups were recorded. Incidence of complications = cases of complication/total cases *100%.

Rescue analgesia

If any severe pain occurred in the two groups of patients one day after the operation, corresponding analgesic measures were implemented. The number of patients in each group administered supplementary analgesia was recorded. Supplementary analgesia rate = cases of supplementary analgesia/total cases *100%. The supplementary analgesia rates were compared between the two groups.

Statistical analysis

The data in this study were analyzed using SPSS 19.0 and plotted using GraphPad Prism 5. The measurement data were represented as the mean ± standard deviation ($\bar{x}$±sd). The comparisons between the two groups were carried out using independent-samples t-tests or repeated-measures ANOVA. The differences in the measurement data at each time point between the two groups were analyzed using Bonferroni post hoc tests. The count data were represented as rates. The comparisons of the count data between the two groups were carried out using chi-square tests. Rank-sum tests were used to analyze the ordinal data. $P<0.05$ was considered significantly different.

Results

Comparison of the general clinical data

A total of 60 patients who underwent gynecological laparotomies in our hospital from March 1, 2020 to September 30, 2020 were recruited for this this retrospective cohort study. The patients were divided into two groups according to the postoperative analgesia method each underwent, with 30 patients administered nonsteroidal analgesics combined with nerve block in the observation group and 30 patients administered nonsteroidal analgesics in the control group. See **Figure 1**. There were no significant differences in terms of age, body mass index, or ASA classification between the two groups ($P>0.05$). See **Table 1**.

Comparison of the intraoperative parameters

There were no significant differences in the operation times, the postoperative recovery times, the sufentanil dosages, the intraoperative blood loss, or the intraoperative blood transfusion rates between the two groups ($P>0.05$). The incidence of emergence agitation in the control group was higher than it was in the observation group ($P<0.01$). See **Table 2**.

Comparison of the postoperative conditions

At T0, there were no significant differences in the MAP, the HR, the VAS scores or the NRS scores between the two groups (all $P>0.05$). At T1, T2, T3, and T4, the MAP, the HR, the VAS

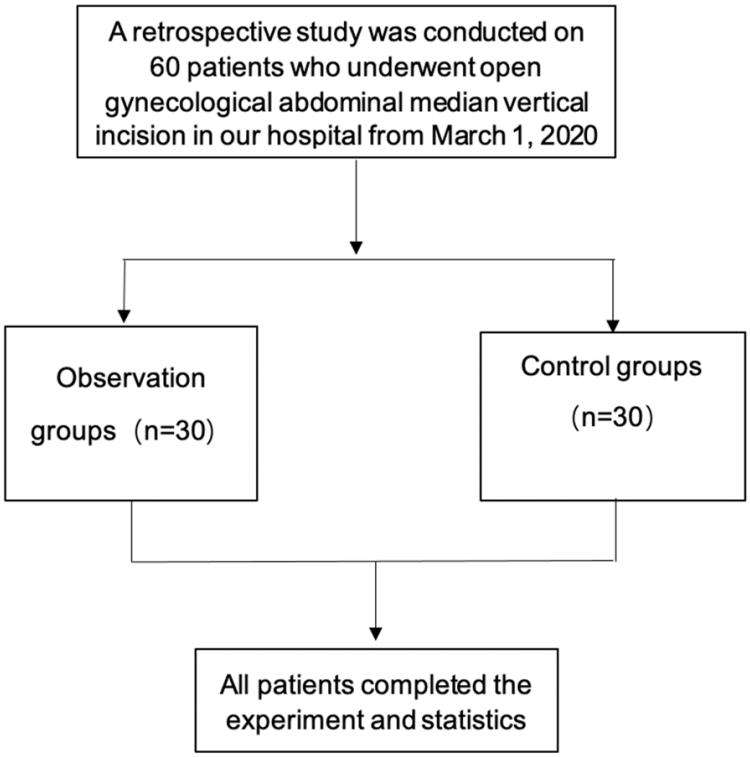

Figure 1. Flow chart of the study.

Table 1. Comparison of general clinical data between the two groups (n, $\bar{x}\pm sd$)

Index	Observation group (n=30)	Control group (n=30)	t/χ^2	P
Age (years)	42.5±13.8	45.8±11.7	0.975	0.334
BMI (kg/m^2)	21.3±3.3	21.0±3.18	0.410	0.684
ASA classification (n)			0.067	0.795
Class I	14	13		
Class II	16	17		
Primary disease (n)			0.034	0.959
Ovarian cancer	8	9		
Cervical cancer	12	11		
Huge uterine fibroids	5	4		
Endometrial carcinoma	5	6		
Hypertension (n)	14	13	0.067	0.795
Diabetes (n)	6	7	0.098	0.754

Note: BMI: body mass index; ASA: American Society of Anesthesiologists.

scores, and the NRS scores in the observation group were lower than they were in the control group (all P<0.05), and the changes in the parameters at T2 were more significant than they were at the other timepoints. See **Table 3**; **Figures 2**, **3**.

Comparison of the inflammatory factors

The postoperative serum inflammatory factor levels, such as IL-6, IL-1β, and TNF-α, in the two groups were higher than they were before the operation (all P<0.001). The postoperative serum inflammatory factor levels in the observation group were significantly lower than they were in the control group (all P<0.01). See **Table 4**.

Comparison of the incidences of complications

There were no significant differences in the incidences of nausea, vomiting, dizziness or lethargy between the two groups (all P>0.05). See **Table 5**.

Comparison of the supplementary analgesia cases

The number of patients requiring supplementary analgesia in the observation group was significantly lower than it was in the control group (P<0.05). See **Table 6**.

Discussion

Pain has been acknowledged as the fifth vital sign, and the impact of pain on patients' quality of life and recover from disease is attracting increased attention. With the development of modern medicine, surgery can effectively alleviate or treat diseases. However, the postoperative pain caused by surgical trauma will affect the surgical effect and the patient's postoperative recovery. Therefore, adequate postoperative analgesia is extremely important. The most commonly-used postoperative analgesics are opioids. Opioids have good analgesic effects but can cause many side effects. Large doses of opioids can cause sig-

Table 2. Comparison of the intraoperative conditions in the two groups ($\bar{x}$±sd)

Index	Observation group (n=30)	Control group (n=30)	t	P
Operation time (min)	105.71±35.25	108.33±34.91	0.292	0.773
Recovery time (min)	23.16±8.42	22.86±7.68	0.144	0.886
Intraoperative blood loss (mL)	367.64±57.68	378.22±51.41	0.750	0.456
Sufentanil dosage (μg)	55.45±15.15	54.55±17.50	0.213	0.832
Blood transfusion rate (%)	16.67	20.00	0.370	0.543
Incidence of emergence agitation (%)	53.33	33.33	8.146	0.004

Table 3. Comparison of the MAP and HR between the two groups ($\bar{x}$±sd)

Group	T0	T1	T2	T3	T4
MAP (mmHg)					
Observation group (n=30)	79.53±18.77	94.93±14.88	90.14±12.45	87.74±15.42	83.48±14.94
Control group (n=30)	82.43±15.31	103.76±17.36	104.74±14.63	95.81±14.28	92.79±15.21
t	0.656	2.115	4.163	2.103	2.135
P	0.515	0.039	0.000	0.040	0.037
HR (bpm)					
Observation group (n=30)	78.65±21.33	88.42±19.37	85.44±15.28	82.34±16.75	78.52±18.61
Control group (n=30)	79.87±20.57	99.68±22.57	99.62±16.63	91.84±14.33	87.87±17.29
t	0.041	2.127	3.440	2.361	2.016
P	0.968	0.038	0.001	0.022	0.048

Note: MAP: mean arterial pressure; HR: heart rate.

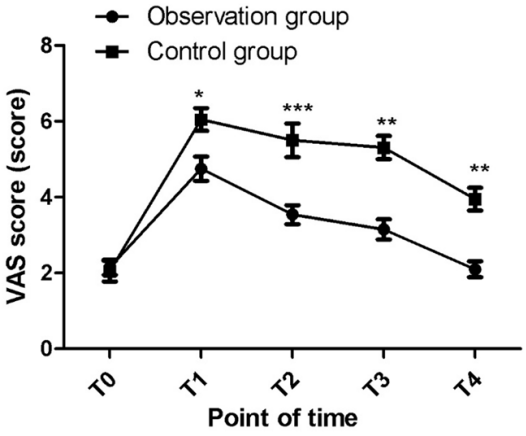

Figure 2. Comparison of the VAS scores between the two groups. Compared with the control group, *P<0.05, **P<0.01, ***P<0.001. VAS: visual analogue scale; T0: before the operation; T1: 1 h after the recovery from anesthesia; T2: 6 h after the recovery from anesthesia; T3: 12 h after the recovery from anesthesia; T4: 24 h after the recovery from anesthesia.

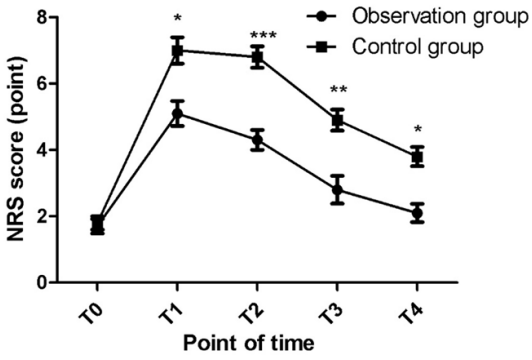

Figure 3. Comparison of the NRS scores between the two groups. Compared with the control group, *P<0.05, **P<0.01, ***P<0.001. NRS: numerical rating scale; T0: before the operation; T1: 1 h after the recovery from anesthesia; T2: 6 h after the recovery from anesthesia; T3: 12 h after the recovery from anesthesia; T4: 24 h after the recovery from anesthesia.

nificant respiratory depression, lethargy, nausea, vomiting, and other adverse reactions [12, 13]. Opioids can also affect a patient's sputum excretions, intestinal peristalsis and offbed activity, postponing the patient's postoperative recovery [14, 15]. Therefore, new analgesic drugs are needed to solve the adverse reactions to opioids. Flurbiprofen axetil is a nonsteroidal anti-inflammatory analgesic [16, 17]. It has advantages such as rapid onset, a

Table 4. Comparison of the inflammatory factors between the two groups ($\bar{x}$±sd)

Time	Observation group (n=30)	Control group (n=30)	t	P
IL-6 (pg/mL)				
Before operation	7.95±1.43	8.33±1.26	1.092	0.279
After operation	17.65±2.31***	24.43±2.88***	10.059	<0.001
IL-1β (pg/mL)				
Before operation	13.57±3.71	12.89±3.82	0.699	0.487
After operation	20.53±4.17***	27.77±3.61***	7.190	<0.001
TNF-α (pg/mL)				
Before operation	21.36±6.05	22.11±6.84	0.450	0.654
After operation	30.41±7.13***	36.18±6.45***	3.287	0.002

Note: Compared with the same group before the operation, ***P<0.001.

Table 5. Comparison of the incidences of complications between the two groups (n, %)

Complication	Observation group	Control group	χ^2	P
n	30	30		
Nausea (%)	16.67	20.00	0.370	0.543
Vomiting (%)	10.00	13.33	0.538	0.463
Dizziness (%)	16.67	13.33	0.437	0.508
Lethargy (%)	20.00	23.33	0.327	0.568

Table 6. Comparison of the supplementary analgesia cases between the two groups

	Observation group	Control group	χ^2	P
n	30	30		
supplementary analgesia rate (%)	10.00	33.33	16.04	<0.001

long action time, and no respiratory depression. Compared with other nonsteroidal anti-inflammatory drugs, flurbiprofen axetil is a lipid microsphere preparation, which makes flurbiprofen axetil a targeted analgesic. It can inhibit platelet cyclooxygenase and the production of prostaglandins, prostacyclin, and blood acid A2 to achieve the analgesic effect. Flurbiprofen axetil can target the injury site to relieve pain caused by wounds and inflammation, enhancing its analgesic effect [11, 18, 19]. A randomized controlled study from abroad, which investigated the use of flurbiprofen axetil and tramadol for postoperative analgesia after abdominal surgery, showed that the postoperative analgesic effect of flurbiprofen axetil group was better than the tramadol group; the VAS scores at rest showed a more significant decrease in the flurbiprofen axetil group than in the tramadol group; and the flurbiprofen axetil group also had a lower incidence of adverse reactions than the tramadol group [20]. However, the single use of flurbiprofen axetil cannot completely relieve pain. Many doctors use opioids in combination with flurbiprofen axetil. Because of opioids' side effects, it is necessary to combine other analgesic methods to form a multimodal analgesia.

Nerve block has become a popular analgesic method in recent years, and it is also a commonly used way to treat patients with chronic pain in the Pain Department. Moreover, nerve block is a local anesthetic method, and it not only has a good analgesic effect, but it also has less impact on the whole body. It is especially suitable for the elderly who are more sensitive to drugs. TAP block injects local anesthetics between the internal oblique and the transversus abdominis muscles, providing good analgesia for the skin, muscles, and fascia of the lateral wall of the anterior abdomen [21-23]. However, a blind puncture through anatomical positioning may cause an incomplete or failed block and damage the intestines through the peritoneum. Therefore, ultrasound-guided nerve block has gradually become a trend. Under the guidance of the ultrasound, the layers of tissues that the needle tip passes through can be clearly observed, and the drug can be accurately injected into the position that needs to be blocked, significantly reducing the injury caused by the puncture. A previous study sh-

owed that comparing the analgesic effects of ultrasound guided TAPB and postoperative wound local infiltration, it was found that bilateral TAP can significantly reduce the pain score at 8-12 hours after surgery [24]. A previous study administered TAPB combined with analgesics to treat postoperative pain after abdominal surgery and found that TAPB can inhibit the stress response during laparoscopic surgery and provide good postoperative analgesia [25]. Another study showed that a TAP block can reduce postoperative pain in patients undergoing laparoscopic cholecystectomy. TAP block combined with flurbiprofen axetil not only provides good surgical analgesia, but it also improves the quality of the patients' recoveries [26].

In this study, compared with flurbiprofen axetil alone, flurbiprofen axetil combined with ultrasound-guided TAP block significantly reduced the VAS and NRS scores, indicating that it can reduce postoperative pain. The blood pressure and heart rate levels in the combined group were significantly lower than they were in the flurbiprofen axetil group. The recovery times were similar in both groups, and the incidences of postoperative nausea, vomiting, dizziness and lethargy did not show significant differences. The most significant difference in the analgesic effect between the two groups was found at 6 h after the operation, probably because of the long analgesic duration of ropivacaine-the analgesic effect of flurbiprofen axetil 6 h after surgery gradually faded, but the effect of ropivacaine continued. From the results of this study, we can also observe that one day after the operations, the supplementary analgesia cases in the group administered flurbiprofen axetil alone were significantly higher than they were in the group administered flurbiprofen axetil combined with TAP block, which proves that the analgesic effect in the combined treatment group lasts longer.

IL-6, IL-1β, and TNF-α are inflammatory factors. IL-6 and IL-1β are secreted by monocytes and play important roles in trauma or the immune-mediated inflammatory response. TNF-α is a pro-inflammatory factor produced by monocytes and can promote the production and release of other inflammatory factors. When a local injury exists, the production of these three inflammatory factors will increase, and they will gather in the injured area and promote pain. A study has confirmed that flurbiprofen axetil has anti-inflammatory and analgesic effects in elderly orthopedic patients. One of its analgesic mechanisms is to reduce the production of the inflammatory factors IL-6 and IL-1β [27]. A previous study showed that analgesics combined with TAP can not only enhance the nerve block effect of ropivacaine, but they can also reduce the use of opioid analgesics, shorten the onset time of local anesthetics, enhance postoperative analgesia and reduce oxidative stress in the body after surgery [28, 29]. Another study also showed that analgesics combined with TAPB can inhibit the stress response in laparoscopic surgery and reduce the release of postoperative inflammatory factors to achieve postoperative analgesia [30]. Therefore, we speculate that the analgesic mechanism of flurbiprofen axetil in gynecological surgery may also be the reduction of the inflammatory factors in the body. From the results of this study, it can be seen that the production of the three inflammatory factors in the blood increased after surgery, which was caused by incision stimulation. However, the production of the inflammatory factors in the blood of the patients treated with flurbiprofen axetil combined with TAP block was significantly lower than it was in the patients treated with flurbiprofen axetil alone. Therefore, it can be speculated that the combined use of TAP block can further reduce the production of inflammatory factors, probably because TAP block can reduce the local inflammation of the wound and achieve the analgesic effect.

There are some shortcomings to this study. This study only studied the analgesic effect within 24 hours after surgery, but not study the specific analgesic effect 24 hours after the operation. Moreover, this study only included a small cohort and limited types of primary diseases. There was no specific study on whether the combined analgesia method still has a good effect on other operations. All the above questions need to be further studied.

This study proves that flurbiprofen axetil has a good analgesic effect. When combined with TAP block, the analgesic effect is significantly increased, and the analgesic time is longer while not increasing the patients' adverse reactions and recovery times. This study provides a certain basis for the clinical application of the

combined analgesic mode, which combines drug analgesia and nerve block. Also, the serum inflammatory factors in the combined analgesia group were reduced, which provides evidence to study the analgesic mechanism of nerve block. In conclusion, flurbiprofen axetil combined with TAP block in patients undergoing gynecological open surgery has a good analgesic effect, so it is worthy of clinical promotion.

Disclosure of conflict of interest

None.

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