



## Effect of dexmedetomidine-induced anesthesia on the postoperative cognitive function of elder patients after laparoscopic ovarian cystectomy

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### ABSTRACT

**Objective:** To investigate the effect of dexmedetomidine at maintenance dose on the postoperative function of elder patients after general anesthesia for laparoscopic ovarian cystectomy.

**Methods:** We enrolled a total of 96 elder patients who were admitted to this hospital for laparoscopic ovarian cystectomy under general anesthesia between March 2015 and March 2017, and divided them into two groups, Group A (n = 48) and B (n = 48). Patients in both groups received the same methods for anesthesia induction and maintenance drugs. At the beginning of operation, patients in Group A received the intravenous injection of dexmedetomidine (0.8 µg/kg) followed by maintenance dose [0.5 µg/(kg h)] to the end of operation, while those in Group B underwent intravenous injection of 0.9% normal saline at the same rate, during which blood pressure, heart rate, oxyhemoglobin saturation and dosage of anesthetics at T1 (5 min after being delivered into the operation room), T2 (immediately after anesthesia induction), T3 (immediately after intubation), T4 (immediately after operation), T5 (immediately after end of operation) and T6 (immediately after extubation). Then, the levels of NSE, IL-6, CRP and HMGB1 were compared between two groups at 24 h before the operation, at the end, 24 h, 3 d and 7 d after operation. Besides, we also compared the postoperative cognitive functions and incidence of adverse reactions at 1 d before, 1, 2, 3 and 7 d after operation through MOCA scales.

**Results:** At T3, T4 and T6, comparisons of the average arterial pressure and heart rate showed that the differences between the two groups had statistical significance ( $p < .05$ ). At the end of operation, and at 24 h, 3 d and 7 d after operation, we found that the levels of IL-6 and CRP in patients of two groups were all significantly elevated when compared with those before operation; at the end of operation and at 24 h and 3 d after operation, the levels of IL-6 and CRP in the Group B were higher than those in the Group A, and the differences had statistical significance ( $p < .05$ ). At the end of operation and at 24 h and 3 d after operation, the levels of NSE and HMGB1 in two group were higher than those before operation, and a more significant elevation was identified in Group B with statistically significant differences ( $p < .05$ ); at 7 d after operation, a decreasing trend was found in the level of HMGB1, which, however, remained higher than the preoperative level, and the level in Group B was still higher than that in Group A with statistically significant differences ( $p < .05$ ). At 2 d after operation, we found that the scores of MOCA in the Group B were remarkably decreased in comparison with the scores in Group A with a statistically significant difference ( $p < .05$ ). Moreover, the incidence rate of postoperative cognitive dysfunction (POCD) in the Group A was significantly lower than that in the Group B, and the difference had statistical significance ( $p < .05$ ).

**Conclusion:** Dexmedetomidine can ameliorate the postoperative cognitive functions of elder patients who received the laparoscopic ovarian cystectomy under general anesthesia, and effectively decrease

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the incidence rate of POCD without any obvious or severe adverse reaction. Thus, it can serve as a kind of adjuvant drug for general anesthesia in clinical practice.

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## 1. Introduction

With an increase in patients requiring operation treatment, the possibility of poor prognosis is also augmenting accompanied with an increase in the number of types, in which POCD has been considered as a severe but the most common type (Chalikonda, 2009). Elder patients, due to the decline in organ functions caused by aging, may suffer from an increase in possibility of POCD induced by the degenerative or pathophysiological variations in tissues and cells. POCD refers to a kind of complications in central nervous system after surgical anesthesia, mainly characterized by the mental disorder, anxiety, personality changes and damaged memory functions in clinical practice, and has been considered as a kind of functional disorder in nervous system. Currently, the pathogenesis of POCD remains elusive in clinical research (Chen et al., 2015). It has been reported that inflammatory responses and abnormal oxygen metabolism in brain are closely associated with the pathophysiological processes of POCD. Meanwhile, anesthetic depth may also affect POCD (Ehrrar et al., 2012). Some studies reported that since there have not yet been effective drugs or treatment methods for POCD, which makes prophylaxis and protection of cognitive functions more important (Ehrrar et al., 2012; Iriola et al., 2011; Steinmetz et al., 2009). Dexmedetomidine is characterized by many effects, such as sedation, analgesia, antagonistic effect on sympathetic activity, and can inhibit the release of inflammatory cytokines, thereby protecting the brain nerves (Bekker and Weeks, 2003). In this study, we enrolled a total of 92 elder patients who underwent laparoscopic ovarian cystectomy under general anesthesia between March 2014 and March 2016 with administration of dexmedetomidine, observed the changes in biochemical indicators and cognitive functions of patients as well as the effect of dexmedetomidine at maintenance dose on postoperative cognitive functions. Detailed information of this study is reported as follows.

## 2. Materials and methods

### 2.1. General material

**Inclusion criteria:** patients aged above 60 years old; patients with the indications of laparoscopic ovarian cystectomy; patients without primary mental disorder or dementia; patients or their family who were informed of the content of study, and signed the written informed consent.

**Exclusion criteria:** patients complicated with the primary diseases in heart, lung, liver, kidney or urinary system; patients who were allergic to dexmedetomidine; patients who were alcoholism; patients who were deaf or mute; patients who voluntarily refused to participate in this study.

**Case selection and grouping:** We enrolled a total of 96 elder patients who were admitted to this hospital for laparoscopic ovarian cystectomy under general anesthesia between March 2015 and March 2017, and divided them into two groups according to their clinical features, Group A ( $n = 48$ ) and B ( $n = 48$ ). In Group A, patients' ages ranged from 65 to 85 years old, while those in Group B ranged from 63 to 85. We found that the differences in age, classification of American Society of Anesthesiologists (ASA), surgical duration and intraoperative bleeding amount showed no statistical significance between the two groups ( $p > .05$ ), suggesting that

these general materials were comparable between the two groups (Table 1).

### 2.2. Methods

Patients in both groups received the same methods for anesthesia induction and maintenance drugs. At the beginning of operation, patients in Group A received the intravenous injection of dexmedetomidine hydrochloride (Jiangsu Hengrui Medicine Co., Ltd.; SFDA approval No. H20090248; specification 2 mL: 200  $\mu\text{g}$ ) at a dosage of 0.8  $\mu\text{g}/\text{kg}$  followed by maintenance dose [0.5  $\mu\text{g}/(\text{kg h})$ ] to the end of operation, while for patients in Group B, they administrated 0.9% normal saline through the same pattern to the end of operation.

Before anesthetic induction, all patients underwent injection of crystalloid solution at a dosage of 5 mL/kg, and endotracheal intubation was chosen for general anesthesia in both groups. For patients in these two groups, they administrated the propofol through Diprifusor TCI system, in which TCI was initiated when the initial concentration of drug in plasma was 2.0  $\mu\text{g}/\text{mL}$  with intravenous injection of sufentanil at a dosage of 0.15  $\mu\text{g}/\text{kg}$ , and the dose of propofol was increased at 1  $\mu\text{g}/\text{mL}$  every 1 min. After bispectral index (BIS) was below 75, TCI system of sufentanil was started to maintain the concentration of drug in plasma at 4 ng/mL followed by intravenous injection of rocuronium bromide at a dosage of 0.8 mg/kg and endotracheal intubation for ventilation. Through adjustment of propofol injection, BIS was maintained between 45 and 55. In Group A, dexmedetomidine was pumped at a rate of 0.5  $\mu\text{g}/(\text{kg h})$ , while in Group B, normal saline in same volume was given. As for the mechanical ventilation during operation, the tidal volume was maintained at 6–8 mL/kg, ventilation rate at 12–14 times/min, and the partial pressure of carbon dioxide in endexpiratory gas (PetCO<sub>2</sub>) at 35–40 mmHg. During the operation, we recorded the blood pressure (BP), heart rate (HR), saturation of pulse oximetry (SpO<sub>2</sub>) and body temperature. At 40 min before the end of operation, pump of dexmedetomidine was withdrawn, and during the drug administration, ephedrine or atropine should be immediately given once the BP was lower than 30% of the baseline or HR was lower than 50 times/min.

### 2.3. Observation indexes

**A. Vital signs:** Blood pressure, heart rate, oxyhemoglobin saturation and dosage of anesthetics at T1 (5 min after being delivered into the operation room), T2 (immediately after anesthesia induction), T3 (immediately after intubation), T4 (immediately after operation), T5 (immediately after end of operation) and T6 (immediately after extubation).

**B. Monitoring the biochemical indexes in blood:** The levels of NSE, IL-6, CRP and HMGB1 were compared between two groups at 24 h before the operation, at the end, 24 h, 3 d and 7 d after operation.

**C. Besides,** we also compared the postoperative cognitive functions and incidence of adverse reactions at 1 d before, 1, 2, 3 and 7 d after operation through MoCA scales, including learning ability, orientation, language, calculation, attention, memory and spatial structure. The total score of MoCA scale was set as 30 points, and higher scores represented better cognitive functions. Patients with

**Table 1**  
Comparison of the general materials between the two groups (n = 48).

Group	Age ( $\bar{x} \pm s$ , years)	ASA classification (I/II, n)	Surgical duration ( $\bar{x} \pm s$ , min)	Intraoperative bleeding amount ( $\bar{x} \pm s$ , mL)	Dose of anesthetics ( $\bar{x} \pm s$ , mg)
Group A	71.89 $\pm$ 31.36	30/18	182.76 $\pm$ 27.24	252.26 $\pm$ 54.27	1493.73 $\pm$ 265.37
Group B	72.06 $\pm$ 32.17	29/19	183.46 $\pm$ 27.26	250.63 $\pm$ 54.48	1498.17 $\pm$ 267.53
t/ $\chi^2$	0.011	0.176	0.162	0.143	0.137
p	0.993	0.679	0.872	0.884	0.891

scores less than 26 points or 2 points lower than the preoperative baseline score would be considered as POCD.

#### 2.4. Statistical methods

In this study, data were processed with SPSS 18.0. Measurement data were presented as ( $\bar{x} \pm s$ ), and *t* test was performed for comparison; ANOVA was applied for comparison of repeated measurement data, and Dunnett-*t* test was carried out for pairwise comparison. Enumeration data were presented as percentage or ratio, and comparison was carried out with chi-square test. *p* < .05 suggested that the difference had statistical significance.

### 3. Results

#### 3.1. Comparison of the hemodynamics at different time points between the two groups

Before operation, comparisons of the average arterial pressure and HR between the two groups showed no statistically significant difference (*p* > .05). At T3, T4 and T6, comparisons of the average arterial pressure and heart rate showed that the differences between the two groups had statistical significance (*p* < .05; Table 2).

#### 3.2. IL-6 and CRP

At the end of operation, and at 24 h, 3 d and 7 d after operation, we found that the levels of IL-6 and CRP in patients of two groups

were all significantly elevated when compared with those before operation; at the end of operation and at 24 h and 3 d after operation, the levels of IL-6 and CRP in the Group B were higher than those in the Group A, and the differences had statistical significance (*p* < .05). At 7 d after operation, we found that the levels of IL-6 and CRP in both groups began to decrease, which, however, remained higher than those before operation, and intergroup comparisons showed that there were no statistically significant differences (*p* > .05; Table 3).

#### 3.3. NSE and HMGB1

At the end of operation and at 24 h and 3 d after operation, the levels of NSE and HMGB1 in two group were higher than those before operation, and a more significant elevation was identified in Group B with statistically significant differences (*p* < .05); at 7 d after operation, a decreasing trend was found in the level of HMGB1, which, however, remained higher than the preoperative level, and the level in Group B was still higher than that in Group A with statistically significant differences (*p* < .05; Table 4).

#### 3.4. Comparison of the cognitive functions between the two groups

One day before operation, we assessed the cognitive functions of the patients in two groups through MoCA scale, and found that they were free from the cognitive dysfunction before operation and the differences had no statistical significance (*p* > .05). Compared with the preoperative cognitive functions, at 2 d after operation, we found that the scores of MOCA were significantly decreased

**Table 2**  
Comparison of the hemodynamics between the two groups ( $\bar{x} \pm s$ ).

Item	Group	T1	T2	T3	T4	T5	T6
MAP (mmHg)	Group A	86 $\pm$ 11	79 $\pm$ 13	90 $\pm$ 11	82 $\pm$ 14	85 $\pm$ 10	90 $\pm$ 9
	Group B	87 $\pm$ 11	81 $\pm$ 14	98 $\pm$ 11	87 $\pm$ 14	86 $\pm$ 12	96 $\pm$ 12
HR (time/min)	Group A	71 $\pm$ 10	54 $\pm$ 6	77 $\pm$ 4	69 $\pm$ 6	72 $\pm$ 10	78 $\pm$ 11
	Group B	71 $\pm$ 11	68 $\pm$ 10	90 $\pm$ 11	77 $\pm$ 8	74 $\pm$ 14	88 $\pm$ 14

**Table 3**  
Comparison of the levels of IL-6 and CRP at different time points between two groups ( $\bar{x} \pm s$ , n = 48).

Group	IL-6 (pg/mL)				
	24 h before operation	At the end of operation	24 h after operation	3 d after operation	7 d after operation
Group A	61.52 $\pm$ 7.17	82.47 $\pm$ 13.48 <sup>a</sup>	117.47 $\pm$ 17.72 <sup>a</sup>	215.23 $\pm$ 35.87 <sup>a</sup>	113.46 $\pm$ 19.62 <sup>a</sup>
Group B	61.63 $\pm$ 7.17	99.27 $\pm$ 17.73 <sup>ab</sup>	137.81 $\pm$ 20.39 <sup>ab</sup>	235.57 $\pm$ 39.67 <sup>ab</sup>	114.28 $\pm$ 19.47 <sup>ab</sup>
<i>t</i>	0.037	4.941	4.902	2.547	0.217
<i>p</i>	0.981	<0.01	<0.01	0.013	0.827
Group	CRP (mg/L)				
	24 h before operation	At the end of operation	24 h after operation	3 d after operation	7 d after operation
Group A	6.56 $\pm$ 3.07	9.73 $\pm$ 5.61 <sup>a</sup>	12.78 $\pm$ 5.84 <sup>a</sup>	15.97 $\pm$ 6.13 <sup>a</sup>	8.07 $\pm$ 3.16 <sup>a</sup>
Group B	6.42 $\pm$ 3.14	12.86 $\pm$ 5.93 <sup>ab</sup>	17.63 $\pm$ 7.69 <sup>ab</sup>	21.74 $\pm$ 9.06 <sup>ab</sup>	8.27 $\pm$ 3.28 <sup>ab</sup>
<i>t</i>	0.182	2.693	3.057	3.307	0.208
<i>p</i>	0.847	0.008	0.003	0.001	0.829

**Table 4**  
Comparison of the levels of NSE and HMGB1 at different time points between two groups ( $\bar{x} \pm s$ ,  $n = 48$ ).

Group	NSE ( $\mu\text{g/L}$ )				
	24 h before operation	At the end of operation	24 h after operation	3 d after operation	7 d after operation
Group A	8.93 $\pm$ 2.57	12.97 $\pm$ 2.86 <sup>a</sup>	17.43 $\pm$ 3.06 <sup>a</sup>	21.96 $\pm$ 4.39 <sup>a</sup>	9.43 $\pm$ 2.28 <sup>a</sup>
Group B	9.06 $\pm$ 2.54	15.86 $\pm$ 3.29 <sup>ab</sup>	21.89 $\pm$ 4.37 <sup>ab</sup>	25.93 $\pm$ 4.86 <sup>ab</sup>	9.84 $\pm$ 2.93 <sup>ab</sup>
<i>t</i>	0.147	4.706	5.418	4.017	0.517
<i>p</i>	0.871	<0.01	<0.01	<0.01	0.59
Group	HMGB1 ( $\mu\text{g/mL}$ )				
	24 h before operation	At the end of operation	24 h after operation	3 d after operation	7 d after operation
Group A	26.17 $\pm$ 11.46	26.94 $\pm$ 11.37 <sup>a</sup>	28.43 $\pm$ 11.53 <sup>a</sup>	35.52 $\pm$ 13.71 <sup>a</sup>	33.76 $\pm$ 13.67 <sup>a</sup>
Group B	25.54 $\pm$ 11.48	31.73 $\pm$ 12.84 <sup>ab</sup>	34.26 $\pm$ 13.49 <sup>ab</sup>	42.17 $\pm$ 15.06 <sup>ab</sup>	40.26 $\pm$ 13.98 <sup>ab</sup>
<i>t</i>	0.192	2.017	2.217	2.263	2.103
<i>p</i>	0.843	0.041	0.027	0.022	0.037

**Table 5**  
Comparison of the MoCA scores between the two groups ( $\bar{x} \pm s$ ).

Group	Before operation	1 d after operation	2 d after operation	3 d after operation	7 d after operation
Group A	28.1 $\pm$ 0.7	27.7 $\pm$ 0.9	27.0 $\pm$ 1.0	27.8 $\pm$ 1.2	28.3 $\pm$ 0.8
Group B	28.0 $\pm$ 0.9	26.5 $\pm$ 0.8	26.4 $\pm$ 0.9	26.8 $\pm$ 0.9	28.2 $\pm$ 0.9

**Table 6**  
Comparison of the incidence and incidence rates of POCD between the two groups.

Group	POCD (n)				No POCD (n)	Incidence rate (%)
	At 1 d after operation	At 2 d after operation	At 3 d after operation	At 7 d after operation		
Group A	0	2	1	0	45	6.3
Group B	2	6	2	0	35	20.9

and the difference had statistical significance ( $p < .05$ ); at 1, 2 and 3 d after operation, the MoCA score in the Group B were remarkably decreased in comparison with the scores in Group A with a statistically significant difference ( $p < .05$ ). As for the intergroup comparison, we found that at 2 d after operation, the MoCA score in the Group B was significantly lower than that in the Group A, and the difference had statistical significance ( $p < .05$ ; Table 5).

One week after operation, we found that there were 3 patients (6.3%) with POCD in the Group A, while in Group B, there were 10 patients (20.9%) with POCD, and the difference had statistical significance ( $p < .05$ ; Table 6).

### 3.5. Postoperative adverse reactions

In these two groups, there were no severe or significant adverse reactions after operation, and the difference between groups showed no statistical significance ( $p > .05$ ).

## 4. Discussion

POCD refers to a kind of disease caused by various factors, such as patient, anesthesia, surgery and postoperative factors, and might involve with the formation of  $\beta$ -amyloid protein, imbalance between neurotransmitter and receptor, damage to the blood-brain barrier and free radical injury; POCD is frequently seen within 1 week after operation under general anesthesia, mostly the 1–3 d after operation and elder patients aged above 65 years old (Bekker and Weeks, 2003). With an increase in age, degeneration in organ functions, degenerative alterations in tissue and cells and the pathophysiological changes make elder patients more susceptible to the onset of POCD (Farag et al., 2006). It has been reported that general anesthesia combined epidural anesthesia can better reduce the occurrence of POCD in comparison with

the simple general anesthesia (An et al., 2011). Meanwhile, it is also reported that during the intraoperative inflammatory responses, the activation of non-specific activators can enhance the postoperative immune responses, thereby resulting in the abnormality in behavior and dysfunction in cognition (Wang et al., 2007).

Dexmedetomidine is a kind of agonist of  $\alpha_2$ -adrenergic receptors with high specificity, and can inhibit the presynaptic release of noradrenaline through mobilizing the  $\alpha_2$  receptor, thereby exerting its effect. It is characterized by various effects, such as sedation, analgesia, anti-anxiety, inhibition of the sympathetic activity, stabilizing the hemodynamics, reducing the dosage of anesthetics and slight inhibitory effect on breath. Once the drugs are delivered to the  $\alpha_2A$  receptors in brain, it will lead to non-rapid-eye movement sleep naturally, but patients can be awakened. Thus, in clinical practice, it has the physiological functions of sedation, hypnosis and lowering the temperature, which are considered as the advantages of dexmedetomidine in altering the cognitive functions after operation.

In this study, we found that the average arterial pressure and heart rate in Group A at T3, T4 and T6 were significantly lower than those in the Group B, but the hemodynamics at the time of intubation or extubation remained more stable, and the differences had statistical significance (Table 2), suggesting that dexmedetomidine can reduce the cardiovascular stress responses caused by intubation or extubation, which can better sustain the stability of hemodynamics of patients (Terrando, 2010).

IL-6, as a kind of pro-inflammatory factor, can serve as an indicator for early diagnosis of tissue injury (Tracey, 2009), and its level can reflect the damage to tissues; stress response to the surgical trauma can lead to the excessive expression of IL-6 (Ramlawi et al., 2006). NSE is a kind of specific acid proteinase secreted by the neurons or neuroendocrine cells, and can be released into the blood once the neurons are stimulated by the ischemia or hypoxia.



HMGB1, as a kind of inflammatory factor in late stage, can promote the activation and aggregation of inflammatory cells, like macrophages, thus causing cascade inflammatory responses, and facilitating the release of IL-6. Besides, the release of HMGB1 can also exacerbate the damage to blood-brain barrier to facilitate the peripheral inflammatory factors to enter the central nervous system, and further aggravate the inflammatory responses (Jiang et al., 2014). CRP can reflect the degree of inflammatory responses (Zhang et al., 2015), and higher levels of CRP represent that the inflammatory response is more severe. In this study, we found that the levels of IL-6, NSE, HMGB1 and CRP were obviously increased, suggesting that there were inflammatory responses in different degrees. It has been reported that dexmedetomidine can significantly decrease the level of plasma inflammatory factor, reduce the incidence of stress response and activation of pro-inflammatory factors, and decrease the immune responses, which shows a certain protective effect on brain nerves, and can effectively decrease the incidence rate of POCD (Balóbangá et al., 2015). In spite of its pathogenesis remaining unclear yet, it is reported that inhibiting the production of inflammatory factors might be associated with the synapse and  $\alpha 2$  adrenergic receptor. Dexmedetomidine can act on the  $\alpha 2$  adrenergic receptor to deliver it to the presynaptic site, thereby promoting the production of lipopolysaccharide to induce the apoptosis of lymphocytes, monocytes and macrophages, and decreasing the production of inflammatory factors and responses (Chen et al., 2015).

The results of this study showed that in Group A, the levels of IL-6 and CRP at 24 h, 3 d and 7 d after operation were significantly lower than those in the Group B, and at 24 h and 3 d after operation, MoCA score of patients in the Group A was significantly higher than that in the Group B, and their incidence rate of POCD was remarkably lower than Group B; after operation, they were free from the significant or severe adverse reactions, which were consistent to the results of previous studies (Taniguchi et al., 2004). Thus, dexmedetomidine can decrease the expression of inflammatory factors, and shows inhibitory effect on the inflammatory responses after the laparoscopic ovarian cystectomy under general anesthesia, which might be correlated with the protective effect of dexmedetomidine on the postoperative cognitive function of patients.

The ISPOCD, consisting of 13 medical centers in 8 nations, had collected the data of 1218 patients who were aged above 60 years old and received the non-cardiac surgery at different time between December 1994 and May 1996, and they found that about 25.8% of patients would suffer from POCD within one week after operation (Tasdogan et al., 2009). In this study, the ratios of POCD occurring within one week after operation were 6.3% and 20.9% in Group A and B, respectively, while after operation, POCD mainly occurred at the first 3 days after operation, and would recover at 7 d after operation. In the study of ISPOCD, age, anesthetic duration, poor education, second operation, postoperative infection and respiratory complications are considered as the risk factors of POCD in early stage after operation (Gerlaeh et al., 2009). In this study, we adopted the random grouping method, and found that there were no statistically significant differences in comparison of the age, surgical duration and education, while those with diseases in other systems or severe intraoperative complications were excluded from this study.

It has been shown that postoperative pains can also affect the cognitive function after operation, and thus, alleviating the postop-

erative pains can significantly ameliorate the postoperative cognitive functions (Li et al., 2015). In this study, we performed assessment with VAS, and found that patients scored less than 4 points, which had maximally reduced the effect of postoperative pains on POCD. Studies also confirmed that inhalation anesthesia can also affect the cognitive functions in an early stage after operation, so we selected the general anesthesia.

In conclusion, dexmedetomidine can ameliorate the postoperative cognitive functions of elder patients who received the laparoscopic ovarian cystectomy under general anesthesia, and effectively decrease the incidence rate of POCD without any obvious or severe adverse reaction. Thus, it can serve as a kind of adjuvant drug for general anesthesia in clinical practice.

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