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Original Article

Role of Dexmedetomidine Infusion on Renal Dysfunction in Patients Undergoing Coronary Artery Bypass Graft Surgery: A Randomized Control Trial

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ABSTRACT

Objective: To find out the effect of Dexmedetomidine infusion on renal function in patients undergoing Coronary Artery Bypass Graft (CABG) surgery.

Study Design: Randomized control trial (RCT- NCT05375188).

Place and Duration of Study: The research was conducted in the Department of Anesthesia, National Institute of Cardiovascular Diseases Karachi Pakistan, from Jun to Sep 2021.

Methodology: 60 patients were allocated randomly into two groups. In Group-D, Dexmetedomidine was given as an infusion of 0.4 µg/kg/h from induction of anesthesia for 24 hours. In Group-C, patients were receiving an equal volume of normal saline. The primary outcome of the study was Serum Creatinine (mg/dl) which was measured 24 hours before the surgery as baseline and then 24 hours and 48 hours after surgery.

Results: In Group-C Serum Creatinine was found to be 0.96 +/- 0.21mg/dl at baseline, 1.02 +/- 0.35 mg/dl after 24 hours and 1.38 +/- 0.47 mg/dl after 48 hours of surgery. In Group-D Serum Creatinine was found to be 0.76 +/- 0.12 mg/dl at baseline, 0.85 +/- 0.17 mg/dl after 24 hours and 0.82+/- 0.24 mg/dl after 48 hours of surgery. *p*-value was found to be <0.001 after 48 hours of surgery.

Conclusion: Dexmetedomidine infusion significantly reduced incidence of acute kidney injury in patients undergoing coronary artery bypass graft surgery.

Keywords: Cardiac surgery-associated acute kidney injury, Dexmetedomidine, Serum creatinine.

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INTRODUCTION

The incidence of cardiac surgery-associated acute kidney injury (CSA-AKI) varies from 5 to 42%.[1] This percentage was found to be 7.86% according to study conducted in Pakistan.[2] 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.[3] The etiology of renal injury is mainly due to elevation of renin levels as a result of sympathetic overactivity in addition to nephrotoxic inflammatory and hemodynamic components.[4] Unfortunately, there is no definite strategy for preventing AKI after cardiac surgery at present.[5]

Dexmedetomidine is a selective and potent α2-adrenoceptor agonist that is used for its anxiolytic, sedative, and analgesic properties.[6] 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.[7,8] Peng *et al.* in his meta-analysis has highlighted the significant role of dexmedetomidine in reducing AKI after bypass surgeries.[9] Then, R.Shi and H-T. Toe have also pointed out the promising renoprotective role of Dexmedetomidine in CABG surgeries.[10]

Kidney Disease Improving Global Outcomes (KDIGO) is one of the latest classifications of identifying AKI and is commonly used in various studies.[11] In 2016, Ammar AS *et al.* in their study documented the reno-protective role of peri-operative dexmedetomidine infusion in cardiac surgery.[4]

Despite having a significant amount of renal derangements in post CABG patients, there is limited data proving renal protection role of dexmedetomidine. Hence, the aim of this study was to use infusion of dexmedetomidine for renal protection in cardiac surgeries.

METHODOLOGY

This study was aimed to compare the trend of changes in serum creatinine and urine output levels up to 48 hours after CABG surgery in patients receiving dex-medetomidine infusion, and see if Dexmede-

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tomidine infusion had any effect on renal function in patients undergoing Coronary Artery Bypass Graft (CABG) surgery in a Tertiary Cardiac Center of Karachi Pakistan. This study, a randomized control trial, was conducted in the Department of Anesthesia & Intensive Care, National Institute of Cardiovascular Diseases (NICVD) Karachi Paksitan, for a period of 3 months from June to September 2021, after approval from (IERB# 66/2021) the ethical review committee of NICVD, Karachi.

Sample Szie: Sample size for the study was calculated using G*Power version 3.1.9.2 using method of sample size calculation for two-sided hypothesis testing of two independent mean. Taking 5% level of significance and 90% power of test, the minimum required sample size of n=6 patients in each group was calculated. Considering the design effect, a sample size of 30 patients in each group was decided. n=60 30(control)+30 (treatment).[4]

Inclusion Criteria: Patients aged between 18 and 65 years, under-going isolated coronary artery bypass grafting, and having ASA physical status Class-IV were included in the study.

Exclusion Criteria: All patients with preoperative renal impairment (elevated creatinine and blood urea nitrogen levels), on diuretic use, preexisting hepatic or pulmonary disease, peripheral vascular disease, previous cardiac surgery, emergency surgery, reopening surgeries, surgeries requiring a deep hypothermic circulatory arrest, preoperative use of inotropes or vasopressors, perioperative use of diuretics, perioperative episode of CPR, preoperative hemoglobin level less than 12 mg/dl, hematological disorders and with morbid obesity were excluded.

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 was done. On the day of surgery in the Operation Theatre (OT), wide bore intravenous cannula (16G) was passed and arterial cannulation was done under local anesthesia in the radial artery. Standard monitors were applied. Propofol at a dose of 1–5 mg/kg in addition to nalbuphine at a dose of 0.1–0.2 mg/kg and atracurium at a dose of 0.6 mg/kg were used to induce anesthesia. A suitable-sized endotracheal tube was inserted, and the patient was connected to IPPV.

We divided a total of 60 patients after informed and written consent, in to two groups using computer generated random allocation based on Bernoulli distribution with probability of success (allocation of treatment group) as 0.50. A list of allocated groups in the sequence of patient number was generated by a statistical expert based on above mentioned statistical parameters. List was accessible to an independent investigator, not involved in patient management, and allocation group was communicated to the management team patient-on-patient basis in order to maintain concealment. An independent team of physicians blinding to the treatment group monitored all the patients after 24 and 48 hours of randomization. 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.

In Dexmedetomidine Group (Group-D), patients received Dexmedetomidine infusion in addition to standard management protocol (0.4 µg/kg/hr), from induction of anesthesia for 24 hours. Whereas, in Control Group (Group-C) patients allocated to this group received equal volume of normal saline as placebo. We have used Kidney Disease Improving Global Outcomes (KDIGO) protocol in order to evaluate incidence of acute kidney injury. This protocol labels an increase in serum creatinine of more than 0.3 mg/dl within a time frame of 48 hours OR volume of urine of less than 0.5 ml/kg/hr for 6 hours, as a case of Acute Kidney Injury.[12]

The primary outcome of the study was Serum Creatinine (mg/dl) which was measured 24 hours before the surgery as baseline and then 24 hours and 48 hours after surgery. The secondary outcomes were incidence of urine output (ml per hour) for up to 48 hours after surgery, operative time, that is, from time of induction of anesthesia till time of skin closure, aortic cross-clamp time, that is, from application of aortic cross-clamping till aortic declamping, CPB time, from connecting the patient to extracorporeal circulation till termination of CPB, total operative time starting from the time of surgical incision till skin closure, duration of ICU stay from transferring the patient from the operating room to the ICU till patient discharge to the ward, episodes of bradycardia and hypotension, dosage of inotropic and hemoglobin levels at baseline, at 24 hours and at 48 hours. Hypotension was defined as decrease in systolic blood

pressure <90 mmHg.[12] Bradycardia was defined as heart rate less than 60 beats/min.[13] An independent team of physicians blinding to the treatment group monitored all the patients after 24 and 48 hours of randomization.

Data was analyzed using IBM SPSS version 21, data was summarized by computing descriptive statistics such as Mean±SD for continuous response variables (including serum creatinine (mg/dl), urine output, and creatinine clearance) and frequency (n%) for categorical response variables. Treatment and control group were compared for baseline characteristics and outcomes by conducting Chi-square test for categorical variables and Independent sample t-test was used for continuous response variables. Relative risk (95% CI) of AKI and other adverse outcomes were computed for treatment groups. Two-sided *p*-value of ≤ 0.05 was taken as criteria for statistical significance.

RESULTS

Both groups had 30 patients each. Group-C had (n=22, 73.3%) males and (n=8, 26.7%) females compared to Group-D which had (n=20, 66.7%) males and (n=10, 33.3%) females. Average age and weight were approximately same in both groups. Group-C had (n=6, 20%) patients Diabetes Miletus, (n=2, 6.7%) with hypertension, (n=6, 20%) smokers and (n=18, 60%) known case of ischemic heart disease (IHD), whereas in Group-D there were (n=6, 20%) diabetic patient, hypertensive, (n=4, 13.3%) and smokers (n=4, 13.3%) known case IHD. Total operative time in Group-C was 310.6±28.2 min vs 318. 7±18.6 min in Group-D (Table-I).

Table-I: Baseline Data and Preoperative Characteristics

	Treatment Group	
	Control	Dexmedetomidine
Total (N)	30	30
Gender		
Male	22 (73.3%)	20 (66.7%)
Female	8 (26.7%)	10 (33.3%)
Age (years)	55.2 ± 9.7	55.4 ± 9.2
Weight (kg)	68.4 ± 10.2	71.9 ± 10.4
Comorbids		
Diabetes Miletus	6 (20%)	6 (20%)
Hypertension	2 (6.7%)	4 (13.3%)
Diabetes and hypertension	4 (13.3%)	10 (33.3%)
History of smoking	6 (20%)	4 (13.3%)
IHD	18 (60%)	10 (33.3%)
CPB time (min)	125.7 ± 20.4	127.3 ± 32.6
Aortic clamp time (min)	97.5 ± 47.2	82.6 ± 26.4
Total Operative time (min)	310.6 ± 28.2	318. 7 ± 18.6

Serum Creatinine in the Group-C was found to be 0.96±0.21 mg/dl, 1.02±0.35 mg/dl and 1.38±0.47 mg/dl at baseline, after 24 hours and after 48 hours of surgery respectively. Whereas, in Group-D, serum creatinine was found to be 0.76±0.12 mg/dl, 0.85±0.17 mg/dl and 0.82±0.24 mg/dl at baseline, after 24 hours and after 48 hours of surgery. The *p*-value for serum creatinine after 48 hours of surgery was <0.001 which is significant (Table-II).

Table-II: Primary and Secondary Outcomes

	Treatment Group		*p*-value
	Control	Dexmedetomidine	
Total (N)	30	30	-
Serum Creatinine (mg/dl)			
Baseline	0.96 ± 0.21	0.76 ± 0.12	<0.001
After 24 hours of surgery	1.02 ± 0.35	0.85 ± 0.17	0.002
After 48 hours of surgery	1.38 ± 0.47	0.82 ± 0.24	<0.001
Hb (g/dl)			
Baseline	13.18 ± 1.44	12.96 ± 2.11	0.649
After 24 hours surgery	10.91 ± 0.89	10.7 ± 1.59	0.538
After 48 hours surgery	10.05 ± 1.11	9.89 ± 1.8	0.680
Amount of Urine (ml/kg/hr)			
After 6 hours	3.32 ± 1.4	2.62 ± 0.73	0.036
After 12 hours	2.44 ± 0.91	2.43 ± 0.93	0.918
After 18 hours	2.19 ± 0.45	1.79 ± 0.46	0.003
After 24 hours	1.79 ± 0.5	1.8 ± 0.4	0.625
After 48 hours	1.69 ± 0.31	1.55 ± 0.45	0.031
Duration of Vasopressor Need (Hours)			
Adrenaline	11.2 ± 13.53	8.17 ± 10.03	0.438
Noradrenaline	20 ± 12.64	15 ± 9.02	0.088
Complications			
Acute Kidney Injury (AKI)	13 (43.3%)	3 (10%)	0.004
Hypotension	09 (30%)	11 (36.7%)	0.492
Bradycardia	2 (6.7%)	0 (0%)	0.492
Length of ICU stay (days)	2.57 ± 0.5	2.57 ± 0.5	>0.999

The requirement for inotropic requirement in patients from both the groups were recorded at an interval of 6 hours for up to 48 hours. The *p*-value of inotropic support when compared between both groups throughout 48 hours was insignificant. In other words, dexmedetomidine infusion did not alter the inotropic support dosage (Table-III).

Table-III: Dosages of Inotropic Support

	Treatment Group		*p*-value
	Control	Dexmedetomidine	
Total (N)	30	30	-
Adrenaline (µg/kg/hr)			
After 6 hours	0.04 ± 0.06	0.03 ± 0.03	0.805
After 12 hours	0.02 ± 0.03	0.01 ± 0.02	0.073
After 18 hours	0.01 ± 0.02	0.01 ± 0.02	0.391
After 24 hours	0.01 ± 0.02	0 ± 0.01	0.965
After 30 hours	0 ± 0.01	0 ± 0.01	0.289
After 36 hours	0 ± 0.01	0 ± 0	0.281
After 42 hours	0 ± 0.02	0 ± 0	0.154
After 48 hours	0 ± 0.02	0 ± 0	0.154
Noradrenaline (µg/kg/hr)			
After 6 hours	0.1 ± 0.2	0.05 ± 0.04	0.357
After 12 hours	0.05 ± 0.06	0.03 ± 0.03	0.220
After 18 hours	0.02 ± 0.04	0.02 ± 0.04	0.253
After 24 hours	0.01 ± 0.03	0.01 ± 0.03	0.122
After 30 hours	0.01 ± 0.03	0 ± 0.02	0.091
After 36 hours	0.01 ± 0.03	0 ± 0.01	0.097
After 42 hours	0.01 ± 0.02	0 ± 0.01	0.313
After 48 hours	0.01 ± 0.02	0 ± 0.01	0.313

DISCUSSION

Acute Kidney Injury post cardiac surgery is a serious issue which causes significant increase in morbidity and mortality which unfortunately have limited management options.[14] Dex-medetomidine has a proven role in organ protection in various studies.[7,8] Soliman and Hussein (2017) in their study, observed a remarkable decrease in blood urea and serum creatinine along with a significant increase in value of creatinine clearance, till the fifth day after CPB, when they gave Dex-medetomidine through the surgery (*p*-value =0.002 for serum creatinine at 48 hours and *p*-value =0.012 for urine output at 48 hours).[15] Similarly, Cho *et al*. in 2016 administered infusion of Dexmedetomidine in their 200 patients undergoing cardiac surgery, saw a reduction in incidence of postoperative AKI in the patients receiving dexmedetomidine (33 cases of AKI in control group vs only 14 cases of AKI in dexmedetomidine group).[16] We used dexmede-tomidine in CABG surgeries to see if it may have a role in renal protection started from the time of induction for up to 24 hours. In this randomized control study, we recruited 60 patients and randomly divided them equally into two groups (30 in each group), Group-C and Group-D. Group-C was control group in which patients received standard management. On the other hand, patients in Group-D were give infusion of dexmedetomidine.

Among the pathogenic mechanisms involved in post CABG acute kidney injury, overactivity of the sympathetic system and decreased renal perfusion are more highlighted.[17,18] More importantly, general anesthesia basically helps in reduction of this sympathetic system activity and hence diminishes risk of injury to the renal system.[19] Dexmedetomidine, on the other hand, attenuates sympathioadrenal hyperac-tivity and helps in decreasing the plasma levels of catecholamines amongst patients undergoing cardiac surgery.[20] Secondly, dexmedetomidine instigates nitric oxide based vasorelaxation. This is based on the background of activating endothelial alpha Type-2 receptors, which is primarily present in renal peritubular vasculature and tubules. Hence, hindering renin, potentially improving glomerular filtration and overall diuresis. Additionally, dexmedetomidine also significantly decrease systemic inflammatory activation, initiation of reactive oxygen species formation, and renal cell death secondary to ischemia/reperfusion injury.[21]

In our study we also evaluated the number of patients developing acute kidney injury post operatively in the two groups. In Group-C, 13 out of 30 patients developed acute kidney injury as per KDIGO protocol. On the contrary, only 3 patients developed acute kidney injury in Group-D, which is again significant as per *p*-value=0.004.

As per our secondary outcomes, there were no significant findings. There was no significant difference in the hemoglobin from baseline up to 48 hours between the two groups. A total of 9 episodes of hypotension was recorded in the control group from the time of induction vs 13 episodes in the Group-D. Whereas, 2 patients in Group-C registered bradycardia in comparison to none in dexmedetomidine group as per definitions.

The *p*-value again remained insigni-ficant (Table-II). In our study, the continuation, of the infusion of dexmedetomidine even after the surgery for up to 24 hours from the time of induction was the highlight. Desborough, in his study, explained the immediate postoperative period, which is 24 hours, during which the inflammatory reactions and activation of sympathetic system involving hemodynamic instability and vital organ damage are at its peak.[22] Hence, our decision to continue the infusion of dexme-detomidine for up to 24 hours could have contributed towards positive findings.

After the surgery, Dexmedetomidine did not cause an increase in inotropic dosage and duration required up to 48 hours (Table-III), which is again a positive finding in developing the role of this drug in

CABG surgeries. We did not notice any increase in duration between two group in terms of ICU stay (Table-III). Thus, the dose of dexmedetomidine which we used in our study apparently is safe and no adverse event was registered.

LIMITATIONS OF STUDY

Firstly, this is a study which was conducted in only one tertiary care hospital. Secondly, patients with preserved cardiac and renal function were involved only. Hence, we cannot explain the role of dex-medetomidine in patients undergoing CABG surgery with deranged cardiac and renal functions. Simultaneously, we did not include investigations in relation to the measurement of plasma levels of catecholamines or any inflammatory markers, which could have shed more light on the mechanism of dexmedetomidine.

CONCLUSION

Our results conclude that, infusion of dexmedetomidine at a dose of 0.4 µg/kg/hr for 24 hours starting at the time of anesthetic induction is a safe dose and reduces the incidence of Acute Kidney Injury (AKI) after CABG.

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Conflict of Interest: None.

Author's Contribution

Following authors have made substantial contributions to the manuscript as under:

HTC: Manuscript writing, concept, critical review

AMK: Concept, Manuscript review, intellectual contribution

SA: Data analysis, interpretation, editing

AA: Manuscript writing, review, editing

MM: Manuscript writing Study design, review

RS: Data collection, Data analysis, interpretation, editing

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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