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Original Research Article

Effect of the combination of dexmedetomidine and sufentanil after laparoscopic cholecystectomy in patients with gallbladder diseases

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Abstract

Purpose: *To investigate the effect of dexmedetomidine plus sufentanil on in-patients after laparoscopic cholecystectomy (LC).*
Methods: *A total of 120 patients with gallbladder disease in Jingxian Hospital, China who were treated with LC were assigned equally to control and study cohorts. Control group received sufentanil, while study group received dexmedetomidine and sufentanil after surgery. The extent of sedation, degree of pain, and dosage of self-controlled analgesia pump drug, were evaluated within 48 h. Serum levels of stress indicators such as cortisol (Cor), norepinephrine (NE), angiotensin II (AngII), reactive oxygen species (ROS), and inflammatory factors: interleukin-17 (IL-17), tumor necrosis factor-alpha (TNF-α), and high-sensitivity C-reactive protein (hs-CRP) were determined.*
Results: *Values of Ramsay sedation scores after surgery in study group were significantly higher than those in control group ($p < 0.05$). The visual analogue scale (VAS) scores were significantly lower in study group than in control group. The self-controlled analgesia pump drug dosages were significantly lower in study cohort ($p < 0.05$). Study cohort had lower levels of Cor, NE, AngII, TNF-α, and hs-CRP after surgery than control cohort, while SOD level was higher in study cohort than in control cohort ($p < 0.05$). There was a significantly lower incidence of adverse reactions in study cohort.*
Conclusion: *The combination of dexmedetomidine and sufentanil as postoperative analgesia in LC significantly improves sedation and analgesia, reduces sufentanil use, alleviates stress response and inflammation, and reduces adverse reactions. Future long-term and large-scale monitoring is required to further validate these findings.*

Keywords: *Laparoscopic cholecystectomy (LC), Dexmedetomidine, Sufentanil, Analgesia, Stress response*

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INTRODUCTION

In the past, traditional open cholecystectomy was commonly used to treat gallbladder diseases. Although this surgical approach provides a wide field of vision which allows for adequate exposure of the surgical area and facilitates the eradication of lesions, it has been gradually phased out due to its long operating time, large surgical incisions, excessive bleeding, and

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numerous postoperative complications. With the development of minimally invasive technology, laparoscopic cholecystectomy (LC) has become the first choice for the treatment of benign gallbladder diseases due to its minimal invasion, low bleeding volume, rapid recovery, and short hospitalization period. Moreover, it effectively prevents the pain caused by traditional open surgery for patients, while achieving good clinical effects [1,2]. Although LC has obvious clinical advantages, it remains an invasive surgery, and patients may experience pain and stress responses during the procedure. To ensure treatment efficacy in patients, it is particularly important to choose appropriate and effective anesthesia and analgesia during the perioperative period [3].

Sufentanil is often used as an opioid analgesic in clinical practice. It has strong lipophilicity; it easily passes through the blood-brain barrier, and it produces significant analgesic effects, with a long duration of action [4]. However, its associated adverse consequences, e.g., depression of respiration, postoperative hyperalgesia, postoperative vomiting/nausea, intestinal obstruction, and urinary retention, may be detrimental to the recovery of patients, resulting in prolonged hospitalization.

Dexmedetomidine is a new, effective and highly selective α2-adrenergic receptor agonist that sedates, alleviates pain and anxiety, and reduces stress response. Dexmedetomidine injection reduces postoperative pain scores, nausea, vomiting, and acute analgesic requirements [5]. Therefore, it is beneficial to combine dexmedetomidine with opioid analgesics so as to reduce the dosage of opioids and reduce the associated side effects. Studies in China have found that the combination of dexmedetomidine and sufentanil exhibits synergistic drug effects which increase the brain tissue exposure level of dexmedetomidine and prolong the duration of sedation [6].

The present study investigated the analgesic effect of dexmedetomidine and sufentanil in patients undergoing laparoscopic cholecystectomy. A total of 120 patients from our hospital were included in the study.

METHODS

General information on patients

This study included 120 patients who were subjected to LC treatment from January 2019 to December 2021 in Jingxian Hospital, Anhui Province, China. The patients were randomly divided into a control group and a study group, with 60 patients in each group. Control cohort comprised 33 male patients and 27 female patients between the ages of 35 - 66 years (mean age = 45.62 ± 11.23 years). Study cohort comprised 29 men and 31 women of ages 33 - 65 years (mean age = 47.62 ± 10.39 years). Gender and age were comparable in the 2 cohorts of patients. Approval for this study was obtained from Jinling Hospital Medical School of Nanjing University (approval no. ETCP202204004). The study was conducted in accordance with the Declaration of Helsinki [7].

Inclusion criteria

The included subjects were those who met the indications for LC treatment, and who agreed to undergo LC surgery; subjects with no allergic reactions to sufentanil and dexmedetomidine, and those who voluntarily signed the informed consent form after being aware of the content of the study.

Exclusion criteria

Patients having surgical contraindications or allergies to sufentanil or dexmedetomidine; those with coagulopathy; subjects with organ failure, and patients with mental illnesses, were excluded.

Procedure and treatment

Patients in both groups underwent general anesthesia during the surgical procedure, with 0.5 mg atropine given intramuscularly before anesthesia. Intravenous access was established for each patient, and an electrocardiogram monitor was connected. Anesthesia induction was achieved with midazolam (0.01 mg/kg) + sufentanil (0.5 g/kg) + rocuronium (0.6 mg/kg), followed by tracheal intubation and mechanical ventilation with a ventilator. During the surgical procedure, propofol (5 g/kg) was infused intravenously every hour, and intermittent doses of sufentanil (0.5 - 1 g/kg) + rocuronium (0.05 g/kg) were used to maintain anesthesia while laparoscopic LC treatment was being performed. After the surgery, patients were connected to a patient-controlled analgesia device. Control cohort was administered sufentanil (1.5 g/kg) diluted with 0.9 % NaCl solution to a volume of 100 mL. Patients in study group were administered sufentanil (1.5 g/kg) + dexmedetomidine (1.0 mg/kg), which was also diluted with 0.9 % NaCl solution to a volume of 100 mL. The patients pressed the pump device for medication, based on their pain tolerance, and all patients were treated with a patient-

controlled analgesia pump for 48 h. The dosage of medication was recorded for each patient.

Evaluation of parameters/indices

Postoperative sedation

The Ramsay sedation score was used to assess postoperative sedation at 6, 12, 24, and 48 h after surgery. The score ranged from 1 to 6, with 1 indicating restlessness and agitation; 2 implying calmness; 3 indicating alertness and sleepiness, and 4 implying that the subject was lightly asleep but could be awakened. Score 5 indicated deep sleep and unresponsiveness, while 6 indicated deep sleep and unresponsiveness.

Degree of pain

Pain was assessed in the two groups of patients at postoperative 6, 12, 24, and 48 h, using the visual analog scale (VAS). The scale had a score range of 0 - 10 points. The higher the score, the more severe the pain. Specifically, 0 points = no pain; 1 - 3 points = mild and tolerable pain; 4 - 6 points = increased pain which was still tolerable, although it affected sleep by the patient, while acute and unbearable pain was scored 7 - 10 points.

Stress indicators

Stress indicator levels in the 2 cohorts before and after surgery were determined at 6 and 12 h: 5 mL of blood was taken from the vein of each patient after overnight fast, at 3-time points: prior to surgery, 6 h after surgery, and 12 h after surgery. After centrifugation, serum was obtained, and the serum levels of cortisol (Cor), norepinephrine (NE), angiotensin II (AngII), and superoxide dismutase (SOD) were determined using radioimmunoassay (RIA) and enzyme-linked immunosorbent assay (ELISA), as appropriate.

Inflammatory cytokines

Prior to surgery, and at 6 and 12 h after surgery, 5 mL of fasting venous blood was taken from each subject. After centrifugation, serum was obtained, and the levels of tumor necrosis factor (TNF-α) and high-sensitivity C-reactive protein (hs-CRP) in the serum were detected by ELISA.

Unwanted reactions

Cases of unwanted reactions were recorded in both cohorts.

Statistical analysis

The data in this study were subjected to statistical analysis using SPSS 25.0. Count data are presented as several cases (n), and the chi-square test was used for intergroup comparisons. Measured results are presented as mean ± standard deviation (SD) and intergroup comparisons were done using *t*-test. Significant differences were assumed at $p < 0.05$.

RESULTS

Clinical data

As shown in Table 1. Gender, age, operation duration and American Society of Anesthesiologists (ASA) classification were comparable in both cohorts, indicating that the two groups were comparable ($p > 0.05$). Thus, the results of this study are usable.

Postoperative Ramsay sedation scores, VAS pain scores

Study cohort had lower Ramsay sedation scores than control cohort at postoperative 6, 12, 24, and 48 h. There were significant differences in the Ramsay scores between the two groups at postoperative 6, 12, and 24 h ($p = 0.0658$), while there was no significant difference in the Ramsay scores between the two groups at postoperative 48 h ($p < 0.05$, Table 2). The VAS scores of study group were significantly low when compared with the control score at 6, 12, 24, and 48 h after surgery ($p < 0.05$). At postoperative 6, 12, 24, and 48 h.

Table 1: Clinical data of the two groups of patients (n=60)

Group	Gender (male/female)	Age (years)	Duration of surgery (min)	ASA classification (Grade I/Grade II)
Control	33/27	45.62±11.23	39.58±11.61	47/13
Study	29/31	47.62±10.39	37.26±12.15	42/18
t/F	0.7307	1.013	1.069	1.043
P-value	0.5839	0.3133	0.2871	0.4044

Table 2: Postoperative Ramsay Sedation Score, VAS Pain Score, and Self-Controlled Analgesia Pump Drug Consumption in the two groups of patients (n=60)

Post-surgery period (h)	Ramsay (point)				VAS score (point)			
	Control	*Study*	*T*	*P-value*	*Control*	*Study*	*t*	*P-value*
6	2.25±0.84	2.55±0.75	2.064	0.0413	4.15±0.97	3.82±0.80	2.033	0.0443
12	2.64±0.79	2.98±0.81	2.328	0.0216	3.75±0.70	3.49±0.63	2.122	0.0360
24	3.31±0.48	3.49±0.39	2.254	0.0260	3.16±0.59	2.78±0.53	3.711	0.0003
48	3.60±0.39	3.69±0.30	1.417	0.1592	2.18±0.49	1.96±0.42	2.641	0.0094

Table 3: Self-controlled analgesia drug usage (mL)

Period (h)	Control group	Study group	*t*	*P*-value
6	10.25±1.09	8.91±1.13	6.611	<0.0001
12	26.33±2.74	24.49±2.48	3.857	0.0002
24	55.68±4.58	49.51±4.37	7.550	<0.0001
48	81.19±7.51	62.64±6.04	14.91	<0.0001

Self-controlled analgesia pump drug consumption

The amount of medication used in the patient-controlled analgesia pump was significantly lower in study cohort ($p < 0.05$; Table 3).

Stress indices levels

The levels of Cor, NE, AngII, and SOD were comparable in the two groups of patients before surgery. However, after surgery, the levels of Cor, NE, AngII, and SOD in both groups increased. Further analysis showed that at 6 and 12 h after surgery, there were significantly lower concentrations of Cor, NE, and AngII in study cohort than in control cohort, while SOD activity was higher in study cohort ($p < 0.05$, Table 4).

Inflammatory cytokine concentrations

Before surgery, the levels of TNF-α and hs-CRP were comparable in both cohorts of patients. However, post-surgery levels of TNF-α and hs-CRP in both groups were significantly increased, when compared to pre-surgery levels, with significantly lower values in study cohort at 6 and 12 h after surgery than in control cohort ($p < 0.05$; Table 5).

Table 4: Data for the two groups of patients before surgery and at 6 and 12 hours after surgery (n=60)

Comparison of stress index levels between the two groups

Period	Cor (nmol/L)				NE (pmol/L)			
	Control	*Study*	*t*	*P-value*	*Control*	*Study*	*t*	*P-value*
Preoperative	118.65±19.51	115.92±18.09	0.7948	0.4283	1592.08±93.71	1611.92±101.83	1.111	0.2690
6 h after	191.59±20.14	180.34±19.27	3.126	0.0022	2584.37±115.72	2368.46±109.88	10.48	<0.0001
12 h after	160.44±20.09	141.97±19.84	34.55	<0.0001	1955.24±95.81	1894.59±96.45	3.456	0.0008

Levels of AngII and SOD at various time points

Period	AngII (ng/L)				SOD (μg/mL)			
	Control	*Study*	*T*	*P*-value	*Control*	*Study*	*t*	*P*value
Preoperative	29.68±2.94	29.31±2.46	0.7476	0.4562	69.18±5.94	70.96±6.16	1.611	0.1098
6 h after	52.91±5.42	47.61±4.92	5.608	<0.0001	81.61±7.55	86.34±7.87	3.359	0.0011
12 h after	36.51±4.28	32.33±3.67	5.743	<0.0001	74.52±6.68	77.66±7.14	2.488	0.0143

Table 5: Inflammatory cytokine levels in the two cohorts of patients before surgery and at 6 and 12 h after surgery (n=60)

Period	TNF-α (ng/L)				hs-CRP (ng/L)			
	Control	*Study*	*t*	*P*-value	*Control*	*Study*	*t*	*P-value*
Preoperative	16.31±1.89	16.78±1.75	1.413	0.1602	15.15±1.82	15.49±1.80	1.029	0.3057
6 h after	25.67±5.48	21.54±4.81	4.387	<0.0001	23.54±2.50	21.35±2.11	5.185	<0.0001
12 h after	18.68±2.14	17.09±1.78	4.425	<0.0001	17.26±1.59	16.38±1.42	3.198	0.0018

Table 6: Incidents of adverse reactions in both cohorts of patients (n=60)

Group	Nausea and vomiting	Respiratory suppression	hypotension	Uroschesis	Overall incidence [n (%)]
Control	5	1	1	3	10 (16.67)
Study	2	0	0	0	2 (3.33)
F					2.434
P-value					0.0295

Incidence of adverse reactions

The main adverse reactions in the two groups of patients were nausea, vomiting, respiratory depression, hypotension, and urinary retention, with significantly higher incidence in study cohort (16.67%) than in control cohort (3.33%) ($p < 0.05$; Table 6).

DISCUSSION

Laparoscopic cholecystectomy reduces postoperative pain, relative to traditional open surgery. However, pain is still the most common complaint in patients. This may prolong hospitalization and delay the resumption of normal activities by patients. If acute pain is not well controlled, it may cause serious adverse consequences on various bodily systems, such as inability to clear respiratory secretions, gastrointestinal obstruction, increased blood pressure and heart rate (HR), sweating, pallor, prolonged bed rest, and increased risk of atelectasis and deep venous thrombosis, all of which ultimately reduce patient's satisfaction with treatment [8]. Therefore, after laparoscopic surgery, it is very important to use an analgesia scheme with the longest duration of postoperative analgesia, the least complications, and the highest level of comfort for the patient.

Opioids are often used for post-surgery relief of pain in clinics. Sufentanil is a derivative of fentanyl, and it produces a stronger analgesic effect and a longer duration of analgesia when compared to fentanyl. However, some adverse reactions caused by sufentanil have limited its application to some extent [9]. The use of dexmedetomidine is currently an area of intensive study on postoperative pain relief in laparoscopic surgery [10,11]. It activates α-adrenergic receptors, reduces catecholamine release into the bloodstream, inhibits sympathetic activity, and induces the hyperpolarization of NE cells, thereby producing sedative and analgesic effects. A previous study showed that dexmedetomidine infusion during LC safely and effectively improved postoperative pain relief during and following elective LC [12].

A study [13] showed that the postoperative analgesic effect of dexmedetomidine when used in combination with sufentanil was better than that of sufentanil alone for laparoscopic gynecological surgery patients, with higher safety and lower incidence of adverse reactions. The postoperative analgesic effects of dexmedetomidine in combination with sufentanil in LC patients were assessed in the present research. It was revealed that sedation ratings of patients in both cohorts at 6, 12, 24, and 48 h post-surgery were between 1 and 5 points, with significantly lower Ramsay scores in study cohort patients at these time points after surgery. This indicates that dexmedetomidine in combination with sufentanil produced a better sedative effect on patients. This may be due to the inhibitory effect of dexmedetomidine on sympathetic activity and endogenous activation of sleep neural pathways [14]. However, Ramsay's scores were comparable in both cohorts at 48 h after surgery. It may be that patients' tolerance to pain increased over time, leading to less agitation. The post-operative VAS pain scores in study cohort were significantly lower than control cohort scores. In addition, the amount of medication used by patients through self-controlled analgesia pumps, and adverse reaction incidents, were lower in study cohort than in control cohort. This indicates that combined use of dexmedetomidine and sufentanil alleviated postoperative pain in LC patients more effectively, reduced sufentanil consumption, and reduced adverse reactions caused by excessive sufentanil use.

The surgical wound resulting from LC treatment may cause the peripheral and central nervous system to be in a state of high sensitivity, leading to the occurrence of stress and inflammatory reactions in patients. Stress reactions involve various indicators such as Cor, NE and AngII, the levels of which directly reflect the degree of stress reaction in patients. Superoxide dismutase is an important antioxidant enzyme that effectively neutralizes toxic oxygen free radicals which reflect the oxidative stress levels of body tissues [15]. Tumor necrosis factor-alpha (TNF-α) and hs-CRP are well-known clinical inflammatory indicators. The present investigation has demonstrated marked increases in levels of Cor, NE, AngII, SOD, TNF-α, and hs-CRP in both groups of patients after

surgery, when compared with values before surgery, suggesting that surgical stimulation caused stress and inflammatory reactions in the patients. After analgesia intervention, the levels of Cor, NE, AngII, TNF-α, and hs-CRP were decreased, with significantly lower values of Cor, NE, AngII, TNF-α, and hs-CRP in study cohort, while SOD activity was significantly higher in control cohort. This indicates that the combined use of dexmedetomidine and sufentanil effectively enhanced antioxidant resistance to stress in the patients. Dexmedetomidine stimulates the vagus nerve, inhibits sympathetic nerve tension, and reduces central NE release, thereby alleviating stress and inflammatory reactions in patients.

Limitations of this study

Firstly, the number of patients was few and the study was carried out in only one center. Secondly, molecular mechanisms for the improved treatment outcomes were not determined and finally, long-term post-operative monitoring beyond 48 h was not done in this study.

CONCLUSION

The combined use of dexmedetomidine and sufentanil for postoperative analgesia in LC is beneficial in improving sedation and analgesic effects, reduces sufentanil usage, alleviates stress and inflammatory responses, and reduces the occurrence of adverse reactions. Therefore, there is a need for long-term and large-scale monitoring of this drug combination to confirm the validity of the findings reported in this study.

DECLARATIONS

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Ethical approval

This study was approved by Jinling Hospital Medical School of Nanjing University (approval no. ETCP202204004).

Availability of data and materials

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

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was performed by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Yan Chen and Xiangliu Liu designed the study, supervised the data collection, and analyzed the data. Gaohua Wang interpreted the data and prepared the manuscript for publication. Haifeng Guo supervised the data collection, analyzed the data and reviewed the draft of the manuscript. Yan Chen and Xiangliu Liu contributed equally to this work and should be considered as co-first authors.

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