ORIGINAL RESEARCH

The Impact of Esketamine Combined with Dexmedetomidine on Laparoscopic Gallbladder Surgery: A Randomized Controlled Trial

Fanyan Hu, MM; Qin Wang, MM; Yongjian Yang, MM; Yajun Liu, MM

ABSTRACT

Objective • To assess the efficacy of combining esketamine with dexmedetomidine in laparoscopic gallbladder surgery.

Methods • We investigated 110 laparoscopic cholecystectomy patients at Jinan Central Hospital, affiliated with Shandong First Medical University, from April 2019 to March 2020. Patients were randomly assigned to the control group (n = 55) or observation group (n = 55). The control group received dexmedetomidine intravenously at 1 μg/kg and a continuous infusion at 0.5 $\mu g \bullet kg^{-1} \bullet h^{-1}$. The observation group received esketamine and dexmedetomidine, with intravenous esketamine at 0.4 mg/kg and a continuous infusion at 0.1 mg/(kg•h). We measured heart rate (HR), systolic blood pressure (SBP), and diastolic blood pressure (DBP) at four-time points: before anesthesia (T0), 30 minutes after anesthesia (T1), extubation (T2), and awakening (T3). We also assessed wake time, post-anesthesia care unit (PACU) stay, and Ramasy and visual analogue scale (VAS) scores at 2, 6, 12, and 24 hours post-surgery.

Results • At T0, no significant changes occurred in HR, SBP, and DBP in both groups ($P > .05$). However, at T1 and T2, HR, SBP, and DBP gradually decreased, with the control group exhibiting lower levels than the observation group ($P < .05$). These levels returned to baseline at T3. PACU residence and wake times showed no significant differences ($P > .05$). At 2 hours post-operation, Ramasy scores significantly dropped in the observation group versus the control group ($P < .05$). At 6, 12, and 24 hours post-operation, Ramasy scores exhibited no significant differences ($P > .05$). Moreover, at 2, 6, and 12 hours post-operation, VAS scores in the observation group were notably lower than in the control group ($P < .05$). At 24 hours post-operation, VAS scores revealed no significant differences ($P > .05$). Adverse reactions within 3 days post-operation did not differ significantly between the groups ($P > .05$).

Conclusions • Combining esketamine with dexmedetomidine enhances the quality of laparoscopic cholecystectomy, alleviates postoperative agitation, accelerates cognitive function recovery, reduces cognitive function impairment, and merits clinical consideration. (*Altern Ther Health Med.* [E-pub ahead of print.])

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INTRODUCTION

Laparoscopic cholecystectomy, a minimally invasive surgical procedure1, has become a crucial approach for treating gallstones and other conditions due to its benefits, including reduced bodily trauma and shorter operation times.[1-2] Nevertheless, some patients experience stress responses triggered by intraoperative factors like pneumoperitoneum and extubation.[2] Additionally, the impact of anesthesia on hemodynamic stability can lead to restlessness during recovery, postoperative cognitive dysfunction, and other adverse reactions. In severe cases, these issues may even risk patient safety.[3]

Assessing the quality of anesthesia is critically important to prevent complications like postoperative restlessness and pain management in patients.[4] Among the ongoing advancements in anesthesia technology, opioid-based general anesthesia has gained widespread use in surgical settings. However, there is growing consensus in favor of adopting multi-modal analgesia, a practice that offers substantial benefits, including reducing opioid use and improving the overall quality of anesthesia.[5,6]

Esketamine, a novel intravenous anesthetic, offers rapid onset, full recovery, minimal respiratory depression, and sedative properties. It also provides analgesic and amnestic effects. Esketamine's impact becomes more significant when combined with dexmedetomidine in reducing opioid consumption and enhancing the overall quality of anesthesia.[7,8] However, scarcity in the existing literature regarding the

combined effect of esketamine and dexmedetomidine highlights the need for a comprehensive study in this area.

Therefore, we conducted this study to bridge the gap by investigating combined effects and highlighting the potential of this promising approach in anesthesia management. The primary aim was to investigate the anesthetic effects of this low-dose esketamine and dexmedetomidine intervention in patients undergoing laparoscopic cholecystectomy to provide valuable clinical insights.

MATERIALS AND METHODS

Study Design

A randomized controlled blind trial was conducted, and we employed a convenient sampling method to enroll 110 patients undergoing laparoscopic cholecystectomy for a drug intervention investigation. These patients were then randomly allocated into two groups: the control group (intervention with dexmedetomidine) and the observation group (intervention with a combination of low-dose esketamine and dexmedetomidine). This study received approval from the Ethics Review Board of Jinan Central Hospital, affiliated with Shandong First Medical University (approval no. 2019-0439). Informed consent was obtained from all participants before the experiment.

Inclusion and Exclusion Criteria

Inclusion criteria: (1) Patients with American Society of Anesthesiologists (ASA) grades I to II; (2) No history of narcotic drug allergies. Patients were excluded if they: (1) had endocrine or immune system diseases; (2) displayed severe dysfunction in liver, heart, lung, or kidneys (Model of End-stage Liver Disease (MELD) > 15; the presence of ascites; mGFR < 60 ml/min/1.73 m^2; exhibited symptoms of heart failure, such as dyspnea or fatigue, with or without physical signs; left ventricular ejection fraction (LVEF) ≥ 50%; FEV1/FVC < 50%); (3) exhibited abnormal cognitive, neurological, or language communication function (assessed using the Montreal Cognitive Assessment (MoCA); criteria for cognitive impairment: illiterate group ≤ 13 points, elementary school group ≤ 19 points, middle school and higher group ≤ 24 points); (4) had coagulopathy dysfunction (PT-INR > 1.6).

Participant Allocation

Using a random number table, the participants were allocated into two groups: the control group (n = 55) and the observation group (n = 55). In the control group, there were 19 females and 16 males. The average age was (46.34±8.91) years, ranging from 26 to 78 years. In the observation group, there were 20 females and 15 males. The average age was (45.17±10.26) years, ranging from 29 to 76 years. No significant differences in gender and age were observed between the two groups ($P > .05$), making them comparable.

Blinding

Eligible patients were randomly assigned to two groups: the control group and the observation group. A statistician, uninvolved in data analysis, generated a computerized list of random numbers and placed them in sealed envelopes. This list determined group allocation. Study coordinators, attending anesthesiologists, and patients remained blinded to the group assignments.

Anesthesia Protocol in Control Group

In the control group, dexmedetomidine at a dose of 1 μg/kg (national drug approval code H20130093) was administered via infusion 10 minutes before the induction with a loading dose. Anesthesia Induction: anesthesia induction involved the administration of 0.6 μg/kg sufentanil (GMC H20205068), 3 to 5 mg/kg propofol (GMC H20051843), and 0.3 mg/kg benzene sulfocisulatracurium (GMC H20213438). Anesthesia Maintenance: during anesthesia maintenance, sevoflurane was administered by inhalation, and dexmedetomidine (national drug approval number H20130093) was infused at a rate of 0.5 μg/(kg•h).

Anesthesia Protocol in Observation Group

In the observation group, a 10-minute pre-induction injection of dexmedetomidine at 1 μg/kg was administered. Anesthesia induction: anesthesia induction involves the administration of esketamine at a dose of 0.4 mg/kg (national drug approval number H20193336), 0.6 μg/kg sufentanil, 3 to 5 mg/kg propofol, and 0.3 mg/kg benzene sulfocisulatracurium. Anesthesia maintenance: during anesthesia maintenance, patients inhaled sevoflurane. A continuous infusion of dexmedetomidine at 0.5 μg/(kg•h) and esketamine at 0.1 mg/(kg•h) was also administered.

Measurement Parameters and Evaluation Criteria

Vital Sign Indicators. The heart rate (HR), systolic blood pressure (SBP), and diastolic blood pressure (DBP) levels in both groups were assessed using a mercury sphygmomanometer at four-time points: before anesthesia (T0), 30 minutes after anesthesia (T1), extubation (T2), and awakening (T3). Additionally, the wake time and post-anesthesia care unit (PACU) retention time were documented for both groups.

Assessment of Agitation. Patients were evaluated for agitation at 2 hours, 6 hours, 12 hours, and 24 hours after awakening, using the Ramsay score commonly employed in intensive care units. The scoring criteria are as follows: 1 point: Patient exhibits irritability, anxiety, and inability to cooperate with treatment. 2 points: Patient cooperates with treatment and remains calm. 3 points: Patient can promptly respond to medical staff inquiries. 4 points: Patient maintains a quiet state and can follow instructions. 5 points: Patient displays poor responsiveness and cannot respond to medical staff on time. 6 points: The patient is in a deep, unarousable sleep state. This approach helped in assessing and recording patients' agitation levels effectively.

Pain Assessment. Pain intensity was assessed using the Visual Analogue Scale (VAS), which employed a scale ranging from 0 to 10. A rating of 10 indicated severe and intolerable pain, while a rating of 0 indicated the absence of pain.

Complications. Occurrence of postoperative complications within 3 days was recorded for both groups, including but not limited to headache, vomiting, pruritus, circulatory depression, and drowsiness.

Sample Size Determination

This study followed a parallel randomized controlled trial design, with Visual Analogue Scale (VAS) scores as the primary outcome measure. Based on previous findings, the expected VAS score was 3.41±0.78 in the control group, and the observation group was anticipated to have a 0.52-point lower score than the control group. Assuming a two-tailed alpha error of 0.01 and a power of 0.90, sample size calculation using Power Analysis and Sample Size (PASS) software (NCSS, Kaysville, Utah, USA) determined a minimum of 49 participants per group. Factoring in an anticipated dropout rate of 10%, the final sample size required for each group was 55.

Statistical Analysis

Data was analysed using IBM SPSS Statistics 19.0 software (IBM, Armonk, NY, USA). The normality of the data distribution was assessed using Kolmogorov-Smirnov and Shapiro-Wilk tests. Normally distributed data are presented as mean ± standard deviation ($\bar{x} \pm s$). Student's t test was employed for between-group comparisons. Categorical variables are expressed as frequency or percentage [n (%)], and group comparisons were performed using the chi-squared test. Multivariate analysis of variance with repeated measures, followed by post hoc tests, was applied to compare multiple groups. A significance level of $P < .05$ was considered statistically significant.

RESULTS

Vital Sign Measurements

At T0, the two groups had no significant differences in HR, SBP, and DBP ($P > .05$). However, at T1 and T2, both groups experienced a gradual decrease in HR, SBP, and DBP levels, with the control group exhibiting lower levels compared to the observation group ($P < .05$). By T3, values had essentially returned to T0 levels, with no significant differences between the two groups ($P > .05$). These results indicate that the observation group maintained relatively stable HR, SBP, and DBP levels. Refer to Table 1.

Measurement of Wake Time and PACU Retention Time

Recovery time and PACU retention time showed no significant differences between the two groups ($P > .05$); refer to Table 2.

Measurement of Agitation Level

Ramsey scores in the control group were lower than those in the observation group 2 hours after surgery ($P < .05$). However, scores did not significantly differ between the two groups at 6, 12, and 24 hours post-surgery ($P > .05$); refer to Table 3.

Table 1. Assessment of Vital Signs in the Study

Project	Group	Cases	T0	T1	T2	T3	F	*P* value
HR (times / min)	Control Group	55	77.33±4.30	71.69±2.57	70.33±3.29	78.62±3.71	77.197	<.001
	Observation Group	55	77.38±4.34	76.16±2.68[a]	75.00±3.12[a]	78.45±3.98	9.403	<.001
t			0.004	79.938	58.521	0.050		
P value			.947	<.001	<.001	0.824		
SBP (mmHg)	Control Group	55	127.84±6.57	115.33±5.92	111.53±5.70	124.62±8.91	63.943	<.001
	Observation Group	55	127.78±6.71	121.35±6.03[a]	117.31±6.38[a]	125.82±8.34	29.028	<.001
t			0.002	27.893	25.139	0.532		
P value			.966	<.001	<.001	0.467		
DBP (mmHg)	Control Group	55	83.56±6.86	75.85±6.23	73.60±6.30	80.84±7.63	23.253	<.001
	Observation Group	55	83.49±7.01	80.31±6.58[a]	78.85±6.53[a]	81.11±6.67	4.560	.004
t			0.003	13.302	18.461	0.040		
P value			.956	<.001	<.001	0.840		

[a] Statistical significance is denoted as $P < .05$ when comparing the observation group to the control group.

Note: The table presents mean values with standard deviations (Mean±SD) for heart rate (HR), systolic blood pressure (SBP), and diastolic blood pressure (DBP) at different time points (T0, T1, T2, T3) in both the control and observation groups.

Table 2. Measurement of Wake Time and PACU Retention Time

Group	Cases	Wake Time	PACU Retention Time
Control Group	55	6.51±2.12	34.12±1.31
Observation Group	55	6.87±2.13	34.21±1.42
t		0.913	0.383
P value		.364	.702

Note: Table 2 displays the measurement results for Wake Time and Post-Anesthesia Care Unit (PACU) Retention Time in both the Control and Observation groups. The values are presented as means with standard deviations (Mean±SD). No statistically significant differences were observed between the two groups in terms of Wake Time and PACU Retention Time.

Table 3. Measurement of Agitation Level

Group	Cases	2 h After Surgery	6 h After Surgery	12 h After Surgery	24 h After Surgery	F	*P* value
Control Group	55	3.11±0.42	3.02±0.30	2.33±0.47	1.98±0.24	122.771	<.001
Observation Group	55	3.76±0.43[a]	3.05±0.36	2.35±0.48	2.02±0.24	260.663	<.001
t		66.023	0.332	0.040	0.659		
P value		<.001	.566	.842	.419		

[a] indicates a statistically significant difference ($P < .05$) between the Control and Observation groups at 2 hours after surgery.

Note: Table 3 presents the measurement of Agitation Level at various time points following surgery in both the Control and Observation groups. Data is expressed as means with standard deviations (Mean±SD).

Table 4. Measurement of Pain Conditions

Group	Cases	2 h After Surgery	6 h After Surgery	12 h After Surgery	24 h After Surgery	F	*P* value
Control Group	55	3.22±0.60	2.96±0.43	2.18±0.55	0.91±0.29	247.244	<.001
Observation Group	55	2.56±0.63[a]	2.13±0.39[a]	0.95±0.36[a]	0.89±0.32	208.529	<.001
t		31.104	115.185	197.232	0.099		
P value		0.001	<.001	<.001	.753		

[a] $P < .001$ compared to the Control group at the corresponding time point, indicating statistically significant differences in pain scores between groups.

Note: Data are presented as mean ± standard deviation.

Measurement of Pain Level

At 2, 6, and 12 hours post-surgery, VAS scores in the observation group significantly decreased compared to the control group ($P < .05$). However, at 24 hours post-surgery, VAS scores did not differ significantly between the two groups; refer to Table 4.

Table 5. Measurement of Incidence of Adverse Reactions

Group	Cases	Headache	Vomiting	Iitching	Inhibition of Circulation	Drowsiness	Incidence Rate (%)
Control Group	55	3	4	2	2	3	14 (25.45)
Observation Group	55	3	3	2	2	3	13 (23.64)
χ^2							0.049
P value							.825

Note: Data are presented as the number of cases. No statistically significant differences in the incidence of adverse reactions were observed between the Control group and the Observation group; χ^2: represents the chi-squared statistic; Incidence rate (%): indicates the percentage of cases experiencing a specific adverse reaction in each group.

Measurement of Adverse Reaction Incidence

Table 5 reveals that there was no significant difference in the incidence of adverse reactions between the two groups ($P > .05$).

DISCUSSION

Laparoscopic cholecystectomy, a minimally invasive surgical approach, has revolutionized the treatment of gallbladder-related diseases. This advanced technique offers reduced trauma, shorter operation times, and improved patient outcomes, making it an important treatment in the management of gallbladder conditions.[10] Due to the typically brief duration of laparoscopic cholecystectomy procedures, anesthetics such as propofol, characterized by their short half-life, are commonly employed for anesthesia.[11-14]

Rapid loss of anesthetic effects upon withdrawal may result in severe pain and adverse reactions for certain patients. Furthermore, central nervous system complications, including cognitive dysfunction and stress disorder syndrome, can manifest due to the influence of surgical stress and individual patient factors.[15-17] Therefore, there is an ongoing need to explore novel anesthesia protocols to address the increasing medical challenges and enhance the overall quality of anesthesia.

Dexmedetomidine is a highly effective and selective α2 adrenergic receptor agonist, and it exhibits a binding affinity to α2 and α1 adrenergic receptors in a ratio of 1600 to 1.[18] In the perioperative period, it serves multiple functions, including sedation, analgesia, anxiety reduction, and sympathetic inhibition. Notably, when combined with opioids, it demonstrates a synergistic analgesic effect, allowing for a significant reduction in opioid dosage.[19,20] Furthermore, dexmedetomidine promotes sympathetic inhibition, preserves hemodynamic stability, and mitigates the stress response.[18-20]

Esketamine, an intravenous anesthetic, possesses both sedative and analgesic properties. It is the right-handed enantiomer of ketamine with a higher potency.[21] Esketamine's primary site of action, like ketamine, is the *N*-methyl-D-aspartic acid (NMDA) receptor, but it exhibits double the affinity of ketamine for this receptor.[22] Intravenous administration of esketamine for 30 seconds results in a short clearance half-life, rapid recovery, mild respiratory depression, and a reduced incidence of psychiatric side effects.[23]

Recent studies have increasingly explored innovative clinical applications of esketamine. One notable area of investigation involves its role as an adjunct to conventional anesthesia and analgesia. Low doses of esketamine have shown promising results in enhancing the effectiveness of anesthesia and analgesia while mitigating the side effects associated with ketamine use.[24] When dexmedetomidine and esketamine are administered in combination, a synergistic drug interaction can be achieved, resulting in desired therapeutic effects.

Blood pressure and heart rate are vital indicators of patient hemodynamic stability and serve as essential parameters for assessing the effectiveness of anesthesia.[25] The findings from this study indicate that, at T1 and T2, the observation group exhibited higher heart rates and blood pressure levels compared to the control group. This result suggests that the adjunctive use of a small dose of esketamine, in combination with dexmedetomidine, significantly mitigated fluctuations in blood pressure and heart rate.

It is evident in findings that the sympathetic effects of esketamine can reduce the sympathetic inhibitory effects of dexmedetomidine, resulting in a positive impact on hemodynamic stability and reduced reliance on vasoactive medications. Additionally, our study results revealed higher Ramsay scores in the observation group compared to the control group.

The pain scores in the observation group were lower than those in the control group at 2, 6, 12, and 24 hours after surgery. This finding suggests that the administration of a low-dose esketamine and dexmedetomidine anesthesia combination was more effective in enhancing sedation and analgesic effects. Consequently, it facilitated smoother surgical procedures and reduced the need for postoperative analgesic medications.

A pharmacological study[26] has demonstrated that the concurrent administration of low-dose esketamine and dexmedetomidine can lead to reduced opioid requirements, enhanced hemodynamic stability, decreased postoperative pain, and an effective reduction in the incidence of postoperative adverse reactions. These findings align with the results obtained in our study.

Furthermore, the data revealed no statistically significant differences between the two groups in terms of recovery time, PACU retention time, or the incidence of adverse reactions. It implies that the use of low-dose esketamine in combination with dexmedetomidine is safe and does not extend the postoperative recovery period for patients. It also does not significantly increase the likelihood of adverse reactions such as vomiting and headache.

Study Limitations

This study, despite its valuable findings, is not without limitations. Firstly, the study was confined to patients within our hospital, which may not fully represent the broader population. Future research could benefit from larger sample sizes and the inclusion of multiple medical centers to enhance the study's generalizability. Additionally, while this study examined the effects of low-dose esketamine and

dexmedetomidine, monitoring the blood concentration of esketamine could further refine dosing recommendations, particularly in consideration of variations in gender, age, and weight among patients. Addressing these limitations in future investigations may provide a more comprehensive understanding of the potential benefits of this combined approach.

CONCLUSION

In conclusion, the utilization of low dose esketamine in combination with dexmedetomidine for laparoscopic gallbladder surgery demonstrates several notable advantages. This combined anesthesia approach not only enhances sedation and analgesic efficacy but also effectively mitigates hemodynamic fluctuations. Importantly, our study findings emphasize the high level of safety associated with this anesthesia regimen. These findings highlight the potential of low-dose esketamine combined with dexmedetomidine as a valuable strategy in laparoscopic gallbladder surgery, offering improved patient comfort and stable perioperative hemodynamics.

CONFLICT OF INTEREST

The authors have no potential conflicts of interest to report relevant to this article.

AUTHORS' CONTRIBUTIONS

FH and YL designed the study and performed the experiments, QW collected the data, YY analyzed the data, FH and YL prepared the manuscript. All authors read and approved the final manuscript.

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