Araştırma / *Research Article*

Urinary Output During the Aortic Cross-Clamping Period in Isolated Coronary Artery Bypass Grafting Surgery: An Indicator of Postoperative Acute Kidney Injury

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İzole Koroner Arter Baypas Cerrahisinde Aortik Kros Klempleme Sırasında Çıkan İdrar Miktarı: Postoperatif Akut Böbrek Hasarının Bir Göstergesidir

ABSTRACT

Objective: Postoperative acute kidney injury (AKI) is a common and serious complication of coronary artery bypass grafting surgery (CABG). In this prospective study, we investigated the efficacy of urinary output during aortic cross-clamping (ACC) in cardiac surgery in determining postoperative AKI.
Methods: This prospective study was performed on patients who underwent isolated coronary artery bypass surgery between January 2016 and April 2017. Patients with an increase of more than 1.5 times in their preoperative creatinine values on their third postoperative day were considered to have acute kidney injury according to RIFLE criteria. The patients were divided into two groups as AKI (+) and AKI (-), regarding presence of AKI.
Results: Acute kidney damage developed in 12 patients out of 146 patients studied. Demographic data, and intraoperative variables were similar between the groups (p>0.05). The urinary output during ACC (mL/kg/h) of the AKI (-) group was significantly higher than that of the AKI (+) group (p=0.045).
Conclusion: Our data have demonstrated that urinary output during ACC and cardiopulmonary bypass (CPB) periods may be a valuable criterion for early diagnosis of AKI. We suppose that, the patients with a urine output less than 3.345 ml/kg/h during the ACC period carry a high risk for postoperative AKI.

Keywords: acute kidney injury, coronary artery bypass greft surgery, urinary output during aortic cross- clamping

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ÖZ

Amaç: Postoperatif akut böbrek hasarı (AKI) koroner arter baypas greft cerrahisinin (CABG) en önemli komplikasyonlardan bir tanesidir. Biz bu prospektif çalışmada, açık kalp cerrahisinin aortik kros klemp (ACC) sırasındaki çıkan idrar miktarının postoperatif AKI belirleme üzerine etkisini araştırdık.
Yöntem: Bu çalışma prospektif olarak Ocak 2016 ile Nisan 2017 tarihleri arasında izole koroner baypas ameliyatı geçiren hastalar üzerinde yapıldı. Postoperatif 3. günde preoperatif kreatinin değerlerinde 1,5 katından fazla artış olan hastalar RIFLE kriterlerine göre akut böbrek hasarı olarak kabul edildi. Hastalar AKI'nin varlığına göre i AKI (+) ve AKI (-) olmak üzere 2 gruba ayrıldı.
Bulgular: Çalışmadaki 146 hastanın 12'sinde akut böbrek hasarı gelişti. Gruplar arasında demografik veriler ve intraoperatif değişkenler birbirine benzerdi (p>0,05). AKI (-) gruptaki ACC sırasındaki çıkan idrar miktarı (ml/kg/saat) AKI (+) gruba göre önemli derecede yüksek bulundu (p=0,045).
Sonuç: Verilerimiz ACC ve kardiyopulmoner baypas sırasındaki çıkan idrar miktarının AKI erken tanısı için değerli bir kriter olabileceğini gösterdi. Biz ACC sırasında idrar çıkışı 3.345 ml/kg/saatin altında olan hastaların postoperatif AKI için yüksek risk taşıdığı düşüncesindeyiz.

Anahtar kelimeler: akut böbrek hasarı, koroner arter baypas greft ameliyatı, aortik kros klemp sırasındaki idrar miktarı

INTRODUCTION

Postoperative acute kidney injury (AKI) is a common and serious complication of coronary artery bypass grafting (CABG) [1]. The incidence of AKI following cardiac surgery varies from 3% to 48%, whereas the incidence of acute renal failure varies between 2% and 15% following CABG. The mortality rate of patients with acute renal failure was reported to be as high as 60% [2].

A number of studies have concluded that determining the risk factors associated with AKI may improve postoperative recovery and perioperative surgical success in open heart surgery [3-6]. Therefore, the identification of risk factors for the development of AKI and initiation of timely interventions are as important as AKI therapy itself. Many factors are known to play a role in the development of AKI. Patient related risk factors in cardiac surgery include age, diabetes mellitus (DM), hypertension (HTN), smoking, decreased glomerular filtration rate, and left ventricular ejection fraction (LVEF), aortic atherosclerosis and early-term surgery following a myocardial infarction or percutaneous cardiac intervention. Surgery- related risk factors for AKI include prolonged cardiopulmonary bypass (CPB) and aortic cross-clamping (ACC) times, hemodilution, hemolysis, inflammatory response syndrome, hemodynamic instability, and nonpulsative flow during CPB [2,3,7-9]. However, the impact of some of these factors, including the urinary output during CABG, on the occurrence of AKI is controversial. According to some studies, there is no relationship between AKI and the amount of urinary output per hour during CABG [10-12]. However, two recent retrospective studies reported that the urine volume during CPB could be used to predict postoperative renal injury [13,14].

ACC in cardiac surgery is an important risk factor for postoperative acute renal failure due to nonpulsatile blood flow. We conjectured that the urine volume during ACC may be a more effective marker of AKI rather than the urine volume during CPB.

In this prospective study, we investigated the efficacy of urinary output during ACC in cardiac surgery in determining postoperative AKI. To the best of our knowledge, this is the first prospective study to make use of urinary output during the ACC period as a predictive marker of AKI.

MATERIAL AND METHODS

This prospective study consisted of patients who underwent isolated CABG between January 2016 and July 2017. Informed consents of the patients enrolled in the study were obtained in the operating room. Approval was obtained from the local ethics committee. Written informed consent was obtained from all participants. The EuroScore values of all the patients were evaluated; only patients with a low to medium risk were included in the study. In total, 252 open heart surgery patients were evaluated. One hundred and six patients were excluded from the study. Exclusion criteria and the number of patients are shown in Figure 1. Thus, 146 patients were finally enrolled in this study.
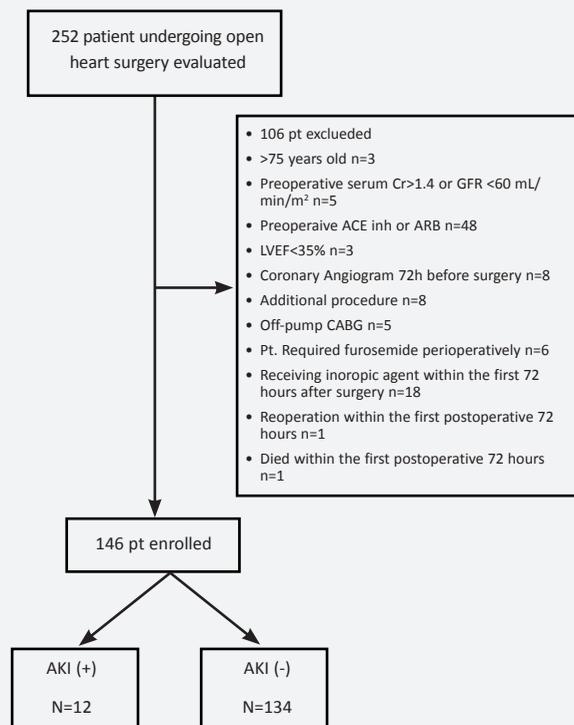

Figure 1.

Patients with more than 1.5-fold increase in their preoperative creatinine values on their third postoperative day were considered to have AKI according to RIFLE criteria [15]. The patients were divided into two groups as AKI(+) and AKI(-), regarding presence of AKI, and then intergroup comparisons were performed.

Demographic data of the patients (gender, age, body mass index [BMI], serum albumin level, LVEF, DM, HTN, and smoking) were recorded. Intraoperative mean perfusion pressure (MPP), postoperative mean arterial pressure (MAP) and central venous pressure (CVP) values, dissolved oxygen tension (pO_2), dissolved carbon dioxide tension (pCO_2), and hemoglobin (HGB) values were recorded. Durations of CPB and ACC, body temperatures during CPB, and the amount of blood and blood products used were recorded. Urinary outputs during ACC and CPB periods were compared between the groups.

Standard IV fluid management with crystalloid replacement was performed in all patients. Crystalloid infusion at a rate of 100 ml/h was performed throughout the operation. Standard anesthetic induction with intravenous propofol, fentanyl, and rocuronium bromide was performed in all patients. Anesthesia was maintained via inhalation of 60% oxygen and 6% desflurane.

Management of CPB
The same surgical team performed all the operations, using a standardized approach, a Terumo roller pump (Terumo Advanced Perfusion System 1, USA), membrane oxygenators (Dideco Compact Flo Evo, USA), mild to moderate (28-32°C) systemic hypothermia and continuous (nonpulsatile) pump flow of 2.2–2.4 L/m². In both groups, the CPB priming solution included 150 ml of 20% mannitol. Myocardial protection was achieved with tepid antegrade blood cardioplegia, and a "hot shot" of 250-500 ml was delivered just prior to removal of the aortic cross-clamping. The MPP was kept in between 60 and 80 mmHg at all times; where, ephedrine or glyceryl trinitrate was used if needed. The acid-base balance was maintained in physiologic levels (pH 7.35-7.45); where sodium bicarbonate was used if needed.

Diuretics was performed in patients with urine volume less than 0.5 ml/kg/h during cardiopulmonary bypass. Hemofiltration was planned in patients for whom no increase in urine volume was seen following diuretics. These patients were excluded from the study.

The hematocrit value during cardiopulmonary bypass was planned to be over 24%. If the hematocrit value falls below 24%, erythrocyte suspension is given.

The activated clotting time was maintained between 480 and 600 sec by heparin infusion. A protamine dose of 0.8 mg/kg was administered to neutralize heparin. Additional protamine was given until the activated clotting time reached 130 sec.

STATISTICAL ANALYSIS
Statistical analysis was performed using IBM SPSS Statistics 22 software. Descriptive statistical methods (mean, median, standart deviation, ratio, frequency) were used for data analysis. Independent sample T test was used for the normally distributed parameters, and Mann Whitney U test for the parameters with nonnormal distribution for intergroup comparisons. Wilcoxon -signed rank test was used while analyzing data within groups. Chi-square test was used for qualitative data.

The risk factors affecting AKI were analyzed using logistic (backward) regression analysis. Evaluation of diagnostic test was used to find the cut- off point for urine volume during cross- clamping period.

The confidence interval of the analysis was %95 and level of significance was p<0.05. Our study performed with 146 patients had a statistical power of 98% and an effect size of 0,49 within 95% confidence interval.

RESULTS

Among 146 patients included in the study, 12 patients had elevated serum creatinine levels (i.e., 1.5 times higher than the baseline). Thus, these patients were considered to have AKI according to RIFLE criteria.

The demographic variables (gender, age, BMI, HTN, DM, smoking and LVEF) were similar among the groups. Preoperative serum albumin value was statistically significantly lower in the AKI(+) than AKI(-) group (p=0.034) (Table 1).

Serum creatinine levels of the groups in the preoperative period were statistically similar (p=0.089). Postoperative serum creatinine level was statistically significantly higher in the AKI(+) group (p=0.001) (Table 2). While serum creatinine levels of AKI(+) patients showed statistically significant increase in the postoperative period (p=0.001), there was a statistically significant decrease in AKI(-) patients (p=0.002).

The CPB and ACC times, body temperatures during CPB surgery, number of vessels bypassed and the

Table 1. The data for demographic variables among the groups.			
	AKI (-) (n=134)	AKI (+) (n=12)	P
Age (year)	61.99±8.20	64.08±8.52	[d]0.401
Gender			
Male	100 (75)	9 (75)	[c]0.641
Female	34 (25)	3 (25)	
Diabetes			
+	70 (52)	7 (58)	[c]0.918
-	64 (48)	5 (42)	
Hypertension			
+	79 (59)	7 (58)	[c]0.956
-	55 (41)	5 (42)	
Smoking			
+	46 (34)	2 (17)	[c]0.179
-	88 (66)	10 (83)	
BMI (kg/m^2)	28.79±4.16 (28.59)	29.41±4.12 (29.08)	[a]0.806
LVEF (%)	56.04±8.57 (59)	53.00±7.73 (55)	[a]0.188
Albumin (mg/dL)	3.64±0.65 (3.9)	3.21±0.60 (3)	[a]0.034*

AKI: Acute Kidney Injury, LVEF: Left Ventricular Ejection Fraction

[a] *Mann Whitney U test: values are given as mean ± standard deviation (median)*
[b] *Fisher exact test: values are given as frequency (percentage)*
[c] *Chi-square test: values are given as frequency (percentage)*
[d] *İndependent Samples T test: mean± standard deviation*
*p<0.05

Table 2. Comparision of creatinine level between the groups.			
	AKI (-) (n=134)	AKI (+) (n=12)	p
Preoperative creatinine (mg/dL)	0.89±0.20 (0.84)	1.1±0.40 (0.96)	[a]0.089
Postoperative 3rd day creatinine (mg/dL)	0.84±0.23 (0.78)	2.18±0.67 (2.325)	[a]0.001*

AKI: Acute Kidney Injury

[a] *Mann Whitney U test: values are given as mean ± standard deviation (median)*

amount of blood products used were similar between the groups. HGB values were similar among the groups in the preoperative and postoperative periods (p>0.05) (Table 3). Also, there was a statistically significant decrease in the postoperative HGB levels of all patients (p=0.001).

The urinary output (mL/kg/h) during CPB and ACC of the AKI(-) group was significantly higher than that of the AKI(+) group (p<0.05) (Table 4).

MPP, PO2, PCO2, values and also fluid balance, MAP and CVP values within the first 72 hours after surgery were found to be similar between the groups (Table 5).

Urinary output less than 3.345 (mL/kg/h) during ACC predicted the presence of AKI with 74.6% sensitivity, 58.3% specificity, 17.07 % positive 95.24%. negative predictive value, 73.29%, accuracy, and relative ratio of 3.59 (Table 6).

Risk factors affecting AKI were analyzed by logistic (backward) regression analysis. While the variables

Table 3. Operative variables among groups.			
	AKI (-) (n=134)	AKI (+) (n=12)	P
Number of vessels (n)	3.40±0.93 (3)	3.82±0.75 (4)	a0.183
Duration of CPB (minutes)	117.85±33.71 (114)	121.42±27.27 (118)	a0.674
Duration of ACC (minutes)	70.40±23.20 (68)	75.25±22.07 (71)	a0.692
CPB temperature (°C)	31.07±1.03 (31)	31.00±0.60 (31)	a0.590
Preoperative HGB (mg/dL)	13.01±1.75 (13)	12.51±1.58 (12.3)	a0.172
Postoperative HGB (mg/dL)	9.17±0.80	9.43±0.64	b0.289
Number of blood products used (units)	0.85±0.92 (1)	1.42±1.56 (1)	a0.265

AKI: Acute Kidney Injury, CPB: Cardiopulmonery Bypass, ACC: Aortic Cross Clamp
a Mann Whitney U test: values are given as mean±standard deviation (median)

Table 4. Comparison of variables for urine output among the groups.			
	AKI (-) (n=134)	AKI (+) (n=12)	P
Urine output during ACC (mL/kg/hour)	5.34±3.14 (4.30)	3.81±2.56 (3.33)	a0.045*
Urine output during CPB (mL/kg/hour)	5.11±2.21 (4.45)	3.71±2.36 (3.30)	a0.046*

AKI: Acute Kidney Injury, ACC: Aortic Cross Clamp, CPB: Cardiopulmonery Bypass
a Mann Whitney U test: values are given as mean±standard deviation (median)
*p<0.05

Table 5. Intraoperative and Postoperative hemodynamic parameters of the groups within the first 72 hours.			
	AKI (-) (n=134)	AKI (+) (n=12)	P
Intraoperative MPP (mmHg)	60.00±4.59 (60)	60.83±1.95 (60)	a0.210
Intraoperative pO$_2$ (mmHg)	256.94±50.11	258.42±44.16	b0.922
Intraoperative pCO$_2$ (mmHg)	36.90±4.96 (36.5)	34.42±3.82 (35.5)	a0.086
Fluid balance within the first 72 hours after surgery (mL)	864.77±861.45 (700)	754.16±433.51 (775)	a0.575
MAP within the first 72 hours after surgery (mmHg)	99.89±12.77 (100)	98.75±11.31 (95)	a0.648
CVP within the first 72 hours after surgery (mmHg)	6.27±1.65 (6)	6.83±1.34 (7)	a0.214

AKI: Acute Kidney Injury, MPP: Mean perfusion pressure, pO$_2$: dissolved oxygen tension,
pCO$_2$: dissolved carbon dioxide tension, CVP: Central venous pressure, MAP: Mean arterial pressure
a Mann Whitney U test: values are given as mean±standard deviation (median)

Table 6. Evaluation of diagnostic tests to determinate cutoff point of urine output during ACC for acute kidney injury.

UO	Sensitivity	Specificity	PPV	NPV	Accuracy	RR
≤3.315	75.4	41.7	13.16	93.52	72.60	2.03
≤3.345	74.6	58.3	17.07	95.24	73.29	3.59
≤3.380	73.9	58.3	16.67	95.19	72.60	3.47
≤3.450	70.9	58.3	15.22	95.00	69.86	3.04

PPV: Positive predictive value , NPV: Negative predictive value
RR: Relative Ratio, UO: Urine Output

Table 7. Results of the logistic regression analysis to predict AKI.

	B	Wald	p	OR	95% C.I.for EXP(B)	
					Lower	Upper
Age (year)	-.033	.367	.545	.967	.869	1.077
Albumin (mg/dL)	-1.436	5.374	.020	.238	.071	.801
BMI (kg/m^2)	-.026	.072	.789	.975	.808	1.175
Diabetes	.516	.359	.549	1.676	.310	9.068
Hypertension	-1.045	1.531	.216	.352	.067	1.841
CPB temperature (°C)	-.287	.498	.480	.751	.338	1.666
Duration of CPB (minutes)	-.008	.135	.714	.992	.952	1.034
Duration of ACC (minutes)	-.011	.135	.714	.989	.931	1.050
Urine output during CPB (mL/kg/hour)	-.263	1.141	.285	.769	.474	1.246
Urine output during ACC (mL/kg/hour)	1.314	2.300	.129	3.720	.681	20.313
Number of blood products used (units)	.999	6.452	.011	2.716	1.256	5.873
Preoperative creatinine (mg/dL)	3.110	5.625	.018	22.421	1.716	292.955
Constant	12.666	.762	.383	316944.201		

AKI: Acute Kidney Injury, BMI: Body mass index, CPB: Cardiopulmonery Bypass, ACC: Aortic Cross Clamp

which were found to be statistically significant or close to significance (p<0.05) by univariate analysis and the variables known to affect AKI in the literature constituted independent variables, AKI was used as the dependent variable. The independent variables were age, serum albumin, BMI, DM, HTN, CPB temperature, the number of blood products used (units), urine volume during CPB, preoperative serum creatinine (mg/dL), CPB time, ACC time and total urine output during ACC (ml/kg/hour) (cut-off value 3.345).

The results of the backward logistic regression test showed that serum albumin, preoperative creatinine and the amount of blood products were used as statistically significant risk factors for AKI. However, the other variables were not statistically significant (Table 7).

None of the patients in either group required renal replacement therapy.

DISCUSSION

AKI is one of the most serious complications of cardiac surgery, resulting in increased rates of patient mortality and morbidity [1,2,16]. In this study, we evaluated urinary output during ACC and CPB times as a criterion for the prediction of AKI. Following cardiac surgery, the urinary outputs of patients with AKI were significantly lower during ACC and CPB surgery than those without AKI. We identified the optimal cut-off value for urinary output during ACC to predict AKI.

The pathogenesis of kidney injury during CPB surgery is complex and involves hemodynamic, inflammatory, and other mechanisms that interact at a cellular level. Previous studies have emphasized the roles of old age, DM, HTN, smoking, and LVEF as risk factors for AKI [8,9]. In our study, these risk factors

and demographic data were similar in both groups. Neugarten et al. concluded that female gender was an independent risk factor for AKI that occurred after cardiothoracic surgery [17]. In the present study, the gender distribution of the patients in the two groups was similar. Findik et al. [18] reported that, low preoperative serum albumin levels were associated with postoperative AKI and increased mortality in patients who underwent isolated coronary artery bypass surgery. Similarly, in the current study, preoperative serum albumin levels in the AKI(+) group were significantly lower than those in the AKI(-) group. In parallel with this finding, the effect of serum albumin level on occurrence of AKI was found to be statistically significant based on the results of logistic regression analysis (p=0.020).

A number of studies have concluded that prolonged CPB and ACC times were risk factors for AKI following cardiac surgery [8,19,20]. Boldt et al. suggested that the postoperative risk of AKI increased in patients when the CPB time exceeded 70 min. [21]. In the present study, the CPB and ACC times were statistically similar between the groups. The ACC and CPB times were not determined as risk factors affecting AKI based on the results of regression analysis. We suppose that, this situation might be a result of the limited number of AKI(+) patients.

The effects of nonpulsatile blood flow on visceral organs during cardiopulmonary bypass are still on debate. Pulsatile blood flow is reported to reduce organ damage due to its beneficial effects on tissue microcirculation and metabolism by reducing peripheral vascular resistance [22]. However, there are also studies mentioning that pulsatile blood flow has no effect on renal functions [23]. All the stages of cardiac surgery effect renal functions. But, we suppose that the most critical stage is ACC period due to initiation of nonpulsatile blood flow. Therefore, we think that there may be a relationship between the urinary output at this period and the occurrence of AKI.

Kron et al. suggested that hypothermia during CPB

reduces renal functions [24]. Regraui et al [25] reported that renal functions at different body temperatures during CPB were not significantly different. In our study, the body temperatures of the patients in both groups were similar.

Various studies have reported that the risk of postoperative AKI increases in accordance with hemodynamic instability and hemodilution, and hematocrit levels less than 25% were detected during CPB [7,26]. In a previous study of patients with normal preoperative renal functions, the patients were divided into two groups. MPP value of one group was adjusted to 50-60 mmHg, and MPP of the other group to more than 70 mmHg [27]. A comparison between these group did not reveal any differences in postoperative renal functions, although intraoperative creatinine clearance values were higher in the group with MPP over 70 mmHg. In the present study, MPP values, preoperative and postoperative HGB levels were similar in the two groups.

In the present study postoperative fluid balance, MAP and CVP values within the first postoperative 72 hours were similar between the groups standardised in terms of major risk factors effective on AKI during postoperative period.

By changing erythrocyte rheology and reducing oxygen transfer to renal cells, hyperoxemia and hypoxemia had exerted negative effects on renal perfusion during cardiopulmonary bypass surgery [28]. In our study, intraoperative pO_2 values were similar between the groups.

In a previous retrospective study, Yilmaz et al. reported that urinary output during CPB surgery was an important indicator of postoperative AKI [13]. Likewise, in a retrospective study, Song et al. concluded that urinary output during CPB surgery was a simple and feasible marker to indicate postoperative AKI [14]. Similarly, in the present study, urinary output during CPB surgery and ACC were significantly lower in the AKI(+) group. Regarding AKI, the cut-off value

for the urinary output during ACC period was found as 3.345 mL/kg/h. As a result, a urinary output less than 3.345 mL/kg/h during ACC was interpreted as an indicator of AKI.

The present study was accepted as an oral presentation at the 23th National Congress of Turkish Society of Thoracic and Cardiovascular Anesthesia and Intensive Care.

In our study, there is no conflict of interest between the authors.

CONCLUSION

Our data have demonstrated that urinary output during ACC and CPB may be a valuable criterion for early diagnosis of AKI. We suppose that, the patients with a urine output less than 3.345 mL/kg/h during ACC period carry a high risk for postoperative AKI.

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