

## Original Article

# Propofol combined with remifentanil reduces the adverse reactions of patients undergoing laparoscopic cholecystectomies

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**Abstract:** Objective: To explore the effectiveness of using isoflurane and propofol combined with remifentanil in laparoscopic cholecystectomies (LC). Methods: A total of 118 patients undergoing LC in our hospital from April 2018 to January 2019 were recruited as the study cohort. 56 of the patients were anesthetized with isoflurane combined with remifentanil during their operations (the IR group), and the other 62 patients were anesthetized with propofol combined with remifentanil during their operations (the PR group). The effects of the two anesthesia methods on the hemodynamics and stress responses were compared, and the postoperative recoveries, adverse reactions, analgesia, and cognitive functions were recorded. Results: Compared with the IR group, the average arterial pressure, heart rate, norepinephrine, and cortisol decreased in the PR group. Compared with the IR group, the total postoperative adverse reaction rate was lower in the PR group. Compared with the IR group, the spontaneous respiration recovery times, the times to opening eyes, and the extubation times were significantly shortened in the PR group. There was no significant difference in the postoperative pain levels between the two groups. Compared with the IR group, the postoperative cognitive function assessment was better in the PR group. Conclusion: Compared with isoflurane combined with remifentanil, propofol combined with remifentanil has a smaller impact on the hemodynamics and cognitive functions of patients undergoing LC, and it causes a more significant reduction in the stress response. In addition, its postoperative adverse reactions are lower, so it is worthy of promoting in clinical practice.

**Keywords:** Propofol, remifentanil, isoflurane, laparoscopic cholecystectomy

## Introduction

Laparoscopic cholecystectomy (LC) is a common surgical operation for treating cholelithiasis, gallbladder polyps, cholecystitis, and other gallbladder diseases [1, 2]. Compared with traditional open surgery, it has the advantages of less trauma, a quick recovery, and only mild pain, so it is widely recognized by doctors and patients [3]. Although LC has been used for about 30 years, it is still a challenge to anesthesiologists because of its great influence on patients' hemodynamics [4, 5]. At present, there is no standard anesthesia scheme that can be used in LC. Therefore, it has always been the focus of LC research to find a safe and effective anesthetic technique.

There are many anesthetic drugs that can be used in LC, and the compatibility effects and

safety of different drugs are different. Propofol, also known as disoprofol, is a widely used anesthetic with a high lipid solubility that can be rapidly induced and recovered from anesthesia during the operation. In addition, it has a good hemodynamic maintainability [6]. Isoflurane is a common anesthetic, and it is mainly used in semi-general anesthesia and general anesthesia, and it can provide sufficient oxygen inhalation during anesthesia [7]. Remifentanil is a new and powerful opioid receptor agonist, and it has a quick onset, is little influenced by liver or kidney dysfunction, has a high metabolic clearance and is easy to control, and it is widely used in various operations [8, 9]. In clinics, remifentanil is often combined with other anesthetics to enhance the anesthetic effect [10]. Previous studies have shown that isoflurane or propofol combined with remifentanil can play a

synergistic role and improve the quality of anesthesia [11, 12]. However, there is currently a lack of clinical data that can be used to compare the application of isoflurane and propofol combined with remifentanyl in LC.

This study was designed to find a safe and effective anesthesia method for LC by comparing the effectiveness of isoflurane combined with remifentanyl in LC and propofol combined with remifentanyl in LC.

## Materials and methods

### Research objects

A total of 118 patients undergoing LC at the College of Medicine, Zhejiang University, Sir Run Run Shaw Hospital from April 2018 to January 2019 were recruited as the study cohort. 56 of the patients were anesthetized with isoflurane combined with remifentanyl during their operations (the IR group), and the other 62 patients were anesthetized with propofol combined with remifentanyl during their operations (the PR group).

Inclusion criteria: patients whose ASA scores were II level or lower [13]. None of the patients had a history of abdominal surgery. Their clinical data were complete, and the patients had no communication problems and signed an informed agreement. All the patients successfully underwent LC.

The exclusion criteria were as follows: patients who had contraindications to the drugs used in this study, patients with severe heart, liver, or kidney function deficiencies, patients who abused drugs or patients with a long-term history of using pain medications, patients with poor compliance and a failure to complete various assessments, patients whose operations were converted to open surgery.

The research was approved by the Ethics Association of our hospital.

### Anesthetic methods

After they entered the operating room, the patients were given an intravenous infusion of lactated Ringer's solution (10 mL/kg) for 30 min, and a mask for oxygen-inspiration was provided for 3 min. Then midazolam (0.04 mg/kg), fentanyl (3 µg/kg), propofol (2 mg/kg) and

vecuronium (0.1 mg/kg) were administered to induce general anesthesia and intubation, and the ventilator control was used during the operation. The patients in the PR group were anesthetized using intravenous infusions of 6~8 mg/(kg·h) propofol and 0.2~0.3 µg/(kg·min) remifentanyl using a micropump. In the IR group, the patients were anesthetized using an intravenous infusion of 4 mg/(kg·h) propofol using a micropump. At the same time, 2%~3% isoflurane was used to maintain the anesthesia. The propofol was discontinued at five minutes before the end of the operation, and the isoflurane was discontinued at 15 minutes before the completion of the operation.

### Outcome measures

The postoperative spontaneous respiration recovery times, the of opening the eyes times, the extubation times, and any major adverse reactions were recorded.

The changes in the hemodynamic indexes, including the mean arterial pressure (MAP) and the heart rate (HR), were recorded before the anesthesia (T1), after the induction of the anesthesia but before the intubation (T2), immediately after the intubation (T3), at 10 min into the operation (T4), and at 10 min after the operation (T5). At the above four time points, the patients' blood was collected and centrifuged to collect the serum. The serum stress indexes [the norepinephrine (NE) and cortisol (Cor) levels] were measured using the ELISA method. The operation was carried out using NE ELISA kits (Shanghai Enzyme-Linked Biology, ml024646) and Cor ELISA kits (Shanghai Enzyme-Linked Biology, ml711149).

The Visual analogue scale pain score (VAS) [14] was used to evaluate the patients' pain levels at 1 h, 6 h, and 12 h after the operations. Painless was 0, mild pain was 1-3 points, pain that affected rest was 4-6 points, and unbearable pain was 7-10.

The mini-mental state scale (MMSE) [15] was used to score the patients' cognitive functions in the two groups at three hours before the operations and at 2 hours, 6 hours, and 12 hours after the operations, with a total possible score of 30. Scores of less than 27 points indicated cognitive impairment, and the lower the score, the higher the degree of impairment.

**Table 1.** A comparison of the two groups' general data ([n (%)],  $x \pm sd$ )

Grouping	IR group (n=56)	PR group (n=62)	$\chi^2/t$	P
Gender			0/379	0.489
Male	36 (64.29)	36 (58.06)		
Female	20 (35.71)	26 (41.94)		
Age/years old	50.27±8.98	52.41±8.11	1.360	0.176
Weight (KG)	66.35±5.78	67.32±6.32	0.867	0.388
Etiology			1.919	0.383
Gallbladder stone	23 (41.07)	18 (29.03)		
Gallbladder polyps	18 (32.14)	23 (37.10)		
Acute cholecystitis	15 (26.79)	21 (33.87)		
ASA evaluation			0.718	0.397
I	30 (53.57)	38 (61.29)		
II	26 (46.43)	24 (38.71)		

*Comparison of the postoperative adverse reactions*

By recording the postoperative adverse reactions, we found that there was no incurable adverse reaction in either group which could not be cured by symptomatic treatment or just healing by itself. The nausea and vomiting, urinary retention, abdominal distension, and restlessness incidences were similar in the two groups, but the total number of people affected in the study group was lower than it was in the IR group ( $P < 0.05$ ) (**Table 3**).

*Comparison of the postoperative analgesia*

By comparing the postoperative pain levels in the two groups, we found that the VAS scores in the IR group were (6.03±1.23), (5.12±1.34), and (3.67±1.24), and the VAS scores in the PR group were (5.87±1.43), (5.23±1.62), and (3.45±1.45) respectively after the operation at 2 h, 6 h and 12 h. There was no significant difference in the VAS scores at each time point after the operations in the two groups ( $P < 0.05$ ) (**Figure 1**).

*Changes in the hemodynamic indexes*

The patients' MAP and HR were recorded, and there was no significant difference in the MAP or HR between the two groups at T1 and T2 ( $P > 0.05$ ), but the MAP and HR of the PR group were lower than they were in the IR group at T3, T4, and T5 ( $P < 0.05$ ) (**Figure 2**).

*Comparison of the stress response indicators*

The patients' NE and Cor were recorded, and there was no significant difference in the NE or Cor between the two groups at T1 or T2 ( $P > 0.05$ ), but the NE and Cor in the PR group were lower than the NE and Cor in the IR group at T3, T4, and T5 ( $P < 0.05$ ) (**Figure 3**).

*Comparison of the cognitive functions*

The cognitive function was assessed using MMSE, and it was found that compared with before the anesthesia, the MMSE scores in the IR group declined significantly at 2 h, 6 h, and 12 h after the operations, but the correspond-

*Statistical processing*

SPSS 18.0 (IBM Corp, Armonk, NY, USA) was used for the statistical analysis, and GraphPad Prism 7 was used to draw the figures. The count data were expressed as a number/percentage [n (%)], and the comparisons between these count data were done using chi-square tests or Fisher exact tests. The measurement data were expressed as the mean number  $\pm$  standard deviation ( $x \pm sd$ ), and the measurement data between the two groups were compared using independent t tests. A single factor analysis of variance was used to compare the means among the multiple groups, and the subsequent pairwise comparisons were conducted using Dunnett-t tests. The difference was statistically significant when  $P < 0.05$ .

**Results**

*Comparison of the general clinical data*

There were no significant differences in the general data such as gender, age, weight, etiology, or ASA evaluation between the two groups ( $P < 0.05$ ) (**Table 1**).

*Comparison of the postoperative recovery*

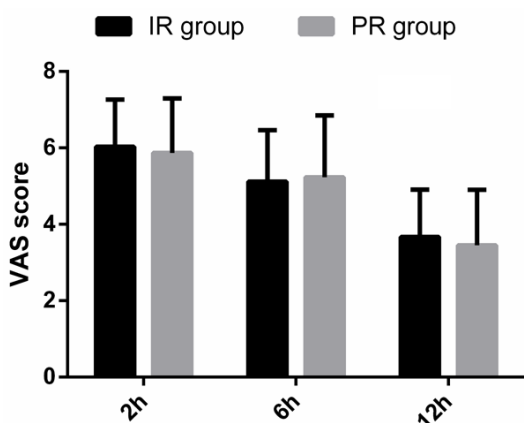
The patients' postoperative recoveries were recorded in both groups, and we found that compared with the IR group, the spontaneous respiration recovery times, the opening eyes times, and the extubation times were shorter in the PR group ( $P < 0.05$ ) (**Table 2**).

**Table 2.** A comparison of the postoperative recovery times (min,  $x \pm sd$ )

Grouping	IR group (n=56)	PR group (n=62)	t	P
Recovery time of spontaneous respiration	10.24±2.98	8.97±2.76	2.403	0.018
Time of opening eyes	13.29±3.22	10.25±3.68	4.753	< 0.001
Extubation time	14.28±3.95	12.11±3.38	3.215	0.002

**Table 3.** A comparison of the postoperative adverse reactions [n (%)]

Grouping	IR group (n=56)	PR group (n=62)	$\chi^2$	P
Nausea and vomiting	6 (10.71)	2 (3.23)	2.611	0.106
Urinary retention	4 (7.14)	3 (4.84)	0.280	0.597
Abdominal distension	5 (8.93)	2 (3.23)	1.715	0.190
Restlessness	3 (5.36)	4 (6.45)	0.063	0.802
Total number of people affected	15 (26.79)	7 (12.90)	4.658	0.031



**Figure 1.** A comparison of the postoperative analgesia. There were no significant differences in the pain scores at 2 h, 6 h, or 12 h after the operations in the two groups.

ing scores in PR group declined significantly at 2 h and 6 h after the operations ( $P < 0.05$ ). Compared with the IR group, the MMSE scores of the PR group were nearly the same before the anesthesia ( $P > 0.05$ ), but the MMSE scores increased at 2 h, 6 h, and 12 h after the operation ( $P < 0.05$ ). (Figure 4).

**Discussion**

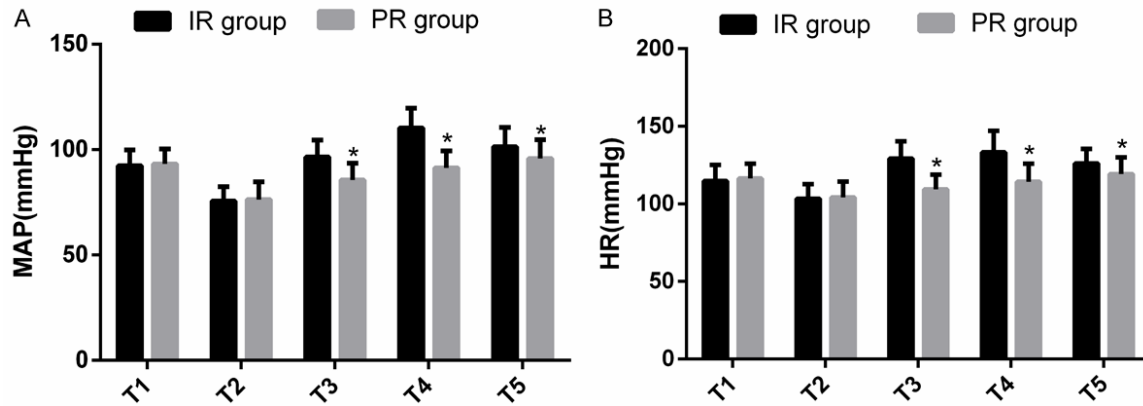
Reasonable and effective anesthetic management is the basis of successful operations and the reduction of postoperative complications [16]. At present, there are many anesthetic drugs that can be used in LC, and different effects will be produced using different combi-

nations of anesthetics. Isoflurane, propofol, and remifentanyl are common anesthetics in surgery. Previous studies have shown that propofol combined with remifentanyl is more valuable than isoflurane combined with remifentanyl in various operations. For example, propofol combined with remifentanyl is more valuable than remifentanyl

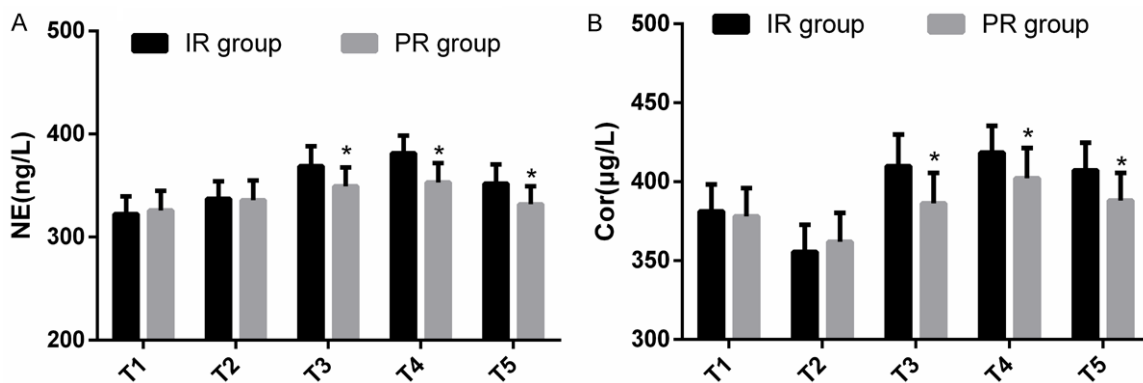
combined with isoflurane during cataract surgery, because the former provides better intraocular pressure and heart rate control for patients [17]. Compared with isoflurane combined with remifentanyl, the anesthetic regimen of propofol combined with remifentanyl can provide doctors with better vision and reduce patients' blood loss in endoscopic sinus surgery [18]. However, there is a lack of clinical data that compares the applications of isoflurane combined with remifentanyl in LC and propofol combined with remifentanyl in LC, so we designed this study.

LC is a common operation. However, a CO<sub>2</sub> pneumoperitoneum will be established during operation, which will disturb patients' respiratory and cardiovascular systems, affect their hemodynamic imbalance, and increase the operation's difficulty [19]. In addition, the establishment of a pneumoperitoneum will also activate the renin-angiotensin-aldosterone system and aggravate the stress reaction, which will lead to postoperative adverse complications and affect patients' lives and health [20]. It has been reported that reducing patients' perioperative stress response can reduce the potential complications, shorten the hospital stays, and enable patients to recover their baseline functional status more quickly [21]. Therefore, the anesthetic programs that have little impact on the patient's body should be selected during anesthesia. We measured patients' hemodynamic indexes during the perioperative period and found that MAP and HR in

The application of propofol combined with remifentanyl in laparoscopic cholecystectomy



**Figure 2.** Changes in the hemodynamic indexes. A. The MAP levels in the PR group were lower than they were in the IR group at T3, T4, and T5. B. The HR levels in the PR group were lower than they were in the IR group at T3, T4, and T5. Note: Compared with the IR group at the same time point, \*represents  $P < 0.05$ .



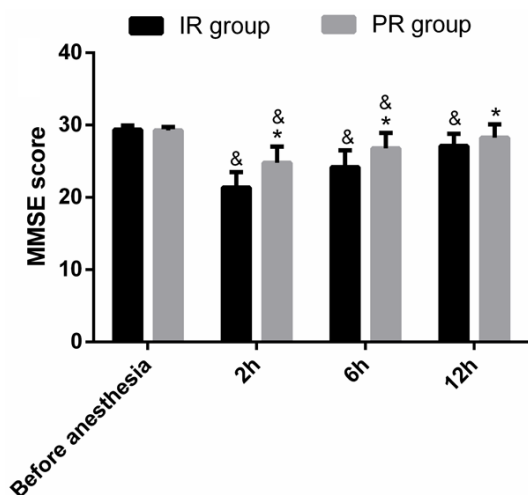
**Figure 3.** Changes in the stress response indicators. A. The NE levels in the PR group were lower than they were in the IR group at T3, T4, and T5. B. The Cor levels in the PR group were lower than they were in the IR group at T3, T4, and T5. Note: Compared with the IR group at the same time point, \*represents  $P < 0.05$ .

PR group decreased at T3, T4 and T5 compared with IR group. Subsequently, we measure the serum levels of Cor and NE in patients during the perioperative period, and the increases of these levels indicated that the stress response was aggravated [22]. The results showed that the Cor and NE levels in the PR group were lower than they were in the IR group at T3, T4, and T5, suggesting that, compared with isoflurane combined with remifentanyl, propofol combined with remifentanyl had less of an impact on the hemodynamics and caused a smaller stress response in the patients undergoing LC. The reason may be that propofol can maximally reduce systemic blood pressure through vasodilation [23]. Postoperative complications have always been a headache for doctors, as they not only affect the patients' recovery, but they also seriously threaten patients' lives [24, 25].

By recording the postoperative adverse reactions in the two groups, we found that there were no serious adverse reactions in the two groups, and any reactions could be cured quickly using symptomatic treatment, but the total number of people affected in the PR group was lower than the number affected in the IR group. This shows that propofol combined with remifentanyl is safer than isoflurane combined with remifentanyl.

As we all know, elderly patients are prone to transient changes in their postoperative cognitive function during laparoscopic surgery, leading to symptoms such as aprosexia, forgetfulness, foggy thinking, and listlessness. In severe cases, postoperative cognitive dysfunction may develop, and it has a negative impact on patients' postoperative rehabilitation [26, 27].





**Figure 4.** Comparison of the cognitive functions. Compared with the pre-anesthesia scores, the MMSE scores in the IR group declined significant at 2 h, 6 h, and 12 h after the operation, but the scores in the PR group declined significantly at 2 h and 6 h after the operation. Compared with the IR group, the MMSE scores in the PR group showed little difference before the anesthesia, but the MMSE scores increased at 2 h, 6 h, and 12 h after the operations. Note: Compared with the IR group at the same time point, \*represents  $P < 0.05$ . &means that compared with that before operation.

Clinical experience reveals that anesthesia is one of the important causes of cognitive dysfunction in patients undergoing surgery. However, excellent anesthesia schemes can reduce the impact of surgery on the cognitive function of patients [28, 29]. Our results showed that the MMSE scores in the PR group were higher than the MMSE scores in the IR group at 2 h, 6 h, and 12 h after the anesthesia, an indication that compared with isoflurane combined with remifentanyl, propofol combined with remifentanyl has a smaller effect on the cognitive function of patients receiving LC. In addition, the results also revealed that the latter also showed advantages in the spontaneous respiration recovery time, the opening eyes time, and the extubation time. The reason may be that propofol takes effect quickly, so its half-life is short, and it can quickly reach the ideal anesthesia depth after being combined with remifentanyl, so as to facilitate the operation.

Although we have proved that propofol combined with remifentanyl has a higher effectiveness in LC than isoflurane combined with remifentanyl, there are still some deficiencies in this

study. First of all, all the research objects came from the same region, and the number of samples was small, which inevitably led to some limitations. Second, the optimal dosage of compatibility between the drugs was not analyzed. It is hoped that these deficiencies can be supplemented in future studies.

To sum up, compared with isoflurane combined with remifentanyl, propofol combined with remifentanyl has a smaller impact on the hemodynamics and cognitive function of patients undergoing LC, and it brings a more significant reduction in the stress response. In addition, the postoperative adverse reactions are lower, so it is worthy of promoting in clinical practice.

#### Disclosure of conflict of interest

None.

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