



Effects of different doses of dexmedetomidine on inflammatory factors and T lymphocyte subsets in elderly patients undergoing laparoscopic surgery

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ABSTRACT

Objective: To investigate the effects of different doses of dexmedetomidine on inflammatory factors and T lymphocyte subsets in elderly patients undergoing laparoscopic surgery.

Methods: from June 2016 to June 2017 in our hospital for laparoscopic surgery of 120 cases of elderly patients, were randomly divided into A group, B group, C group, D group of 30 cases, all patients underwent intravenous inhalational anesthesia, A, B, C in three groups were given dexmedetomidine before induction of anesthesia. Fixed loading dose of 0.5 $\mu\text{g}/\text{kg}$, after intubation respectively with dexmedetomidine 0.2 $\mu\text{g}/(\text{kg}\cdot\text{h})$, 0.5 $\mu\text{g}/(\text{kg}\cdot\text{h})$, 0.8 $\mu\text{g}/(\text{kg}\cdot\text{h})$ after continuous infusion to surgery, D group at the same time with the same volume of physiological saline. Before induction of anesthesia (T_0), 24 h after operation (T_1), 72 h after operation (T_2) of venous blood interleukin-1 were measured beta (IL-1 beta), interleukin-2 receptor (sIL-2R) and interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-alpha) and T lymphocyte subsets ($\text{CD}3^+$, $\text{CD}4^+$, $\text{D}8^+$). **Results:** the T_1 of the 4 groups of sIL-2R, IL-6, IL-1 beta, TNF-alpha and T_0 levels were significantly higher than, and A group, B group and C group than in D group, B group and C group than in A group, B group and C group had no significant difference; group IL-1, sIL-2R, IL-6, TNF-beta and alpha level of T_1 decreased significantly, and A group, B group and C group than in D group, B group and C group than in A group, B group and C group had no significant difference. T_1 of the 4 groups of $\text{CD}3^+$, $\text{CD}4^+$, $\text{D}8^+$, $\text{CD}4^+/\text{CD}8^+$ and T_0 decreased significantly, and A group, B group and C group than in D group, B group and C group than in A group, B group and C group had no significant difference; T_2 D group $\text{CD}3^+$, $\text{CD}4^+$, $\text{D}8^+$, $\text{CD}4^+/\text{CD}8^+$ lower than T_1 , and A group, B group, C group, $\text{CD}3^+$, $\text{CD}4^+$, $\text{D}8^+$, $\text{CD}4^+/\text{CD}8^+$ higher than that of D group, B group, C group, $\text{CD}3^+$, $\text{CD}4^+$, $\text{D}8^+$, $\text{CD}4^+/\text{CD}8^+$ higher than that of A group, B group, C group no significant difference. **Conclusion:** Dexmedetomidine can inhibit the inflammatory reaction and improve the immune function in elderly patients undergoing laparoscopic surgery, and the effect of middle and high dose is more significant.

1. Introduction

Laparoscopic surgery has the advantages of less trauma and

quicker recovery, and is more likely to be treated with laparoscopic minimally invasive surgery in elderly patients. Preoperative anxiety, anesthesia, surgical trauma, intraoperative bleeding, postoperative pain, stress and other factors can cause patients with inflammation and immune suppression, especially in elderly patients, due to organ compensatory function decline, more susceptible to immune suppression and cognitive dysfunction[1]. Studies have shown that dexmedetomidine can reduce stress response, reduce proinflammatory cytokines secretion, improve postoperative

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immune function and cognitive function in elderly patients with general anesthesia, and there is correlation with the dose[2]. The purpose of this study was to investigate the effects of different doses of dexmedetomidine on inflammatory factors and T lymphocyte subsets in elderly patients undergoing laparoscopic surgery.

2. Clinical information

2.1. General information

Methods from June 2016 to June 2017, 120 cases of elderly patients undergoing laparoscopic surgery in our hospital were randomly divided into group A, group B, group C and group D. A group of 30 cases, 17 cases were male, 13 were female; age ranged from 60 to 75 years old, the average (66.8 ± 4.2) years old; weighing 55 to 72 kg, the average (61.8 ± 8.6) kg; type of disease: 13 cases of colorectal surgery, 7 cases of urinary surgery, 5 cases of genital surgery, the other 5 cases. B group of 30 cases, 18 cases were male, 12 were female; age ranged from 61 to 76 years old, the average (67.2 ± 5.1) years old; weighing 57 to 70 kg, the average (62.2 ± 7.9) kg; type of disease: 14 cases of colorectal cancer, 7 cases of urinary surgery, 5 cases of genital surgery, the other 4 cases. C group of 30 cases, 17 cases were male, 13 were female; age ranged from 61 to 75 years old, the average (65.9 ± 5.1) years old; weighing 56 to 71 kg, the average (62.2 ± 7.9) kg; type of disease: 13 cases of colorectal surgery, 6 cases of urinary surgery, 6 cases of genital surgery, the other 5 cases. D group of 30 cases, 19 cases were male, 11 were female; age ranged from 62 to 77 years old, the average (66.2 ± 5.3) years old; weighing 56 to 73 kg, the average (62.8 ± 9.2) kg; type of disease: 12 cases of colorectal surgery, 9 cases of urinary surgery, 4 cases of genital surgery, the other 5 cases. There was no significant difference in age, sex, weight and disease type between the 4 groups ($P > 0.05$).

2.2. Inclusion and elimination criteria

Inclusion criteria: heart, lung, liver and kidney function is normal; the American Society of anesthesiologists (ASA) grade II - III; with good compliance of patients and their families; and signed the informed consent. Exclusion criteria: significant bradycardia, arrhythmia, atrioventricular block; combined immune, endocrine, blood diseases and mental diseases; the recent application of hormone or immunosuppressive drugs; related to taboo or allergy; incomplete information cases.

2.3. Method

All patients underwent static inhalation combined intubation and general anesthesia. Before entering operation room for 30 min 0.5 mg, 0.1 g phenobarbital atropine intramuscular injection with fentanyl 3 $\mu\text{g}/\text{kg}$, 1 mg/kg, 2 mg/kg propofol vecuronium anesthesia; tracheal intubation and mechanical ventilation, tidal volume control in 8-10 mL/kg, respiratory rate at 12-14/min; intraoperative propofol 4 mg/(kg.h) and rocuronium 0.8 mg/(kg.h), seven isoflurane 1.5-2.0 minimum alveolar concentration to maintain anesthesia. A, B, C in three groups were given before induction of anesthesia with dexmedetomidine (Jiangsu Hengrui medicine, Zhunzi H20090248) loading dose of 0.5 $\mu\text{g}/\text{kg}$ after tracheal intubation in A group dexmedetomidine 0.2 g/(kg.h), B group with dexmedetomidine 0.5 $\mu\text{g}/\text{kg}$ C in dexmedetomidine 0.8 $\mu\text{g}/\text{kg}$ after continuous infusion to surgery, D group at the same time with the same volume of physiological saline

2.4. Observation index

Before induction of anesthesia (T_0), 24 h after operation (T_1), 72 h after operation (T_2) of venous blood, centrifugal extraction determination of serum interleukin ELISA-1 beta (IL-1 beta), interleukin-2 receptor (sIL-2R) and interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-alpha), kit provided by Shanghai Institute of biological products, the determination of T lymphocyte subsets by flow cytometry ($\text{CD}3^+$, $\text{CD}4^+$, $\text{D}8^+$), kit was purchased from American BD company.

2.5. Statistical processing

The data were analyzed by SPSS 19.0 software, count data was checked by χ^2 , and measured data by t test, By means of Mean \pm SD, The difference was statistically significant between $P < 0.05$. $P < 0.05$ is statistically significant.

3. Result

3.1. Comparison of inflammatory factors at different time points

The levels of IL-1, sIL-2R, IL-6 and TNF- in T_0 of 4 groups were not statistically significant ($P > 0.05$). T_1 of the 4 groups of sIL-2R, IL-6, IL-1 beta, TNF- alpha and T_0 levels were significantly

Table 1.

Comparison of inflammatory factors at different time points.

Group	time	IL-1 β (pg/mL)	sIL-2R (pg/mL)	IL-6 (pg/mL)	TNF- α (pg/mL)
A group	T ₀	2.38±0.68	59.75±7.46	10.27±5.32	47.63±12.84
	T ₁	6.41±0.79 ^{*△}	98.24±6.74 ^{*△}	27.16±4.15 ^{*△}	89.63±13.52 ^{*△}
	T ₂	5.03±0.76 ^{*#△}	82.68±5.84 ^{*#△}	19.54±5.32 ^{*#△}	73.44±11.42 ^{*#△}
B group	T ₀	2.36±0.62	60.13±7.52	10.31±5.48	48.17±13.17
	T ₁	5.30±0.87 ^{*△※}	90.36±7.42 ^{*△※}	22.95±4.17 ^{*△※}	81.74±12.85 ^{*△※}
	T ₂	3.46±0.65 ^{*#△※}	71.34±5.28 ^{*#△※}	13.67±3.84 ^{*#△※}	59.52±10.31 ^{*#△※}
C group	T ₀	2.37±0.62	60.07±6.79	10.26±5.28	47.76±13.11
	T ₁	5.19±0.75 ^{*△※}	88.25±7.15 ^{*△※}	22.29±4.35 ^{*△※}	78.57±12.63 ^{*△※}
	T ₂	3.19±0.77 ^{*#△※}	68.53±6.29 ^{*#△※}	13.28±3.76 ^{*#△※}	57.54±9.78 ^{*#△※}
D group	T ₀	2.36±0.64	60.08±6.81	10.31±5.47	47.78±13.36
	T ₁	8.08±1.14 [*]	123.74±7.65 [*]	40.16±6.47 [*]	128.37±18.67 [*]
	T ₂	6.57±0.62 ^{*#}	95.34±7.52 ^{*#}	25.27±4.36 ^{*#}	97.62±17.54 ^{*#}

Note: compared with T₀ ^{*}P<0.05, compared with T₁ [#]P<0.05, compared with D group P<0.05, compared with the A group P<0.05.

Table 2.

Comparison of T lymphocyte subsets at different time points.

Group	time	CD3 ⁺ (A/μL)	CD4 ⁺ (A/μL)	CD8 ⁺ (A/μL)	CD4 ⁺ /CD8 ⁺
A group	T ₀	986.38±152.71	621.51±76.33	388.64±62.50	1.65±0.19
	T ₁	685.47±132.41 ^{*△}	427.36±71.51 ^{*△}	286.74±41.35 ^{*△}	1.37±0.31 ^{*△}
	T ₂	718.63±99.36 ^{*△}	449.12±68.41 ^{*△}	302.34±27.84 ^{*△}	1.40±0.21 ^{*△}
B group	T ₀	987.69±148.64	623.48±77.21	387.96±61.83	1.66±0.20
	T ₁	796.75±102.36 ^{*△}	511.08±81.36 ^{*△}	303.45±37.36 ^{*△}	1.51±0.17 ^{*△}
	T ₂	802.47±129.64 ^{*△※}	515.64±85.92 ^{*△}	319.42±43.81 ^{*△※}	1.55±0.24 ^{*△※}
C group	T ₀	988.27±149.38	623.52±75.63	386.48±53.17	1.66±0.22
	T ₁	805.53±104.81 ^{*△}	517.62±78.24 ^{*△}	311.35±31.34 ^{*△}	1.54±0.23 ^{*△}
	T ₂	821.63±124.74 ^{*△※}	525.94±79.35 ^{*△※}	318.27±34.66 ^{*△※}	1.57±0.21 ^{*△※}
D group	T ₀	987.17±150.83	620.65±77.74	390.12±65.16	1.65±0.22
	T ₁	607.84±95.28 [*]	356.57±65.44 [*]	268.51±43.69 [*]	1.25±0.16 [*]
	T ₂	519.63±79.39 ^{*#}	304.58±69.71 ^{*#}	239.47±39.81 ^{*#}	1.12±0.21 ^{*#}

Note: compared with T₀ ^{*}P<0.05, compared with T₁ [#]P<0.05, compared with D group P<0.05, compared with the A group P<0.05.

higher than (*P*<0.05), and A group, B group and C group than in D group (*P*<0.05), B group and C group than in A group (*P*<0.05), B group and C group had no significant difference (*P*>0.05); T₂ of the 4 groups of IL-1, sIL-2R, IL-6, TNF-, beta alpha level and T₁ decreased significantly (*P*<0.05), and A group, B group and C group than in D group (*P*<0.05), B group and C group than in A group (*P*<0.05), B group and C group had no significant difference (*P*>0.05). See Table 1.

3.2. Comparison of T lymphocyte subsets at different time points

T₀, CD3⁺, CD4⁺, D8⁺ and CD4⁺/CD8⁺ levels were not statistically significant in the 4 groups (*P*>0.05). T₁ of the 4 groups of CD3⁺, CD4⁺, D8⁺, CD4⁺/CD8⁺ and T₀ decreased significantly (*P*<0.05), and A group, B group and C group than in D group (*P*<0.05), B group and C group than in A group (*P*<0.05), B group and C group had no significant difference (*P*>0.05); T₂ D group CD3⁺, CD4⁺, D8⁺, CD4⁺/CD8⁺ lower than T₁ (*P*< 0.05), and A group, B group, C group, CD3⁺, CD4⁺, D8⁺, CD4⁺/CD8⁺ higher than that of D group (*P*<0.05), B group, C group, CD3⁺ CD4⁺, D8⁺, CD4⁺/CD8⁺ higher than that

of A group (*P*<0.05), B group, C group no significant difference (*P*>0.05). See Table 2.

4. Discussion

The elderly patients with poor physique, low tolerance of anesthesia, with surgical trauma, preoperative anxiety, anesthesia, intraoperative bleeding, low temperature, stress and other factors can induce inflammatory reaction and the influence of immune state, leading to many complications, including cognitive dysfunction is a common seriously affect the quality of life in patients[3]. Laparoscopic surgical trauma, can effectively remove abdominal lesions, but anesthesia, CO₂ pneumoperitoneum will cause the stress reaction of patients, respiratory and circulatory system disorders, endocrine disorders, inflammatory factors rise higher, adverse effects on the central nervous system of patients[4]. Dexmedetomidine is a novel and highly selective alpha 2 adrenergic receptor agonist, combined with brainstem vasomotor central alpha 2-AR, inhibition of central to synthesis and release of norepinephrine, decreased parasympathetic tension, play a central role in anti sympathetic;

dexmedetomidine has analgesic and anti anxiety effects, can make patients entered the natural non REM sleep, has certain anesthetic effect in a certain dose range, and the influence on cognitive function in patients with small; dexmedetomidine can reduce the stress reaction of patients, inhibiting inflammatory reaction, reduce the release of inflammatory cytokines, improve the immune function of patients with[5-7].

Surgical trauma can cause a large number of inflammatory factors released in the body, leading to a significant increase in serum levels of IL-1, beta, sIL-2R, IL-6, TNF-alpha and so on. TNF-alpha is the biological effect of cytokines, has dual biological effects, under normal circumstances, TNF-alpha has anti infection and anti tumor effect, when more than a certain range, and other inflammatory factors to promote the development of the disease, elevated levels of TNF-alpha, alpha kappa B/NF can activate TNF-alpha signal Pathfinder, injury of endothelial cells. The inflammatory factors through the blood-brain barrier, causing tissue edema, the synaptic connection function, cause of postoperative cognitive dysfunction[8]. IL-6 is a multifunctional cytokine, is not only a key component of inflammatory mediators in the network, but also with a variety of diseases, closely related to the development, IL-6 can cause the release of excitatory amino acids and free radicals in vivo, the increase in oxygen free radicals and produce neurotoxicity, which causes central nervous system inflammatory response[9]. Hypoxic ischemic brain injury, glial cells are destroyed, resulting in increased release of IL-1 beta, causing brain tissue through the immunological mechanism of excessive inflammation and reperfusion injury, that the relationship between the IL-1 beta and central nervous system diseases closely[10]. SIL-2R from activated T lymphocyte membrane receptor protein, as a combination of low affinity receptors on the cell membrane with IL-2, inhibit its biological activity, regulation of immune cell proliferation, thereby inhibiting the immune response[11]. There are research reports[12], dexmedetomidine can reduce perioperative stress and inflammation, and reduce the levels of IL-2, IL-6 and TNF-alpha. Some scholars of gastrectomy in elderly patients received dexmedetomidine load of 0.5 g/kg, and 0.2 g/kg, 0.5 g/kg, 0.8 g/kg continuous infusion to the end of surgery, and compared with the normal saline group, the T₁, T₂ IL-6, IL-1 beta, TNF- alpha. Were lower than those in the saline group, and 0.5 g/kg and 0.8 g/kg group was lower than that of 0.2 g/kg group, that different concentrations of dexmedetomidine infusion in elderly patients with abdominal surgery can reduce inflammatory reaction, and high dose was more significant[7]. This study shows that the T₁ of the 4 groups of sIL-2R, IL-6, IL-1 beta, TNF- alpha and T₀ levels were significantly higher than ($P<0.05$), and A group, B group and

C group than in D group ($P<0.05$), B group and C group than in A group ($P<0.05$), B group and C group had no significant difference ($P>0.05$) T₂; 4 groups of IL-1, sIL-2R, IL-6, TNF-beta and alpha level of T₁ decreased significantly ($P<0.05$), and A group, B group and C group than in D group ($P<0.05$), B group and C group than in A group ($P<0.05$), B group and C group had no significant difference ($P>0.05$). It is suggested that continuous infusion of middle and high dose dexmedetomidine can inhibit the release of inflammatory factors and reduce the damage of central nervous system in elderly laparoscopic surgery.

The immune status is an important factor affecting the prognosis of patients during the perioperative period. T lymphocyte subsets are sensitive indicators to reflect the immune dysfunction of the body, which can indicate the immune status and balance level[13]. Anesthesia and surgical trauma can lead to inhibition of immune function in patients with general anesthesia, especially the cellular immune function in elderly patients can damage, inhibition of T cells, NK cells and related cytokines, affect the prognosis of patients[14]. Studies have shown that[6], inflammatory response and immune suppression can damage the central nervous system, suggesting that immunosuppression and inflammatory response are the main mechanisms of cognitive dysfunction. It is reported that[15], dexmedetomidine 0.4-1.0 ug/kg can interfere with the acute psychological stress during local anesthesia, and can improve the postoperative immune function. Some scholars believe that[16], perioperative dexmedetomidine can reduce the number of elderly patients undergoing laparoscopic surgery in T cells and NK cells, and the dose dependence, that high doses of dexmedetomidine can improve the immune function of patients. This study shows that the T₁ of the 4 groups of CD3⁺, CD4⁺, D8⁺, CD4⁺/CD8⁺ and T₀ decreased significantly ($P<0.05$), and A group, B group and C group than in D group ($P<0.05$), B group and C group than in A group ($P<0.05$), B group and C group had no significant difference ($P>0.05$) T₂; D group CD3⁺, CD4⁺, CD8⁺, CD4⁺/CD8⁺ T₁ ($P<0.05$), and lower than that of A group, B group, C group, CD3⁺, CD4⁺, CD8⁺, CD4⁺/CD8⁺ higher than that of D group ($P<0.05$), B group, C group, CD3⁺ CD4⁺, D8⁺, CD4⁺/CD8⁺ higher than that of A group ($P<0.05$), and B group C group showed no significant difference ($P>0.05$). It is suggested that continuous infusion of middle and high dose dexmedetomidine can effectively improve the immune function in elderly patients undergoing laparoscopic surgery.

To sum up, dexmedetomidine can inhibit the inflammatory reaction and improve the immune function in elderly patients undergoing laparoscopic surgery, and the effect of middle and high dose is more significant.

Reference

- [1] Huang Yong, Zhu Xuanjin, Liu Jianwei. Safety of laparoscopic surgery for elderly patients with colorectal cancer. *J Pract Med* 2015; **31**(4): 556-558.
- [2] Meng Yun, Zhang Hua, Yu Yonghao. Effects of dexmedetomidine on cognitive function in elderly patients undergoing laparoscopic surgery and postoperative cerebral oxygen saturation. *Tianjin Univ J* 2016; **22**(1): 66-68.
- [3] Su Xiaohua, Su Hong, Cai Qiaoying. The application of general anesthesia combined with epidural anesthesia in the operation of elderly patients. *Medical Res Educ* 2016; **33**(3): 10-15.
- [4] Xiao Xifeng, Jiang Feng, Zhang Wanlin. Impact of gynecological laparoscopic surgery and open surgery on acute oxidative stress response and energy metabolism. *J Shaanxi Med J* 2015; **44**(8): 1015-1017.
- [5] Zhang Huanhuan, Li Yang, Teng Xiufei. Observation of the effect of dexmedetomidine combined with sufentanil on postoperative analgesia in gynecological laparoscopic surgery. *J China Med Univ* 2016; **45**(4): 333-336.
- [6] Tan Xinglong, Huang Chunliu. Influence of dexmedetomidine on brain metabolism and early postoperative cognitive function in elderly patients undergoing laparoscopic surgery. *Jilin Med Univ* 2016; **37**(3): 552-554.
- [7] Wang Li, Wang Yi, Leng Yan. The magazine, combined with different concentrations of dexmedetomidine on general anesthesia for subtotal gastrectomy in elderly patients with cognitive dysfunction of the immune effect. *Modern Tradit Chin Med Western Med* 2017; **26**(5): 550-553.
- [8] Qin Chengwei, Wu Jizhi. The influence of dexmedetomidine on the amount of sevoflurane in laparoscopic gastric cancer surgery and the detection of serum inflammatory factors. *Chin J Modern Med* 2014; **24**(34): 38-41.
- [9] Huang Qiaowen, Cai Lisheng. The effect of dexmedetomidine on cytokines in elderly patients under general anesthesia during laparoscopic colorectal surgery stress levels and postoperative effect. *Chin Clin Pharmacol Ther* 2016; **21**(7): 802-805.
- [10] Luo Wenwen, Wang Ying, Hu Bin. The influence of dexmedetomidine on IL-1, IL-6 and TNF-alpha in elderly patients with gastric cancer during perioperative period. *Chin Hosp Pharm* 2016; **36**(9): 134.
- [11] Deng Aiqin, Deng Zhilian, Xu Lin. Effects of different doses of dexmedetomidine on inflammatory factors in patients undergoing laparoscopic surgery for uterine malignancies. *Guangdong Med Univ* 2016; **37**(10): 1549-1551.
- [12] Zhang Jingyi. Influence of dexmedetomidine on perioperative period inflammatory factor and stress reaction in patients with gynecological laparoscopic operation. *Drug Eval Res* 2016; **39**(4): 631-634.
- [13] Pi Zhibing, Lin Hai, Xu Xuzhong. Effects of different doses of dexmedetomidine in elderly patients undergoing laparoscopic surgery analgesia and stress and immune function. *Chin J Clin Pharmacol* 2015; **31**(17): 1709-0712.
- [14] Lin Liurong, Wu Bingbing, Lin Lanying. Dexmedetomidine on laparoscopic surgery for colorectal cancer in elderly patients with postoperative cognitive dysfunction and serum neuron specific enolase, 100 beta protein, tumor necrosis factor alpha level. *China J Gerontol* 2017; **37**(6): 1463-1465.
- [15] Zhang Yiwen, Xing Zumin, Xu Yinghua. Different doses of dexmedetomidine in elderly patients with laparoscopic node cognitive dysfunction early after surgery of rectal cancer. *J Southern Med Univ* 2014; **34**(5): 743-746.
- [16] Feng Yanling, Yang Xiaolei, Qian Xiaomin. Effects of different doses of dexmedetomidine on postoperative cognitive function and inflammatory factors in elderly patients undergoing laparoscopic gallbladder surgery. *Modern Med* 2016; **44**(11): 1499-1503.