A prospective randomized comparative pilot trial on extended daily dialysis versus continuous venovenous hemodiafiltration in acute kidney injury after cardiac surgery

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Background and objectives
Acute kidney injury (AKI) requiring dialysis after cardiac surgery is accompanied by high mortality. Continuous venovenous hemodiafiltration (CVVHDF) and extended daily dialysis (EDD) are commonly used for critically ill patients with AKI. The aim of this prospective randomized comparative pilot trial was to compare the efficacy of CVVHDF and EDD in patients with AKI after cardiac surgery.
Patients and methods
A total of 80 patients who developed AKI and who needed renal replacement therapy (RRT) after cardiac surgery were included in this prospective randomized comparative trial. Patients were randomized to receive either CVVHDF or EDD. The outcomes assessed were renal recovery, mortality rate at day 30, and cost of RRT in the ICU.
Results
Both groups were comparable with respect to demographic data and APACHE II score. The frequencies of renal recovery and mortalities were comparable in both groups. The cost of RRT was significantly lower in the EDD group compared with the CVVHDF group ($P < 0.001$).
Conclusion
Both CVVHDF and EDD are effective in patients with AKI after cardiac surgery, with EDD having the advantage of lower cost.

Keywords:
acute kidney injury, cardiac surgery, continuous venovenous hemodiafiltration, extended daily dialysis

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Introduction

The new term for acute renal failure is acute kidney injury (AKI), which is particularly used in critical care medicine. It denotes a clinical syndrome of rapid decrease in renal excretory function and consequent decrease in urine output, accumulation of metabolic acids, creatinine, and urea, and increased potassium and phosphate concentrations [1]. In critically ill patients, AKI is rather common; its incidence has been reported to reach 30–60% [2]. Definition of AKI has reached a consensus with the RIFLE (risk, injury, failure, loss, end stage) criteria that are supported by the Acute Kidney Injury Network (AKIN) with minor modifications [1,3].

Cardiac surgery is a significant risk factor for AKI. The overall incidence of AKI after adult cardiac surgery is between 5 and 10% [4] depending on preoperative renal function and the complexity of cardiac surgery [5]. The type of surgery affects the risk for AKI and the postoperative pattern of serum creatinine. Complex and on-pump cardiac surgeries are associated with significantly higher risk of postoperative AKI and greater incidence of severe AKI requiring dialysis [6]. Under normal circumstances, the serum creatinine level decreases by 0.1–0.2 mg/dl following cardiac surgery. If the creatinine level increases by only 0.3 mg/dl within 48 h, the patient is considered to suffer from stage 1 AKI according to AKIN [7].

Adequate hydration is known to reduce the risk of developing AKI [8]. During the postoperative period after cardiac surgery, the main problem is excessive extracellular fluid and not dehydration. Thus, intravascular hypovolemia is the main cause of AKI, which requires rapid correction to preserve end-organ perfusion. In patients after cardiac surgery, the cardiac index should be maintained at greater than 2 l/min/m^2 in the immediate postoperative period to prevent gross hypovolemia [9].

Patients with AKI are treated using renal replacement therapy (RRT) to substitute metabolic functions of the kidney until renal recovery. It helps to correct acid–base and electrolyte imbalance and remove toxins. The RRT process encompasses ultrafiltration for water transport and diffusion and convection for solute transport [10].

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Two classes of RRT are available depending on the duration of therapy: intermittent and continuous. Continuous venovenous hemodiafiltration (CVVHDF) is a commonly used continuous modality. Extended daily dialysis (EDD) is an intermittent dialysis with a prolonged duration and low flow rates, and it is performed daily. EDD combines the advantages of intermittent and continuous techniques [11].

To our knowledge, no randomized comparative study has compared between CVVHDF and EDD in patients with AKI after cardiac surgery. The aim of the current randomized comparative pilot trial was to assess the efficiency of EDD as against CVVHDF in patients with AKI after cardiac surgery.

Patients and methods

Study design

This is a prospective, randomized, comparative pilot study comparing CVVHDF as against EDD in patients who needed RRT after cardiac surgery. After approval by the ethical committee of our institution, written informed consent was obtained from each patient or his relatives before enrollment into the study.

Population

The study included 80 patients who developed AKI after cardiac surgery and who needed RRT. RRT was initially guided by the RIFLE criteria for stage 1 AKI: a doubling in the serum creatinine level and/or urine output less than 0.5 ml/kg for 12 h.

Exclusion criteria were: age less than 18 years, systolic blood pressure less than or equal to 85 mmHg at the time of consent, chronic renal impairment, patients who needed dialysis before cardiac surgery, participation in another research study, and refusal of the patient.

Study procedures

Patients were randomized to receive either CVVHDF or EDD. A vascular access for dialysis was obtained in all patients by insertion of a Mahukar double-lumen hemodialysis catheter. A radial artery catheter was inserted for invasive blood pressure monitoring and blood sampling.

CVVHDF was performed with either a multifiltrate continuous renal replacement therapy (CRRT) machine (Fresenius Medical Care, Bad Homburg, Germany) or a Prismaflex machine (Gambro). CVVHDF session was given daily and continuously until recovery of the renal functions or death of the patient. The ratio of dialysate to replacement fluid was 1 : 2. The effluent flow was 35 ml/kg/h. Blood flow was 150–200 ml/min. EDD was performed using a 4008S machine (Fresenius Medical Care). EDD was given daily until recovery of the renal functions or death of the patient. The duration of the EDD session was 6–8 h, with a blood flow of 100–200 ml/min, and a dialysate flow of 300 ml/min.

In both groups, the ultrafiltration volume, defined as the net fluid lost by the machine per hour, was determined by the attending physician. Bicarbonate buffer solutions were used. A loading bolus of 5000 IU of heparin was administered inside the circuit before allowing blood to pass into the filter, and then a continuous intravenous heparin infusion was given at a rate of 500–1000 IU/h to maintain the ACTT for 180–220 s or PTT for 65–85 s.

Measurements

The APACHE II score was computed at admission to the ICU. Baseline vital signs and hemodynamic and laboratory data were recorded just before the start of the study and then recorded daily. Laboratory measurements included serum creatinine, blood urea nitrogen (BUN), and creatinine clearance estimated using the Cockcroft–Gault formula. The incidence of renal recovery in survivors, defined as dialysis-independence at hospital discharge among survivors, was recorded in both groups (%). The ultrafiltration volume was recorded daily. Hemodynamic measurements included heart rate, central venous pressure, and systolic and diastolic arterial blood pressures. The number and doses of vasopressors used during the study period were recorded.

The cost of RRT for each patient was determined on the basis of the cost of the sessions of CVVHDF and EDD during the patient's stay in the ICU, including only the cost of the dialysis solutions used during the sessions and the cost of consumables of the RRT machines, such as the dialysis set and filters used.

Endpoints

The primary endpoint was the frequency of renal recovery in survivors. The secondary endpoints were mortality at day 30, length of stay in the ICU, and cost of RRT.

Statistical analysis

Data are presented as mean ± SD or % and are compared using the Student *t*-test or the χ^2-test. All statistical analyses were performed using the SPSS (SPSS Inc., Chicago, Illinois, USA) software package. A *P*-value of less than 0.05 was considered significant.

Results

Between January 2010 and February 2013, 89 patients were considered for inclusion in the study. Three patients were excluded because they died before the start of RRT and six patients refused to participate in the study. Eighty patients were randomized to treatment with either CVVHDF (the CVVHDF group) or EDD (the EDD group), with 40 patients in each group. Patients' baseline characteristics at the time of enrollment in the study were comparable in both groups (Table 1). In our institution, the incidence of AKI after cardiac surgery between January 2010 and February 2013 was 4.2%; only 27% of these patients needed RRT.

The frequency of renal recovery among the survivors and the ultrafiltration volumes were comparable in both groups (Table 2). In both groups, the serum creatinine level and BUN were significantly decreased, whereas the creatinine clearance was significantly increased at the end of the study compared with that at baseline ($P < 0.05$). Serum creatinine, BUN, and the creatinine clearance were comparable in both groups (Table 3). The mortality rate and length of stay in the ICU were comparable in both groups (Table 2). The cost of RRT was significantly lower in the EDD group compared with the CVVHDF group ($P < 0.001$).

The hemodynamic measurements including the heart rate and systolic and diastolic arterial blood pressures were comparable in both groups. The number of patients on vasopressors was comparable in both groups (Table 4). Transient attacks of hypotension (systolic blood pressure<80 mmHg) occurred in one patient in the CVVHDF group and in two patients in the EDD group. All were reversed by decreasing the rate of ultrafiltration and infusing 20% albumin.

Discussion

In the management of AKI in the ICU, the main question is what to use: CRRT or intermittent hemodialysis (IHD). CRRT is recommended for hemodynamically unstable patients to allow for continuous adjustment of intravascular volume and solute removal, with correction of metabolic acidosis. This allows correction of hypervolemia [12]. A further query is the type of CRRT to be used. The difference between CRRT modalities lies in the main mechanism of clearance: simple diffusion as in CVVHD, convection in CVVH, or a combination of both in CVVHDF. The latter is advocated by some investigators on the basis of the safety and efficiency of the technique, despite lacking evidence [13].

EDD combines the advantages of IHD and CRRT. This technique is devised to use the standard IHD machine technology to provide slower solute and fluid removal in CRRT. It has been shown to be safe and effective in the treatment of AKI in critically ill patients, with an advantage of lower cost compared with CRRT, in addition to hemodynamic tolerability [14]. In another study, it was reported that EDD is a safe and

Table 1 Baseline characteristics of the two studied groups

Variables	EDD group (n = 40)	CVVHDF group (n = 4)	P-value
Age (years)	46 ± 18	49 ± 17	NS
Male sex	28 (70)	24 (60)	NS
Weight (kg)	81 ± 12	79 ± 13	NS
APACHE II score	23.3 ± 6.2	22.9 ± 5.9	NS
Causes of AKI[a]			
Hypotension	20 (50)	24 (60)	NS
Hypovolemia and bleeding	4 (10)	4 (10)	NS
Sepsis	10 (25)	12 (30)	NS
Nephrotoxins	6 (15)	4 (10)	NS
Vasopressors[b]			
Patients on dobutamine	16 (40)	20 (50)	NS
Patients on dopamine	4 (10)	6 (15)	NS
Patients on norepinephrine	10 (25)	8 (20)	NS
Patients on epinephrine	4 (10)	8 (20)	NS
Indications for cardiac surgery			
Coronary artery bypass graft	24 (60)	30 (75)	NS
Valve procedures	14 (35)	10 (25)	NS
Combined operations	2 (5)	0 (0)	NS
Laboratory values			
Serum creatinine (mg/dl)	3.7 ± 1.1	3.9 ± 1	NS
BUN (mg/dl)	72 ± 28	75 ± 22	NS
Creatinine clearance (ml/min)	39 ± 24	42 ± 21	NS

Data are presented as mean ± SD or number (%). AKI, acute kidney injury; APACHE II score, Acute Physiology and Chronic Health Evaluation Score II, ranges from 0–71, with higher scores indicating higher severity of illness; BUN, blood urea nitrogen; CVVHDF, continuous venovenous hemodiafiltration; EDD, extended daily dialysis. [a]More than one cause may be present. [b]Patients may or may not need vasopressors. $P \leq 0.05$ is considered significant when compared with the other group.

Table 2 Patients' outcome

Variables	EDD group (n = 40)	CVVHDF group (n = 40)	P-value
Mortality rate at day 30	7 (17.5)	9 (22.5)	NS
Length of stay in the ICU (days)	23 ± 5	19 ± 8	NS
Renal recovery in survivors	21 (63.63)	23 (74.19)	NS
Ultrafiltration volume (ml/72 h)	5680 ± 750	6300 ± 870	NS
Cost of RRT ($)	984.6 ± 615.4	4384.6 ± 2135.3	<0.001

Data are presented as mean ± SD or number (%). CVVHDF, continuous venovenous hemodiafiltration; EDD, extended daily dialysis; RRT, renal replacement therapy.

Table 3 Renal functions

Variables	Baseline	24 h	48 h	72 h	*P*-value
Serum creatinine (mg/dl)					
EDD group	3.7 ± 1.1	3.1 ± 0.9	2.1 ± 1.1*	2.1 ± 0.9*	≤0.05
CVVHDF group	3.9 ± 1	2.2 ± 0.9*	1.3 ± 0.5*	1.1 ± 0.3*	≤0.05
BUN (mg/dl)					
EDD group	72 ± 28	63 ± 18	46 ± 14*	38 ± 1.4*	≤0.05
CVVHDF group	75 ± 22	39 ± 27*	31 ± 15*	26 ± 12*	≤0.05
Creatinine clearance (ml/min)					
EDD group	39 ± 24	45 ± 13	59 ± 9	71 ± 14*	≤0.05
CVVHDF group	42 ± 21	57 ± 14	71 ± 13*	74 ± 14*	≤0.05

Data are presented as mean ± SD. BUN, blood urea nitrogen; CVVHDF, continuous venovenous hemodiafiltration; EDD, extended daily dialysis. *Significant difference compared with baseline in the same group; $P \leq 0.05$.

Table 4 Hemodynamic variables

Variables	Baseline	24 h	48 h	72 h	*P*-value
Heart rate (beats/min)					
EDD group	82 ± 19	77 ± 17	76 ± 15	80 ± 12	NS
CVVHDF group	84 ± 16	85 ± 11	78 ± 12	78 ± 10	NS
Systolic blood pressure (mmHg)					
EDD group	123 ± 15	127 ± 10	118 ± 17	127 ± 14	NS
CVVHDF group	119 ± 14	120 ± 17	126 ± 9	122 ± 13	NS
Diastolic blood pressure (mmHg)					
EDD group	64 ± 13	72 ± 15	70 ± 11	67 ± 12	NS
CVVHDF group	63 ± 11	67 ± 11	74 ± 13	72 ± 11	NS

Data are presented as mean ± SD. CVVHDF, continuous venovenous hemodiafiltration; EDD, extended daily dialysis.

effective substitute for CRRT with respect to solute clearance and hemodynamic stability. It was associated with lower incidence of clotting and anticoagulation therapy [15].

However, no studies have evaluated the outcome of EDD compared with that of CRRT modalities. We believe that the current study is the first to address the comparison between CVVHDF and EDD in the management of AKI after cardiac surgery. In the current pilot study, CVVHDF and EDD resulted in comparable frequency of renal recovery among the survivors (63.63 vs. 74.19%, respectively; $P = 0.704$) as well as mortality ($P = 1.000$). The cost of RRT was significantly lower in the EDD group compared with the CVVHDF group ($P < 0.001$).

Many studies have investigated the difference in outcome between CRRT and intermittent techniques to examine the general belief that the continuous method results in better outcome because of the slow protracted nature. However, these studies failed to demonstrate any difference in outcome between the two approaches [16–22].

Another theoretical advantage of CRRT is better hemodynamic stability, but several controlled trials have been unable to prove this benefit [16,17–21,23]. In our study, the hemodynamic measurements were comparable in both groups. It was suggested that the hemodynamic stability of CRRT could be attributed partly to slow dialysis and fluid removal, as well as to heat loss and hypothermia [19], which improves venous return and blood pressure [24]. Cooling the dialysate can produce a similar effect on IHD in patients with AKI as practiced in chronic hemodialysis [25]. However, the hemodynamic benefit of CRRT was not reflected by a difference in survival.

EDD is a hybrid therapy with benefits of both CRRT and IHD. Its major advantages are system flexibility and reduced costs [26]. Flexibility lies in the duration and intensity of treatment in which blood and dialysate flow and the rate of ultrafiltration can be tailored to the real needs of the patient. Studies comparing EDD with CRRT revealed similar hemodynamic responses [14,15,27,28].

The cost of therapy for critically ill patients needs to be recognized for therapeutic decisions. Care in the ICU is extremely expensive. We believe that the lower cost of EDD is suitable for developing countries such as Egypt. In our study, the cost of RRT was significantly lower in the EDD group compared with the CVVHDF group ($P<0.001$). This result correlates with a previous study in which the authors reported that the cost of CRRT was more than double that of intermittent RRT [29]. This was also confirmed in another multicenter and multinational study [30].

However, controlled trials comparing the outcome of EDD with that of CRRT in large populations are still lacking. The results of the current study suggest that CVVHDF and EDD are effective in patients with AKI after cardiac surgery, with EDD having the advantage of lower cost. The small size of this study limits the ability to draw definitive conclusions; however, it can be viewed as a pilot study to be followed by larger ones involving a larger population in a multicenter setting comparing the two modalities in different situations encountered in the ICU, not only following cardiac surgery. Another limitation of the current study is that the treatment was not blinded; hence, any bias cannot be excluded.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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