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Renal Function after Coronary Artery Bypass Graft Using Dexmedetomidine

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ABSTRACT

Acute kidney injury (AKI) is defined by 0.3 mg/dL increase in serum creatinine (SCr) and is associated with higher incidence of postoperative mortality after coronary artery bypass graft (CABG). There are few clinical studies on the effect of dexmedetomidine (DEX) on renal function. We evaluated AKI after coronary artery bypass graft with and without cardiopulmonary bypass (CPB) under anesthesia with DEX. **Method:** In this retrospective study, we performed serial analysis of serum creatinine (SCr) up to 48 hours after surgery in 286 patients who underwent CABG. We tested the similarity between groups, evaluating patients separately for use of CPB and DEX. Each patient was evaluated for his or her SCr at the following points in time: preoperative, immediately postoperative, 24 hours postoperative, and 48 hours postoperative. Preoperative SCr was used as the baseline value for each patient. If the SCr increased ≥0.3 mg/dL in at least one of the periods, the patient was classified as having AKI. We also assessed the risk for AKI in patients with altered preoperative SCr (values between 1.1 to 2.0 mg/dL for women or 1.3 to 2.0 mg/dL for men) compared to patients with normal SCr. **Results:** The groups were similar for preoperative weight, age, and altered SCr. Patients were anesthetized with DEX and who underwent CPB exhibited higher incidence of AKI ($p = 0.043$). Without CPB, there was higher incidence of AKI after using DEX ($p = 0.066$). **Conclusion:** Anaesthesia with DEX increased the incidence of AKI after myocardial revascularization surgery in patients who underwent CPB.

Keywords: Acute Kidney Injury; Dexmedetomidine; Cardiopulmonary Bypass; Coronary Artery Bypass Graft

1. Introduction

Acute kidney injury (AKI) [1,2] is defined by 0.3 mg/dl increase in serum creatinine (SCr) and is associated with higher incidence of postoperative mortality after myocardial revascularization surgery [3-7]. As indicated by its pathophysiology, AKI has multifactorial causes, including low cardiac output, hypoperfusion, hypovolemia, diabetes mellitus, age ≥ 65 years old, emergency surgery, renal ischemia, use of cardiopulmonary bypass (CPB), and adopted rewarming method after CPB [7-15]. There is 30% incidence of AKI in patients undergoing myocardial revascularization and approximately 1% will require dialysis [7,8,16].

Dexmedetomidine (DEX) is an α_2-adrenoceptor agonist with α_2/α_1 selectivity of 1600:1. Doses between 0.2 - 0.6 μg/kg/h promote sedation, anxiolysis, hypnosis, and analgesia with little or no change in breathing [17]. DEX acts on three types of α_2 receptors (A, B, and C). The α_{2A} has been described in the periphery and α_{2B} and α_{2C} in the central nervous system (CNS). In the periphery, the presynaptic receptors inhibit noradrenaline release, while post-synaptic receptors determine vasoconstriction. DEX acts on central receptors, causing sympatholysis, sedation, and antinociception [18]. In the cardiovascular system, DEX reduces heart rate, peripheral vascular resistance, and indirectly, myocardial contractility, cardiac output, and systemic pressure. Incidences of bradycardia and hypotension have been associated with loading dose. Under anesthesia, DEX drastically reduces the minimum alveolar concentration (MAC) [19]. In cardiac surgery, DEX reduces catecholamine plasma concentrations, maintains hemodynamic stability, and increases urinary output [20]. Despite maintaining antidiuretic hormone (ADH) concentration, another α_2 agonist, clonidine, increases diuresis and creatinine clearance on the first night after surgery [21]. Thus, with respect to renal function,

DEX may be a promising agent for use in myocardial revascularization surgery. Therefore, we conducted a retrospective study to assess the effect of using DEX intraoperatively on postoperative renal function in patients who underwent myocardial revascularization surgery with and without CPB.

2. Methods

This retrospective study was approved by the appropriate ethics authority (Ref: 120/2011) and registered with REBEC (Ref: U1111-1128-4201). Written informed consent was waived by the ethics committee. We selected patients who underwent anaesthesia for myocardial revascularization between January 2008 and December 2011. We excluded patients who met the following exclusion criteria: underwent emergency surgery and catheterization within less than 72 hours before the operation, had ≥2 mg/dl serum creatinine (SCr) before surgery, had incomplete data, and patients with continued use of α_2 agonist. Patients were divided into the following groups based on use of CPB and DEX:

Group $G_{(CPB)}$—CPB patients

Group $G_{(Control)}$—non-CPB patients

Group $G_{(CPB + DEX)}$—CPB patients who received DEX

Group $G_{(DEX)}$—non-CPB patients who received DEX

For $\mathbf{G_{(CPB)}}$ and $\mathbf{G_{(Control)}}$, the anesthesia protocol began with 3 to 5 mg of intravenous midazolam. Standard ASA monitors were attached, and radial artery catheterization was used for monitoring mean arterial pressure. We injected 20 to 30 μg/kg fentanyl, 0.3 mg/kg etomidate, and 0.08 mg/kg pancuronium. Anaesthesia was maintained by isoflurane titration according to hemodynamic response using 60% O_2 as carrier. Mean arterial pressure was maintained between 60 and 90 mmHg. We used metaraminol or ephedrine for short episodes of hypotension, noradrenaline for episodes of low peripheral vascular resistance, dobutamine to increase cardiac inotropism, and sodium nitroprusside or nitroglycerin for hypertensive crisis.

For $\mathbf{G_{(CPB+DEX)}}$ and $\mathbf{G_{(DEX)}}$, we used DEX at 0.5 μg/kg/h dose immediately after venipuncture and monitoring without loading dose, then reducing the fentanyl dose to 10 to 20 μg/kg. Use of isoflurane and vasoactive agents was kept the same as for $\mathbf{G_{(CPB)}}$ and $\mathbf{G_{(Control)}}$.

To start CPB, the patients were anticoagulated with sodium heparin (4 mg/kg) or until reaching activated clotting time (ACT) higher than 480 seconds. During CPB, nonpulsatile flow was used with target mean arterial pressure from 50 to 80 mmHg. Temperature was measured with a nasopharyngeal thermometer and maintained between 30˚C and 35˚C during CPB.

To quantify AKI rates in patients who underwent CABG with and without CPB, we used the results from tests routinely performed at the following *time points*: preoperative (M_{pre}), immediately postoperative (M_{iPO}), 24 hours postoperative (M_{PO24}), and 48 hours postoperative (M_{PO48}). These data were collected by reviewing electronic records available in the TASY® program, version 2.6, developed and licensed by Whebsistemas. The following were used as criteria to define AKI: AKIN (*Acute Kidney Injury Network*), ≥0.3 mg/dl increase in SCr concentration, or ≥50% increase in SCr concentration from baseline within at least 48 hours without urine output analysis [1]. Each patient was evaluated for SCr concentration at *time points* starting from M_{pre}. The SCr concentration at each *time point* was compared to that in M_{pre}. If at least one of these comparisons between *time points* indicated ≥0.3 mg/dl increase in SCr concentration, the patient was classified as having AKI. We also assessed risk for AKI in patients with altered preoperative SCr (values between 1.1 mg/dl and 2.0 mg/dl for women or 1.3 mg/dl and 2.0 mg/dl for men) compared to patients with normal SCr.

The statistical analysis aimed to test whether there was significant difference in incidence of AKI when using DEX, thus we separated patients who underwent CPB from those who did not. We considered Student t-test for independent samples in comparing two groups with respect to quantitative variables. We considered Fisher exact and Chi-square tests in assessing the association between qualitative variables. Values were considered statistically significant at $p < 0.05$.

3. Results

We evaluated 543 patients, of whom 257 patients were excluded because they met the exclusion criteria. A total of 286 patients were included in the statistical study, distributed as follows: G_{CPB}, 157 patients; $G_{CPB + DEX}$, 50 patients; $G_{control}$, 55 patients; and G_{DEX}, 24 patients.

We confirmed similarity between groups for weight, age, preoperative SCr, and incidences of hypertension (HTN) and diabetes mellitus (DM) preoperatively, for samples with and without CPB (see **Tables 1** and **2**).

Analysis of the results tested if there was some other factor associated with the AKI studied. Among the groups that underwent CPB or not, we separately tested weight, age, and altered preoperative SCr concentration up to 2 mg/dl. For those patients who did not undergo CPB and received DEX or not, only age ($p = 0.008$), but not weight ($p = 0.912$) or altered SCr ($p = 0.488$), was associated with higher incidence of AKI. Incidence of AKI was higher in the group that received DEX, even in patients who did not undergo CPB, but without statistical significance ($p = 0.066$) (**Figure 1**).

For groups that underwent CPB, the DEX factor was associated with a higher incidence of AKI ($p = 0.043$; beta error of 0.273) (**Figure 2**). In these patients, age ($p = 0.224$), weight ($p = 0.067$), and altered SCr up to 2 mg/dl

Table 1. Testing similarity of the groups that were submitted to CPB and that received or did not receive DEX, for weight, age, and altered preoperative serum creatinine concentration up to 2 mg/dl.

Variable	DEX	n	Mean	Median	Minimum	Maximum	Standard deviation	p-value*
Age	Without	157	64.0	64.0	36.0	87.0	9.0	0.755
	With	50	64.4	65.0	39.0	82.0	9.8	
Weight	Without	157	74.7	73.0	45.0	116.0	13.4	0.347
	With	50	72.8	72.5	44.0	97.0	11.7	
Altered Pre-Op. Creatinine	Without	157	1.20	1.18	0.63	1.98	0.28	0.171
	With	50	1.14	1.15	0.72	1.60	0.24	

*Student t-test for independent samples.

Table 2. Testing similarity of the groups that were not submitted to CPB and that received or did not receive DEX, for weight, age, and altered preoperative serum creatinine concentration up to 2 mg/dl.

Variable	DEX	n	Mean	Median	Minimum	Maximum	Standard deviation	p-value*
Age	No	55	61.8	65.0	34.0	85.0	11.9	0.097
	Yes	24	65.5	67.0	48.0	78.0	7.2	
Weight	No	55	73.8	73.0	47.0	119.0	13.8	0.862
	Yes	24	73.2	72.5	40.0	101.0	15.7	
Alt. Pre-Op. Creatinine	No	55	1.11	1.10	0.68	1.92	0.28	0.649
	Yes	24	1.08	1.13	0.71	1.44	0.23	

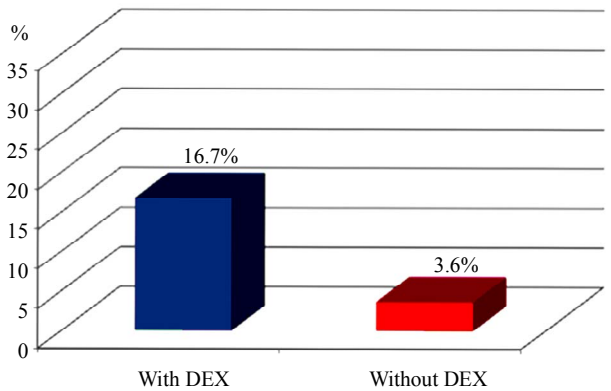

Figure 1. Percentage of cases with acute kidney injury (AKI) according to DEX use in patients who were not submitted CPB (p = 0.066; beta error of 0.831).

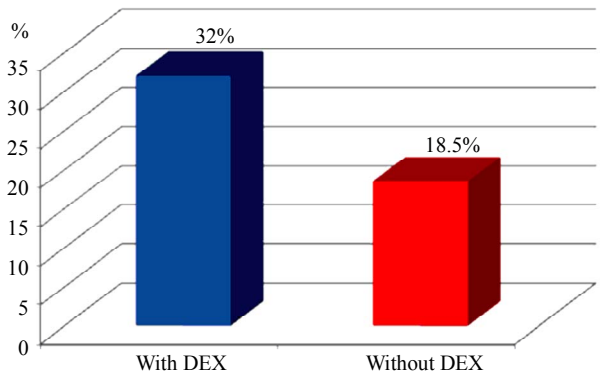

Figure 2. Percentage of acute kidney injury cases in patients who were submitted to CPB according to DEX use (p = 0.043; beta error of 0.273).

(p = 0.364) exhibited no statistically significant association with AKI.

4. Discussion

In this study, we found higher incidence of AKI in groups that received DEX regardless of CPB use. We also observed similarity for preoperative creatinine, sex, age, weight, and incidence of HTN and DM in the sample studied, further validating the results of this retrospective study. The age factor was associated with increased incidence of AKI in the non-CPB group, as expected for changes associated with aging [13,22]. Although, age is not necessarily a risk factor, other studies corroborate the results found for the non-CPB group [3-7].

SCr is a late biomarker of AKI. Although other biomarkers, such as KIM-1 (*Kidney Injury Molecule*), NAG (*N-acetyl-B-D-glucosaminidase*), NGAL (*Neutrophil Gelatinase Associated Lipocalin*), IL-18 (Interleukin 18), or cystatin C seem promising, the present definition of AKI is still based on altered serum creatinine concentration

and urine output [23-25]. Urinary output can increase the sensitivity for diagnosing AKI, but as this parameter is used to determine the phase of AKI, very constant measurements are required, which poses considerable difficulty in clinical practice [26]. Current clinical practices do not emphasize small SCr increases, which are often attributed to laboratory variation. However, the coefficient of variation of SCr with modern analyzers is relatively small and therefore 0.3 mg/dL increases are unlikely to be caused by laboratory variation [27]. According to Tolpin and colleagues [5], even subclinical increases are associated with worse prognosis. However, there is an overall consensus that diagnostic criteria should only be applied when optimal hydration status has been established [1].

CPB is an AKI-independent risk factor in renal function after myocardial revascularization surgery. The causes contributing to CPB as a risk factor are still being studied, but several factors have been proposed, such as hypothermia and rewarming, oxygen delivery to the kidneys (renal DO_2), perfusion method employed, perfusion pressure, and CPB duration itself [4,6,10,14,15,28,29]. Each factor would partially contribute to some kind of injury. Because the SCr values obtained before surgery are similar enough among all patients studied, this could emphasize intraoperative factors as probable determinants of AKI, including use of CPB and DEX.

Kulka and colleagues [21] studied preoperative treatment of patients undergoing myocardial revascularization with clonidine (4 μg/kg intravenously) and believe that this other agonist α_2 prevented renal function deterioration in patients, probably by reducing the sympathetic nervous system response. These authors' conclusion was based on studying creatinine clearance in patients treated with agonist α_2 compared to creatinine clearance in untreated patients. At three days after surgery, the clearances of the two groups were equal. However results from additional clinical trials are still necessary.

An *in vitro* experiment with human kidney cells and *in vivo* experiment with mice demonstrated that DEX activates the cell survival signal, phosphorylated AKT antibody (pAKT) via α_2 adrenoceptors, to reduce cell death and release the nuclear protein HMGB1 (*high mobility-group box*-1) in the plasma, inhibiting TLR4 (*toll-like receptor* 4) signaling, where both HMGB1 and TLR4 determine renal protection and play a central role in coordinating inflammatory responses in renal ischemia and reperfusion. DEX also has protective properties for organs as well as cytoprotective and anti-inflammatory effects, protecting against renal injury after ischemia and reperfusion. The authors of the study believe that, if extrapolated to clinical practice, their results indicate that DEX determines renal protection against ischemia and reperfusion injuries [30].

In contrast, other authors of histological studies found that using DEX in rats caused dilation, degeneration, and necrosis of renal tubules after hemorrhage of 30% of volemia, without replacing this loss. However, there was reduced renal vascular resistance in organ function, with increased glomerular filtration and renal filtration fraction [31].

In this retrospective study it was not possible to obtain a precise conclusion due to the sample size. Missing data, emergency surgeries, and other exclusion criteria left us with a small sample, especially for the non-CPB group. However, we found that DEX increased the incidence of AKI in the CPB group. In patients without CPB use, DEX was not considered an independent risk factor for AKI because p-value was 0.066, which would only indicate a statistically significant trend with a larger sample power. Thus, more patients are probably necessary to demonstrate if DEX is also a risk factor for AKI in patients not undergoing CPB.

5. Conclusion

In conclusion, albeit with a small sample, we observed that DEX behaved as an independent risk factor for increased incidence of AKI after CABG in patients who used CPB. For the non-CPB group, our sample was too limited to reach a conclusion.

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