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Original Article

Effect of dexmedetomidine combined with propofol on stress response, hemodynamics, and postoperative complications in patients undergoing laparoscopic cholecystectomy

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Abstract: Objective: This research was designed to probe the effect of dexmedetomidine combined with propofol on stress response, hemodynamics, and postoperative complications in patients undergoing laparoscopic cholecystectomy. Methods: Altogether 144 patients who underwent laparoscopic cholecystectomy in the Beibei Traditional Chinese Medical Hospital, the Sixth People's Hospital of Chongqing from January 2018 to July 2020 were research subjects. The control group (CG) (n=68) received propofol continuous pumping sedation, while the research group (RG) (n=76) was given dexmedetomidine combined with propofol continuous pumping sedation. The quality of postoperative recovery and incidence of postoperative complications of the two groups were observed and compared. The hemodynamic indexes (HR, SpO_2 and MAP) before anesthesia induction (T0), tracheal intubation (T1), at the commencement of operation (T2), at the end of operation (T3), and extubation (T4) were observed. The stress response indexes (Cortisol, ACTH and norepinephrine, NE) were monitored, and the scores of pain, anxiety and cognitive dysfunction before and after operation were evaluated. Results: Compared with the CG, the incidence of postoperative complications in the RG was lower, and the quality of postoperative recovery (time of breathing recovery, eye opening, consciousness and extubation) was better. Besides, the hemodynamic indexes of the RG were more stable, and the levels of stress indexes Cortisol, ACTH, and NE were lower. The RG had VAS and SAS scores that were lower, and MMSE scores were higher. Conclusion: Dexmedetomidine combined with propofol can effectively alleviate the stress response of patients undergoing laparoscopic cholecystectomy, stabilize perioperative hemodynamics, and reduce postoperative complications.

Keywords: Dexmedetomidine, propofol, laparoscopic cholecystectomy, stress response, hemodynamics

Introduction

Cholelithiasis and cholecystitis are the most familiar benign gallbladder diseases clinically [1]. Surgical treatment is the most important treatment [2]. With the development of minimally invasive concepts and technology, laparoscopic surgery has become a crucial way of surgery [3]. Under general anesthesia, laparoscopic cholecystectomy (LC) is a surgical method to observe the abdominal cavity and gallbladder through laparoscope and perform cholecystectomy by making incisions of about 10 mm in the navel, right axillary front line and costal midline, and near the xiphoid process in the middle of upper abdomen. Carbon dioxide gas is injected into the abdominal cavity after it is punctured with a needle, the insufflator is connected to maintain proper pressure, and the necessary instruments are placed [4-6]. Compared with conventional open cholecystectomy (OC), it has minimally invasive tissue, less pain, and postoperative pulmonary complications, and quick recovery. Thus, it has been highly recognized by doctors and patients, and widely used in clinical practice [7, 8] as the gold standard for treating cholecystolithiasis, cholecystitis, polyp of gallbladder, and other diseases [9]. Anesthesia is the key to LC, and anesthesia and surgical trauma inevitably cause a series of changes in stress response, postoperative pain, immune function, cognitive function, and hemodynamics [10, 11]. Therefore, a rational choice of anesthetic drugs and schemes has important clinical significance for reducing the body's response to noxious stimuli [12].

Propofol is a traditional intravenous general anesthetic. It has quick and short effects, strong anesthetic efficacy, quick onset, rapid and stable recovery and few adverse reactions, and is widely used clinically [13]. Some studies have shown that propofol can inhibit the secretion of adrenal cortical hormone, and can reduce cortisol and catecholamine, but these quickly returns to the preoperative level after drug withdrawal [14, 15]. Dexmedetomidine (Dex) is a new type of agonist of 2-adrenergic receptor with high selectivity [16]. Research has shown that Dex has been widely used in auxiliary anesthesia because of its good sedative, analgesic, antisympathetic, and non-respiratory inhibitory effects [17]. It reduces sympathetic activity by decreasing the release of norepinephrine, which leads to a decrease of blood pressure (BP) and heart rate (HR). It also reduces the dosage of anesthetics and opioid analgesics during operation [18].

At the moment, there are few studies on propofol combined with dexmedetomidine in laparoscopic cholecystectomy. Hence, in this research, patients undergoing laparoscopic cholecystectomy were given propofol combined with dexmedetomidine, in order to explore the influence of this scheme on postoperative stress response, hemodynamics, and the incidence of complications.

Materials and methods

General data

Totally 144 patients undergoing laparoscopic cholecystectomy in the Beibei Traditional Chinese Medical Hospital, the Sixth People's Hospital of Chongqing from January 2018 to July 2020, were selected as the research objects. Thereinto, the control group (CG) (n=68) received propofol continuous pumping sedation, while the research group (RG) (n=76) was given dexmedetomidine combined with propofol continuous pumping sedation. In the RG, there were 45 males and 31 females, aged from 25 to 70, (50.77±3.48) years old on average. In the CG, there were 38 males and 30 females, aged from 28 to 68, with an average age of (51.13±3.72) years.

Inclusion and exclusion criteria

Inclusion criteria were as follows: (1) All met the diagnostic criteria for benign diseases of gallbladder [19] and the indications of laparoscopic cholecystectomy; (2) All patients were receiving laparoscopic surgery for the first time; (3) The American Society of Anesthesiologists (ASA) [20] was classified as Grades I-II; (4) This research was approved by the Ethics Committee of our hospital. Both the subjects and their families were informed, and they signed the full informed consent form.

Exclusion criteria were as follows: (1) There were contraindications for surgical anesthesia; (2) Those who were allergic to the drugs used in this research; (3) Those who took sedatives or antidepressants before surgery and had a history of opioid addiction; (4) Patients with coagulation dysfunction; (5) Patients with chronic diseases such as hypertension and diabetes; (6) Patients with severe primary organ diseases, such as cardiovascular diseases, respiratory diseases, liver and kidney insufficiency; (7) Patients with cognitive impairment, central nervous system and severe peripheral nerve diseases.

Anesthesia methods

All patients were fasted and forbidden to drink for 8 h before operation. After patients entered the operating room, the venous access was opened, and the vital signs, including BP, oxygen saturation, HR, and electrocardiogram, were closely monitored by Dash 4000 monitor. Meanwhile, the Bispectral Index (BIS) was monitored by American BIS monitor. In view of patients' body mass and other parameters, the dose of corresponding anesthetic was calculated to induce anesthesia. Patients in both groups were given 0.15 mg/kg vecuronium bromide (Xinbai Pharmaceutical Co., Ltd., Nanjing, China, H20067267), 2 μg/kg fentanyl (Langfang Branch of China National Pharmaceutical Group Industry Co., Ltd., China, H20-123297), and 1.5 mg/kg propofol (Sichuan Guorui Pharmaceutical Co., Ltd., Leshan, China, H20030115). Those in the CG were given 0.15 μg/(kg·min) remifentanil (Yichang Renfu Pharmaceutical Co., Ltd., China, H20030197) and 4.5 mg/(k·gh) propofol (Sichuan Guorui Pharmaceutical Co., Ltd., Leshan, China, H20030115) by intravenous target control to maintain anesthesia, and vecuronium bromide (Xinbai Pharmaceutical Co., Ltd., Nanjing, China, H20067267) could be added if necessary. Patients in the RG were given a loading dose of dexmedetomidine (Jiangsu Hengrui Pharmaceutical Co., Ltd., Lianyungang, China, H20090248) 0.5 μg/kg within 10 min before anesthesia induction, and intravenous injection was completed within 10 min. Afterwards, 0.15 μg/(kg·min) remifentanil (Yichang Renfu Pharmaceutical Co., Ltd., China, H20030197) and 4.5 mg/(kg·h) propofol (Sichuan Guorui Pharmaceutical Co., Ltd., Leshan, China, H20030115), and 0.5 μg/(kg·h) dexmedetomidine (Jiangsu Hengrui Pharmaceutical Co., Ltd., Lianyungang, China, H20090248) were added for continuous infusion until the end of operation.

Outcome measures

(1) The incidence of postoperative complications was observed. (2) The quality of postoperative recovery was observed: time of postoperative breathing recovery, eye opening, consciousness, and extubation. (3) Hemodynamic indexes: the hemodynamic indexes before anesthesia induction (T0), endotracheal intubation (T1), at the commencement of operation (T2), at the end of operation (T3), and at extubation (T4) were observed and recorded, including HR, oxygen saturation (SpO_2), and mean arterial pressure (MAP). (4) Oxidative stress response indexes: 5 mL venous blood was collected from both groups of patients before operation and 24 h after operation. The levels of cortisol (Cor), adrenocorticotropic hormone (ACTH) and norepinephrine (NE) before and 24 h after operation were tested by ELISA. This research was conducted in strict accordance with the kit instructions of human Cor ELISA (Shanghai Hengfei Biotechnology Co., Ltd., China, CEA462Ge-1), ACTH and NE ELISA (Shanghai Jingkang Bioengineering Co., Ltd., China, JK-(e)-A905, JK-(a)-5709). (5) Pain score: the pain before and 24 h after operation was evaluated by Visual analogue scale (VAS) [21]; 0 is painless; less than 3 points is mild pain that can be tolerated; 4-6 is divided into patients with pain that affects sleep, but can still be tolerated; a score of 7-10 means that patients have gradually intense pain that affects sleep. The lower the score, the lighter the pain symptoms. (6) Postoperative cognitive function indicators: the cognitive function of both groups before and 24 h after operation was assessed by the Minimum Mental State Examination (MMSE) [22]. The total score is 30 points, and 27-30 is normal; 21-26 is mild disorder; 10-20 is moderate disorder; 0-9 is a severe disorder. The higher the score, the better the cognitive function is. (7) Anxiety score: the anxiety of patients in both groups before and 24 h after operation was assessed by Self-rating Anxiety Scale (SAS) [23]. The total score of SAS scale is 100 points: 50-70 indicates mild anxiety, 71-90 indicates moderate anxiety, and > 90 means severe anxiety; the higher the score, the more serious the anxiety is.

Statistical methods

SPSS24.0 (IBM Corp, Armonk, NY, USA) was employed for statistical analysis, and the pictures were drawn by GraphPad Prism 7. The counting data were expressed by (n (%)) and compared by Chi-square test. The measured data were represented by mean ± standard deviation (x ± sd) and compared by independent-samples T test. The comparison before and after treatment was made by paired t-test, the data at different time points within the group were analyzed by one-way ANOVA, and pairwise comparison at different time points within the group was assessed by SNK-q method. If $P < 0.05$, a difference was considered significant.

Results

General data

There was no marked difference in clinical baseline data such as gender, age, body mass index (BMI), operation time, place of residence, nationality, education background, history of smoking and drinking, or fracture causes and types between the two groups ($P > 0.05$) (**Table 1**).

Comparison of postoperative complications between both groups of patients

The incidence of postoperative complications was 6.58% in the RG, which was markedly

Table 1. Comparison of clinical baseline data between two groups (n (%))/(x ± sd)

Category	Research group (n=76)	Control group (n=68)	t/χ^2	P
Gender			0.162	0.686
Male	45 (59.21)	38 (55.88)		
Female	31 (40.79)	30 (44.12)		
Age (years)	50.77±3.48	51.13±3.72	0.599	0.549
BMI (kg/m^2)	22.83±2.15	22.36±2.23	1.287	0.200
Operation time (min)	48.32±3.84	49.07±3.42	1.232	0.220
Disease type			0.567	0.451
Cholecystitis	28 (36.84)	21 (30.88)		
Gallstone	48 (63.16)	47 (69.12)		
Place of residence			0.241	0.623
City	40 (36.84)	33 (30.88)		
Countryside	36 (63.16)	35 (69.12)		
Marriage			0.316	0.573
Married	60 (78.95)	51 (75.00)		
Unmarried	16 (21.05)	17 (25.00)		
Education background			0.013	0.906
≥ high school	25 (32.89)	23 (33.82)		
< high school	51 (67.11)	45 (66.18)		
History of smoking			1.653	0.198
Yes	36 (47.37)	25 (36.76)		
No	40 (52.63)	43 (63.24)		
History of hypertension			0.316	0.573
Yes	21 (27.63)	16 (23.53)		
No	55 (72.37)	52 (76.47)		
History of diabetes			0.022	0.881
Yes	13 (17.11)	11 (16.18)		
No	63 (82.89)	57 (83.82)		

lower than that in the CG (26.46%) (P < 0.05) (**Table 2**).

Comparison of postoperative recovery quality between both groups

The time of respiratory recovery, eye opening, consciousness and extubation in the RG were dramatically shorter than those in the CG (P < 0.001) (**Table 3**).

Comparison of hemodynamic indexes between both groups of patients

In the RG, HR, SpO_2, and MAP did not change dramatically at T0, T1, T2, T3, and T4 (P > 0.05). There was no marked difference in HR between T1 and T0 in the CG (P > 0.05), while T2-T4 were markedly higher than T0 and dramatically higher than the RG at the same time. SpO_2 in the CG did not change dramatically at T0, T1, T2, T3, and T4, and there was no marked difference compared with the RG in the meantime (P > 0.05). There was no obvious difference in MAP between T1 and T0 in the CG (P > 0.05), while T2-T4 were markedly higher than T0 and obviously higher than those in the RG at the same time (**Figure 1**).

Comparison of oxidative stress response indexes between two groups of patients

Before operation, there was no obvious difference in serum Cor, ACTH, and NE between the CG and the RG (P > 0.05). Serum Cor, ACTH, and NE in the two groups were markedly higher than those before operation at 24 h after operation, and were dramatically lower in the RG than those in the CG at the same time (**Figure 2**).

Comparison of VAS scores between both groups of patients

There was no marked difference in VAS scores between the two groups before operation (P > 0.05), and the scores in the RG were dramatically lower than those in the CG at 24 h after operation (**Figure 3**).

Comparison of MMSE scores between both groups

Before operation, there was no obvious difference in MMSE scores between the two groups (P > 0.05). Twenty-four hours after operation, the scores were markedly lower than those before operation, and those of the RG were dramatically higher than in the CG (**Figure 4**).

Comparison of SAS scores between both groups

Before operation, there was no marked difference in SAS scores between the two groups (P

Table 2. Comparison of postoperative complications between the two groups (n (%))

Group	n	Nausea and vomiting	Dysphoria	Urinary retention	Hypotension	Respiratory depression	Total incidence rate
Research group	76	2 (2.63)	1 (1.32)	0 (0.00)	2 (2.63)	0 (0.00)	5 (6.58)
Control group	Sixty-eight	7 (10.29)	4 (5.88)	3 (4.41)	3 (4.41)	1 (1.47)	18 (26.46)
χ^2	-	-	-	-	-	-	10.580
P	-	-	-	-	-	-	0.001

Table 3. Comparison of postoperative recovery quality between the two groups (x ± sd, min)

Group	Respiratory recovery time	Eye opening time	Safe consciousness time	Withdrawal time
Research group (n=76)	6.88±2.13	9.12±3.01	20.03±4.08	30.16±5.25
Control group (n=68)	11.53±3.02	12.54±3.27	29.86±4.85	49.86±6.55
t	10.760	6.535	13.200	20.010
P	< 0.001	< 0.001	< 0.001	< 0.001

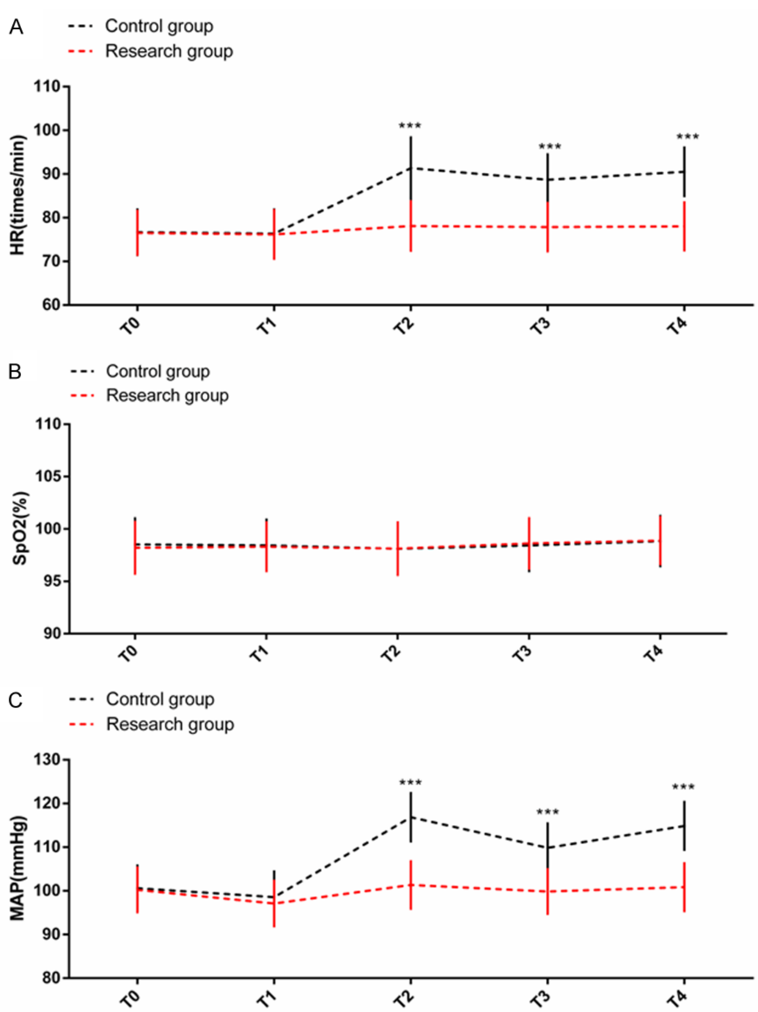

Figure 1. Comparison of hemodynamic indexes between both groups. A: The HR of CG is markedly higher than that of T0 at T2-T4, and is dramatically higher than that of RG at the same time. B: The SpO_2 in the CG does not change markedly from T0 to T4, and there is no obvious difference compared with the RG simultaneously. C: The MAP of CG is dramatically higher than that of T0 at T2-T4, and is markedly higher than that of RG concurrently. Note: ***P < 0.001.

> 0.05). Twenty-four hours after operation, the scores of patients increased markedly, and the RG was dramatically lower than the CG (**Figure 5**).

Discussion

Laparoscopic cholecystectomy is considered the first choice to treat benign diseases of gallbladder. Compared with traditional open surgery, it has less trauma and quick recovery, thus it is widely used clinically [24]. However, effective and safe anesthetic drugs and methods are the key to success. Shallow anesthesia can increase BP, HR, and myocardial oxygen consumption, while deep anesthesia can cause postoperative adverse reactions such as poor quality of recovery and postoperative cognitive dysfunction [25, 26]. Hence,

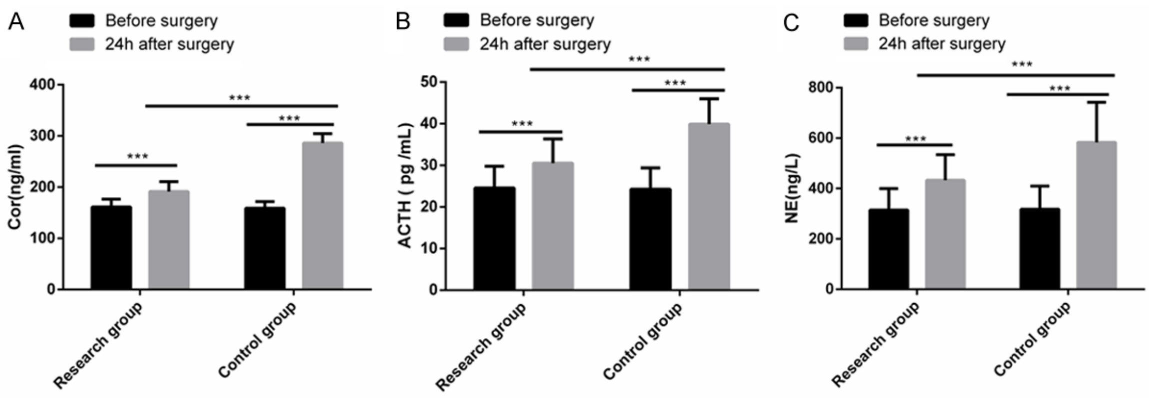

Figure 2. Comparison of oxidative stress response indexes between both groups. Serum Cor (A), ACTH (B), and NE (C) in both groups are markedly higher than those before operation, and the RG is dramatically lower than the CG. Note: ***P < 0.001.

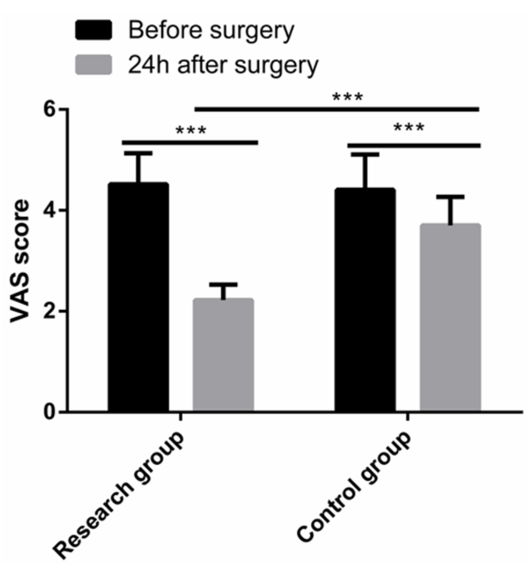

Figure 3. Comparison of VAS scores between both groups. The VAS scores of patients in the RG are markedly lower than those in the CG at 24 h after operation. Note: ***P < 0.001.

selecting anesthetic drugs and schemes rationally is quite significant to the smooth implementation of surgery and the prognosis.

This research manifested that the incidence of postoperative adverse reactions such as nausea, vomiting, respiratory depression, and restlessness in the RG was dramatically lower than that in the CG; it indicated that dexmedetomidine combined with propofol could reduce the incidence of postoperative complications in laparoscopic cholecystectomy. Meanwhile, we also observed and compared the postoperative recovery quality of both groups of patients. The results signified that the time of postoperative respiratory recovery, eye opening, consciousness, and extubation of the RG were dramatically shorter than those of the CG. This revealed that dexmedetomidine combined with propofol had more advantages in the postoperative recovery quality of patients, and markedly improved the postoperative recovery of patients. Zhang *et al.* [27] found that the anesthesia scheme of dexmedetomidine combined with propofol in laparoscopic gastrointestinal tumor resection could effectively stabilize intraoperative hemodynamics, relieve postoperative pain and restlessness, and improve postoperative recovery quality, which was similar to our research results. Kim *et al.* [28] confirmed that the anesthesia mode of propofol combined with dexmedetomidine in hand surgery with brachial plexus block could stabilize the hemodynamics and perioperative adverse reactions of patients. In this study, we found that HR, SpO_2 and MAP in the RG were markedly more stable than those in the CG at T2-T4, which was similar to the results of Kim. All surgical patients will have different degrees of stress response, which directly affects the surgical effect and prognosis [29]. Li *et al.* [30] discovered that dexmedetomidine was added to patients undergoing radical resection of esophageal cancer by thoracoscopy combined with laparoscopy on the basis of propofol and remifentanil anesthesia, which could effectively reduce the stress response during the perioperative period and relieve the postoperative pain. Furthermore, we monitored the stress response of two groups of patients, and found that the serum stress indicators Cor, ACTH

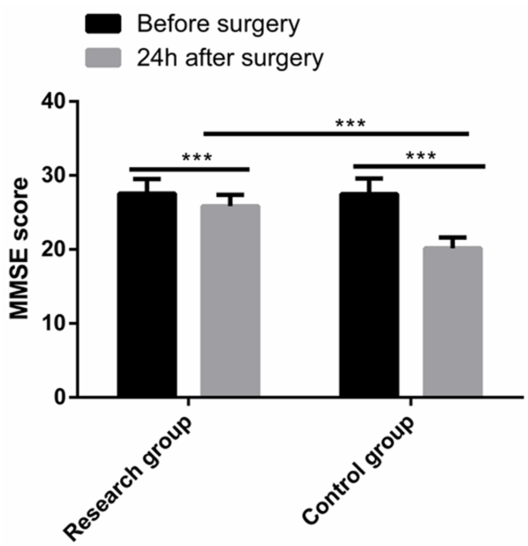

Figure 4. Comparison of MMSE scores between both groups. Twenty-four hours after operation, the scores of patients in both groups decrease dramatically, and the RG is markedly higher than the CG. Note: ***P < 0.001.

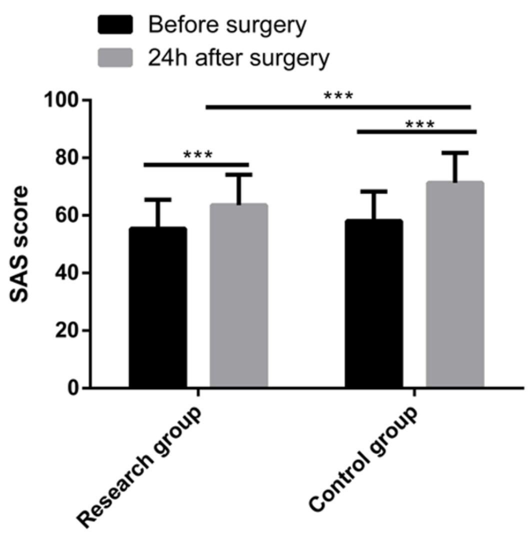

Figure 5. Comparison of SAS scores between both groups Twenty-four hours after operation, the scores of patients in both groups increase markedly, and the RG is dramatically lower than the CG. Note: ***P < 0.001.

and NE in the RG were markedly lower than those in the CG. This suggests that dexmedetomidine combined with propofol could markedly reduce the stress response of patients and alleviate their harm, which is consistent with the research results of Li *et al*. MMSE is a common tool to evaluate postoperative cognitive function of patients undergoing surgery. We evaluated their cognitive function before and after surgery. The results manifested that the postoperative cognitive function of patients in the RG was markedly higher than that in the CG, indicating that the anesthesia scheme of dexmedetomidine combined with propofol could improve postoperative cognitive dysfunction of patients undergoing surgery. Li *et al*. [31] found that dexmedetomidine combined with propofol could reduce the incidence of postoperative cognitive dysfunction in elderly patients undergoing hip or knee replacement, which was similar to our results. We also assessed the pain and anxiety of postoperative patients; results showed that the VAS and SAS scores in the RG were dramatically lower than those in the CG, which also indicated that patients receiving dexmedetomidine combined with propofol anesthesia could better relieve postoperative pain and anxiety. Zeng *et al.* [32] found that in thoracic surgery, dexmedetomidine combined with propofol could reduce postoperative pain, enhance analgesic effect, and decrease the dosage of propofol, which was similar to our results.

In general, dexmedetomidine combined with propofol can effectively alleviate the stress response of patients undergoing laparoscopic cholecystectomy, stabilize perioperative hemodynamics, reduce postoperative complications, and improve cognitive function, reduce pain and anxiety, and promote rehabilitation. The innovation of this study is that it combines the advantages of propofol and dexmetomidine in anesthesia, and makes up for the effect of propofol on patients' hemodynamics, so as to achieve the purpose of smooth operation. However, this study also has some shortcomings. For example, we could also analyze patients' treatment compliance and influencing factors, and the risk factors of postoperative rehabilitation. In the future, we will study the above aspects.

Disclosure of conflict of interest

None.

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