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Effect of Dexmedetomidine on Inflammatory Response in Aortic Dissection

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ABSTRACT

Objective: To study the effect of dexmedetomidine (Dex) on perioperative inflammatory response in aortic dissection (AD) patients.

Methods: From June 2020 to June 2022, 50 patients with Stanford type B AD underwent endovascular stent-graft exclusion (EVAR) at our hospital. They randomly were assigned to two groups (*N* = 25): the control group (C group) and the Dex group. Patients in the Dex group received 0.5ug/kg Dex intravenously 10 minutes before induction of anesthesia and 0.5μg/kg/h Dex during the intervention until 15 minutes before the end of surgery. In contrast, the C group received the same volume of normal saline at the same time points. The two groups were induced and maintained with the same anesthetic agents. Venous blood samples were taken 3 days before operation (T1), 1 day before operation (T2), 1 day after operation (T3) and 3 days after operation (T4) to detect levels of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and white blood cell count (WBC).

Results: At T3 and T4, CRP and ESR in the Dex group were significantly improved compared with those in the C group.

Conclusion: Dexmedetomidine can reduce the inflammatory reaction of aortic dissection.

INTRODUCTION

Aortic dissection (AD) is a rare cardiovascular disease with a high mortality rate characterized by aortic membrane rupture and the formation of intramural hematoma [Zeng 2018]. In recent years, the prevalence of AD has increased, and younger patients are being affected more and more. The advent of aortic replacement and interventional therapy significantly has reduced the mortality rate of AD patients. In general, the pathological process of AD is complex and closely related to the infiltration of inflammatory cells in the aortic wall [Wang 2021]. Dexmedetomidine (Dex) is widely used in the perioperative period of cardiovascular surgery as it can block the signal transduction of the blue nucleus near the fourth ventricle, activate the 2 adrenergic receptors, and act as a sedative. Dex has been shown modulate the release of anti-inflammatory and pro-inflammatory cytokines, thereby reducing the inflammatory response [Wang 2020; İşcan 2018]. This study assesses the effect of Dex on perioperative inflammatory response in AD patients and provided a reference for perioperative medication in such patients.

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MATERIAL AND METHODS

From June 2020 to June 2022, our hospital admitted and managed 50 patients with Stanford type B aortic dissection using endovascular aortic repair (EVAR). The study's inclusion criteria are as follows: no gender, age limit, ASA grade I-II, no heart, brain, kidney and other important organ function injury. Enrolled patients randomly were divided into 2 groups (*N* = 25): the control group (C group) and Dex group. This study was approved by the Medical Ethics Committee of our hospital (2022 Teaching No.002), and informed consent was signed by the patients and their families prior to enrollment.

Following admission, vital signs closely were monitored, a thorough preoperative assessment was performed, strict blood pressure and heart rate control, analgesia, and complete bed rest were implemented. EVAR was performed 3 to 5 days after remission of acute inflammation. After entering the operation room, venous access was established; ECG, SpO2, BIS, invasive arterial pressure, and body temperature were monitored accordingly. The Dex group received 0.5μg/kg of Dex infusion (Jiangsu Hengrui Pharmaceutical Co Ltd.) intravenously 10 minutes before anesthesia induction, and 0.5μg/kg/h of Dex was given throughout the intervention and stopped 15 minutes before the end of surgery. The C group received the same volume of normal saline. Anesthesia was induced by intravenous injection of midazolam 0.04mg/kg, propofol 1.0-2.0mg/kg, cis-atracurium 0.1-0.15mg/kg and sufentanil 0.3-0.4μg / kg. The patients were ventilated using tracheal intubation and mechanical ventilation to maintain a PaCO2 of 35 ~ 45 mmHg. Anesthesia maintenance was achieved using intravenous infusion of propofol 3-5mg/kg/h, remifentanil 0.1- 0.2μg/kg/min, cis-atracurium 8mg/h. BIS and body temperature were maintained at 45-55 and 36-37 , respectively. Sufentanil 5μg was given 10 minutes before the end of the intervention. Patients were taken to the PACU following surgery, and the tracheal tube was removed while the patients were awake. During the perioperative period, vasoactive drugs were used to maintain

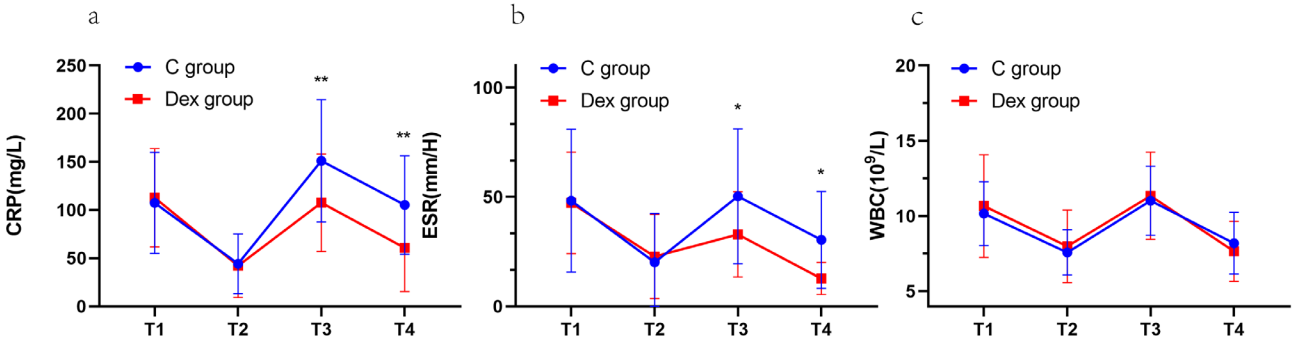

Figure 1. Comparison of perioperative serum inflammatory cytokine concentrations in patients. A refers to the comparison of CRP values between the two groups. B refers to the comparison of ESR values between the two groups. C refers to the comparison of WBC counts between the two groups. T1, T2, T3, and T4 represent 3 days before the operation, 1 day before the operation, 1 day after the operation and 3 days after the operation, respectively. *P < 0.05, **P < 0.01

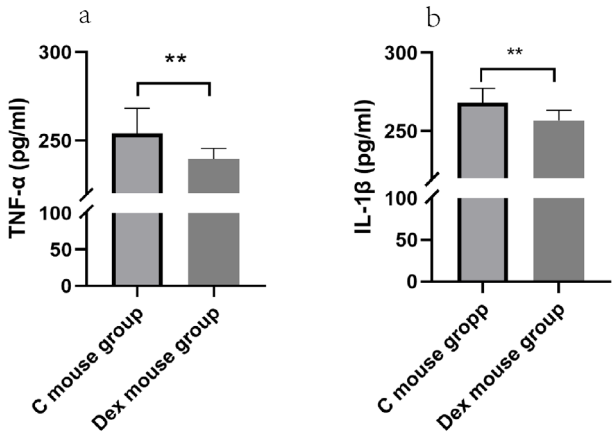

Figure 2. Comparison of serum inflammatory factors in AD mice. *P < 0.05, **P < 0.01

the hemodynamic stability of patients, and controlled hypotension was induced during stent implantation. Venous blood samples were taken 3 days before the operation, 1 day before the operation, 1 day after the operation, and 3 days after the operation. C-reactive protein (CRP) was detected by immune transmission turbidimetry; erythrocyte sedimentation rate (ESR) was analyzed using a capillary photometer imaging method; and white blood cell (WBC) count, as well as the changes in perioperative inflammatory indicators, were observed.

Statistical methods: SPSS 17.0 software was used for all statistical analyses. The mean±standard deviation (X ± s) was used for normal distribution, the analysis of variance (ANOVA) was used for repeated measurement design, and the two independent samples t-test was used for randomized block design. The enumeration data were compared with the X test. P < 0.05 was considered statistically significant.

RESULTS

General information and operation index of the patients: The general information and operation index showed no statistical significance (P > 0.05), as shown in Table 1. (Table 1)

Comparison of perioperative serum levels of inflammatory factors: CRP and ESR levels significantly were different between the two groups at T3 and T4, while no significant difference was found, in terms of WBC count. (Figure 1)

DISCUSSION

Stanford type B AD (TBAD) is a life-threatening cardiovascular disease with a 5-year mortality rate of 30% to 40% [Fattori 2013; Afifi 2015]. EVAR is increasingly being used in endovascular repair to treat TBAD since it is less invasive and has a lower mortality rate when compared with traditional surgical methods. Although the exact etiology of AD is unknown, a large body of evidence suggests that inflammatory factors play a key role in the development of AD [Anzai 2015; Son 2015; Zhang 2016]. Numerous inflammatory cell infiltrates, including neutrophils and macrophages, were found to be enriched in human AD specimens and animal AD aortas [Anzai 2015; Son 2015; Zhang 2016; Ye 2018; Ju 2013]. Gavazzi and Liu et al. previously reported that lowering the oxidative stress level could reduce AD incidence [Gavazzi 2007; Liu 2016]. Proinflammatory cytokines cause immune disorders and amplify the inflammatory response in blood vessels, resulting in excessive loss of aortic vascular smooth muscle cells, vascular remodeling and expansion, leading to the development of AD. In contrast, anti-inflammatory cytokines can alleviate the inflammatory response, promote vascular tissue repair, and inhibit AD occurrence, implying that inflammation is closely linked to the occurrence of AD.

Clinical studies have shown that Dex has a protective effect on important organs. Dex's main biological mechanism for organ protection is its anti-inflammatory effects [Zhao 2022]. The anti-inflammatory effect of Dex may be related to its ability to inhibit the expression of inflammatory molecules when it binds to α2-adrenergic receptors on macrophages [Szelényi 2000] or by increasing norepinephrine uptake (suppression of the immune response) when it binds to

Table 1. Comparison of general data and operation index between the two groups (N = 50, $\bar{X}$±S)

Group	Age (years)	BMI (kg/m^2)	Operation time (min)	Fluid infusion volume (ml)	ASA grade (I/II)
C group	55±15	24±4	107±11	1020±68	2/23
Dex group	54±12	25±4	100±13	1042±118	3/22

α2-adrenergic receptors on central nervous system synapses [Klimscha 1997; Maes 2000; Lai 2009]. In addition to the main biological effects of α2AR agonists, DEX has confirmed the anti-inflammatory effect of α2AR agonists by reducing inflammatory cytokines (such as TNF-α and IL-6) in vitro, in vivo, and in clinical experiments [Hofer 2009; Qiao 2009]. To summarize, the anti-inflammatory effects of DEX are achieved by inhibiting TLR4/NF-κB [Gu 2011; Levey 2017; Yang 2015; Lameire 2013], JAK2-STAT3 [Lankadeva 2019; Si 2013], and NF-κB/COX-2 [Yao 2015] pathways. DEX also increases the release of acetylcholine (ACh) through an anti-sympathetic effect; it combines with α7nAChR on immune cytomembranes and exerts anti-inflammatory effects via the cholinergic pathway [Gu 2011; Si 2013; Miksa 2009; Ohta 2020]. Although it is known that the onset and progression of AD will result in a series of inflammatory and stress responses, few studies have focused on the use of Dex as an adjuvant treatment for AD patients.

In our study, we found that the CPR, ESR and WBC values of AD patients after admission (T1) were significantly higher than the normal value, suggesting that the patients were in an acute inflammatory phase. Considering that surgery performed in an acute inflammatory period could lead to an increase in perioperative mortality and adverse postoperative complications, it is critical to control the blood pressure, reduce the heart rate, administer anti-inflammatory drugs, and manage symptoms in a timely manner (except for acute aortic rupture, deterioration of the condition requiring emergency surgery). EVAR was performed selectively when the patient's condition deteriorated and the patient's inflammation index decreased (T2). We found that both patient groups had elevated serum inflammation index on T3, possibly due to the surgical stress on postoperative day 1. After Dex treatment, the inflammation index increase was significantly lower compared with the control group. Patients' serum inflammatory cytokines decreased significantly three days after surgery, and inflammatory indicator concentrations improved significantly after Dex treatment. The above observations suggest that Dex can reduce the inflammatory response of AD and is beneficial to the recovery of AD patients. Although the anti-inflammatory mechanisms by which Dex inhibits inflammation are not fully understood, previous studies have shown that Dex can reduce pro-inflammatory cytokines, such as IL-6 and TNF-α, in septic patients and can reduce pro-inflammatory cytokines and CRP during anesthesia in surgical patients [Zamani 2016; Li 2015]. This is in line with our findings, which revealed that Dex could significantly reduce CRP and ESR levels, implying that Dex could alleviate the inflammatory response in patients with aortic dissection. In our experiment, however, there was no significant difference in WBC count, and previous research found that Dex could reduce the plasma concentration of inflammatory cytokines in rats with endotoxin-induced shock in a dose-dependent manner [Taniguchi 2008]. As a result, larger sample sizes or higher Dex doses are required in future studies. After admission, patients with aortic dissection require strict heart rate, blood pressure, and analgesic medication control. Dex as a highly selective alpha 2 adrenoceptor agonist, because of its sedation, analgesia and hemodynamic stability, it cannot only be used in surgery during anesthesia, but can also play a very important role in patients with admission and postoperative management. Our research group previously found that the acute phase of AD patients with sympathetic nerve excitability significantly increased. It is difficult to manage the blood pressure within the ideal range using conventional antihypertensive drugs; however, adding Dex to conventional antihypertensive drug treatment has been shown to significantly reduce the dosage of antihypertensive drugs and effectively control blood pressure and heart rate. We hypothesize that this is related to the mechanism by which Dex reduces inflammatory cytokines. In the future, our research team will increase the clinical research sample size, increase the perioperative Dex action time in patients, and study the molecular mechanism of Dex anti-inflammatory in animal models using high-throughput sequencing and other biological methods.

Collectively, our study shows that Dex can effectively reduce the perioperative systemic inflammatory response in AD patients.

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