Renal-protective effect of dexmedetomidine during cardiac surgery with cardiopulmonary bypass: a prospective, randomized, double-blind, placebo-controlled study

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Background and objectives
Postcardiac surgery-associated acute kidney injury (AKI) is associated with up to 60% mortality rates of all cardiac surgery patients. This study aimed to study the renal-protective effect of dexmedetomidine in reducing the incidence of AKI following cardiac surgery.
Patients and methods
A total of 40 patients scheduled for cardiac surgery with cardiopulmonary bypass (CPB) were randomly allocated into two equal groups. In the study group, dexmedetomidine was given as an infusion of 0.4 μg/kg/h from induction of anesthesia till the end of surgery while in the control group, the patients received an equal volume of normal saline. The primary outcome of this study was the level of serum neutrophil gelatinase-associated lipocalin. The secondary outcomes were serum creatinine, hemodynamic parameters, operative time, aortic cross-clamp time, CPB time, and duration of ICU stay.
Results
Intraoperative and postoperative time variables and number of patients who developed hypotension were comparable between groups. Bradycardia developed more frequently in the dexmedetomidine group than in the placebo group. Serum neutrophil gelatinase-associated lipocalin after 2 h showed a statistically significant difference between groups. Serum creatinine showed no statistically significant difference between groups.
Conclusion
Dexmedetomidine could have a protective role in renal function during cardiac surgery using the CPB.

Keywords:
cardiac surgery, cardiopulmonary bypass, dexmedetomidine, renal-protective effect

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Introduction

The incidence of cardiac surgery-associated acute kidney injury (CSA-AKI) varies from 5 to 42% [1]. It is associated with up to 60% mortality rates of all cardiac surgery patients. Severe CSA-AKI is independently associated with three to eight-fold higher perioperative mortality, prolonged ICU and hospital length of stay, and increased cost of care. The risk of death related to AKI remains elevated for 10 years after cardiac surgery regardless of other risk factors, even for those patients with complete renal recovery [2].

Dexmedetomidine is a selective and potent α2-adrenoceptor agonist that is used for its anxiolytic, sedative, and analgesic properties [3,4]. It decreases central nervous system sympathetic outflow in a dose-dependent manner and has opioid-sparing analgesic effects. There is increasing evidence of its organ-protective properties against ischemic and hypoxic injury, including cardioprotection, neuroprotection, and renoprotection [5,6].

Currently, the standard diagnostic tests for AKI detection are monitoring of serum creatinine concentration and urine output, both of which are markers of renal function but not kidney injury [7]. Owing to the limitations of existing tests of kidney function, there is considerable interest in novel biomarkers of AKI [8]. Neutrophil gelatinase-associated lipocalin (NGAL) fulfills many of the characteristics essential for a useful AKI biomarker. NGAL represents a significant component in the pathophysiology of the disease. NGAL concentration in urine or plasma increases rapidly in a dose-dependent manner that is proportional to the degree of renal damage. NGAL is expressed early after kidney damage when such injury is still potentially limitable or reversible. NGAL also allows differentiation between the causes of AKI (intrinsic

vs. transient 'prerenal' AKI), risk stratification, therapy monitoring, and prognostication concerning the need for acute dialysis, duration of hospital stay, and mortality. NGAL is noninvasive, clinically actionable, and reliably measurable on available standardized clinical platforms. Furthermore, the marker incrementally adds value to the baseline clinical risk assessment, potentially enabling physicians to intervene early to limit the extent of kidney injury [9]. This study aimed to study the renal-protective effect of dexmedetomidine in reducing the incidence of AKI following cardiac surgery.

Patients and methods

This prospective, randomized, double-blind, placebo-controlled, parallel design study was performed after approval of the ethics committee of Faculty of medicine, Benha University. The study was conducted among 40 patients. Their ages ranged between 18 and 65 years and class II and III ASA physical status scheduled for cardiac surgery with cardiopulmonary bypass (CPB, valve replacement, and coronary artery bypass grafting); the patients were evaluated between August 2016 and March 2019 in Benha University Hospitals. All patients were involved in the study after written informed consent was obtained.

Patients with preoperative renal impairment (elevated creatinine and blood urea nitrogen levels) and diuretic use, preexisting hepatic or pulmonary disease, peripheral vascular disease, previous cardiac surgery, emergency surgery, surgeries requiring a deep hypothermic circulatory arrest, preoperative use of inotropes or vasopressors, diabetic patients, preoperative hemoglobin level less than 12 mg/dl, hematological disorders or morbidly obese patients were excluded from the study. These patients were allocated randomly into two equal groups. An online randomization program was used to generate a random number list (http://www.randomizer.org/). Patient randomization numbers were concealed in opaque envelopes which were opened by the study investigator. In the study group (group I), dexmedetomidine was given as an infusion of 0.4 μg/kg/h from induction of anesthesia till the end of surgery. In the control group (group II), the patients received an equal volume of normal saline. The staff involved in the clinical care and members of the study group obtaining the data were blinded to randomization for the period of data achievement and analysis. Group allocation was revealed after the final statistical analysis. Preoperatively, careful assessment of the cardiovascular system and investigations for the exclusion criteria and routine investigations which included complete blood count, coagulation profile, liver, and renal function tests, blood grouping, chest radiography, ECG, and echocardiography were done. In the preanesthetic room, wide bore intravenous cannula was inserted, and a blood sample was taken for baseline serum NGAL and creatinine measurements. Supplemental O_2 (2–3 l/min) via the nasal cannula was applied after premedication. Midazolam (0.01–0.02 mg/kg) and fentanyl (0.5 μg/kg) during arterial cannulation were given to the patients as premedication. An arterial line was applied under local anesthesia in the radial artery after Allen's test was performed. In the operative room, pulse oximeter (SpO_2), a five-lead ECG, and invasive arterial blood pressure monitoring were applied. Doses of induction were adjusted according to the hemodynamics and myocardial function of the patient. Anesthesia was induced by propofol (1–5 mg/kg) in addition to fentanyl (1–2 μg/kg) and cisatracurium (0.1–0.2 mg/kg). Face mask ventilation with oxygen for 3 min and finally, a suitable-sized endotracheal tube was inserted, and the patient was connected to IPPV, which was adjusted to maintain a $PaCO_2$ of between 30 and 35 mmHg. Anesthesia was maintained with an inhalational agent (isoflurane) (1–2%) in 70% oxygen with the intent to maintain the mean arterial blood pressure and heart rate within 20% of the baseline. Cisatracurium 3 μg/kg/min was administered to maintain muscle relaxation throughout the procedure. After induction of anesthesia, central venous line, urinary catheter, and temperature probe were inserted in the lower third of the esophagus. Before skin incision additional fentanyl (5–10 μg/kg) was injected. Arterial blood gases, serum Na and K, hematocrit, and blood glucose were measured after induction of anesthesia, during CPB, after weaning from CPB and according to needs. Activated clotting time was measured at baseline, 5 min after heparin administration, during CPB, and finally after reversal of heparin with protamine sulfate. The primary outcome of the study was the level of serum NGAL (ng/dl), which was measured preoperatively as a baseline and 2 h after CPB. The secondary outcomes were serum creatinine at baseline and 2 h post-CPB, incidence of postoperative hypotension (systolic blood pressure <90 mmHg), incidence of postoperative bradycardia (heart rate<60), operative time from induction of anesthesia till skin closure, aortic cross-clamp time from application of aortic cross-clamping till aortic declamping, CPB time from connecting the patient to extracorporeal circulation till termination of CPB, duration of ICU stay from transferring the patient from the operating room to the ICU till patient discharge to the ward.

Statistical analysis

Data analysis was done by using statistical analysis of social sciences (IBM, New York, New York, USA), version 16. Quantitative data were presented as mean ±SD and were analyzed by using the unpaired Student's *t* test. Qualitative data were presented as numbers (frequency) and were analyzed using the χ^2 test. A *P* value less than 0.05 was considered statistically significant, and a *P* value less than 0.01 was considered statistically highly significant. The sample size was calculated according to a pilot study for the first five patients in each group. An α error=0.05 (two-tailed) and a power of 80% was assumed to detect an assumed clinically significant difference (effect size *d*=1.0068) between the measurements of the level of NGAL after 2 h (primary outcome). Seventeen patients in each group were found to be satisfactory. We considered 20 patients in each group to overcome the dropout.

Results

Fifty patients were approached for participation in the study. Seven declined participation and 43 patients consented to participate. Of these, three were lost before randomization because of cancellation or rescheduling of their surgical procedures. Therefore, 40 patients inclusively were randomly assigned to treatment (Fig. 1).

Demographic characteristics and duration of surgery were comparable between groups (Table 1).

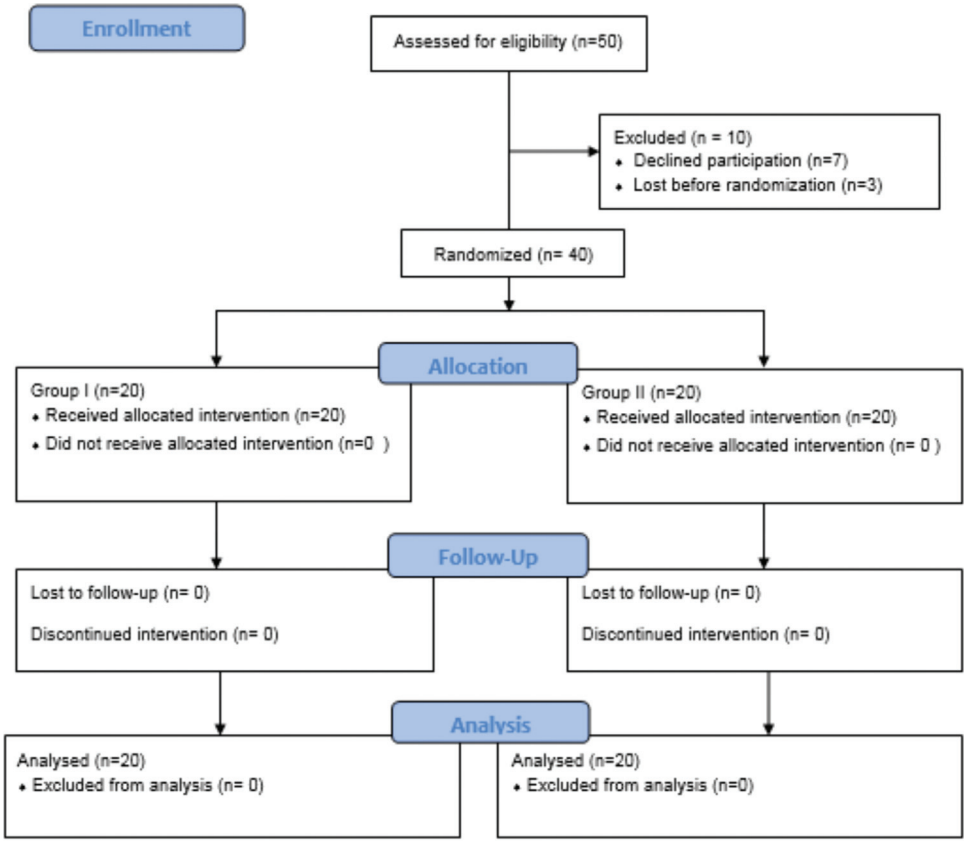
Intraoperative and postoperative time variables and the number of patients developed hypotension were comparable between both groups. Bradycardia developed more frequently in the dexmedetomidine group than in the placebo group (*P*=0.025) (Table 2).

Table 1 Demographic characteristics and duration of surgery

	Group I	Group II	*P* value
Age (years)	48.25±11.95	42.65±7.35	0.08
Weight (kg)	78.55±6.96	73.05±11.37	0.073
Sex (male : female)	6 (30) : 14 (70)	5 (25) : 15 (75)	0.72
ASA (II : III)	18 (90) : 2 (10)	19 (95) : 1 (5)	0.54
Duration of surgery (min)	268±51.25	283.5±57.69	0.37

Data are presented as mean±SD except for sex and ASA, which are presented as *n* (%).

Figure 1



Consort flow diagram.

Table 2 Intraoperative and postoperative variables

	Group I	Group II	*P* value
Aortic cross-clamp time (min)	68.75 ±14.49	72±12.5	0.45
Bypass time (min)	122.75 ±31.18	128 ±17.94	0.51
Duration of ICU (day)	2.4±0.82	2.65 ±0.48	0.24
Duration of postoperative ventilation (h)	14.3±6.81	15.65 ±4.53	0.46
Hypotension	7 (35)	8 (40)	0.74
Bradycardia	5 (25)	12 (60)	0.025*

Data are presented as a mean±SD except for hypotension and bradycardia are presented as *n* (%). *Significant changes.

Table 3 Laboratory data

	Group I	Group II	*P* value
NGAL baseline (ng/ml)	89.45 ±14.15	92.7 ±12.65	0.44
NGAL 2 h postoperative (ng/ml)	118.25 ±20.81	186.25 ±75.88	0.0004*
Creatinine baseline (mg/dl)	0.76±0.13	0.81±0.13	0.19
Creatinine 2 h postoperative (mg/dl)	0.99±0.24	1.05±0.13	0.35

Data are presented as mean±SD. NGAL, neutrophil gelatinase-associated lipocalin. *Significant changes.

As regards laboratory data, baseline serum NGAL showed no statistically significant difference, but after 2 h serum NGAL showed a statistically highly significant difference between groups. Both baseline and after 2 h, serum creatinine showed no statistically significant difference between groups (Table 3).

Discussion

Risk factors for AKI are common among patients undergoing cardiac surgery. Many of these factors are not changeable, such as advanced age, hypertension, hyperlipidemia, and peripheral vascular disease. Other factors are specific to the anesthetic, surgical, and ICU management, and physicians should be aware of these factors to eliminate or mitigate their effects [10].

NGAL has been identified as one of the most sensitive and specific biomarkers for predicting AKI after cardiac surgery [11,12].

Dexmedetomidine has a possible protective effect on CSA-AKI [13].

This study demonstrated that there is a protective role of dexmedetomidine on renal function during cardiac surgery using the CPB, indicated by serum NGAL as an early detector.

Ammar *et al.* [14] revealed that dexmedetomidine provided some degree of protection to the kidney during cardiac surgery as evidenced by lower levels of urinary specific kidney proteins (beta-NAG, alpha-1-M, GST-pi, GST-alpha) combined with lower levels of serum proinflammatory cytokines (tumor necrosis factor-α and interleukin-1β) and lower values of noradrenaline and cortisol. Furthermore, the dexmedetomidine group showed higher creatinine clearance and lower serum cystatin C.

Ji *et al.* [15,16] were agreeable with this study. They concluded that post bypass infusion of dexmedetomidine is associated with a significant decrease in the incidence of mild AKI in these cardiac surgical patients with preoperative normal renal function and mild chronic kidney disease. The post bypass use of dexmedetomidine is also associated with a significant decrease in in-hospital, 30-day mortality, and the incidence of overall postoperative complications.

Balkanay *et al.* [12] also agreed with this study. They revealed that post bypass dexmedetomidine infusion could be useful in preventing the aggravation of AKI.

Jo *et al.* [17] made a trial that was agreeable with us. They concluded that intraoperative dexmedetomidine infusion might reduce the incidence of AKI and the incidence of post CBP eGFR decline after pediatric congenital heart surgery under CPB.

Bayram *et al.* [18] were agreeable with us also. They said that the use of dexmedetomidine during pediatric angiography as an adjuvant to sedative agents is effective in preventing renal injury due to contrast media. Shi and Tie [13] conducted a meta-analysis regarding dexmedetomidine for CSA-AKI. They reported that dexmedetomidine might be a promising prevention strategy for CSA-AKI.

Honore *et al.* [19] had some comments about the meta-analysis of Shi and Tie. They said that the work of Shi and Tie must be interpreted with caution as the potential protective role of dexmedetomidine in CSA-AKI can only be reliably appreciated when type and duration of surgery, patient characteristics and comorbidities, right heart hemodynamics, and perioperative therapeutic strategies are considered. Furthermore, it requires comparison with other relevant sedatives and a more thorough insight into dexmedetomidine-mediated effects on compartmental renal blood flow distribution and renal microcirculation.

However, some studies went against this study. Salah *et al.* [20] compared the effects of a continuous infusion of dexmedetomidine versus placebo. They reported that the use of dexmedetomidine infusion did not alter renal function in terms of serum creatinine or creatinine clearance but was associated with an increase in urinary output in the first 24 h postoperatively.

Leino *et al.* [21] also showed that the use of intravenous dexmedetomidine did not alter renal function in that cohort of relatively low-risk elective coronary artery bypass grafting patients although it was associated with an increase in urinary output as compared with placebo. Another meta-analysis made by Li *et al.* [22] reported that there was no significant difference in the incidence of AKI.

On the other hand, many experimental studies had been performed to determine the protective role of dexmedetomidine on renal function. The Chen *et al.* [23] study demonstrated that dexmedetomidine protected against acute stress-induced renal tubular injury, which may be effective by regulating NE release, strengthening the antioxidative stress system, reducing ROS production, and inhibiting JNK phosphorylation, thereby downregulating the expression of key proteins in the mitochondria-dependent pathway. This study offers a theoretical basis for the future development of new anti-stress drugs and guidance for the clinical application of dexmedetomidine as an anti-stress agent.The Si *et al.* [24] study demonstrated that dexmedetomidine treatment results in a partial, but significant, attenuation of renal damage.

Gu *et al.* [25] studied the protective role of dexmedetomidine on ischemia-reperfusion induced kidney injury *in vitro* and *in vivo*. They concluded that *in vitro*, dexmedetomidine decreased the incidence of cell death in a dose-dependent manner while *in vivo*, dexmedetomidine preserved the tubular architecture and reduced cell death. So, the level of renal dysfunction was minimized, and renal failure was prevented. The organ-protective effect was abolished with α_2 adrenoreceptor antagonist, indicating that dexmedetomidine acted in an α_2 adrenoreceptor-dependent manner.

Sugita *et al.* [26] investigated whether a continuous infusion of dexmedetomidine could improve ischemic reperfusion injury in rats. They showed that continuous infusion of dexmedetomidine reduced renal dysfunction compared with pentobarbital.

Conclusion

This study demonstrated that dexmedetomidine could have a protective role in renal function during cardiac surgery using the CPB.

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Conflicts of interest

There are no conflicts of interest.

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