Effects of dexmedetomidine on postoperative pain and early cognitive impairment in older male patients undergoing laparoscopic cholecystectomy

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Abstract. The primary aim of the present study was to investigate the effect of dexmedetomidine (DEX) on postoperative pain and early cognitive impairment in old male patients, who underwent laparoscopic cholecystectomy (LC). A total of 97 old patients, subjected to LC at the 980 Hospital of the Joint Service Support Force of the People's Liberation Army of China, were randomly divided into two groups, namely the DEX and normal saline groups. Patients in the DEX group received an intravenous infusion of 0.8 μg/kg DEX within 10 min following general anesthesia, followed by a maintenance infusion of 0.5 μg/(kg/h). Furthermore, patients in the normal saline group were treated with an equivalent volume of normal saline. Cognitive function was assessed using the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA) tests at 6 h, 1, 2 and 3 days, postoperatively. The incidence of postoperative cognitive dysfunction (POCD) and postoperative adverse events were recorded for both groups. In addition, the Visual Analogue Scale (VAS) pain score was utilized to assess the pain level of all patients, while the Quality of Recovery-15 (QoR-15) scale was employed to analyze the postoperative recovery results. Therefore, the MoCA score was higher in the DEX group compared with the normal saline group at 6 h and day 1 postoperatively. Additionally, the MMSE score was higher at 6 h postoperatively in the DEX group compared with the normal saline group. Correspondingly, the incidence of POCD was lower in the DEX group compared with the normal saline group at 6 h and day 1, after LC (P<0.05). VAS score in resting state for patients in the DEX group was significantly lower compared with the normal-saline group (P<0.05). Furthermore, the QoR-15 scale score in patients in the DEX group was notably increased compared with the normal saline group on the first and second days after the operation (P<0.05). Overall, the present study verified that the continuous infusion of DEX at a rate of 0.5 μg/(kg/h) during LC could effectively reduce the incidence of early POCD and alleviate postoperative pain in old male patients, thus facilitating postoperative recovery.

Introduction

Postoperative cognitive dysfunction (POCD) is a common early symptom affecting the central nervous system following operation and anesthesia. This phenomenon is commonly observed in old patients undergoing general surgical procedures and is characterized by a decline in cognitive function, including postoperative anxiety, impaired memory, reduced attention and even personality changes. All the aforementioned manifestations can impede postoperative recovery (1). The onset of POCD can exacerbate postoperative complications, prolong hospital stay and impose significant burdens on society and family (2). Current research has suggested that both the age of patients and the nature of surgery can significantly affect the manifestations of POCD (3). However, further studies are needed to fully elucidate the triggers of postoperative cognitive impairment. Consequently, clinicians and anesthetists should pay considerable attention to the occurrence and preventive measures against POCD.

Dexmedetomidine (DEX), a highly selective α2 receptor agonist, possesses anti-inflammatory, sedative, analgesic, anxiolytic, anti-sympathetic and mild respiratory depressant properties. Furthermore, it exerts a protective effect on postoperative cognitive function (4), while it has been reported that it is effective in preventing anesthesia-induced postoperative delirium (5). A meta-analysis by Yu *et al* (6) indicated that DEX was associated with a reduced risk of POCD in old adults. Therefore, it was hypothesized that DEX could stand out among the drugs with the highest potential to reduce the incidence of POCD in older adults subjected to non-cardiac surgery (7). DEX plays a crucial role in multimodal analgesia approaches and is an integral part of enhanced recovery

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after surgery protocols, thus contributing to satisfactory postoperative outcomes. The efficacy of DOX in alleviating postoperative pain is notable when used during nerve blocks, with several studies highlighting its superiority over other agents in the perioperative setting. It has been also reported that DEX exhibits neuroprotective effects (8-11).

The quality of recovery-15 (QoR-15) serves as a tool for assessing the quality of postoperative and postanesthetic recovery. Therefore, DEX yields higher satisfaction scores, possibly due to its effect on reducing pain, postoperative nausea and vomiting. Although previous literature reviews have primarily focused on POCD in patients undergoing cardiovascular and non-cardiac surgery, several studies have suggested that DEX can improve POCD (6-7). Despite the possible beneficial effects of DEX on perioperative patients, the role of DEX in laparoscopic cholecystectomy (LC) has not been well established. Therefore, the present study aimed to evaluate the efficacy of intraoperative use of DEX on preventing POCD and relieving postoperative pain in old patients undergoing LC, thus taking the opportunity to outline the relevant clinical evidence supporting the application of DEX in elderly patients subjected to LC.

Materials and methods

General information. In the present study, a total of 97 old patients who underwent LC under general anesthesia between January 2022 and January 2023 at the 980 Hospital of the Joint Service Support Force of the People's Liberation Army of China (Shijiazhuang, China) were enrolled. The patients were allocated into the DEX (n=53) and normal saline (n=44) groups. The inclusion criteria were as follows: i) Male patients; ii) aged 65-75 years; iii) patients with an American Society of Anesthesiologists (ASA) score of class I-II; iv) patients diagnosed with gallstones or cholecystitis and subjected to LC; and v) patients with Simple Intelligent Mental State Scale (MMSE) score of ≥24 on the first preoperative day. Furthermore, the exclusion criteria were the following: Patients i) with cancer; ii) with intraoperative changes in surgical procedures; iii) with allergies to anesthetic medications; iv) suffering from psychiatric disorders or had a history of psychotropic drug use; v) with history of drug abuse; and vi) with underlying systemic diseases. Underlying systemic diseases are chronic metabolic diseases requiring long-term treatment. These encompass a range of basic diseases across various systems in the human body, such as chronic bronchitis, bronchial asthma and chronic obstructive pulmonary disease in the respiratory system; high blood pressure and coronary heart disease in the circulatory system; chronic gastritis, peptic ulcer and viral hepatitis in the digestive system; chronic glomerulonephritis in the urinary system; diabetes, hyperthyroidism, hypothyroidism in the endocrine system, rheumatoid arthritis, systemic lupus erythematosus, osteoarthritis, Sjögren's syndrome, gout and other rheumatism-related diseases can be categorized as co-morbidities. The present study was approved by the Ethics Committee of the 980 Hospital of the Joint Service Support Force of the People's Liberation Army of China (approval no. 2021-KY-86; Shijiazhuang, China) and informed consent was obtained from all patients or their families.

Drug administration. For an hour during the operation all patients received general anesthesia, with venous access established upon entering the operation room. Prior to anesthesia, electrocardiogram, heart rate, oxygen saturation measured by a pulse oximeter and blood pressure were monitored. Patients in the DEX group received 0.8 μg/kg DEX (Jiangsu Hengrui Medicine Co., Ltd.) intravenously within 10 min prior to induction, followed by a maintenance infusion of 0.5 μg/(kg/h). Correspondingly, patients in the normal saline group received an equivalent volume of normal saline. For the induction of general anesthesia, propofol (2.0-2.5 mg/kg) and sufentanil (0.3 μg/kg) combined with rocuronium (0.6 mg/kg) were employed. Following endotracheal intubation, sevoflurane (2-3%), sufentanil [0.3 μg/(kg/min)] and propofol (4-5 mg/kg/h) were administered intravenously to maintain anesthesia. Therefore, patients in the DEX group were treated with a combination of five narcotic drugs, while those in the normal saline groups with four. All patients were subjected to mechanical ventilation throughout the operation. The electroencephalography double-frequency index was maintained between 45 and 60. The peak airway pressure was controlled <25 cmH_2O, while the end-tidal CO_2 pressure was maintained between 37-45 mm Hg.

Evaluation indicators. In the present study, two evaluation systems, namely MMSE and Montreal Cognitive Assessment (MoCA), were utilized and POCD was diagnosed when both scores met the diagnostic criteria for POCD. When the score of patients met only one of the diagnostic criteria, then the patients were not diagnosed with POCD. These scores were recorded on day 1 prior operation and at 6 h, 1, 2 and 3 days postoperatively. Score assessment was performed by clinicians with relevant experience and rigorous training. The evaluation personnel were relatively fixed. The diagnosis of POCD complied with the 'Guidelines for the Diagnosis and Treatment of Dementia and Cognitive Disorders' developed by the Dementia and Cognitive Impairment Group of the Chinese Academy of Neurology (12). When the postoperative score decreased by more than three points compared with the preoperative one on the MOCA and MMSE scale, a decline in postoperative cognitive function was considered. According to the POCD evaluation standard, scores of 28-30, 24-27, 19-23 and 0-18 points, indicated normal, mild, moderate and severe cognitive impairment, respectively. The visual analog score (VAS) in the resting state was also recorded at day 1, 2 and 3, postoperatively. The VAS scores ranged from 0 to 10, with higher scores indicating increased pain levels. Furthermore, the QoR-15 score, ranging from 0 (not occurred) to 10 (always present) was employed to assess the QoR of patients at day 1 prior surgery and at days 1, 2 and 3 after operation. Adverse reactions during the surgical operations were observed in both groups.

Statistical analysis. Statistical analysis was performed using SPSS 20.0 software (IBM Corp.). Count data are expressed as the mean ± standard deviation or n (%). All count data were analyzed using unpaired t-test, Fisher's exact and Chi-square tests. $P<0.05$ was considered to indicate a statistically significant difference.

Table I. Characteristics of patients with cholecystitis or gallstones who underwent laparoscopic cholecystectomy among the two groups.

Characteristics	DEX group (n=53)	Normal-saline group (n=44)	P-value
Age (year)	69.5±6.4	68.9±7.1	0.251
Hight (cm)	172.2±4.9	174.2±2.1	0.514
Weight (cm)	73.1±6.7	77.5±5.8	0.061
Education (year)	7.8±2.5	7.3±2.9	0.082
Length of surgery (min)	60.1±3.4	58.5±3.8	0.213
ASA status, n (%)			0.659
I	28 (52.8%)	21 (47.7%)	
II	25 (47.2%)	23 (52.3%)	
Duration of surgery (min)	55±2.4	54±3.7	0.729
intraoperative bleeding (ml)	47±5.7	49±4.9	0.620
Smoking, n (%)	30 (56.7%)	26 (59.1%)	0.892
Drinking, n (%)	35 (66.03%)	25 (56.8%)	0.823

Values are presented as the mean ± standard deviation or number (percentage). DEX, dexmedetomidine.

Table II. Comparison of postoperative MMSE and MoCA scores.

	MMSE score				MoCA score			
Postoperative period	DEX group	Normal-saline group	T-value	P-value	DEX group	Normal-saline group	T-value	P-value
6 hours	23.49±2.04	20.52±2.87	5.451	0.009	25.34±1.22	21.24±2.51	6.121	0.007
1 day	25.12±1.31	25.01±1.21	4.211	0.059	26.97±0.67	23.01±2.05	4.894	0.013
2 day	27.56±0.75	26.48±0.39	1.032	0.231	26.04±1.23	27.15±0.82	3.673	0.076
3 day	28.12±1.32	28.01±1.79	2.321	0.324	27.38±0.43	27.62±0.51	1.127	0.432

T-tests were used to compare the MMSE scores and MoCA scores of patients at different postoperative periods. MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; DEX, dexmedetomidine.

Results

Effect of DEX on MMSE and MoCA scores. There were no significant differences in the general data, including age, weight, height, educational level, operation time and ASA status between the DEX and normal saline groups (Table I). The MMSE and MoCA scores were compared between the two groups and the results revealed that MMSE score was significantly higher in patients in the DEX group at 6 h after surgery compared with the normal saline group (P<0.05). Furthermore, MoCA score was also notably higher in the DEX group at both 6 h and day 1 after LC compared with the normal saline group (P<0.05; Table II). The aforementioned findings suggested that DEX could be associated with a reduced early incidence of POCD in old patients undergoing LC.

DEX is associated with the lack of adverse events following LC. The incidence of POCD and postoperative agitation were significantly lower in the DEX group compared with the normal saline group (P<0.05), while there were no significant differences in the incidence of other postoperative adverse reactions between the two groups (P>0.05; Table III). This result could be ascribed to the capacity of DEX on diminishing postoperative delirium (5).

DEX is associated with reduced VAS score and enhanced QoR-15 scale score. VAS score was utilized to evaluate the postoperative pain levels. Therefore, patients in the DEX group revealed significantly lower VAS score on days 1 and 2 post-operatively compared with those in the normal saline group (P<0.05). However, no significant differences were obtained between the two groups at day 3 after LC (P>0.05; Table IV), thus indicating that DEX could effectively alleviate pain within the first two days after LC. Furthermore, when comparing preoperative QoR-15 scale score between the two groups, patients in the DEX group exhibited a significantly higher postoperative QoR-15 scale score compared with those in the normal saline group on days 1 and 2 after surgery (P<0.01). No significant differences were recorded between the two groups preoperatively and at day 3 after LC (P>0.05; Table V). The aforementioned findings affirmed that DEX could enhance the recovery of patients during the early postoperative period.

Table III. Comparison of the incidence of POCA and other postoperative side effects.

Postoperative side effects	DEX group (n=53)	Normal-saline group (n=44)	P-value
POCD	3 (5.6%)	8 (18.2%)	0.024
Postoperative nausea	2 (3.8%)	4 (9.1%)	0.617
Postoperative agitation	1 (1.9%)	7 (16.3%)	0.006
Postoperative hypotension	0 (-)	3 (7.0%)	0.322
Postoperative bradycardia	1 (5.7%)	3 (7.0%)	0.809
Postoperative drowsiness	3 (1.9%)	4 (9.1%)	0.423

Fisher exact tests were used to compare postoperative side effects between two groups. Data are presented as n (%). POCA, at least a 3-point decrease in their MoCA and MMSE score compared with the baseline. POCD, postoperative cognitive dysfunction; DEX, dexmedetomidine.

Table IV. Comparison of VAS scores at rest.

Postoperative period	DEX group	Normal-saline group	T-value	P-value
1 day	1.69±0.21	2.12±0.24	5.132	0.012
2 days	2.81±0.29	3.25±0.26	4.871	0.031
3 days	1.21±0.18	1.33±0.25	4.822	0.619

Data are presented as the mean ± standard deviation. DEX, dexmedetomidine.

Table V. Comparison of the scores of the QoR-15 scale.

Perioperative period	DEX group	Normal-saline group	T-value	P-value
1 day before surgery	140.7±4.1	143.1±3.6	1.91	0.195
1 day after surgery	123.7±4.3	109.7±4.3	5.923	0.001[a]
2 days after surgery	126.5±4.6	118.4±2.1	7.821	0.005[a]
3 days after surgery	134.6±5.1	135.1±2.9	8.821	0.727

Data are presented as the mean ± standard deviation; [a]P<0.05. QoR-15, Quality of Recovery-15; DEX, dexmedetomidine.

Discussion

Cholecystitis and gallstones are prevalent conditions in hepatobiliary surgery and LC stands as the preferred minimally invasive surgical approach for their treatment (13). The increase in the elderly population has risen the incidence of gallbladder inflammation among the elderly, thus supporting the enhanced attention that should be paid to postoperative complications associated with LC (14).

Among these complications, POCD is considered as the most common postoperative complication in elderly. Typically manifesting within the first postoperative weeks, the incidence of POCD ranges from ~10 to 54% (15). As a common complication of anesthesia, POCD can be associated with several factors, such as central nervous system inflammation and neurotransmitter abnormalities (16). It has been reported that several other factors can affect the onset of POCD, including age (>65 years), lower educational level, cognitive impairment, high-risk surgical procedures, postoperative complications, infections and pain (17). Perioperative stress response acts as an inducing factor for POCD and is associated with an increased risk of complications and prolonged hospital stays, thus adversely affecting patient recovery. Therefore, strategies to minimize the incidence of POCD are urgently needed for clinical practitioners. Currently, there is no widely accepted index for the diagnosis of POCD (18). Commonly, POCD is diagnosed based on MMSE and MoCA scores or several neuropsychological tests (NTBs), such as Wechsler intelligence scale and clinical dementia rating scale tests. MMSE and MoCA tests consist of 20 items and take between 5 and 10 min to complete. However, NTBs take ~2 h to complete by the patient (19,20). Long time evaluation is not suitable for hospitalized patients, especially in postoperative ones. Comparison of MoCA and MMSE scores with those of NTBs showed that these were aligned. The validity and feasibility of the MoCA and MMSE scores could further support their use in place of NTBs, since they could save time and relieve the burden of the patient (21). A well-constructed screening tool should be brief, easy to complete, with favorable psychometric properties, generalizable to older patients and preferably completed

by patients themselves or by non-healthcare professionals. Therefore, MoCA and MMSE tests could be more suitable for assessing the postoperative cognitive function of old patients. In the present study, consistent with previous studies, the MMSE and MoCA tests, which are common diagnostic methods, were employed to diagnose POCD (22,23).

DEX possess sedative, analgesic, anxiolytic and sympathetic nerve blockade effects. The ability of DEX to enhance nerve blockade and reduce the onset time of local anesthetics has led to its widespread clinical use in recent years (24-27). It has been also reported that DEX exhibits several immunological functions, including reducing cytokine secretion and white blood cell counts (28) and stabilizing C-reactive protein levels, thus contributing to myocardial protection (29). More specifically, DEX has the potential to safeguard cognitive function via inhibiting inflammatory responses and reducing stress, eventually preventing the occurrence of POCD (30-32). Conventionally, it has been considered that DEX can protect postoperative cognitive function (33,34). In the present study, the MMSE and MoCA tests were utilized to evaluate cognitive function. Therefore, the results revealed that the MMSE score was significantly higher in Group A at 6 h postoperatively ($P<0.05$). Furthermore, MoCA score was substantially higher at 6 h and day 1 postoperatively ($P<0.05$). The aforementioned results supported the protective effect of DEX on early postoperative cognitive function in patients undergoing LC.

A previous study demonstrated that varying doses of DEX displayed different effects on POCD (35). Low doses of DEX could not effectively reduce the incidence of POCD. Therefore, in the present study, an intravenous infusion of 0.8 μg/kg DEX was administrated within 10 min prior to induction, followed by a maintenance infusion of 0.5 μg/(kg/h). Consistent with the studies by Li *et al* (36) and Ran *et al* (37), the results of the present study indicated that a particular dose of DEX could effectively reduce the incidence of POCD in elderly patients.

Extensive clinical observations and animal experiments have established an association between postoperative pain and the onset of POCD. Therefore, adequate pain control, achieved through the appropriate use of DEX, could present a viable method for preventing POCD (38,39). In the present study, significantly lower VAS score was recorded in the DEX group on the first and second postoperative days compared with the normal-saline group ($P<0.05$), thus indicating that DEX could effectively alleviate postoperative pain in patients undergoing LC.

However, the underlying mechanism of POCD remains unknown. Previous studies suggested that the analgesic properties of DEX could be triggered by several mechanisms, including transversus intrathecal and abdominis plane block (40,41).

Postoperative recovery is a complex and multidimensional process, which is affected by several factors. Evaluating the QoR of the patients has gained increasing attention as a mean of assessing the overall quality of health after general anesthesia. Prior or on the day of surgery, patients were asked to complete the QoR-15 questionnaire, which served as a measure of baseline (relatively healthy) status. QoR-15 test can be a valuable outcome measure in perioperative clinical trials, before or after the operation and for assessing the effects of changes on healthcare delivery for quality assurance purposes. Consistent with the concept of fast-track recovery, it offers a benchmark for optimizing anesthesia strategies (42). This approach is practical, feasible and straightforward in assessing postoperative recovery (43). In the present study, the QoR-15 scale was employed to evaluate postoperative QoR in all patients. The results indicated that patients in the DEX group showed significantly higher QoR-15 scores compared with the normal saline group on the first and second day after LC, thus suggesting that DEX could enhance analgesic effects, prolong nerve block and improve patient recovery.

Anesthetics, including DEX, are a prerequisite for LC. The present study aimed to investigate whether DEX could prevent the adverse drug reactions in patients who underwent LC. Drug-related side effects, such as postoperative heart rhythm abnormalities, blood pressure changes, agitation and nausea, can occur after the use of anesthetics. A previous study by Zucker *et al* (44) suggested that women experienced adverse drug reactions, nearly twice as often as men. However, it was not clear whether the differences in the incidence of postoperative adverse events were due to the use of DEX or to sex differences. Therefore, to reduce the effect of the sex on the results of the present study, female patients were excluded.

However, the present study has certain limitations. Firstly, its reproducibility could be constrained, primarily due to the challenge of repeated postoperative cognition assessments, especially among less educated patients. Secondly, patient selection lacked categorization based on sex and age. Furthermore, in the present study, only the short-term cognitive function was evaluated, while the long-term cognitive function in elderly patients was neglected. Lastly, the exclusion of female patients could also be considered as a limitation of the present study.

The typical duration of cancer patient surgery in that area of the body lasts ~4-8 h. The dosage of DEX varies depending on the duration of the operation. Therefore, the cumulative dosage of DEX applied for patients with cancer in that area of the body ranges ~2-4 μg/kg (45). However, in the present study, the duration of LC (~1 h) in 53 patients with cholecystitis or gallstones and the dosage of DEX applied were almost the same. Therefore, the cumulative dosage of DEX in patients with cholecystitis or gallstones was ~0.5 μg/kg. Due to the longer and different duration of surgery in patients with cancer, the doses of anesthesia used in such patients vary, which make it more difficult to assess the effect of different doses of anesthesia and postoperative side effects in old patients. Analyzing the effect of different doses of anesthesia and postoperative adverse reactions require further investigation and is beyond the scope of the present study. Therefore, patients with cancer were excluded and the study only focused on the effect of DEX on postoperative adverse reactions in non-tumor patients.

In summary, further research is needed to enhance the applicability of these findings, particularly within the context of patients undergoing LC. To the best of the authors' knowledge, this was the first study on cognitive dysfunction in older patients undergoing LC. Two questionnaire systems were employed in the present study, which supported the effectiveness of DEX in preserving cognition function and managing pain, thus further contributing to the existing knowledge.

Overall, the results of the present study suggested that treatment of patients undergoing LC with DEX could effectively

diminish the incidence of POCD and relieve postoperative pain in the elderly, thus indicating that DEX exerted favorable analgesic effects and a safety profile, thus being considered as a valuable and promising candidate for clinical promotion and application.

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Availability of data and materials

The data generated in the present study are not publicly available due to patient privacy but may be requested from the corresponding author on reasonable request.

Authors' contributions

YLF and WXS contributed to the study conception and design and performed material preparation, data collection and analysis. YLF wrote the first draft of the manuscript. QTZ, ZLW and QW participated in data analysis and drew the figures in this manuscript. YLF and WXS confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of the 980 Hospital of the Joint Service Support Force of the People's Liberation Army of China (approval no. 2021-KY-86; Shijiazhuang, China) and informed consent was obtained from all patients or their families.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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