Effect of parecoxib sodium on the pain and stress response in female patients after laparoscopic operation

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Abstract

Objective:
To investigate the effects of intravenous parecoxib sodium to post-laparoscopic female patients on pain, cortisol and Adreno-corticotropic-hormone (ACTH) level at different time points, and provide reference to clinical analgesia regimen. Methods: A total of 45 female patients undergoing selective laparoscopic operation were randomly divided into 3 groups (n = 15). Group P1 received parecoxib sodium (40 mg) 30 min before skin cutting; Group P2 received parecoxib sodium (40 mg) at time of skin suture; Group P0 was the control group (don't use parecoxib sodium). The three groups were tested the cortisol and adrenocorticotropic hormone before surgery and 30 min after surgery. The analgesic effects were evaluated with VAS score and 24-hour analgesic effect satisfaction. Noninvasive blood pressure (NIBP), mean arterial pressure (MAP), heart rate (HR), and blood oxygen saturation (SpO2) were recorded before anesthesia induction, just after tracheal extubation, and 5 min, 15 min, 30 min, 4 hr. and 8 hr. after tracheal extubation. Results: There were no significant differences between the groups with respect to age, weight, the duration of operation, and the preoperative cortisol and ACTH ($P > 0.05$). The post-operative cortisol and ACTH were significantly different in three groups ($P < 0.05$). HR and MAP were of significant differences in the three groups ($P < 0.05$). HR and MAP at different time points in each group were significantly different ($P < 0.05$). The VAS score was of significant differences in the three groups ($P < 0.05$). The 24-hour analgesic effect satisfaction was significantly different in the three groups ($P < 0.05$). Conclusions: Preemptive analgesia by parecoxib sodium can efficiently reduce the postoperative pain, postoperative stress duration and prevent general anesthesia patients from the stress response of extubation. Analgesia effect after 24 hour of the operation is good and no significant adverse effects are observed in this duration. The preemptive analgesia effects between skin cutting and skin suture are of no significance.

Keywords

Parecoxib sodium; postoperative pain; stress response, cortisol; ACTH.

1. Introduction

1.1 Study object

With the improvement of life quality, patients' demand for medical services and technologies has also been constantly improved, for instance, they require for minor surgical injuries, small pain, quick repair of wounds, and good therapeutic effect. Due to small incision and quick repair and leaving scarcely any clear scars after operation, laparoscopic surgery is chosen by increasing patients, who also require no pain after surgery. There are including depression and the effects on memory,

increasing patients' psychological and physiological burden. This clinical study is to seek a more desirable and safe anesthesia program to alleviate postoperative pain and stress response in patients receiving laparoscopic surgery.

1.2 Internal environment changes to stress resistance

After nociceptive stimulus (such as surgery or trauma), inflammatory reactions can lead to the release of inflammatory mediators and algogenic substances, including histamine, bradykinin, lysosomal enzyme, 5-hydroxytryptamine, prostaglandin, complement, and leukotriene B4. In addition to direct pain, those stimulating factors can also cause tissue edema and vascular dilatation, which increases the sensitivity of the effect receptors and reduces the pain threshold, further leading to peripheral hyperalgesia [1].

Stress response is the coordinated response of multiple systems and organs in the body, including at least the nervous system, endocrine system and immune system. When the body is suddenly exposed to strong and harmful stimuli such as trauma, surgery and pain, hypothalamus pituitary secretion causes the changes of hormones in blood. That is acute stress. It responds to external stimulus and thus makes the internal environment stable. But excessive stress can cause adverse reactions and diseases. The longitudinal study by Schoorlemmer RMM et al. [2] and retrospective study by Lipiner Friedman D et al. [3] have found that higher levels of cortisol in the body were associated with higher mortality risk, and significantly correlated with chronic diseases in older people. A previous study found that hormones in the stress response have the potential to inhibit the immune system and increase the chances of cancer cell growth in the body [4]. Therefore, in surgical treatment, it is necessary to avoid unnecessary stress and strengthen the anti-stress measures.

For example, with too great surgical stress, neuroendocrine hormones can lead to ischemic injury of renal gastrointestinal tract, mass consumption of energy, and stress cardiovascular injury, which may inhibit tissue regeneration, affect wound healing, and cause stress hyperglycemia. In case of severe pain stimulation, the hypothalamic-pituitary-adrenal axis activity increases, resulting in the release of various hormones and the increase of catecholamine content in the blood [5], which leads to the increases of heart rate, cardiac contraction and blood pressure. Additionally, there showed that the blood glucose was significantly higher in patients after surgical stress than that before surgery, indicating that patients with diabetes or patients with abnormal blood glucose may face higher risk of postoperative blood glucose abnormalities. Because excessive stress causes less use of glucose and the increase of glycogen decomposition, inducing stress hyperglycemia, or exceeded renal sugar threshold causes stress glycosuria. The body also showed more changes in response to stress resistance.

After surgery with general anesthesia, tracheal extubation period is an important transition point, which lasts from the end of the operation to the patient's spontaneous breathing and mental recovery. The stress response in this period can be characterized by shortness and irregularity of breath, elevated blood pressure, mental recovery, rapid increase of heart rate, and restlessness, which is due to shallower anesthesia, pain in the surgery incision, prolonged localized body compression, stimulation of oral secretions and catheters. It is generally believed that moderate stress is a beneficial physiological response to the human body. However, excessive stress response can increase the incidence of complications during the tracheal extubation period. It may increase the risk of heart failure, pulmonary edema or cerebral hemorrhage before surgery in patients with cardiovascular disease.

1.3 Use of premedication

In the 20th century, Crile GW et al. [6] first proposed the concept of preemptive analgesia. Preemptive analgesia is to give analgesic measures before pain stimulus to eliminate or reduce the pain message to the central nervous system, achieving good postoperative analgesia effect, reducing the postoperative complications and the days of hospitalization after the operation [7]. At present, the commonly used clinical analgesic drugs after surgery include opioids, local anesthetics, and non-steroidal

anti-inflammatory drugs (NSAIDs). The commonly used postoperative analgesic methods are subcutaneous analgesia, epidural analgesia and intravenous analgesia, among which the last is used mostly.

The application of opioid analgesic drugs is inevitable for intubation under general anesthesia in laparoscopic surgery. On one hand, opioids have potent analgesic effect. On the other hand, there are subtypes of opioid receptors (μ、κ、δ) in human body, which interact with each other to exert analgesic effect. As an opioid drug, morphine used for postoperative analgesia has serious side effects, including respiratory depression, asphyxia, bradycardia and skin itch, and can increase the risk of apnea after extubation. In addition, it is very addictive, so it is seldom used for continuous analgesia after operation.

As a NSAID, parecoxib sodium is a new kind of specific highly-selective cyclooxygenase-2 (COX-2) inhibitor, with less adverse reaction in clinical application, high safety and good tolerance. It inhibits the expression of peripheral COX-2 and reduces the peripheral synthesis of Prostaglandin, thus playing an anti-inflammatory and analgesic effect. It can also inhibit the expression of central COX-2 and reduces the central synthesis of Prostaglandin, thus effectively reducing PGE2 level in cerebrospinal fluid [8]. Selective parecoxib sodium has the same effect as non-selective NSAIDs, or even has better analgesic and anti-inflammatory effects. Because it does not produce gastrointestinal and renal complications associated with the suppression of COX-1. In addition, the analgesic mechanism of parecoxib sodium and opioid analgesics are different, so there is no risk of apnea after extubation. There shows that the application of non-steroidal anti-inflammatory drugs in the perioperative period can effectively reduce the changes in heart rate and blood pressure at extubation and recovery period, not prolonging the waking period or increasing adverse effects.

1.4 Effect changes at different time of administration

Preemptive analgesia program has long been used in clinical anesthesia, but it is not specific, systematic and scientific, and most doctors do it with experience. Previous studies evidenced that non-steroidal anti-inflammatory drugs used for preemptive analgesia can reduce postoperative visual analog scale (VAS) score, indicating their analgesic effect, but the studies failed to show that perioperative medication at different time points is difference in effects.

Presently, increasing patients choose laparoscopic surgery and require no pain and quick and safe recovery after surgery. Study at home and abroad have shown that preemptive analgesia has certain effect on postoperative analgesia, and NSAIDs such as parecoxib sodium are popular in clinical application with less adverse reaction, good tolerance and little effect on the respiratory and gastrointestinal systems, effectively reducing stress response in the extubation period. However, it is rarely studied at which time point the drug could give the maximum therapeutic effect in the perioperative period. This study targets to explore appropriate medication time points, to effectively suppress stress response and achieve satisfactory postoperative analgesic effect.

2. Materials and Methods

2.1 Study objects

2.1.1 General information

A total of 45 female patients undergoing laparoscopic operation (hysteromyoma and cyst resection) with general anesthesia.

2.1.2 Data resource

The patients were from The First Affiliated Hospital of Jinan University.

2.1.3 Grouping

The 45 female patients were randomly divided into 3 groups (n = 15). Group P1 received parecoxib sodium (40 mg) 30 min before skin cutting; Group P2 received parecoxib sodium (40 mg) at time of

skin suture; Group P0 was the control group (not use parecoxib sodium). Anesthesia and operation are performed by the same group of doctors and are the first surgery in the morning.

2.1.4 Inclusion criteria

The patients were included, who were ASA I and II patients receiving selective laparoscopic operation (hysteromyoma and cyst resection), aged from 18 to 50 years, weighted ranging 45 - 75 kg, with no abnormality in preoperative heart, liver, kidney, lung, coagulation or blood glucose, and Hct > 30% and Hb > 100g/L.

2.1.5 Exclusion criteria

The patients were excluded, who changed to laparotomy during the operation, received tracheal intubation more than 1 time, showed allergic reactions during the operation, had the duration of operation over 120 min, or had used NSAIDs 24 h before surgery.

2.2 Main experimental drugs and instruments

2.2.1 Main experimental drugs

(1) Multiple Electrolytes Injection (Plasma-Lyte A): Shanghai Baxter Healthcare Ltd.

(2) Succinylated gelatin (4%) - Gelofusine: German B. Braun

(3) Fenranyl citrare injection

(4) Remifentanil injection

(5) Propofol Injection - Jing An

(6) Atracurium besylate

(7) Midazolam Injection

(8) Ramosetron

(9) Parecoxib Sodium for Injection: Pfizer Pharmaceuticals Ltd.

2.2.2 Anesthesia and monitoring instruments

(1) WATO EX-60 anesthesia machine: Shenzhen MINDRAY Biomedical Electronic Co., Ltd.

(2) Beneview T5 monitor: Shenzhen MINDRAY Biomedical Electronic Co., Ltd.

2.2.3 Experimental reagents and instruments

(1) Cortisol kits (100 test/box): American Abbott (μg/dL Cortisol x 27.6 = nmol/L Cortisol)

(2) AXSYM automatic immune analyzer: American Abbott

(3) Adreno-corticotropic-hormone (ACTH) kits (Siemens IMMULITE®2000): Siemens Medical Diagnostic Products (Shanghai) Co., Ltd. (SHD)

(4) Immunoassay Analyzer System (Siemens IMMULITE®2000): Siemens Medical Diagnostic Products (Shanghai) Co., Ltd. (SHD)

2.3 Experimental procedure and methods

2.3.1 Before anesthesia induction

All the patients were injected with Hyoscine (0.3 mg) before entering the operating room, with routine monitoring of electrocardiogram (ECG), blood oxygen saturation (SpO2) and noninvasive blood pressure (NIBP). Two venous blood samples (each 3 ml) were extracted to test the serum Cortisol and plasma ACTH before anesthesia induction. Intravenous drip of 4% succinylated gelatin (500 ml) and injection of ramosetron (0.3 mg) was administrated in patients' upper limb. The patients in the Group P1 received parecoxib sodium (40 mg) 20 min before intubation; Group P0 received normal saline (5 ml) 20 min before intubation.

2.3.2 Anesthesia induction and intubation

Anesthesia induction was performed for all the patients by intravenous injection of midazolam (0.1 mg/kg; no more than 5 mg), fentanyl (4 μg/kg), propofol (2.0 mg/kg) and atracurium besylate (0.6 mg/kg). Oral intubation was carried out after giving muscle relaxant 300 seconds. Women are

generally given the number 7.0 endotracheal intubation. After successful intubation, the patient was connected to anesthesia ventilator for mechanical ventilation. The tidal volume was set at 8 - 10 ml/kg, respiratory rate at 12 - 16 bpm, inspiratory/expiratory ratio at 1: 2, and partial pressure of end-tidal carbon dioxide (PETCO2) at 35 ~ 45 mmHg (1 mmHg = 0.133 Kpa).

2.3.3 Perioperative anesthesia management

After successful oral intubation, continuous pumping of remifentanil (0.1-0.2 μg/kg·min) and propofol (6 -10 mg/kg·h) was carried out from the open venous channel to maintain intravenous anesthesia, with intermittent intravenous injection of atracurium besylate (0.1-0.2 mg/kg). Intravenous infusion was maintained with plasma Lyte A. During the operation, the heart rate was maintained stable, the average arterial pressure was maintained at ± 20% of the basic value, PETCO2 maintained at 35 - 45 mmHg, and SpO2 at 99% - 100%. For group P2, intravenous injection of parecoxib sodium (40 mg) (diluted in 5 ml normal saline) was performed 5 min before skin suture with the surgeon's permission.

2.3.4 Recovery and extubation

After the surgeon completed the operation, the patient shall stop using any anesthetic drugs immediately. Extubation was performed when the patient's spontaneous respiratory rate was 16 ~ 24 bpm and regular, tidal volume > 6 ml/kg in spontaneous breathing, swallowing reflex recovered, SpO2 > 95% after mechanical ventilation was stopped, and responded to calling. The patient was escorted to PACU for observation.

2.3.5 PACU observation and treatment

All patients were taken to the PACU for observation (30 - 45 min). Two venous blood samples (each 3 ml) were extracted 30 min after extubation to test the serum Cortisol and plasma ACTH. Adverse reactions and pain intensity (VAS score) of the patients were observed in PACU. When the VAS score > 6, those patients who had analgesic requirement, were given intravenous injection of Tramadol (1 - 1.5 mg/kg; maximum single dose of 100 mg) for analgesia, which was recorded. When fully awake and stable, the patient was sent back to the ward by special person.

2.3.6 Time points and content of the records

Recording time points: before anesthesia induction (T0), just after tracheal extubation (T1), and 5 min (T2), 15 min (T3), 30 min (T4), 4 hr. (T5) and 8 hr. (T6) after tracheal extubation. Recording content: heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), blood oxygen saturation (SpO2), nausea, vomiting, VAS score, analgesia methods and special situations (Appendix 2).

2.3.7 Follow-up

Postoperative follow-up was carried out on all the patients 24 h after the operation; postoperative pain and adverse reactions were recorded, including nausea, vomiting, coughing, dizziness, restlessness, intraoperative consciousness, sleep conditions, and postoperative analgesic measures. The patient scored for the analgesic effect satisfaction, ranging from very good (5 points), good (4 points), satisfied (3 points), poor (2 points), and very poor (1 point).

2.4 Statistical methods

All the data were analyzed using SPSS13.0 statistical software and presented by mean ± standard deviation. One-way ANOVA was used to compare the measurement data of multiple groups at the same time. Repeated measures ANOVA was used to compare the hemodynamic parameters and the test data of multiple groups at different time points. Rank sum test was for abnormal distribution. The *t* test and variance analysis were used for comparison in the group. The enumeration data were tested using χ^2. $P < 0.05$ was considered to be significantly different.

3. Results

3.1 Baseline characteristics of the three groups

There were no significant differences between the three groups with respect to age, weight and the duration of operation ($P > 0.05$).

Table 1 Baseline characteristics of the patients in the three groups

Group	Age (years)	Weight (kg)	Duration of operation (min)
P1	33.93 ± 8.35	54.63 ± 6.00	77.80 ± 17.61
P2	33.40 ± 9.30	55.20 ± 8.10	75.13 ± 14.95
P0	31.93 ± 9.45	57.90 ± 7.32	72.73 ± 18.38

Notes: $P > 0.05$.

3.2 Comparison of Cortisol and ACTH in the three groups

1. Compared with that before anaesthesia induction, the Cortisol level in the group P1 was significantly lower 30 min after extubation ($P < 0.05$).
2. Compared with that before anaesthesia induction, the Cortisol level in the group P2 was significantly lower 30 min after extubation ($P < 0.05$).
3. Compared with that before anaesthesia induction, the ACTH level in the group P1 was significantly lower 30 min after extubation ($P < 0.05$).
4. Compared with that before anaesthesia induction, the ACTH level in the group P2 was significantly lower 30 min after extubation ($P < 0.05$).
5. The Cortisol level 30 min after extubation in the group P1 was significantly lower than that in the group P0 ($P < 0.05$).
6. The Cortisol level 30 min after extubation in the group P2 was significantly lower than that in the group P0 ($P < 0.05$).
7. There were no significant differences in the Cortisol level 30 min after extubation between the group P1 and group P2 ($P > 0.05$).
8. The ACTH level 30 min after extubation in the group P1 was significantly lower than that in the group P0 ($P < 0.05$).
9. The ACTH level 30 min after extubation in the group P2 was significantly lower than that in the group P0 ($P < 0.05$).
10. There were no significant differences in the ACTH level 30 min after extubation between the group P1 and group P2 ($P > 0.05$).

Table 2 Comparison of Cortisol and ACTH of the patients in the three groups

Group	CORTISOL (before anesthesia induction) (nmol/L)	CORTISOL (30 min after tracheal extubation) (nmol/L)	ACTH (before anesthesia induction) (pg/ml)	ACTH (30 min after tracheal extubation) (pg/ml)
P1	497.71 ± 205.62	348.07 ± 141.55[ab]	27.45 ± 17.20	9.64 ± 8.75[ab]
P2	543.50 ± 194.98	324.97 ± 138.29[ab]	35.54 ± 14.87	13.60 ± 10.02[ab]
P0	531.27 ± 117.89	556.75 ± 271.18	36.83 ± 16.87	34.79 ± 19.52

Notes: [a], $P < 0.05$ Compared with that before anesthesia induction; [b], $P < 0.05$ compared with the P0 group.

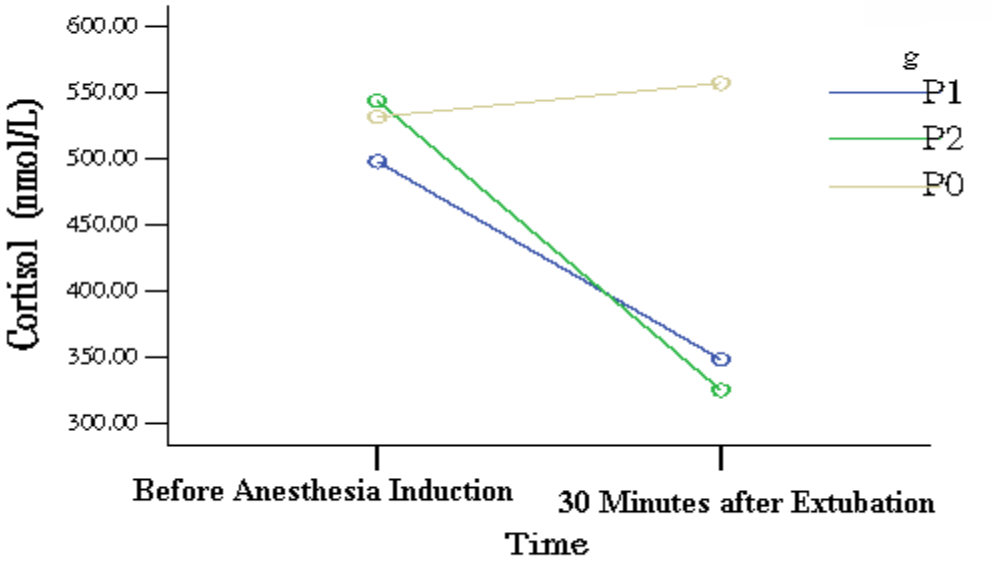

Figure 1 Change of cortisol in three groups

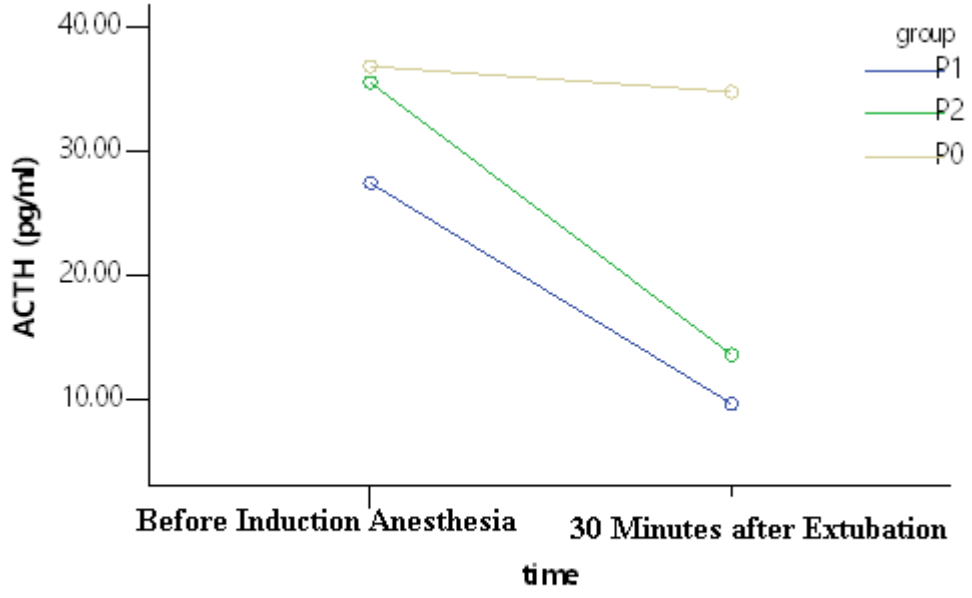

Figure 2 Change of ACTH in three groups

3.3 Changes of HR and MAP at different time points in the three groups

Changes of HR in the three groups

1. Compared with the group P0, the group P1 showed significantly lower HR at T1, T2, T3, T4, T5 and T6 ($P < 0.05$).

2. Compared with the group P0, the group P2 showed significantly lower HR at T1, T2, T3 and T4 ($P < 0.05$).

3. Compared with the group P1, the group P2 showed significantly higher HR at T5 and T6 ($P < 0.05$).

Changes of MAP in the three groups

1. Compared with the group P0, the group P1 showed significantly lower MAP at T1, T2, T3, T4 and T5 ($P < 0.05$).

2. Compared with the group P0, the group P2 showed significantly lower MAP at T1, T2, T3, T4 and T5 ($P < 0.05$).

3. There were no significant differences in the changes of MAP in the group P1 and P2 ($P > 0.05$).

Changes of HR at different time points in the same group

1. Compared with T0, the group P0 showed significantly higher HR at T1, T2, T3 and T4 ($P < 0.05$).

2. Compared with T1, the group P0 showed significantly lower HR at T2, T3, T4, T5 and T6 ($P < 0.05$).

3. There were no significant differences in the changes of HR at different time points in the same group ($P > 0.05$).

Changes of MAP at different time points in the same group

1. Compared with T0, the group P0 showed significantly higher MAP at T1, T2, T3 and T4 ($P < 0.05$).

2. Compared with T1, the group P0 showed significantly lower MAP at T5 and T6 ($P < 0.05$).

3. There were no significant differences in the changes of MAP at different time points in the same group ($P > 0.05$).

Table 3 Data on haemodynamics at different time points in the three groups

Items	Group	T_O	T_1	T_2	T_3	T_4	T_5	T_6
HR (bpm)	P1	78.6 ± 8.4	86.1 ± 10.4*	81.8 ± 10.7*	80.6 ± 8.4*	80.5 ± 8.2*	77.6 ± 6.9*	79.7 ± 7.4*
	P2	82.3 ± 8.7	91.0 ± 9.0*	87.8 ± 8.7*	83.5 ± 4.4*	83.4 ± 3.9*	83.5 ± 5.8#	85.9 ± 7.5#
	P0	84.3 ± 9.2	100.1 ± 7.8a	96.3 ± 6.8ab	91.1 ± 9.2ab	90.5 ± 8.3ab	87.1 ± 12.9b	85.3 ± 10.0b
MAP (mmHg)	P1	84.2 ± 11.0	91.5 ± 5.7*	87.2 ± 6.0*	86.5 ± 6.4*	86.1 ± 6.4*	82.1 ± 6.6*	82.5 ± 9.8
	P2	87.1 ± 10.0	93.7 ± 6.3*	88.5 ± 9.7*	89.3 ± 10.0*	89.1 ± 10.0*	85.9 ± 9.6*	85.0 ± 7.0
	P0	87.6 ± 7.2	102.3 ± 5.4a	100.3 ± 6.3a	100.5 ± 9.4a	100.5 ± 9.4a	93.7 ± 6.3b	88.3 ± 7.3b

Notes: *, $P < 0.05$ compared with the P0 group; #, $P < 0.05$ compared with the P1 group; a, $P < 0.05$ compared with T0; b, $P < 0.05$ compared with T1.

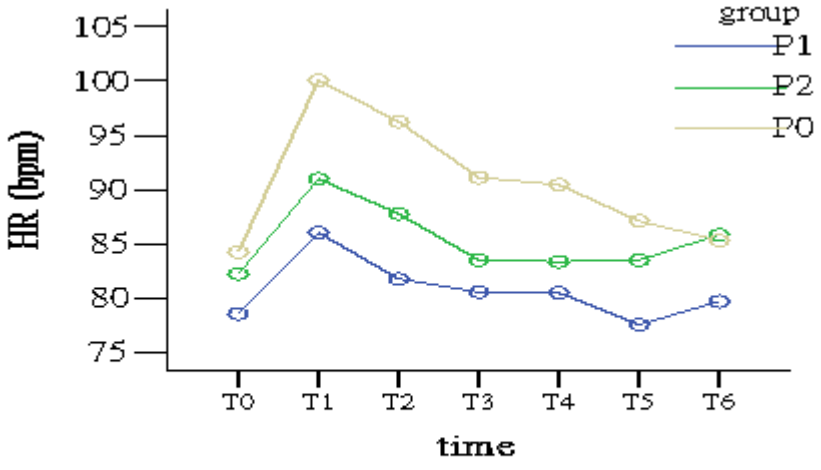

Figure 3 Change of HR at each time in three groups

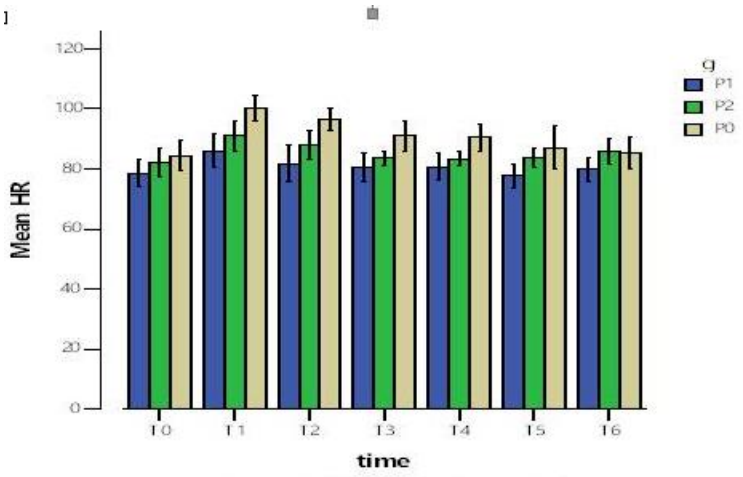

Figure 4 Comparison of HR at each time in three groups

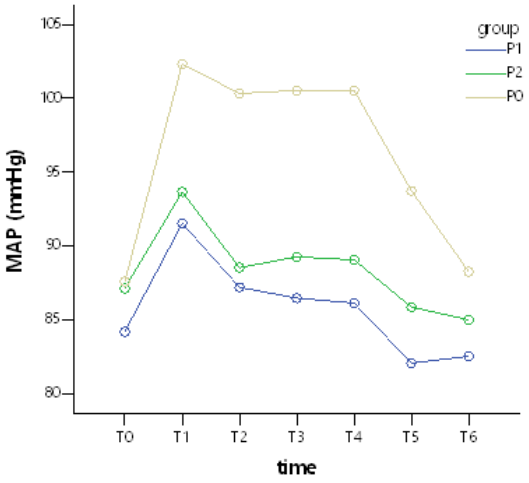

Figure 5 Change of MAP at each time in three group

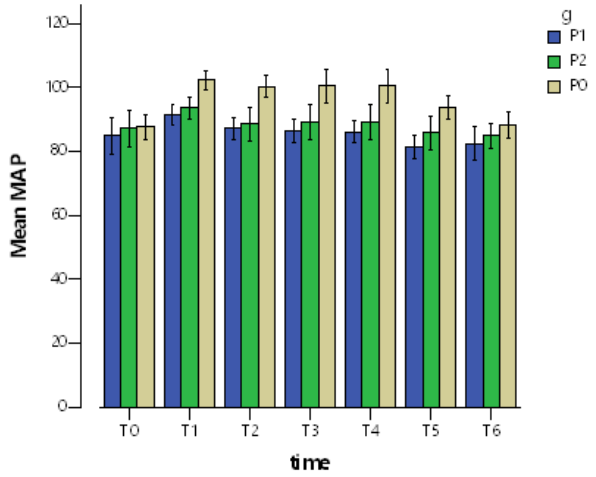

Figure 6 Comparison of MAP at each time in three groups

3.4 Changes of VAS score at different time points in the three groups

1. Compared with the group P0, the group P1 showed significantly lower VAS score at T1, T2, T3, T4, T5 and T6 ($P < 0.05$).

2. Compared with the group P0, the group P2 showed significantly lower VAS score at T1, T2, T3, T4, T5 and T6 ($P < 0.05$).

3. There were no significant differences in the changes of VAS score in the group P1 and P2 ($P > 0.05$).

Table 4 VAS score at different time points in the three groups

Group	T2	T3	T4	T5	T6
P1	3.3 ± 1.8*	2.8 ± 1.4*	2.5 ± 1.0*	2.1 ± 0.9*	1.6 ± 0.7*
P2	3.7 ± 1.4*	3.5 ± 1.2*	3.1 ± 1.1*	2.7 ± 1.2*	2.0 ± 1.2*
P0	4.8 ± 0.8	4.4 ± 0.5	4.1 ± 0.4	4.1 ± 0.4	4.1 ± 0.6

Notes: *, $P < 0.05$ compared with the P0 group.

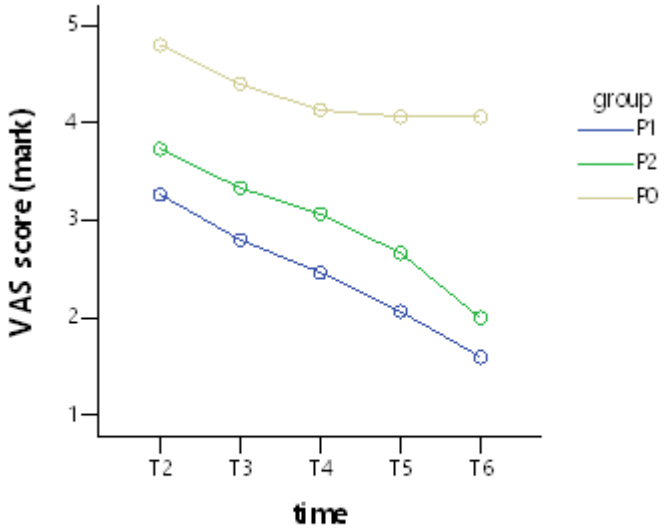

Figure 7 Change of VAS score at each time in three groups

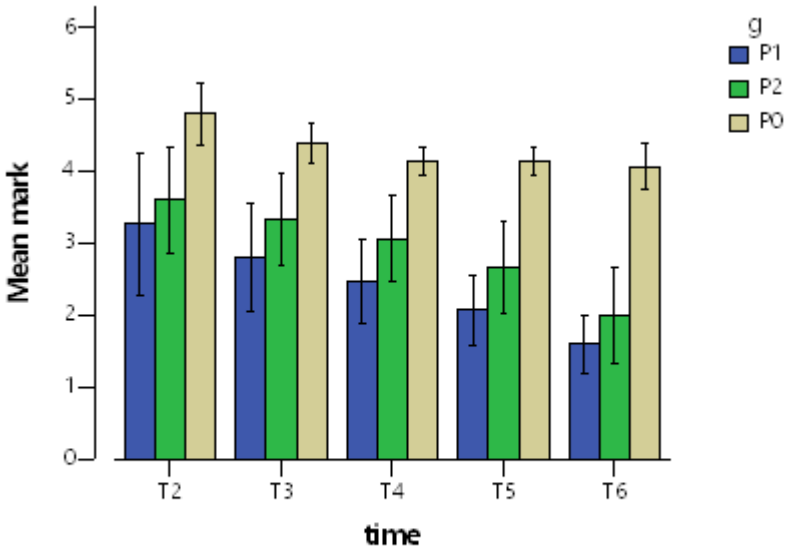

Figure 8 Comparison of VAS score at each time in three groups

3.5 24-hour analgesic effect satisfaction in the three groups

1. Compared with the group P0, the group P1 and P2 showed significantly higher 24-hour analgesic effect satisfaction ($P < 0.05$).

2. Compared with the group P2, the group P1 showed significantly higher 24-hour analgesic effect satisfaction ($P < 0.05$).

Table 5 Data on 24-hour analgesic effect satisfaction in the three groups

Group	n	24-hour analgesic effect satisfaction
P1	15	3.93 ± 0.70^{ab}
P2	15	3.13 ± 0.52^{a}
P0	15	2.27 ± 0.60

Notes: [a], $P < 0.05$ compared with the P0 group; [b], $P < 0.05$ compared with the P2 group.

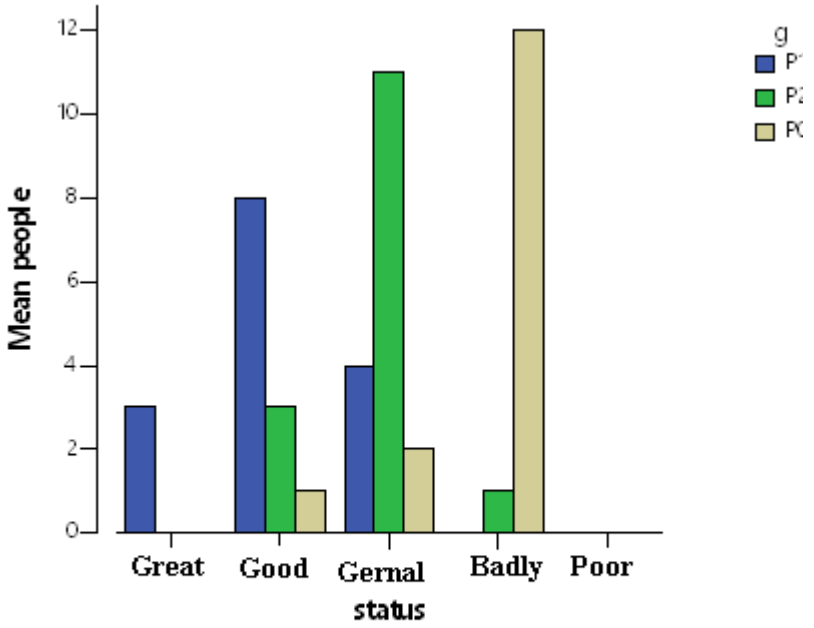

Figure 9 Comparison of 24-hour analgesic effect satisfaction in three groups

4. Discussion

With the development of China, medical endoscopic technique is progressing and more extensively applied. Compared with laparotomy, endoscopic surgery has the advantages of less trauma, faster postoperative recovery and shorter hospitalization time. Additionally, with small and inconspicuous endoscopic surgical incision, it is more welcome to patients. In particular, for patients with basic diseases, they will face more risks if receiving operations. They require rapid onset and short duration for anesthesia to maintain appropriate depth of anesthesia, and hemodynamic and respiratory stability. When selecting anesthetic drugs and adjuvant drugs, early and quick recovery and discharge of the patients is paid more attention. Currently, with the improvement of people's life quality, increasing patients demand no pain after operation and no obvious adverse reactions, greatly increasing the technical requirements of anesthesia management. However, it is inevitable to apply anesthetic drugs properly in the operation, and some adverse reactions of these drugs are inevitable. Fortunately, the use of adjuvant drugs can avoid unnecessary effects and certain adverse reactions. In this study, a reasonable time point of administration was explored through different time points of administration.

There was no significant difference in preoperative age, weight, heart rate, blood pressure and duration of operation of the patients in this study, indicating that the patients in this study were generally comparable. In order to elucidate the effect of adjuvant drugs on postoperative pain relief, the following study data excluded the use of opioids in postoperative pain relief.

Some studies believed that serum Cortisol level after surgery was significantly higher than that before surgery, which indicates that there is stress response during the operation, and the body activates the neuroendocrine system to maintain the balance of the internal environment. Stress can be divided into acute and chronic stress according to the length of its occurrence. Acute stress refers to varying degrees of changes in blood hormones through hypothalamus pituitary secretion after a sudden exposure of the body to strong and harmful stimuli, such as trauma, surgery and pain. In addition to elevated serum Cortisol level in stress response, many different hormones are affected, such as Growth hormone, ACTH, and anti-diuretic hormone (ADH). Literature has shown that the physiological response caused by stress is the body's resistance to the stress environment at that time, which is beneficial to a certain extent. However, when the physiological response caused is excessive or lasts too long, it will have an impact on individual health [9], manifested as elevated blood pressure, increased heart rate, abnormal blood glucose, gastrointestinal discomfort, and abnormal urine and mood. The individual will generate great energy and accelerate metabolism to eliminate the damage caused by stress. In turn, stress can cause excessive physiological response to the individual, which will affect the body's environmental status and health. It has been shown that serum Cortisol can directly or indirectly affect cognition and participate in emotional abnormalities, such as anxiety and depression, during stress. The hippocampal part of brain is closely related to glucocorticoids, and high levels of glucocorticoids disturb the balance of glucocorticoids and mineralocorticoids in the body under long-term or intense stress. The function of mineralocorticoids is then relatively impaired or inhibited, clinically manifested as cognitive defects caused by stress [10]. All of the above-mentioned adverse effects are caused by the stress response.

As early as the 20th century, clinical anesthesiologists have noticed the adverse effects of strong stress response on the body. Crile GW et al. [6] proposed the concept of preemptive analgesia, but there is no large-scale and systematic application in clinical practice. Preemptive analgesia is to give analgesia measures before pain stimulation, thus to reduce postoperative complications and shorten hospitalization after surgery, which is correlated to reducing the adverse or potential effects of stress on the body. There are many indicators of stress response. Research has shown that neuroticism does not affect ACTH response due to opioid receptor blockade. But in the same ACTH response, high levels of Cortisol response occur in highly neurotic individuals, which indicates that in normal groups, highly neurotic individuals already have HPA axis changes [11], and that Cortisol changes due to psychological factors such as high stress. Therefore, Cortisol and ACTH were both used as stress indicators in this study to eliminate individual neuroticism differences. In the perioperative period, human blood Cortisol concentration will increase according to the degree of surgical invasion, and the peak will be reached 24 hours after surgery. In this study, preemptive analgesia was used by giving parecoxib sodium (40 mg) at different points in the perioperative period. The results show that compared with that before anesthesia induction, the group P1 and P2 showed significantly lower serum Cortisol 30 min after extubation (Figure 1), and compared with the group P0 (556.75 ± 271.18), group P1 (348.39 ± 141.55) and P2 (324.00 ± 138.29) showed significantly lower serum Cortisol 30 min after extubation. Generally, serum Cortisol level is 116 nmol/L ~1060 nmol/L in the morning and 47 nmol/L ~458 nmol/L in the afternoon. And there was no significant difference in serum Cortisol level between the group P1 and P2. On the one hand, opioid analgesics were used in this study to block some pain and stimulation; on the other hand, parecoxib sodium was injected in the experimental groups. Because parecoxib sodium has the effect of blocking pain, and can block endogenous stimulation such as inflammation caused by tissue injury, thus improving intraoperative analgesia effect. The author speculates that the reason why the patient's serum Cortisol level increased obviously on the first day after surgery may be that the metabolism and scavenging of sedatives gradually reduce

the pain threshold of the body, and the patient feels pain and Cortisol gets high. It will be further studied in this respect with modified experiments.

Plasma ACTH was also tested as a stress indicator because serum Cortisol may change under the influence of psychological mood. The study results showed that compared with that before anesthesia induction, the group P1 and P2 showed significantly lower plasma ACTH 30 min after extubation (Figure 2), and compared with the group P0 (34.79 ± 19.52), group P1 (9.64 ± 8.75) and P2 (13.60 ± 10.02) showed significantly lower plasma ACTH 30 min after extubation. Generally, plasma ACTH level is 0 ~ 46 pg/ml. According to the research results of Tyrka AR et al. [12] and Pessina P et al. [13], Cortisol and ACTH in the body are related to each other, but cause different effects in the body. Serum Cortisol and plasma ACTH both as indicators of stress response, the former is affected by a highly neurotic environment, while the latter is not. Nevertheless, perioperative injection of parecoxib sodium can significantly reduce postoperative Cortisol and ACTH level. It is generally believed that when stimulated by severe pain, the activity of hypothalamic-pituitary-adrenal axis increases, leading to the release of various stress hormones and the increase of the content of catecholamine in the blood [5], which will accelerate the heart rate, and increase the cardiac contractility and the blood pressure. Another study showed that patients' blood glucose significantly increased after surgical stress compared with that before surgery. This study shows that patients' heart rate in P1 group at T1, T2, T3, T4, T5 and T6, and in P2 group at T1, T2, T3 and T4 were lower than that in P0 group at corresponding time points, the HR of group P1 and group P2 was lower than that of group P0, and compared with group P1, P2 group showed higher HR at T5 and T6 (Figure 3 and Table 3). Additionally, patients' MAP in P1 and P2 group at T1, T2, T3, T4 and T5 group were lower than that in P0 group at corresponding time points (Figure 5 and Table 3); compared with T0, only group P0 showed increased HR and MAP at T1, T2, T3 and T4 (Figure 3,5 and Table 3); compared with T1, group P0 showed decreased HR at T2, T3, T4, T5 and T6 and MAP at T5 and T6 (Table 3). The results in group P0 suggested hemodynamic changes or stress reactions in extubation. There was no significant difference at different time points in P1 and P2 groups, suggesting that the administration of parecoxib sodium during surgery can avoid the stress response during extubation and does not increase the risk of cardiovascular accidents. The results indicate that administration of parecoxib sodium as an auxiliary analgesic drug during perioperative period can effectively inhibit the stress response and make HR and MAP relatively stable.

Briefly summarized, perioperative single administration of parecoxib sodium (40 mg) can effectively reduce postoperative serum Cortisol and plasma ACTH, and can make HR and MAP relatively stable at tube extraction and after extubation. It is may be due to the presence of COX (COX-1, COX-2 and COX-3). COX-1 is an essential protein for maintaining physiological needs, which can promote the synthesis of prostaglandin for human physiological needs, help to maintain renal blood flow, regulate the external vascular resistance, protect stomach mucosa, and regulate platelet aggregation. COX-2, the most prominent inducible protein, is rarely seen in tissue. However, when cells are exposed to inflammatory cytokines such as endotoxin, TNF and IL-1, a large amount of COX-2 is induced, which promotes the synthesis of inflammatory PG and causes inflammatory response. The functionality of COX-3 has not yet been fully explained. At present, many scholars believe that NSAIDs plays different roles in different COXs, causing anti-inflammation, analgesia or adverse reactions [14-16].

The NSAIDs used in this study was parecoxib sodium with selective inhibition of COX-2. Its IC50 of COX-1 and COX-2 is 140 μmol/L and 0.005 μmol/L, respectively. Obviously, its selective inhibition on COX-2 is 28,000 times stronger than that on COX-1 [17]. Consequently, it can be more effective in inhibiting the synthesis of COX-2 and PGs, and in anti-inflammation and analgesia, which helps to reduce the effect of surgical stress on tissue and make postoperative serum Cortisol, plasma ACTH, HR and MAP to be relatively stable.

Pain has been defined by the International Association for the Study of Pain (IASP) as the experience of unpleasant feelings and emotions associated with potential or actual tissue injury. Although limited

to the subjects' assessment of perceived pain intensity, VAS score as a short-term pain assessment measure, is often used in clinical evaluation of pain relief measures, with advantages in convenient management and scoring [25]. Pain after extubation is usually due to shallower anesthesia, pain in the surgery incision, and prolonged localized body compression. Therefore, VAS score was used to measure the pain intensity at different time points in this study. When the VAS score > 6, the patient was given intravenous injection of Tramadol (1 ~ 1.5 mg/kg; maximum single dose of 100 mg) under the patient's analgesic requirement, which was recorded. Tramadol is a non-morphine central analgesic drug, mainly acting on the central nervous system. It activates the "analgesic system" by activating morphine receptors, used to alleviate acute and chronic pain. At the recommended dose, it is of low drug resistance and causes no respiratory inhibition or significant effect on hemodynamics. Therefore, in this study, only two patients in the P0 group required analgesia, which was of no statistical significance. The results showed that the VAS score of group P1 and P2 were lower than that of group P0 at 5 min, 15 min, 30 min, 4 h and 8 h after extubation (Table 4). It may be explained by that tissue injury induced inflammation in the operation process, and COX-2 was then induced by a variety of inflammatory cytokines, prompting the synthesis of PGs and aggravating inflammation and tissue damage [30]. Then the patients' pain threshold decreased and their sensitivity to pain increased, and that explains why the VAS score of P0 group was relatively high. In addition, the patients in the group P1 and P2 were pretreated with parecoxib sodium for analgesia, and no increase in VAS score was observed after surgery. Parecoxib sodium can reduce PGs synthesis and inhibit inflammatory damage in vivo by selectively inhibiting the expression of peripheral and central COX-2, and therefore the postoperative pain intensity was reduced or the patients' pain threshold was increased. So parecoxib sodium is a dual analgesic drug [19].

Postoperative follow-up was carried out for all the patients 24 h after the operation; postoperative pain and adverse reactions were recorded, including nausea, vomiting, coughing, dizziness, restlessness, intraoperative consciousness, sleep conditions, and postoperative analgesic measures. Then each of the patients scored for the analgesic effect satisfaction. Although it is comparatively subjective, patients' subjective feelings should not be underestimated. Because the patients' comfort after discharge depends on the doctor's management and medication skills. The results showed that there was no statistically significant difference in nausea, vomiting, cough, sleep status, and postoperative analgesia during the 24 h postoperative follow-up visit. However, it was found that the analgesia satisfaction in P1 and P2 groups was higher than that of P0 group (Table 5). According to the study made by Luscombe et al. [20] found that compared with the control group, the 1 h postoperative cough pain score in the parecoxib sodium group was significantly decreased, with no significant difference in the postoperative recovery quality score, and the parecoxib sodium group showed lower incidence of headache 24 h after surgery. The author believes that it is related to the administration of parecoxib sodium in the perioperative period, which inhibits the expression of COX-2 and increases the pain threshold.

It is controversial on the time points of preemptive analgesia in regard to the effectiveness of analgesia [21-23]. The author chooses a representative summary to express it. In 2002, Moiniche S et al. [24] found that preemptive analgesia before skin cutting was not superior to analgesic treatments after skin cutting in alleviating postoperative pain. According to the results of this study, no significant difference was found in the postoperative ACTH and Cortisol, as well as the HR and MAP at tube drawing and different time points after extubation in P1 and P2 group, but compared with the group P0, group P1 and P2 showed lower postoperative ACTH and Cortisol level, and only P0 group showed higher HR and MAP at tube drawing and 5 min, 15 min, 30 min after extubation (Figure 1, 2, 3 and 5). The results also showed that there was no significant difference in VAS score after extubation between group P1 and group P2, but the VAS score of group P0 was relatively high (Figure 7). In the 24 h postoperative follow-up visit, the analgesic effect satisfaction scores of the three groups were P1 (3.93 ± 0.70), P2 (3.13 ± 0.52), and P0 (2.27 ± 0.60), and the number of patients rated very good and good was higher in the P1 group than that in the P2 group (Figure 9). That may be related to the time of administration.

The inflammatory factors are not induced to express or stimulated before skin cutting, and the peripheral and central COX-2 has been pre-inhibited by parecoxib sodium, which enhances the tolerance of the body to stress. Although there was no significant difference in serum Cortisol, plasma ACTH, HR and MAP at 30 min after surgery, the analgesic effect satisfaction score of group P1 (3.93 ± 0.70) was higher than that of group P2 (3.13 ± 0.52). Therefore, the analgesic effect satisfaction was better with the administration of 40 mg of parecoxib sodium before skin cutting (Table 5).

In addition, a large number of literatures have shown that parecoxib sodium, which selectively inhibits COX-2, has good and accurate analgesia effect after surgery, with few adverse reactions. However, compared with traditional NSAIDs, parecoxib sodium lacks antiplatelet effect and cannot be used to prevent cardiovascular embolism. Furthermore, parecoxib sodium can inhibit prostaglandin synthesis and may lead to deterioration of kidney function and fluid retention. Therefore, when used in patients with hepatic and renal insufficiency, hypertension and cardiac insufficiency, the advantages and disadvantages should be weighed, and the situation should be closely observed.

The recommended dosage of parecoxib sodium is 40 mg for intravenous injection or slow intramuscular injection for deeper muscles. The maximum daily dose is 80 mg and it cannot be used continuously over 3 days. For the patients aging no less than 65 years or weighing less than 50 kg, the initial dose should be reduced to half of the normal dosage, with a daily maximum of 40 mg.

5. Conclusion

Through analgesic treatment at different time points in the perioperative period, this study investigated the change of postoperative serum Cortisol, plasma ACTH, hemodynamics, and VAS score, and the effect on patients' postoperative pain relief and stress response after the administration of parecoxib sodium, with the aim to find out the optimal duration of administration for patients with the lowest stress response and postoperative pain. Through the above research, the following conclusions are drawn.

1. Administration of parecoxib sodium before skin cutting or during skin suture can effectively reduce postoperative serum Cortisol and plasma ACTH of patients, indicating that both can reduce postoperative stress response.

2. Administration of parecoxib sodium before skin cutting or during skin suture can maintain the HR and MAP relatively stable at and after extubation, and provide a good and stable time for tube removal.

3. Administration of parecoxib sodium before skin cutting or during skin suture can effectively reduce VAS score within 24 h after extubation, with good analgesia effect and no obvious adverse reactions.

4. Administration of parecoxib sodium before skin cutting is not superior to the analgesic treatments during skin suture, manifested as no significant differences in serum Cortisol, plasma ACTH 30 min after surgery and 24 h VAS score, despite higher 24-hour analgesic effect satisfaction score.

6. Competing Interests

The authors declare that they have no competing interests.

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