

## Original Article

# Application effect of sevoflurane combined with remifentanil intravenous inhalation anesthesia in patients undergoing laparoscopic radical resection of cervical cancer

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**Abstract:** Objective: To determine the application effect of sevoflurane combined with remifentanil intravenous inhalation anesthesia in patients undergoing laparoscopic radical resection of cervical cancer (LRHCC). Methods: The clinical data of 127 patients with cervical cancer (CC) who received LRHCC in Henan Provincial People's Hospital during January 2017 and June 2021 were retrospectively analyzed. Among them, 60 patients anesthetized by propofol combined with remifentanil were assigned to the control group (Con group), while the rest 67 anesthetized by sevoflurane combined with remifentanil to the research group (Res group). The following items of the two groups were compared: the changes of heart rate and blood pressure before anesthesia (T0), at 30 min after anesthesia (T1) and 10 min after surgery (T2), anesthetic effect, stress substance contents, anesthesia recovery, changes in brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF), Mini-Mental State Examination (MMSE) scores, and adverse reactions. Results: The heart rate and blood pressure at T1 and T2 were notably different between the two groups ( $P < 0.05$ ). In contrast to the Con group, the Res group showed a greatly better recovery effect of anesthesia and presented notably lower levels of adrenaline and GLU (all  $P < 0.05$ ). 10 min after surgery, the Con group showed lower levels of BDNF and NGF than the Con group. After surgery, the MMSE scores in the Res group were higher than that of the Con group, and the two groups had no significant difference in the incidence of adverse reactions ( $P > 0.05$ ). Conclusion: In contrast to propofol combined with remifentanil anesthesia, intravenous inhalational anesthesia with sevoflurane combined with remifentanil can exert a stronger anesthetic effect in patients receiving LRHCC, with a high safety.

**Keywords:** Sevoflurane, remifentanil, radical hysterectomy for cervical cancer, anesthetic effect, cognitive function

## Introduction

Cervical cancer (CC) is a disease closely associated with human papillomavirus infection. With an increasing incidence in recent years, it ranks the fourth most pervasive gynecological cancer worldwide, the seventh most pervasive cancer and the second most pervasive gynecological cancer in China [1-3]. In 2014, there were approximately 102,000 cases of CC in China, among which the death toll reached approximately 30,400 cases [4]. Most patients with early CC can be treated with surgery and with a

high cure rate. For example, the cure rate of radical hysterectomy exceeds 80%, and patients have a 5-year survival of over 90% [5, 6]. Currently, laparoscopic radical hysterectomy for cervical cancer (LRHCC) is wide applied in clinical practice, with features of less trauma and blood loss, milder pain, and milder inflammation than traditional open surgery [7].

Different kinds of anesthesia during surgery exerts different influences on hemodynamics, stress response, and cognitive function recovery of patients [8, 9]. Combined anesthesia is

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recommended for surgery, because various anesthetic drugs can deliver a synergistic and stronger anesthetic effect and can help patients to regain consciousness [10]. Sevoflurane is a novel anesthetic with advantages of small dosage for muscle relaxant, promoting calm response and stabilizing hemodynamics of patients during operation, and contributing to quick and thorough recovery after operation [11]. Remifentanyl is a strong ultrashort-acting opioid analgesic widely applied in general anesthesia and sedation in intensive care unit [12]. It can be metabolized rapidly through plasma esterase. Therefore, after termination of remifentanyl infusion, respiratory depression caused by opioids will disappear almost immediately, so that tracheal intubation can be removed as early as possible, and the time in ICU can be minimized [13]. Postoperative cognitive dysfunction is a common complication after anesthesia. Patients with cognitive dysfunction usually suffer memory and language disorders and declines in information acquisition, mental concentration and understanding, decision-making function and social adaptability within several days or even weeks after anesthesia [14]. At present, the clinical application of sevoflurane combined with remifentanyl in patients undergoing LRHCC is rare, and the anesthetic effect, safety and postoperative recovery in patients undergoing the surgery is still unclear. We hypothesize that intravenous inhalational anesthesia with sevoflurane combined with remifentanyl can deliver better anesthetic effect and substantially alleviate postoperative cognitive dysfunction.

Accordingly, in this retrospective study, the anesthetic effect of intravenous inhalational anesthesia with sevoflurane combined with remifentanyl in patients underwent LRHCC and its effect on cognitive function was investigated.

### Materials and methods

#### *Clinical data of patients*

Totally 127 patients with CC who received LRHCC in Henan Provincial People's Hospital during January 2017 and June 2021 were enrolled, and their clinical data were retrospectively analyzed. Among them, 60 patients anesthetized by propofol combined with remifentanyl were assigned to the control group (Con

group), while the rest 67 anesthetized by sevoflurane combined with remifentanyl were assigned to the research group (Res group). This study was carried out with approval of the Ethics Committee of Henan Provincial People's Hospital, and the patients or their family member had signed the informed consent.

**Inclusion criteria:** Patients confirmed with CC at Ia-IIa stage by cervical biopsy according to the diagnostic criteria in line with relevant guidelines [15]; patients who met indications of LRHCC; patients with detailed case data; patients meeting the anesthesia indications; patients with ASA grade  $\leq$  II [16]; and patients without obvious cognition, communication, vision or consciousness disorder. **Exclusion criteria:** Patients with autoimmune diseases, hypertension, diabetes, or cardiovascular or cerebrovascular diseases; patients who were given laparotomy instead halfway; patients with heart, liver or lung dysfunction; patients with infection or insufficient coagulation function; patients unable to complete the test independently; and patients with unfavorable compliance.

#### *Anesthesia methods*

Before surgery, both groups were fasted for 12 h, and then injected intramuscularly with 0.5 mg penehyclidine hydrochloride to establish a venous access. Their vital signs were monitored after they entered the operating room. Each of them was given 0.05-0.1 mg/kg midazolam, 0.8 mg/kg rocuronium bromide, and 2-4  $\mu$ g/(kg·h) remifentanyl (Specification: 2 mg/piece; manufacturer: Nwha Pharmaceutical Co., Ltd., State Food and Drug Administration (SFDA) approval number: H20143315) via intravenous drip after 3 minutes of oxygen inhalation. After 3 minutes, they were intubated, and an anesthesia machine was adopted to maintain the pneumoperitoneum pressure at 1.60-1.86 kPa, tidal volume at 8-10 mL/kg, and respiratory rate at 13-16 times/min. Patients in the Con group were anesthetized by propofol (Specification: 20 mL: 200 mg, manufacturer: Xi'an Libang Pharmaceutical Co., Ltd., SFDA approval number: H19990282) at 4-8 mg/(kg·h) via intravenous drip, while those in the Res group were anesthetized by inhalation of 1%-3% sevoflurane (Specification: 100 mL; manufacturer: Shanghai Hengrui Pharmaceutical Co., Ltd., SFDA approval num-

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ber: H20070172) and intermittently instilled with 0.2 mg/kg rocuronium bromide during surgery. Sevoflurane and propofol were terminated during incision suture, and all anesthetics were terminated when the patient was extubated.

### *Specimen collection and detection*

Before anesthesia (T0), at 30 min after anesthesia (T1) and 10 min after surgery (T2), 5 ml radial artery blood was extracted from each patient, followed by addition of heparin solution for plasma preparation. Then adrenaline content, brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) levels in the plasma were quantified by ELISA with corresponding kits from Germany IBL company (ELISA kit for adrenaline: item number: AE91026Hu, Shanghai AMEKO Biotechnology Co., Ltd.; ELISA kit for BDNF: item number: JL11683-48T, Shanghai Jianglai Biotechnology Co., Ltd.; ELISA kit for NGF: item number JL18187-48T, Shanghai Jianglai Biotechnology Co., Ltd.). A blank well, a well for standards, and a well for samples to be determined were set, respectively. Sample diluent and horseradish peroxidase (HRP)-labeled assay antibody were added into micropores except the sample pores. Unbound biotinylated antibodies were fully washed off, followed by addition of HRP-labeled avidin and the second rinse. Finally, TMB substrate was added for color development. TMB turned blue under catalysis and turned yellow under the action of acid. A microplate reader (Thermo Scientific FC automatic microplate reader, Thermo Fisher Scientific) was used to determine the optical density at 450 nm, on which corresponding concentration was converted from the standard curve. Moreover, a blood glucose meter was adopted for blood glucose (GLU) determination.

### *Outcome measures*

*Primary outcome measures:* Anesthetic effect including anesthesia maintenance time and extubation time in the two groups was evaluated, and the levels of BDNF and NGF in both groups at T0 and T2 were analyzed. In addition, the Mini-Mental State Examination (MMSE) was adopted to evaluate cognitive function at 24 h before surgery and at 6 and 24 h after surgery [17]. With a total score of 30 points, a MMSE score <27 points indicates cognitive

dysfunction, and a lower score indicates more severe cognitive dysfunction.

*Secondary outcome measures:* Hemodynamic indexes (heart rate (HR) and blood pressure (BP)) of the two groups were evaluated, and the concentrations of adrenaline and blood GLU in plasma were analyzed. In addition, the anesthesia recovery and adverse reactions in the two groups were recorded.

### *Statistical analyses*

SPSS 20.0 (Cabit Information Technology Co., Ltd., Shanghai, CN) was used for statistical analyses, and Prism 8 (SOFTHEAD Software Technology Co., Ltd., Shenzhen, China) was for figure rendering. Counting data (%) were expressed as n (%) analyzed using the chi-square test. Measurement data in normal distribution were expressed as (mean  $\pm$  SD), and comparison between groups was conducted using the independent-samples T test, while comparison within groups before and after therapy was conducted using the paired t test. Comparison of data at different time points was conducted using repeated analysis of variance, and the pairwise comparison of BR and HR among different time points was conducted using the Bonferroni method. \* means  $P < 0.05$  and \*\*\* means  $P < 0.001$ .  $P < 0.05$  denotes a remarkable difference.

## Results

### *General clinical data*

Comparison of general clinical data between the two groups revealed no significant difference regarding age, body mass index (BMI), smoking history, alcohol abuse history, place of residence, and tumour size ( $P > 0.05$ ). So, the two groups of patients were comparable (**Table 1**).

### *Changes of BR and HR in the two groups*

The changes in HR and BR at T0, T1 and T2 were compared between the two groups. No significant difference was observed between the two groups in HR and BP at T0 ( $P > 0.05$ ). HR and BP in both groups increased greatly at T1 than those at T0 (both  $P < 0.05$ ), with greatly lower HR and BP in the Res group than those in the Con group (both  $P < 0.05$ ). HR and BP in both

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**Table 1.** Comparison of general clinical data between two groups

Factors	Control group (n=60)	Research group (n=67)	t/ $\chi^2$ value	P-value
Age (Y)	40.5±6.4	41.6±6.1	0.991	0.324
BMI (kg/m <sup>2</sup> )	22.45±2.26	23.14±2.34	1.686	0.094
Smoking history			0.683	0.409
Yes	23 (38.33)	21 (31.34)		
No	37 (61.67)	46 (68.66)		
Alcohol abuse history			3.164	0.075
Yes	29 (48.33)	22 (32.84)		
No	31 (51.67)	45 (67.16)		
Place of residence			1.484	0.223
Urban area	34 (56.67)	45 (67.16)		
Rural area	26 (43.33)	22 (32.84)		
Tumor size			1.392	0.238
<2 cm	41 (68.33)	39 (58.21)		
≥2 cm	19 (31.67)	28 (41.79)		
Menopause or not?			1.037	0.309
Yes	36 (60.00)	46 (68.66)		
No	24 (40.00)	21 (31.34)		
ASA classification			0.664	0.415
Class I	27 (45.00)	35 (52.24)		
Class II	33 (55.00)	32 (47.76)		
FIGO staging			1.424	0.491
IA2	15 (25.00)	20 (29.85)		
IB1	26 (43.33)	32 (47.76)		
IB2	19 (31.67)	15 (22.39)		
Pathohistological type			1.295	0.524
Squamous cell carcinoma	32 (53.33)	40 (59.70)		
Adenocarcinoma	20 (33.33)	22 (32.84)		
Adenosquamous carcinoma	8 (13.33)	5 (7.46)		

groups decreased greatly at T2 than those at T1 ( $P<0.05$ ), with greatly lower HR and BP in the Res group than those in the Con group (both  $P<0.05$ ) (**Figure 1**).

### Comparison of anesthetic effects

According to comparison of anesthetic effects between the two groups, the two groups had no significant difference in anesthetic maintenance time ( $P>0.05$ ), while the Res group experienced notably earlier extubation time than the Con group ( $P<0.001$ ) (**Table 2**).

### Changes of stress substance contents

According to the ELISA results, the two groups were not significantly different in adrenaline and GLU levels at T0 (both  $P>0.05$ ). Adrenaline

and GLU in both groups increased greatly at T1 than those at T0 (both  $P<0.001$ ), with notably lower levels of them in the Res group than those in the Con group (both  $P<0.001$ ). Adrenaline and GLU levels in both groups decreased greatly at T2 than those at T1 (both  $P<0.001$ ), with notably lower levels of them in the Res group than those in the Con group (both  $P<0.001$ ) (**Figure 2**).

### Anesthesia recovery

According to comparison of anesthesia recovery between the two groups, the Res group experienced significantly earlier spontaneous breathing recovery time, anesthesia recovery time, and language recovery time than the Con group (**Table 3**).

### Changes in BDNF and NGF

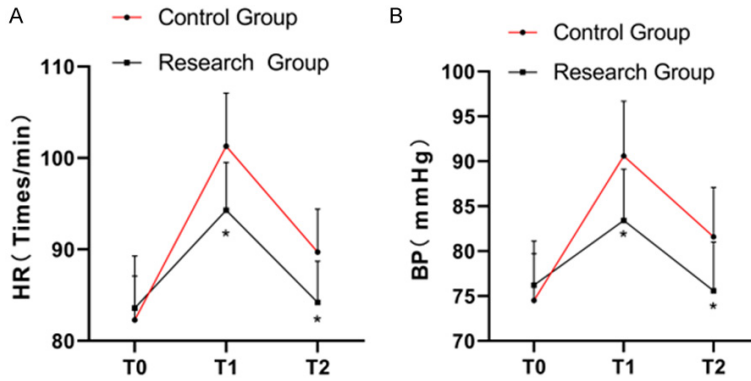
According to the results of ELISA, there was no significant difference between

the two groups in BDNF and NGF levels at T0 ( $P>0.05$ ), and BDNF and NGF in both groups decreased greatly at T2 than those at T0 ( $P<0.05$ ), with higher plasma levels of them in the Res group than those in the Con group (**Figure 3**).

### Comparison of MMSE scores

MMSE scores of the two groups were not notably different at 24 h before surgery ( $P>0.05$ ). At 6 h after surgery, MMSE scores of both groups decreased greatly (both  $P<0.001$ ), with a significantly lower MMSE score in the Con group than that in the Res group ( $P<0.001$ ). At 24 h after surgery, the Res group got a notably higher MMSE score than the Con group ( $P<0.05$ ) (**Figure 4**).

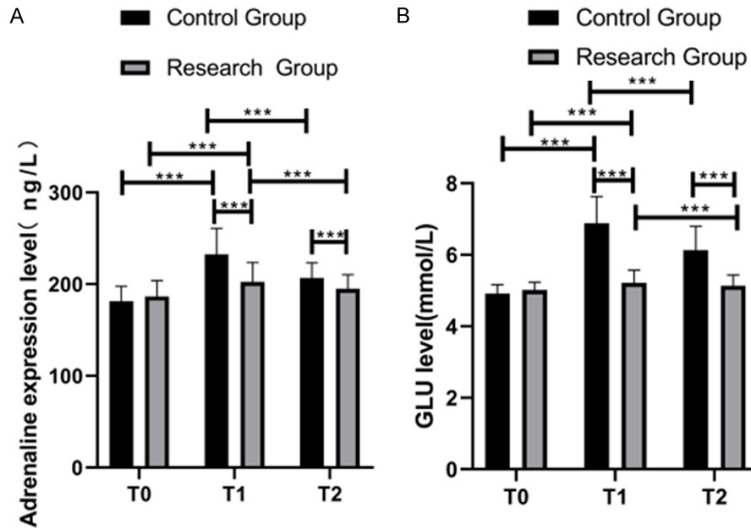
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**Figure 1.** Changes in heart rate (A) and blood pressure (B) of the two groups of patients. Note: T0: Before anesthesia, T1: at 30 min after anesthesia, T2: 10 min after surgery, Using independent-sample t test, compared to the same time in control group, \*P<0.05.

**Table 2.** Comparison of anesthetic effects between two groups

Group	Anesthesia maintenance time (min)	Extubation time (min)
Control group (n=60)	165.24±14.78	11.47±1.73
Research group (n=67)	161.35±16.49	9.35±1.21
T-value	1.939	8.068
P-value	0.166	<0.001



**Figure 2.** Changes in adrenaline (A) and GLU (B) level in the two groups. Note: T0: before anesthesia, T1: at 30 min after anesthesia, T2: 10 min after surgery; \*\*\*P<0.001, compared using independent-sample t test between groups and paired t test within group.

## Incidence of adverse reactions

According to statistics of adverse reactions in the two groups, there was no significant differ-

ence between the two groups in the incidence of adverse reactions (P>0.05, Table 4).

## Discussion

CC is a pervasive cancer worldwide. Thanks to the extensive implementation of the cell screening program, it can be diagnosed at an earlier stage and get timely treatment, so some countries and regions have shown a significant decrease in the incidence and mortality of CC [18, 19]. For patients with early CC, surgery can remarkably improve their cure and survival rates [20]. Different kinds of anesthesia can exert different effects on the prognosis of patients during surgery, so choosing an appropriate anesthesia method is crucial for postoperative recovery of patients.

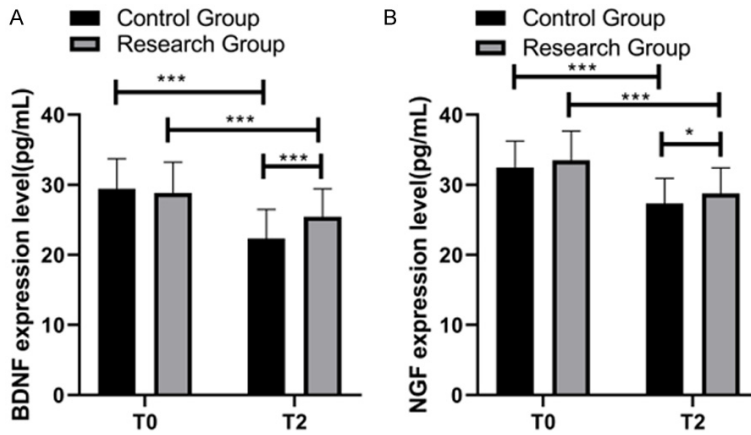
In surgical anesthesia, combined anesthesia with different drugs requires a lower dosage of each drug and may deliver a stronger anesthetic effect while lowering the incidence of side effects as compared with single administration [21]. We applied intravenous inhalational anesthesia with sevoflurane combined with remifentanyl in LRHCC to study the anesthetic effect of this combined anesthesia and its influence on patients' cognitive function. The Con group was given propofol combined with sevoflurane for anesthesia, while the Res group was given sevoflurane combined with remifentanyl for intravenous inhalational anesthesia.

Firstly, we compared the hemodynamic changes of the two groups, and found a notable fluctuation of HR and BP in the Con group and a slight fluctuation of them in the Res group. The

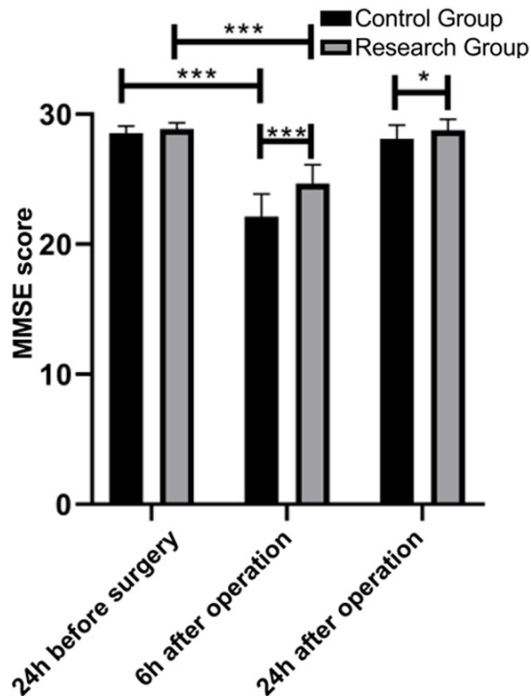
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**Table 3.** Comparison of anesthesia recovery between two groups

Group	Spontaneous breathing recovery time (min)	Anesthesia recovery time (min)	Language recovery time (min)
Control group (n=60)	8.31±1.65	9.26±2.04	12.05±2.17
Research group (n=67)	6.12±1.24	6.81±1.53	8.16±1.76
T-value	8.509	7.705	11.14
P-value	<0.001	<0.001	<0.001



**Figure 3.** Changes in the expression levels of BDNF (A) and NGF (B) in the two groups. Note: T0: before anesthesia, T2: 10 min after surgery; \*P<0.05, \*\*\*P<0.001, compared using independent-sample t test between groups and paired t test within group.



**Figure 4.** Comparison of MMSE scores between the two groups. Note: \*\*\*P<0.001, compared using independent-sample t test between groups and paired t test within group.

data imply that sevoflurane combined with remifentanyl contributes to more stable heart rate and blood pressure. Then we compared the anesthetic effects of the two groups, and found similar anesthesia time but notably earlier extubation time in the Res group as compared with Con group. In addition, the Res group showed more stable levels of adrenaline and blood glucose than the Con group. The results denote that sevoflurane combined with remifentanyl anesthesia contributes to earlier extubation time and higher anesthetic effect, and can alleviate stress reaction and pain of patients. Sevoflurane is a novel inhalation anesthetic featured with aromatic smell, little irritation to the respiratory tract and contributions to quick recovery of patients [22]. Remifentanyl is an ultra-short opioid receptor agonist. It can quickly achieve the

blood-brain balance in one minute in human body, and can be hydrolyzed rapidly in tissue fluid and blood, so it is advantageous in quick action, short maintenance time, no accumulation in body, and quick recovery [23]. Thus, we inferred that sevoflurane combined with remifentanyl anesthesia could effectively alleviate the stress reaction of patients during LRHCC, and maintain more stable heart rate, blood pressure and anesthetic effect in surgical patients. Haraldsen et al. [24] have revealed the stronger ability of sevoflurane than propofol in contributing to better hemodynamics. Similar to our results, in one study by Ren et al. [25], sevoflurane combined with remifentanyl anesthesia demonstrated a higher clinical efficacy than propofol combined with remifentanyl in cesarean section of pregnant women with gestational hypertension and showed its ability to alleviate stress response of pregnant women. Afterwards, we compared the anesthesia recovery between the two groups. According to the results, the Res group experienced earlier spontaneous breathing recovery time, anesthesia recovery time, and language recovery time than the Con group, which indicated that sevo-

**Table 4.** Comparison of incidence of adverse reactions between two groups

Group	Dizziness	Vomiting	Convulsion	Pain	Total
Control group (n=60)	4 (6.67)	1 (1.67)	1 (1.67)	4 (6.67)	10 (16.67)
Research group (n=67)	3 (4.48)	2 (2.98)	1 (1.49)	3 (4.48)	9 (13.43)
$\chi^2$ -value					0.260
P-value					0.610

flurane combined with remifentanil anesthesia could bring an earlier wake-up and consciousness regain to patients. In one study by Sun et al. [26], remifentanil combined with sevoflurane promoted shorter extubation time, faster anesthesia recovery and body rehabilitation but lower incidence of cough at awakening and restlessness as compared with those with sevoflurane alone for anesthesia maintenance. This agrees with our research.

Old age and high prevalence of complications are contributing factors of cognitive dysfunction after operation [27]. Different anesthesia methods exert different impacts on postoperative cognitive function. BDNF and NGF are biological indicators for evaluating patients' cognitive function, and the low expression of them indicates cognitive dysfunction [28, 29]. Postoperative cognitive dysfunction may last for weeks or months after operation, seriously compromising the health of patients [30]. In our study, the two groups were not different significantly in plasma BDNF and NGF before anesthesia, but after surgery, lower levels of BDNF and NGF were found in the Res group than those in the Con group. We also compared MMSE scores of the two groups, and found notably higher MMSE scores of patients in the Res group than those in the Con group. The data suggest that sevoflurane combined with remifentanil anesthesia may reduce postoperative cognitive dysfunction and accelerate postoperative recovery. One study by Sun et al. [31] has revealed that sevoflurane anesthesia can substantially lower the incidence of postoperative cognitive dysfunction as compared with propofol. It may be explained by the fact that sevoflurane takes effect faster and can be cleared faster. At the end of the study, we counted the incidence of adverse reactions between the two groups and found no notable difference. The incidence of adverse reactions in the Res group was 13.43%, indicating that sevoflurane combined with remifentanil anes-

thesia was safe and worthy of clinical promotion.

However, this study still has some limitations: First, remifentanil was used in a single dose, various concentrations can be compared to find out the ideal anesthetic concentration. Second, only few clinical detection indicators were detected. We will address them in future research.

In conclusion, this study has verified that compared with propofol combined with remifentanil, sevoflurane combined with remifentanil for anesthesia can exert a stronger anesthetic effect in patients receiving LRHCC, with advantages of less stress response and milder cognitive dysfunction. Also, it has a high safety, thus, it is worthy of clinical promotion.

#### Disclosure of conflict of interest

None.

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