Fenoldopam Reduces the Incidence of Renal Replacement Therapy After Cardiac Surgery

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Objective: **To investigate whether a continuous 48-hour infusion of fenoldopam, 0.1 μg/kg/min, reduced the need for renal replacement therapy in patients with acute renal injury after cardiac surgery.**

Design: **Case-matched study.**

Setting: **Teaching hospital.**

Participants: **Ninety-two patients.**

Interventions: **Patients who developed acute renal injury (defined as serum creatinine doubling or oliguria) after cardiac surgery received a continuous infusion of fenoldopam, 0.1 μg/kg/min, (46 patients) for 48 hours. They were case matched with 46 patients who developed acute renal injury, had similar baseline characteristics, and received standard treatment (hemodynamic support to obtain a mean arterial pressure >60 mmHg, fluid administration to increase central venous pressure >10 mmHg, and loop diuretics to maintain a urine output >0.5 mL/kg/h). Renal replacement therapy was started when acute renal injury became oligoanuric, when serum creatinine increased >4 mg/dL or 3 times basal value, or in the presence of severe hyperkalemia (K >6.5 mmol/L) or severe acidemia (pH < 7).**

Measurements and Main Results: **Patients in the fenoldopam group had a reduced need for renal replacement therapy (8 patients, 17%) with respect to case-matched controls (18 patients, 39%; $p = 0.037$). The length of intensive care unit stay (median [interquartile range]) was similar in the 2 groups: fenoldopam group, 5 days (3-9 days), and control group, 10 days (3-16 days, $p = 0.15$).**

Conclusions: **Given the limitations of case-matched studies, fenoldopam may be useful in avoiding renal replacement therapy in patients who develop acute renal injury after cardiac surgery.**

KEY WORDS: fenoldopam, acute renal failure, acute renal injury, renal replacement therapy, cardiac surgery, kidney

A RECENT META-ANALYSIS[1] suggested that fenoldopam reduces acute renal failure (ARF), the need for renal replacement therapy (RRT), and mortality in critically ill patients admitted to intensive care units (ICUs) or undergoing major surgery. Fenoldopam mesylate, a benzazepine derivative, is the first selective dopamine-1 receptor agonist approved for clinical use.[2] It acts predominantly as a vasodilator and as a diuretic, and it is increasingly used for its renoprotective properties.

The risk of ARF after cardiac surgery is high.[3] Established measures to prevent and treat renal dysfunction are limited to adequate hydration, optimization of the hemodynamic status with inotropes and/or vasodilators, elimination of medications with adverse effects on renal function, and correction of acid-base or metabolic imbalances associated with renal insufficiency.

The role of fenoldopam in cardiovascular surgical patients has been studied by different authors. No effect emerged for low doses or short-term use,[4] whereas other authors using fenoldopam, 0.1 μg/kg/min, for longer periods (mostly 48 hours) showed suggestive trends toward improvement in renal function and/or a reduced need for RRT.[5-9] Therefore, the authors conducted a case-matched study in high-risk cardiac surgical patients to show whether fenoldopam, 0.1 μg/kg/min, administered for 48 hours could reduce the need for RRT after cardiac surgery in patients with ongoing acute renal injury.

METHODS

The study was performed according to the principles of the Declaration of Helsinki. The ethical committee approved the study protocol. Patients provided written informed consent. The setting was a 15-bed postcardiac surgery ICU in a tertiary hospital.

Patients 18 years of age or older undergoing cardiac surgery were included in the study protocol if they developed acute renal injury within 48 hours after cardiac surgery as defined by the following established criteria[10]: urinary output <0.5 mL/kg/h for 24 hours or postoperative serum creatinine >2 times preoperative serum creatinine and >1.4 mg/dL. Exclusion criteria included preoperative dialysis, glaucoma (because of the risk of increased intraocular pressure with fenoldopam), and allergy to fenoldopam or its infusion components such as metabisulfite or sulfites.

The study group consisted of consecutive patients who received fenoldopam (Corlopam R; Hospira, McPherson, KS) at 0.1 μg/kg/min for 48 hours in addition to standard management of hemodynamic support (dobutamine, 5-7.5 μg/kg/min, if necessary to obtain a mean artery pressure >60 mmHg; the second drug used was norepinephrine), fluid administration to increase central venous pressure >10 mmHg, and loop diuretics to maintain a urine output (UO) >0.5 mL/kg/h with a maximum dosage for furosemide of 1,000 mg/d followed by the use of ethacrynic acid in nonresponders. Fenoldopam was supplied as a sterile, lyophilized powder in vials containing 25 mg, reconstituted with bacteriostatic water for intravenous injection. The solution was administered by continuous infusion through a central venous catheter.

Forty-six patients with the same characteristics and inclusion criteria undergoing cardiac surgery in the previous year were selected as controls. The selection of patients in the control group was based on a 1:1 case-control study. For each case in the study group, a control patient was randomly matched as follows: same age, sex, EuroSCORE, and operation. Furthermore, all perioperative routine management was unchanged in the control group; the same hemodynamic support, hydration, and loop diuretics were administered.

All patients received standard monitoring and anesthesia. Heparin, 300 IU/kg, was given to maintain the activated coagulation time >400

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seconds, and it was reversed with protamine. Cardiopulmonary bypass (CPB) was conducted with an institutional custom pack including a coated membrane oxygenator, with mild hypothermia (32°-33°C). Pump flow was set at 2.4 L/min/m^2. Perfusion pressure on pump was maintained at 50 mmHg, and norepinephrine was used if necessary. No patient received epsilon aminocaproic acid or aprotinin. At the end of the surgical procedure, patients were transferred to the ICU and weaned from the ventilator as soon as they met the following criteria: hemodynamic stability, no major bleeding, normothermia, and consciousness with adequate pain control. Transfer out of the ICU was performed when the SpO_2 was >94% on an F_IO_2 of <0.5 by facemask, adequate cardiac stability with no significant arrhythmias, chest tube drainage <50 mL/h, UO >0.5 mL/kg/h, no inotropic or vasopressor therapy, and no seizure activity.

The hypothesis tested was that fenoldopam would improve renal function reducing the need for RRT after cardiac surgery. Secondary outcomes were represented by the serum creatinine concentration at ICU discharge, time on mechanical ventilation, and ICU length of stay.

RRT was started when acute renal injury became oligoanuric (UO <20 mL/h) for more than 6 hours, when serum creatinine increased >4 mg/dL or 3 times basal values, or in the presence of severe hyperkalemia (K >6.5 mmol/L) or severe acidemia (pH < 7.0). Renal support was provided by continuous venovenous hemofiltration through a double-lumen catheter inserted into a femoral, internal jugular, or subclavian vein. The blood pump was set to deliver 120 to 150 mL/min, aiming for an ultrafiltration rate of 1.5 to 2 L/h in the pre- or postdilution mode with bicarbonate buffer in the solution. Anticoagulation of the extracorporeal circuit was maintained with a heparin infusion (200-1,000 U/h) through the inflow side of the circuit.

The collected variables were age, sex, EuroSCORE, emergent (unscheduled) surgery, previous cardiac surgery (redo), hypertension, diabetes (on oral or insulin treatment), atherosclerosis, CRF (serum creatinine >1.4 mg/dL), hemodynamic instability (MAP <60 mmHg or need for inotropic agent), duration of CPB and cross-clamping, the simplified acute physiology score at admission to the ICU, surgical revision, hemodynamic support (at least 2 inotropic drugs), need for intra-aortic balloon pump, UO <0.5 mL/kg/h for at least 24 hours, multiple transfusions (more then 4 red cell units or 1 L of fresh plasma), sepsis (when an infectious source was seen in a patient with body temperature >38°C or <36°C, heart rate >90 beats/min, respiratory rate >20 breath/min, or $PaCO_2$ <32 mmHg, white blood cells >12,000/mm^3 or <4000/mm^3), assumption of nephrotoxic drugs (antibiotics [aminoglycosides and glycopeptides] or radiocontrast agents) within the previous 48 hours, and serum creatinine.

Sample-size calculations were based on a 2-sided α error of 0.05 and 80% power. Based on previous experience, the authors anticipated a need for RRT of 60% in this high-risk population and assumed a reduction to 30% in patients treated with fenoldopam. It was calculated that a sample size of 46 patients per group was needed. Therefore, the total study population was $2 \times 46 = 92$ patients. Data were analyzed by the use of Epi Info 2002 software (CDC, Atlanta, GA) and SAS software, version 8 (SAS Institute, Cary, NC). Patients were case matched by age, sex, EuroSCORE, and operation with patients who did not receive fenoldopam. Preoperative patient characteristics, individual risk factors, and intraoperative course were compared by univariate analysis. Data are reported as percentage or as mean ± standard deviation or, for variables not normally distributed, as median and 25th to 75th percentile.

Dichotomous data were compared by using a chi-square test with the Yates correction or a Fisher exact test when appropriate. Continuous measures were compared by analysis of variance or the Mann-Whitney *U* test when appropriate. Two-sided significance tests were used throughout the analysis. Stepwise multivariate linear regression analysis was used to determine independent predictors of cTnI release, and results are reported as odds ratios (ORs) with 95% confidence intervals.

RESULTS

In the study period, 92 patients undergoing cardiac surgery were investigated, 46 patients receiving fenoldopam case matched with 46 control patients receiving standard treatment. Preoperative characteristics, surgical procedures, and intraoperative data are described in Table 1. Serum creatinine values at baseline and at diagnosis of acute renal injury together with peak and discharge values are shown in Table 2.

Patients in the fenoldopam group had a reduced need for RRT (8 patients, 17%) with respect to controls (18 patients, 39%; $p = 0.037$). Time on RRT was 10 ± 9 days in the

Table 1. Perioperative Characteristics of 92 High-Risk Patients Who Underwent Cardiac Surgery, Had Acute Renal Injury, and Were Treated With Fenoldopam or With Standard Treatment

	Control Group (n = 46)	Fenoldopam Group (n = 46)	*p* Value
Preoperative characteristics			
Age (y)	65 ± 14.8	69 ± 9.2	0.2
Female sex, n (%)	21 (46%)	21 (46%)	0.9
EuroSCORE	8 ± 2.6	9 ± 3.5	0.4
Hypertension on treatment, n (%)	21 (46%)	29 (63%)	0.2
Diabetes, n (%)	17 (37%)	10 (22%)	0.2
Chronic renal failure, n (%)	8 (17.4%)	8 (17.4%)	0.9
Hemodynamic instability	9 (20%)	8 (17%)	0.9
Previous cardiac surgery (redo), n (%)	10 (22%)	12 (26%)	0.8
Emergent surgery, n (%)	17 (37%)	18 (39%)	0.9
Type of cardiac surgery			
Coronary artery bypass surgery	14 (30%)	11 (24%)	0.6
Valvular surgery	18 (39%)	23 (50%)	0.4
Aortic and other surgery	14 (30%)	12 (26%)	0.8
Perioperative data			
Duration of CPB (min)	116 ± 61	108 ± 52	0.5
Duration of cross-clamp (min)	66 ± 38	68 ± 34	0.8
Inotropic support, n (%)	34 (74%)	33 (72%)	0.9
Intra-aortic balloon pump, n (%)	7 (15%)	6 (13%)	0.9
Multiple transfusion, n (%)	11 (24%)	10 (22%)	0.9
Surgical revision, n (%)	3 (6%)	3 (6%)	0.7
SAPS II	34 ± 7	35 ± 9	0.6
Diuresis during the first 24 ICU hours (mL)	3,515 ± 1,395	3,403 ± 1,603	0.4
When acute renal injury was diagnosed			
Nephrotoxic drugs in the last 48 h, n (%)	18 (39%)	16 (35%)	0.8
Sepsis, n (%)	13 (28%)	16 (35%)	0.7
Oliguria, n (%)	8 (17%)	6 (13%)	0.8
Dobutamine, n (%)	15 (32%)	15 (32%)	0.9
Norepinephrine, n (%)	4 (9%)	3 (6%)	0.5
Ethacrynic acid, n (%)	6 (13%)	6 (13%)	0.9

Abbreviation: SAPS II, simplified acute physiology score (II) at ICU admission.