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Article

Effects of oxycodone hydrochloride and dezocine on hemodynamics and levels of inflammatory factors in patients receiving gynecological laparoscopic surgery under general anesthesia

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We aimed to compare the effects of oxycodone hydrochloride and dezocine on hemodynamics and inflammatory factors in patients receiving gynecological laparoscopic surgery under general anesthesia. A total of 246 patients were divided into group A and B (n=123). Hemorheology indices were recorded 5 min after anesthesia (T0), 1 min after pneumoperitoneum (T1), when position was changed 5 min after pneumoperitoneum (T2), 15 min after pneumoperitoneum (T3), 1 min (T4) and 5 min (T5) after position was restored. Visual analogue scale scores 1, 2, 6, 12, 24 and 48 h after operation were recorded. Postoperative adverse reactions and visceral pain were observed. The expression levels of inflammatory factors were detected by enzyme-linked immunosorbent assay 12 h after operation. Compared with group A, group B had higher heart rate and mean arterial pressure at T2, lower central venous pressure and cardiac output at T1-T3, and higher systemic vascular resistance at T1-T5 ($P<0.05$). The incidence rate of pain syndrome in group A was lower ($P<0.05$). Group A had lower tumor necrosis factor-alpha and interleukin-6 expression levels and higher interleukin-10 level than those of group B ($P<0.05$). For gynecological laparoscopic surgery, oxycodone preemptive analgesia has superior outcomes to those of dezocine.

Keywords: Gynecological laparoscopic surgery. Oxycodone hydrochloride. Dezocine. Hemodynamics. Inflammatory factor.

INTRODUCTION

Due to small trauma in gynecological laparoscopic surgery, postoperative pain is relatively mild, but the visceral pain caused by intraoperative traction and injury is inevitable. Intra-abdominal injury secondary to hysterectomy or ovariectomy, and shoulder pain induced by abdominal wall expansion because of pneumoperitoneum or sub-diaphragmatic stimulation can easily lead to adverse reactions such as agitation during recovery and respiratory depression, seriously affecting the patients' postoperative recovery. Although opioid analgesics exert analgesic effects, they may inhibit the respiratory center and aggravate the adverse reactions during recovery (Cho *et al.*, 2019; Aktan, Akbayrak, 2020). As a new opioid analgesic, oxycodone is a semi-synthetic pure opioid receptor agonist, which acts on the central nervous system and smooth muscle. It can well suppress agitation during recovery, with sedative and anti-anxiety effects (Park *et al.*, 2015; Zhao *et al.*, 2020). Oxycodone is a μ and κ receptor agonist, and its effect on relieving visceral pain is superior to that of a simple receptor agonist. Besides, dezocine is a novel mixed-type opioid receptor agonist, with equivalent role to

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that of morphine in treating acute nociceptive pain and few adverse reactions (Wang *et al*., 2017). Preemptive analgesia is to take measures before the noxious stimulus occurs, and to delay inflammatory stress response through reducing the expressions of inflammatory factors (Zhou *et al*., 2018; Zhu *et al*., 2019). In this study, therefore, the effects of oxycodone hydrochloride and dezocine on the preemptive analgesia of gynecological laparoscopic surgery were compared, aiming to provide new ideas for the clinical selection of appropriate anesthesia methods.

MATERIAL AND METHODS

General information

Sample size was estimated according to $N=4[\frac{(Z_{A/2}+Z_{A}}{ä}]^2$, where N is the number of required samples, $Z_{\alpha/2}$ is 1.96 (Z value corresponding to α=0.05), Zβ is 0.84 (Z value corresponding to type II error probability β which is 0.20), and δ is 0.6 (allowable error). N was calculated as 87, so no fewer than 87 cases should be included in each group.

A total of 246 patients scheduled to undergo gynecological laparoscopic surgery in our hospital from January 2019 to November 2020 were prospectively selected. Inclusion criteria: (1) Patients with preoperative American Society of Anesthesiologists grade I-II; (2) those aged 20-56 years old; (3) those undergoing laparoscopic ovarian cyst removal. Exclusion criteria: (1) Patients with severe diseases in the heart, liver or lung; (2) those with history of opioid allergy; (3) those complicated with diabetes mellitus or hyperglycemia; (4) those unable to cooperate due to severe mental disorders; (5) pregnant or lactating woman. The patients were divided into group A and group B (n=123) according to the odd/even number of visits. In group A, the patients were aged 21-55 years old, with an average of (38.5±3.8) years old; the body weight was 46-76 kg, with an average of (62.7±6.5) kg. In terms of educational level, there were 36 cases of junior high school or below, 60 cases of senior high school, and 27 cases of junior college or above. In group B, the patients were aged 20-56 years old, with an average of (39.2±3.5) years old; the body weight was 45-77 kg, with an average of (62.5±6.4) kg. In terms of educational level, there were 33 cases of junior high school or below, 57 cases of senior high school, and 33 cases of junior college or above. The two groups had similar baseline clinical data such as age, body weight and educational level (P>0.05), and they were comparable. The research protocol was approved by the medical ethics committee of our hospital on December 2nd, 2018 (approval No. LL20181202823), and all patients were informed and signed the informed consent.

METHODS

The patients were deprived of food for 12 h and water for 8 h before operation. After the patients entered the operating room, the venous channel was opened, and the blood pressure, heart rate (HR), pulse oxygen saturation (SpO_2), partial pressure of end-tidal carbon dioxide [$P(CO_2)$] and bispectral index (BIS) were monitored. Target-controlled infusion of propofol and remifentanil was used for anesthesia and induction (BCP-100 infusion pump, Beijing Slgo Medical Technology Co., Ltd., China). After the loss of consciousness through anesthesia induction, vecuronium bromide was injected intravenously at 0.1 mg/kg, followed by tracheal intubation for mechanical ventilation (tidal volume: 6.8 mL/kg, respiratory rate: 12-15 times/min, inspiration/expiration ratio: 1:1.5-1:2), and $P(CO_2)$ was kept at 35-45 mmHg (1 mmHg=0.133 kPa). During operation, the target concentrations of propofol and remifentanil were adjusted according to the patients' conditions, vecuronium bromide was injected intermittently to maintain muscle relaxation, and BIS was maintained at 40-60. At 1 h before the end of operation, the administration of muscle relaxant was stopped, and intravenous anesthesia was terminated at an appropriate time according to the operation conditions. At 10 min before pneumoperitoneum, group A was given oxycodone at 0.1 mg/kg, and group B was given dezocine at 0.1 mg/kg. Before extubation, the effect of muscle relaxant was antagonized (1 mg of neostigmine + 0.55 mg of atropine) when necessary. When intraoperative HR was lower than 50 times/min, the target concentration of remifentanil was reduced or atropine was intravenously injected. When the systolic blood pressure was lower than 80 mmHg, the target concentration of propofol was reduced or vasopressors were used. At 20 min before the end of operation, 5 mg of tropisetron was applied for both groups.

Observation indices

(1) Preoperative blood biochemical test: 3 mL of fasting peripheral blood was drawn the next morning after admission, and then liver function, kidney function and blood glucose were detected. (2) Intraoperative recording of hemorheology indices: HR, mean arterial pressure (MAP), central venous pressure (CVP), systemic vascular resistance (SVR) and cardiac output (CO) were recorded at 5 min after anesthesia (T0), 1 min after pneumoperitoneum (T1), when the position was changed at 5 min after pneumoperitoneum (T2), 15 min after pneumoperitoneum (T3), 1 min (T4) and 5 min (T5) after the position was restored. The incidence of adverse reactions such as arrhythmia, hypercapnia, subcutaneous emphysema, air embolism and postoperative nausea and vomiting was observed and recorded. (3) Evaluation of analgesic effect: The visual analogue scale (VAS) score (0 point: no pain, 10 points: the severest pain) was recorded in the resting state, and that upon admission was used as the basic control value. The VAS score of resting pain and dynamic pain was also recorded at 1, 2, 6, 12, 24 and 48 h after operation. The occurrence of adverse reactions and pain syndrome after laparoscopic surgery was observed. None of VAS evaluators knew the analgesia plan or clinical indices of patients. (4) Detection of serum inflammatory factors: 5 mL of peripheral blood was collected at the equivalent analgesia scoring point 12 h after operation, and centrifuged. The supernatant was collected and stored at 4°C. Then the serum levels of tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), IL-8, IL-10 and transforming growth factor-beta (TGb-β) were detected using enzyme-linked immunosorbent assay kits according to the instructions.

Statistical analysis

SPSS 23.0 software was used for statistical analysis. Measurement data were expressed as mean ± standard deviation, and the independent *t* test was performed for intergroup comparison. Intergroup comparisons at multiple time points were conducted by the repeated measures analysis of variance. First, the intergroup differences and the differences of measured values at each time point were analyzed. If there were differences, the independent-sample t test was used to compare the intergroup differences at each time point, and the SNK-q test was employed to compare the time differences of each group. The χ^2 test was performed for intergroup comparison of numerical data. $P<0.05$ suggested statistically significant difference.

RESULTS

Surgical indices

There were no significant differences in systolic blood pressure, diastolic blood pressure, fasting plasma glucose, aspartate aminotransferase, alanine aminotransferase, creatinine, pneumoperitoneum time, operation time and intraoperative blood loss between the two groups ($P>0.05$) (Table I).

TABLE I - Surgical indices

Item	Group A (n=123)	Group B (n=123)	P
SBP (mmHg)	114.89±11.24	112.38±12.02	0.298
DBP (mmHg)	74.5±5.4	74.6±4.9	0.387
FPG (mmol/L)	4.93±0.45	4.96±0.43	0.557
AST (U/L)	20.51±2.34	20.64±2.13	0.893
ALT (U/L)	14.29±2.13	14.89±2.03	0.743
Creatinine (μmol/L)	62.38±6.23	61.28±6.24	0.872

TABLE I - Surgical indices

Item	Group A (n=123)	Group B (n=123)	P
Pneumoperitoneum time (min)	83.49±5.84	83.56±5.79	0.388
Operation time (min)	100.29±11.23	101.43±10.27	0.754
Intraoperative blood loss (mL)	245.37±18.27	243.28±17.24	0.543
P(CO_2) (mm Hg)	43.37±1.32	43.56±1.28	0.893

ALT: alanine aminotransferase; AST: aspartate aminotransferase; DBP: diastolic blood pressure; FPG: fasting plasma glucose; P(CO2): partial pressure of end-tidal carbon dioxide; SBP: systolic blood pressure.

VAS scores at different time points

The two groups had similar VAS scores at different time points (P>0.05) (Table II).

TABLE II - VAS scores at different time points

Item	Time	Group A (n=123)	Group B (n=123)	P
VAS in a resting state	1 h	3.38±0.45	3.43±0.49	0.374
	2 h	3.13±0.38	3.20±0.39	0.445
	6 h	2.99±0.39	3.03±0.37	0.782
	12 h	2.43±0.34	2.51±0.32	0.893
	24 h	1.65±0.29	1.76±0.24	0.473
	48 h	0.98±0.13	1.04±0.21	0.507
VAS in a motion state	1 h	4.99±0.45	5.02±0.44	0.662
	2 h	4.71±0.39	4.95±0.38	0.483
	6 h	4.41±0.43	4.47±0.39	0.489
	12 h	3.73±0.56	3.85±0.42	0.783
	24 h	1.92±0.34	1.95±0.35	0.823
	48 h	1.49±0.34	1.50±0.33	0.745

VAS: Visual analogue scale.

Intraoperative hemodynamic indices

HR, MAP and SVR significantly increased in the two groups at T1-T3 compared with those at T0 (P<0.05). CVP significantly rose in the two groups at T2, while it significantly declined in group B at T1 and T3 (P<0.05). CO significantly declined in the two groups at T1-T3 (P<0.05). Compared with group A, group B had significantly higher HR and MAP at T1 and T2, lower CVP and CO at T1-T3, and higher SVR at T1-T5 (P<0.05). No patients suffered from hypercapnia, subcutaneous emphysema or air embolism (Table III).

TABLE III - Intraoperative hemodynamic indices

Item	Group	Case No.	T0	T1	T2	T3	T4	T5
HR (bpm)	A	123	79.82±5.48	100.76±6.18*	97.45±5.43*	99.43±4.89*	77.48±4.32	76.84±4.38
	B	123	80.42±4.32	104.72±5.94*#	105.42±5.02*#	99.79±4.58*	79.75±4.45	78.92±4.35
MAP (mmHg)	A	123	75.44±4.53	83.74±5.02*	83.29±5.11*	85.89±5.23*	75.43±4.76	74.38±4.82
	B	123	74.98±4.49	88.96±4.52*#	88.84±4.67*#	88.62±4.63*	75.74±4.72	76.24±4.76
CVP (cmH_2O)	A	123	6.69±0.67	6.49±0.63	6.95±0.54*	6.75±0.63	6.41±0.57	6.92±0.61
	B	123	6.58±0.71	5.89±0.59*#	6.32±0.52*#	6.10±0.56#	7.11±0.58	6.85±0.60
SVR (DNS/S·CM5)	A	123	998.28±89.28	1623.38±102.38*	1712.34±113.24*	1536.78±123.28*	965.43±67.32	922.35±91.23
	B	123	1000.22±90.24	2019.26±103.45*#	2267.39±115.27*#	1649.28±131.29*#	1016.34±71.26#	1094.56±94.32#
CO (L/min)	A	123	6.22±0.58	5.75±0.62*	5.85±0.49*	5.87±0.51*	6.23±0.61	6.33±0.73
	B	123	6.24±0.61	5.67±0.59*#	5.57±0.51*#	5.49±0.49*#	6.19±0.59	6.14±0.62

CO: Cardiac output; CVP: central venous pressure; HR: heart rate; MAP: mean arterial pressure; SVR: systemic vascular resistance. *P<0.05 *vs.* T0, #P<0.05 *vs.* group A.

Levels of serum inflammatory factors

After operation, group A had lower serum levels of TNF-α and IL-6 (P<0.05) and higher level of IL-10 than those of group B (P<0.05). The two groups had similar expression levels of IL-8 and TGb-β (P>0.05) (Table IV).

TABLE IV - Levels of serum inflammatory factors (ng/mL)

	TNF-α	IL-6	IL-8	IL-10	TGb-β
Group A (n=123)	42.09±4.89	16.27±1.23	24.67±2.36	20.78±3.28	42.31±4.32
Group B (n=123)	49.27±4.92	20.78±1.25	25.09±2.42	17.64±3.24	41.92±4.32
P	<0.001	<0.001	0.873	<0.001	0.192

IL: Interleukin; TGb: transforming growth factor; TNF: tumor necrosis factor.

Incidence of adverse reactions

The two groups had similar numbers of cases with adverse reactions including nausea, dizziness, fever and pruritus (P>0.05). The incidence rate of pain syndrome after laparoscopic surgery in group A was significantly lower than that of group B (P<0.05) (Table V).

TABLE V - Adverse reactions and pain syndrome after laparoscopic surgery (n)

Group	Adverse reaction				Pain syndrome after laparoscopic surgery	
	Nausea	Dizziness	Fever	Pruritus	Shoulder pain	Abdominal pain
Group A (n=123)	30	9	5	6	13	17
Group B (n=123)	29	11	4	6	29	33
P	0.983	0.873	0.287	1.000	<0.001	<0.001

DISCUSSION

Pneumoperitoneum during gynecological laparoscopic surgery leads to postoperative shoulder pain, sub-diaphragmatic and abdominal pain which are all moderate pain and important factors affecting the patients' hospital stay and recovery (Sao *et al.*, 2019; Korolkiewicz *et al.*, 2020). Dezocine is an opioid receptor agonist-antagonist, which exerts agonistic effects on κ receptors and partial agonistic effects on μ receptors, without typical μ receptor dependence (Li *et al.*, 2019). Oxycodone hydrochloride is a mixed-type opioid receptor agonist, with agonistic effects on both κ and μ receptors. It works mainly for the central nervous system and smooth muscle, which is more effective for treating visceral pain than other potent opioids. Visceral pain is the dominant pain after gynecological laparoscopic surgery (Kucharz *et al.*, 2015).

In this study, the VAS score in the resting state and motion states at different time points of oxycodone group were slightly better than those of dezocine group, indicating that the two drugs had similar analgesic effects. The incidence rate of adverse reactions had no significant difference between the two groups, but there were significantly fewer cases of shoulder pain and abdominal pain in oxycodone group than those in dezocine group, suggesting that the therapeutic effect of oxycodone on visceral pain and pain syndrome after laparoscopic surgery surpassed that of dezocine, which may be related to the distribution and bioavailability of oxycodone (Kim *et al.*, 2015). Moreover, dezocine group had significantly higher HR, MAP and SVR, but significantly lower CO than those of oxycodone group at T1 and T2. Probably, the diaphragm caused by intraoperative pneumoperitoneum, intraoperative peritoneal traction and visceral pain easily resulted in significant hemodynamic changes. CO_2 pneumoperitoneum can increase myocardial oxygen consumption and even cause myocardial ischemia, thus inducing adverse cardiovascular reactions in the perioperative period. Meanwhile, pneumoperitoneum increases plasma catecholamine, renin-angiotensin, vasopressin and prostaglandin, thus causing peripheral vasoconstriction, which is related to the visceral pain induced by mechanical compression. Hence, oxycodone was more effective for treating the visceral pain caused by pneumoperitoneum than dezocine, which may be related to the short onset time of oxycodone.

In this study, the equivalent VSA score was used as the baseline, and the expressions of serum inflammatory factors in the two groups were compared after gynecological laparoscopic surgery, aiming to compare the effects of the two drugs on postoperative inflammatory stress response. Inflammatory factors, which are classified into pro-inflammatory and anti-inflammatory factors, compete and keep relatively balanced (Cicchese *et al.*, 2018). Pain can promote the increase in pro-inflammatory factors, and inhibit anti-inflammatory factors, further leading to inflammatory stimuli and cascades (Kuffler, 2020). Inflammatory response, as a cascade reaction controlled by multiple mechanisms of pro-inflammatory and anti-inflammatory factors, causes non-specific damage to human tissues. Pro-inflammatory cytokines include TNF-α, IL-6 and IL-8, while anti-inflammatory factors include IL-10 and TGb-β (Han *et al.*, 2019). Given that the inflammatory cascade peaks at 12 h after operation (Laughlin *et al.*, 2020), the research time

point was selected at 12 h after operation in this study, and blood samples were collected. Oxycodone better promoted the expressions of anti-inflammatory factors and reduced those of pro-inflammatory factors than dezocine, thereby keeping the balance of inflammatory factors, preventing postoperative immune stress response, and reducing the damage of immune stress to tissues. Possibly, oxycodone has significantly better effects on alleviating visceral pain than dezocine, works quickly and reaches peak plasma concentration within 5 min after administration, thus rapidly relieving pain. Moreover, the elimination half-life of oxycodone is as short as about 3.5 h, and its plasma concentration can reach the steady state fast, thereby attenuating the stress response to intraoperative pneumoperitoneum and reducing the release of catecholamine. Collectively, oxycodone is more helpful than dezocine in keeping the balance of inflammatory factors, which benefits the intraoperative hemodynamic stability and recovery of immune function after gynecological laparoscopic surgery.

In conclusion, in gynecological laparoscopic surgery, preemptive analgesia using oxycodone hardly affects the hemodynamics during operation, relieves the postoperative pain syndrome caused by visceral traction, better promotes the expressions of anti-inflammatory factors, inhibits the expressions of pro-inflammatory factors, and keeps the balance of inflammatory factors, with superior effects to those of dezocine.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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