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Original Research Article

Effect of combined application of sevoflurane and remifentanil on laparoscopic surgery, postoperative recovery time and stress response

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Abstract

Purpose: *To investigate the effect of application of sevoflurane and remifentanil on laparoscopic surgery, and its effect on patients' postoperative recovery time and stress response.*
Methods: *Ninety patients undergoing laparoscopic surgery in Zhongshan City People's Hospital, Guangdong Province, China were selected and randomly divided into propofol group (PG) and sevoflurane group (SG), with 45 patients in each group. Patients in PG were anesthetized with combination of propofol and remifentanil, while those in SG received combination of sevoflurane and remifentanil. Patients' heart rate (HR), stroke volume (SV) and mean arterial pressure (MAP) were tested before anesthesia induction (T1), after intubation (T2), 15 min after pneumoperitoneum (T3), and after extubation (T4), in order to evaluate the stability of vital signs in the patients.*
Results: *At T2, T3, and T4, HR, SV, and MAP were more stable in SG than in PG ($p < 0.05$). At T3 and T4, the levels of ET-1, noradrenaline (NE) and cortisol (Cor) were significantly lower in SG than in PG ($p < 0.05$). Furthermore, postoperative recovery time, spontaneous breathing time, time taken to open the eyes under command, and orientation recovery time were shorter in SG than in PG ($p < 0.05$). After awakening, SG had significantly higher Ramsay score than PG ($p < 0.05$).*
Conclusion: *The combined use of sevoflurane and remifentanil for anesthesia in patients undergoing laparoscopic surgery results in stable vital signs, facilitates recovery after surgery, improve quality of recovery, and reduce stress response. Therefore, the combination anesthesia merits further mechanistic and large-scale investigation before clinical application.*

Keywords: *Laparoscopic surgery, Remifentanil, Sevoflurane, Recovery time, Stress response*

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INTRODUCTION

Laparoscopic surgery is a newly developed micro-invasive treatment characterized by minimal trauma, reduced scars, and rapid recovery. It has resulted in significant progress in the treatment of hepatobiliary, spleno-pancreatic, gastrointestinal, thoracic, and gynecological diseases. However, during the course of pneumoperitoneum, CO_2 affects blood circulation which, in combination with stimulation by anesthetic drugs, generates adverse effects on the stability of vital signs of patients. This negatively affects surgery and patients'

postoperative recovery [1-4]. Therefore, much attention has been paid to studying anesthesia for laparoscopic surgery. For many years, propofol and remifentanil have been used for anesthesia in clinics. Propofol produces quick effect, and it is associated with fast postoperative recovery. However, it depresses the respiratory center and reduces blood pressure. In order to make up for the disadvantages of propofol and reduce the dose used while guaranteeing its anesthetic effect, it is possible to replace it with sevoflurane. It has been reported that sevoflurane is a halogen inhalation anesthetic with rapid onset and minimal irritation to the circulatory and respiratory systems, when used for anesthesia maintenance [5,6]. At present, there are limited studies on the anesthetic effect of sevoflurane in laparoscopic surgery. Therefore, the present study was aimed at investigating the effect of application of combination of sevoflurane and remifentanil on patients undergoing laparoscopic surgery, and its effect on recovery time, stress response, and vital signs.

METHODS

Enrollment and grouping of patients

Ninety (90) patients who underwent laparoscopic surgery in Zhongshan City People's Hospital**,** Guangdong Province, China, from March 2020 to February 2021 served as subjects in this study. They were randomly divided into propofol group (PG) and sevoflurane group (SG), with 45 patients in each group. The study was approved by the Ethics Committee of Zhongshan City People's Hospital (approval no. 20200103), and it was carried out in line with the principles of the Declaration of Helsinki, as revised in 2013 [7]. Signed written informed consents were obtained from the patients and/or guardians.

Inclusion and exclusion criteria

Inclusion criteria

Patients in the following categories were included in this study: those who met the surgical indicators, and who underwent laparoscopic surgery for the first time, patients with ASA grades I and II, and those who show high level of cooperation with the researchers.

Exclusion criteria

Patients who were allergic to, or dependent on the anesthetic drugs used, those with serious organ diseases such as liver, kidney, heart, lung and other organ failures, and those with large pelvic and abdominal masses, were excluded from the study. In addition, patients who had diaphragmatic hernia or abdominal hernia, and those with dispersive peritonitis complicated with intestinal obstruction, were excluded.

Treatments

All patients were fasted for 8 h, and 0.3 mg of atropine hydrochloride infusion was administered *via* intramuscular injection 30 min before surgery. Anesthesia was induced in both groups using sufentanil (5 μg/kg), midazolam (0.1 mg/kg) and rocuronium bromide (0.6 mg/kg) *via* intravenous injection. Oro-tracheal intubation was performed. The anesthesia machine was connected, and mechanical ventilation was conducted during surgery for adjustment of respiratory frequency and tidal volume [8]. For anesthesia maintenance, patients in SG inhaled 7 % sevoflurane (Shanghai Hengrui Pharmaceutical Co. Ltd; specification: 120 mL; NMPA approval no. 19990027). Propofol (Sichuan Guorui Pharmaceutical Co. Ltd; specification: 10 ml/0.1 g; NMPA approval no. H20040079) was intravenously pumped into patients in PG at the rate of 8 mg/kg/h. Then, remifentanil hydrochloride (Jiangsu Nhwa Pharmaceutical Co. Ltd; specification: 1 mg; NMPA approval no. H20143314) was continuously pumped into patients in both groups at a constant rate of 0.15 μg/kg/min [9,10]. Ten (10) min before the end of the surgery, the administration of sevoflurane and propofol was stopped, while remifentanil administration was stopped at the end of the surgery. Finally, 0.05 mg of fentanyl was administered for analgesia.

Determination of treatment outcomes

Prior to surgery, statistical analysis was carried out on patients' general information such as age, gender, BMI, ASA grade, surgery type, hypertension, hyperlipidemia, diabetes, smoking history and drinking history. Patients' heart rate (HR), stroke volume (SV) and mean arterial pressure (MAP) were tested before anesthesia induction (T_1), after intubation (T_2), 15 min after pneumoperitoneum (T_3), and after extubation (T_4), in order to evaluate the stability of vital signs. At T_1, T_3 and T_4, endothelin-1 (ET-1) level was measured with enzyme linked immunosorbent assay (ELISA), while noradrenaline (NE) and cortisol (Cor) levels were measured with radioimmunoassay to evaluate stress response. Patients' recovery time, spontaneous breathing time, time taken to open eyes under command, and orientation recovery time were recorded.

Quality of recovery was evaluated with the Ramsay scale at the time of waking up, 30 min after waking up, and 1 h after waking up. A score of 6 points showed that the patient was asleep and did not respond to calls, and 5 points indicated that they were asleep but responded sluggishly to calls. Moreover, a score of 4 points meant shallow sleep from which the patient could be woken up, while a score of 3 points showed drowsiness, with fast response to calls. A score of 2 points indicated that the patient was awake and exhibited good responses, while a score of 1 point denoted restlessness.

Before anesthesia, and at 4 h and 9 h after surgery, cognitive function was evaluated in the patients using the 30-point Mini-Mental State Examination (MMSE) scale. The scores on this scale were directly proportional to cognitive function.

Statistical analysis

The SPSS version 21.0 software was used for statistical analysis. Measurement data are expressed as mean ± standard deviation (SD), and comparison between two groups was done with *t*-test. Enumeration data are expressed as numbers and percentages (n (%)), and two-group comparison was done with chi square χ^2 test. Differences were considered statistically significant at $p < 0.05$.

RESULTS

General information on patients

There were no statistically significant differences between the two groups with respect to general information such as gender, age and disease type ($p > 0.05$), as listed in Table 1.

Stability of vital signs

At T_2, T_3 and T_4, vital signs such as HR, SV and MAP were more stable in SG than in PG ($p < 0.05$). These results are shown in Table 2.

Stress response

At T_3 and T_4, there were lower levels of ET-1, NE and Cor in patients in SG than in those in PG ($p < 0.05$). Details are shown in Table 3.

Table 1: General information on patients (n = 45)

Parameter	PG	SG	χ^2/t	*P*-value
Age (years)	44.93±7.01	45.42±7.55	0.3190	0.7504
BMI (kg/m^2)	22.64±3.08	23.15±3.14	0.7778	0.4388
Male/female	27/18	25/20	0.1822	0.670
ASA grade			***0.1852***	***0.667***
I	26 (57.78)	28 (62.22)		
II	19 (42.22)	17 (37.78)		
Surgery type			***0.3041***	***0.581***
Cholecystectomy	18 (40)	17 (37.78)		
Gastrointestinal surgery	13 (28.89)	12 (26.67)		
Gynecologic operation	7 (15.56)	9 (20)		
Others	7 (15.56)	7 (15.56)		
Hypertension	13 (18.89)	15 (33.33)	0.2074	0.649
Hyperlipidemia	10 (22.22)	7 (15.56)	0.6527	0.419
Diabetes	6 (13.33)	9 (20)	0.7200	0.396
Drinking history	31 (68.89)	28 (62.66)	0.4429	0.506
Smoking history	24 (53.33)	23 (51.11)	0.0445	0.833

Table 2: Vital signs in the two groups

Group	Indicator	T_1	T_2	T_3	T_4
PG	HR (bpm)	83.67±8.40	75.88±7.39	79.66±7.25	88.09±7.72
SG		84.15±8.39	80.24±8.40	83.91±8.06	84.05±8.15
t/P		0.27/0.79	2.61/0.01	2.63/0.01	2.41/0.02
PG	SV (mL)	63.21±6.39	55.21±5.57	58.24±5.49	67.06±6.41
SG		62.96±6.37	60.10±6.09	62.14±6.18	63.15±6.06
t/P		0.39/0.70	3.97/0.0001	3.16/0.0021	3.00/0.0036
PG	MAP	96.11±9.24	82.09±8.27	98.86±9.50	105.04±9.68
SG	(mmHg)	95.88±6.18	88.98±8.59	92.87±9.16	97.53±9.31
t/P		0.14/0.89	3.88/0.0002	3.04/0.0031	3.75/0.0003

Table 3: Stress response in each group

Group	Indicator	T_1	T_3	T_4
PG	ET-1 (mmol/L)	76.15±7.48	107.85±9.88	93.75±9.32
SG		75.96±7.47	94.06±9.67	85.78±8.64
t/P		0.12/0.90	6.69/< 0.05	4.21/0.0001
PG	NE (nmol/L)	1.18±0.26	1.42±0.47	1.32±0.34
SG		1.17±0.31	1.15±0.33	1.16±0.35
t/P		0.17/0.87	3.15/0.0022	2.20/0.0305
PG	Cor (nmol/L)	319.98±30.65	420.02±37.46	385.26±33.53
SG		321.03±30.54	389.55±36.04	343.17±29.81
t/P		0.16/0.87	3.93/0.0002	6.29/< 0.05

Table 4: Postoperative recovery (min)

Group	Recovery time	Spontaneous breathing time	Time to open eyes under command	Orientation recovery time
PG	16.71±2.83	15.88±2.27	18.44±2.49	20.09±2.53
SG	11.90±2.09	11.28±2.05	15.23±2.14	16.61±2.12
t	9.2729	10.2001	6.6310	7.1505
P-value	<0.001	<0.001	<0.001	<0.001

Table 5: Ramsay scores (mean ± SD)

Group	At the time of waking up	30 min after waking up	60 min after waking up
PG	1.60±0.43	1.31±0.32	1.39±0.30
SG	3.61±0.58	2.78±0.41	2.51±0.64
t	18.6749	18.9601	10.6295
P-value	<0.001	<0.001	<0.001

Table 6: MMSE scores in the two groups of patients

Group	Pre-anesthesia	Postoperative 4 h	Postoperative 8 h
PG	28.63±2.39	21.17±2.14	25.26±2.41
SG	28.32±2.35	23.25±2.30	27.34±2.27
t		4.4414	4.2145
P-value		<0.001	0.0001

Postoperative recovery

The postoperative recovery time, spontaneous breathing time, time to open eyes under command, and orientation recovery time of patients in SG were shorter than those of patients in PG ($p < 0.05$), as presented in Table 4.

Recovery quality

After waking up, SG patients had significantly higher Ramsay scores than patients in PG ($p < 0.05$). Details are listed in Table 5.

Mental state status

After surgery, patients in SG had significantly better MMSE scores than those in PG ($p < 0.05$), as presented in Table 6.

DISCUSSION

Laparoscopic technique, also called “quality-of-life preserving surgery” in modern medical practice, is a very advanced surgical method developed in the 21st century. The technique has been widely used in the treatment of several diseases in the clinics. However, there is a requirement for establishment of CO_2 pneumoperitoneum pressure during the surgery for enhanced view of the intra-abdominal region. In addition, the traumatic nature of the surgery causes fluctuations in vital signs of patients such as heart rate and blood pressure, as well as increases in stress response. As a result, there is an increasing need for an appropriate anesthesia in laparoscopic surgery for maintenance of stability of patients’ vital signs, reduction of stress stimulation, and enhancement of the quality of recovery. In laparoscopic surgery, there is very intensive surgical stimulus within minutes before

the end of the procedure. Thus, there is need for an appropriate depth of anesthesia. In this respect, the choice of opioid anesthesia is crucial, and remifentanil is exactly the first opioid chosen for that purpose [11,12].

Propofol, the only intravenous anesthetic suitable for minimally invasive surgery, has rapid onset and fast recovery, and it depresses the respiratory system, leading to transient respiratory arrest. Moreover, propofol decreases blood pressure and induces mild excitement in anesthesia. In a study involving retrospective analysis of data of 63 patients who underwent laparoscopy hysterectomy under anesthesia with propofol and remifentanil, statistics showed that 91.6 % of the patients presented different degrees of nausea, vomiting and pain during the recovery period [13]. Previous studies have shown that the use sevoflurane for child patients required low doses of muscle relaxant, with the anesthesia resulting in induction of more calmness and more stable intraoperative hemodynamics, as well as fast recovery and full awakening after surgery [14-16]. In another study, it was reported that the use of sevoflurane in combination with an appropriate amount of remifentanil prolonged recovery time of patients and improved the quality of recovery [17].

The present study was carried out due to limited investigations involving application of sevoflurane in laparoscopic surgery. Therefore, in this study, propofol was replaced with inhalation anesthetic, with the aim of enhancing the effectiveness and safety of anesthesia for laparoscopic surgery. The results showed that sevoflurane stabilized patients' hemodynamics, reduced stress response and produced high quality of postoperative awakening. Patients in SG had more stable vital signs such as HR, SV and MAP at T_2, T_3 and T_4, and lower levels of ET-1, NE and Cor at T_3 and T_4 than those in CG. In addition, postoperative awakening time, spontaneous breathing time, time taken to open eyes under command, and orientation recovery time were shorter in SG, with higher Ramsay scores and better MMSE scores, when compared with patients in PG. These results indicate that the combination of sevoflurane and remifentanil resulted in better effects in laparoscopic surgery than the combination of propofol and remifentanil. This was because surgical trauma, anesthesia stimulus and CO_2 pneumoperitoneum caused fluctuations in HR, SV, MAP and other vital signs; and increased stress response, resulting in raised levels of ET-1, NE and Cor; vasodilatation and systolic dysfunction, and unstable vital signs.

Remifentanil anesthesia had a rapid onset and an analgesic effect. At low doses, remifentanil is effectively metabolized by non-specific esterase (NSE), while an excessive dose of remifentanil affects heart rate, blood pressure, and cognitive function of patients. In addition, propofol produces inhibitory effects on the circulatory and respiratory system. Therefore, the combination of remifentanil and propofol was less favorable for stabilizing the vital signs of patients. Sevoflurane, a novel inhalation anesthetic, has better physical properties than existing inhalation anesthetics, with a blood gas fraction coefficient of only 0.59, rapid onset, low tissue uptake, and faster awakening in patients.

Compared with strong inhalation anesthetics, it has weaker potency but a higher MAC value (1.7 %). Besides, sevoflurane is safer due to low adverse effect on the circulatory system. Moreover, it has no adverse impact on the myocardial conduction system, no stimulatory effect on the respiratory tract, and no noticeable effect on the pituitary and adrenal glands. It has been reported that patients who were anesthetized with sevoflurane were awake about 10 min after surgery, but they experienced sudden awakening and restlessness [18].

In this study, the use of sevoflurane in combination with remifentanil prolonged the awakening time of patients but significantly enhanced awakening quality. Thus, there was a synergistic effect between the two. It should be noted that sevoflurane, which is metabolized in the body by hepatic cytochrome P-450, is not suitable for patients with increased intracranial pressure. In addition, due to its unstable chemical properties, sevoflurane generates five kinds of hydrolysates when in contact with soda lime. It may also reduce blood glucose level. Therefore, there is need for more studies to determine the optimum dose of sevoflurane for use in laparoscopic surgery.

Limitations of the study

Due to the research cost, only 90 patients were selected for comparative analysis in this single-center study. Therefore, multi-center studies with a larger sample size are required to validate the findings in the present study.

CONCLUSION

The combined use of sevoflurane and remifentanil for anesthesia in patients undergoing laparoscopic surgery results in stable vital signs, facilitate fast recovery after surgery, improves quality of recovery, and reduces stress response.

Thus, the combination of sevoflurane and remifentanil may be considered a suitable substitute in view of the shortcomings of propofol/remifentanil combination. However, more elaborate studies should be carried out to validate this finding.

DECLARATIONS

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Ethical approval

The study was approved by the Ethics Committee of Zhongshan City People's Hospital (approval no. 20200103).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Yong Chen conceived and designed the study, analyzed and interpreted the experimental data. Yong Chen and Hongkai Lin drafted the manuscript and revised the manuscript for important intellectual contents. Yong Chen and Hongkai Lin read and approved the final manuscript.

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