Journal of Clinical Anesthesia 40 (2017) 33–38

Contents lists available at ScienceDirect

Journal of Clinical Anesthesia

Original contribution

The effect of dexmedetomidine on renal function in patients undergoing cardiac valve replacement under cardiopulmonary bypass: A double-blind randomized controlled trial

Mingyu Zhai, MM [a,b], Fang Kang, MD [b], Mingming Han, MM [b], Xiang Huang, MM [b], Juan Li, PhD [a,b,*]

[a] School of Medicine, Shandong University, Ji nan, Shandong, China
[b] Department of Anesthesiology, Anhui Provincial Hospital, Anhui Medical University, Hefei, Anhui, China

ARTICLE INFO

Article history:
Received 11 December 2016
Received in revised form 29 March 2017
Accepted 31 March 2017
Available online xxxx

Keywords:
Dexmedetomidine
Cardiopulmonary bypass
Cardiac valve replacement
Acute kidney injury

ABSTRACT

Study objective: We attempted to explore the effect of Dex on renal function in patients with cardiac valve replacement under cardiopulmonary bypass (CPB).
Design: We designed a prospective, randomized, placebo-controlled, single-center, parallel-arm double-blind trial.
Setting: Operating room.
Patients: Seven-two eligible patients were randomly divided into Dex group and placebo group.
Interventions: Dexmedetomidine (Dex) (0.6 $\mu g \cdot kg^{-1}$) was administered in patients of Dex group at 15 min before anesthesia induction, followed by a treatment of 0.2 $\mu g \cdot kg^{-1} \cdot h^{-1}$ Dex until the end of operation. Patients in placebo group were treated with normal saline equally.
Measurements: The levels of serum urea nitrogen (BUN), creatinine (Cr), neutrophil gelatinase-associated lipocalin (NGAL), urine interleukin-8 (IL-18) and superoxide dismutase (SOD) activity were tested before anesthesia induction (T1) and after operation at 0, 12 h, 24 h and 72 h (T2–5). The urine output during operation and the post-operative complication of acute kidney injury (AKI) were recorded.
Main results: The levels of BUN and Cr were significantly increased at T5, and similar findings were found in the levels of NGAL and urine IL-18 at T3 and T4. The SOD activity was significantly declined at T2 and T3 in the two groups. The levels of BUN and Cr at T5 and the NGAL level at T3 and T4 were significantly lower in Dex group, comparable to placebo group. The intraoperative urine output was significantly increased and the postoperative incidence of AKI was significantly lower in Dex group.
Conclusions: Dex may attenuate the renal injury and decrease the incidence of AKI in patients undergoing cardiac valve replacement under CPB.

1. Introduction

Cardiac surgery under cardiopulmonary bypass (CPB), is the main cause for the abnormal physiological perfusion, thrombosis and local kidney ischemia hypoxia injury, which may progress to different degrees of acute kidney injury (AKI) [1,2]. AKI is a recognized complication following CPB and correlates with high mortality and postoperative care costs [3,4]. Renal protection should be considered during cardiac surgery with CPB, and optimization of perioperative medications may be an important strategy.

Dexmedetomidine (Dex), served as a highly selective α_2 adrenoceptor agonist, is characterized by sedation, analgesia and anxiolytic property. It has been shown that Dex has advantages in reducing anesthetic requirements, enhancing hemodynamic stability and providing sedation following cardiac surgery [5,6]. As its wide application in cardiac surgery under CPB, Dex has shown significant effect on reducing the postoperative lung and brain injury [7,8]. However, the safety and effect on of Dex for renal protection is controversial. Sugita et al. have reported that continuous infusion of Dex alleviates renal ischemia reperfusion injury in rat kidney [9], while Kari et al. have suggested that intravenous Dex does not show protective effect on the renal function but increases the urinary output. Whether Dex is able to attenuate the

* Corresponding author at: Department of Anesthesiology, The South District of Anhui Provincial Hospital, No.1 Swan Lake Road, Shushan District, Hefei, Anhui 230036, China.
E-mail address: lijuan0807@hotmail.com (J. Li).

http://dx.doi.org/10.1016/j.jclinane.2017.03.053
0952-8180/

renal injury in patients undergoing cardiac valve replacement under CPB remained to be solved.

In the present study, we designed the prospective study to explore the effect of Dex on kidney function in patients subjected to cardiac valve replacement under CPB.

2. Materials and methods

2.1. Study population

This clinical study was performed according to the consolidated standard of reporting of trials (CONSORT) guidelines. Approved was obtained from the Ethics Committee of Anhui Provincial Hospital, Anhui Medical University, and this study was registered at Chinese Clinical Trial Registry (ChiCTR) with the number of ChiCTR-TRC-14004832. All the included patients or their parents had signed the written informed consents before this study. Between February 2014 to December 2014, patients aged from 18 to 75 years with reduced physical status classified as ASA (American Society of Anesthesiologists) II or III and heart failure as NYHA (New York Heart Association) II or III were enrolled in this study. The eligible patients were subjected to cardiac valve replacement under CPB. The exclusion criteria contained patients with atrioventricular block, heart block, severe left ventricular dysfunction with left ventricular ejection fraction (LVEF) ≤ 40% and those treated with α_2-adrenoceptor agonist within two weeks before surgery. During the experimental period, the cases present with obvious kidney dysfunction (Cr ≥ 1.5 mg/dL, CysC < 1.1 mg/L and BUN > 9.0 mmol/L), hypertension III, and diabetes were also excluded.

2.2. Groups

The eligible patients were randomly assigned to two groups based on the computer generated random numbers, but they were blinded to the assigned group. At the operating room, the patients were anesthetized with intramuscular injection of morphine at 0.2 mg/kg (no >10 mg for each patient) by the same anesthesiologist who was blinded to this study design.

In the Dex group, patients received Dex intravenously at 0.6 $\mu g \cdot kg^{-1}$ over 15 min before anesthesia, and then injected with 0.2 $\mu g \cdot kg^{-1} \cdot h^{-1}$ Dex during the entire operation period. For the patients in placebo group, the 0.9% normal saline with the same volume was administered. All the drugs used were prepared by the same nurse who was blinded to the study design. The mean arterial pressure (MAP) of patient was monitored by the cannulation of left radial artery under local anesthesia. A double-lumen central venous catheter was cannulated to monitor central venous pressure (CVP) and collect blood samples. In addition, the administration of Ringer's solution at 8–10 mL/kg was performed for patients.

2.3. Surgery

Anesthesia was induced with 0.02 mg/kg midazolam, 0.6 μg/kg sufentanil, and 0.2 mg/kg etomidate. After tracheal intubation with 0.9 mg/kg rocuronium, mechanical ventilation was performed with FiO_2 70% to maintain the end-tidal carbon dioxide partial pressure at 35–45 mm Hg (1 kPa = 7.5 mm Hg). The target range of BIS (bispectral index) was 40–60 and the fluctuation of blood pressure was <20%.

All the operation procedures were performed by the same surgeon team, with the application of CPB machine Terumo-Sarns (Sarns Japanese Company, U.S. subsidiary of Terumo, USA) and Cobe membrane oxygenator (Sorin Corporation, Italy). The surgeries were performed under the standard hypothermic CBP (30–32 °C) with bicaval cannulation and left ventricular vent tube via the right superior pulmonary vein. During the CPB, the following parameters were maintained, such as ACT (activated clotting time) > 480 s, Hct 20–25%, perfusion flow rate 2.0–2.4 $L \cdot m^{-2} \cdot min^{-1}$, pH value of 7.35–7.45, $PaCO_2$ 35–45 mm Hg (1 kPa = 7.5 mm Hg), Hct 25%–30%, and rewarming rate of 0.20–0.25 °C/min. Dopamine and dobutamine infusions were applied to maintain the stable blood pressure after opening the ascending aorta.

2.4. The blood and urine parameters measurements

Blood samples (4 mL) were obtained from the right internal jugular vein at 5 different time points: before anesthesia induction (T1) and after aortic unclamping at 0 (T2), 12 h (T3), 24 h (T4), 72 h (T5). A small volume of the blood sample was used for red blood cell specific volume (Hct) measurement and the remaining for the detections of serum levels of creatinine (Cr), blood urea nitrogen (BUN), neutrophil gelatinase-associated lipocalin (NGAL) and the activity of superoxide dismutase (SOD). The concentrations of serum BUN and Cr were measured with OLYMPUS automatic biochemical analyzer according to the Sarcosine oxidase method. The protein levels of serum NGAL and urine IL-18 were assayed by enzyme-linked immunosorbent assay (ELISA) following the manufacture's instruction of the ELISA kit (Bioporto Company, Denmark and Shanghai Yueyan Institute of Biotechnology Ltd.). The activity of SOD was measured based on the Xanthine oxidase method (Nanjing Jiancheng Biological Pharmaceutical Co., Ltd.). The same reaction was performed in duplicate. During CPB process, the blood concentration of patient was diluted, which may affect the accuracy of measurement results. Thus, in this study, all the data were controlled by the individual Hct values (correction value = preoperative Hct / sample Hct × measured value).

2.5. Outcomes

After surgery, the surgery type such as mitral valve replacement (MVR), aortic valve replacement (AVR), double valve replacement (DVR) for patients were recorded, as well as the aortic clamping time, surgery duration, and CPB time. The drainage within 48 h post-operation, tracheal extubation time, the urine output during the entire period of surgery and at day 1 and day 2 post-operation were all measured.

The incidence of AKI was observed according to the diagnosis criteria of the Risk, Injury, Failure, Loss, and End-stage renal disease classification (RIFLE) [10]. Other adverse events, such as re-operation, cardiac arrest, liver function failure and persistent coma were also recorded.

2.6. Statistical analysis

The power analysis of the number of patients required in this study was performed using Stata software. All the data were expressed as mean ± SD (standard deviation) or numbers (percentages). Differences between groups were compared by using the independent *t*-test or Mann–Whitney rank sum test. Changes in the laboratory data were analyzed by two-way analysis of variance (ANOVA). All the *P* values were two sided, and $P < 0.05$ was considered statistically significant. All the data manipulations and statistical analyses were conducted with the application of SPSS software version 18.0.

3. Results

The power analysis suggested that the number of patients was calculated to be 31 in each group, when alpha = 0.0500 and power = 0.8000. Finally, 72 patients were included in our study and the eligible patients were randomly divided into the Dex and placebo group ($n = 36$/each group). All the patients received the planned surgical procedure and no patients withdrew from the study (Fig. 1). After CPB, 7 cases in Dex group and 8 cases in placebo group received dopamine treatment. In addition, 3 cases in each group were subjected to dobutamine infusion to maintain the stable blood pressure. As shown in Table 1, the mean age of patients in Dex and placebo group was 45 ± 10 and 47 ± 11 years old, respectively. The male patients accounted for 44.4% in placebo group and 47.2% in Dex group ($P = 0.833$). The baseline demographic characteristics were similar between the two groups ($P > 0.05$). Besides, there