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Original Article

The effects of dexmedetomidine on post-operative cognitive dysfunction and inflammatory factors in senile patients

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Abstract: Objective: To evaluate the effect of dexmedetomidine on post-operative cognitive dysfunction (POCD) and possible action mechanisms. Methods: A total of 148 aged surgical patients were divided into two groups, which were treated with dexmedetomidine (Dex group) or normal saline (control group) during general anesthesia. The incidence of POCD one day after surgery was evaluated using Mini-Mental State Examination and serum levels of interleukin 6 (IL-6) and tumor necrosis factor α (TNF-α) were measured using ELISA. The correlation between the two cytokines and POCD was evaluated using quartile division assay. Results: The incidence of POCD was 9.20% and 21.31% in Dex and control groups, respectively. It is significantly different between the two groups ($P < 0.05$). The levels of IL-6 and TNF-α were significantly increased after surgery, as compared to before surgery ($P < 0.05$). Compared to control group, Dexmedetomidine significantly inhibited the increase of post-operative IL-6 and TNF-α levels ($P < 0.05$). The incidence of POCD was significantly different between quartile divisions of IL-6 and TNF-α ($P < 0.05$). *Pearson* correlation analysis showed that IL-6 and TNF-α were positively correlated with the POCD ($r = 0.689$, $P = 0.043$ and $r = 0.711$, $P = 0.038$, respectively). Conclusions: The results demonstrate that dexmedetomidine reduces the incidence of POCD in aged patients, and inflammation suppression may underlie the action mechanism.

Keywords: Dexmedetomidine, inflammation, POCD, quartile division

Introduction

Aged patients frequently undergo cognitive dysfunction after surgery, which is characterized by mental derangement, anxiety, personality changes and memory impair. These changes in mental, personality, social and cognitive ability after surgery are commonly called post-operative cognitive dysfunction (POCD) [1]. POCD severely interferes in the compliance of postoperative treatment, and reduces the prognosis and life quality. How to prevent and treat the incidence of POCD in aged patients is a highly concerned question for clinical practitioners. Investigations have shown occurrence of POCD is related with proinflammatory response. Dexmedetomidine, an anesthesia and sedation drug, has been revealed to improve POCD [2]. Clinical research also showed dexmedetomidine decreased the perioperative proinflammatory response [3]. Therefore, it is speculated some correlation exists between POCD and inflammation. In the present study, we retrospectively evaluated the effect of dexmedetomidine on POCD in aged patients and possible mechanisms.

Materials and methods

General information

In the retrospective study, a total of 148 cases of aged patients were selected from Jan 2012 through June 2013 in our Hospital. These cases had complete clinical documents. All these patients received time-selection surgery under

Table 1. MMSE and incidence of POCD

	Cases size (n)	MMSE		POCD (n, (%))
		Before surgery	After surgery	
Dex group	87	28.24 ± 5.18#	25.86 ± 4.10*,**	8 (9.20)**
Control group	61	28.51 ± 5.42	23.29 ± 4.59*	13 (21.31)

*$P < 0.05$ *vs* before surgery, **$P < 0.05$ *vs* control group, #$P > 0.05$ *vs* control group.

I~III grade of general anesthesia according to the grading of American Society of Anesthesiologists. No patients had history of psychosis. These cases included 75 cases of fracture surgery, 36 cases of prostate removal, 31 cases of gallbladder surgery, and 6 cases of radical resection of rectal carcinoma. These research subjects were divided into dexmedetomidine (Dex) group and control group. In Dex group, there were 87 cases, including 56 males and 31 females. The ages were 61~89 years (average 70.6 ± 4.2). The body weights were 45~95 kg (average 65.8 ± 5.8). The educational levels of these patients included illiteracy (11), elementary education (21), secondary education (37) and above (20). In ASA grading, there were 31 cases of Grade I, 47 cases of II and 9 cases of Grade III. There were 61 cases in control group, including 38 males and 23 females. The ages were 61~92 years (average 71.4 ± 4.9). The body weights were 47~94 kg (average 66.2 ± 5.5). The educational levels of these patients included illiteracy (8), elementary education (16), secondary education (23) and above (14). In ASA grading, there were 22 cases of Grade I, 32 cases of II and 7 cases of Grade III. No significant difference between the two groups was seen in age, sex, body weight, educational levels and ASA grading ($P > 0.05$).

Anesthesia

The patients in the two groups received regular preoperative fasting. They were given 5 mg diazepam (oral) and 0.5 mg atropine (intramuscular) 30 min before surgery, and 30-min oxygen inhalation through mask. Venous channels were made and ECG, vital signs and blood oxygen saturation were regularly monitored. Drugs for anesthesia induction were fentanyl (2.0~4.0 μg/kg), propofol (1.0 mg/kg) and vecuronium bromide (0.1 mg/kg). After successful anesthesia, anesthesia was maintained by propofol through micropump, and accompanied by discontinuous fentanyl and vecuronium bromide. At 10 min after stable anesthesia, patients in Dex group were given 0.5 μg/kg dexmedetomidine (intravenous) at concentration of 0.5 μg/mL. The injection time was 10 min. Dexmedetomidine was then maintained in 0.2 μg/kg. h until 30 min before the end of surgery. The patients in control group were given same manipulation as in Dex group except dexmedetomidine was replaced by normal saline.

POCD

POCD was evaluated using Mini-Mental State Examination (MMSE) one day before and after surgery. The parameters in MMSE included orientation, memory, attention, calculation, recollection and linguistic ability. The scores range was 0~30. Scores < 24 were considered POCD.

Proinflammatory cytokines measurement

In one day before and after surgery, i.e. 10 min before MMSE test, 3 ml venous blood was extracted from elbow. Serum was isolated by regular centrifuge. Serum levels of interleukin 6 (IL-6) and tumor necrosis factor α (TNF-α) were measured using ELISA according to the manufacturer's instructions (Shenzhen Jingmei Biology Engineering CO., Ltd).

Correlation analysis between POCD and cytokines

The correlation between POCD and cytokines was first evaluated using quartile division assay. Three quartiles (Q1, Q2, Q3) were decided by ranging the values of IL-6 or TNF-α from small toward big. They were Q1 = (87 + 1)/4 = 22, Q2 = (87 + 1)/2 = 44, and Q3 = (87 + 1) ×3/4 = 66, which were further divided four divisions (q1, q2, q3, q4). The difference of POCD incidence in the four divisions was compared. *Pearson* analysis was also performed to evaluate the correlation between POCD and the two cytokines.

Statistical analysis

Data were analyzed with SPSS 12.0 software. The successive data are presented as x ± s, and analyzed with Kruskal-Wallis. Enumeration data are presented as percentage (%), and were analyzed with X^2 test. The correlation

Table 2. The levels of IL-6 and TNF-α before and after surgery

	Cases size (n)	IL-6 (ng/L)		TNF-α (ng/L)	
		Before surgery	After surgery	Before surgery	After surgery
Dex group	87	49.44 ± 9.25#	69.04 ± 12.14*,**	45.28 ± 8.99#	64.82 ± 9.71*,**
Control group	61	51.02 ± 10.49	86.48 ± 13.51*	46.20 ± 9.42	75.74 ± 10.39*

*$P < 0.05$ *vs* before surgery, **$P < 0.05$ *vs* control group, #$P > 0.05$ *vs* control group.

Table 3. The incidence of POCD in the quartile divisions of IL-6

quartile division	Cases size (n)	IL-6 (ng/L)	POCD (n (%))
q1	22	57.96 ± 10.16	0 (0.00)
q2	22	65.27 ± 10.62	1 (4.55)
q3	22	70.34 ± 11.82	2 (9.09)
q4	21	83.24 ± 14.82	5 (22.73)

Table 4. The incidence of POCD in the quartile divisions of TNF-α

quartile division	Cases size (n)	TNF-α (ng/L)	POCD (n (%))
q1	22	55.28 ± 11.27	0 (0.00)
q2	22	61.94 ± 10.72	1 (4.55)
q3	22	66.18 ± 11.71	2 (9.09)
q4	21	76.41 ± 14.20	5 (22.73)

analysis was performed with *Pearson* analysis. $P < 0.05$ was considered statistically different.

Results

MMSE and incidence of POCD

Preoperative and postoperative MMSE and incidence of POCD were shown in **Table 1**. The MMSE scores were significantly decreased after surgery, as compared to before surgery in both groups, especially in control group ($P < 0.05$). The postoperative MMSE in Dex group was significantly higher than that in control group ($P < 0.05$). No significant difference of preoperative MMSE was seen between the two groups ($P > 0.05$). The incidence of POCD was significantly lower in Dex group than that in control group ($P < 0.05$).

The levels of IL-6 and TNF-α before and after surgery

The serum levels of IL-6 and TNF-α were listed in **Table 2**. The levels of IL-6 and TNF-α one day after surgery were significantly increased as compared to before surgery in both Dex and control groups ($P < 0.05$), while their preoperative levels were not significantly different ($P > 0.05$). Dex treatment significantly decreased the postoperative levels of IL-6 and TNF-α ($P < 0.05$).

The relationship between POCD and the quartile divisions of IL-6

The cases were divided into four divisions according to the IL-6 values from small to big. The incidence of POCD was significantly increased with the IL-6 levels ($P < 0.05$, **Table 3**).

The relationship between POCD and the quartile divisions of TNF-α

Similar as IL-6, the incidence of POCD was significantly increased with the TNF-α levels ($P < 0.05$, **Table 4**).

The Pearson correlation analysis between proinflammatory factors and POCD

Pearson correlation analysis showed serum level of IL-6 was positively correlated with the incidence of POCD ($r = 0.689$, $P = 0.043$). Similarly, serum level of TNF-α was also positively correlated with the incidence of POCD ($r = 0.711$, $P = 0.038$).

Discussion

With the economic development and improvement of living standards, China is gradually entering aged society. The continuous advancement of medical technologies makes it possible that more and more aged people receive surgical treatment. This results in higher and higher incidence of POCD, which subsequently causes a great burden to hospitals, families and society. However, the mechanism of POCD is not clear until now. It is generally believed that POCD is closely related with patients' own situation, surgery and anesthesia. Other studies showed inflammation could play an important role in the occurrence of POCD [4-6].

IL-6 plays an important role in defense, immune and inflammatory responses in the body, and

affects cell growth and differentiation of the central nervous system (CNS). IL-6 also affects brain functions, including learning and memory ability. Intracranial IL-6 expresses mainly in microglia, neurons and astrocytes, and is involved in brain injury. Normal concentration of IL-6 participates in neuron protection and repair. In contrast, higher concentration of IL-6 exacerbates the damages of microglia and neuron [7]. These effects may be mediated by influencing synaptic plasticity and neural development [8, 9]. TNF-α is cytokine secreted by macrophages. It possesses wide bioactivity, and plays an important role in immune regulation, inflammation regulation, and neural, endocrine and many other systems. TNF-α participates in a variety of life activities including eating, sleep, and autonomic activities. Recent investigations showed that TNF-α may also participate in learning and memory process, and exert important effects on the pathological process of POCD [10]. The possible mechanisms of TNF-α in POCD include affecting synaptic plasticity and inhibiting the growth and differentiation of neuronal processes.

In the present study, the research cases were divided into four divisions using quartile division method according to the magnitude of IL-6 and TNF-α. The results showed a significant difference of POCD incidence between the four divisions. The incidence of POCD was increased with the increase of the levels of IL-6 and TNF-α, indicating a positive correlation between the incidence of POCD and IL-6 or TNF-α level. Further, *Pearson* correlation analysis revealed IL-6 was positively correlated with the incidence of POCD ($r = 0.689$, $P = 0.043$). Similarly, TNF-α was positively correlated with the incidence of POCD ($r = 0.711$, $P = 0.038$). These results demonstrate the closely correlation between inflammation and the occurrence of POCD.

Dexmedetomidine is a highly selective alpha-2 adrenergic receptor agonist. It is widely used in the treatment of sedation, analgesic and anti-anxiety. Indeed, in the present study, dexmedetomidine revealed a significantly improvement on the incidence of POCD to 9.2% from 21.31% in control group. In recent years, dexmedetomidine has exhibited anti-inflammatory activity, which may mediate protective effect on the body. The action mechanisms involving anti-inflammatory activity of dexmedetomidine may be considered as following [11, 12]. ① Activate central alpha-2 adrenergic receptor, and inhibit sympathetic excitation, then activate cholinergic anti-inflammatory pathway and lower the levels of proinflammatory factors. ② inhibit monocyte-macrophages, and regulates the release of TNF-α. ③ control the release of IL-6, TNF-α and other factors by regulating nuclear factor Kappa B. In the present study, dexmedetomidine significantly decreased the serum levels of IL-6 and TNF-α, as compared to in control group, suggesting the anti-inflammatory activity of dexmedetomidine.

Summary, these results showed dexmedetomidine markedly decreased the incidence of POCD and release or/and expression of IL-6 and TNF-α. These results suggest the protective effect of dexmedetomidine on POCD is mediated by the inhibition of inflammatory response. Further pharmacological studies are needed to prove the speculation.

Disclosure of conflict of interest

None.

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