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Original Article

Effects of dexmedetomidine on anesthesia recovery period and postoperative cognitive function of patients after robot-assisted laparoscopic radical cystectomy

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Abstract: Objective: The purpose of the study was to evaluate the neuroprotective effect of dexmedetomidine on anesthesia recovery period and postoperative cognitive function of patients after robot-assisted laparoscopic radical cystectomy and ileal conduit diversion. Methods: A total of 40 elective patients who would undergo robot-assisted laparoscopic radical cystectomy and ileal conduit diversion. They were randomly divided into two groups in a double-blind manner. After pneumoperitoneum established, all patients adopted 40° trendelenberg position. Mean arterial pressure (MAP), heart rate (HR), and bispectral index (BIS) of each patient were recorded at four moments respectively, namely the end of surgery (T_0), palinesthesia (T_1), extubation (T_2), 10 min after extubation (T_3). Results: In the dexmedetomidine group, the mean arterial pressure and heart rate decreased at T_1 and T_2 compared with controls ($P<0.05$); in addition, the delirium rating scale was lower than the latter ($P<0.05$) while Ramsay sedation score was significantly higher ($P<0.05$). POCD was observed on 28 patients, containing 17 controls and 11 dexmedetomidine individuals, one day after operation, and 21 patients (12 controls, 9 dexmedetomidine people) five days after operation. One- and five-day after operation, the levels of TNF-α, NSE and IL-6 in the dexmedetomidine group were significantly lower than those in the control group ($P<0.05$), and serum SOD significantly increased in the former ($P<0.05$). Conclusion: Dexmedetomidine had a neuroprotective effect on anesthesia recovery and postoperative period of the elderly patients undergone robot-assisted laparoscopic radical cystectomy, which might be related to the reduction of inflammatory reaction induced by dexmedetomidine.

Keywords: Dexmedetomidine, robot, trendelenberg position, postoperative cognitive dysfunction, neuroprotection

Introduction

Robotic laparoscopic radical surgery for bladder cancer is a new developed minimally invasive surgery. Previous researches [1-3] for this surgery have shown that long time peneumoperitoneum and excessive head-down tilt increase the permeability of blood cerebrospinal fluid barrier. And then with cerebral vascular expansion, cerebral blood flow increase and CO_2 retention, H^+ gets into brain cells, which results in intracellular acidosis and tends to induce internal environment disturbance. Compared with the common aparoscopic surgery, it is possessed with long awakening time after operation and patients tend to appear psychomotor agitation in anesthesia recovery, which are caused by such factors as stress reaction, trauma, anesthesia, bleeding and transfusion during operation, reduced cerebral blood flow and hypotension. Patients operated with robotic laparoscopic radical surgery adopt the position of Trendelenberg that can better expose the plevic organs. However, the large dip head-down tilt with long time increases cerebral blood flow and the possibility of encephaledema as well as causes obstacles of the oxygen metabolism in brain tissues. Besides, with operation time lengthened, the influences will expand [3, 4].

In recent years, it has been a research hotspot to prevent post operative cognitive dysfunction by using some drugs. Dexmedetomidine (DEX)

which plays a role in the protection of brain and nerve, is a new-style α_2 adrenergic agonists with high selectivity and is the dextroisomer of medetomidine. The proportion of the combination for DEX with α_2 and α_1 adrenergic receptors is 1620:1. This study aimed to detect the influence of DEX applied in the robotic laparoscopic radical surgery on the anesthesia recovery period and post operative cognitive function for the elderly, as well as investigate its neuroprotective effect and mechanism.

Materials and methods

Ethical review

This study was approved and supervised by the Ethics Committee of Chinese PLA general hospital. All the participants gave consent forms.

Subjects and grouping

40 patients (aged from 45-80 years) performed with robotic laparoscopic radical surgery were selected in this study. According to the classification criterion of American Society Anesthesiologists (ASA), these patients were divided into I-III level. The body mass index of the patients ranged from 18 kg/m^2 to 25 kg/m^2. Patients with diseases, such as serious disease of cardiovascular system, chronic obstructive pulmonary disease, diseases of severe hepatic and renal dysfunction, endocrine and metabolic disease, central nervous system disease and acute upper respiratory infection were excluded. The patients with following conditions were not taken into this study: taking drugs (sedative, antidepressant, and anxiolytic), drug dependence, excessive drinking, severe visual and hearing disorders and so on. By methods of random number table, double blind and placebo control, 40 patients (34 males and 6 females) were divided into two groups-control group and DEX group. There were 20 patients in each group, including 3 females. In control group, normal saline (NS) was put in a 50 mL injector. In DEX group, 2mg DEX (Jiangsu Hengrui Medicine Co., Ltd.) was diluted with NS to blend 50 mL solution. Before the end of this study, all the patients and experimenters didn't know what would be done on the patients.

Medication

In case group, DEX was intravenously infused to the patients who were conducted by sequence intubation with the speed of 0.8 μg/(kg.h) for 10 minutes, and then followed by a constant speed of 0.3 μg/(kg.h) until 30 minutes before the end of operation. The controls were given the same dose of NS. With the same anesthesia method, all patients took no drugs before operation and were tested with invasive blood pressure, electrocardiogram and pulse oxygen saturation after being pushed into the operating room. The patients were initially performed with drugs for induction of anesthesia. The drugs injected to vein in sequence were as follows, 1-2 mg/kg diprivan (Swedish Astrazeneca), 0.3 μg/kg fentanyl (Yichang People Happiness Co,. Ltd.), 0.2 mg/kg atracurium besylate (British GlaxoSmithKline Co,.). After tracheal intubation, the patients were conducted with mechanical ventilation by connecting to Datex-Ohmeda Aestiava/5 anesthetic machine (GE Co,. America). The anesthetic machine was set as follows: initial respiratory rate of 12 times/min, inspiration:expiration=1:2, tidal volume of 8 mL/kg and oxygen concentration of 70%, to detect the partial pressure of carbon dioxide in endexpiratory gas. Sevoflurane (Abbott Laboratories) of 0.6 minimum alveolar concentration (MAC) was continuously inhaled for maintenance of anesthesia. Vein was injected with diprivan and remifentanil (Yichang People Happiness Pharmaceutical Co,. Ltd.) to keep the bispectral index (BIS) as 40-60. During operation, fentanyl and atracurium besylate were injected into vein as required. 0.1 mg fentanyl and 4 mg ondansetron were processed with intravenous injection 30 minutes before the end of operation. The patients were performed by Trendelenberg position with 40° incline after the establishment of pneumoperitoneum. Legs were spread outward and were put up, presenting lithotomy position. Robot system was put between the legs with support arms on the abdomen of patients. After skin incision on belly, CO_2 was inserted with a gas flow rate of 14 L/min by versus needle. In order to obtain better visual fields during the operation, pneumoperitoneum pressure ranged from 15 mmHg to 20 mmHg. Trocar and endoscope imaging system were put into lateral abdominal wall to finish the excision of bladder prostate and seminal vesicle (excision of womb and the accessories for female patients) with the help of robot. After cleanness for the positions (para-aortic lymph nodes, inferior vena caval lymph nodes, sacral lymph nodes, external iliac lymph nodes, internal iliac lymph

nodes, obturator lymph nodes and bladder surrounding lymph nodes) finished, pneumoperitoneum was stopped and the patients were adjusted to horizontal position to finish the surgery of ileal neobladder. DEX or NS was stopped injecting to all patients 30 minutes before the end of operation. Anesthetics and intravenous mediation stopped after abdominal closure and skin closure, respectively. The pneumoperitoneum time during operation was 160±38 minutes (minimum duration: 120 min; maximum duration: 210 min). During operation, the blood pressure of patients was maintained at 105-130/60-90 mmHg (1 mmHg=0.133 kPa). If blood pressure was under 100/60 mmHg, 5 mg ephedrine (Shenyang No.1 Pharmaceutical Co,. Ltd.) should be injected into patients immediately to avoid the adverse effect caused by hypotension on hemodynamics. The hypotension time of all the patients was less than 5 minutes.

Observation and recordance indexes

The mean values of artery pressure (MAP), heart rate (HR), and BIS of the patients at four time points (T_0: the moment when the surgery was ended; T_1: the moment when the patients woke up from surgery; T_2: the moment of extubation; T_3: 5 minutes after extubation) were recorded. (2) The Ramsay sedation scale was as follows: 1 point: dysphoric; 2 point: calm; 3 point: sleepy and inarticulate, but rapid response to instructions; 4 point: asleep, but able to be awakened; 5 point: sluggish response to calls; 6 point: deep asleep or anesthetic, and no response to calls. The postoperative comfort scale was detailed as follows: 0 point: continuous pain; 1 point: painlessness in a calm state, but severe pain when taking deep breaths or coughing; 2 point: painlessness in a lying and calm state, but slight pain when taking deep breaths or coughing; 3 point: painlessness when taking deep breaths; 4 point: painlessness when turning over or coughing. Postoperative delirium rating scale (DRS) was performed on patients, and whether the patients had any of such adverse reactions as nausea, vomiting and laryngeal edema before leaving the post anesthesia care unit (PACU) was observed. Visual analogue scale (VAS) was illustrated as follows: 0: painlessness; and 10: serious pain. All patients were sent to the PACU after the surgery for observation. The patients were called their names every 5 minutes, and the Ramsay scores were recorded. 30 minutes after the endotracheal tube was pulled out, comfort scale was recorded until the patients became totally conscious and could clearly speak out identities and telephone numbers thereof. (3) Preoperative cognitive function test and postoperative cognitive dysfunction (POCD) test were respectively performed. Neuropsychological test of all patients was conducted on the last day before surgery, the first day after surgery, and the fifth day after surgery, respectively. Standard deviations of values on various test items before the surgery were calculated. Then the differences on test data between before and after surgery were compared. When at least one standard deviation of a certain test item was reduced compared to before surgery, then the test item showed postoperative dysfunction. When postoperative dysfunction happened on two or more test items of a patient, then the patient suffered POCD. The following 6 examinations for neuropsychological test were adopted for evaluating various cognitive domains such as memory, attention and mental speed: ① mini mental state examination (MMSE); ② digit span test (DSPT); ③ digit symbol test (DSYT); ④ trail making test (TMT); ⑤ words recall test (WRT); and ⑥ verbal fluency test (VFT). For DSPT, 19 items of time and place orientation, language, memory, attention, reading comprehension, and drawing were tested and the highest score was 30. For DSPT test, an array of numbers were read to the patients, and the patients were required to retell the numbers in a positive sequence and an inverted sequence respectively, and scores would be given according to the accuracy in retelling. As respect to DSYT, an array of numbers and symbols in one-to-one correspondence were provided, then the patients were asked to match the numbers with the symbols within 90 seconds, and scores were recorded according to the answer accuracy. About TMT, the patients were requested to connect a series of numbers with lines in a certain order, and the time used would be recorded so that the speed and memory of the patients could be tested. In WRT test, the patients were provided with a group of words. After reading the words for a period of time, the patients were asked to recall the words and scores were given according to the accuracy. In VFT test, to determine language competence,

Table 1. MAP, HR, BIS of in 2 groups of all time points (n=20)

Time point	MAP/(mmHg)	HR/(bpm)	BIS
Group C			
T_0	95±11	65±12	55±5
T_1	119±15★	80±11★	86±6
T_2	121±19★	92±15★	89±5
T_3	118±15★	78±10★	88±6
Group D			
T_0	97±10	71±11	55±5
T_1	105±17※	69±10※	85±6
T_2	100±19※	73±14※	89±6
T_3	98±15※	67±13※	89±7

※P<0.05 vs. control; ★P<0.05 vs. T_0.

Table 2. Comparison of Ramsay sedation score, delirium rating, comfort score and VAS score in 2 groups (n=20)

	Group C	Group D
Ramsay sedation score	1.3±0.2	2.0±0.3※
Delirium rating	17.4±5.2	13.2±2.7※
Comfort score	2.3±0.4	2.2 ±0.2
VAS score	3.3±0.2	3.4±0.4

※P<0.05 vs. control.

the patients were required to speak out as many vegetable names as possible within 1 minute. (4) The serological test was conducted. Blood samples were collected from each patient on the last day before surgery, the first day after surgery, and the fifth day after surgery respectively to examine the content of neuron specific enolase (NSE), tumor necrosis factor alpha (TNF-α), superoxide dismutase (SOD) and interleuki-6 (IL-6) in serum. (5) Intraoperative conditions: the intraoperative blood-gas analysis results and end-tidal $PaCO_2$ results were observed and recorded.

Statistical processing

All the data were expressed by $\bar{x}$±s. The statistical processing was performed by SPSS 13.0. Comparisons between groups were conducted with t-test, and χ^2 test was adopted to compare the enumeration data. *P*<0.05 was considered as the statistically significant level.

Results

At T_1 and T_2 moments, the patients in DEX group had significantly lower MAP and HR than the patients in the control group (*P*<0.05). For the patients in the control group, the MAP and HR thereof at T_1 and T_2 moments were higher than those at T_0 moment (*P*<0.05) (**Table 1**). Compared with controls, patients in the DEX group showed lower DRS (*P*<0.05) and higher Ramsay scores (*P*<0.05) (**Table 2**). Differences in the content of NSE, SOD, IL-6, and TNF-α between two groups were not statistically significant (*P*>0.05). On the first and fifth day after surgery, serum contents of NSE, IL-6, and TNF-α in the DEX group were obviously lower than those of control group (*P*<0.05), while the DEX group had apparently higher serum content of SOD than the control group (*P*<0.05) (**Table 3**). On the first day after surgery, 7 patients suffered POCD in the control group and 3 patients in DEX group. On the fifth day after surgery, 4 patients suffered POCD in controls and 1 patient in the DEX group (*P*<0.05). Differences in propofol consumption between the two groups showed statistical significance (*P*<0.05). However, there was no remarkable differences in the consumption of opioid drugs between two groups (*P*>0.05). Monitoring indexes at different time points of the two groups were also compared. For patients in both groups, the $PaCO_2$ level after pneumoperitoneum and Trendelenberg posture were higher than its basic 60 minutes after level 15 minutes after tracheal intubation. No statistical significance was observed in the differences of $PaCO_2$ level at different time points (*P*>0.05, **Table 4**).

Discussion

Researches have shown that α_2 adrenergic receptor is a transmembrane G protein-coupled receptor widely distributed in central nervous system, peripheral nervous system and autonomic ganglia, and the density thereof is the highest in pontine nucleus, parahippocampal gyrus and locus coeruleus [5]. The main function of DEX is to activate α_2 adrenergic receptors with high selectivity so that α_2 adrenergic receptors can act on the locus coeruleus of the central nervous system, the spinal cord of the peripheral nervous system and central and peripheral neurotransmitters to achieve sedative and hypnotic effects, analgesic effect, and the effect of antagonism on sympathetic activity respectively. The cerebral protection effect of DEX was firstly discovered by Hoffman et al. [6]. Based on the rat model of incomplete cerebral ischemia, they found that DEX pretreat-

Table 3. Concentration of NSE, SOD, IL-6 and TNF-α in 2 groups of all time points (n=20)

Time point	NSE (ng/ml)	SOD (U/ml)	IL-6 (pg/mL)	TNF-α (pg/mL)
C group (n=50)				
Before operation	11.1±1.4	126.2±6.2	<1.5	10.6±1.7
1 day after operation	19.6±3.5	92±11.1	32.3±8.9	19.8±2.7
5 day after operation	15.0±4.2	100.4±9.2	7.8±4.9	12.7±2.2
D group (n=50)				
Before operation	12.0±1.5	123.3±7.8	<1.5	11.5±1.9
1 day after operation	13.6±2.5※	107.4±9.6※	17±7.3※	12.9±1.1※
5 day after operation	12.0±1.2※	120.0±6.9※	4.8±1.3※	5.6±1.8※

※P<0.05 vs. control.

Table 4. Intraoperative detection index between two groups (n=20)

Time point	$PetCO_2$	PaO_2 (mmHg)	$PaCO_2$ (mmHg)	PH (mmHg)
Group C				
15 min after intubation	30±2	440±72	37±4	7.39±0.40
Pneumoperitoneumn	38±6★	443±63	42±13	7.28±0.83★
60 min after trendelenberg	45±7★	400±45	60±11★	7.20±0.74★
Stop pneumoperitoneumn	33±3	387±75	41.±5	7.31±0.52
Group D				
15 min after intubation	31±2	430±74	37±4	7.35±0.40
Pneumoperitoneumn	39±6★	435±63	44±12★	7.27±0.81
60 min after trendelenberg	46±7★	409±49	58±10★	7.19±0.44★
Stop pneumoperitoneumn	34±5	390±69	43.±5	7.31±0.61

★*P*<0.05 vs. 15 min after intubation.

ment could greatly reduce the catecholamine level in serum and improve the neurological and histopathological results, and there existed a dose-dependent relationship. In the case of cerebral ischemia reperfusion, DEX can reduce levels of NO and TNF-α, and increase the SOD activity so that nerve injuries can be avoided. Furthermore, DEX can mitigate vasospasm through inhibiting releasing of catecholamine in cerebral tissues, which can prevent the brain injuries caused by subarachnoid hemorrhage [7-9]. Also, DEX can avoid damages to hippocampus, thalamus, and cortex caused by the inhaling of isoflurane dose independently as well as the long-term impact of isoflurane on neurocognitive functions [10]. Additionally, DEX can confer protection to traumatic brain injuries, the mechanism of which may be associated with the function of relieving inflammatory reactions [11].

In the present study, compared to the control group, the haemodynamics index was more stable in recovery period and the volume of vasoactive drugs was significantly lower in DEX group, suggesting DEX have the function of reducing stress response during tracheal extubation. Moderately sedative and analgesic effects of DEX could effectively ease the pain of patients caused by extubation in awakening period and the cardiovascular reactions caused by stress response in tracheal extubation period. The discomfort in tracheal extubation period could be released by using adequate doses of DEX without delaying the extubation time. DEX had dual roles of sedation and analgesia that could restrain the sympathetic excitability of nervus centralis, reduce the release of epinephrine and norepinephrine, and lessen the sympathetic reaction caused by extubation. The best effect of DEX was to produce a sedation state similar to the normal sleep state that patients can be awakened. This characteristic of DEX was conducive to the nursing and observation on patients undergoing general anesthesia in waking up period.

The patients in DEX group had lower DRS scores and higher Ramsay sedation scores

after surgery and felt much more comfortable in anesthesia recovery period with less restless times. The favorable cosurgery of patients suggested preferable sedation and relieving anxiety effects of DEX that were helpful for patients going through the stimulation caused by extubation smoothly and comfortably. DEX could combine with norepinephrine receptors in the brain, spinal marrow and all over the body to change the norepinephrine systematically, which might be the reason for deliration. But there still existed the possibilities of patients in DEX group taking less propofols and deliriant sedatives. In the present study, the propofol dosage of DEX group was less than that of control group, and the BIS of two groups maintained at level of 40~60. Then we accordingly adjusted the anesthetic and decelerated the maintenance infusion rate of propofol properly. However, due to the lackage of corresponding objective analgesia indexes, we adjusted the infusion rate of remifentanil only by experiences and therefore, inconsistent analgesic might occur.

The $PaCO_2$ content of the two groups in our study raised 60 min after pneumoperitoneum and Trendelenberg and was higher than its basic level 15 min after endotracheal intubation. The differences of PaO_2 content were not significant at different times. DEX had no effect on the respiratory acidosis caused by pneumoperitoneum, so the variation tendency of the two groups was consistent. The rising of $PaCO_2$ content led to the increase of cerebral blood flow (CBF). However, the studies showed that DEX could significantly reduce the intracranial pressure of permissive hypercapnia patients compared with propofol and kept the balance of cerebral oxygen supply and demand [12]. This function of DEX might be related to the vasoconstriction caused by the influence of dexmedetomidine on the α_2 receptors of arterial circle of Willis, arteriola and pial arterial smooth muscle.

Our research found that 1 d and 5 d after the surgery, serum levels of NSE, IL-6 and TNF-α in DEX group were obviously decreased compared with control group and contrarily, serum level of SOD increased evidently. As an important initial cytokine affecting several cells, TNF-α motivates a series of cascade reaction at the cellular and subcellular level to induce the waterfall-like release of the cytokines such as IL-1, IL-6 and IL-8 [13]. It can also promote the aggregation and activation of leukocytes at the inflammatory site to release a variety of inflammatory mediators (platelet-activating factor, NO and oxygen radical). By raising the influence of adhesion molecules on vascular endothelial to prompt the occurrence of leukocyte adhesion, peripheral vascular and capillary leakage and tissue injury, TNF-α damages the organs, tissues and cells of the whole body. DEX is found to significantly inhibit the expression of TNF-α and improve the activity of protein kinases in previous study [14]. IL-6 is one of the important inflammatory mediators occurred in mononuclear cells and vascular endothelial cells. It can stimulate the proliferation of activated B lymphocyte and the generation of immunoglobulin. IL-6 can also stimulate the liver to produce acute phase reactive proteins and thus to catalyze and enlarge the inflammatory reaction and toxic effect. High concentration of IL-6 directly damages vascular endothelial cells, promotes the immune adhesion and the formation of microthrombus, and inhibits endothelial repair, then causes highly permeable blood vessel [15]. SOD is an endogenous free radical scavenger that its consumption will increase with the enhanced content of free radical, so it indirectly reflects the production situation of free radicals in vivo. SOD activity mediately reflects the damage degree of oxygen free radicals on cells. Studies on animals have shown that in rabbit global cerebral ischemia-reperfusion model, DEX decreases the content of NO and increases the activity of SOD, which demonstrated that DEX can reduce the ischemia-reperfusion injury during such process [16]. Ayoglu et al. proved that DEX had the effect of relieving the oxidative stress response occurring in the process of subarachnoid hemorrhage in rabbits. NSE is a neurochemical marker of cerebral injury that can be used as the early diagnosis indicator of early cerebral ischemic injury, especially subclinical brain damage [17]. With a half-life of 4 h, NSE is relatively stable in the fluid and has no cross reaction with non-neuronal enolase. NSE was proved by Cooper to be a biochemical criterion of neuron damage and a effective indicator of detecting the dead number of neurons [18]. Furthermore, some studies showed that serum IL-6 was positively correlated with the level of NSE among patients with brain damage, and NSE was the direct marker of neurons injury [19]. Also it was

confirmed that the higher serum level of IL-6 predicted more severe the inflammatory response of brain tissues and neuron damage were, and higher the postoperative cognitive dysfunction (POCD) rate [20].

The usage of DEX in anesthesia recovery period reduced the number of patients with POCD at Day 1 and Day 5. Until now, there were still no unified standards on the diagnosis of dysfunction of cognitive ability. Theoretically, the dysfunction of cognitive ability after surgery can be diagnosed by POCD. The diagnosis of POCD is mainly depending on neuropsychological test. Formatting cognitive assessment scale can improve the interview efficiency of the clinicians with patients. Quantifying the cognitive function is the main method in the diagnosis of POCD at present. The present study evaluated the cognitive function using cognitive assessment scale A before surgery and cognitive assessment scale B after surgery. Besides neuropsychological assessment scale, people have been trying to find a more objective examination index to diagnose and evaluate POCD, such as magnetic resonance imaging (MRI) and brain electrophysiological for the examination of biological indicator in cerebrospinal fluid and blood. Regrettably, whether these objective determinations could be used for POCD or not because of poor specificity sparked considerable controversies, so we should dialectically treat the associated test results. Our study detected two inflammatory factors, namely IL-6 and TNF-α, to assist the POCD assessment while neuropsychological test was still needed for the final diagnosis and assessment of POCD. The statistical significance differences existed in the cognitive scale scores and NSE between two groups in the present study manifested that DEX can indeed alleviate the cerebral injury after robot-assisted laparoscopic radical surgery for bladder cancer and protect the central nervous of the patients in a certain degree.

Disclosure of conflict of interest

None.

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