Crit Care Shock (2022) 25:253-262

Prophylactic low dose furosemide infusion effect on cardiac surgery patients with renal dysfunction: A randomized controlled trial

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Abstract

***Objectives*: Preoperative renal dysfunction increases the risk of postoperative renal failure and mortality in cardiac surgery patients. Studies investigating the protective effect of furosemide in cardiac surgery were mostly conducted in patients with normal renal function. This study aimed to evaluate the effect of prophylactic low-dose furosemide in cardiac surgery patients with mild to moderate renal dysfunction.**

***Design*: Double-blind randomized controlled trial.**

***Setting*: This study was conducted at a cardiovascular surgery center.**

***Patients and participants*: Eighty-seven patients of elective cardiac surgery with mild to moderate renal dysfunction (estimated glomerular filtration rate [eGFR] 30-89 ml/min/1.73 m^2).**

***Interventions*: Prophylactic furosemide infusion (2 mg/h) or 0.9% NaCl infusion (2 ml/h) was administered and continued for a total of 12 hours.**

***Measurement and results*: We examined blood samples at 12, 24, 48, and 120 hours after infusion started to measure the change in eGFR. A decrease in eGFR ≥20% was considered a worsening of renal function, while ≥20% increase in eGFR was recovering of renal function. We compared the requirement for therapeutic furosemide infusion and renal replacement therapy in both groups.**

The incidence of decreasing eGFR at the 12th, 24th, and 48th-hour was higher in the control compared to the furosemide group. Increasing eGFR at the 120th-hour was the same in both groups. Subjects in the furosemide group required less administration of therapeutic furosemide infusion than the control group. Renal replacement therapy was needed more in the furosemide group than in the control group.

***Conclusions*: Low-dose furosemide infusion can reduce the incidence of worsening renal function, and the need for therapeutic furosemide infusion, but does not prevent the usage of renal replacement therapy.**

Key words: Furosemide, glomerular filtration rate, renal dysfunction, cardiac surgery.

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Introduction

Renal dysfunction increases the risk of mortality in patients undergoing cardiac surgery, which is associated with the degree of preoperative renal function. The degree of decreased renal function is described by the glomerular filtration rate (GFR) according to the definition of Kidney Disease: Improving Global Outcome (KDIGO). Estimated glomerular filtration rate (eGFR) of 30-89 ml/min/1.73 m^2 is classified as mild-moderate renal dysfunction. Cardiac surgery patients with pre-existing renal dysfunction are at risk for deterioration in renal function or may even progress to acute or chronic renal failure. These risks are higher in surgeries that

require the use of cardiopulmonary bypass (CPB), due to extreme physiological conditions that lead to hemodynamic instability and inflammatory stimulation. (1-4)

Diuretics are widely used in post-cardiac surgery as a treatment strategy for postoperative acute kidney injury (AKI) to prevent anuria. Theoretically, furosemide has the protective effect of blocking the K/Na/Cl cotransporter process in ascending limb of the loop of Henle, hence decreasing energy demand in the renal. Fakhari et al. reported that prophylactic furosemide infusion has a renal protective effect in adult cardiac surgery patients with normal renal function. Other studies have assessed the effects of furosemide as a renal protection strategy, but none were specifically implemented in patients with preexisting renal dysfunction. (5-7)

This study aimed to evaluate the effect of prophylactic low-dose furosemide infusion in patients with mild-moderate renal dysfunction (eGFR 30-89 ml/min/1.73 m^2) who underwent elective cardiac surgery with CPB.

Methods and materials

This study was conducted from May to December 2021 after receiving approval from the Ethics Committee. The protocol for this double-blind randomized controlled study was registered on clinical trial gov (ID: NCT04919564). Patients were provided with a full explanation of the study and signed a written consent form to participate. The patients were allowed to leave the study at any point. Inclusion criteria were patients aged 18-65 years with left ventricle ejection fraction (LVEF) >40%, mild to moderate renal dysfunction (eGFR 30-89 ml/min/1.73 m^2) who underwent elective cardiac surgery with CPB. Exclusion criteria were patients with stage 4-5 chronic renal failure, history of renal replacement therapy, LVEF<40%, undergoing emergency or repeated surgery, complex heart disease, congenital heart disease, aortic vascular surgery, massive bleeding, sepsis, or currently participating in another research. Drop-out criteria were hemodynamically unstable (with persistent hypotension, supported with >2 inotropic drugs or >2 vasoactive drugs, on intra-aortic balloon pump [IABP], or on extracorporeal membrane oxygenation [ECMO]), cardiogenic shock, prolonged CPB time, crisis or severe pulmonary hypertension, redo surgery for any reason, postoperative bleeding, and anaphylactic shock.

Regarding the high prevalence of deteriorating renal function after on-pump cardiac surgery (15-60%), we aimed for a 30% reduction, statistical power of 80%, and a significance level of 5%, the sample size was calculated as 41 patients for each group. Anticipating a 10% loss of follow-up, we assigned a total of 90 patients to the furosemide (n=45) and control (n=45) groups.

Patients were randomized to receive either a control group (0.9% NaCl 2 ml/h) or a treatment group (50 mg furosemide in 50 ml NaCl 0.9%, 2 ml/h) according to a list that was prepared by the assigned research center staff (who was not involved in the conduction of the study), using randomization software at 1:1 ratio. Those who participated in conducting the study interventions were blinded to treatment solutions. eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.

In the operating room, patients were set up with a monitoring device and provided a premedication with midazolam 0.1 mg/kg of body weight (kg BW) followed by the induction of anesthesia with fentanyl (5-10 mcg/kg BW), propofol (1-2 mg/kg BW), and rocuronium (1-2 mg/kg BW), intravenously. All monitoring and procedures, including anesthesia, CPB, and surgery, were conducted according to standard operational procedures and routine treatments were done as indicated. After induction, we started the treatment solution at the rate of 2 ml/h and continued in the intensive care unit (ICU) for a total of 12 hours. The treatment solution contained 50 mg furosemide in 50 ml of NaCl 0.9% in the furosemide group or NaCl 0.9% in the control group. In the management of CPB, all patients were given furosemide 20 mg and mannitol 2.5 ml/kg BW added to the priming fluid, and then the patient was given mannitol 2.5 ml/kg BW during rewarming or infusion during CPB. The priming fluid used was Ringerfundin, 0.9% NaCl, gelatin, and/or 20% albumin. The cardioplegic fluid used a routine solution with antegrade administration. Anesthesia maintenance was continued according to the anesthesiologists. Continuous ultrafiltration was done while CPB was running. Hemodynamic targets during CPB were mean arterial pressure (MAP) >50 mmHg and hemoglobin >9 g/dl. The indication of vasopressor use during CPB was when the MAP<50 mmHg.

After surgery, all patients were transferred to the ICU, intubated, sedated, and monitored as in the operating room. After 12 hours, treatment infusion was terminated, and then the first blood sample was drawn to measure blood urea nitrogen (BUN) concentration, serum creatinine, and eGFR. Sampling was repeated on the 24th, 48th, and 120th hour. Blood sampling can be done in another ward after the patient has been transferred from the ICU. The criteria for transfer were assessed according to pro-

cedures and indications.

If the patient's diuresis was less than 0.5 ml/kg BW/h for 6 hours, continuous furosemide 20 mg was given intravenously followed by infusion starting from 10 mg/h, which can be increased to a maximum of 40 mg/h. If the patient has renal failure or severe worsening of renal function as indicated by serum creatinine values >4 mg/dl, eGFR<30 ml/min/1.73 m^2, diuresis <0.3 ml/kg BW/h for 24 hours, or anuria for 12 hours, or refractory electrolyte imbalance, the patient was indicated for either continuous renal replacement therapy (CRRT) or intermittent hemodialysis according to the standard procedures.

The collected data were as follows: demographics, intra-, and postoperative characteristics and outputs, and primary variables which were alteration in GFRs, the need for furosemide infusion therapy, and renal replacement therapy. Secondary variables such as length of stay in ICU, hospital, and in-hospital mortality were also included.

The data obtained were analyzed using the SPSS 25.0 software program (SPSS Inc., Chicago, IL, USA). Statistical analyses included descriptive analysis to assess the size of the distribution (incidence) of the variable characteristics of the research subjects, and differential analysis using the chi-square test (if n>5) or the Fisher exact test (if n<5). The normality of the data distribution was tested by the Kolmogorov-Smirnov test. If the data distribution was normal, the analysis was done through two independent-sample t-tests. If the data distribution was not normal, the analysis was done through the Mann-Whitney test. p-values less than 0.05 were considered statistically significant.

Results

Of a total of 90 patients, 3 patients were excluded (1 patient with incomplete data and 2 patients who underwent IABP intraoperative installation); hence, there were 87 patients who met the requirements: 43 subjects in the furosemide group and 44 subjects in the control group (**Figure 1**).

Table 1 shows the demographic and characteristics of the patients studied. The distribution of average age, gender, weight, height, and LVEF between the two groups was not significantly different. Comparing type of operation, comorbid score, history of angiotensin-converting enzyme inhibitor (ACEi)/angiotensin receptor blocker (ARB) medication, history of diuretic therapy, and renal dysfunction preoperative category between the two study groups did not show any significant differences.

Table 2 shows the perioperative characteristics and outcomes of the study, all surgeries were performed with an aortic clamp procedure, mannitol administration, and ultrafiltration procedure. The duration of the aortic clamp, CPB procedure, and the duration of surgery were not significantly different between groups. Inotropic requirements during surgery and administration of fresh frozen plasma (FFP) were not significantly different in the two groups. Intraoperative packed red cell (PRC) transfusion in the furosemide group was significantly different compared to the control group (27 vs 15 patients, p-value 0.007).

In the ICU, inotropic use, PRC, and FFP transfusion were not significantly different between the two groups. However, vasopressor use was significantly different between the furosemide group and the control group (19 vs 11 patients, p-value 0.049). Although the duration of mechanical ventilation, serum lactate values, and the incidence of postoperative complications in the two groups were not significantly different, the duration of ventilator use was longer in the furosemide group. The lactate value and incidence of postoperative complications were lower in the furosemide group (2.6 mmol/l and 20.9%) compared to the control group (2.8 mmol/l and 25%). The urine output in the pre-pump period was significantly different in the furosemide group compared to the control group (p-value 0.002), whereas in the on-pump, post-pump, 24h, and 48h periods were not significant. Preoperative serum creatinine and BUN in the furosemide group were higher than in the control group, while the preoperative GFR was lower. However, in comparison of 12h, 24h, 48h, and 120h, the serum creatinine, BUN, and eGFR values of the two groups did not differ and the data analysis did not show significant differences. Comparisons of the postoperative renal dysfunction category between the two groups are shown in **Table 2** and **Figure 2**. In the furosemide group, there were fewer patients with severe renal dysfunction compared to the control group (5 vs 9 patients).

As primary variables, we compared alterations in eGFR values, the need for therapeutic furosemide infusion, and renal replacement therapy (RRT) usage postoperatively in **Table 3**. The furosemide group had a lower proportion of patients experiencing a decline of eGFR in 12h, 24h, and 48h than the control group, and the difference was significant in the 48h sample (27 vs 48 patients, p-value 0.047). The highest proportion of patients who suffered a worsening GFR was in the 24h of the furosemide group, while in the control group it was in the 48h samples. Although the comparison of increased eGFR in 120h samples between the two groups was not significantly different, the proportion in furo-

semide groups was higher. The furosemide group had a significantly lower proportion of patients who needed therapeutic furosemide infusion (10-40 mg/h) than the control group (10 vs 23 patients, p-value 0.005). Although the comparison of RRT requirements between the two groups was not significantly different, there were more patients with RRT usage in the furosemide group than in the control group.

Table 4 shows the comparison of the length of hospital stay in the furosemide group with the control group, and it was significantly different (8 vs 6 days, p-value 0.02). Meanwhile, the in-hospital mortality incidence was the same between the two groups.

Discussion

Extracorporeal circulation, the complexity of cardiac surgery, and uneventful hemodynamic changes in the perioperative period affect renal vascular bed and oxygenation in renal structures. All of these processes lead to a decline in postoperative renal function and this incidence will be higher in patients with preoperative renal dysfunction. It is important to maintain renal function perioperatively to prevent an irreversible decline in renal function. In addition to maintaining stable hemodynamic conditions and reduced CPB time, several supportive medical agents have also been introduced to reduce the incidence of declining renal function in cardiac surgery. (6,8)

Determining the degree of renal dysfunction is very important for predicting the outcome of cardiac surgery patients. Although serum creatinine is routinely used in clinical practice to determine renal function, it can be affected by several factors such as sex, age, ethnicity, diet, and muscle mass. In patients with a GFR reduction of up to 50%, serum creatinine can remain within the normal limit. In this study, we measured eGFR as a parameter for renal function alteration. GFR is reported as a better parameter in detecting, evaluating renal dysfunction, and predicting postoperative outcomes compared to creatinine. (7,9)

Furosemide is hypothesized to possess a renal protective effect in cardiac surgery. Furosemide inhibits the Na-K-2Cl transporter in the ascending part of the loop of Henle, thus reducing oxygen demand and consumption. Nevertheless, it shows various responses in different patients in concordance with baseline renal function. Therefore, it will be ineffective in oliguric acute renal injury. (9-12)

A previous study that assessed furosemide's protecting and rescuing properties in cardiac surgery-associated acute kidney injury have not shown convincing evidence. Even though furosemide is capable of establishing a polyuria state, it did not improve renal function, the requirement of dialysis, or the long-term outcome. Lassnigg even suggested an increased risk for renal impairment in patients receiving furosemide. Different methods and doses were applied in the trials, to obtain better applications of furosemide as a renal protective agent. A study conducted by Fakhari et al. supports the finding that furosemide infusion has renal protective effects during on-pump cardiac surgery in patients with normal renal function, as shown by normal diuresis, eGFR, and serum creatinine. In contrast, Mahesh and colleagues failed to demonstrate those benefits. (7,13,14)

In this randomized controlled trial, we found that patients receiving furosemide have higher diuresis during the intraoperative period up until 24 hours since the drug was initially administered, and it persisted for several hours after the drug was discontinued. Furosemide-induced diuresis may be considered a method of decreasing renal oxygen demand and consumption, which protects the kidneys from ischemia. Although baseline serum creatinine was higher and baseline eGFR was lower in the furosemide group, values in the next samples were comparable between the furosemide and control groups. We applied a 20% change in eGFR as a threshold value to determine whether subjects experienced decreasing or increasing renal function based on several works of literature and previous classifications (Acute Kidney Injury Network [AKIN] and Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease [RIFLE]), which used 25% as the low threshold. We monitored that 61% of the subjects (53 patients) in both groups, involving 22 patients in the furosemide group and 31 patients in the control group, experienced a GFR decrease in the first sample, and then this incremented until the third sample. A significant difference occurred in the third sample, where 27 patients in the furosemide group and 36 patients in the control group experienced a ≥20% decrease in eGFR compared to the baseline value. In the fourth sample, 22 patients in the furosemide group and 23 in the control group, who had a decreased GFR, sustained a ≥20% increase in GFR compared to the third sample. Enhancement of renal function occurred probably as a response to glomerular structure autoregulation to decrease GFR in order to limit volume depletion. This response may still occur even after the insult was resolved, which leads to fluid retention, thereby macular edema and worsening renal function. Furosemide will ameliorate fluid retention by enhancing diuresis but is unable to decrease any renal injury that has happened, nor decrease creatinine

levels. Some studies have considered that furosemide could be harmful because its usage is encouraging a significant delay in RRT. (5,10,15,16)
Worsening renal dysfunction is characterized by a decrease in GFR, and manifests as a decrease in diuresis. The degree of oliguria correlates with the occurring renal injury. Aiming at volume status control, physicians will try to use diuretics to convert the oliguric to a non-oliguric condition which is associated with lower mortality rates. The study conducted by Hamishehkar et al. showed furosemide has no harmful effects on renal function in patients with AKI; thus, it might be suggested as one of the treatment modalities in these patients with AKI. Intravenous diuretic administration is often employed to augment urine output in oliguric patients with AKI prior to initiation of RRT. However, the dose applied for this purpose is remarkably high, ranging from 10 to 40 mg/h, and cumulatively totals 960 mg/day, continuously. In this study, the requirement for therapeutic furosemide infusion was more significant in the control group than in the furosemide group. The prophylactic low dose furosemide infusion for 12 hours in the furosemide group was able to help in maintaining a continuous smooth postoperative diuresis in most patients which decreased the requirement of therapeutic furosemide infusion in this group. (10,15)
In patients with renal failure, furosemide has been proven to be ineffective. We found that the incidence of acute kidney failure requiring dialysis was 5.7% (5 of 87 patients), and the outcome of postoperative renal function was different from patients with normal kidney function. This outcome strengthens the claim that preoperative renal dysfunction is a strong independent factor in the occurrence of AKI to postoperative acute renal failure (ARF). In this study, the prophylactic low-dose furosemide did not prevent the requirement of RRT. Although the difference was not statistically significant, more patients in the furosemide group required RRT than in the control group. This result might be because the condition in which patients in the furosemide group did not respond well to therapeutic furosemide infusion that needed to be intervened with RRT or could be related to the theory that furosemide did not directly improve ARF in terms of creatinine or other substances clearance, mainly in the severely injured kidney. (7,12,14,16-19)
The systematic review by Ahmed and colleagues concluded that furosemide treatment did not prevent mortality, need for dialysis, and length of hospital stay. In our study, there was a significant difference in the length of hospital stay. Length of stay in ICU was also longer in the furosemide group although it was not significant. The incidence of in-hospital mortality in both groups was the same. (7,18,20)
Several limitations are identified in this study. First, we included patients with mild to moderate renal dysfunction, where the range of eGFR values was large from >30-89 ml/min/1.73 m^2. However, since the random distribution of these categories into both groups was comparable, the results were accountable. Then, the decisions of giving the therapeutic dose of furosemide infusion and the use of renal replacement therapy were given to the consultant on duty, although there were specific indications determined in the research protocol, we considered that the decision from the consultant of that day was the best decision at that time. Essentially, delaying therapy is not an option that can be tolerated by the research subjects.

Conclusions

This study did not demonstrate a convincing protective effect of prophylactic low-dose furosemide infusion for cardiac surgery patients with preoperative mild-moderate renal dysfunction. Even though low-dose furosemide could reduce the incidence of worsening renal function and the need for a high therapeutic dose of furosemide infusion, it did not prevent the requirement for renal replacement therapy.

Acknowledgment

The authors would like to express the highest gratitude to our patients who participate in this study, and to our research team who were involved throughout the whole process. Sincere gratitude to the Adult Cardiovascular Surgical team, the surgeons, anaesthesiologists, intensivists, nurses, perfusionists, and all medical staff for their assistance and cooperation in the research.

Authors' contributions

PA designed and performed the experiment, analyzed the data, contributed the materials tools for this experiment, wrote the draft, and critically revised the paper. JH, AS, and ARS designed the experiments, analyzed the data, contributed material tools for this experiment, contributed to writing the draft, and critically revised the paper.

Conflict of interest

No external funding was received for this study. The authors declare that they have no conflict of interest.

Table 1. Patients' demographic and preoperative characteristics

Variable	Group		p-value
	Furosemide (n=43)	Control (n=44)	
Age (years), mean±SD	59±7	57±8	0.251
Weight (kg), mean±SD	68.4±10.7	67±15.6	0.640
Height (cm), mean±SD	161.9±8.1	160.6±7.5	0.465
Gender - Male, n (%) - Female, n (%)	 36 (83.7) 7 (16.3)	 32 (72.7) 12 (27.2)	 0.215
Type of operation - CABG, n (%) - Valve, n (%)	 35 (81.4) 8 (18.6)	 29 (65.9) 15 (34.1)	 0.102
LVEF (%), mean±SD	57.4±9.3	55.1±9.7	0.262
Comorbid - Score 1-2, n (%) - Score 3-4, n (%) - Score >4, n (%)	 39 (90.7) 3 (7.0) 1 (2.3)	 41 (93.2) 3 (6.8) 0 (0)	 0.998 0.953 1.000
History of ACEi/ARB - Yes, n (%) - No, n (%)	 28 (65.1) 15 (34.9)	 31 (70.5) 13 (29.5)	 0.594
History of diuretics - Yes, n (%) - No, n (%)	 18 (41.9) 25 (58.1)	 24 (54.5) 20 (45.5)	 0.236
Renal dysfunction - Mild (eGFR 60-89 ml/min/1.73 m^2), n (%) - Moderate (eGFR 30-59 ml/min/1.73 m^2), n (%)	 20 (46.5) 23 (53.5)	 22 (50.0) 22 (50.0)	 0.745

Legend: SD=standard deviation; CABG=coronary artery bypass graft; LVEF=left ventricle ejection fraction; ACEi=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker; eGFR, estimated glomerular filtration rate.

Table 2. Perioperative characteristics and outcomes of patients in furosemide and control groups

Variables		Group		p-value
		Furosemide	Control	
Aortic cross-clamp, n (%)		43 (100)	44 (100)	N/A
Aortic cross-clamp time (minutes), median (min-max)		51 (25-263)	49 (25-268)	0.855
CPB duration (minutes), median (min-max)		97 (49-283)	95.5 (53-294)	0.622
Surgical duration (minutes), median (min-max)		265 (124-616)	268.5 (105-510)	0.835
Use intraoperative inotropic, n (%)		26 (60.5)	28 (63.6)	0.761
Use intraoperative vasopressor, n (%)		3 (7.0)	0 (0)	0.116
Use intraoperative mannitol, n (%)		42 (97.7)	44 (100)	0.494
Ultrafiltration during CPB, n (%)		43 (100)	44 (100)	N/A
Use intraoperative PRC, n (%)		27 (62.8)	15 (34.1)	0.007
Use intraoperative FFP, n (%)		16 (37.2)	18 (40.9)	0.724
Use inotropic in ICU, n (%)		31 (72.1)	28 (65.1)	0.486
Use vasopressor in ICU, n (%)		19 (45.2)	11 (25.0)	0.049
Use PRC in ICU, n (%)		20 (46.5)	23 (52.3)	0.591
Use FFP in ICU, n (%)		5 (11.6)	5 (11.5)	1.000
MV time (hours), median (min-max)		13.58 (2.25-152)	11.33 (2.42-44)	0.517
Postoperative serum lactate (mg/dl), median (min-max)		2.6 (0.9-13)	2.8 (0.8-15)	0.936
Postoperative complication(s), n (%)		9 (20.9)	11 (25.0)	0.652
Urinary output (ml), median (min-max)	Pre-pump	100 (0-1500)	50 (0-700)	0.002
	On-pump	400 (0-2500)	400 (50-2300)	0.643
	Post-pump	500 (50-2100)	500 (200-2020)	0.519
	Intraoperative	1000 (340-5000)	1000 (360-4500)	0.819
	24h	2450 (111-4990)	2100 (475-3860)	0.035
	48h	2500 (1400-5160)	2460 (265-4335)	0.481
Creatinine (mg/dl), median (min-max)	Preoperative	1.29 (0.86-1.14)	1.15 (0.09-1.91)	0.080
	12h	1.55 (0.96-3.49)	1.47 (0.75-3.32)	0.447
	24h	1.69 (0.91-3.09)	1.54 (1.02-5.57)	0.832
	48h	1.59 (0.84-4.08)	1.56 (0.84-6.67)	0.855
	120h	1.43 (0.70-3.01)	1.40 (0.71-4.09)	0.610
BUN (mg/dl), median (min-max)	Preoperative	17 (9-36)	16.5 (9-32)	0.862
	12h	22 (0.96-70)	22 (12-43)	0.715
	24h	27 (14-65)	29.5 (15-91)	0.521
	48h	31 (11-75)	34 (16-87)	0.077
	120h	29 (14-136)	25 (12-110)	0.842
eGFR (ml/min/1.73 m^2), median (min-max)	Preoperative	56 (30-88)	67.5 (35-89)	0.442
	12h	45 (14-84)	46 (19-99)	0.983
	24h	39 (21-87)	39.5 (10-73)	0.668
	48h	41 (15-89)	41.5 (9-84)	0.581
	120h	49 (22-103)	50 (15-98)	0.640
Postoperative renal dysfunction, n (%)	mild (eGFR 60-89 ml/min/1.73 m^2)	16 (37.2)	16 (36.4)	0.516
	moderate (eGFR 30-59 ml/min/1.73 m^2)	22 (51.2)	19 (43.2)	0.756
	severe (eGFR<30 ml/min/1.73 m^2)	5 (11.6)	9 (20.5)	0.343

Legend: CPB=cardiopulmonary bypass; PRC= packed red cell; FFP=fresh frozen plasma; ICU=intensive care unit; MV=mechanical ventilation; BUN=blood urea nitrogen; eGFR=estimated glomerular filtration rate; N/A=not available.

Table 3. Primary variables outcomes

Variables	Groups		p-value
	Furosemide	Control	
Decreased eGFR values at:			
- 12h, n (%)	22 (51.2)	31 (70.5)	0.065
- 24h, n (%)	28 (65.1)	35 (79.5)	0132
- 48h, n (%)	27 (62.8)	36 (81.8)	0.047
Increased eGFR at ≥120h, n (%)	22 (51.2)	23 (52.3)	0.918
Therapeutic dose furosemide infusion, n (%)	10 (23.3)	23 (52.3)	0.005
Use renal replacement therapy, n (%)	4 (9.3)	1 (2.3)	0.202

Legend: eGFR=estimated glomerular filtration rate.

Table 4. Secondary variable outcomes

Variables	Groups		p-value
	Furosemide	Control	
ICU stay (hours), median (min-max)	27 (13-340)	24 (9-384)	0.104
Hospital stay (days), median (min-max)	8 (4-30)	6 (4-18)	0.020
In-hospital mortality, n (%)	1 (2.3)	1 (2.3)	N/A

Legend: ICU=intensive care unit; N/A=not available.

Figure 1. Consort flow diagram

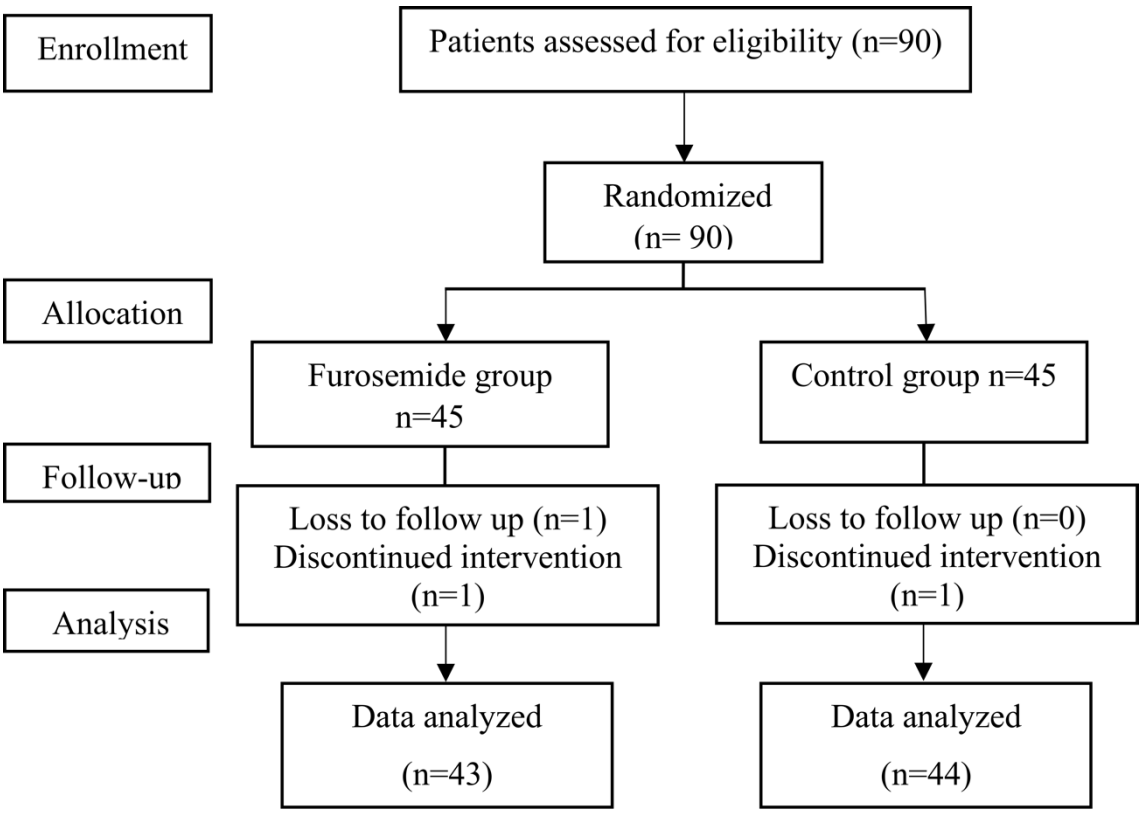
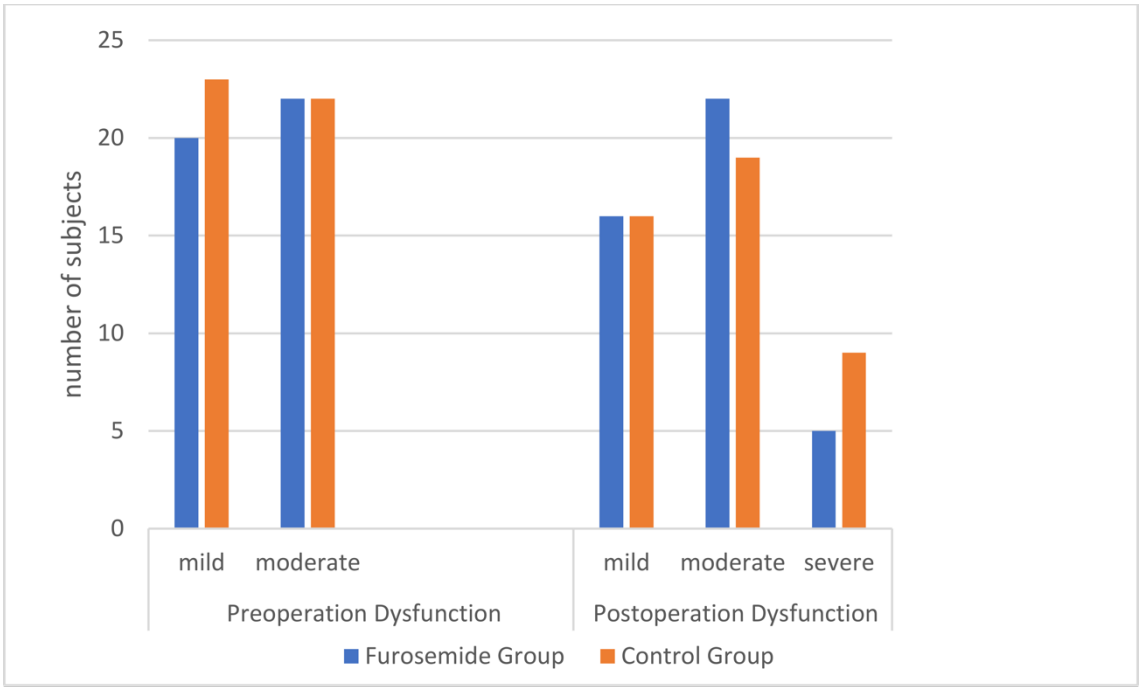


Figure 2. Incidence of preoperative and postoperative renal dysfunction



References

1. Berger AK, Herzog CA. CABG in CKD: untangling the letters of risk. Nephrol Dial Transplant 2010;25:3477-9.
2. Husain-Syed F, Ferrari F, Sharma A, Danesi TH, Bezerra P, Lopez-Giacoman S, et al. Persistent decrease of renal functional reserve in patients after cardiac surgery-associated acute kidney injury despite clinical recovery. Nephrol Dial Transplant 2019;34:308-17.
3. Gandhi A, Husain M, Salhiyyah K, Raja SG. Does perioperative furosemide usage reduce the need for renal replacement therapy in cardiac surgery patients? Interact Cardiovasc Thorac Surg 2012;15:750-5.
4. Shavit L, Hitti S, Silberman S, Tauber R, Merin O, Lifschitz M, et al. Preoperative hemoglobin and outcomes in patients with CKD undergoing cardiac surgery. Clin J Am Soc Nephrol 2014;9:1536-44.
5. Vives M, Hernandez A, Parramon F, Estanyol N, Pardina B, Munoz A, et al. Acute kidney injury after cardiac surgery: prevalence, impact and management challenges. Int J Nephrol Renovasc Dis 2019;12:153-66.
6. Di Tomasso N, Monaco F, Landoni G. Renal protection in cardiovascular surgery. F1000Res 2016;5:1-11.
7. Fakhari S, Bavil FM, Bilehjani E, Abolhasani S, Mirinazhad M, Naghipour B. Prophylactic furosemide infusion decreasing early major postoperative renal dysfunction in on-pump adult cardiac surgery: a randomized clinical trial. Res Rep Urol 2017;9:5-13.
8. Loef BG, Henning RH, Navis G, Rankin AJ, van Oeveren W, Ebels T, et al. Changes in glomerular filtration rate after cardiac surgery with cardiopulmonary bypass in patients with mild preoperative renal dysfunction. Br J Anaesth 2008;100:759-64.
9. Yuan S-M. Acute Kidney Injury after Cardiac Surgery: Risk Factors and Novel Biomarkers. Braz J Cardiovasc Surg 2019;34:352-60.
10. Hamishehkar H, Sanaie S, Fattahi V, Mesgari M, Mahmoodpoor A. The Effect of Furosemide on the Level of Neutrophil Gelatinase-associated Lipocalin in Critically Hospitalized Patients with Acute Kidney Injury. Indian J Crit Care Med 2017;21:442-7.
11. Ortega-Loubon C, Fernandez-Molina M, Carrascal-Hinojal Y, Fulquet-Carreras E. Cardiac surgery-associated acute kidney injury. Ann Card Anaesth 2016;19:687-98.
12. Bayat F, Faritous Z, Aghdaei N, Dabbagh A. A study of the efficacy of furosemide as a prophylaxis of acute renal failure in coronary artery bypass grafting patients: A clinical trial. ARYA Atheroscler 2015;11:173-8.
13. Mahesh B, Yim B, Robson D, Pillai R, Ratnatunga C, Pigott D. Does furosemide prevent renal dysfunction in high-risk cardiac surgical patients? Results of a double-blinded prospective randomised trial. Eur J Cardiothorac Surg 2008;33:370-6.
14. Lassnigg A, Donner E, Grubhofer G, Presterl E, Druml W, Hiesmayr M. Lack of renoprotective effects of dopamine and furosemide during cardiac surgery. J Am Soc Nephrol 2000;11:97-104.
15. Doddakula K, Al-Sarraf N, Gately K, Hughes A, Tolan M, Young V, et al. Predictors of acute renal failure requiring renal replacement therapy post cardiac surgery in patients with preoperatively normal renal function. Interact Cardiovasc Thorac Surg 2007;6:314-8.
16. Kunt AT, Akgun S, Atalan N, Bitir N, Arsan S. Furosemide infusion prevents the requirement of renal replacement therapy after cardiac surgery. Anadolu Kardiyol Derg 2009;9:499-504.
17. Ho KM, Power BM. Benefits and risks of furosemide in acute kidney injury. Anaesthesia 2010;65:283-93.
18. Winther-Olesen M, Moller MH, Johansen KK, Aasvang EK. Effects of post-operative furosemide in adult surgical patients: A systematic review and meta-analysis of randomised clinical trials. Acta Anaesthesiol Scand 2020;64:282-91.
19. Perez-Valdivieso JR, Monedero P, Vives M, Garcia-Fernandez N, Bes-Rastrollo M, GERDCC. Cardiac-surgery associated acute kidney injury requiring renal replacement therapy. A Spanish retrospective case-cohort study. BMC Nephrol 2009;10:27.
20. Ahmed US, Iqbal HI, Akbar SR. Furosemide in acute kidney Injury-A Vexed Issue. Austin J Nephrol Hypertens 2014;1:1-3.