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ORIGINAL ARTICLE / ÖZGÜN MAKALE

The effects of perioperative goal-directed therapy on acute kidney injury after cardiac surgery in the early period

Perioperatif hedefe yönelik tedavinin kardiyak cerrahi sonrası erken dönem akut böbrek hasarı üzerine etkileri

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ABSTRACT

Background: This study aims to investigate the effects of goal-directed fluid therapy on the development of acute kidney injury in the perioperative period in patients undergoing cardiopulmonary bypass.

Methods: Between November 2019 and May 2021, a total of 60 patients (46 males, 14 females; mean age: 62.5±9.6 years; range, 44 to 76 years) who were scheduled for elective coronary artery bypass grafting or valve surgery under cardiopulmonary bypass were included in the study. The patients were divided into two groups as the study group (Group S, n=30) and control group (Group C, n=30). The patients in Group C were treated with standard therapy, while the patients in Group S were treated with goal-directed fluid therapy. The Kidney Disease: Improving Global Outcomes (KDIGO) classification and renal biomarkers were used for the evaluation of acute kidney injury.

Results: Acute kidney injury rates were similar in both groups (30%). Postoperative fluid requirement, intra-, and postoperative erythrocyte suspension requirements were significantly lower in Group S than Group C (p=0.002, p=0.02, and p=0.002, respectively). Cystatin-C was lower in Group S (p<0.002). The kidney injury molecule-1, glomerular filtration rate, and creatinine levels were similar in both groups. The length of hospital stay was longer in Group C than Group S (p<0.001).

Conclusion: Although goal-directed fluid therapy does not change the incidence of acute kidney injury in patients undergoing cardiac surgery, it can significantly decrease Cystatin-C levels. Goal-directed fluid therapy can also decrease fluid and erythrocyte requirements with shorter length of hospital stay.

Keywords: Acute kidney injury, cardiac surgery, goal-directed therapy.

ÖZ

Amaç: Bu çalışmada kardiyopulmoner baypas yapılan hastalarda perioperatif dönemde hedefe yönelik sıvı tedavisinin akut böbrek hasarı gelişimi üzerindeki etkileri incelendi.

Çalışma planı: Kasım 2019 - Mayıs 2021 tarihleri arasında kardiyopulmoner baypas altında elektif koroner arter baypas greftleme veya kapak cerrahisi yapılması planlanan toplam 60 hasta (46 erkek, 14 kadın; ort. yaş: 62.5±9.6 yıl; dağılım, 44-76 yıl) çalışmaya alındı. Hastalar çalışma grubu (Grup S, n=30) ve kontrol grubu (Grup C, n=30) olmak üzere iki gruba ayrıldı. Grup C'deki hastalar standart tedavi ile tedavi edilirken, Grup S'deki hastalar hedefe yönelik sıvı tedavisi ile tedavi edildi. Akut böbrek hasarının değerlendirilmesinde Böbrek Hastalığı: Küresel Sonuçların İyileştirilmesi (KDIGO) sınıflandırması ve renal biyobelirteçler kullanıldı.

Bulgular: Akut böbrek hasar oranları her iki grupta da benzerdi (%30). Ameliyat sonrası sıvı gereksinimi, ameliyat sırası ve sonrası eritrosit süspansiyon gereksinimi Grup S'de, Grup C'ye kıyasla anlamlı düzeyde düşük idi (sırasıyla, p=0.002, p=0.02 ve p=0.002). Sistatin-C, Grup S'de anlamlı düzeyde düşük bulundu (p<0.002). Böbrek hasarı molekülü-1, glomerüler filtrasyon hızı ve kreatinin düzeyleri her iki grupta da benzerdi. Hastanede kalış süresi Grup S'ye kıyasla Grup C'de daha uzundu (p<0.001).

Sonuç: Hedefe yönelik sıvı tedavisi kalp cerrahi yapılan hastalarda akut böbrek hasarı görülme sıklığını değiştirmese de, Sistatin-C düzeyini anlamlı olarak düşürebilir. Ayrıca hedefe yönelik sıvı tedavisi ile sıvı ve eritrosit gereksinimi azaltılabilir ve hastanede kalış süresi kısaltılabilir.

Anahtar sözcükler: Akut böbrek hasarı, kalp cerrahisi, hedefe yönelik tedavi.

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Acute kidney injury (AKI) after open heart surgery is the second most common cause of all-cause AKI.[1] The rate of cardiac surgery associated-AKI ranges from 5 to 60%.[1-3] Previous studies have shown that even small deterioration of kidney functions has been associated with prolonged length of hospital stay, higher costs, and impaired outcomes.[4,5] Most of these problems are reversible within days to weeks of occurrence, but relevant studies over the past decade have demonstrated that there is an association between AKI, chronic kidney disease, and end-stage renal disease.[6-8] Therefore, the development of effective approaches to the prevention of AKI is necessary to reduce both the charge of chronic kidney disease and other significant mortality and morbidities.[6,9] The setup of cardiopulmonary bypass (CPB), amount and type of fluids used for anesthesia induction, volume replacement therapy and pump-priming, extended hypotension time, development of venous congestion, and nephrotoxic drugs usage are the main reasons for the AKI development.[10-12]

Inadequate kidney perfusion and hypoxia contribute to the pathogenesis of postoperative AKI. Low cardiac output, low flow, blood pressure, and low oxygen delivery can associate with tissue ischemia during and after cardiac surgery. Maintaining adequate intravascular volume and organ perfusion pressures are protective against hypoperfusion.[13,14] On the other hand, venous congestion plays a role in the pathophysiology of AKI.[15]

The aim of goal-directed fluid therapy (GDT) is to improve systemic oxygen delivery (DO_2) to tissues. For this purpose, it uses fluids, blood transfusions and/or inotropes, accompanied by an algorithm.[16] Recently, the monitors using minimally invasive techniques make possible continuous cardiac output, systemic vascular resistance index (SVRI), and DO_2. These technologies use pulse counter (pressure based) and esophageal Doppler (flow based). These new technologies are expanding the application of GDT. Meta-analyses and clinical studies suggest that the GDT strategy performed in high-risk patients undergoing cardiac surgery reduces the 30-day mortality, reduces major complication ratios, and decreases intensive care unit (ICU) and hospital length of stay.[16-22] Furthermore, GDT is a strongly recommended component of cardiac surgical enhanced recovery.[9] However, in cardiac surgery, the importance of GTD on kidney injury has not been mentioned adequately in the literature.[21-23]

In the present study, we aimed to investigate the impact of the GDT-employed approach on perioperative AKI in patients undergoing CPB in the early postoperative period. Our second objective was to investigate the possible factors leading to AKI (ejection fraction [EF], cardiac output, cross-clamp [CC] duration, pump balance, and CPB duration).

PATIENTS AND METHODS

This single-center, prospective, stratified randomized study was conducted at Manisa Celal Bayar University Hafsa Sultan Hospital, Department of Anesthesiology and Cardiovascular Surgery between November 2019 and May 2021. A total of 72 patients aged ≥18 years who were scheduled for elective coronary artery bypass grafting (CABG) or valve surgery with CPB were included in the study. Those with preoperative renal disease and/or high creatinine levels (>1.2 mg/dL) (n=7), undergoing hemodialysis (n=4), and contraindication to insert esophageal Doppler probe (n=1) were excluded from the study. Finally, a total of 60 patients (46 males, 14 females; mean age: 62.5±9.6 years; range, 44 to 76 years) were included. The patients were randomized as stratified according to the EuroSCORE II scoring system and left ventricular EF (LVEF) for patients undergoing cardiac surgery by using a random-number table during the preoperative visit.

The patients were divided into two groups as the study group (Group S, n=30) and control group (Group C, n=30). The patients in Group C were treated with standard therapy, while the patients in Group S were treated with GDT.

Hemodynamic management protocol

In Group S, stroke volume index (SVI)-guided management was followed according to the decision tree guidelines (Figure 1). The SVI and the other hemodynamic data were monitored by esophageal Doppler (CardioQ-ODM+, Deltex, Chichester, UK).[24] An esophageal probe was inserted gently into the middle esophagus of patients after anesthesia induction. An SVI of greater than 30 mL/beat/m^2 was targeted. When the SVI was below that value, a volume of 250 mL of balanced electrolyte solution (Isolyt S, Koçak Farma, Istanbul, Türkiye) was infused. The fluid replacement was repeated with 5-min intervals, until there was no more increase and/or was decreased than 10% in SVI. Colloids (3 balanced electrolyte solutions: 1 colloid) were used only, when fluid replacement with crystalloids was not sufficient to optimize preload. When hemodynamic instability (mean arterial pressure [MAP] ≤65 mmHg) occurred perioperatively, firstly fluid responsiveness was evaluated. If SVI was still under target value, then corrected flow time (FTc)

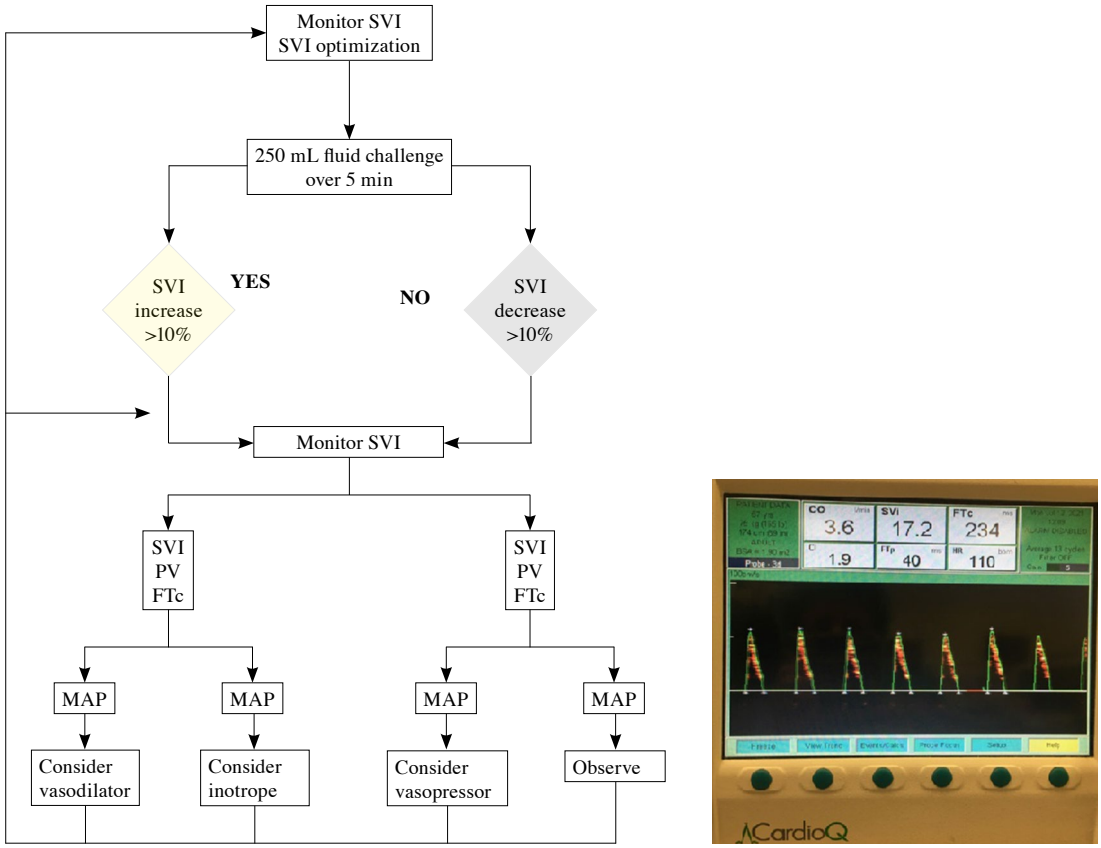

Figure 1. Goal-directed therapy algorithm protocol guided in the study group by esophageal Doppler monitoring parameters.

SVI: Stroke volume index; PV: Peak velocity; FTc: Corrected flow time; MAP: Mean arterial pressure.

(330-360 msec), peak velocity (PV) (140-(age of patient)=cm/in), SVRI (1,500 to 2,500 dyn/s/cm^5/C), cardiac index (CI >2.5 L/min/m^2) were evaluated. For keeping those parameters in normal ranges, infusion of inotropic (dobutamine; 3 to 5 µg/kg/h and/or adrenaline 0.05 µg/kg/min) and/or vasoconstrictor (noradrenaline; 0.02 to 1.5 µg/kg/min) and/or vasodilator (nitroglycerin; 0.1 µg/kg/h) agents were infused (Figure 1). Cardiac rhythm and frequency were optimized. The GDT protocol application was continued, until the weaning of ventilation in the postoperative care unit. After extubation, the patient's SVI was followed with transthoracic echocardiography. In Group C, according to standard clinical practice, fluids and/or inotropic-vasoactive drugs were administered to keep the MAP above 65 mmHg. If the MAP was lower than target values, the fluid (balanced crystalloid, colloid, or blood or blood products) was given until central venous pressure (CVP) at 8 to 10 mmHg. lf the MAP was still below 65 mmHg, inotropic agents and/or vasoconstrictor agents were begun according to the decision of the operation team. Heart rate optimization was also considered.

Anesthesia and CPB management

Anesthesia induction was similar in all cases. Anesthesia was induced with fentanyl (3 to 5 µg/kg), midazolam (0.1 mg/kg), and rocuronium bromide (0.6 mg/kg). Maintenance of anesthesia was continued with fentanyl (0.2 to 0.3 mg/h) infusion and intermittent bolus midazolam (2 mg/h) and rocuronium bromide (20 mg/h) and 2% sevoflurane in 50% O_2: 50% air mixture was applied. The cases were ventilated with a tidal volume of 6 mL/kg in a volume-controlled manner.

The CPB management was performed according to the routine protocol of the clinic. The patients were administered 300 U/kg of heparin before cannulation, and activated clotting time (ACT) was maintained over 400 sec during CPB. Sevoflurane inhalation anesthesia and fentanyl (0.2 to 0.4 mg/h) infusion were continued during CPB. Bolus midazolam (2 mg/h) and rocuronium (20 mg/h) were administered

intermittently. Myocardial protection was performed using intermittent, tepid, high-potassium blood antegrade and retrograde cardioplegia of 1,500 mL initially and was repeated after 20 min. The CPB was performed using a membrane oxygenator and roller pump, maintaining the arterial partial oxygen pressure levels between 150 and 200 mmHg. The mean perfusion flow rate was kept at 2.1 to 2.6 L/min/m^2 adjusted to according to body surface area (BSA) and temperature. When CPB was terminated, heparin was antagonized.

Blood management was applied similarly in both groups. In all patients, hemoglobin (Hb) was targeted at >7 g/dL during CPB and >8 g/dL after weaning from CPB. In cases with critical lesions, Hb was kept at >9 g/dL.

Data collection

The hemodynamic data of the cases (MAP, CVP) were recorded at 10 min after induction (t1), 4 h (t2), 24 h (t3), and 48 h (t4) in the postoperative ICU. Additionally, in Group S, the SVI, CI, SVRI, and (DO_2) were monitored continuously via esophageal Doppler monitoring and recorded at the study data collection time. Blood samples for biochemical markers (creatinine, glomerular filtration rate [GFR], kidney injury molecule-1 [KIM-1], and cystatin-C) analysis were collected at baseline (t1) and at t2, t3, and t4.

Renal failure was determined according to the Kidney Disease: Improving Global Outcomes (KDIGO) classification. In terms of biochemical parameters, renal failure was determined with serum creatinine, GFR, cystatin-C, and KIM-1. Patients' risk factors, medications, cardiac surgery type, age, BSA, EF, EuroSCORE II, operation time, CPB duration, CC duration, ventilation duration, ICU stay, hospitalization duration and total requirement of an inotrope, vasoconstrictor, and vasodilator agents was recorded.

Randomization

Stratified randomization was performed for predetermined risk factors. All patients were assigned to one of four predetermined stratification categories considering EuroSCORE II and EF, which have shown an association with AKI in patients undergoing cardiac surgery.[25-27] The order of the permuted sets was randomly determined by Internet-based software.

Statistical analysis

Statistical analysis was performed using the Statistica for Windows version 12.5 software (StatSoft, Inc., OKC, USA). The distribution characteristics of the variables were determined using the Shapiro-Wilk or Kolmogorov-Smirnov tests. Continuous data were expressed in mean ± standard deviation (SD) or median and interquartile range (IQR), while categorical data were expressed in number and frequency. In the comparison of two independent groups, the Student t-test or analysis of variance (one-way or repeated measure ANOVA) was used for parametric variables, and the Mann-Whitney U test was used for non-parametric continuous variables. The inter-group post-hoc comparisons of variables with significant two-way (group-time) interaction with the ANOVA test were made with the Tukey honestly significant difference test. The Fisher exact test for two or Pearson chi-square (χ^2) tests were used to compare inter-group categorical variables. Independent factors affecting the formation of postoperative AKI were investigated using the Forward Stepwise Binary Logistic Regression analysis. The estimation accuracy was confirmed by the backward removal method of the same analysis. For correlation analysis between variables, the Pearson product-moment or Spearman rank-order method was used according to the distribution feature of the variable. A *p* value of <0.05 was considered statistically significant.

RESULTS

There was no statistically significant difference between the groups in terms of age, BSA, EF, EuroSCORE II, medications and surgical procedures (p>0.05) (Table 1).

Table 2 shows stratified randomization blocks according to preoperative risk factors.

Duration of operation, duration of CPB, duration of CC, ventilation, and length of stay in the ICU were similar between the groups (p>0.05, Table 3). Length of hospital stay was significantly higher in Group C than in Group S (9 [8.9-9.7] *vs*. 8 [7.8-8.6], respectively, p<0.001). Inotrope, vasoconstrictor, and vasodilator requirements were not statistically significant between the groups (p>0.05).

The hemodynamic properties during the study periods are shown in Table 4. CVP and lactate values were statistically significantly similar between the groups at all time points (p>0.05). The SVI, CI, SVRI, and DO_2 values were kept within the normal range in Group S.

While intraoperative fluid consumption was similar in both groups, the postoperative fluid requirement was statistically significantly lower in Group S (Group S: 2780±780 mL, Group C: 3402±680 mL, p=0.002, Table 5). On the other hand, Group C had

Table 1. Preoperative demographic variables of the Group Control (C) and Group Study (S)

	Group S (n=30)					Group C (n=30)					
	n	%	Mean±SD	Median	IQR	n	%	Mean±SD	Median	IQR	*p*
Age (year)			62.2±9.3					62.3±10.6			1.000
Body surface area (m^2)			1.85±0.19					1.82±0.16			0.511
EuroSCORE				3	2-5				3.5	2-4	0.709*
Ejection fraction (%)				45	45-60				45	45-55	0.821*
Hypertension	14	47				16	53				0.835
Diabetes mellitus	16	53				15	50				1.00
Atrial fibrillation	2	7				1	3				1.000
Cerebrovascular event	0	0				1	3				1.00
COPD	5	17				8	27				0.541
ACEI-ARB	3	10				8	27				0.239
β-Blocker	20	67				15	50				0.331
Calcium channel blocker	0	0				3	10				0.218
Nitrate	7	23				12	40				0.337
Diuretic	4	13				9	30				0.217
Operation type											0.211**
CABG	21	70				25	83				
Single valve replacement	6	20				5	17				
Double valve replacement	2	7				0	0				
AVR + MVR + CABGX1	1	3				0	0				

SD: Standard deviation; IQR: Interquartile range; COPD: Chronic obstructive pulmonary disease; ACEI: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker; CABG: Coronary artery bypass grafting; * Mann-Whitney U tests; ** Pearson chi-square (χ^2) tests.

Table 2. Stratified randomization blocks according to preoperative risk factors

Stratified randomization blocks (n=60)	EuroSCORE	Left ventricle ejection fraction (%)	Group S	Group C
I (n=16)	<4	≥50	8	8
II (n=14)	<4	<50	7	7
III (n=12)	≥4	≥50	6	6
IV (n=18)	≥4	<50	9	9

EuroSCORE: European System for Cardiac Operative Risk Evaluation.

Table 3. Intraoperative characteristics of the cases

	Group S (n=30)			Group C (n=30)			
	Mean±SD	Median	IQR	Mean±SD	Median	IQR	*p*
Operation time (min)	240±23			253±39			0.121
CPB time (min)	109±29			103±22			0.532
CC time (min)	73±29			68±22			0.441
Ventilation time (h)	12.6±2.9			11.0±2.4			0.119
ICU stay duration (day)		2	2-3		2	2-3	0.633*
Hospital stay duration (day)		8	8-9		9	9-10	<0.001*
Dopamine, total (mg)	55.6±13.2			49.6±15.2			0.113
Noradrenaline, total (mg)		0.96	0.35-1.21		1.00	0.54-1.19	0.821*
Nitrogliserine, total (mg)		0.54	0-1.2		0.66	0-1.6	0.714*

SD: Standard deviation; IQR: Interquartile range; CPB: Cardiopulmonary bypass; CC: Cross-clamp; ICU: Intensive care unit; * Mann-Whitney U tests.

Table 4. The hemodynamic parameters of the groups during the study periods

	Data collection time				
	Preoperative	t2	t3	t4	
	Mean±SD	Mean±SD	Mean±SD	Mean±SD	*p*
CVP (mmHg)					0.142
Group S	7.2±2.3	7.3±3.3	8.1±2.4	8.3±3.1	
Group C	7.3±1.8	8.7±3.0	9.7±2.8	9.0±2.7	
Lactate (mmol/L)					0.523
Group S	0.9±0.34	2.2±0.8	1.6±0.7	1.2±0.6	
Group C	1.0±0.37	1.7±1.0	1.5±1.4	1.1±0.4	
SVI (mL/m^2)					0.134
Group S	29.2±9.7	29.2±7.0	28.9±6.6	31.4±6.2	
CI (L/min/m^2)					0.091
Group S	2.2±0.9	2.6±0.7	2.4±0.7	2.1±0.8	
SVRI (dyn/s/cm^5/m^2)					0.831
Group S	2.865±1.444	2.763±965	2.820±1.515	2.793±1.413	
DO_2I (mL/min)					0.441
Group S	649±233	644±170	639±210	658±201	

SD: Standard deviation; t2: Postoperative 4th hour; t3: Postoperative 24th hour; t4: Postoperative 48th hour; CVP: Central venous pressure; SVI: Stroke Volume Index; CI: Cardiac Index; SVRI: Systemic Vascular Resistance Index; DO_2: Oxygen delivery Index; * Repeated measures ANOVA test; ** Tukey HSD test.

Table 5. Comparison of fluid requirement and balances between group Control (C) and Group Study (S) in the perioperative period

	Group S (n=30)	Group C (n=30)	
	Mean±SD	Mean±SD	*p*
Intraoperative fluid (mL)	1.867±599	2.075±585	0.225
Postoperative fluid (mL)	2.780±780	3.402±680	0.002*
Intraoperative balance (mL)	566±804	985±580	0.021
Postoperative balance (mL)	-752±453	207±615	<0.001*
CPB balance (mL)	-358±388	-273±373	0.432

SD: Standard deviation; CPB: Cardiopulmonary bypass; * Student-t test.

Table 6. Requirement of blood and blood products in group Control (C) and Group Study (S) in the perioperative period

	Group S (n=30)		Group C (n=30)		
	Median	IQR	Median	IQR	*p*
Intraoperative ES (U)	0	0.2-0.6	1	0.5-0.9	0.02*
Postoperative ES (U)	1	0.5-1.0	2	1.3-2.3	0.002*
Intraoperative FFP (U)	1	0.5-1.0	1	0.6-0.9	0.725
Postoperative FFP (U)	1.5	1.3-2.2	2	1.3-2.3	0.331

IQR: Interquartile range; ES: Erythrocyte suspension; FFP: Fresh frozen plasma; * Mann-Whitney U test.

significantly more positive balance intraoperatively and in ICU (p=0.02 and p<0.001, respectively, Table 5). Intraoperative erythrocyte suspension (ES) requirement was statistically significantly lower in Group S than those in Group C (Group C: 0 [0.2-0.6]; Group S: 1 [0.5-0.9]; p=0.02, Table 6). Similarly, the postoperative ES requirement was significantly lower in Group S (Group C: 1 [0.5-1.2]; Group S: 2 [1.3-2.3];

p=0.002). Intra- and postoperative fresh frozen plasma (FFP) requirements were similar in both groups. Intraoperative apheresis thrombocyte was required in only one case in Group S. Thrombocyte suspension was required in three patients from the postoperative study group and seven patients from the control group (p>0.05).

The changes in the GFR and creatinine values were similar between the groups (p=0.7 and p=0.3, respectively, Figure 2a, b). The change of cystatin-C over time was statistically significant between the groups (p<0.002). Cystatin-C was significantly higher in Group C at 24 and 48 h postoperatively (p<0.02 and p<0.04, respectively, Figure 2c). The changes in KIM-1 values were similar between the groups over time (p=0.8).

The incidence of AKI and the stages of KDIGO in the patients were similar between the groups (p>0.05) (Table 7). Acute kidney injury developed in nine (30%) cases in each group. All of the patients with AKI were observed at the postoperative 24th hour (t3). There was no new case detected at the postoperative 48th hour (t4). The independent factors affecting the formation of postoperative AKI were investigated separately in both groups. The variables included in the analysis were age, EF, EuroSCORE II, hematocrit (preoperative), MAP (preoperative), intraoperative noradrenalin requirement and groups. All cases were included in this analysis, and Cystatin-C, intraoperative noradrenalin requirement and EuroSCORE II were found to be independent risk factors for the development of AKI postoperative period. The increase in the EuroSCORE II increased

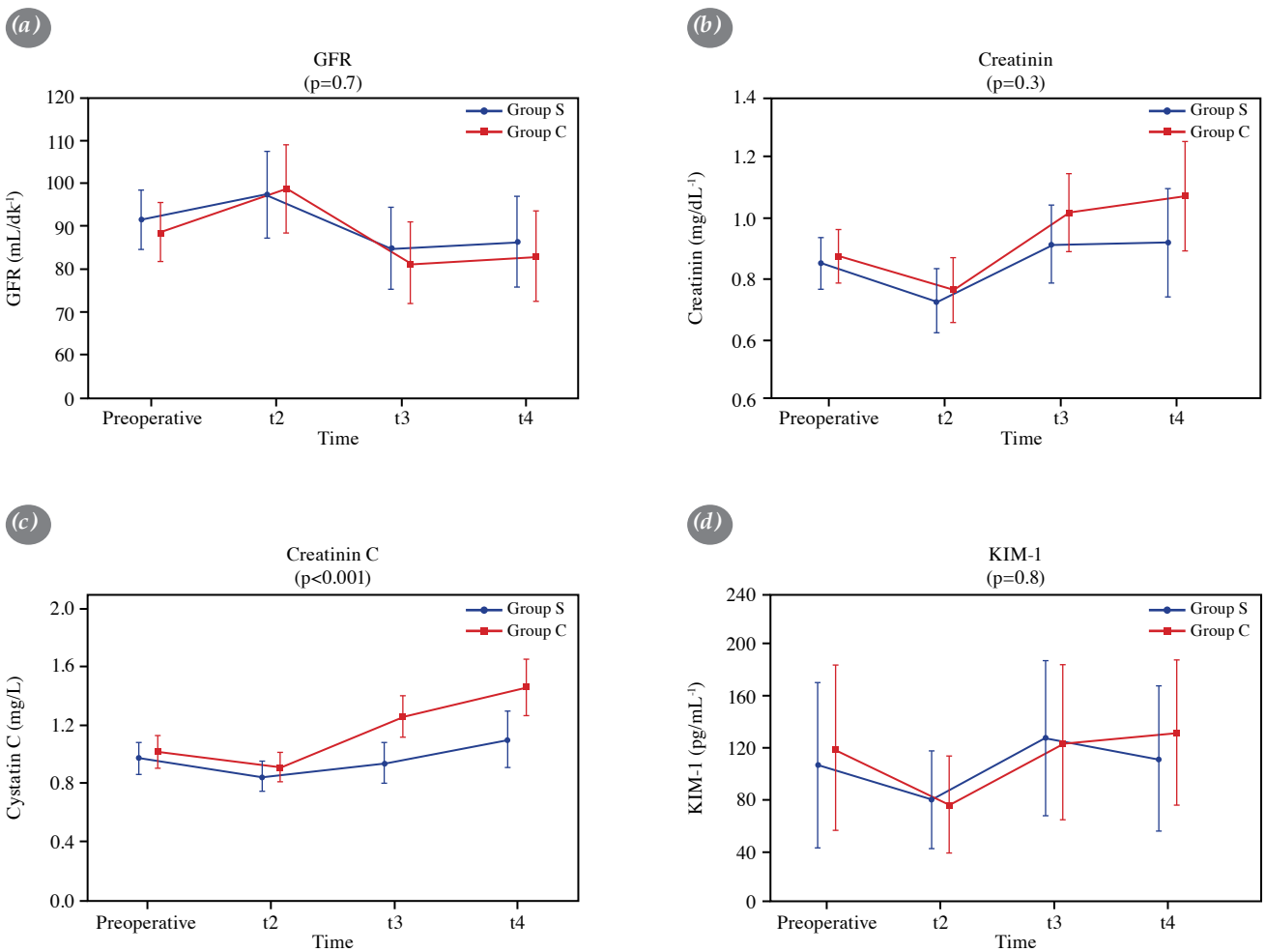

Figure 2. Biochemical parameters in the study and control groups. **(a)** Comparison of GFR in groups. **(b)** Change in creatinine over time in groups. **(c)** Comparison of cystatin-C change over time in groups. p<0.04 in t3; Tukey HSD test, p<0.02 in t4; Tukey HSD test. **(d)** KIM-1 change in groups over time in groups.

KIM-1: Kidney Injury Molecule-1; GFR: Glomerular filtration rate; Vertical bars expressed 95% Confidence interval. Repeated measures ANOVA test; t1: preoperative, t2: postoperative 4th hour; t3: postoperative 24th hour; and t4: postoperative 48th hour.

Table 7. The incidence of AKI, the stages of KDIGO of the patients and the distribution of AKI patients within study times and in Group Control (C) and Group Study (S)

		AKI		KDIGO			
		n	%	I	II	III	*p*
t2	Group S	2	7	1	0	1	0.624
	Group C	4	13	3	0	1	
t3	Group S	7	23	4	0	3	0.715
	Group C	5	17	2	0	3	
t4	Group S	7	23	4	1	2	0.827
	Group C	6	20	4	0	2	
All time	Group S	9	30	5	1	3	0.836
	Group C	9	30	6	0	3	

AKI: Acute kidney injury; KDIGO: Kidney Disease: Improving Global Outcomes; t2: Postoperative 4th hour; t3: Postoperative 24th hour; t4: Postoperative 48th hour; Pearson chi-square test.

Table 8. Independent risk factors for the development of AKI

		OR	95% CI	*p
For all patients	EuroSCORE	0.61	0.38-0.97	0.022
	Cystatin-C level	0.26	0.001-0.56	0.043
	Noradrenalin requirement	0.74	0.55-0.98	0.042

OR: Odds ratio; CI: Confidence interval; EuroSCORE: European System for Cardiac Operative Risk Evaluation; * Forward stepwise binary logistic regression analysis.

the AKI rate by 0.61 times, the increase in Cystatin-C level increased AKI rate 0.26 times and increase in noradrenalin consumption increased the AKI ratio by 0.74 times ($p<0.02$, $p<0.04$, and $p<0.04$, respectively) (Table 8).

DISCUSSION

In the present study, AKI occurred with similar frequency in the management of GDT and the standard treatment in patients undergoing cardiac surgery. The incidence of AKI was 30% in both groups, as well. Postoperative fluid requirement and intra- and postoperative ES requirement were significantly lower in patients with managed GDT than those in Group C. Intra- and postoperative fluid balances were poorer in Group S than Group C. While Cystatin-C was lower in patients treated with GDT, the other biomarkers such as KIM-1, GFR, and creatinine did not differ significantly between the two groups. The length of hospital stay was shorter in patients treated with GDT.

In our study, different from our routine practice, we managed the patients in Group S with GDT to observe its effect on AKI. Firstly, whether or not the patients had hemodynamic instability in Group S, we check the patients for fluid replacement in the operation room and postoperative care unit. The fluid replacement was repeated with 5-min intervals, until there was no more increase than 10% in SVI. Thus, it ensured the optimum SVI and optimum perfusion. Then, we followed the hemodynamic parameters according to the decision tree guidelines. The incidence of AKI was not different between GDT and standard therapy. Similarly, Osawa et al.[16] reported that a GTD decreased the 30-day mortality, but did not affect the occurrence of AKI as defined by Acute Kidney Injury Network (AKIN) classification in high-risk patients undergoing cardiac surgery.[16] Contrary to our study, recent meta-analyses and some clinical studies have shown that GDT reduces significantly the risk for AKI after cardiac surgery.[21-23] Johnston et al.[21] reported that their observational retrospective cohort study regarding the goal-directed volume resuscitation protocol depended on the patient fluid responsiveness significantly reduced the rate of AKI after cardiac surgery. The lowest postoperative GFR within seven days of surgery and the Risk, Injury, Failure, Loss of Kidney Function, and End-stage Kidney Disease (RIFLE) classification criteria were used to determine AKI. Meersch et al.[22] reported that the development

of AKI was significantly lower in the group receiving GDT. They evaluated the severity of AKI according to KDIGO criteria and followed the patients from the first 72 h to postoperative Day 90. They attributed this positive result to the reduction of volume overload and organ edema with GDT. They showed that tissue edema led to the development of postoperative AKI and the worsening of pre-existing AKI. Thomson et al.[23] reported that the incidence of postoperative AKI was lower in patients followed with a GDT protocol targeting SVmax for the first 8 h after cardiac surgery, compared to those treated with standard treatment. Their method for defining the AKI was the AKIN criteria based on the change in creatinine concentration and not including urine output.

Although our study showed that GDT did not decrease the incidence of AKI and did not change creatinine levels compared to the standard method in patients undergoing cardiac surgery, Cystatin-C levels were significantly lower in the GDT group than in the standard treatment group at postoperative 24th and 48th h. Additionally, Cystatin-C level at the postoperative 4th h was an independent risk factor for the development of AKI. Similar to our study, kidney damage without an apparent decline in kidney function, indicating creatinine-negative but biomarker-positive AKI, might be observed in ICU patients.[29-32] Our study results can be attributed to the fact that timely diagnosis of AKI may involve a broader panel of diagnostic tools. Also, our study suggested that Cystatin-C could be used for the early prediction of AKI associated with cardiac surgery.[32] According to many studies in the literature, an elevation in serum creatinine may be a late marker for AKI development.[14,32]

In our study, the postoperative fluid requirement and ES requirement were significantly decreased with the use of GDT. This approach may prevent unnecessary fluid challenges which contribute to AKI and the GDT protocol was individual for our patients. Similar to our study, Parke et al.[25] reported that algorithm-guided fluid administration (guided stroke volume variation) reduced the amount of fluid given compared to usual care in cardiac surgery patients in their multi-center, randomized-controlled study. They also found that the rate of AKI in groups was similar. Contrary to our results, Osawa et al.[16] showed that patients treated with GDT received a greater volume of intravenous fluids than the usual care group. They also reported that there was no significant difference in the ES transfusion. Either anemia or ES transfusion may lead to AKI by directly harming the kidney or increasing the susceptibility of patients to simultaneous kidney damage. On the other hand, Ginglio et al.[13] reported that the total volume of fluid was not significantly different between the GDT and the control group in their meta-analysis study which explored the effect of GDT on postoperative complications in major abdominal and orthopedic surgical procedures. The causes of these differences may be high heterogeneity in cases and surgery as mentioned above. While the intraoperative fluid balance was similar between the groups, the postoperative balance was poorer in the GDT group. The requirement of fluid postoperatively was also less in the patients treated with GDT compared to the Group C.

Although the amount of fluid given and presence of negative balance led to increase the use of vasopressor medications in Group S, the incidence of AKI was similar between the groups in our study. Similarly, it was shown that protocolized algorithms for fluid therapy led to decrease in fluid loading and increase in the use of vasopressors or diuretics medications; however, the rate of AKI remained unchanged.[25] There are studies in the literature showing that both negative and positive fluid balances may be associated with an increased risk of renal injury.[33,34] In our institutions, slightly negative fluid balance is preferred during and after cardiac surgery to prevent severe complications such as lung edema and cognitive disfunctions.

In accordance with our institutional practice, we applied a balanced electrolyte solution primarily for resuscitation and management during the perioperative period and ICU stay. Colloid (3 crystalloid: 1 colloid) was applied only, when fluid replacement with crystalloids was not sufficient to optimize preload (n=3, Gelofusine®, Braun Medical, Istanbul, Türkiye). While fluid therapy increases preload and optimizes the stroke volume, it creates concerns that can lead to dilutional anemia, coagulopathy and hypoproteinemia with hemodilution in cardiac surgery. To prevent these concerns, there are no evidence-based fluid therapy suggestions specifying the dosage of fluids (for both crystalloids and colloids) or the time of fluid applied in the literature.[35,36] Recently, protocols that provide hemodynamic stability with targeted therapies have been shown to be more effective than fluid type and quantity on outcomes of patients undergoing cardiac surgery.[25,35] Not only fluid status, but oxygenation (DO_2) and Hb content should be kept at optimum levels according to period of cardiac surgery and patient's characteristics.[35]

In the current study, we perfused all patients according to conventional perfusion guidance during the CPB period. Pump flow was adjusted based on

the BSA and temperature. We followed DO_2 during and after cardiac surgery in Group S, but not during CPB. Recent multi-center, prospective, randomized-controlled studies have shown that the goal-directed perfusion (GDP) strategy, in which pump flow is adjusted based on the DO_2, is more effective in reducing the risk of cardiac surgery-associated AKI compared to conventional perfusion guidance.[35] The concept of GDP aims to maintain the DO_2 on CPB above the critical value (260 to 270 mL/min/m^2) and prevent insufficient oxygen delivery. Therefore, postoperative outcomes can be improved during the CPB period.[37] However, some authors found a correlation between perioperative DO_2 and postoperative AKI.[38] Mini-CPB has also an increasingly preferred method in the CPB period in recent years. It has certain benefits of shed blood partition, biocompatible coating of the circuit and reduced prime volume. Mini-CPB circuits demonstrate improved homeostasis, reduced perioperatively homologous blood and blood products transfusion requirement, and reduced incidence of renal failure after CPB.[39,40] These systems during CPB can be used with GDT during cardiac surgery.

Optimal fluid administration prevents hypovolemia and end-organ hypoperfusion resulting from inadequate fluid resuscitation and, also the adverse effects of anemia, hypoproteinemia formation resulting from excessive fluid administration. Therefore, optimizing volume status and hemodynamics may reduce the occurrence of coronary surgery-associated AKI. In addition, the length of hospital stay was significantly shorter in the patients who received GDT than those in Group C in our study. Similarly, recent meta-analyses favor the GDT approach to standard therapy in terms of mortality rate and postoperative complications, including length of stay in the ICU and hospital.[16-19]

The main limitation to our study is relatively small sample size in both groups. This study was conducted during the novel coronavirus disease 2019 (COVID-19) pandemic. Due to the postponement of elective operations in this period, the targeted number of patients could not be reached. Due to our small sample size, high odds ratio numbers for significant independent risk variables may not have been achieved. The study may also have limited external validity given its single-center design. Therefore, further adequately powered multi-center studies are needed to confirm our results. Finally, the patients included in our study had no kidney injuries. Thus, these findings should be confirmed in patients with preexisting kidney injury.

In conclusion, goal-directed therapy should be considered in the foreground, as it shortens the length of hospital stay and reduces the unnecessary fluid load in patients who are scheduled for cardiac surgery. Cystatin-C can be used as a more eligible early phase renal injury biomarker in the evaluation of acute kidney injury in the early postoperative period.

Ethics Committee Approval: The study protocol was approved by the Manisa Celal Bayar University Faculty of Medicine Clinical Research Ethics Committee (date: 11.11.2019, no: 57). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Idea/concept, design: İ.Ö., T.Ö., Control/supervision: D.A., F.Y., Data collection and/or processing: İ.Ö., D.A., F.Y., Analysis and/or interpretation: D.A., F.Y., Literature review: A.Ş., İ.H.Ö., T.Ö., Writing the article: İ.Ö., T.Ö., A.Ş., İ.H.Ö., Critical review: T.Ö., A.Ş., İ.H.Ö., Fundings: MCBU, BAP., Materials: İ.Ö., D.A., F.Y.

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