Original Article
Clinical study of the combined use of dexmedetomidine and remifentanil in patients with coronary heart disease undergoing 3D laparoscopic surgery with EEG bispectral index monitoring

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Abstract: Objective: This study sought to investigate the safety and clinical outcomes associated with the combined administration of dexmedetomidine (Dex) and remifentanil (Rem) in patients with coronary heart disease undergoing three-dimensional (3D) laparoscopic surgery, with concurrent monitoring of the electroencephalography (EEG) bispectral index. Methods: This study is of a retrospective nature and involved a total of 60 patients with coronary heart disease who underwent 3D laparoscopic surgery at our hospital between June 2020 and September 2021. In a double-blind manner, these patients were randomly assigned to two groups: the control group (Group I), which consisted of 30 patients, and the treatment group (Group II) receiving a combination of Dex and Rem, also comprising 30 patients. The study's primary objective was to compare and assess the treatment outcomes in these two patient groups. Results: Patients in Group II who developed postoperative coronary heart disease experienced a significant reduction in blood pressure, heart rate, and electrocardiogram values ($P<0.05$). Additionally, Group II exhibited lower bispectral index (BIS) and visual analog scale (VAS) values ($P<0.05$). Conclusion: In patients with coronary heart disease undergoing 3D laparoscopic surgery, the intraoperative use of Dex combined with Rem anesthesia offers several advantages. It helps stabilize hemodynamics, reducing the risk of myocardial ischemia, and significantly alleviates postoperative pain, all without increasing the likelihood of adverse postoperative reactions. Furthermore, this approach effectively dampens the intraoperative and postoperative stress response, facilitating enhanced recovery after surgery (ERAS). Overall, the clinical impact is positive, safe, and reliable.

Keywords: Dex, Rem, coronary heart disease, 3D laparoscopic surgery, ERAS

Introduction

Multiple studies have provided evidence that a significant portion of the country's population, approximately one-fifth, which translates to around 290 million individuals, is affected by cardiovascular disease. Within this group, 11 million individuals suffer from coronary heart disease [1]. Hence, it is crucial to consider the treatment of coronary heart disease and the postoperative recovery of these patients.

The use of 3D laparoscopy, with its three-dimensional visual capabilities and minimally invasive nature, has empowered surgeons to perform more precise procedures, resulting in smaller scars and quicker postoperative recoveries [2]. Particularly for elderly patients with coronary heart disease undergoing 3D laparoscopic surgery, the benefits are pronounced. Surgeons can work with greater precision, anatomical details are clearer, patient trauma is significantly reduced, intraoperative hemodynamics remain stable, and the risk of myocardial ischemia is significantly diminished [3]. Additionally, 3D laparoscopic surgery effectively mitigates both intraoperative and postoperative stress responses without elevating the incidence of postoperative adverse reactions, leading to accelerated recovery [4]. The clinical results of 3D laparoscopic surgery in elderly patients with coronary heart disease are highly

satisfactory, with the procedure being deemed safe and reliable [5].

Remifentanil, a fentanyl μ-type opioid receptor agonist, has rapid penetration of the blood-brain barrier in the human body within approximately 1 minute and swift hydrolysis in tissues and blood [6]. As a result, it offers fast onset of action and short maintenance time, making it a primary choice for analgesia in clinical practice [7]. However, the adverse reactions associated with opioid agonists, such as nausea, vomiting, and respiratory depression, have spurred the search for improved analgesic options [8]. Dexmedetomidine, a relatively selective α_2 receptor agonist, exerts sedative, anti-anxiety, hypnotic, analgesic, and sympathetic nerve-blocking effects, along with the potential to reduce stress reactions [9]. Simultaneously, this drug can reduce the required amount of anesthetics, enhance hemodynamic stability during surgery, and lower the incidence of myocardial ischemia. However, Dex alone is insufficient to achieve the desired level of surgical anesthesia [10].

In recent years, the concept of "ERAS" (Enhanced Recovery After Surgery) has focused on reducing stress related to the physiological and psychological trauma experienced by surgical patients [11]. It involves a multidisciplinary approach encompassing surgery, anesthesia, nursing, and nutrition, all aimed at promoting rapid rehabilitation [12]. Therefore, this study selected patients with coronary heart disease who underwent 3D laparoscopic surgery at our hospital to assess the clinical effectiveness and safety of using dexmedetomidine in combination with remifentanil for intraoperative anesthesia. The study also aimed to determine whether this approach is suitable for ERAS.

Materials and methods

Normal information

This study is a retrospective analysis involving a total of 60 patients diagnosed with coronary heart disease, all of whom underwent 3D laparoscopic surgery at our hospital between June 2020 and September 2021. Notably, each of these patients exhibited a clean bill of health with no ST-T changes or arrhythmia in their pre-surgery electrocardiograms (ECG) following medication. Employing a double-blinded app-

roach, the patients were randomly divided into two groups: the control group (Group I), consisting of 30 patients, and the dexmedetomidine group (Group II), also comprising 30 patients.

Throughout the study, various parameters were meticulously monitored and documented at distinct time points. These included measurements taken at the onset of the operation (T_1), the initiation of CO_2 pneumoperitoneum (T_2), the cessation of CO_2 pneumoperitoneum (T_3), and post-operatively upon exiting the operating room (T_4). The recorded data encompassed dynamic changes in patients' blood pressure, heart rate, and other critical vital signs at each of these time points, as well as ST-T variations in their ECG readings during the surgical procedure. Additionally, the study considered the bispectral index (BIS) values measured at these time points and pain scores recorded one hour post-operation and immediately after leaving the operating room. Pain levels were assessed utilizing the visual analog scale (VAS), with scores ranging from 0 indicating the absence of pain to 10 signifying severe and unbearable pain.

The inclusion criteria for this study encompassed elderly patients and those presenting with preoperative conditions such as hypertension, coronary heart disease, arrhythmia, hypertension, and myocardial ischemia. Specifically, the study enrolled patients who exhibited no ST-T changes in their electrocardiograms and no arrhythmia after receiving preoperative drug treatment. Additionally, patients with an ASA score of I-II were eligible for inclusion. The study encompassed a range of surgical procedures, including those related to the stomach, liver, gallbladder, spleen, colon, rectum, and uterus. In contrast, individuals with severe hypertension and those with a history of peptic ulcers, severe arrhythmia, or heart disease, particularly when heart function exceeded grade 3, were excluded from participation in the study.

Methods

Anesthesia: All patients fasted for 8 h and avoided water for 4 h before the operation. Sufentanil 0.2-0.3 μg/kg, propofol 1.5-2 mg/kg, and cisatracurium besylate 0.2 mg/kg were used for the induction of anesthesia, and a quick induction tracheal intubation was per-

formed. A no. 7.5 reinforcement wire tracheal catheter was used for male patients, while a 7.0-gauge reinforced wire tracheal catheter was utilized for female patients. Intraoperative maintenance was performed using combined intravenous inhalation anesthesia: 30 patients in Group I were anesthetized using plasma target-controlled pump injection of remifentanil (speed of 1-2 ng/mL) and combined inhalation of sevoflurane simultaneously. The patients in Group II were administered dexmedetomidine (speed 1 g/mL) combined with remifentanil plasma target control (speed 1-2 ng/mL) pump injection and sevoflurane inhalation. The patients were monitored using the EEG bispectral index (sufentanil and cisatracurium besylate were added as needed using the BIS), muscle relaxation and other means. After surgery, the patient's consciousness and various reflexes were restored, the tracheal tube was withdrawn after the patient naturally awakened, and the patient was transferred to the intensive care unit. Patient-controlled intravenous analgesia (PCIA) was not used for self-controlled analgesia within 1 h after the surgery.

Anesthesia monitoring: The Dräger anesthesia system (Germany) was used to regularly monitor the vital signs of all patients after entering the operating room, including the heart rate (HR), downward shifts of the ECG ST-T, and blood pressure using two limb and three chest leads. The systolic blood pressure (SBP), diastolic blood pressure (DBP), blood oxygen saturation (SPO_2), bispectral index (BIS), muscle relaxation, and the concentration of inhaled and exhaled sevoflurane were also measured.

EEG bispectral index monitoring: The Bispectral Index (BIS) is a measure that assesses the linear components (frequency and power) of an electroencephalogram (EEG) and further analyzes the non-linear relationships (phase and harmonics) between the component waves. Specifically, after the patient has entered the surgery room, the first step is to properly prepare the skin in the area where the electrode will be attached. This entails thoroughly cleaning and drying the skin to ensure an optimal connection. This is critical for achieving accurate BIS monitoring. Subsequently, we affix the electrode patch to the designated area on the patient's skin and ensure it is securely in place by gently pressing around it. Then, the electrode patch is firmly pressed for 5 seconds, which helps establish a solid connection with the patient's skin. Next, the BIS sensor is connected to the electrode patch and it is linked to the patient cable. The sensor and cable are responsible for transmitting the patient's brain activity data to the monitoring equipment. Once all the electrodes turn green, indicating their proper functioning, we proceed to enter the sensor inspection interface. This step is crucial to verify that the electrodes are accurately detecting the patient's brain activity. Subsequently, the BIS monitoring can commence. The BIS monitor will provide a numerical value that reflects the patient's level of consciousness: A BIS value of 100 signifies that the patient is in an awake state. A BIS value of 0 represents the complete absence of brain electrical activity, which may occur during deep anesthesia or in specific medical conditions. Generally, a BIS value in the range of 85-100 is considered normal. A BIS value between 65-85 indicates a sedative state. A BIS value between 40-65 suggests an anesthetic state. A BIS value below 40 may indicate burst suppression, signifying very deep anesthesia or a severe medical condition.

Muscle relaxation monitoring: The stimulation electrode leads and sensor leads are connected to the TOF-Watch main unit. The ulnar nerve, is monitored with the adductor pollicis muscle in the thumb being the standard monitoring site. The distal electrode is placed at the intersection of the adductor pollicis muscle and the ulnar nerve near the wrist, and the proximal electrode is placed about 2-3 centimeters from the elbow on the ulnar nerve. The sensor's larger surface must be facing the palmar aspect of the thumb. The muscle relaxation monitoring metric involves four consecutive stimulations (TOF) delivered within a 2-second interval. This monitors the muscle response after administering neuromuscular blocking agents and measures the TOF ratio (T_4/T_1). T_4/T_1 is the fundamental indicator for assessing the effectiveness of muscle relaxation.

Statistical analysis: SPSS 20.0 statistical software package was used to perform all statistical analyses. All experimental data are expressed as the mean ± standard deviation ($\overline{X}\pm S$). The measured data showing differences between the two groups were compared by one

Table 1. Clinical events ($\overline{X}\pm S$)

	Group I	Group II	P
Age, years	59.54±9.56	59.27±9.86	0.919
Weight, kg	62.39±13.80	64.07±10.53	0.617
Height, cm	162.14±7.56	165.93±5.74	0.055
ASA	9/21	10/20	0.925
Operative time, hr	2.40±1.04	3.16±1.31	0.093

Table 2. Comparison of blood pressure between the two groups of patients ($\overline{X}\pm S$)

Group	N	NBP	T_1	P	T_2	P	T_3	P	T_4	P
Group I	30	SBP	144.89±21.61		112.25±18.69		117.71±11.99		134.36±14.35	
		DBP	87.57±10.91		73.64±13.42		73.60±9.47		84.64±10.16	
Group II	30	SBP	146.03±19.19	0.838	119.67±12.18	0.041	114.17±10.01	0.241	124.93±14.87	0.021
		DBP	88.77±12.62	0.712	47.56±3.03	0.040	73.50±10.41	0.969	81.43±12.01	0.046

T_2: Dex maintains a stable intraoperative circulation, injected at a rate of 1 μg/ml. Blood pressure fluctuations are relatively small, and hemodynamics are stable. Therefore, the circulation fluctuations of group I are larger than those of group II.

Table 3. Comparison of HR between the two groups of patients ($\overline{X}\pm S$)

Group	N	T_1	P	T_2	P	T_3	P	T_4	P
Group I	30	77.57±14.85		71.25±16.31		74.46±14.18		85.35±13.58	
Group II	30	79.57±16.30	0.640	66.57±13.51	0.048	67.70±11.06	0.046	78.13±9.90	0.029

Table 4. ST-T downshift in the two groups of patients at each time point ($\overline{X}\pm S$)

Group	N	T_1	P	T_2	P	T_3	P	T_4	P
Group I	30	0.05±0.02		0.11±0.06		0.15±0.04		0.15±0.04	
Group II	30	0.04±0.03	0.090	0.05±0.05	<0.001	0.04±0.04	<0.001	0.04±0.03	<0.001

way analysis of variance (ANOVA), and counted data were compared by χ^2 tests. P<0.05 indicated a significant difference.

Results

As illustrated in **Table 1**, there were no significant differences in age, height, weight, American Society of Anesthesiologists status, or operative time between the two groups of patients (P>0.05).

We compared the blood pressure of the two groups of patients at each time point. The values at T_1 and T_3 were not significantly different (P>0.05), but there were significant differences at T_2 and T_4 between the two groups (P<0.05). Group I had significantly higher values than Group II (**Table 2**).

Comparing the heart rate in the two groups of patients at T_1, there was no significant differ-

ence (P>0.05), but there were significant differences at T_2, T_3, and T_4 between the two groups (P<0.05). Patients in Group I had significantly higher heart rates than those in Group II (**Table 3**).

The downward shift in the ST-T of the dim sum electrogram at T_1 was not significantly different between the two groups (P>0.05). However, there were significant differences at T_2, T_3, and T_4 between the two groups (P<0.05). Patients in Group I had significantly higher shifts than those in Group II (**Table 4**).

The BIS values of the two groups of patients at each time point from T_1 and T_4 were not significantly different (P>0.05), but there were significant differences at T_2 and T_3 between the two groups (P<0.05). Patients in Group I had significantly higher BIS values than those in Group II (**Table 5**).

Table 5. BIS status of the two groups of patients at each time point ($\overline{X}$±S)

Group	N	T_1	T_2	P	T_3	P	T_4	P
Group I	30	0	59.04±10.55		57.29±14.25		86.29±6.88	
Group II	30	0	44.07±5.99	<0.001	43.63±5.60	<0.001	86.97±8.59	0.0749

Table 6. BIS status of the two groups of patients at each time point ($\overline{X}$±S)

Group	N	Out of operation	1 h later	P
Group I	30	0	3.39±1.06	
Group II	30	0	1.03±0.59	0.001

We compared the pain score (VAS score) of the two groups of patients at T_4. There was no significant difference (P>0.05). However, there was a significant difference 1 h after the operation (P<0.05). Patients in Group I had significantly higher scores than those in Group II (**Table 6**).

Discussion

In recent years, rapid advancements in medical science have brought international attention to the concept of rapid rehabilitation in surgical models [13]. One such approach, ERAS, relies on evidence-based medical data to minimize the physiological and psychological trauma experienced by surgical patients and reduce their stress responses [14]. Within this context, the role of the anesthesiology department is paramount. They are responsible for managing perioperative pain, ensuring circulatory and respiratory stability, restricting fluid infusion, and facilitating early postoperative activities [15]. It is widely recognized that surgical trauma triggers a stress response in the body, which can impede the patient's rapid recovery [16]. Moreover, many elderly patients have a history of cardiovascular disease, making them particularly vulnerable. Surgical trauma can suppress cellular immunity, increase postoperative inflammation, and contribute to cardiovascular and cerebrovascular issues [17]. Thus, maintaining stability throughout the perioperative process is crucial. In response to these challenges and following multidisciplinary consultations, a series of anesthesia plans have been developed. The primary goals of our anesthesia strategy are to maintain a pain-free environment throughout the surgical procedure, reduce complications and stress, and accelerate postoperative recovery.

This study prioritized the establishment and maintenance of hemodynamic stability during the induction of general anesthesia. The general anesthesia induction protocol consisted of administering sufentanil at a dosage of 0.2-0.3 μg/kg, propofol at 1.5-2 mg/kg, and cisatracurium besylate at 0.2 mg/kg. This was followed by a rapid induction and tracheal intubation. Male patients received a 7.5-gauge reinforced wire tracheal catheter, while female patients were provided with a 7.0-gauge reinforced wire endotracheal catheter. Particular care was taken to minimize manipulation-related stimulation during tracheal intubation, and any drop in the patient's blood pressure was controlled within the range of 15%-20%.

Subsequently, intraoperative maintenance was carried out using a combined intravenous and inhalation anesthesia approach. In Group I, which included 30 patients, anesthesia was achieved through the plasma target-controlled pump injection of remifentanil (at a rate of 1-2 ng/mL) and simultaneous inhalation of sevoflurane. In Group II, the other 30 patients received dexmedetomidine (at a rate of 1 g/mL) in combination with plasma target-controlled remifentanil (at a rate of 1-2 ng/mL) and concurrent sevoflurane inhalation. Moreover, this study employed the advanced Dräger anesthesia system for continuous monitoring of vital signs, encompassing heart rate (HR), the downward shift of the electrocardiogram's ST-T wave, and blood pressure, considering two limb and three chest leads. The systolic blood pressure (SBP), diastolic blood pressure (DBP), blood oxygen saturation (SPO_2), bispectral index (BIS), muscle relaxation, and the concentration of inhaled and exhaled sevoflurane were also recorded. All patients received supplementary doses of sufentanil and cisatracurium besylate as necessary, guided by BIS monitoring and muscle relaxation monitoring during the operation. The Dräger anesthesia system offers multiple monitoring and ventilator modes, ensuring not only the timely administration of intraoperative medications and maintaining a satisfactory depth of anesthesia

but also the preservation of a patient's hemodynamics and respiratory stability, thereby ensuring the safety of the anesthesia.

Finally, following the surgery, patients' consciousness and various reflexes were restored. The tracheal tube was removed once patients spontaneously awakened and were subsequently transferred to the intensive care unit. Notably, self-controlled analgesia through patient-controlled intravenous analgesia (PCIA) was not employed within the first hour post-operation. Importantly, both groups of patients did not exhibit significant respiratory depression or circulatory depression at the one-hour post-surgery mark. Moreover, they did not report adverse reactions such as dizziness, nausea, vomiting, or lethargy.

This study demonstrated that the combined use of dexmedetomidine and remifentanil plasma target-controlled pump injection can adequately stabilize the circulatory state of patients with coronary heart disease. Therefore, patients in Group II had larger values at T_2 and T_4 and maintained relatively stable hemodynamics, and the changes in blood pressure and heart rate were significantly smaller than those of Group I. Simultaneously, the degree of decrease in ST-T of the ECG in Group II was also significantly lower than that of the control group. Dexmedetomidine can improve the stability of hemodynamics during surgery and reduce the incidence of myocardial ischemia [18]. A satisfactory state of anesthesia is achieved when a patient maintains adequate analgesia, sedation, and muscle relaxation during the operation. Remifentanil is a short-acting opioid with a strong analgesic effect, a fast onset, fast metabolism, and no accumulation [19]. It is suitable for the maintenance of intraoperative anesthesia [20]. Dexmedetomidine is a relatively selective α_2 receptor agonist with strong selectivity, a short half-life, and sedative, anti-anxiety, hypnotic, analgesic, and sympathetic nerve block effects [21]. The drug can also be used to reduce the dosage of anesthetics [22]. Dexmedetomidine can be used clinically to sedate patients where intubation and ventilation are started during intensive care treatment [23]. Therefore, the BIS value of the patients at each time point from T_2 and T_3 was also significantly higher in Group I than in Group II. The BIS is an indicator reflecting the depth of anesthesia during surgery. The BIS can remain relatively stable at higher values, indicating that dexmedetomidine has a better sedative effect.

Postoperative pain can produce a series of adverse effects, which are primarily manifested as an increased load on the cardiovascular system and increased oxygen consumption, further leading to increased cardiovascular events, reduced postoperative respiratory function recovery, a postoperative hypercoagulability state, reduced postoperative immune function, delays in postoperative gastrointestinal function recovery, changes in chronic pain, and increased hospitalization costs [24, 25]. Analgesia is achieved with remifentanil by activating the central and peripheral nerve opioid receptors [26]. While opioids themselves are prone to causing excessive sedation and respiratory and circulatory depression, remifentanil also has serious adverse reactions, such as vomiting, dizziness, and drowsiness [27]. This study demonstrated that the pain scores of the patients in Group II 1 h after the operation were significantly lower than those of the patients in Group I; their pain was reduced, the stress response was less, and no adverse reactions occurred. Considering that dexmedetomidine use reduces the intraoperative dosage of sufentanil, it has a greater impact on ERAS, can speed up ERAS, and can significantly reduce postoperative pain in patients without increasing the incidence of postoperative adverse reactions.

In conclusion, our research underscores the pivotal role of anesthesia in advancing ERAS principles for patients with coronary heart disease undergoing surgery. Through the strategic use of dexmedetomidine and remifentanil, we established a robust foundation for stable hemodynamics, reduced stress responses, and enhanced postoperative pain management. We advocate for the integration of our findings into clinical practice, contributing to the evolution of patient-centric, evidence-based surgical care.

These findings highlight the authors' dedication to improving patient outcomes and emphasize the impact of this anesthesia approach within the context of ERAS and surgeries for patients with coronary heart disease. However, limitations of the current study include a relatively small sample size, limited

diversity in surgical types, and stringent inclusion criteria. To address these shortcomings, future research is anticipated to encompass larger sample sizes, a wider array of surgical procedures, and more inclusive criteria. This expansion aims to extend the benefits to a broader population of coronary heart disease patients.

Disclosure of conflict of interest

None.

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