Journal of Clinical Anesthesia 75 (2021) 110498

Contents lists available at ScienceDirect

Journal of Clinical Anesthesia

journal homepage: www.elsevier.com/locate/jclinane

Original Contribution

Dexmedetomidine reduces acute kidney injury after endovascular aortic repair of Stanford type B aortic dissection: A randomized, double-blind, placebo-controlled pilot study

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ARTICLE INFO

Keywords:
Endovascular aortic repair
Stanford type B aortic dissection
Dexmedetomidine
Acute kidney injury
Renal function

ABSTRACT

Study objective: To determine the effect of dexmedetomidine on acute kidney injury (AKI) following endovascular aortic repair (EVAR) for Stanford type B aortic dissection (TBAD).
Design: Randomized, double-blind, placebo-controlled, pilot study.
Setting: University Hospital.
Patients: 102 TBAD patients undergoing EVAR procedures were enrolled. Patients with dissection involving aortic arch or renal artery were excluded.
Interventions: Patients were randomly assigned, in a 1:1 ratio, to a dexmedetomidine group (intravenous dexmedetomidine 0.4 μg/kg/h immediately after anesthesia induction and 0.1 μg/kg/h after extubation, which was maintained until 24 h) or a normal saline control group.
Measurements: The primary outcome was the incidence of AKI within the first two days after surgery, based on the Acute Kidney Injury Network (AKIN) criteria. The secondary outcomes included serum cystatin C and estimated glomerular filtration rate on postoperative days 1, 2, and 7, and in-hospital need for renal replacement therapy (RRT). Long-term outcomes included RRT and all-cause mortality.
Main results: Ninety-eight patients completed the study (dexmedetomidine, $n = 48$; control, $n = 50$). AKIN stage 1 AKI occurred in 3/48 (6.3%) patients receiving dexmedetomidine, compared with 11/50 (22%) patients receiving normal saline (odds ratio = 0.24, 95% CI: 0.07 to 0.89, $P = 0.041$). This difference remained significant after adjusting for baseline covariates (adjusted odds ratio = 0.21, 95% CI: 0.05 to 0.84; $P = 0.028$). Dexmedetomidine led to a lower serum cystatin C on postoperative day 1 (median [IQR] mg/L: 1.31 [1.02–1.72] vs. 1.58 [1.28–1.96]). There were no between-group differences in other secondary or long-term outcomes. During the follow-up (median = 28.4 months), 1 patient in the dexmedetomidine group and 3 patients in the control group required RRT.
Conclusions: Dexmedetomidine reduced the incidence of AKI in TBAD patients after EVAR procedures. The long-term benefits of dexmedetomidine in this patient population warrant further investigation.
Trial registration: ChiCTR-IPR-15006372.

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https://doi.org/10.1016/j.jclinane.2021.110498
Received 22 April 2021; Received in revised form 23 August 2021; Accepted 29 August 2021
Available online 3 September 2021

1. Introduction

Stanford type B Aortic Dissection (TBAD) is a life-threatening disease, with a 5-year mortality rate of 30%–40% [1,2]. The prevalence of TBAD is approximately 3 per 100,000 people annually [3]. Endovascular aortic repair (EVAR) with a stent graft is increasingly performed to treat TBAD, which is less invasiveness and leads to a lower mortality rate when compared to a conventional surgical approach [4,5]. During EVAR procedures, surgical stress, inflammatory responses, and the use of iodinated contrast medium may increase the risk of postoperative acute kidney injury (AKI) [6]. Studies reported that the incidence of AKI after EVAR procedures was about 15%–20%, which was associated with a decreased long-term survival and compromised quality of life after surgery [7,8]. The prevention and treatment for renal dysfunction following EVAR procedures remain challenging.

Dexmedetomidine is a highly selective α2 adrenoreceptor agonist which produces sedation, analgesia, and hemodynamic stabilization by reducing the sympathetic tone [9,10]. Pre-clinical studies showed that dexmedetomidine protected against renal ischemia-reperfusion injury by inhibiting inflammatory responses, suppressing apoptosis, and attenuating oxidative stress [11,12]. A clinical study suggested that dexmedetomidine alleviated AKI and suppressed the decline of post-bypass estimated glomerular filtration rate (eGFR) in cardiac surgical procedures [13]. In addition, a recent randomized controlled trial reported that dexmedetomidine reduced the incidence of AKI after aortic surgery and reduced the length of hospital stay [14]. However, the impact of dexmedetomidine on renal outcomes after EVAR procedures for TBAD patients has yet to be elucidated.

Therefore, this study was designed to investigate the effects of perioperative dexmedetomidine administration on postoperative AKI after EVAR procedures for TBAD patients. We hypothesized that a 24-h dexmedetomidine treatment would reduce the incidence of AKI and improve renal outcomes in TBAD patients undergoing EVAR procedures.

2. Methods

2.1. Study design

This investigator-initiated, randomized, double-blind, placebo-controlled trial was approved by the Institutional Review Board of The First Affiliated Hospital of Soochow University (IRB No. 2015–026) and written informed consent was obtained from all participants. The trial was registered at the Chinese Clinical Trial Registry (No. ChiCTR-IPR-15006372, Date of registration: May 10, 2015) prior to patient enrollment. The study was conducted according to the guidelines of the Consolidated Standards of Reporting Trials (CONSORT).

2.2. Inclusion and exclusion criteria

The inclusion criteria of this study were patients ≥18 years with American Society of Anesthesiologists physical (ASA) status III, who were diagnosed as TBAD with lesions in the descending thoracic aorta and/or abdominal aorta and scheduled to undergo elective EVAR procedures. The diagnosis of TBAD was according to preoperative computed tomography angiography (CTA) imaging, which was confirmed by aortic digital subtraction angiography (DSA) in the operating room at the beginning of the procedures.

The exclusion criteria included sick sinus syndrome, severe bradycardia (heart rate [HR] < 50 beats/min), left ventricular ejection fraction <30% or heart failure, atrioventricular block, allergy to α2 adrenoreceptor agonist, lesions involving aortic arch or renal artery, or refusal to participate. If the approach was changed to another surgical procedure (open surgery and/or need for fenestrated or branched stent), the patient was also excluded.

2.3. Randomization and blinding

An independent anesthesia assistant performed the online randomization with a 1:1 ratio and permuted block sizes of 2 and 4. According to the randomly generated sequence, patients were randomly assigned to either a dexmedetomidine group or a control group. The allocation concealment was guaranteed using identical opaque sealed envelopes. An independent anesthesia nurse prepared the study medications, either dexmedetomidine or normal saline, according to the random codes. The study medications were stored in identical 50 mL syringes and placed in bags that were labelled with the patient numbers only. The patients, anesthesiologists, postoperative observers, and other medical staff were all unaware of the group allocation until the final analysis was completed.

2.4. Anesthesia

Patients did not receive sedative or analgesic medications preoperatively. In the operating room, a standard monitoring included electrocardiography, noninvasive cuff blood pressure, pulse oximetry, and temperature. Patients received bispectral index (BIS, Aspect Medical Systems, Newton, MA) monitoring. After the placement of radial artery line under local anesthesia, radial artery pressure was continuously monitored. In addition, stroke volume (SV), stroke volume variation (SVV), and cardiac output (CO) were monitored using the FloTrac/Vigileo system (Edwards Lifesciences, Irvine, CA).

General anesthesia was induced with propofol 1.5 mg/kg, sufentanil 0.4 μg/kg, and cisatracurium 0.2 mg/kg in this sequence. After endotracheal intubation, a controlled mechanical ventilation was conducted with a tidal volume of 8 mL/kg and a respiratory rate of 12–15 times/min, which aimed to maintain the end-tidal carbon dioxide at 35–45 mmHg and pulse oxygen saturation ≥ 95%. The fraction of inhaled oxygen was 40% in air. General anesthesia was maintained with 1%–3% sevoflurane inhalation, with a continuous measurement of end-tidal sevoflurane concentration. The depth of anesthesia was adjusted to BIS values within 40–60. The BIS-guided anesthesia together with anesthetic-gas concentration measurement is routinely used in our patients undergoing major surgery, for the purpose of providing a better anesthesia care during surgery. Additional doses of sufentanil and cisatracurium were given intraoperatively if necessary. The nasopharyngeal temperature was maintained within 36–37 °C using a warming blanket. Iodixanol injection solution (Visipaque, GE Healthcare Ireland, Cork, Ireland) was used as the contrast medium for all patients. Intravenous ondansetron 4 mg was administered for prophylaxis of postoperative nausea and vomiting. Following the EVAR procedures, patients were transferred to a cardiovascular intensive care unit (ICU) where they were weaned and extubated. Patients received a continuous hemodynamic monitoring including electrocardiography, noninvasive cuff blood pressure, radial artery pressure, SV, SVV, and CO until discharge from the ICU.

2.5. Study interventions

For the dexmedetomidine group, intravenous dexmedetomidine was given at a rate of 0.4 μg/kg/h, which was started immediately after anesthesia induction and then decreased to 0.1 μg/kg/h after tracheal extubation in the ICU. The dexmedetomidine treatment maintained for a total of 24 h. The dosing regimen of dexmedetomidine in this study was based on the previous studies [15,16], and it is generally within the current clinical norms. For the control group, normal saline was given in the same fashion as dexmedetomidine.

2.6. Hemodynamic management

All patients received a goal-directed fluid therapy until the end of mechanical ventilation. The aim of this fluid therapy was to maintain the

SVV < 10% using Lactated Ringer's solution together with hydroxyethyl starch 6% 130/0.4 boluses, which has been utilized in our patients undergoing major non-cardiac surgery [17]. Hypotension was defined as mean arterial pressure (MAP) < 65 mmHg or ≥ 20% reduction in MAP from baseline, and bradycardia was defined as HR < 50 beats/min. Hypertension was defined as systolic blood pressure > 160 mmHg, and tachycardia was defined as HR > 100 beats/min. Intraoperative hypotension was treated with intravenous ephedrine 6–10 mg or phenylephrine 50–100 μg, and bradycardia was treated with intravenous atropine 0.5 mg. Postoperative hemodynamic events (including hypotension, hypertension, tachycardia, and bradycardia) with interventions in the ICU were recorded. Interventions for hypotension included norepinephrine infusion and/or intravenous fluids, and intervention for bradycardia was use of atropine. Interventions for hypertension and tachycardia included use of nicardipine, urapidil, nitroglycerin, or esmolol. If severe hypotension or bradycardia persisted after interventions, the study intervention was stopped and unmasking of the group allocation occurred.

2.7. AKI prevention strategy

The risk of postoperative AKI was evaluated preoperatively using the Acute Kidney Injury Risk Index. This index was based on the number of risk factors: age ≥ 56 years, male sex, congestive heart failure, hypertension, diabetes mellitus-oral or insulin therapy, emergency surgery, abdominal surgery, ascites, and renal insufficiency-mild or moderate (preoperative serum creatinine >106.1 μmol/L [18]. The Acute Kidney Injury Risk Index classes range from I to V: class I (0, 1, or 2 risk factors), class II (3 risk factors), class III (4 risk factors), class IV (5 risk factors), and class V (≥ 6 risk factors). A preoperative class ≥ III indicates a moderate to high risk of AKI postoperatively [19].

To prevent postoperative renal dysfunction in our patients, we implemented a bundle of perioperative care, including (1) optimization of hemodynamic status using the SVV-based goal-directed fluid therapy, (2) prevention and timely interventions for both hypotensive and hypertensive episodes, (3) discontinuation of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers therapy in the morning of surgery, (4) avoidance of nonsteroidal anti-inflammatory drugs, (5) avoidance of nephrotoxic antibiotics such as aminoglycosides, (6) maintenance of normoglycemia, (7) diuretics not used for the purpose of renal protection, but only for treatment of fluid overload or edema symptoms, (8) use of a minimal contrast volume by using automated contrast injectors and small catheters, and (9) perioperative monitoring of serum creatinine, serum cystatin C, and urine output.

2.8. Study outcomes

The primary outcome was the incidence of AKI that occurred on postoperative day (POD) 1 or 2, based on the Acute Kidney Injury Network (AKIN) criteria [20]. Serum creatinine levels were assessed at 10:00 am on POD 1 and 2, and urine output was measured hourly through the urinary catheter. For patients with AKI, serum creatinine was monitored daily or more frequently when needed. The secondary outcomes included serum cystatin C and eGFR measured on POD 1, 2, and 7, and in-hospital need for renal replacement therapy (RRT). The eGFR was estimated using the Chronic Kidney Disease Epidemiology Collaboration equation (http://ckdepi.org/equations/gfr-calculator/) [21].

Other outcomes included the incidences of in-hospital complications (stroke, pneumonia, cognitive dysfunction, deep venous thrombosis, and mesenteric venous thrombosis), length of ICU stay, length of postoperative hospital stay, 30-day need for RRT, and 30-day mortality. Postoperative cognitive dysfunction was assessed twice daily (8:00 and 20:00) during the hospitalization by trained physicians using the Mini-Mental State Examination tool [22]. The definitions of postoperative complications are shown in Supplementary Table 1.

Long-term follow-up was carried out via telephone and by reviewing electronic medical records until May 30, 2021. Long-term outcomes included need for RRT after hospital discharge and all-cause death.

2.9. Perioperative data

The perioperative data included the incidence of intraoperative hypotension and bradycardia, medications for intraoperative hemodynamic events, intraoperative fluid infusion and urine output, intraoperative sufentanil consumption, serum lactic acid at the end of surgery, dose of contrast medium, SVV and CO values at the end of surgery and at the end of mechanical ventilation, duration of surgery, time to extubation, and the incidence of hemodynamic events with interventions in the ICU.

2.10. Sample size calculation

The sample size was calculated a priori using the PASS software (version 11.0.7; NCSS, Kaysville, UT, USA). Our preliminary data showed that 18.2% TBAD patients without receiving dexmedetomidine experienced AKI after EVAR procedures, which is in line with the recent literature [8]. Studies suggested that dexmedetomidine reduced the incidence of AKI after cardiac surgery (a 17% reduction from 33% to 14%) [15] or after cardiac angiography (a 26.7% reduction from 36.7% to 10%) [23]. The therapeutic effect of dexmedetomidine on AKI after EVAR procedures for TBAD is unknown. Based on these reports and our previous data, we hypothesized that the dexmedetomidine treatment would lead to a 15% reduction in the AKI incidence in our patients. To detect such a difference with a statistical power of 80% at a one-sided α level of 0.05 (H1: P1 [treatment group proportion] < P2 [control group proportion]), we estimated that 44 patients in each group would be needed. Considering a possible dropout rate of 15%, we finally allocated 102 patients, with 51 in each group.

2.11. Statistical analysis

Normal distribution of data was assessed using the Kolmogorov–Smirnov test. Continuous variables are expressed as mean ± standard deviation (SD) or median (interquartile range, IQR), and categorical variables are presented as number of patients (percentage). Data were analyzed using independent *t*-test, Mann-Whitney *U* test, Chi-squared test, or Fisher exact test, as appropriate. The effect size of dexmedetomidine vs. normal saline control was assessed using the odds ratio (OR) or difference with 95% confidence interval (CI).

In addition, we conducted several post hoc analyses: (1) the changes of serum cystatin C from baseline to POD 1, 2, and 7; (2) the number of patients with eGFR decrease >25%, 50%, or 75% from baseline to POD 1, 2, and 7; (3) long-term outcomes (need for RRT and all-cause mortality); (4) AKI incidence, changes of serum cystatin C, number of patients with eGFR decrease, and long-term outcomes were adjusted for baseline covariates (hypertension, diabetes, serum creatinine, eGFR, and serum cystatin C) using multivariate logistic regression or generalized linear model; and (5) subgroup analysis for the incidence of AKI, according to age, hypertension history, lesion location, and hydroxyethyl starch use.

All analyses were performed based on the modified intent-to-treat population, including all randomized patients who had undergone their EVAR procedures and received the study treatment. We expected that missing data would be uncommon in this study, and imputation of missing data was not planned. Statistical analyses were conducted using the SPSS software (version 19.0; IBM SPSS, Chicago, IL, USA), and graphs were plotted using the GraphPad Prism software (version 9.00; GraphPad, San Diego, CA, USA). All tests were two-sided, with a *P* value <0.05 indicating a statistically significant difference.

3. Results

3.1. Study flow

From December 2016 to October 2020, a total of 110 patients were screened for eligibility. Of 8 patients who were excluded after screening, 5 patients did not meet the eligibility criteria (3 with dissection lesions affecting renal artery in the preoperative CTA imaging, 1 having second degree atrioventricular block, and 1 requiring emergent surgery), and 3 patients declined to participate. Of 102 patients randomized, surgical procedures were switched in 3 patients (undergoing open surgery and/or need for fenestrated or branched stent), and 1 patient withdrew the consent before anesthesia. Finally, 98 patients completed this study (dexmedetomidine, $n = 48$; control, $n = 50$). Unmasking of group allocation did not occur. All patients received single stent EVAR procedures to treat TBAD. Three patients in the dexmedetomidine group and 4 patients in the control group were lost to follow-up after hospital discharge, leaving 91 patients with their long-term data available for analysis (dexmedetomidine, $n = 45$; control, $n = 46$) (Fig. 1).

3.2. Patient characteristics

Patients' demographics and baseline characteristics are shown in Table 1. The mean age was 58.7 years old in the dexmedetomidine group and 60.5 years old in the control group. Most patients (about 84%) were male sex. A higher number of patients in the control group than in the dexmedetomidine group had history of hypertension (72% vs. 60.4%) and diabetes (10% vs. 8.3%), without having significant between-group differences. All patients were at ASA status III. Based on the Acute Kidney Injury Risk Index classification, 10.4% of patients in the dexmedetomidine group and 6% of patients in the control group were at class III, and no patients were at class IV or V.

3.3. Perioperative data

The perioperative data are presented in Table 2. Compared with the control group, the dexmedetomidine treatment did not increase the incidence of intraoperative hypotension or bradycardia, or the percentage of patients requiring medications for those hemodynamic events. No patient had severe hypotension or bradycardia that persisted after interventions. The two groups are comparable in terms of intraoperative fluid infusion, urine output, sufentanil consumption, serum lactic acid at the end of surgery, dose of contrast medium, SVV and CO values, duration of surgery, and time to extubation. For postoperative hemodynamic events with interventions in the ICU, the two groups are also comparable, except that a lower number of patients in the

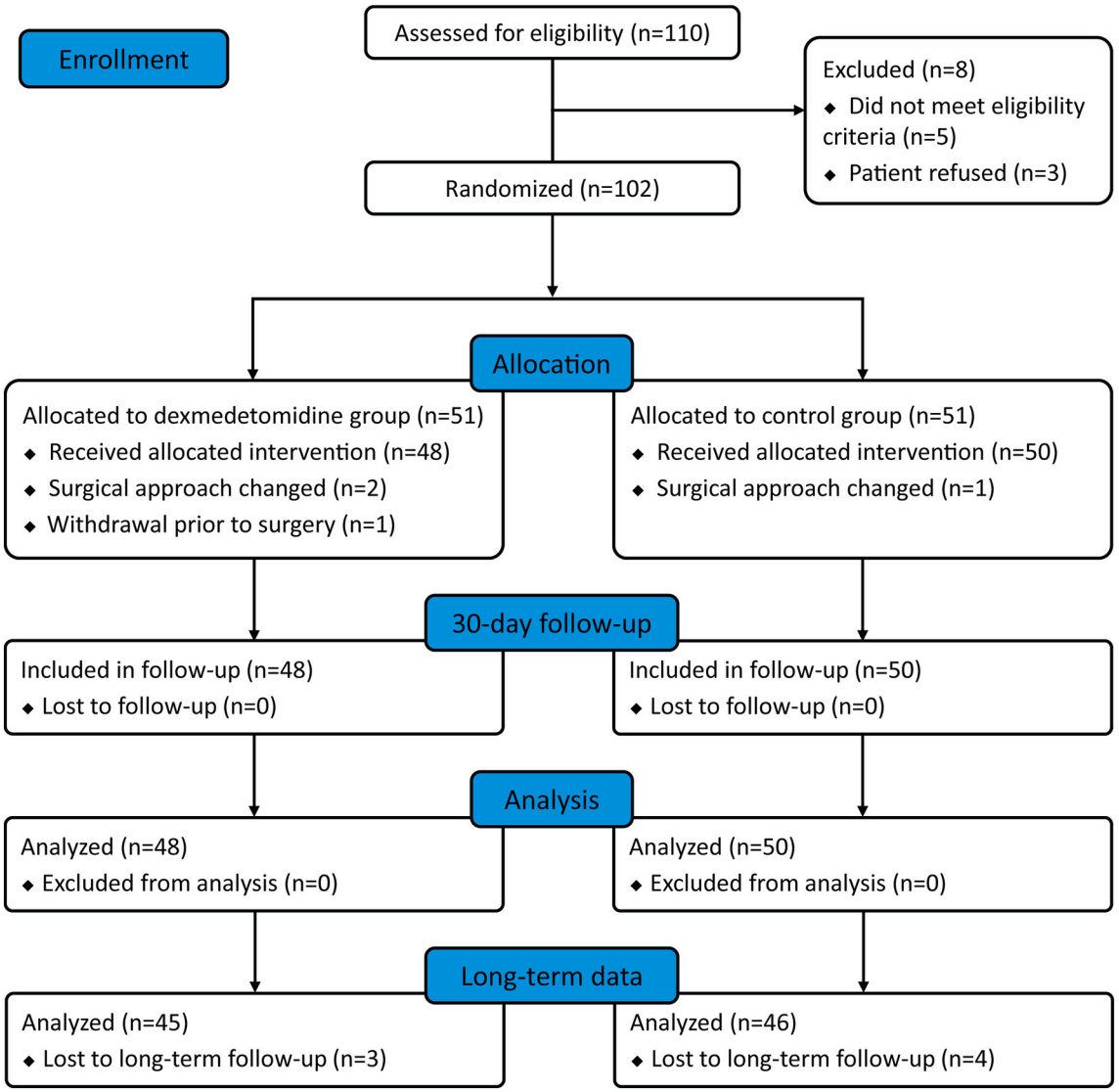

Fig. 1. CONSORT flowchart.

Table 1
Baseline characteristics.

	Dexmedetomidine (n = 48)	Control (n = 50)	P value
Demographics			
Age (years)	58.7 ± 11.4	60.5 ± 12.5	0.471
Female sex	8 (16.7%)	8 (16%)	0.929
Body mass index (kg/m^2)	25.2 ± 4.3	24.3 ± 3.3	0.221
Comorbidities			
Hypertension	29 (60.4%)	36 (72%)	0.225
Diabetes	4 (8.3%)	5 (10%)	1.000
Coronary artery disease	3 (6.2%)	3 (6%)	1.000
Cerebral vascular disease	2 (4.2%)	1 (2%)	0.613
Preoperative laboratory data			
Hemoglobin (g/L)	131.3 ± 15.4	128.3 ± 15.5	0.348
Lactic acid (mmol/L)	1.07 ± 0.29	1.11 ± 0.36	0.552
Serum creatinine (μmol/L)	79.6 ± 26.1	76.4 ± 20.7	0.504
eGFR (mL/min)	94.9 ± 23.2	91.8 ± 23.2	0.508
Serum cystatin C (mg/L)	1.23 ± 0.46	1.32 ± 0.49	0.355
Preoperative medication			
Calcium channel blockers	15 (31.2%)	18 (36%)	0.619
Beta blockers	4 (8.3%)	5 (10%)	1.000
Renin-angiotensin system inhibitors	14 (29.2%)	16 (32%)	0.761
Diuretics	3 (6.2%)	2 (4%)	0.674
Statins	7 (14.6%)	8 (16%)	0.846
Lesion location			
Descending thoracic aorta only	20 (41.7%)	24 (48%)	0.529
Abdominal aorta involved	28 (58.3%)	26 (52%)	
Acute Kidney Injury Risk Index class [a]			
I	29 (60.4%)	25 (50%)	0.282
II	14 (29.2%)	22 (44%)	
III	5 (10.4%)	3 (6%)	

Data are mean ± standard deviation or number of patients (percentage).
eGFR, estimated glomerular filtration rate.
[a] Acute Kidney Injury Risk Index class (I to V, with a higher class indicating a higher risk of AKI postoperatively).

dexmedetomidine group had hypertension requiring intervention than in the control group (33.3% vs. 58%). Hypotension and bradycardia with intervention in the ICU were uncommon in both groups. No patient needed transfusion perioperatively.

3.4. Primary outcome

AKI within the first postoperative two days occurred in 3 of 48 (6.3%) patients receiving dexmedetomidine infusion, compared with 11 of 50 (22.0%) patients receiving normal saline (OR = 0.24, 95% CI: 0.07 to 0.89; P = 0.041) (Table 3). All AKI patients were at AKIN stage 1. The details of diagnosis and duration of postoperative AKI are shown in Supplementary Table 2. Two patients and 5 patients (4.2% vs. 10%) showed AKI on POD 1, and 3 patients and 11 patients (6.3% vs. 22%) had AKI on POD 2, in the dexmedetomidine and control groups, respectively. The 7 AKI patients on POD 1 still experienced AKI on POD 2. Among 14 AKI patients on POD 2, one patient in the control group had both serum creatinine increase and urine output decrease, and no patient fulfilled the AKI definition according to urine output decrease alone. The median duration of AKI was 2 (IQR, 1–8) days and 3 (IQR, 2–6) days in the dexmedetomidine and control groups, respectively.

The subgroup analysis for the incidence of AKI is depicted in Fig. 2. For the effects of dexmedetomidine vs. control on the AKI incidence, there was no significant heterogeneity between the subgroups of age (< 60 y vs. ≥ 60 y), hypertension history (no vs. yes), lesion location (descending thoracic aorta only vs. abdominal aorta involved), or hydroxyethyl starch use (< 500 mL vs. ≥ 500 mL).

Table 2
Perioperative data.

	Dexmedetomidine (n = 48)	Control (n = 50)	P value
Intraoperative hemodynamic events			
Hypotension	20 (41.7%)	18 (36%)	0.565
Bradycardia	9 (18.8%)	5 (10%)	0.216
Medications for intraoperative hemodynamic events			
Ephedrine	14 (29.2%)	11 (22%)	0.416
Phenylephrine	12 (25%)	10 (20%)	0.553
Atropine	9 (18.8%)	5 (10%)	0.216
Intraoperative fluids and urine output			
Lactated Ringer's solution (mL)	830 (600–1000)	800 (600–1000)	0.878
Hydroxyethyl starch 6% 130/0.4 (mL)	480 (400–520)	480 (380–510)	0.781
Urine output (mL/h)	150 ± 66	132 ± 58	0.150
Intraoperative sufentanil (μg/kg)	0.67 ± 0.22	0.71 ± 0.20	0.356
Serum lactic acid at the end of surgery (mmol/L)	1.10 ± 0.32	1.14 ± 0.36	0.562
Contrast medium (iodixanol, mL/kg)	2.35 ± 0.46	2.43 ± 0.44	0.361
SVV at the end of surgery (%)	7.5 ± 2.4	6.8 ± 2.1	0.127
SVV at the end of mechanical ventilation (%)	8.2 ± 2.0	8.8 ± 3.2	0.271
CO at the end of surgery (L/min)	4.97 ± 0.88	4.81 ± 0.78	0.361
CO at the end of mechanical ventilation (L/min)	5.71 ± 1.11	5.65 ± 1.05	0.790
Duration of surgery (min)	120 ± 73	134 ± 80	0.394
Time to extubation (min)	79 (35–125)	76 (30–174)	0.884
Hemodynamic events in the ICU			
Hypotension with intervention	4 (8.3%)	3 (6%)	0.712
Bradycardia with intervention	1 (2.1%)	0 (0%)	0.490
Hypertension with intervention	16 (33.3%)	29 (58%)	0.014
Tachycardia with intervention	1 (2.1%)	6 (12%)	0.112

Data are mean ± standard deviation, median (interquartile range), or number of patients (percentage).
SVV, stroke volume variation; CO, cardiac output; ICU, intensive care unit.

3.5. Secondary and other outcomes

Serum level of cystatin C on POD 1 was significantly lower in the dexmedetomidine group than in the control group (1.31 [IQR, 1.02–1.72] mg/L vs. 1.58 [IQR, 1.28–1.96] mg/L; difference = −0.28 mg/L, 95% CI: −0.47 to −0.09 mg/L; P = 0.004) (Table 3, Supplementary Fig. S1A). However, serum creatinine did not differ on POD 1 between the two groups (Supplementary Fig. S1B). There were no between-group differences in the other secondary outcomes (Table 3). The dexmedetomidine group had a reduced length of postoperative hospital stay (10.0 ± 2.3 days vs. 11.1 ± 2.4 days). No patient needed RRT or died during postoperative 30 days.

3.6. Long-term outcomes and post hoc analyses

After adjusting for baseline covariates, the incidence of AKI was still significantly lower in the dexmedetomidine group than in the control group (adjusted OR = 0.21, 95% CI: 0.05 to 0.84; P = 0.028) (Table 4). The median changes of serum cystatin C on POD 1 was 0.14 (IQR, −0.06–0.45) mg/L and 0.40 (IQR, 0.09–0.71) mg/L in the dexmedetomidine and control groups, respectively. The between-group difference was −0.26 mg/L (95% CI: −0.45 to −0.08 mg/L; P = 0.005) in the unadjusted analysis, and was −0.28 mg/L (95% CI: −0.48 to −0.09 mg/

Table 3
Postoperative outcomes.

	Dexmedetomidine (n = 48)	Control (n = 50)	Odds ratio or difference (95%CI)	*P* value
Primary				
Acute kidney injury	3 (6.3%)	11 (22%)	0.24 (0.07 to 0.89)	0.041
Secondary				
Serum cystatin C at POD 1 (mg/L)	1.31 (1.02–1.72)	1.58 (1.28–1.96)	−0.28 (−0.47 to −0.09)	0.004
Serum cystatin C at POD 2 (mg/L)	1.36 (1.19–1.73)	1.53 (1.26–2.07)	−0.15 (−0.35 to 0.01)	0.073
Serum cystatin C at POD 7 (mg/L)	1.21 (1.00–1.53)	1.35 (1.02–1.61)	−0.08 (−0.25 to 0.09)	0.358
eGFR at POD 1 (ml/min)	91.3 ± 20.7	85.4 ± 23.2	5.85 (−2.98 to 14.68)	0.192
eGFR at POD 2 (ml/min)	88.5 ± 21.7	82.2 ± 24.2	6.23 (−3.00 to 15.48)	0.183
eGFR at POD 7 (ml/min)	94.3 ± 20.3	88.3 ± 22.2	6.01 (−2.55 to 14.57)	0.167
In-hospital need for RRT	0 (0%)	0 (0%)	–	1.000
Other				
Stroke	1 (2.1%)	1 (2%)	1.04 (0.06 to 17.15)	1.000
Pneumonia	3 (6.2%)	4 (8%)	0.77 (0.16 to 3.62)	1.000
Cognitive dysfunction	2 (4.2%)	6 (12%)	0.32 (0.06 to 1.67)	0.269
Deep venous thrombosis	2 (4.2%)	1 (2%)	2.13 (0.19 to 24.30)	0.613
Mesenteric venous thrombosis	0 (0%)	1 (2%)	0 (0 to 9.38)	1.000
Length of ICU stay (day)	2 (1–2)	2 (1–2)	0 (0 to 0)	0.674
Length of postoperative stay (day)	10.0 ± 2.3	11.1 ± 2.4	−1.1 (−2.05 to −0.15)	0.024
In-hospital mortality	0 (0%)	0 (0%)	–	1.000
30-day need for RRT	0 (0%)	0 (0%)	–	1.000
30-day mortality	0 (0%)	0 (0%)	–	1.000

Data are mean ± standard deviation, median (interquartile range), or number of patients (percentage).
POD, postoperative day; eGFR, estimated glomerular filtration rate; RRT, renal replacement therapy; ICU, intensive care unit.

L; $P = 0.004$) after adjustment. The dexmedetomidine group had a lower number of patients with eGFR decrease >25% on POD 1 (2 of 48 vs. 5 of 50) and POD 2 (3 of 48 vs. 9 of 50). No patient had eGFR decrease >50% or 75%.

To assess the long-term outcomes, patients were followed-up for a median of 28.4 (IQR, 16.2–40.5) months. There were no significant between-group differences in need for RRT or all-cause mortality (Table 4). All 3 patients requiring RRT in the control group were diagnosed with postoperative AKI after the EVAR procedures. During the follow-up period, 1 patient in each group died of cancer, 1 patient in the dexmedetomidine group died of gastrointestinal hemorrhage, and 3 patients in the control group (including 2 cases who had postoperative AKI and needed RRT after hospital discharge) died due to infection, stroke, and unknown reasons. The details of deceased patients during the long-term follow-up are shown in Supplementary Table 3.

4. Discussion

In this study, the 24-hour dexmedetomidine treatment reduced the incidence of AKI in TBAD patients following EVAR procedures. In addition, the dexmedetomidine group had lower serum cystatin C and changes of serum cystatin C on POD 1 than in the control group. These between-group differences remained statistically significant after adjustment for baseline covariates. To the best of our knowledge, this is the first randomized controlled trial to suggest that dexmedetomidine could reduce the AKI incidence in TBAD patients undergoing EVAR procedures.

The deterioration of renal function following EVAR procedures has been reported previously [24–26]. The contrast medium containing iodixanol is a critical risk factor for postoperative renal dysfunction, leading to contrast-induced nephropathy [27–29]. Stress response and inflammation induced by surgical procedures further exacerbate renal dysfunction [30]. The American College of Radiology recommended the use of AKIN criteria for the diagnosis of contrast-induced nephropathy [31,32]. Therefore, postoperative AKI in our patients was assessed using the AKIN criteria. Owing to our AKI prevention strategy incorporating the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, all AKI patients in this study were at AKIN stage 1, and no patient developed severe AKI (stage 2 or 3). Our dexmedetomidine treatment for a total of 24 h led to a reduced occurrence of AKI events after EVAR procedures in TBAD patients. When using the Risk, Injury, Failure, Loss of kidney function, End-stage renal disease (RIFLE) criteria and utilizing GFR decrease >25% as a criterion for AKI, we also found a lower number of patients with GFR decrease >25% in the dexmedetomidine group on POD 1 and 2, but the between-group difference did not achieve a statistically significant level. However, a major limitation of the RIFLE criteria is that it underestimates the impact of a small increase in serum creatinine on postoperative morbidity and mortality [33]. Using the RIFLE criteria, the number of patients with AKI may be underestimated. To overcome this, the AKIN criteria which takes into account a small creatinine increase (≥ 0.3 mg/dL or 26.5 μmol/L) has been introduced and widely used [20].

Currently, AKI is diagnosed by assessing increased serum creatinine or decreased urine output. Several AKI diagnostic systems have been developed, including the RIFLE, AKIN, and KDIGO [6]. However, the identification and early intervention of AKI may be delayed, because detecting changes of serum creatinine or urine output has a relatively late diagnostic presentation. It is reported that any measurable increase in serum creatinine does not occur until more than half of active nephrons are damaged (GFR < 40 mL/min/1.73m^2) [34]. Over the recent years, several novel and specific biomarkers such as cystatin C and neutrophil gelatinase-associated lipocalin have emerged for early AKI detection [34–36]. Studies suggested that monitoring the concentration of serum cystatin C helped to identify the early stage of contrast-induced nephropathy [37,38]. In our study, 7 patients showed AKI on POD 1, and 14 patients had AKI on POD 2, based on serum creatinine increase using the AKIN criteria. The dexmedetomidine group had lower serum levels of cystatin C and changes of serum cystatin C on POD 1, while serum creatinine did not differ on POD 1 between the two groups. These results suggest that dexmedetomidine treatment alleviated renal dysfunction following EVAR procedures and that assessing serum levels of cystatin C exhibited an early diagnostic value.

Several meta-analyses have evaluated the renoprotective effects of dexmedetomidine after cardiac surgery. Peng, et al. reported that dexmedetomidine reduced the AKI incidence from 18.3% to 10.9% [39], Liu, et al. found AKI incidence decreasing from 12.3% to 8.6% [40], and Li, et al. showed AKI incidence in pediatrics decreasing from 38.8% to 23.9% [41]. In our study, dexmedetomidine reduced the incidence of AKI from 22% to 6.3% (i.e., a 15.7% reduction) after EVAR procedures for TBAD. It seems that dexmedetomidine could offer a stronger renal protective effect in this patient population. There are some explanations for our findings. First, studies showed that administration of contrast media reduced renal blood flow via enhancing intrarenal vasoconstriction and inhibiting vasodilation [42,43], whereas dexmedetomidine attenuates sympathy–adrenal hyperactivity, inhibits renin release, and

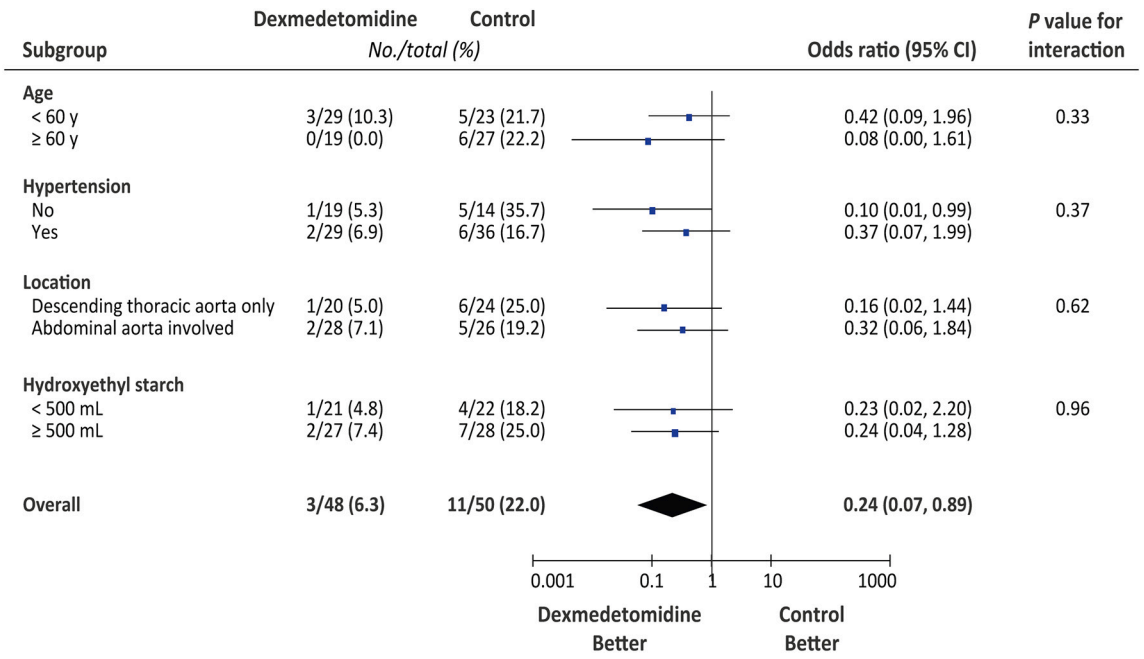

Fig. 2. Subgroup analysis for the incidence of AKI, according to age, hypertension history, lesion location, and hydroxyethyl starch use.

Table 4
Results of post hoc analyses.

	Dexmedetomidine (n = 48)	Control (n = 50)	Odds ratio or difference (95%CI)	*P* value	Adjusted odds ratio or difference (95%CI) [a]	Adjusted *P* value [a]
Primary outcome						
Acute kidney injury	3 (6.3%)	11 (22%)	0.24 (0.07 to 0.89)	0.041	0.21 (0.05 to 0.84)	0.028
Other renal outcomes						
Changes of serum cystatin C on POD 1 (mg/L)	0.14 (−0.06–0.45)	0.40 (0.09–0.71)	−0.26 (−0.45 to −0.08)	0.005	−0.28 (−0.48 to −0.09)	0.004
Changes of serum cystatin C on POD 2 (mg/L)	0.30 (0.01–0.43)	0.42 (0.11–0.68)	−0.12 (−0.32 to 0.01)	0.065	−0.16 (−0.32 to 0.01)	0.057
Changes of serum cystatin C on POD 7 (mg/L)	0.13 (−0.05–0.28)	0.17 (−0.13–0.40)	−0.04 (−0.16 to 0.14)	0.867	−0.02 (−0.17 to 0.13)	0.775
eGFR decrease >25% on POD 1	2 (4.2%)	5 (10%)	0.39 (0.08 to 2.01)	0.436	0.33 (0.06 to 1.90)	0.216
eGFR decrease >25% on POD 2	3 (6.3%)	9 (18%)	0.30 (0.08 to 1.06)	0.122	0.28 (0.07 to 1.13)	0.074
eGFR decrease >25% on POD 7	2 (4.2%)	2 (4%)	1.04 (0.16 to 6.87)	1.000	1.12 (0.14 to 8.74)	0.915
Long-term outcomes						
Renal replacement therapy	1 (2.2%) (n = 45)	3 (6.5%) (n = 46)	0.33 (0.02 to 2.28)	0.617	0.32 (0.03 to 3.39)	0.340
All-cause death	2 (4.4%) (*n* = 45)	4 (8.7%) (*n* = 46)	0.49 (0.09 to 2.21)	0.677	0.64 (0.09 to 4.45)	0.648

Data are median (interquartile range) or number of patients (percentage).
POD, postoperative day; eGFR, estimated glomerular filtration rate; CI, confidence interval.
[a] Adjusted for baseline covariates (hypertension, diabetes, serum creatinine, eGFR, and serum cystatin C) using multivariate logistic regression or generalized linear model.

promotes renal vasodilation, leading to an enhanced GFR and increased urine output [10,44,45]. Second, dexmedetomidine has been shown to effectively reduce the incidence of AKI from 36.7% to 10% (i.e., a 26.7% reduction) after cardiac angiography, suggesting a strong protective effect of dexmedetomidine against contrast-induced AKI [23]. Last, from the perspective of molecular mechanisms, pretreatment with an α2 adrenoreceptor agonist (dexmedetomidine or clonidine) protected against radiocontrast-induced nephropathy in mice, as reflected by reduced plasma creatinine, alleviation of renal tubular necrosis and apoptosis, and decreased cortical tubule vacuolization [46].

This 24-h dexmedetomidine treatment showed a favorable safety profile, without an increase in hypotension or bradycardia events during the EVAR procedures or in the ICU. We found that all hypotension and bradycardia episodes in our patients were transient. This is attributable to the relative low doses of dexmedetomidine used in this study without a loading dose. Dexmedetomidine administered at a loading dose (such as 1 μg/kg/h over 10 min) followed by a maintenance infusion is often used for sedation or monitored anesthesia care in diagnostic procedures. A loading dose of dexmedetomidine in general anesthesia may increase the risk of hypotension and bradycardia [47], whereas hypotension is a critical determinant of postoperative renal dysfunction [6]. Previous studies suggested that dexmedetomidine infusion at a rate of 0.4 μg/kg/h, without a loading dose, reduced the incidence of AKI after cardiac or aortic surgery [14,15]. Furthermore, postoperative dexmedetomidine administration at a low dose (i.e., 0.1 μg/kg/h) has been shown to enhance postoperative care through improving sleep quality and reducing delirium after non-cardiac surgery [16]. For these reasons, we used this dosing regimen of dexmedetomidine (i.e., 0.4 μg/kg/h and then 0.1 μg/kg/h) in our patients, without a loading dose.

After the EVAR procedures, medications are often needed to treat

hypertension in TBAD patients, and our results showed that the dexmedetomidine infusion reduced the proportion of patients who required interventions for hypertension in the ICU. A recent study suggests that the reduction of length of stay may be due to the reduction in delirium for patients undergoing major non-cardiac and cardiac surgery [48]. Although we found a reduction of one day of postoperative hospital stay associated with dexmedetomidine, there are many confounding variables affecting the length of stay in this study. Thus, whether dexmedetomidine could enhance postoperative recovery of TBAD patients after EVAR procedures needs further investigation.

This study has several limitations. First, patients were excluded if the dissection lesion involved aortic arch or renal artery or when the surgical procedure was changed. In addition, we only included patients with ASA status III, because patients with a poor preoperative status (ASA class $\geq$ IV) had a significantly worse outcome compared to patients with ASA class III (1-year survival rate, 28.6% vs. 92.6%) [49]. By doing so, we optimized the uniformity of patients in this study. However, we suggest that further studies are needed for patients with higher ASA class, lesion involving renal artery, decreased GFR, or renal dysfunction before surgery. Second, our study was powered for the primary outcome of postoperative AKI, so the current sample size precludes any firm statistical or clinical inferences for the secondary and long-term outcomes. Third, hydroxyethyl starch 6% 130/0.4 was used in the SVV-guided fluid therapy. While the effects of hydroxyethyl starch on renal function remain controversial [50,51], recent studies showed that modern hydroxyethyl starch 6% 130/0.4 as part of goal-directed fluid therapy was associated with better outcomes than a traditional or a crystalloid-based fluid therapy, without short- or long-term renal injury after major surgery [52–56]. Last, this study was conducted at a single center, and our perioperative care of keeping TBAD patients after EVAR procedures weaned and extubated in the ICU and having continuous SV and CO monitoring until ICU discharge is probably not the standard practice in many other institutions. Therefore, further studies are required to confirm the potential generalization of our findings and to determine the long-term benefits of dexmedetomidine in EVAR procedures for TBAD patients.

In conclusion, this pilot study suggests that perioperative dexmedetomidine treatment reduces the incidence of AKI following EVAR procedures in TBAD patients. Our findings justify a larger multicenter study to investigate the renoprotective benefits and long-term outcomes of dexmedetomidine in this patient population.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jclinane.2021.110498.

Declarations of interests

The authors declared no competing interests. The manufacturer of dexmedetomidine (Jiangsu Hengrui Medicine Co, Ltd., Jiangsu, China) had no role in the study design, data collection, statistical analysis, data interpretation, or manuscript preparation.

Funding

This study was supported by the National Natural Science Foundation of China (82072130 and 81873925 to FHJ), Natural Science Foundation of Jiangsu Province (BK20191171 to FHJ), and Science and Technology Development Plan Clinical Trial Project (SLT201909 to FHJ).

Acknowledgements

We would like to thank the patients, research assistants, anesthesia and surgical nurses, and all other healthcare providers for their support and participation in this study.

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