Anesthetic Effects of Dexmedetomidine Combined with Nalbuphine in Patients Undergoing Laparoscopic Cholecystectomy and its Impact on Nutritional Status

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AIM: Laparoscopic cholecystectomy (LC) is a common surgical procedure for the removal of the gallbladder. Effective anesthesia is crucial for ensuring patient comfort and safety during LC. Dexmedetomidine, a selective α2-adrenergic agonist, is widely used as an adjunct to anesthesia due to its sedative and analgesic properties. Nalbuphine, a synthetic opioid analgesic, is also employed for pain management during various surgical procedures. This study aimed to determine the anesthesia effects of dexmedetomidine combined with nalbuphine on patients undergoing LC and its impact on their nutritional status.

METHODS: The clinical records of 100 patients who underwent LC at Wuhan No.1 Hospital between January 2021 and January 2022 were analyzed retrospectively. Forty-six patients who received intravenous dexmedetomidine (0.4 µg/kg) were assigned to the control group, while fifty-four patients who received intravenous nalbuphine (0.2 mg/kg) and dexmedetomidine (0.4 µg/kg) were assigned to the study group. The outcomes compared between the two groups included heart rate (HR), mean arterial pressure (MAP), Riker sedation-agitation scale (RSAS) scores, visual analogue scale (VAS) scores, duration of operation, awakening time from anesthesia, extubation time, adverse reactions, and nutrition-related indicators before and after surgery.

RESULTS: There were no significant differences in MAP between the groups at the same time point ($p > 0.05$). However, at T1 and T3, the study group had significantly lower HR compared to the control group ($p < 0.05$), with no significant differences in HR at other time points ($p > 0.05$). The study group exhibited significantly lower RSAS scores compared to the control group ($p < 0.01$). No significant differences were observed between the groups in terms of duration of operation, awakening time from anesthesia, and extubation time ($p > 0.05$). At 6 hours post-operation, there were no significant differences in VAS scores between the groups ($p > 0.05$), but at 12, 24, and 48 hours post-operation, the study group had significantly lower VAS scores compared to the control group ($p < 0.0001$). No significant inter-group difference was observed in the total incidence of adverse reactions ($p = 0.180$). Additionally, one week after surgery, the study group exhibited significantly higher levels of albumin, prealbumin, transferrin, and total protein compared to the control group ($p < 0.0001$).

CONCLUSIONS: Dexmedetomidine combined with nalbuphine provides a superior anesthetic effect compared to dexmedetomidine alone in patients undergoing LC. This combination effectively controls hemodynamic fluctuations during the recovery period and reduces agitation without affecting the awakening time from anesthesia. These findings suggest that this combination is beneficial and worth promoting.

Keywords: dexmedetomidine; nalbuphine; laparoscopic cholecystectomy; anesthetic effect; adverse reactions

Introduction

Laparoscopic cholecystectomy (LC), a minimally invasive procedure, is characterized by relatively less trauma and rapid post-operative recovery [1]. However, the procedure involves invasive manipulation of the diaphragm and gallbladder triangle, which can trigger stress in patients, reducing the safety of the operation and increasing the incidence of adverse events [2, 3]. In addition, after operation, patients often experience pain, and upon regaining consciousness, some may exhibit negative emotions such as agitation and anxiety due to their physical condition, mental state, and pain tolerance. These factors can compromise their overall well-being, reduce their willingness to cooperate with post-operative care, and prolong their recovery [4].

Anesthesia is a critical component in clinical practice for stabilizing the physiological state of patients during LC and facilitating the smooth progression of the surgery [3]. With the advancements in medical technology, there is a growing recommendation for the use of combined anesthesia in LC [5]. Dexmedetomidine, a widely used sedative in clinical settings, is an adrenergic receptor agonist that selectively targets α2 adrenoceptors, providing sedative and analgesic effects while inhibiting sympathetic nerve activity [6, 7]. Nalbuphine, a common opioid receptor agonist-antagonist, can act on κ receptor to produce sedative and analgesic in-

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fluence after binding to μ, κ and δ receptors, and can also act on μ receptor to produce partial antagonism [8, 9]. The combined use of dexmedetomidine and nalbuphine in LC has not been extensively investigated.

Therefore, this study aimed to evaluate the anesthetic effects of dexmedetomidine combined with nalbuphine in patients undergoing LC, providing a reliable reference for future anesthesia protocols in such surgeries.

Methods and Materials

Sample Data

The clinical records of 128 patients who underwent LC at Wuhan No.1 Hospital between January 2021 and January 2022 were retrospectively analyzed.

Inclusion and Exclusion Criteria

Inclusion criteria: (1) Patients who underwent LC; (2) individuals classified as American Society of Anesthesiologists (ASA) class I or II; (3) patients aged between 18 and 45 years; (4) patients with detailed clinical data; (5) individuals with a body mass index (BMI) $\leq$30 kg/m^2.

Exclusion criteria: (1) Individuals who had taken painkillers or other drugs affecting research results within two weeks prior to admission; (2) patients with uncontrolled high blood pressure; (3) patients with liver or kidney dysfunction; (4) patients with endocrine, metabolic, or neurological disorders; (5) patients with a history of alcohol addiction; (6) individuals allergic to the drugs used in the study.

Sample Screening

Out of the initial 128 patients, 100 met the inclusion criteria of this study following a rigorous screening process. Among them, 46 patients were allocated to the control group and anesthetized with intravenous dexmedetomidine. The remaining 54 patients were assigned to the study group and anesthetized with intravenous nalbuphine and dexmedetomidine.

Anesthesia Scheme

Every patient was required to fast for at least 8 h before surgery. Upon arrival in the operating room, patients received oxygen via a mask, and venous access was established. Vital signs were monitored, including blood pressure, body temperature, heart rate (HR), Electrocardiogram (ECG), and blood oxygen saturation.

Anesthesia induction: Patients received intravenous injections of 1.50 mg/kg propofol (Sichuan Guorui Pharmaceutical Co., Ltd., Leshan, China; State Food and Drug Administration (SFDA) approval no.: H20040079; 10 mL:1 g), 0.5 μg/kg sufentanil injection (Yichang Humanwell Pharmaceutical Co., Ltd., SFDA approval no.: H20054172, Yichang, China; specification: 2 mL:100 μg), and 0.15 mg/kg atracurium besilate (Jiangsu Heng Rui Pharmaceutical Co., Ltd., Lianyungang, China, SFDA approval no.: H20183042; 5 mL:10 mg). Tracheal intubation was performed 3 minutes later. During the operation, the oxygen flow was maintained at 2 L/min, and the partial pressure of carbon dioxide at the end of expiration was 30–35 mmHg.

Intraoperative anesthesia maintenance: Anesthesia was maintained with intravenous infusions of 0.05–2.00 μg/(kg·min) remifentanil and 4.0–6.0 mg/(kg·h) propofol, with mean arterial pressure (MAP) maintained within 20% of the pre-anesthesia levels.

After cholecystectomy, the control group received 0.4 μg/kg dexmedetomidine hydrochloride (Yangtze River Pharmaceutical Group, Taizhou, China; SFDA approval no.: H20143195; specification: 1 mL:0.1 mg) via intravenous pump over 10 minutes, followed by 5 mL of 0.9% NaCl. The study group received the same dexmedetomidine regimen, followed by 0.20 mg/kg nalbuphine hydrochloride (Yichang Humanwell Pharmaceutical Co., Ltd., Yichang, China; SFDA approval no.: H20130127, 2 mL:20 mg) intravenously. Anesthetic drugs were discontinued post-operation, and patients were transferred to the anesthesia monitoring room. Upon regaining spontaneous breathing, patients received 1.0 mg neostigmine methylsulfate and 0.5 mg atropine intravenously to antagonize residual muscle relaxants. Extubation was performed once extubation criteria were met, and patients were returned to the ward after stabilization of vital signs. The same surgical team performed all surgeries.

Table 1. Baseline data.

Factors	Study group (n = 54)	Control group (n = 46)	χ^2	*p*-value
Age				
≥45 years old	25	26	1.039	0.308
<45 years old	29	20		
Gender				
Male	20	25	3.008	0.083
Female	34	21		
BMI				
≥23 kg/m^2	30	22	0.595	0.441
<23 kg/m^2	24	24		
ASA classification				
Class I	35	28	0.166	0.684
Class II	19	18		
History of smoking				
Yes	15	16	0.570	0.450
No	39	30		
Place of residence				
Rural areas	36	25	1.585	0.208
Urban areas	18	21		

BMI, body mass index; ASA, American Society of Anesthesiologists.

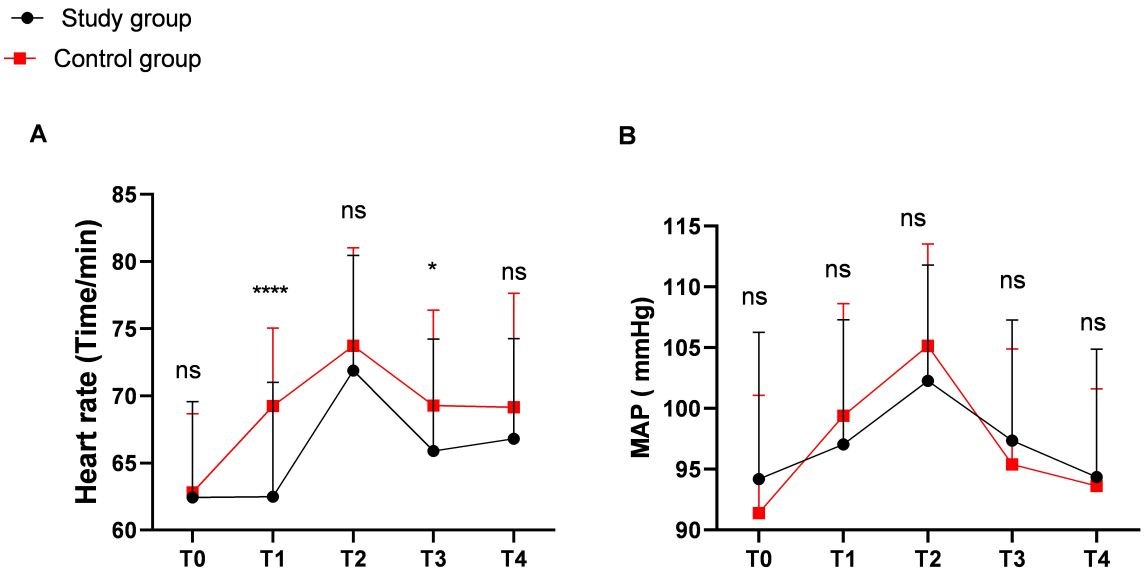

Fig. 1. Inter-group comparison of heart rate and MAP at different time points. (A) Comparison of heart rate at different time points between the two groups. (B) Comparison of MAP at various time points between the two groups. Notes: $^{ns}p > 0.05$; $^{*}p < 0.05$; $^{****}p < 0.0001$. For the study group, n = 54; for the control group, n = 46. MAP, mean arterial pressure.

Outcome Measures

Primary outcome measures: (1) HR and MAP were recorded at the end of operation (T0), before extubation (T1), immediately after extubation (T2), 5 minutes after extubation (T3), and 10 minutes after extubation (T4). (2) The Riker sedation-agitation scale (RSAS) was adopted to evaluate the agitation of each patient during the recovery period [10]. It has 7 points in total, and a smaller score implies better sedative effect. Scores of >4 points indicate agitation and scores of ≤4 points indicate sedation. (3) The visual analogue scale (VAS) was used for scoring and comparing the pain degree at 6 h, 12 h, 24 h and 48 h after operation in the two groups [11], with lower scores indicating less pain. Secondary outcome measures: (1) The duration of operation, awakening time from anesthesia and extubation time of the two groups were compared. (2) Albumin, prealbumin, transferrin and total protein: One day before surgery and one week after surgery, 4 mL fasting venous blood samples were acquired from every patient, followed by centrifugation for supernatant collection, and the levels of albumin, prealbumin, transferrin and total protein were determined by an automatic biochemical analyzer. (3) Adverse reactions in the two groups were recorded and analyzed.

Statistical Analyses

Data were processed using SPSS 20.0. (IBM Corp, Armonk, NY, USA) [3]. Measurement variables were described as mean ± SD, with independent-sample *t*-tests and paired *t*-tests or repeated measures analysis of variance (ANOVA) used for inter-group and intra-group comparisons. Categorical data were expressed as percentages (%) and compared using the chi-square (χ^2). A *p*-value < 0.05 was considered statistically significant. Data visualization was performed using GraphPad 8 (Graph Pad Software Co., Ltd., San Diego, CA, USA) [5].

Results

Baseline Data

A comparison of baseline data between the two groups revealed no significant differences in age, sex, BMI, or ASA classification. ($p > 0.05$, Table 1).

Comparison of Heart Rate (HR) and Mean Arterial Pressure (MAP)

Both groups exhibited a similar trend in heart rate (HR) and mean arterial pressure (MAP), with values initially increasing and then decreasing, reaching their peak at T2. No significant inter-group difference was observed in MAP at the same time point ($p > 0.05$). However, the study group demonstrated significantly lower HR at T1 and T3 compared to the control group ($p < 0.05$), while no significant differences were observed at the other time points ($p > 0.05$, Fig. 1).

Comparison of Agitation during Recovery

The study group had significantly lower Riker sedation-agitation scale (RSAS) scores compared to the control group ($p < 0.01$, Fig. 2).

Table 2. Incidence of adverse reactions [n (%)].

Group	Nausea and vomiting	Dizziness	Respiratory depression	Total adverse reactions
Study group (n = 54)	0 (0.00)	2 (3.70)	1 (1.85)	3 (5.56)
Control group (n = 46)	4 (8.70)	1 (2.17)	2 (4.35)	7 (15.22)
p-value	0.042	>0.999	0.593	0.180

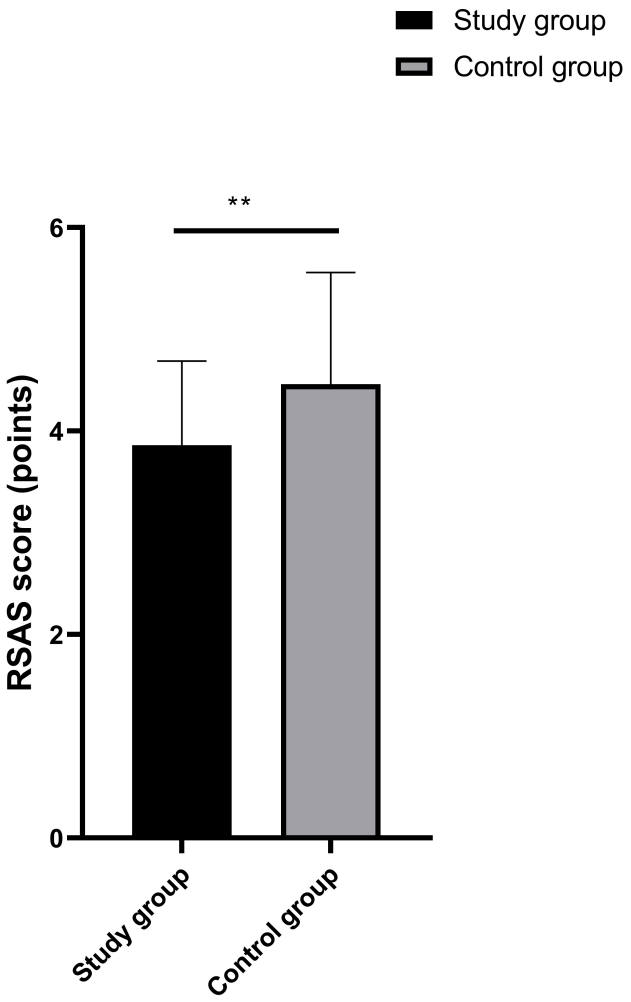

Fig. 2. Inter-group comparison of agitation during recovery. Notes: $^{**}p < 0.01$. For the study group, n = 54; for the control group, n = 46. RSAS, Riker sedation-agitation scale.

Comparison of Duration of Operation, Awakening Time from Anesthesia, and Extubation Time

There were no significant differences between the two groups regarding the duration of operation, awakening time from anesthesia, and extubation time ($p > 0.05$, Fig. 3).

Comparison of Pain

No significant inter-group difference was observed in VAS scores at 6 hours post-operation ($p > 0.05$). However, at 12, 24, and 48 hours post-operation, the study group had significantly lower VAS scores compared to the control group ($p < 0.0001$, Fig. 4).

Incidence of Adverse Reactions

In the study group, there were 2 cases of dizziness and 1 case of respiratory depression, totaling 3 cases of adverse reactions. In the control group, there were 4 cases of nausea and vomiting, 1 case of dizziness, and 2 cases of respiratory depression, totaling 7 cases of adverse reactions. No significant inter-group difference was observed in the total incidence of adverse reactions ($p = 0.180$, Table 2).

Albumin, Prealbumin, Transferrin, and Total Protein Levels in the Two Groups

One day before surgery, there were no significant inter-group differences in the levels of albumin, prealbumin, transferrin, and total protein ($p > 0.05$). After treatment, the levels of these proteins increased significantly in both groups ($p < 0.0001$), with the study group showing more notable increases ($p < 0.0001$, Fig. 5).

Discussion

Laparoscopic cholecystectomy (LC) is a minimally invasive surgical technique frequently employed in hepatobiliary surgery, primarily for patients with cholecystolithiasis, gallbladder polyps, and other conditions requiring cholecystectomy [12]. Previous research indicates that LC offers a shorter recovery time compared to conventional open surgery, but post-operative pain can still be significant, potentially prolonging patient recovery [13, 14, 15]. Therefore, choosing an appropriate and effective anesthesia method is crucial for patient comfort and surgical safety [16].

Dexmedetomidine is a highly selective $\alpha 2$ adrenergic receptor agonist known for its analgesic and sedative effects and ability to stabilize hemodynamics [17, 18]. Nalbuphine, an opioid receptor agonist-antagonist, provides analgesia and sedation with fewer side effects and is effective for visceral pain management, making it an ideal post-operative analgesic drug [19]. This study investigated the combined anesthetic effects of dexmedetomidine and nalbuphine on patients undergoing LC.

Firstly, the study compared and analyzed HR and MAP between the two groups. The HR and MAP of both groups peaked at extubation. No significant inter-group difference was observed in MAP at any time point (T0, T1, T2, T3, and T4). However, the study group exhibited significantly lower HR at T1 and T3 compared to the control group, with no significant difference at other time points. The results showed that compared to the control group, the fluctuation amplitude of hemodynamics in the study group was

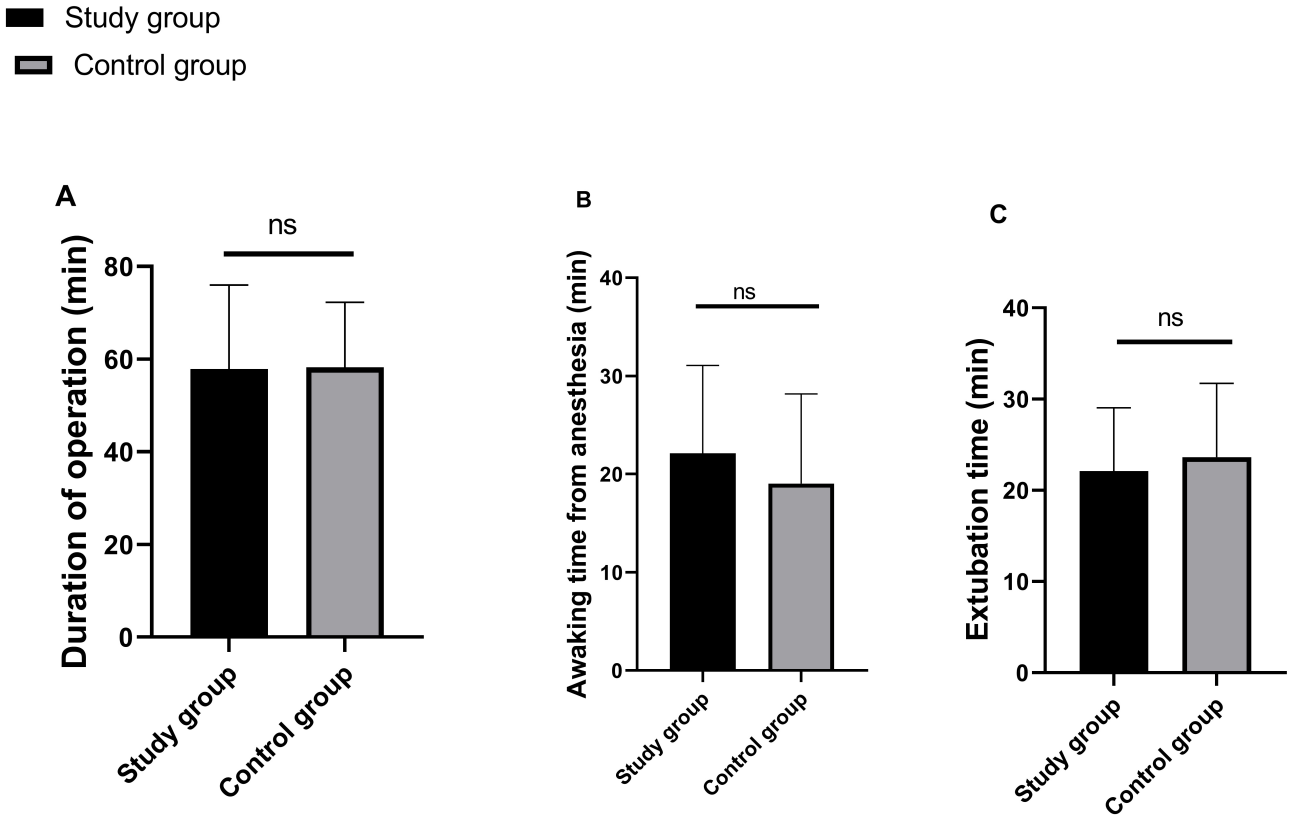

Fig. 3. Inter-group comparison of duration of operation, awakening time from anesthesia, and extubation time. (A) Comparison of duration of operation between the two groups. (B) Comparison of awakening time from anesthesia between the two groups. (C) Comparison of extubation time between the two groups. Notes: $^{ns}p > 0.05$. For the study group, n = 54; for the control group, n = 46.

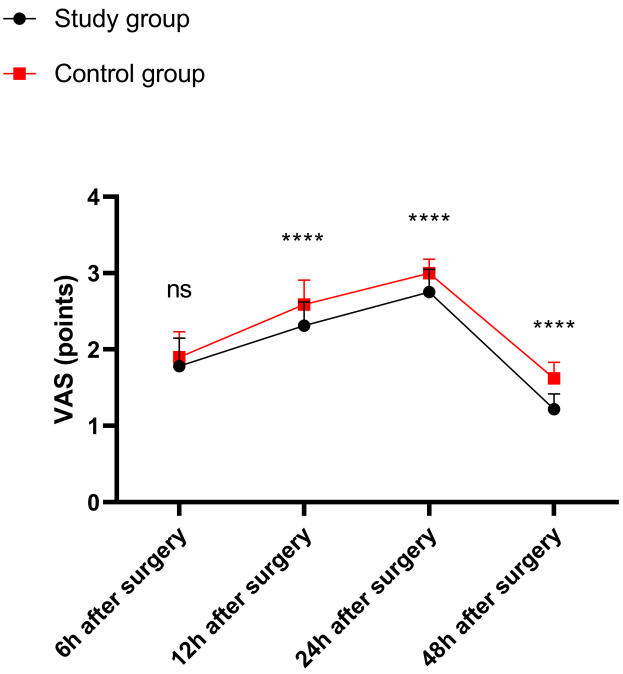

Fig. 4. Comparison of VAS scores between the two groups. Notes: $^{ns}p > 0.05$; $^{****}p < 0.0001$. For the study group, n = 54; for the control group, n = 46. VAS, visual analogue scale.

more stable, indicating that dexmedetomidine combined with nalbuphine was more helpful for maintaining hemodynamic stability during extubation. The possible reasons are as follows: Dexmedetomidine can reduce the sympathetic nerve activity and the release of norepinephrine from nerve endings and vasoconstrictor factors in blood, and inhibit the fluctuation of hemodynamics during extubation [20], while nalbuphine can effectively relieve the pain caused by extubation and reduce the occurrence of stress reaction [21].

The study group also had significantly lower RSAS scores compared to the control group, indicating that dexmedetomidine combined with nalbuphine could provide substantially increased sedation effect. Additionally, no significant differences were observed between the two groups regarding the duration of operation, awakening time from anesthesia, and extubation time, suggesting that nalbuphine does not adversely affect these parameters.

The VAS score is a frequently-adopted method to evaluate pain intensity [11]. In this study, at 6 h after operation, no significant inter-group difference was observed regarding VAS scores, but at 12 h, 24 h and 48 h after operation, the study group had significantly lower VAS scores compared to the control group. This shows that the study group has less pain than the control group, and the analgesic effect of dexmedetomidine+nalbuphine is more obvious than that of

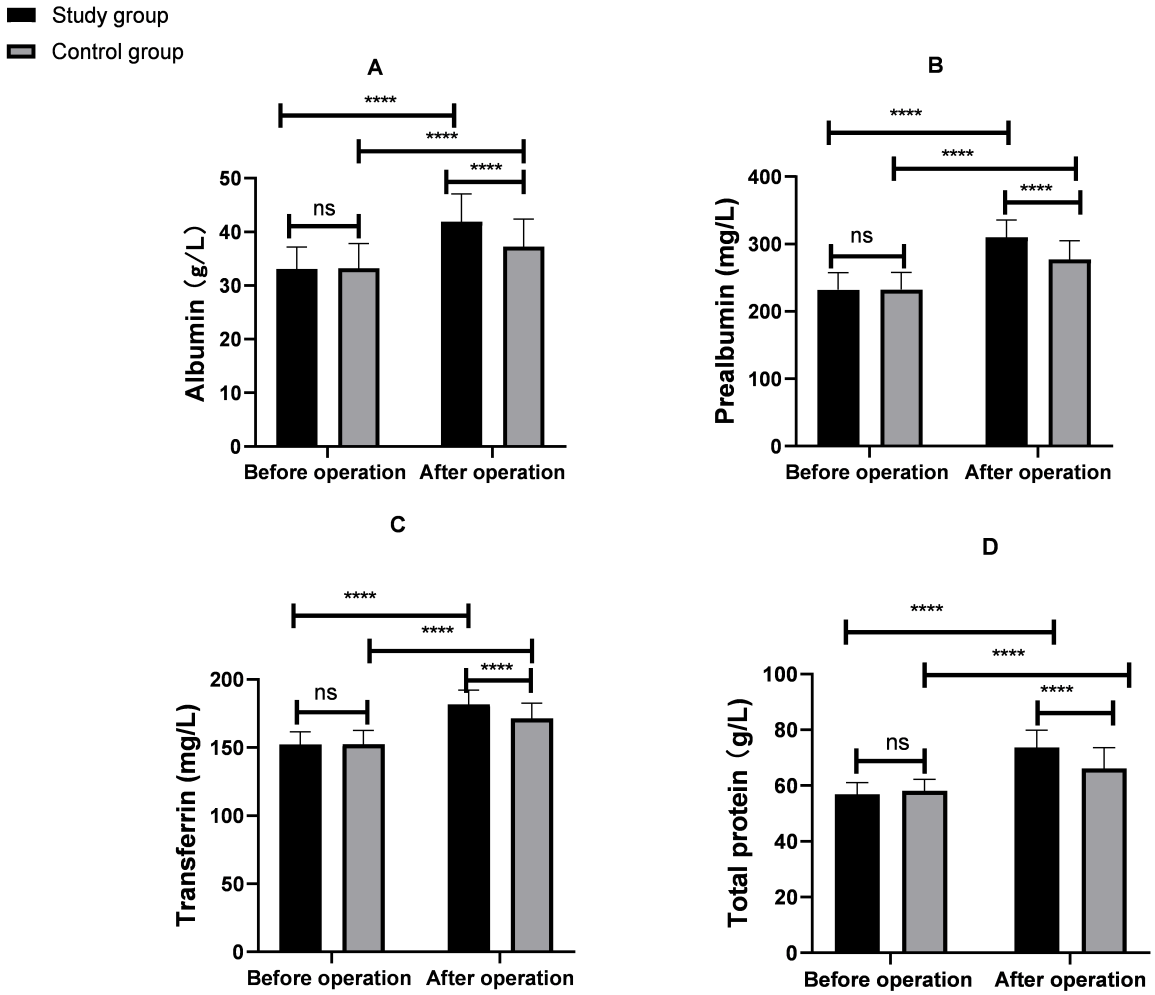

Fig. 5. Inter-group comparison of albumin, prealbumin, transferrin, and total protein levels. (A) Comparison of albumin levels between the two groups. (B) Comparison of prealbumin levels between the two groups. (C) Comparison of transferrin levels between the two groups. (D) Comparison of total protein levels between the two groups. Notes: $^{ns}p > 0.05$; $^{****}p < 0.0001$. For the study group, n = 54; for the control group, n = 46.

dexmedetomidine alone. Liu *et al*. [22] have found that the application of nalbuphine plus dexmedetomidine can lower the pain and improve sedation of patients after laparoscopic follicular resection and promote their recovery, which supports the results of this current study.

Furthermore, our study observed a lower incidence of adverse reactions in the study group compared to the control (5.55% vs.15.22%). Although the difference was not statistically significant, possibly due to the small sample size and variability within each group, the findings suggest a trend towards reduced adverse reactions with the addition of nalbuphine. Future studies with larger sample sizes are needed to confirm these findings.

One week after surgery, the study group exhibited significantly higher levels of albumin, prealbumin, transferrin, and total protein compared to the control group. This improvement in nutritional status may be due to the positive effects of dexmedetomidine on post-operative gastrointestinal recovery [23] and the ability of nalbuphine to lower post-operative nausea and vomiting, thereby enhancing patient comfort and nutrient intake and absorption. Raghuraman [24] also reported nalbuphine as a useful adjunct to intrathecal local anesthetics, citing its prolonged duration of analgesia, anti-pruritic and anti-shivering properties, and reduced incidence of respiratory depression, nausea, and vomiting. Furthermore, surgical stimulation and stress response often lead to metabolic disturbances, including protein breakdown and negative nitrogen balance. Combining dexmedetomidine and nalbuphine may help mitigate these disturbances by reducing surgical stimulation and stress responses, thereby contributing to the maintenance of nitrogen balance and protein. This promotes the utilization and absorption of nutrients in patients.

This study has several limitations, including a limited sample size that may introduce bias and the absence of long-term follow-up to assess the prognosis of patients. Future studies should involve larger sample sizes and extended follow-up periods to provide more comprehensive and reliable data on the anesthetic effects of dexmedetomidine plus nalbuphine in LC patients.

Conclusions

Compared to dexmedetomidine alone, the combination of dexmedetomidine and nalbuphine provides a superior anesthetic effect in patients undergoing LC. This combination effectively controls hemodynamic fluctuations during the recovery period and reduces agitation without affecting the awakening time from anesthesia. Therefore, it is a valuable anesthesia strategy worthy of promotion.

Availability of Data and Materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

YY and LZ formed the research. YY and WJY designed this study. YY, LZ and WJY performed the research. YY and WJY collected and analyzed the data. LZ and WJY have been involved in drafting the manuscript. All authors have been involved in revising it critically for important intellectual content. All authors gave final approval of the version to be published. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

Ethical approval was granted by the Ethics Committee of Wuhan No.1 Hospital (ethical approval number: TW903210). This study adhered to the principles of the Declaration of Helsinki. This study is retrospective in nature, involving the analysis of existing data without direct interaction with participants. So the informed consent from individual participants was exempted by Wuhan No.1 Hospital.

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Conflict of Interest

The authors declare no conflict of interest.

References

[1] Jiang B, Ye S. Pharmacotherapeutic pain management in patients undergoing laparoscopic cholecystectomy: A review. Advances in Clinical and Experimental Medicine: Official Organ Wroclaw Medical University. 2022; 31: 1275–1288.

[2] Barazanchi AWH, MacFater WS, Rahiri JL, Tutone S, Hill AG, Joshi GP, *et al*. Evidence-based management of pain after laparoscopic cholecystectomy: a PROSPECT review update. British Journal of Anaesthesia. 2018; 121: 787–803.

[3] Toleska M, Dimitrovski A. Is Opioid-Free General Anesthesia More Superior for Postoperative Pain Versus Opioid General Anesthesia in Laparoscopic Cholecystectomy? Prilozi (Makedonska Akademija Na Naukite i Umetnostite. Oddelenie Za Medicinski Nauki). 2019; 40: 81–87.

[4] Lee J, Hur MH. The Effects of Aroma Essential Oil Inhalation on Stress, Pain, and Sleep Quality in Laparoscopic Cholecystectomy Patients: A Randomized Controlled Trial. Asian Nursing Research. 2022; 16: 1–8.

[5] Zhao SY, Lu XH, Lyu SG, Shan YY, Miao CH. Effects of remimazolam versus propofol on postoperative recovery quality in elderly patients undergoing thoracoscopic laparoscopic radical esophagectomy. Zhonghua Yi Xue Za Zhi. 2023; 103: 1303–1309. (In Chinese)

[6] Chima AM, Mahmoud MA, Narayanasamy S. What Is the Role of Dexmedetomidine in Modern Anesthesia and Critical Care? Advances in Anesthesia. 2022; 40: 111–130.

[7] Wang W, Ma Y, Liu Y, Wang P, Liu Y. Effects of Dexmedetomidine Anesthesia on Early Postoperative Cognitive Dysfunction in Elderly Patients. ACS Chemical Neuroscience. 2022; 13: 2309–2314.

[8] Yu P, Zhang J, Zou Y, Wang J. Effect of Preventive Analgesia with Nalbuphine and Dexmedetomidine in Endoscopic Sinus Surgery. Pain Research & Management. 2022; 2022: 2344733.

[9] Yu P, Zhang J, Wang J. Nalbuphine for spinal anesthesia: A systematic review and meta-analysis. Pain Practice: the Official Journal of World Institute of Pain. 2022; 22: 91–106.

[10] Zhong L, Shen K, Zhai S, Chen T, Tao Q, Chen L, *et al*. Application of sedation-agitation scale in conscious sedation before bronchoscopy in children. Medicine. 2019; 98: e14035.

[11] Sung YT, Wu JS. The Visual Analogue Scale for Rating, Ranking and Paired-Comparison (VAS-RRP): A new technique for psychological measurement. Behavior Research Methods. 2018; 50: 1694–1715.

[12] Cirocchi R, Kwan SH, Popivanov G, Ruscelli P, Lancia M, Gioia S, *et al*. Routine drain or no drain after laparoscopic cholecystectomy for acute cholecystitis. The Surgeon: Journal of the Royal Colleges of Surgeons of Edinburgh and Ireland. 2021; 19: 167–174.

[13] Jensen SAMS, Fonnes S, Gram-Hanssen A, Andresen

K, Rosenberg J. Long-term mortality and intestinal obstruction after laparoscopic cholecystectomy: A systematic review and meta-analysis. International Journal of Surgery (London, England). 2022; 105: 106841.
[14] Liang J, Tian XF, Yang W. Effect of Humanistic Nursing on Preoperative Anxiety, Postoperative Pain Relief and Prognosis of Colorectal Cancer Patients. Journal of Modern Nursing Practice and Research. 2021; 1: 9.
[15] Matsumoto J. Intracellular pigment translocation and color changes in lower vertebrates (author's transl). Tanpakushitsu Kakusan Koso. Protein, Nucleic Acid, Enzyme. 1978; 23: 349–360. (In Japanese)
[16] Warner MA, Arnal D, Cole DJ, Hammoud R, Haylock-Loor C, Ibarra P, *et al*. Anesthesia Patient Safety: Next Steps to Improve Worldwide Perioperative Safety by 2030. Anesthesia and Analgesia. 2022; 135: 6–19.
[17] Trifa M, Tumin D, Tobias JD. Dexmedetomidine as an adjunct for caudal anesthesia and analgesia in children. Minerva Anestesiologica. 2018; 84: 836–847.
[18] Chen R, Sun S, Li Y, Dou X, Dai M, Wu Y, *et al*. Efficacy and safety evaluation of dexmedetomidine for postoperative patient controlled intravenous analgesia: A systematic review and meta-analysis. Frontiers in Pharmacology. 2022; 13: 1028704.
[19] Gao XN, Nie XY, Gao JL, Heng TF, Zhang YQ, Hua L, *et al*. Pharmacokinetic Study of Nalbuphine in Surgical Patients Undergoing General Anesthesia with Varying Degrees of Liver Dysfunction. Drug Design, Development and Therapy. 2022; 16: 2383–2393.
[20] He H, Peng W, Luan H, Shi C, Tu W. The effect of dexmedetomidine on haemodynamics during intracranial procedures: a meta-analysis. Brain Injury. 2018; 32: 1843–1848.
[21] Gong Y, Zhang Y, Tao S. Nalbuphine for analgesia after fracture surgery and its effect on circulating inflammatory factors. Experimental and Therapeutic Medicine. 2018; 15: 859–863.
[22] Liu X, Song J, Zhang Y, Zhang Y, Hu X. Different Doses of Nalbuphine Combined with Dexmedetomidine in Laparoscopic Oophorocystectomy. Medical Science Monitor: International Medical Journal of Experimental and Clinical Research. 2021; 27: e930197.
[23] Lu Y, Fang PP, Yu YQ, Cheng XQ, Feng XM, Wong GTC, *et al*. Effect of Intraoperative Dexmedetomidine on Recovery of Gastrointestinal Function After Abdominal Surgery in Older Adults: A Randomized Clinical Trial. JAMA Network Open. 2021; 4: e2128886.
[24] Raghuraman MS. Intrathecal nalbuphine–Will it gain wider acceptance?–A narrative review. Egyptian Journal of Anaesthesia. 2017; 33: 289–293.