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The Preventive Effect of Dexmedetomidine Against Delirium in Patients with Aortic Dissection: A Retrospective Cohort Study

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ABSTRACT

Background: Dexmedetomidine (DEX) is often used to reduce the incidence of delirium in intensive care unit (ICU) patients. However, it was found in our clinical practice that the incidence of delirium in some patients with aortic dissection (AD) remained high even after using DEX. The aim of the present study was to clarify whether the protective effects of DEX against delirium were different between Stanford type A and B AD patients during ICU stay.

Methods: Data of patients with Stanford type A or B AD who were treated in the ICU of our hospital between 2015 and 2018 retrospectively were reviewed. They were divided into four groups: A1 group (Stanford type A AD patients using DEX), A2 group (Stanford type A AD patients without using DEX), B1 group (Stanford type B AD patients using DEX), and B2 group (Stanford type B AD patients without using DEX). Patients in A1 and B1 groups received intravenous administration of DEX within 1 h admission to the ICU and after surgery or stent implantation at a loading dose of 1 μg/kg, followed by continuous infusion of 0.2–0.7 μg/(kg·h) for >24 h. The mortality rate, delirium incidence, length of ICU stay, and drug administration were compared between the four groups.

Results: After intravenous administration of DEX, the delirium incidence in B1 group was reduced significantly compared with that in B2 group (2.8% vs. 17.8%, P = 0.04), while there was no significant difference between A1 and A2 group (20.8% vs. 24.3%, P = 0.7). However, DEX administration significantly reduced the use of anti-hypertensive drugs (P = 0.04) and morphine (P = 0.02) in Stanford type A AD patients.

Conclusion: The use of DEX reduced the incidence of delirium in Stanford type B AD patients during ICU stay, therefore reducing the risk of medical accidents and risk of rupture of the aortic dissecting aneurysm. The preventive effect of DEX against delirium in Stanford type A AD patients was not obvious, and whether increasing the dosage of DEX could enhance the therapeutic efficacy in this group of patients needs to be further observed in future studies.

INTRODUCTION

Aortic dissection (AD) is the most devastating emergency and severe disease in cardiovascular surgery, which is characterized by acute onset and a high mortality rate [Wu 2018; Lau 2019] with the age-dependent incidence reaching 3.5-6/100,000 and 10/100,000 person-years in the general population and elderly individuals, respectively [Chiu 2016]. AD is generally accompanied by tearing pain and hypertension, and the perioperative treatment of which mainly includes sedation, analgesia, blood pressure control, and rupture prevention [Wee 2019; Endlich 2016]. According to the Stanford Classification in Acute Aortic Dissection [Sievers 2020; Rylski 2017], AD comprises two types – A and B. But recent studies have revealed the occurrence of the non-A non-B AD type.

Dexmedetomidine (DEX) is a highly selective α2 adrenergic agonist which exerts sedative and analgesic effects without inhibiting respiration [Hosokawa 2010; Seto 2016] and thus has a high application value in AD patients. Several recent studies have demonstrated that DEX reduces or even prevents the incidence of postoperative delirium in critically ill patients in the intensive care unit (ICU) [Wang 2017; Su 2016; Rudolph 2011]. But most of these studies did not classify the patients into specific disease types, and few addressed the AD typing, knowing that clinical treatments differ with the pathological changes of different types of AD. For instance, Stanford type A AD is generally treated with open thoracotomy, while Stanford type B AD is mainly treated with endovascular graft exclusion (EVGE) using coated stents [Wang 2016].

We observe in our clinical practice that the incidence of delirium in some AD patients using DEX remains high. The aim of the present retrospective study was to investigate the effectiveness of DEX in preventing delirium in Stanford type A or B AD patients during ICU stay. Our results demonstrated that continuous DEX infusion decreased the occurrence of delirium in Stanford type B AD patients but not in Stanford type A AD patients, but it decreased the use of anti-hypertensive drugs and analgesics in Stanford type A AD patients.

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MATERIALS AND METHODS

Study design and patient inclusion: The electronic medical records of all the patients treated for AD in the ICU of our hospital between January 2015 and December 2018 retrospectively were reviewed, and ICU data were extracted. Exclusion criteria were: 1) coma when presenting to the ICU; 2) single or multiple organ failure; 3) mean artery pressure (MAP) <60 mmHg; 4) cardio-pulmonary resuscitation (CPR) administration; 5) bradycardia with heart rate (HR) <55 bpm; and 6) incomplete clinical data. According to the disease type and whether they received continuous DEX infusion during ICU stay, patients were classified into four groups: 1) Stanford type A AD patient group receiving DEX treatment (A1 group), 2) Stanford type A AD patient group without receiving DEX treatment (A2 group), 3) Stanford type B AD patient group receiving DEX treatment (B1 group), and 4) Stanford type B AD patient group without receiving DEX treatment (B2 group). The study protocol was approved by the Ethics Committee of the said hospital [KS1993]. Informed consent was waived due to its retrospective nature.

ICU management: As sedation and analgesia are the main treatments in the perioperative period of AD patients, all patients were given blood pressure (BP) control after admission to the ICU, and the specific dosage of antihypertensive drugs varied from patient to patient. According to the Guidelines on the Diagnosis and Treatment of Aortic Diseases, updated by the European Society of Cardiology in 2014 [Erbel 2014], metoprolol was initially applied to control BP in all four groups. In patients with decreased HR but no overt BP reduction, nicardipine hydrochloride and sodium nitroprusside concomitantly were administered. The target for BP control was systolic blood pressure (SBP) between 100 and 120 mmHg. To maintain renal perfusion, MAP was maintained above 60 mmHg and urine volume above 1 ml/kg/h. For pain management, visual analog scale (VAS) scores (1-10 points) were used to assess patients' pain. Morphine was administered for analgesia in patients with VAS scores >3. In the A1 and B1 groups, based on the standard treatment, intravenous administration of DEX was started in the ICU department within 1 h of hospitalization and after surgery or stent implantation with loading injection of 1 μg/kg, followed by continuous infusion of 0.2–0.7 μg/(kg·h) >24 hours. DEX was administered at 400 μg in 46 ml normal saline (NS). The following baseline data were collected at admission: demographics including age, sex, smoking and underlying diseases (hypertension, diabetes, ischemic heart disease and acute kidney injury), surgical treatment, and Stanford AD classification.

Outcome assessment: The primary outcome was the incidence of delirium. The secondary outcomes were the mortality rate and length of ICU stay, and dosage of antihypertensive drugs and morphine. Delirium was evaluated according to the confusion assessment method for the intensive care unit (CAM-ICU) [Gusmao-Flores 2012]. In detail, the patients meeting the first two items and one of the latter two were diagnosed with delirium: 1) acute onset of mental status changes or fluctuating course; 2) inattention; 3) disorganized thinking; and 4) altered level of consciousness (other conscious states than complete consciousness, such as alert, somnolence, lethargy, and coma). A decrease in antihypertensive drugs and morphine was defined as any decrease in antihypertensive or morphine doses within 24h after DEX initiation.

Statistical analysis: The sample size was calculated using the PASS 15 software. According to clinical work experience and previous literature [Wu 2018; Lau 2019], the incidence of postoperative delirium in AD was about 25%-35%, and the incidence in the control group was 30%. It is expected that the prevention of postoperative delirium in the treatment groups in this study could reduce the incidence by 20%, i.e., the incidence in the prevention groups should be 10%. Using α=0.05 (two-sided), 1-β=0.8, and equal group size, the sample size was 70 in each group, totaling 140.

SPSS 21.0 (IBM SPSS, USA) was used for statistical analysis. Quantitative data are presented as the mean ± standard deviation (SD). Independent samples t-test was performed for group pair comparisons. Repeated measures analysis of variance (ANOVA) was performed for quantitative data with repeated measurements. The chi-square test or Fisher's exact test was carried out for comparing qualitative data. Two-sided $P < 0.05$ was considered statistically significant.

RESULTS

General patient characteristics: After reviewing the electronic medical records, 168 patients met the inclusion criteria, including 101 in Stanford type A AD group, and 67 in Stanford types B AD group. Sixteen patients in Stanford type A group were excluded from analysis because of presenting coma in the ICU (N = 3), single or multiple organ failure (N = 7), MAP <60 mmHg (N = 6), and/or CPR administration (N = 2), including five patients who had more than one of these conditions. In addition, three patients in Stanford type B AD group were excluded for MAP <60 mmHg at ICU presentation. Finally, the A1, A2, B1 and B2 groups comprised 48, 37, 36 and 28 patients, respectively. There were no significant differences in the baseline characteristics between the A1 and A2 groups, or the between B1 and B2 groups. (Table 1) All patients in the A1 and A2 groups received surgery under cardiopulmonary bypass, while only 25 patients (69.4%) and 20 patients (71.4%) in the B1 and B2 groups received descending aortic stent implantation, respectively. The other patients in the B1 (11, 30.6%) group and B2 group (8, 28.6%) received conservative treatment (Table 1).

Delirium incidence and mortality rates: In the A1 and A2 AD groups, 10 (20.8%) and nine (24.3%) patients presented delirium, and seven (14.6%) and six (16.2%) patients died, respectively, showing no significant differences in delirium incidence (P = 0.70), mortality rate (P = 0.83), and length of ICU stay (P = 0.67) between the two groups. In the B1 and B2 AD groups, one (2.8%) and five (17.8%) patients presented delirium, and two (5.6%) and one (3.6%) patient died, respectively, showing no significant difference in the mortality rate (P = 0.70) and length of ICU stay (P = 0.81) between the two groups; however, the delirium incidence in the B2 group was significantly higher than in B1 group (P = 0.04). (Table 2)

Table 1. Baseline characteristics of the patients

Characteristics	Stanford type A			Stanford type B		
	A1 (*N* = 48)	A2 (*N* = 37)	*P*	B1 (*N* = 36)	B2 (*N* = 28)	*P*
Age (years)	58±5	56±7	0.82	55±9	57±5	0.84
Gender (M/F)	34 (70.8)/14 (29.2)	26 (70.2)/11 (29.7)	0.96	24 (66.7)/12 (33.3)	17 (60.7)/11 (39.3)	0.62
Smoking history	25 (52.1)	18 (48.6)	0.75	15 (41.7)	12 (42.9)	0.92
Marfan syndrome	15 (31.2)	11 (29.7)	0.88	7 (19.4)	5 (17.9)	0.87
Hypertension	30 (62.6)	21 (56.8)	0.59	25 (69.4)	20 (71.4)	0.86
Diabetes	21 (43.8)	14 (37.8)	0.58	12 (33.3)	12 (42.9)	0.44
Cardiac insufficiency	2 (4.2)	1 (2.7)	0.71	0 (0)	0 (0)	1.00
Acute renal injury	18 (37.5)	14 (37.8)	0.98	3 (8.3)	1 (3.5)	0.44
Depression	0 (0)	0 (0)	1.0	0 (0)	0 (0)	1.00
Tumor history	0 (0)	1 (2.7)	0.25	0 (0)	0 (0)	1.00
Mechanical ventilation	42 (87.6)	36 (97.3)	0.43	32 (88.9)	23 (88.5)	0.44
Pulmonary infection	12 (25.0)	10 (27.0)	0.83	1 (2.8)	0 (0)	0.37
Surgical treatment						
Total arch replacement	8 (16.7)	6 (16.2)	0.78	0 (0)	0 (0)	1.00
Stented elephant trunk	20 (41.7)	13 (35.1)	0.66	0 (0)	0 (0)	1.00
Bentall procedure	12 (25.0)	15 (40.5)	0.34	0 (0)	0 (0)	1.00
David procedure	8 (16.7)	3 (8.1)	0.41	0 (0)	0 (0)	1.00
Endovascular stent-graft exclusion	0 (0)	0 (0)	1.00	25 (69.4)	20 (71.4)	0.85
Conservative treatment	0 (0)	0 (0)	1.00	11 (30.6)	8 (28.6)	0.88

Table 2. Mortality rate, ICU stay and delirium incidence

	Stanford type A			Stanford type B		
	A1 (*N* = 48)	A2 (*N* = 37)	*P*	B1 (*N* = 36)	B2 (*N* = 28)	*P*
Delirium incidence, n (%)	10 (20.8)	9 (24.3)	0.70	1 (2.8)	5 (17.8)	0.04
Mortality rate, n (%)	7 (14.6)	6 (16.2)	0.83	2 (5.6)	1 (3.6)	0.70
ICU stay (days)	6±1	7±1.2	0.67	3±1.3	4±1.1	0.81

Use of anti-hypertensive drugs: The use of anti-hypertensive drugs in the A1 group was significantly lower than in the A2 group ($P = 0.04$), but comparable between the B1 and B2 groups ($P = 0.13$), although fewer patients in the B1 group used anti-hypertensive drugs as compared with those in the B2 group. (Table 3)

Use of morphine: The dose of morphine used was 0.1 (0-0.2) mg/kg in the A1 group and 0.2 (0.1-0.3) mg/kg in the A2 group, indicating a significant difference between the two groups ($P = 0.02$). Meanwhile, the dose of morphine used in the B1 group was 0.1 (0-0.2) mg/kg and 0.1 (0.025-0.2) mg/kg in the B2 group, showing no significant difference between the two groups ($P = 0.13$). (Table 4)

DISCUSSION

The present study found that continuous DEX infusion reduced the use of anti-hypertensive drugs and analgesics in Stanford type A AD patients and decreased the delirium incidence in Stanford type B AD patients.

Rupture of the aortic dissecting aneurysm is the main cause of mortality in AD patients. BP management, analgesia, sedation and immobilization are effective methods for preventing this situation [Fukui 2018]. However, effective BP management is generally difficult to achieve by use of a single anti-hypertensive drug, and combined application of 2-3 anti-hypertensive drugs is generally required for most

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Table 3. Use of anti-hypertensive drugs

	Stanford type A			Stanford type B		
	A1 (*N* = 48)	A2 (*N* = 37)	*P*	B1 (*N* = 36)	B2 (*N* = 28)	*P*
Using multiple anti-hypertensive drugs, n	13 (27.1)	18 (48.6)	0.04	9 (25.0)	12 (42.9)	0.13
Using single anti-hypertensive drugs (n)	35 (72.9)	19 (51.4)	-	27 (75.0)	16 (57.1)	-

Table 4. Use of morphine (mg/kg)

	Stanford type A			Stanford type B		
	A1 (*N* = 48)	A2 (*N* = 37)	*P*	B1 (*N* = 36)	B2 (*N* = 28)	*P*
Dose of morphine	0.1 (0-0.2)	0.2 (0.1-0.3)	0.02	0.1 (0-0.2)	0.1 (0.025-0.2)	0.13

patients [Guerrero-Garcia 2018]. The current study showed that DEX administration in patients with Stanford type A AD significantly reduced the use of anti-hypertensive drugs and the required morphine dose. In addition to its sedative effect, DEX is a highly selective α2 adrenergic agonist which could effectively inhibit the production of stress-related catecholamine [Chen 2020], and also exert a synergistic effect with opioids, thus reducing the dose of sedatives and attenuating the impact of morphine on respiration [Xu 2016]. Although this phenomenon was not observed in Stanford type B AD patients, we speculate that it may be because the incidence of pain and the dosage of antihypertensive drugs in Stanford type B AD patients were lower than in type A AD patients.

Previous studies have demonstrated that DEX can reduce the delirium incidence in critically ill patients [Shehabi 2019; Shi 2019; Skrobik 2018]. However, we found that this effect in Stanford type A AD patients was not so obvious as in Stanford type B AD patients, and the specific mechanism may need to be further studied in the future. In view of the current knowledge about AD, it may be associated with the unique characteristics of this disease. First, the tearing of Stanford type A AD could affect the ascending aorta and the three vessels of the aortic arch, which could influence the cerebral blood flow and increase the delirium incidence. Second, the duration of extracorporeal circulation is prolonged in patients with Stanford type A AD, in whom the incidence of postoperative cerebral complications is as high as 17.2% [Conzelmann 2012; Merkle 2019]. Although using brain-protecting technologies (e.g., deep hypothermic circulatory arrest and selective antegrade cerebral perfusion) could reduce cerebral damage, brain-related complications, including transient brain dysfunction, could not be completely prevented. Delirium is the most common clinical manifestation of transient brain dysfunction, with an incidence as high as 15%-33.6% after operation [Liu 2017; Shi 2019], which is consistent with the delirium incidence (22.4%) in our study. Previous studies have demonstrated that DEX could reduce the incidence and course of delirium [Shehabi 2009]. As we did not record the duration of delirium in some patients in this study, no related analysis could be conducted, and prospective studies are required to address this issue. We found that DEX could reduce delirium occurrence in Stanford type B AD cases without affecting the use of anti-hypertensive drugs and morphine dose. This also may be associated with the characteristics of this disease. For instance, the tearing of Stanford type B AD occurs at the distant left subclavian artery, making this disease type not as dangerous as Stanford type A AD, with lower rates of incidence of tearing pain, rupture, and bleeding compared with Stanford type A AD.

Hypotension and bradycardia are the major adverse reactions after administration of DEX at the recommended dose of ≤1.4μg/(kg4u) [Keating 2015]. The highest maintenance dose of DEX in this study was 1.0μg/ (kg·h). As shown above, 18 patients had MAP <60 mmHg within 30 min of DEX administration, including 16 Stanford type A AD cases. HR was not overly changed after discontinuation of the DEX treatment in these patients. However, the preoperative levels rapidly were restored after fluid expansion, suggesting that the observed changes might be associated with insufficient blood volume. Intraoperative blood loss and postoperative blood oozing easily could induce insufficient blood volume in AD patients. Therefore, sufficiently increasing blood volume by DEX administration effectively could prevent rapid BP dropping.

There some limitations in this study. First, it is a single-center retrospective study with inherent shortcomings. Second, the sample size was relatively small, and ICU stay was not long enough. Therefore, time-effectiveness and delayed responses in patients administered with DEX could not be analyzed. Third, whether discontinuation of DEX therapy would increase the use of other drugs and the delirium incidence need to be verified. Further studies also are required to investigate whether DEX could stabilize the circulation, reduce stress reactions, and prolong patient survival for surgical treatment.

In summary, the use of DEX reduced the incidence of delirium in patients with type B AD during ICU stay, which could also prevent the occurrence of medical accidents caused

by delirium in such patients. Although the use of DEX did not seem to affect the incidence of delirium in patients with Stanford type A AD, it could decrease the use of antihypertensive drugs and morphine in these patients, probably through its synergistic effect with these drugs.

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