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Original Article

Application of sevoflurane combined with remifentanil anesthesia in laparoscopic radical hysterectomy for cervical cancer

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Abstract: Objective: To explore the effects of sevoflurane combined with remifentanil anesthesia on the physical stress and immunologic function of patients undergoing laparoscopic radical hysterectomy for cervical cancer. Methods: The clinical data of 74 patients undergoing laparoscopic radical hysterectomy for cervical cancer were retrospectively analyzed. Patients were divided into two groups according to the different anesthesia methods, among which 37 cases received propofol and remifentanil anesthesia were set as a control group (CG), and 37 cases received sevoflurane and remifentanil anesthesia were set as an observation group (OG). Results: The OG showed a lower heart rate, Ramsay score and bispectral index than the CG 30 min after the start of the surgery and at the end of the surgery. The levels of glucagon, angiotensin II and cortisol in the OG were lower than those in the CG upon skin incision, at the end of surgery, and at 1 h after surgery ($P < 0.05$). The levels of $CD3^+$ and $CD4^+$ of the OG were higher than those of the CG at 1 d and 3 d after surgery. In terms of Montreal Cognitive Assessment and Mini-Mental State Examination scores 1 d after surgery, the OG was higher than the CG. Conclusion: Sevoflurane combined with remifentanil anesthesia for patients undergoing laparoscopic radical hysterectomy for cervical cancer is superior to propofol and remifentanil, and can ensure stable hemodynamics and mitigate physical stress, so it is worthy of clinical application.

Keywords: Laparoscopic radical hysterectomy, cervical cancer, sevoflurane, remifentanil, physical stress, immunologic function, cognitive function

Introduction

Cervical cancer is a common malignant tumor in the female reproductive system. It is the second most common malignant tumor after breast cancer and the third leading cause of cancer-related death in women worldwide [1]. Wang et al. studied the long-term trend of cervical cancer incidence and mortality in China from 1993 to 2017 and found that the incidence and mortality of cervical cancer in China decreased from 1993 to 1998 and increased from 2008 to 2015. Joinpoint regression model results showed that from 1993 to 2017 the standardized incidence of cervical cancer in women increased from 9.54/100,000 to 10.88/100,000 [AAPC (95% CI) = 0.6 (0.3, 0.9), P < 0.05], while the standardized mortality decreased from 4.88/100,000 to 4.48/100,000 [2]. Surgical resection and chemoradiotherapy are the current options for the treatment of cervical cancer. Due to disease factors, patients undergoing radical hysterectomy for cervical cancer already have a low cellular immune function. Surgical trauma and anesthesia effects can cause different degrees of stress responses in the body, inhibit the lymphatic and reticuloendothelial systems, reduce the tropism of neutrophils, decrease the activity of monocytes and further decrease the immunity of patients, thus increasing the incidence of postoperative infections and other complications [3, 4]. Laparoscopic minimally invasive radical hysterectomy for cervical cancer has become the latest preferred method for the treatment of early cervical cancer due to its advantages of less surgical trauma, less bleeding and rapid recovery, but the anesthesia relat-

ed stress reactions may inhibit the immunity to a certain extent [5]. Therefore, it is of great concern to select a reasonable anesthesia method to mitigate the physical stress reaction and anesthetic inhibition of immunologic function.

Remifentanil is a μ-type receptor agonist that can reach blood-brain equilibration within 1 minute after injection, with rapid onset and short maintenance time. Its analgesic effect depends on the dosage of the drug, and it does not accumulate in the body even after prolonged or repeated injections [6]. Sevoflurane is a new type of halogen inhalation anesthetic. When taking sevoflurane, a small dosage of muscle relaxant is required. The patient usually has a stable reaction to the drug during the induction period, which also has little influence on intraoperative hemodynamics, and generally is being followed by a quick and thorough postoperative recovery [7]. Propofol has a quick anesthetic effect and short induction duration. Both drugs are widely used in clinical anesthesia in recent years. However, propofol has a more significant influence on hemodynamic indices of patients and shows an increased stress response, which leads to certain adverse effects on the quality of postoperative recovery. In this study, the effects of sevoflurane combined with remifentanil anesthesia on the stress response, immune function, and cognitive function of patients undergoing laparoscopic radical hysterectomy for cervical cancer were observed.

Materials and methods

Patient selection

We analyzed the data of patients who underwent laparoscopic radical hysterectomy for cervical cancer from January 2018 to June 2019 in Hubei Provincial Hospital of Traditional Chinese Medicine. Patients anesthetized with sevoflurane combined with remifentanil were included in an observation group (OG). Patients who were anesthetized with propofol combined with remifentanil were included in a control group (CG) by Propensity Score Matching (PSM) of 1:1 with the OG according to five factors, including age, operation time, clinical staging, body mass index (BMI) and ASA classification. Inclusion criteria: (1) patients who were diagnosed with cervical cancer by magnetic resonance imaging and pathological biopsy according to relevant criteria in Obstetrics and Gynecology [8], and underwent laparoscopic radical hysterectomy; (2) patients with no coagulation disorders and autoimmune disease, no history of blood transfusion, and no history of pelvic surgery or hormonotherapy or surgical treatment in the past 3 months; (3) patients who did not receive radiotherapy and chemotherapy before surgery; (4) patients who were at clinical stages Ia2-IIa2; (5) patients with classes I-II according to ASA classification. Exclusion criteria: (1) patients with other tumors, severe internal diseases, cognitive dysfunction, acute or chronic systemic infection, or insufficiency of liver, lung or kidney; (2) patients with a history of drinking; (3) patients who were allergic to anesthetics.

Determination of sample size

Since this was a retrospective analysis, PSM was used to match the number of cases in both groups. For the corroboration of the analysis, we also cross-referenced the sample size calculation for the number of cases in the prospective study. If the intraoperative serum cortisol concentration increased by 10% in the OG compared to pre-anesthesia and 25% in the CG compared to pre-anesthesia, we set $\beta \leq 0.1$, power = 90% and $\alpha = 0.05$ of significance level (two-sided), and the calculated sample size for each group was 35 cases. The clinical data of patients in the OG (n = 37) and CG (n = 37) who met the inclusion and exclusion criteria were screened from the electronic record database and included in this study. This study has been approved by the Ethics Committee of Hubei Provincial Hospital of Traditional Chinese Medicine.

Methods

The two groups of patients received laparoscopic radical hysterectomy for cervical cancer. Fasting for 8 h before surgery, patients received intramuscular injection of 0.5 mg atropine (Tianfang Pharmaceutical Co., Ltd., China) at 30 min before anesthesia, and intramuscular injection of 10 mg diazepam (Shandong Xinyi Pharmaceutical Co., Ltd., China). Then, the upper limb vein channels were opened, the monitoring of the electrocardiogram and depth of anesthesia was connected, the left radial artery was punctured and catheterized to monitor arterial pressure, and oxygen masks were provided. In the CG, 1% propofol at 2 mg/kg and remifentanil at 3 μg/kg were given for

anesthesia, and vecuronium at 0.1 mg/kg was given intravenously after consciousness disappeared. Tracheal intubation was conducted for mechanical ventilation with a tidal volume of 10 mL/kg, respiratory rate from 10 to 12 times/min, and respiration ratio of 1:1.5. Anesthesia maintenance: propofol at 4 to 8 mg/(kg·h) (Xi'an Libang Pharmaceutical Co., Ltd., Xi'an, China) and vecuronium at 1 μg/(kg·min) (Anhui Welman Pharmaceutical Co., Ltd., Hefei, China) were provided by pump injection. The OG was given a target-controlled infusion of remifentanil (Jiangsu Nhwa Pharmaceutical Co., Ltd., Xuzhou, China), and the plasma concentration was set to 3 ng/mL. Sevoflurane was given by inhalation (Shanghai Xiyuan Biotechnology Co., Ltd., China) at the same time, starting with a concentration of 0.5%, then gradually increasing by 0.5-4% as the number of breaths increased. The concentration was increased once every 2 to 3 breaths. The oxygen flow was set to 4 L per minute. Vecuronium bromide (0.1 mg/kg) was given intravenously after the patient lost consciousness, followed by mechanical ventilation with tracheal intubation and a tidal volume of 10 mL/kg. Remifentanil was continuously injected and sevoflurane was continuously inhaled. Anesthesia was discontinued after surgery. Intraoperative bispectral index (BIS) was used to determine the depth of anesthesia, which was maintained at 40-60 in both groups.

Outcome measures

The main outcome measures included glucagon (GLU), angiotensin II (AngII) and cortisol (Cor). Other indicators were secondary outcome measures.

Hemodynamic indices

Mean arterial pressure (MAP) and heart rate (HR) were measured before anesthesia, at 30 min after the start of the surgery, at the end of the surgery, and at 1 h after surgery.

Physical stress indices

Blood sample (3 mL) was collected from the veins of the patients before anesthesia, upon skin incision, at the end of the surgery and at 1 h after surgery. The samples were centrifuged at 3000 r/min for 10 min to measure the GLU, AngII and Cor levels using enzyme-linked immunosorbent assay.

Immunologic function indices

Blood sample (4 mL) was collected from the veins before, at 1 d, 3 d and 7 d after surgery, and the plasma was collected by centrifugation at 3000 r/min for 10 min. The plasma (50 μL) was taken and mixed with 5 μL of anti-human T lymphocyte subsets monoclonal antibody (BM company, USA), followed by labeling sequentially and placing at room temperature for 15 min in the dark. Afterwards, 200 μL of red blood cell lysate (BM company, USA) was added, mixed and placed at room temperature for 15 min in the dark. A horizontal centrifuge was used for 5 min of centrifugation, with the speed adjusted to 1200 r/min, and the supernatant was discarded. Subsequently, 400 μL of phosphate buffer was added and centrifuged at 1200 r/min for 5 min, the supernatant was discarded, and PBS was added. The $CD3^+$, $CD4^+$, and $CD8^+$ were measured using CytoFLEX Flow Cytometer (Beckman Coulter Co., Ltd.), and CELL Quest software was used to analyze the results.

Intraoperative sedation effects

BIS and the changes of Ramsay score were observed before anesthesia, at 30 min after the start of the surgery, at the end of the surgery, and at 1 h after surgery. The Ramsay score was used to observe intraoperative sedation. The Ramsay scoring criteria were as follows: 1 point: anxious and upset; 2 points: conscious, quiet and cooperative; 3 points: somnolent but compliant with directives; 4 points: light sleep and awakening rapidly; 5 points: sleeping with blunt reaction; 6 points: deep sleep and unable to be wakened. Points above 5 indicated excess sedation.

Anesthesia effects

The onset time of muscle relaxant, duration, extubation time and wake-up time were recorded. Neuromuscular transmission velocity was measured with a musculorelaxation accelerometer, and Train of Four (TOF) stimuli were given at 40 mA every 15 s to the ulnar nerve in all patients via two surface electrodes. The evoked potentials of the thumb were determined by a TOF-Watch SX accelerometer (Organon, the Netherlands) in uncalibrated mode. Three consecutive TOF measurements (separated by 15 s) were obtained, and the average value was

Table 1. Intergroup comparison of general data (mean ± SD, *n*)

Group	*n*	Average age (years)	BMI (kg/m^2)	Operation time (min)	Intraoperative blood loss (mL)	Clinical staging			ASA classification	
						Ia2	Ib2	IIa2	I	II
OG	37	45.25±7.48	24.54±1.73	268.33±23.54	494.83±58.59	20	12	5	27	10
CG	37	46.15±6.87	24.72±1.75	273.23±25.37	490.57±60.82	21	10	6	25	12
χ^2/t		0.521	0.445	0.861	0.307	0.297			0.259	
P		0.604	0.658	0.392	0.760	0.862			0.611	

OG: Observation Group; CG: Control Group; BMI: Body Mass Index.

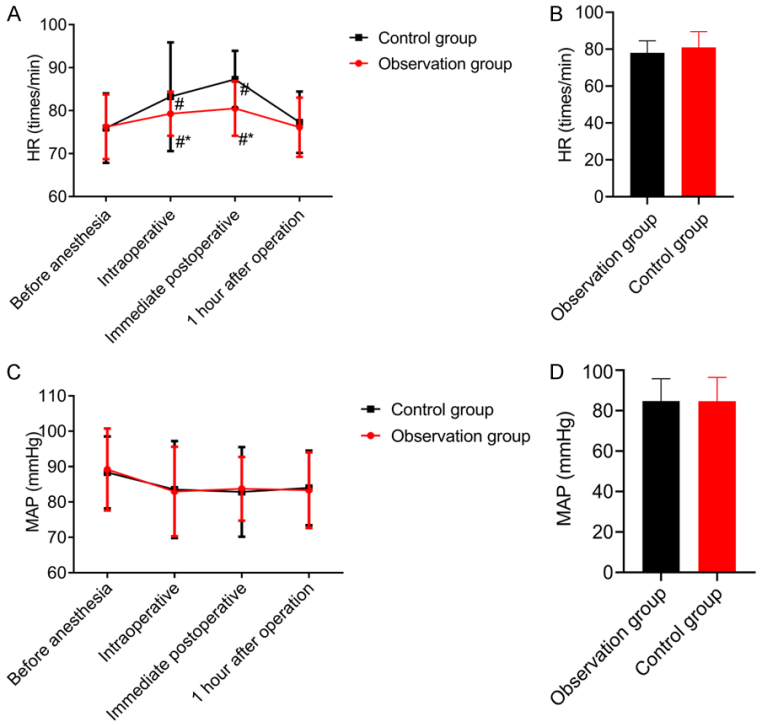

Figure 1. Comparison of hemodynamics between the two groups. A, B: Heart rate (HR); C, D: Mean arterial pressure (MAP). Compared with the control group, $^*P < 0.05$; compared with before anesthesia, $^\#P < 0.05$. Post-hoc Bonferroni test was performed to compare HR ($P < 0.05$ when comparing the observation group with the control group) and MAP ($P > 0.05$ when comparing the observation group with the control group).

taken as the final TOF. TOF ratios ≥ 0.9 and < 0.9 were used as criteria to determine complete or incomplete recovery of neuromuscular block.

Cognitive function

The cognitive status of the patients was observed before surgery, and at 1 day and 7 days after surgery. Montreal Cognitive Assessment (MoCA) was adopted for evaluated. MoCA covered 7 dimensions: language, attention, direction, visuospatial abilities, abstract thinking, memory and recall. With a full score of 30 points, patients with education period less than 12 years received an extra point. The Mini-Mental State Examination (MMSE) scale focused on the direction and attention, with a full score of 30 points. Patients obtaining a score under 27 were recognized with cognitive dysfunction. A higher score reflects better cognitive function in both scales.

Anesthesia-related adverse reactions

The adverse reactions of anesthesia, including nausea, vomiting, hypotension, bradycardia, shivering, oversedation and dysphoria, were recorded from the end of anesthesia to the end of recovery period.

Statistical analysis

Statistical analysis was performed with Statistical Package for Social Science (SPSS) 25.0. Measurement data were expressed as mean ± standard deviation (mean ± SD). The independent *t*-test was used to compare the means between the two groups, and the paired t-test was used to compare the means before and after surgery in the same group. The characteristics of dynamic changes at different time points were compared using the repeated measures analysis of variance, followed by post-hoc Bonferroni test. The counting data were expressed as % and compared using the χ^2 test. For all statistical comparisons, significance was set at $P < 0.05$.

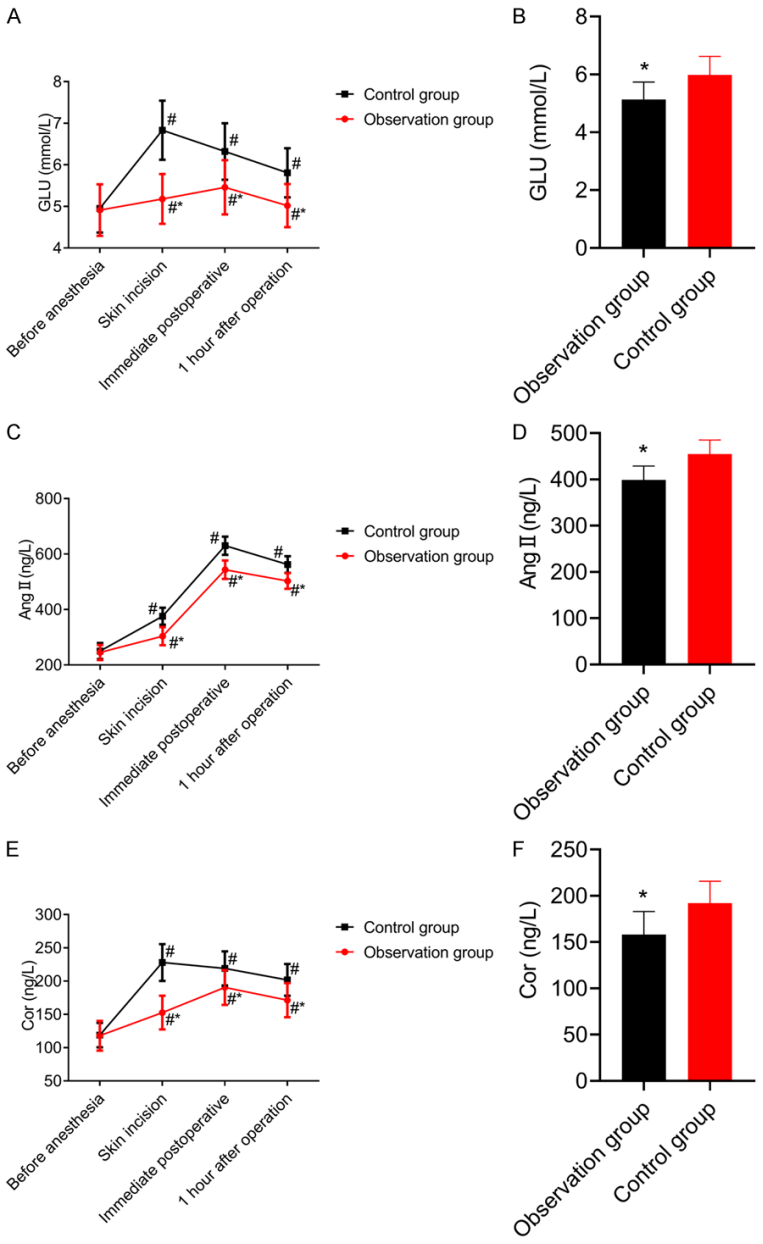

Figure 2. Comparison of body stress indicators between the two groups. A, B: Glucagon (GLU); C, D: Angiotensin II (AngII); E, F: Cortisol (Cor). Compared with the control group, $^{*}P < 0.05$; compared with before anesthesia, $^{\#}P < 0.05$. Post-hoc Bonferroni test was performed to compare GLU, AngII and Cor ($P < 0.05$ when comparing the observation group with the control group).

Results

Comparison of clinical data between the two groups

Age, body mass index, operation time, intraoperative blood loss, clinical staging and ASA classification were not statistically different between the two groups ($P > 0.05$), showing comparability (**Table 1**).

Intergroup comparison of hemodynamics changes

Before anesthesia, no statistically significant difference was observed in HR and MAP between the two groups ($P > 0.05$). There was no significant difference in MAP at 30 min after the start of the surgery and at the end of the surgery between the two groups ($P > 0.05$). While the HR in the OG was lower than that in the CG at 30 min after the start of the surgery and at the end of the surgery ($P < 0.05$), suggesting that sevoflurane combined with remifentanil anesthesia was more beneficial to hemodynamic stability during laparoscopic radical hysterectomy for cervical cancer (**Figure 1**).

Intergroup comparison of physical stress indices

Before anesthesia, the two groups were not statistically different in GLU, AngII and Cor ($P > 0.05$). The levels of GLU, AngII, and Cor upon skin incision, at the end of the surgery and at 1 h after surgery were significantly higher than those before anesthesia in both groups ($P < 0.05$). In addition, they were significantly lower in the OG than those in the CG at the same time point ($P < 0.05$). It suggested that sevoflurane combined with remifentanil anesthesia was more beneficial to reducing the stress response in patients undergoing laparoscopic radical hysterectomy for cervical cancer (**Figure 2**).

Intergroup comparison of immunologic function indices

Statistical difference was not found in $CD3^{+}$, $CD4^{+}$ and $CD8^{+}$ between the two groups before surgery ($P > 0.05$). At 1 d and 3 d after surgery, the $CD3^{+}$ and $CD4^{+}$ were higher in the OG than

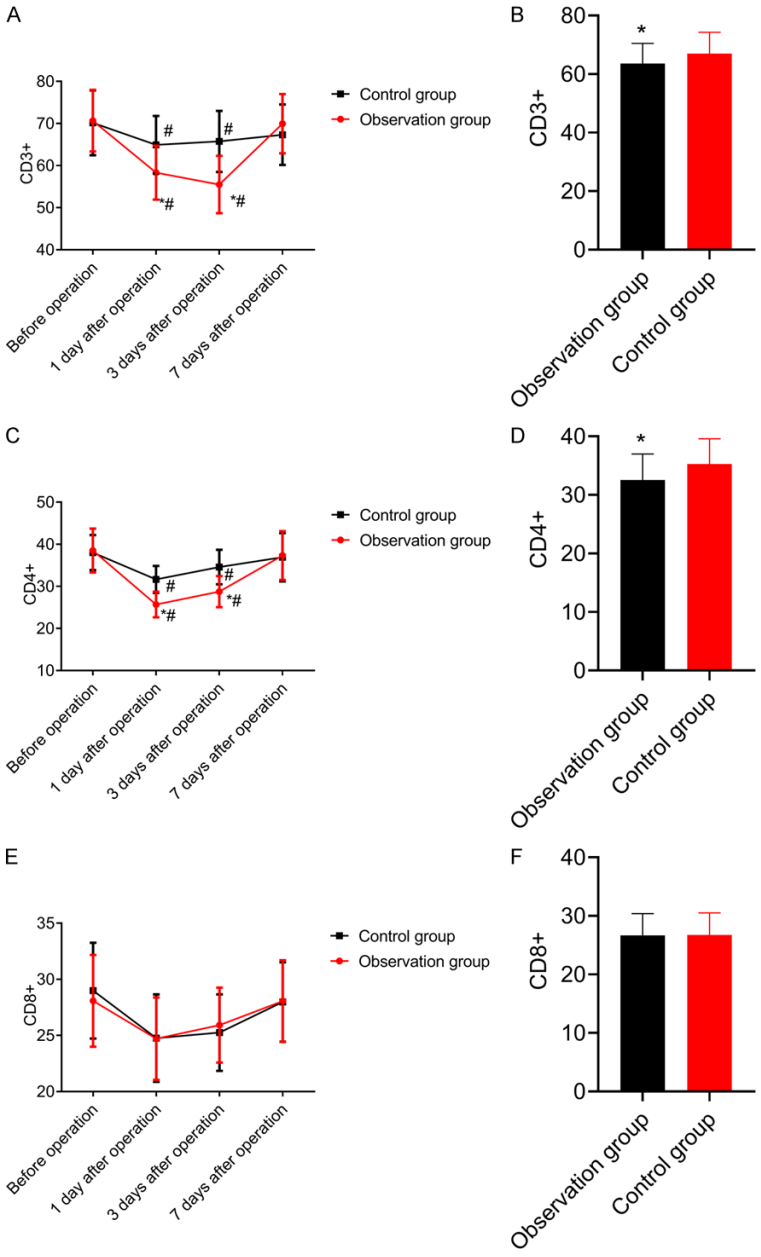

Figure 3. Comparison of immune function indexes between the two groups. A, B: $CD3^+$; C, D: $CD4^+$; E, F: $CD8^+$. Compared with the control group, $^*P < 0.05$; compared with before anesthesia, $^\#P < 0.05$. Post-hoc Bonferroni test was performed to compare $CD3^+$ and $CD4^+$ ($P < 0.05$ when comparing the observation group with the control group) and $CD8^+$ ($P > 0.05$ when comparing the observation group with the control group).

those in the CG ($P < 0.05$), whereas at 7 d after surgery, the $CD3^+$ and $CD4^+$ showed no statistical difference between the two groups ($P > 0.05$). Besides, there was no significant difference in $CD8^+$ between the two groups at each time point after surgery ($P > 0.05$). These results indicated that sevoflurane combined with remifentanil anesthesia could improve perioperative cellular immune function in patients undergoing laparoscopic radical hysterectomy for cervical cancer (**Figure 3**).

Intergroup comparison of sedation effects

Statistical difference was not found in Ramsay score and BIS before anesthesia and at 1 h after surgery between the two groups ($P > 0.05$). Lower Ramsay score and BIS at 30 min after the start of the surgery and at the end of the surgery were observed after anesthesia, and the two were significantly lower in the OG than those in the CG at the same time point ($P < 0.05$). This suggested that sevoflurane combined with remifentanil anesthesia had a better anesthetic and sedation effect in patients undergoing laparoscopic radical hysterectomy for cervical cancer (**Figure 4**).

Intergroup comparison of the onset time of muscle relaxant, duration, extubation time and wake-up time

The onset time of muscle relaxant, extubation time, and wake-up time were shorter in the OG than those in the CG ($P < 0.05$). The longer duration in the CG suggested that sevoflurane combined with remifentanil anesthesia had a better anesthetic and sedative effect in patients undergoing laparoscopic radical hysterectomy for cervical cancer, and the postoperative recovery was faster (**Figure 5**).

Intergroup comparison of MoCA and MMSE

The difference between the two groups in MoCA and MMSE scores before surgery and at 5 d after surgery was not statistically significant

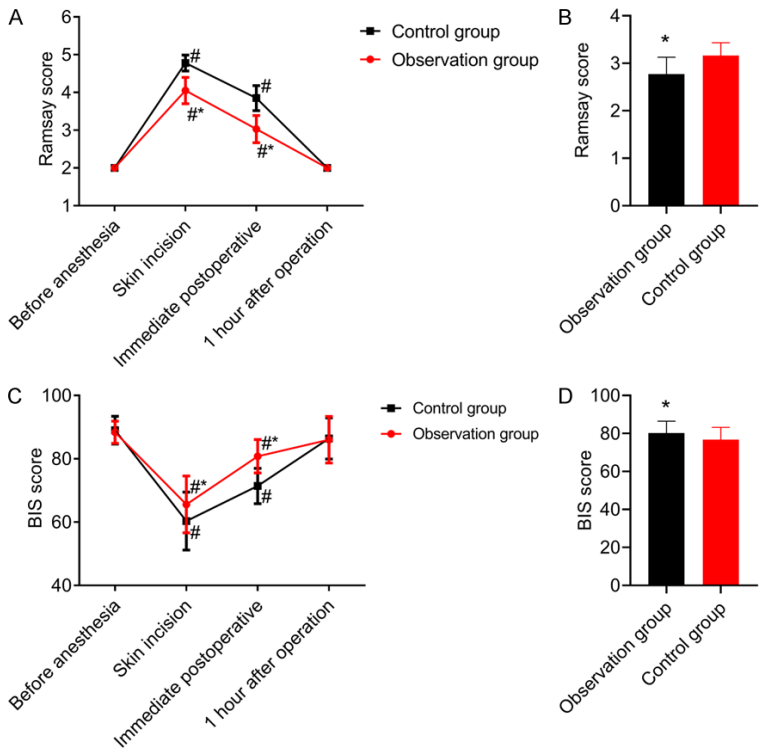

Figure 4. Comparison of anesthetic and sedation effects between the two groups (mean ± SD). A, B: Ramsay score; C, D: Bispectral index (BIS) score. Compared with the control group, $^{*}P < 0.05$; compared with before anesthesia, $^{\#}P < 0.05$. Post-hoc Bonferroni test was performed to compare Ramsay score and BIS score ($P < 0.05$ when comparing the observation group with the control group).

($P > 0.05$). At 1 d after surgery, the MoCA and MMSE scores of the OG were higher than those of the CG ($P < 0.05$), showing that sevoflurane combined with remifentanil anesthesia had a small effect on the cognitive function of patients undergoing laparoscopic radical hysterectomy for cervical cancer, and the patients recovered better (**Figure 6**).

Intergroup comparison of anesthesia-related adverse reactions

The total incidence of anesthesia-related adverse reactions was 29.73% in the OG, which was lower than 70.27% in the CG ($P < 0.05$), indicating that sevoflurane combined with remifentanil anesthesia during laparoscopic radical hysterectomy for cervical cancer had fewer adverse reactions and higher safety (**Table 2**).

Discussion

Sevoflurane blood and air partition coefficient is 0.63-0.69. Its anesthesia induction is rapid, and the patient can enter an anesthesia state within 2 min. Sevoflurane has little influence on the patient's hemodynamics, and patients wake up quickly after surgery [9]. After remifentanil enters the human body, it can quickly reach the blood-brain barrier and can be rapidly metabolized. It has the advantages of fast onset and short maintenance time. Yang et al. [10] applied sevoflurane combined with remifentanil anesthesia in laparoscopic surgery for patients with acute cholecystitis and found that they could play a synergic effect, stabilize hemodynamics and reduce stress response. According to the results of this study, at 30 min after the start of the surgery and at the end of the surgery, the HR was lower in the OG than that in the CG.

GLU, AngII and Cor are important indices to reflex physical stress reactions arising from trauma and anesthesia, which may lead to metabolic disturbance and stress hyperglycemia [11]. In the meantime, the increased release of catecholamines during stress reaction can affect the function of the cardiovascular system and increase the serum AngII and Cor [12, 13]. In this study, the results showed that upon skin incision, at the end of surgery and 1 h after surgery, the GLU, AngII and Cor were lower in the OG than those in the CG, which results are similar to the findings reported in a previous study [12]. The reason may be that sevoflurane combined with remifentanil anesthesia has the characteristics of controlled depth of anesthesia, which reduces the metabolism time of anesthetic drugs in the blood, and effectively reduces the stress response of anesthetic drugs to the body [14-16].

In addition, the results showed that the OG exhibited higher $CD3^{+}$ and $CD4^{+}$ compared with the CG at 1 d and 3 d after surgery, suggesting that sevoflurane combined with remifentanil anesthesia can improve the perioperative cellular immune function of patients undergoing

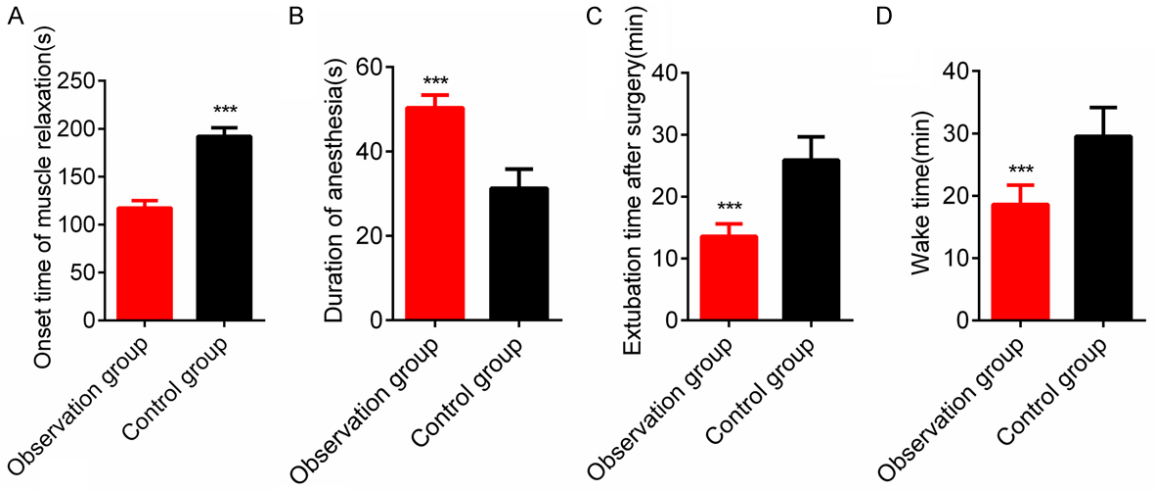

Figure 5. Intergroup comparison of onset time of muscle relaxation, duration, extubation time and wake-up time. A: Onset time of muscle relaxation; B: Duration of anesthesia; C: Extubation time; D: Wake-up time. Compared with the control group, $^{***}P < 0.001$.

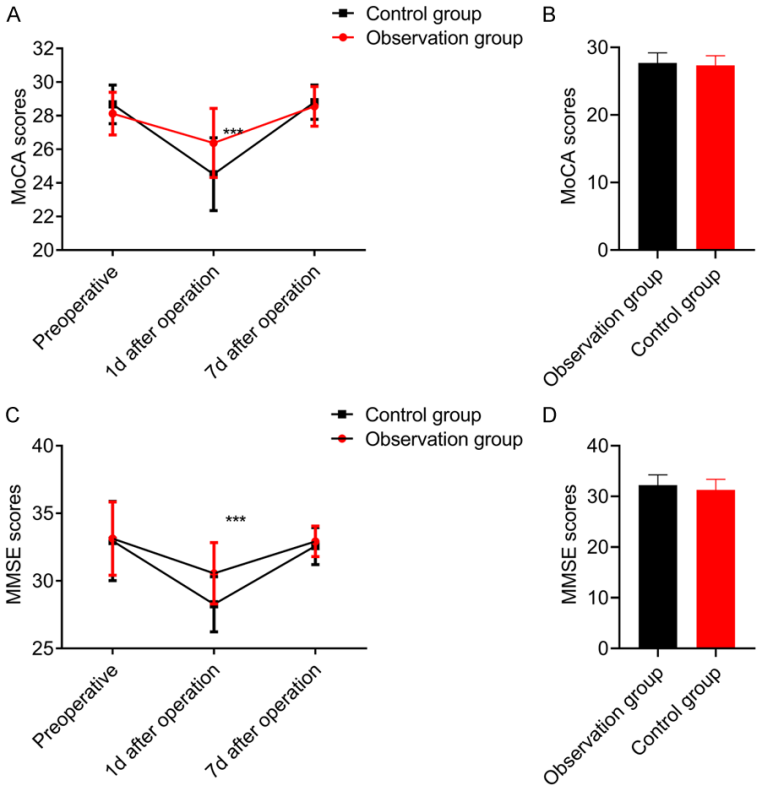

Figure 6. Intergroup comparison of MoCA and MMSE scores. A, B: Montreal Cognitive Assessment (MoCA) score; C, D: Mini-Mental State Examination (MMSE) score. Compared with the control group, $^{***}P < 0.001$. Post-hoc Bonferroni test was performed to compare MoCA score and MMSE score ($P > 0.05$ when comparing the observation group with the control group).

laparoscopic radical hysterectomy for cervical cancer. Yin et al. [17] showed that compared with intravenous anesthesia alone, sevoflurane combined with anesthesia significantly reduced the perioperative immune function of patients with hepatitis and cirrhosis, and the postoperative immune function recovered faster. This finding is similar to the results of our study.

This study also found lower Ramsay scores and BIS at 30 min after the start of the surgery and at the end of the surgery, shorter onset time of muscle relaxant, extubation time and wake-up time, longer duration, and higher MoCA and MMSE scores at 1 d after surgery in the OG, as well as a total anesthesia-related incidence of adverse reactions of 29.73% in the OG and 70.27% in the CG, which are consistent with the previous reports [18-20]. The result of this study indicated that sevoflurane combined with remifentanil anesthesia achieve a better sedation effect, faster onset, fewer adverse reactions, faster postoperative recovery and less cognitive impairment after surgery.

Table 2. Intergroup comparison of adverse reactions [*n* (%)]

Group	*n*	Nausea and vomiting	Low blood pressure	Bradycardia	Shivering	Oversedation	Dysphoria	Total incidence
OG	37	1 (2.70)	2 (5.41)	2 (5.41)	2 (5.41)	1 (2.70)	3 (8.11)	11 (29.73)
CG	37	2 (5.41)	5 (13.51)	6 (16.22)	3 (8.11)	3 (8.11)	7 (18.92)	26 (70.27)
χ^2		0.006	0.691	0.569	0.001	0.295	1.141	12.162
P		0.981	0.412	0.463	0.977	0.589	0.289	0.001

OG: Observation group; CG: Control group.

This study also has some shortcomings. In general, compared with propofol, sevoflurane has a higher incidence of postoperative nausea and vomiting, immunosuppression, respiration-related adverse reactions and cognitive defects, but some data in this study contradict this point. Nevertheless, some reports are consistent with this study. For example, Cao et al. [21] reported that compared with propofol anesthesia, sevoflurane inhalation anesthesia was more conducive to stabilizing the intraoperative hemodynamics and respiratory dynamics and reducing the stress response in elderly patients undergoing laparoscopic cholecystectomy, suggesting that it is a safe and reliable anesthesia method. This difference may be because the number of cases in this study is small, and middle-aged patients around 45 years old, who may have better tolerance, were selected. In the future study, we will expand the number of cases and conduct a multicenter study for in-depth exploration.

In conclusion, sevoflurane combined with remifentanil anesthesia can maintain hemodynamic stability and mitigate physical stress, and are superior to propofol and remifentanil anesthesia in patients undergoing laparoscopic radical hysterectomy for cervical cancer, so it is worthy of clinical application.

Disclosure of conflict of interest

None.

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