Furosemide infusion prevents the requirement of renal replacement therapy after cardiac surgery

Furosemid infüzyonu kalp cerrahisi sonrası renal replasman tedavi ihtiyacını önlemektedir

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ABSTRACT

Objective: Acute kidney injury (AKI) is a devastating complication following cardiac surgery and the ideal management is controversial. This prospective, randomized, open-label and double-blinded study analyzed the renoprotective effects of furosemide infusion and intermittent bolus therapy administered with dopamine infusion in cardiac surgical patients.
Methods: Between August 1, 2007 and July 31, 2008, 100 adult patients undergoing elective coronary artery bypass surgery (CABG) surgery with normal renal function (creatinine <1.4 mg/dl) were enrolled in the study. The patients were randomized for the comparison of intermittent (Group 1, n=50, 1mg-3mg/kg) and continuous infusion of furosemide (Group 2, n=50, 10mg/ml). Continuous variables were expressed as mean ± SD and compared by unpaired Student's t test or ANOVA for repeated measures. Statistical significance was assumed if p value was <0.05.
Results: Renal replacement therapy (RRT) was used in 5% of patients (all in group 1, p=0.028). The 30-day mortality was 5%. Only 2 patients became hemodialysis dependent in group 1. Group 2 patients showed a continuous and higher urine output postoperatively than group 1 (p<0.001). Both groups had significant increase in peak postoperative serum creatinine values (p<0.001), however peak postoperative creatinine-clearance was significantly lower in group 1 (p<0.001).
Conclusion: Acute kidney injury necessitating RRT makes a small percentage of patients undergoing cardiac surgery and if RRT is not required the survival is excellent. Continuous infusion of furosemide seems to be effective in promoting diuresis and decreasing the need for RRT. However further multicenter studies with different doses of furosemide are required to confirm these results.
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Key words: Acute kidney injury, coronary artery bypass surgery, furosemide, renal replacement therapy

ÖZET

Amaç: Akut böbrek yetmezliği (ABY) kalp cerrahisi sonrası gelişen önemli bir komplikasyondur ve tedavisi tartışmalıdır. Bu prospektif, randomize, açık, çift kör çalışmanın amacı dopamin infüzyonu eşliğinde sürekli veya bolus furosemid uygulamasının renal koruyucu etkilerini analiz etmektir.
Yöntemler: Çalışmaya 1 Ağustos 2007 ve 31 Temmuz 2008 tarihleri arasında izole koroner arter baypas cerrahisi uygulanan 100 erişkin hasta dahil edildi. Hastalar bolus (Grup 1, n=50,1-3mg/kg) veya infüzyon (Grup 2, n=50,10mg/ml) furosemidin renal koruyuculuğu karşılaştırılmak üzere randomize edildi. Devamlı değişkenler ortalama ± SS olarak belirtildi ve Student's t testi veya ANOVA (tekrarlı ölçümler varyans analizi) testleri kullanıldı. Önemlilik p <0.05 düzeyinde değerlendirildi.
Bulgular: Renal replasman tedavisi (RRT) %5 hastada uygulandı, cerrahiden 40-55 saat sonra başlandı (ortalama 46.25±6.75 saat) ve 5.7 gün devam edildi. RRT uygulanan bütün hastalar grup 1'de yer alıyordu (p=0.028). Otuz gün mortalitesi %5 olarak tespit edildi (ölümler grup 1'de, p=0.028). Taburculuk öncesi ortalama kreatinin düzeyi 1.49±0.71 mg/dl idi, sadece grup 1'de bulunan 2 hasta hemodiyaliz bağımlı hale geldi. Grup 2 hastalarının postoperatif idrar çıkışları grup 1 hastalarına göre devamlı ve daha fazla idi (p<0.001). Her iki grubun postoperatif en yüksek serum kreatinin değeri anlamlı derecede arttı (her iki grupta p<0.001). Ancak grup 1 hastalarının postoperatif en yüksek kreatinin klirens değerleri anlamlı derecede düşük bulundu (p<0.001).
Sonuç: Renal replasman tedavisi gerektiren ABY kalp cerrahisi hastalarının çok küçük bir yüzdesinde görülmektedir ve eğer RRT gerekmemişse bu hastaların sağkalım profili oldukça iyidir. Sürekli furosemid infüzyonunun diürezi artırmakta ve RRT ihtiyacını azaltmakta etkili olduğu gözlenmiştir. Ancak çok merkezli ve değişik dozlarda furosemid kullanılarak yapılmış çalışmalar gerekmektedir. *(Anadolu Kardiyol Derg 2009; 9: 499-504)*
Anahtar kelimeler: Akut böbrek yetmezliği, koroner arter baypas cerrahisi, furosemid, renal replasman tedavisi

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Introduction

Acute kidney injury (AKI) is a devastating complication following cardiac surgery. Its incidence ranges from 1% to 40% (1-3). About 2-15 % of patients with AKI require renal replacement therapy (RRT) and this situation is associated with an increased mortality rate that can be as high as 60% (4). Age, diabetes mellitus, preexisting renal dysfunction, severe arteriosclerosis of the aorta, hypertension and impaired left ventricular function are the major risk factors for the development of AKI (5-7). Intraoperative renal hypoperfusion, nonpulsatile flow, inflammatory response syndrome due to cardiopulmonary bypass and genetic polymorphisms are also important causative factors of AKI (8-10).

There is still an ongoing debate about the prevention and treatment of AKI following cardiac surgery. Several agents such as dopamine, loop diuretics and mannitol have been used for this purpose. There are many studies in the literature about the role of these agents in prevention of AKI, however, a definite consensus has not been reached (4, 11). Additionally there is still debate about how to administer these drugs in cardiac surgery.

The purpose of the current study was to compare the renoprotective effects of continuous furosemide infusion and intermittent furosemide bolus therapy administered with dopamine infusion in cardiac surgical patients.

Methods

Patients

After we received institutional review board approval and written informed patient consent 100 adult patients undergoing elective isolated coronary artery bypass grafting surgery (CABG) with normal renal function (baseline serum creatinine value <1.4 mg/dl) were enrolled in the study. The trial was undertaken on all consecutive CABG patients between August 1, 2007 and July 31, 2008. The study subjects were randomly assigned for the comparison of the renoprotective effects of intermittent (Group 1, 50 patients) and continuous infusion of furosemide (Group 2, 50 patients) in conjunction with renal doses of dopamine. Patients who were on either hemodialysis or peritoneal dialysis, patients undergoing operations other than or in conjunction with CABG were excluded.

Kidney injury was interpreted according to RIFLE classification (12) that is explained as R: Risk, I: Injury, F: Failure, L: Loss and E: End-stage kidney disease (Table 1).

CABG procedure

All operations were performed in a standardized approach by a Jostra HL-20 roller pump (Jostra AG, Hirrlingen, Germany), membrane oxygenators (Jostra Quadrox, Hirrlingen, Germany), and a 40 µm arterial blood filter (Jostra AG, Hirrlingen, Germany). Mild to moderate (28-32°C) hypothermia and pulsatile flow of 2.2 to 2.4 L/ m^2 were used. Myocardial protection was achieved with tepid antegrade blood cardioplegia. Perfusion pressure was kept over 70 mmHg in all times. Aprotinine was not used in any of the patients. Induction and maintenance of general anesthesia with endotracheal intubation were standardized an all the patients (phentanyl, midazolam, pancuronium and isoflurane in oxygen with air).

Table 1. RIFLE classification (adapted from reference 12)

	GFR Criteria	Urine Output Criteria
Risk	Increased plasma creatinine X1.5	<0.5 mL.kg^{-1}.h^{-1} X 6 hours
Injury	Increased plasma creatinine X2	<0.5 mL.kg^{-1}.h^{-1} X 12 hours
Failure	Increased plasma creatinine X3 or acute plasma creatinine ≥350 µmol/L or acute rise ≥44 µmol/L	<0.3 mL.kg^{-1}.h^{-1} X 24 hours or anuria X 12 hours
Loss	Persistent acute renal failure= complete loss of kidney function >4 weeks	
ESKD	End-stage kidney disease (>3 months)	

ESKD - end-stage kidney disease, GFR - glomerular filtration rate

Postoperative management

Postoperatively patients were followed in intensive care unit (ICU) according to protocols of our institution. Electrocardiography, systemic mean arterial pressure, central venous pressure, pulmonary artery and wedge pressures, cardiac output and index, arterial blood gases, chest tube output and hourly urine output were monitored. Serum electrolytes were measured in conjunction with arterial blood gas measurement. Fluid and electrolyte imbalances were corrected immediately with appropriate management. Hematocrit values <25% were corrected with erythrocyte suspension administration.

The renoprotective regimen was started according to the urine output criteria of RIFLE meaning urine output less than 0.5 ml/kg/h within 6 hours after surgery. These patients were in the R (Risk) group according to RIFLE classification.

Group 1 patients received undiluted (10 mg/ml, administered within 1 to 2 minutes) 1 mg to 3 mg/kg of furosemide intravenously every 4 hours up to a cumulative maximum of 500 mg in 24 hours (13).

Group 2 patients received continuous intravenous infusion of furosemide at 2 ml/h. The concentration of the drug was 10 mg/ml (250 mg in 50 ml of 0.9% sodium chloride). The infusion rate was doubled every 2 hours if 1ml/kg/h urine output could not be reached.

As previously described both Group 1 and 2 patients received renal doses of dopamine infusion in conjunction with furosemide at 2-3 µg/kg/min. Mannitol either intermittently or in a continuous infusion manner was not administered to any group. The study medication was continued until discharge of the patient from the ICU or 48 hours after surgery.

Daily blood urea nitrogen (BUN), serum and urea creatinine and serum electrolytes were measured uniformly in all patients until discharge from hospital. Preoperative and postoperative creatinine clearances and peak creatinine clearance were calculated according to the formulations reported in the literature (11, 14).

The indication criteria for RRT were determined by our staff nephrologists and they were the same for both of the study groups. These criteria included; hyperkalemia (>6 mmol/l), anuria or oliguria <0.5ml/kg/h for 12 hours and metabolic acidosis.

Vascular access was with a dual lumen catheter via a central venous vein. Patients were heparinized to achieve activated clotting time of 200 seconds. Fresenius polysulfone filter (Fresenius Medical care AG, Bad Homburg, Germany) was used for filtration.

Statistical analysis

All statistics were performed using SPSS version 11.0 for Windows (SPSS Inc. Chicago, IL, USA). Continuous variables were expressed as mean ± SD and were compared by unpaired Student's t test or ANOVA for repeated measures (2x2 factorial design) with Bonferroni corrections. Comparison between groups for categorical variables was made by Chi-square test. Survival analysis was performed by Kaplan-Meier method and Log rank test was performed for comparison of both groups. Statistical significance was assumed if *p* value was <0.05.

Results

Patient demographics and operative data are shown in Table 2. Preoperative patient characteristics and intraoperative data did not assure statistical significance between the two groups. The preoperative mean serum creatinine was 1.12±0.17 mg/dl in group 1 and 1.10±0.20 mg/dl in group 2 (p=0.338). Postoperative peak serum creatinine levels were found to be higher in group 1 patients than group 2 (2.17±0.87 and 1.28±0.35 respectively, p<0.001). Group 2 patients revealed higher amounts of urine output than group 1 patients and this was statistically significant (2.68±0.95 and 1.21±0.60, p<0.001).

Postoperative results are summarized in Table 3. Postoperative and peak creatinine clearance values did not show statistically significant difference compared to preoperative values in group 2 (p=0.051 and p=0.063), whereas intermittent administration of furosemide in group 1 patients resulted in lower levels of postoperative and peak creatinine clearance values (p<0.001 and p<0.001).

RRT was used in 5% of patients (all patients were in group 1, p=0.028). The creatinine value before commencement of RRT was 3.84±0.91 mg/dl. RRT was started 40 to 55 hours after surgery (mean 46.25±6.75 h) and used for 5.7 days. The mean creatinine level was 1.49±0.71 mg/dl prior to hospital discharge and only 2 patients became hemodialysis dependent in group 1.

Intraaortic balloon pump support was required in 8% of patients (5 patients in group 1 and 3 patients in group 2). Prolonged ventilatory support was necessary in 4% of patients (3 patients in group 1 and 1 patient in group 2) and two of them required a tracheostomy. The mean ICU stay time was 42.46±36.84 hours in group 1 and 28.64±10.82 hours in group 2 (p=0.014), in-hospital stay time was 5.78±3.29 days in group 1 and 4.52±0.99 days in group 2 (p=0.011).The 30-day mortality rate was 5% and all of the patients were in group 1 (p=0.028). Three patients died due to low cardiac output and multiorgan failure. These patients required RRT. One patient died due to mesentery artery ischemia and one due to cerebrovascular accident. The overall mortality at the end of the follow-up was 8% (7 patients in group 1 and 1 patient in group 2). Log rank test for survival revealed a higher overall mortality for group 1 (χ^2= 4.82, p= 0.028) (Fig. 1).

Discussion

Our results suggested that continuous infusion of furosemide with renal dose of dopamine increased the urine output and resulted in higher levels of peak postoperative creatinine clearances than intermittent furosemide regimen.

Table 2. Baseline and perioperative characteristics of patients

Clinical characteristics	Group 1* (n=50)	Group 2** (n=50)	p[a]
Age, years	65.8±9.2	65.3±10.0	0.796
Female, %	16	28	0.114
Body mass index, kg/m^2	26.90±4.19	25.84±2.60	0.133
Hypertension, n	20	22	0.689
Diabetes mellitus, n	20	17	0.539
Hyperlipidemia, n	20	18	0.684
CPB time, min	70.32±18.20	74.20±11.18	0.526
Cross-clamp time, min	38.16±12.36	39.30±12.32	0.797
LV function, %	40.0±5.1	42.0±5.2	0.142
Serum creatinine, mg/dl	1.12±0.17	1.08±0.2	0.338
Creatinine clearance, ml/min	86.74±9.65	85.20±9.66	0.427
Blood urea nitrogen, mg/dl	15.8±2.0	16.3±2.0	0.269
Euroscore, points	4.66±30.00	3.86±27.00	0.069

Data are presented as Mean±SD and proportions
*Group 1, furosemide administered intermittently with renal dose of dopamine infusion
**Group 2, furosemide administered as continuous infusion with renal dose of dopamine infusion
[a]Chi-square and unpaired Student's t tests
CPB - cardiopulmonary bypass, LV - left ventricle

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Table 3. Comparison between preoperative and postoperative parameters within the groups

Variables	Preoperative	Postoperative	F	p***
Urine output, ml/kg/h				
Group 1*	0.84±0.08	1.21±0.60	19.2	<0.001
Group 2**	0.86±0.80	2.68±0.95	179.4	<0.001
interaction			82.1	<0.001
Serum Cr, mg/dl				
Group 1*	1.12±0.17	1.68±0.40	87.7	<0.001
Group 2**	1.08±0.21	1.17±0.19	15.4	<0.001
interaction			54.0	<0.001
Serum Cr, pre vs peak, mg/dl				
Group 1*	1.12±0.17	2.17±0.87	71.6	<0.001
Group 2**	1.08±0.21	1.28±0.35	13.4	<0.001
interaction			39.1	<0.001
CC, ml/min				
Group 1*	86.74±9.65	42.24±11.04	451.6	<0.001
Group 2**	85.20±9.66	77.24±26.15	3.9	0.051
interaction			65.9	<0.001
CC, pre vs peak, ml/min				
Group 1*	86.74±9.65	34.43±10.56	636.3	<0.001
Group 2**	85.20±9.66	77.12±28.30	3.6	0.063
interaction			87.6	<0.001

Data are presented as Mean±SD
*Group 1, furosemide administered intermittently with renal dose of dopamine infusion
**Group 2, furosemide administered as continuous infusion with renal dose of dopamine infusion
***ANOVA for repeated measures (2x2 factorial design) with Bonferroni corrections.
CC - creatinine clearance, Cr - creatinine, pre-preoperative

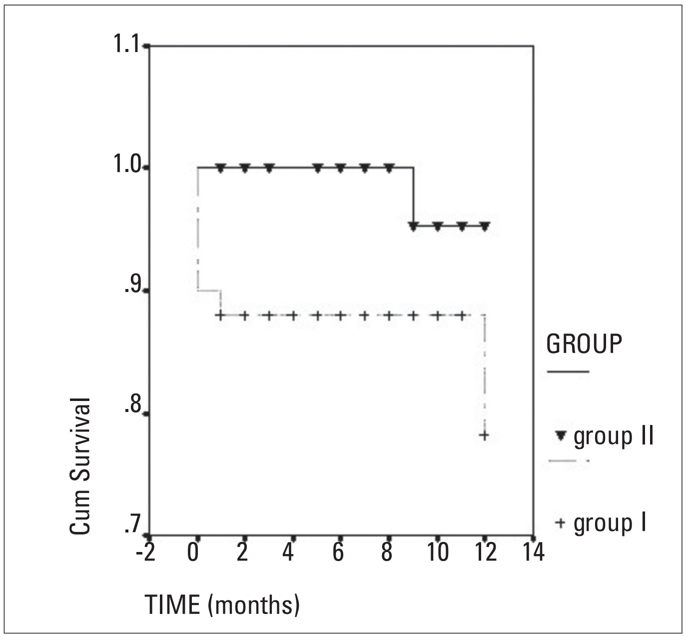

Figure 1. One-year Kaplan-Meier survival curve in group 1 and group 2, respectively
(7 patients in group 1 and one patient in group 2, χ^2= 4.82, p=0.028 in Log rank test)

Postoperative AKI requiring RRT has an independent effect on morbidity and early mortality. It is reported that the overall mortality due to this complication is 40-80% (11). Mortality is higher with intermittent use of hemofiltration than continuous RRT in acute postoperative period. This is suggested to be due to continuous removal of fluid and toxins with continuous RRT (15, 16).

The exact mechanism of postoperative AKI is still unclear. Many strategies are suggested to prevent this dreadful complication of cardiac surgery. These include, use of some pharmacological agents as mannitol, furosemide and dopamine, hydration of patient, keeping the perfusion pressures higher (>70mmHg) (4).

Furosemide is a loop diuretic that inhibits the active resorption of sodium and chloride in the ascending loop of Henle reducing oxygen requirement. It promotes diuresis as well as results in vasodilation of cortical vessels. Augmentation of renal blood flow decreases the concentration of nephrotoxic agents thus prevents tubular obstruction (17).

Dopamine is another widely used agent for prevention of AKI in many cardiovascular ICU. Renal dose dopamine (2-3µg/kg/min) acts through dopaminergic receptors and results in diuresis, natriuresis, increase in renal blood flow and glomerular filtration rate (18).

There are many studies in the literature about the use of furosemide and dopamine in prevention of AKI. Copeland and associates (19) stated that continuous infusion of furosemide may be useful for a gentle and sustained diuresis. Similarly, Gulbis et al. (20) reported continuous infusion of furosemide as an effective and safe method of diuresis in cardiac surgery. In a study by Sirivella et al (4), infusion of a solution composed of mannitol, furosemide and dopamine promoted diuresis and decreased the need for dialysis. In contrast to these studies Lassnigg et al. (11) suggested renal-dose dopamine was ineffective and furosemide led to renal dysfunction after cardiac surgery.

The present study demonstrates that RRT was required in 5% of patients. All the patients were in group 1 that received intermittent boluses of furosemide. Furosemide infusion with simultaneous administration of renal-dose dopamine led to the continuous and higher amounts of urine output compared to the other group. This condition prevented volume overload in patients who are hemodynamically unstable after cardiac surgery. Intermittent boluses of furosemide however caused fluctuations in the amounts of urine output thus these patients required greater amounts of fluid replacement and also had uncontrollable electrolyte imbalances. Volume overload and eventual pulmonary edema led to increased ratio of RRT use in group 1 patients. These results are consistent with the literature (21, 22).

There are many studies in the literature that used furosemide infusion, however none of them come to a decision about its dosage. In the present study, we used the dose recommended by Bojar et al. (13) that is 10 mg/ml. We increased the dose whenever necessary to reach urine output of 1 ml/kg/h. The infusion was continued until the patient was discharged from ICU or 48 hours after surgery. These maneuvers all could lead to the prevention of group 2 patients from RRT use.

Overall, both groups had significant increase in peak postoperative serum creatinine values however the peak postoperative creatinine clearance was lower in the patients who received intermittent boluses of furosemide. This is thought to be due to steady state urine output achieved with continuous infusion of furosemide.

It is well known that RRT use leads to increased stay times in ICU and hospital, increased cost and mortality eventually. Thus, RRT commencement was delayed until the urine output was <0.5 ml/kg/h for 12 hours. Besides RRT was used immediately whenever hyperkalemia, acidosis or pulmonary edema were diagnosed.

Study limitations

There are some limitations to our study. First, the patients were selected in a general manner rather than specific. Second limitation is that the study does not include a dopamine alone group, this was because we administered intermittent boluses of furosemide (out of study protocol criteria) in any of the patients that we think oliguria or volume overload according to pulmonary wedge pressures. Last limitation is the small number of patients in each group.

Conclusion

In summary, AKI occurring after cardiac surgery causes multiple postoperative complications and leads to prolonged hospitalization, increased costs, and eventually increased rate of mortality. Fortunately, AKI necessitating RRT makes a small percentage of patients undergoing cardiac surgery and if RRT is not required the survival of these patients with AKI is excellent.

Continuous infusion of furosemide seems to be effective in promoting diuresis and decreasing the need for RRT. However further multicenter studies with larger number of patients and different doses of furosemide are required to confirm these results.

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