Revista Argentina de Clínica Psicológica
2020, Vol. XXIX, N°5, 665-669
DOI: 10.24205/03276716.2020.1062

Inhibitory Effects of Parecoxib Sodium on Hyperalgesia Induced by Anesthesia using Remifentanil in Combination with Sevoflurane

Jie Zhang[a], Xinfa Liu[a], Tongtao Shen[b*]

Abstract

AIM: To evaluate the inhibitory effects of parecoxib sodium on hyperalgesia induced by anesthesia using remifentanil in combination with sevoflurane.

MATERIALS AND METHODS: A total of 180 ASA I-II patients who received laparoscopic surgery from January 2017 to February 2018 were selected and randomly divided into a control group (group A) and a parecoxib sodium group (group B) (n=90). Intravenous inhalational anesthesia was performed. The same induction method was used by both groups. Anesthesia was maintained with 0.2-0.4 μg/(kg·min) remifentanil and 1.5%-3.5% sevoflurane. For group B, 40 mg parecoxib sodium was administered intravenously before suture. Mean arterial pressure (MAP), heart rate (HR) and oxygen saturation (SpO2) before surgery (T0), after surgery (T1), upon recovery (T2), immediately after extubation (T3), 10 min after extubation (T4) and 30 min after extubation (T5), as well as postoperative recovery time, extubation time, Ramsay score, verbal rating scale (VRS) score and adverse reactions were recorded.

RESULTS: The SpO2 values of both groups hardly changed at all time points. Group B had basically the same MAP and HR values at all time points (P>0.05). The MAP and HR values of group A at T2, T3, T4 and T5 were significantly higher than those at T0 and those of group B (P<0.05). The Ramsay score upon recovery and postoperative VRS score of group B were significantly better than those of group A (P<0.05). Group B did not suffer from respiratory depression, nausea, vomiting or agitation. In contrast, group A had 1 case of nausea and vomiting, and 18 cases of agitation. The incidence rate of agitation in group A significantly exceeded that of group B (P<0.05).

CONCLUSIONS: Parecoxib sodium has significant inhibitory effects on hyperalgesia after anesthesia using remifentanil in combination with sevoflurane, without increasing adverse reactions.

Keywords: Parecoxib Sodium, Remifentanil, Sevoflurane, Hyperalgesia

1. Introduction

Pain is a common symptom and unpleasant sensation of most diseases [1]. It has been considered as the fifth vital sign after breathing, pulse, blood pressure and body temperature [2]. Particularly, postoperative pain burdens patients both physically and psychologically, also affecting their recovery [3-5]. Opioids are currently the most commonly used analgesic drugs. As the main drugs for preoperative induction, anesthetic assistance and combined general anesthesia, opioids have been widely applied to clinical practice for postoperative analgesia and chronic pain relief [6]. However, opioids may also cause acute tolerance and hyperalgesia [7].

Remifentanil is a new synthetic and ultra-short-acting μ-receptor opioid typified by fast onset, short duration of action, rapid elimination regardless of age, gender and weight, continuous infusion without accumulation and metabolism independent of liver or renal function [8]. Remifentanil is actually the first ultra-short-acting opioid which has thus been widely used for general anesthesia, postoperative analgesia and labor analgesia. Nevertheless, remifentanil also induces side effects like other opioids do, such as dose-dependent respiratory depression, intraoperative bradycardia and hypotension, thoracic wall rigidity, immediate disappearance of

[a]Department of Anesthesiology, The Hospital Affiliated to Medical School of Yangzhou University (Taizhou People's Hospital), Taizhou 225300, Jiangsu Province, P. R. China
[b]Department of Anesthesiology, Affiliated Hospital of Yangzhou University, Yangzhou 225001, Jiangsu Province, P. R. China
**Corresponding Author: Tongtao Shen*

analgesic effects after withdrawal, and risk of acute postoperative hyperalgesia [9]. Until now, the relationship of remifentanil with postoperative secondary hyperalgesia has attracted widespread attention.

Parecoxib sodium is a highly selective cyclooxygenase-2 (COX-2) inhibitor that can suppress both central and peripheral COX-2 expressions and reduce corresponding prostaglandin synthesis, thereby exerting analgesic and anti-inflammatory effects, alleviating hyperalgesia and inducing mild side effects [10,11]. Due to rapid onset and long duration of action, parecoxib sodium even has stronger analgesic effects than those of morphine [12-14]. Parecoxib sodium should be used before the analgesic effects of opioids disappear, because it cannot antagonize the roles of prostaglandin-like algogenic substances that already exist, failing to mitigate sensible pain. Therefore, we herein focused on the inhibitory effects of parecoxib sodium on hyperalgesia after anesthesia by using remifentanil plus sevoflurane.

2. Materials and Methods

BASELINE CLINICAL DATA

This study has been approved by the ethics committee of our hospital, and written consent has been obtained from all patients. A total of 180 ASA I-II patients who received laparoscopic surgery from January 2017 to February 2018 were selected, including 99 males and 81 females aged between 20 and 58 years old. Their BMI values ranged from 23.21 to 26.79 kg/m^2. All patients did not suffer from cardiovascular and respiratory diseases, or contraindications for parecoxib sodium. There were 66 cases of laparoscopic cholecystectomy, 63 cases of laparoscopic gynecologic surgery, 27 cases of laparoscopic hernia repair and 24 cases of laparoscopic varicocele ligation. They were randomly divided into a control group (group A) and a parecoxib sodium group (group B) (n=90).

ANESTHESIA METHODS

Intravenous inhalational anesthesia was performed for both groups. Anesthesia induction was conducted using 0.05 mg/kg midazolam, 2 mg/kg propofol, 1 μg/kg remifentanil (batch No. H20180197, Yichang Renfu Pharmaceutical Co., Ltd., China) and 0.6 mg/kg atracurium. Mechanical ventilation was carried out after endotracheal intubation to maintain the end-tidal partial pressure of carbon dioxide at 35-45 mmHg. Anesthesia was maintained with 0.2-0.4 μg/(kg·min) remifentanil and 1.5%-3.5% sevoflurane, and atracurium was intermittently administered to keep muscle relaxation. Sevoflurane administration was stopped before suture, and remifentanil was continuously pumped until the end of surgery. For group B, 40 mg parecoxib sodium (batch No. J20180045, Hisun Pfizer Pharmaceutical Co., Ltd., China) was intravenously injected 20 min before the end of surgery. After surgery, the patients were sent to the recovery room and extubated after they woke up. After extubation, the patients were observed for 30 min and inquired of pain state. No patient used antagonists, wake-up drugs or analgesic pump.

DETECTION INDICES

After entering the operating room, all patients were routinely monitored for mean arterial pressure (MAP), electrocardiogram and oxygen saturation (SpO_2). The wake-up time and extubation time were recorded. Ramsay sedation scoring: 1 point, unrest and irritability; 2 points, quiet cooperation; 3 points, sleepiness but being able to obey instructions; 4 points, sleep state but being able to be woken up; 5 points, respiratory retardation; 6 points, deep sleep state while being unable to be woken up. 2~4 points: Appropriate sedation; 5~6 points: excessive sedation. Verbal rating scale (VRS) scoring: 0 point, no pain; 1-point, mild pain; 2 points, moderate pain; 3 points, severe pain. The incidence rates of adverse reactions during recovery were recorded. MAP, heart rate (HR) and SpO_2 were recorded before surgery (T0), after surgery (T1), upon recovery (T2), immediately after extubation (T3), 10 min after extubation (T4) and 30 min after extubation (T5).

STATISTICAL ANALYSIS

All data were analyzed by SPSS 16.0 software, and subjected to normal distribution and variance homogeneity tests. The categorical data were expressed as mean ± standard deviation, and intergroup comparisons were performed by the independent-samples t test. The numerical data were represented as percentage, and intergroup comparisons were conducted with the χ^2 test. $P<0.05$ was considered statistically significant.

3. Results

BASELINE CLINICAL DATA

The two groups had similar age, BMI, gender ratio, surgical type, surgical time, postoperative recovery time, extubation time and dose of remifentanil ($P>0.05$) (Table I).

Table 1. **Baseline clinical data.**

	Group A (n=90)	Group B (n=90)	t/χ^2	*P*
Age (year)	48.79±5.47	49.02±5.51	0.281	0.779
BMI (kg/m^2)	24.28±2.31	24.41±2.29	0.379	0.705
Gender			0.023	0.879
Male	54 (60.00)	55 (61.11)	*	
Female	36 (40.00)	35 (38.89)		
Surgical type			0.780	0.854
Laparoscopic cholecystectomy	34 (37.78)	32 (35.56)	*	
Laparoscopic gynecologic surgery	32 (35.56)	31 (34.44)		
Laparoscopic hernia repair	14 (15.56)	13 (14.44)		
Laparoscopic varicocele ligation	10 (11.10)	14 (15.56)		
Surgical time (min)	53.27±8.27	53.52±7.98	0.206	0.837
Recovery time (min)	8.29±2.34	8.31±2.28	0.058	0.954
Extubation time (min)	12.76±3.15	12.88±3.14	0.256	0.799
Dose of remifentanil (μg)	865.42±45.32	871.24±46.27	0.852	0.395

*χ^2 test

MAP, HR AND SpO_2 VALUES AT DIFFERENT TIME POINTS

The SpO_2 values of both groups hardly changed at all time points. Group B had basically the same MAP and HR values at all time points (P>0.05). The MAP and HR values of group A at T2, T3, T4 and T5 were significantly higher than those at T0 and those of group B (P<0.05) (Table II).

Table 2. **MAP, HR and SpO_2 values at different time points.**

	Group A (n=90)	Group B (n=90)
MAP (mmHg)		
T0	86.13±8.18	86.47±8.22
T1	83.78±8.02	83.81±7.92
T2	98.37±8.57*, #	87.34±7.65
T3	101.27±8.24*, #	88.29±6.73
T4	103.29±7.95*, #	87.96±6.43
T5	99.08±8.04*, #	86.98±6.52
F_{time}	35.187	
P_{time}	<0.001	
$F_{intergroup}$	26.546	
$P_{intergroup}$	<0.001	
HR (bpm)		
T0	79.28±5.29	79.84±5.36
T1	72.78±5.46	76.27±4.39
T2	99.67±6.71*, #	80.98±4.46
T3	102.42±7.01*, #	82.19±5.02
T4	104.89±7.25*, #	83.27±5.11
T5	102.19±7.09*, #	84.23±4.96
F_{time}	182.28	
P_{time}	<0.001	
$F_{intergroup}$	134.27	
$P_{intergroup}$	<0.001	
SpO_2 (%)		
T0	98.89±0.29	99.01±0.28
T1	99.29±0.43	98.87±0.29
T2	99.37±0.23	99.17±0.21
T3	98.98±0.22	99.34±0.22
T4	99.34±0.28	98.45±0.23
T5	99.56±0.23	99.36±0.24
F_{time}	0.768	
P_{time}	0.326	
$F_{intergroup}$	0.548	
$P_{intergroup}$	0.492	

RAMSAY AND VRS SCORES

The Ramsay score upon recovery and postoperative VRS score of group B were significantly better than those of group A (P<0.05) (Table III).

Table 3. **Ramsay and VRS scores.**

	Group A (n=90)	Group B (n=90)	t	*P*
Ramsay score (point)	1.72±0.35	2.65±0.41	16.367	0.779
VRS score (point)	2.34±0.40	0.79±0.12	35.211	<0.001

POSTOPERATIVE RESPIRATORY DEPRESSION, NAUSEA, VOMITING OR AGITATION

Group B did not suffer from respiratory depression, nausea, vomiting or agitation. In contrast, group A had 1 case of nausea and vomiting, and 18 cases of agitation. The incidence rate of agitation in group A significantly exceeded that of group B (P<0.05) (Table IV).

Table 4. **Postoperative respiratory depression, nausea, vomiting or agitation.**

	Group A (n=90)	Group B (n=90)	χ^2	*P*
Respiratory depression	0 (0.00)	0 (0.00)	0.000	1.000
Nausea and vomiting	1 (1.11)	0 (0.00)	1.006	0.316
Agitation	18 (20.00)	0 (0.00)	20.000	<0.001

4. Discussion

Hyperalgesia can be defined as the excessively nociceptive response to invasive or non-invasive stimuli caused by damage or inflammation of the peripheral tissues. This kind of paresthesia is characterized by decreased pain threshold or hypersensitivity to normal pain stimuli and is usually divided into two subtypes, i.e. primary hyperalgesia and secondary hyperalgesia [15]. Peripheral nociceptors are sensitized so that normal low-intensity stimuli that should not cause pain can also cause pain, and this situation is called primary hyperalgesia. Secondary hyperalgesia occurs when the central nociceptors are sensitized. In cases of tissue damage, the response to normal harmless stimuli is enhanced (touch-induced pain, or allodynia). The enhanced response is caused by not only mechanical and thermal stimuli from the injured areas (primary hyperalgesia), but also by mechanical stimuli from the undamaged areas around the damaged ones (secondary hyperalgesia). These changes result from increased excitability of neurons in the dorsal horn of the spinal cord after injury, i.e. central sensitization. Spontaneous pain at the operative site and the primary mechanical hyperalgesia might be more closely related to acute pain [16] Researches have verified that hyperalgesia induced by high-dose opioid drugs is closely related to their pharmacokinetics. Remifentanil has a rapid onset and fades quickly, and it is more likely to result in hyperalgesia [17]. Our study showed that the pain score of group A after remifentanil anesthesia was significantly higher than that of group B even in minimally invasive laparoscopic surgeries. Among the pain-generating inflammatory factors, prostaglandins, which are called pain amplifiers, play an important role in the transmission of pain sense in spinal cord and are involved in the production of hyperalgesia [18]. Prostaglandins can stimulate the release of substance P by activating or dissimilating ions into cells and lead to the imbalance of the transmitter in normal sensory processes. Parecoxib sodium belongs to selective COX-2 inhibitor and has fast onset and long-lasting analgesic effect. It works 7-13 min after a single intravenous injection of 40 mg and lasts for 6-12 h, with strong analgesic effect. Compared with traditional non-selective COX-2 inhibitors, it can significantly reduce the incidence of gastrointestinal reactions, and does not affect platelet aggregation and coagulation time. Now it has been widely used in clinics [19].

Tröster et al. reported that preventive usage of 40 mg of parecoxib sodium prevented hyperalgesia in (71.3 ± 7) % of cases administrated with remifentanil at 0.1 μg/(kg·min), while the placebo only worked in (46.4 ± 17) % of cases [20]. Herein, intravenous injection of 40 mg of parecoxib sodium before the end of operations effectively inhibited the hyperalgesia induced by remifentanil anesthesia of 0.2-0.4 μg/(kg·min) and insure stable vital signs and high quality of post-anesthesia wake-up. It did not increase adverse reactions such as respiratory depression, nausea, emesis and agitation, and did not prolong the recovery and extubation time. Parecoxib sodium suppresses hyperalgesia by inhibiting the expression of peripheral COX-2 and decreasing the synthesis of peripheral prostaglandins, thus exerting analgesic

and anti-inflammatory effects. It also inhibits the expression of central COX-2 and reduces the synthesis of central prostaglandins, being capable of both peripheral and central analgesia [21].

5. Conclusions

In summary, intravenous injection of 40 mg of parecoxib sodium before the end of surgery effectively inhibited hyperalgesia induced by remifentanil withdrawal without increasing adverse reactions. The patients recovered quickly and had stable hemodynamics. Hence, parecoxib sodium may be safely applied in clinical practice.

References

[1] Fernández DM, Wagner S, Kalinowski M, et al.: Naming the pain in requirements engineering. Empir Softw Eng, 2017; 22(5):2298-338.

[2] Purser L, Warfield K, Richardson C: Making pain visible: an audit and review of documentation to improve the use of pain assessment by implementing pain as the fifth vital sign. Pain Manag Nurs, 2014; 15(1):137-42.

[3] Højer Karlsen AP, Geisler A, Petersen PL, Mathiesen O, Dahl JB: Postoperative pain treatment after total hip arthroplasty: a systematic review. Plos One, 2015; 156(1):8-30.

[4] Hinther A, Nakoneshny SC, Chandarana SP, Wayne Matthews T, Dort JC: Efficacy of postoperative pain management in head and neck cancer patients. J Otolaryngol Head Neck Surg, 2018; 47(1):29.

[5] Chapman CR, Vierck CJ: The Transition of Acute Postoperative Pain to Chronic Pain: An Integrative Overview of Research on Mechanisms. J Pain, 2017; 18(4):359.e1-38.

[6] Dowell D, Haegerich TM, Chou R: CDC Guideline for Prescribing Opioids for Chronic Pain--United States, 2016. JAMA, 2016; 315(15):1624-45.

[7] Kim SH, Stoicea N, Soghomonyan S, Bergese SD: Intraoperative use of remifentanil and opioid induced hyperalgesia/acute opioid tolerance: systematic review. Front Pharmacol, 2014; 5:108.

[8] Kamata M, Tobias JD: Remifentanil: applications in neonates. J Anesth, 2016; 30(3):449-60.

[9] Koppert W, Sittl R, Scheuber K, Alsheimer M, Schmelz M, Schüttler J: Differential modulation of remifentanil-induced analgesia and postinfusion hyperalgesia by S-ketamine and clonidine in humans. Anesthesiology, 2003; 99(1):152-9.

[10] Luscombe KS, Mcdonnell NJ, Muchatuta NA, Paech MJ, Nathan EA: A randomised comparison of parecoxib versus placebo for pain management following minor day stay gynaecological surgery. Anaesth Intensive Care, 2010; 38(1):141-8.

[11] Reuben, Scott S: Update on the role of nonsteroidal anti-inflammatory drugs and coxibs in the management of acute pain. Curr Opin Anaesthesiol, 2007; 20(5):440-50.

[12] Watanabe T, Minakami H, Sakata Y, et al.: Effect of labor on maternal dehydration, starvation, coagulation, and fibrinolysis. J Perinat Med, 2001; 29(6):528-34.

[13] Glass PS, Gan TJ, Howell S: A review of the pharmacokinetics and pharmacodynamics of remifentanil. Anesth Analg, 1999; 89(4 Suppl):7-14.

[14] Beers R, Camporesi E: Remifentanil update: clinical science and utility. CNS Drugs, 2004; 18(15):1085-104.

[15] Fletcher D, Martinez V: Opioid-induced hyperalgesia in patients after surgery: a systematic review and a meta-analysis. Br J Anaesth, 2014; 112(6):991-1004.

[16] Crile GW: The kinetic theory of shock and its prevention through anoci-association (shockless operation). Lancet, 1913; 182(4688):7-16.

[17] Gupta A, Fant F, Axelsson K, et al.: Postoperative analgesia after radical retropubic prostatectomy: a double-blind comparison between low thoracic epidural and patient-controlled intravenous analgesia. Anesthesiology, 2006; 105(4):784-93.

[18] Richebé P, Rivat C, Laulin JP, Maurette P, Simonnet G: Ketamine improves the management of exaggerated postoperative pain observed in perioperative fentanyl-treated rats. Anesthesiology, 2005; 102(2):421-8.

[19] Noveck RJ, Laurent A, Kuss M, Talwalker S, Hubbard RC: Parecoxib Sodium does not Impair Platelet Function in Healthy Elderly and Non-Elderly Individuals. Clin Drug Invest, 2001; 21(7):465-76.

[20] Tröster A, Sittl R, Singler B, Schmelz M, Schüttler J, Koppert W: Modulation of remifentanil-induced analgesia and postinfusion hyperalgesia by parecoxib in humans. Anesthesiology, 2006; 105(5):1016-23.

[21] Luan YH, Wang D, Yu Q, Chai XQ: Action of β-endorphin and nonsteroidal anti-inflammatory drugs, and the possible effects of nonsteroidal anti-inflammatory drugs on β-endorphin. J Clin Anesth, 2017; 37:123-8