

The association of blood transfusion and acute kidney injury in diabetic coronary artery bypass grafting patients

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ABSTRACT

Objectives: This study aims to investigate the association between blood transfusion and acute kidney injury (AKI) in diabetic coronary artery bypass grafting (CABG) patients.

Patients and methods: Between October 2016 and September 2019, a total of 270 elective CABG patients with diabetes (62 males, 208 females; mean age: 63.2±9.3 years; range, 40 to 86 years) were retrospectively analyzed. The patients were divided into two groups according to presence of cardiac surgery-related AKI. Risk factors were compared between the groups.

Results: No significant difference was found between the groups in terms of baseline characteristics, except for body mass index, EuroSCORE II, and platelet count. The significant factors in the univariate analysis were included in the logistic regression. Only blood transfusion was found to be associated with AKI with red blood cell, fresh frozen plasma, platelet, and complete transfusions ($p<0.001$, $p<0.001$, $p=0.002$, and $p<0.001$, respectively).

Conclusion: Our study results suggest that perioperative red blood cell, fresh frozen plasma, platelet, and complete transfusions are associated with postoperative AKI in diabetic CABG patients.

Keywords: Acute kidney injury, blood transfusion, coronary artery bypass grafting, diabetes mellitus.

Coronary artery bypass grafting (CABG) is safely performed with low mortality and morbidity rates thanks to the increased surgical experience in recent years. Despite the increase in surgical experience, CABG may demand additional medical requirements that bring along inevitable complications. Blood transfusions are one of the most common requirements accompanying CABG and may result in undesirable side effects, such as acute kidney injury (AKI).^[1]

Blood transfusion is frequently required after cardiac operations and the causes for transfusion requirement are several. Surgical bleeding during both the intra- and postoperative periods is very common in CABG patients.^[2] Antiaggregant and/or anticoagulant medications are frequently used during the perioperative period. The use of a cardiopulmonary bypass may lead to coagulopathy as a result of platelet dysfunction and a deteriorated coagulation cascade. Fluid replacement, particularly with crystalloids to provide hemodynamic stability, may cause dilutional anemia. All these factors play a role in the need for blood transfusion after CABG surgery.^[3,4]

Blood transfusions are associated with AKI in CABG patients.^[5,6] Meanwhile, anemia itself has been shown as another cause of AKI.^[7] Maintaining a balance is important not to cause anemia, while also avoiding an unnecessary blood transfusion.

Patients undergoing CABG surgery have a high rate of diabetes mellitus. Diabetes mellitus increases the complication rates associated with AKI, impaired wound healing, and mortality.^[8,9] As diabetic patients are more susceptible to postoperative complications, special implementations with these patients may provide better outcomes after CABG. This is why we

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have given a special interest in investigating the group of diabetic patients.

In this study, we aimed to investigate the risk factors, particularly blood transfusions in diabetic CABG patients, associated with AKI.

PATIENTS AND METHODS

The single-center, retrospective study was conducted at Kütahya Health Sciences University, Evliya Çelebi Training and Research Hospital, Department of Cardiovascular Surgery between October 2016 and September 2019. A total of 270 elective CABG patients with diabetes (62 males, 208 females; mean age: 63.2 ± 9.3 years; range, 40 to 86 years) who were followed up to two weeks until discharge were included in the study. All patients included in the study were elective CABG patients, all of whom had normal regulation of blood glucose at least one week before surgery to eliminate the negative effects of uncontrolled blood glucose. Patients with emergency CABG surgery, off-pump surgery, simultaneous operations with CABG, cardiac reoperations, preoperative renal impairments, and in-hospital mortality were excluded from the study to standardize the results and avoid potential pre-existing negative impacts on renal function. All patients were operated at the same center using the same anesthesia, cardiopulmonary bypass, and operation protocols. Data including baseline demographic characteristics and follow-up were retrieved from hospital database. A written informed consent was obtained from each patient. The study protocol was approved by the Kütahya Provincial Health Directorate Ethics Committee (No: 2021/16). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Acute kidney injury was classified in accordance with the Kidney Disease: Improving Global Outcomes (KDIGO) criteria.^[10] The patients' final measurement values before surgery were defined as the baseline measurements. The serum creatinine level at 48 h after surgery was recorded. An increase in baseline creatinine of over 50% (i.e., 0.3 mg/dL increase) was defined as Stage 1 AKI, an increase of $\geq 100\%$ as Stage 2 AKI, and an increase of $\geq 200\%$ as Stage 3 AKI. None of the patients had Stage 2-3 AKI. The patients having no AKI constituted the AKI-negative group, while the patients diagnosed with Stage 1 AKI constituted the AKI-positive group. The estimated glomerular

filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration Equation (CKD-EPI) and the Cockcroft-Gault formula for estimating creatinine clearance (CrCl).^[11]

Administering red blood cell (RBC) transfusion was decided, when a hematocrit level below 25% or hemoglobin level below 8 g/dL was detected in the perioperative period. Administering a fresh frozen plasma (FFP) transfusion was decided, when the international normalized ratio was above 1.4 or activated clotting time or activated partial thromboplastin time was two-times higher than the baseline value. Administering a platelet transfusion was decided, when a platelet count was below 100 ($10^3/\mu\text{L}$) and ongoing hemorrhage or drainage was detected.

The primary outcome measure of the study was AKI as defined in accordance with the KDIGO criteria.

Statistical analysis

Statistical analysis was performed using the Jamovi version 1.2.27 software (<https://www.jamovi.org>). The Shapiro-Wilk test, skewness and kurtosis values, histograms, and *Q/Q* plots have been used to identify distribution patterns. Descriptive data were expressed in mean \pm standard deviation (SD) or median (interquartile range [IQR]) for continuous variables and in number and frequency for categorical variables, where applicable. For the nominal variables, the chi-square test was used to compare the groups. As the number of patients with postoperative AKI was less than 30 ($n=19$), the Mann-Whitney U test was used to compare the non-parametric data. Multivariate analysis was performed on the variables which were found to be statistically significant in the univariate analysis or that are established risk factors as defined in the literature. A *p* value of <0.05 was considered statistically significant.

RESULTS

Of all 270 elective diabetic CABG patients included in the study, 19 patients were in the AKI-positive group with Stage 1 AKI, while 251 were in the AKI-negative group. Among the patients, 118 (43.7%) had hypertension. There was no significant difference in the baseline demographic characteristics of the groups including age, sex, presence/lack of hypertension, chronic pulmonary disease, and

Table 1 Baseline demographic and clinical characteristics of patients											
	AKI-negative (n=251)					AKI-positive (n=19)			p		
	n	%	Mean±SD	Median	Min-Max	n	%	Mean±SD		Median	Min-Max
Age (year)			62.9±9.3					66.8±8.45		0.073	
Female	190	75.7				18	94.7			0.057	
Hypertension	112	44.6				6	31.6			0.269	
Chronic pulmonary disease	41	16.3				0	0			0.056	
Peripheral vascular disease	60	23.9				5	26.3			0.813	
Body mass index (kg/m ²)			27.9±4.0					25.4±4.6		0.010	
EF			48.6±9.9					47.9±10.2		0.794	
EuroSCORE II				1.86	1.29-3.10				2.45	1.81-3.78	0.024
Baseline laboratory values											
Hematocrit (%)			39.3±5.6					40.2±4.1		0.526	
Hemoglobin (g/dL)			13.5±1.9					13.9±1.4		0.434	
Platelet (10 ³ /μL)				239	201-286				209	185-235	0.045
Creatinine (mg/dL)				1.00	0.86-1.17				1.03	0.84-1.21	0.582
Creatinine clearance (mL/min)			81.8±26.7					70.0±21.4		0.062	
Glomerular filtration rate (mL/min/1.73 m ²)			64.9±20.7					56.9±19.8		0.106	
AKI: Acute kidney injury; SD: Standard deviation; Min: Minimum; Max: Maximum.											

AKI: Acute kidney injury; SD: Standard deviation; Min: Minimum; Max: Maximum.

Table 2
Comparison of patient groups according to postoperative renal measurements and perioperative blood transfusion

	AKI-negative (n=251)			AKI-positive (n=19)			<i>p</i>
	Mean±SD	Median	Min-Max	Mean±SD	Median	Min-Max	
Creatinine (postoperative)		1.06	0.92-1.23		1.32	1.22-1.54	<0.001
CrCl (postoperative)	70.3±23.4			45.6±15.0			<0.001
eGFR (postoperative)	60.1±19.2			39.7±11.3			<0.001
Perioperative blood transfusion							
RBC (unit)	1.6±1.3			4.0±1.3			<0.001
FFP (unit)	2.8±1.3			4.4±1.6			<0.001
Platelet (unit)		0	0-0		0	0-1	0.002
nonRBC (unit)	3.1±1.6			5.3±2.3			<0.001
Complete transfusion (unit)	4.7±2.5			9.2±3.2			<0.001

AKI: Acute kidney injury; CrCl: Creatinine clearance; eGFR: Estimated glomerular filtration rate; FFP: Fresh frozen plasma; RBC: Red blood cell.

peripheral vascular disease; and baseline hematocrit, hemoglobin, and creatinine levels, except for the body mass index, EuroSCORE II, and baseline platelet count (Table 1).

Postoperative renal measurements such as creatinine levels, CrCl, and eGFR revealed statistically significant differences between the groups (Table 2). Of the patients, 41 had no RBC transfusion during the perioperative period; all patients had at least one unit of transfusion (RBC or non-RBC transfusion). The AKI-positive group was found to have higher transfusion rates, including RBC ($p<0.001$), FFP ($p<0.001$), platelet ($p=0.002$), and complete ($p<0.001$) transfusions. None of the patients had any permanent postoperative renal impairment.

The factors found to be significant in the univariate analysis and the established risk factors described in the literature for AKI were examined (Table 3). For renal impairment, the eGFR was taken into account to represent renal function. No statistically significant relationship was found for age, hypertension, EuroSCORE II, or baseline eGFR with AKI in the logistic regression analysis. Perioperative RBC transfusions, non-RBC transfusions (summation of the FFP and platelet transfusions), and complete transfusions were found to be associated with AKI. The $R^2_{\text{Nagelkerke}}$ was greater than 20% and accuracy exceeded 90% for all three univariate logistic regression analyses, all of which had values of $p<0.001$.

Table 3
Univariate logistic regression analysis results for acute kidney injury

	Odds ratio	95% CI	<i>p</i>	$R^2_{\text{Nagelkerke}}$	Accuracy
Age	1.050	0.995-1.108	0.075	-	-
Hypertension	0.573	0.211-1.555	0.274	-	-
EuroSCORE II	1.093	0.912-1.310	0.336	-	-
Baseline eGFR	0.981	0.958-1.000	0.107	-	-
RBC (unit)	2.572	1.838-3.597	<.001	0.335	91.9%
nonRBC (unit)	1.829	1.423-2.352	<.001	0.216	93.7%
Complete transfusion (unit)	1.543	1.321-1.802	<.001	0.310	93.7%

CI: Confidence interval; eGFR: Estimated glomerular filtration rate; RBC: Red blood cell.

The receiver operating characteristic (ROC) curve analysis was performed for the statistically significant variables (i.e., RBC, non-RBC, and complete transfusions) to define a cut-off value for each; however, reliable cut-off values could not be obtained due to the limited number of patients in the AKI-positive group. The statistically insignificant results of the ROC analysis are not presented.

DISCUSSION

Diabetic patients are prone to complications after CABG surgery, and a special interest and implementations are required during the perioperative period. Diabetic CABG patients are at an increased risk for cerebrovascular disease, AKI, sternal infections, and mortality and require transfusions more often.^[12] Diabetes mellitus is an independent risk factor for AKI, even when blood transfusions are not considered. Endothelial dysfunction and impaired microcirculation are considered to be responsible for its pathogenesis.^[12,13]

Several factors have been found to be associated with increased blood transfusion. According to Klein et al.,^[14] age, sex, body surface area, logistic EuroSCORE, preoperative hemoglobin and creatinine were associated with increased blood transfusion.

Blood transfusions are a specific topic that may complicate and lead to AKI in CABG patients and requires a rigorous approach.^[15] Cardiovascular surgeons tend to avoid redundant blood transfusions, and studies defining the safe limits for blood transfusion have been previously published.^[16] Restrictive or liberal thresholds for RBC transfusions were investigated by Mazer et al.^[17] The transfusion criteria were defined as a hemoglobin level of <7.5 mg/dL for the restrictive threshold approach and a hemoglobin level of <9.5 mg/dL for the liberal threshold approach. The study showed the restrictive threshold approach to not be inferior to the liberal threshold approach with respect to mortality, infection, neurological complications, pulmonary impairment, and AKI. The six-month follow-up results of the study also supported the initial results.^[18]

Lower body mass index, higher logistic EuroSCORE II, and lower preoperative platelet counts in our cohort were found to be associated with Stage 1 AKI. Receiving blood transfusion during the perioperative period was also found to be associated

with a higher incidence of Stage 1 AKI in terms of RBC, FFP, platelet, and complete transfusions.

In their propensity score-matched retrospective study, Kocyigit et al.^[19] found receiving blood transfusion not to be associated with new-onset dialysis or discharge creatinine level in diabetic CABG patients. The Koster et al.'s^[20,21] studies also found no significant association between blood transfusion and renal impairment in terms of RBC and apheresis platelet concentrates. However, according to Amini et al.,^[22] AKI was associated with RBC transfusions and diabetes, in addition to advanced age, on-pump cardiac surgery, and prolonged mechanical ventilation.

Although blood transfusions have been shown to be associated with negative outcomes, postoperative anemia after CABG surgery is also related to the increased morbidity.^[23] To maintain vital functions at the cellular level and avoid anemia induced hypoxia, keeping hemoglobin levels within the safe range, while avoiding unnecessary blood transfusions is essential.

The use of erythropoietin, oral or intravenous iron replacement, and a predeposit autologous donation may help prevent blood transfusions in the preoperative period. During the intraoperative and early postoperative periods, the use of tranexamic acid and cell salvage may be beneficial. Minimal invasive approaches including thoracoscopic, robotic-assisted, or transcatheter techniques are applicable. Endoscopic harvesting of the saphenous vein may also have relevance.^[24-26]

Our study presents the results from a limited number of patients. This is the main limitation of the study. The Stage 1 AKI-positive group had a low number of patients; as such, propensity score-matching may not be applicable. Variables that may affect renal impairment such as how many years the patient has been diagnosed as diabetic, their insulin use and dosage amounts, glycated hemoglobin (HbA1c) levels, drainage amounts, use of inotropic agents, and presence of an intra-aortic balloon pump were not studied. This is another limitation of our study. The retrospective design of the study is the third limitation. However, a sample of patients from a single cardiac center provides similar surgical and anesthetic management for the entire study group, which relatively strengthens the results of our study.

In conclusion, our study results suggest that perioperative RBC, FFP, platelet, and complete

transfusions are associated with postoperative AKI among diabetic CABG patients. Further large-scale, prospective, randomized-controlled studies are needed to gain a better understanding of blood transfusion-associated AKI in this population.

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