Extended Daily Dialysis in Acute Renal Failure
A New Therapeutic Approach

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Introduction. Although intermittent hemodialysis (IHD) is the standard therapy in patients with acute renal failure, it is associated with several drawbacks. Extended daily dialysis (EDD) has been described as a compromise between IHD and continuous therapies and could potentially overcome problems associated with IHD.

Materials and Methods. We compared EDD with IHD each administered in 15 patients with acute renal failure. The IHD was administered 4 hours per session thrice weekly, while EDD was given for 8 hours per session daily with the same machines at similar blood and dialysate flow rates. Treatment outcome, metabolic control, and hemodynamic stability were assessed in the patients of each group.

Results. A total of 140 EDD treatment sessions and 82 IHD sessions were administered. Patients in the EDD and the IHD groups received a mean of 74.67 ± 29.70 hours and 21.73 ± 5.99 hours of dialysis, respectively ($P < .001$). The median urea reduction ratio in the EDD group was significantly higher (83.82% versus 64.66%, $P < .001$). Patients on EDD showed faster normalization of deranged metabolic parameters. Hemodynamically, EDD was better tolerated compared to IHD. The median predialysis mean arterial pressure in the EDD and IHD patients were 103.3 mm Hg and 100 mm Hg, respectively, while the postdialysis values were 78.6 mm Hg and 73 mm Hg, respectively.

Conclusions. Extended daily dialysis appears to be a promising technique for dialysis in moderately ill patients having up to 2 organ failures.

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INTRODUCTION

Acute renal failure (ARF) is a common final outcome of various primary renal and nonrenal diseases. The treatment options in patients with ARF include peritoneal dialysis, intermittent hemodialysis (IHD) and continuous renal replacement therapies (CRRT).

Conventional hemodialysis in ARF is fraught with several problems particularly in patients with severe concomitant illnesses such as sepsis, acute respiratory distress syndrome or multiorgan failure. The rapid solute removal during short intermittent hemodialysis sessions produces large fluctuations in urea and electrolyte levels with a high chance of development of dysequilibrium syndromes. Hypotension is a serious complication and may require premature termination of dialysis in up to 5% of the sessions.[1] Patients with ARF receive fluids in the form of parenteral nutrition, antibiotics, and pressor support. Since most patients are oligo-anuric, adequate fluid removal during dialysis is essential, so that the patient's nutrition and treatment are not affected.[2] Hemodynamic compromise is a major impediment towards the

goal of achieving reasonable fluid homeostasis in patients with ARF, since removal of large amounts of fluid during the short IHD sessions tends to produce hypotension. In addition, with IHD, issues such as hemodynamic compromise and vascular access complications have a tendency to reduce the delivered dialysis dose, especially in view of the short treatment sessions of about 4 hours. Studies have linked the delivered dialysis doses to the final outcome in ARF.[3] The required dialysis dose for ARF is believed to be higher than that for CRF, because of alterations in the peripheral circulation, solute and water exchange among the tissue and the body compartments, and altered metabolism in this population.[4] Thus, it is well-appreciated that the IHD is not the ideal therapy for ARF, its major shortcoming being the rapid removal of solutes and fluid that is, in general, responsible for all the major complications seen with this modality. Continuous therapies are believed to be more physiological since they remove solutes slowly over several hours, mimicking a native kidney function.

All the aforesaid problems occurring with the IHD are addressed by the CRRT. However, continuous therapies have several inherent disadvantages. Continuous renal replacement therapy is prohibitively expensive, needs specialized equipment, is manpower intensive, and requires stricter anticoagulation to prevent extracorporeal blood clotting. Financial and manpower constraints have kept CRRT out of the reach of the majority of the population in the developing world.

To circumvent these problems, we designed a treatment plan that requires conventional hemodialysis machines, but the dialysis was performed daily over an extended duration for each session—extended daily dialysis (EDD). It is hypothesized that EDD would provide advantages, similar to CRRT, over conventional hemodialysis. The principle aim of our study was to compare the differences in the clinical outcome, hemodynamic stability, and metabolic control between the EDD and IHD treatment protocols, and to determine whether the EDD provided results superior to IHD.

MATERIALS AND METHODS

Patients

Between March 2005 and April 2006, a total of 30 consecutive patients admitted to the Lok Nayak Hospital in New Delhi, India, with a diagnosis of ARF were enrolled in the study. The study protocol was approved by the institutional ethics committee. Acute renal failure was defined as kidney dysfunction documented by a serum creatinine level equal to or greater than 2.0 mg/dL or an increase in serum creatinine of more than 50% over the baseline value.[5] Indications for initiation of dialysis therapy were fluid overload unresponsive to diuretics; uremic symptoms such as persistent nausea, vomiting, or encephalopathy; and severe metabolic acidosis or hyperkalemia not responding to medical treatment. Patients with the following characteristics were excluded from the study: age greater than 60 years or less than 14 years, preexisting renal insufficiency (baseline serum creatinine level equal to or greater than 2.0 mg/dL, bilateral contracted kidneys on ultrasonography, or persistent urinary abnormalities), and more than 2 failing organs at the time of inclusion.

A detailed history was obtained with emphasis on preexisting medical conditions, symptoms attributable to uremia, and the likely cause of the acute deterioration in kidney function. Vital signs, details of pressor support, level of consciousness, presence of sepsis,[6] and provision of enteral or parenteral nutrition were recorded. The number of failing organs was determined and used as a measure of disease severity (Appendix). The degree of dysfunction or failure of the individual organs was not taken into account.

Treatment

The patients were alternately assigned into the EDD group and conventional IHD group; ie, the first patient underwent EDD, the second one underwent IHD, and so on. Extended daily hemodialysis was administered for 8 hours per session, daily, and conventional IHD, 4 hours per session thrice a week. Other aspects of dialysis treatment including dialysis machines, dialysis membranes, anticoagulants, dialysate, and blood flow rates remained the same for both groups.

Vascular access was obtained using a dual-lumen femoral catheter. In both groups, dialysis was performed using Tina dialysis machines (Baxter Health Care, Deerfield, IL, USA) at a blood flow rate of 150 mL/min to 300 mL/min, as per angio-access using polysulfone F6 dialyzer

(Fresenius, Bad Homburg, Germany). Dialysate flow rate was kept at 500 mL/min in the IHD and 300 mL/min in the EDD groups. Ultrafiltration was prescribed during dialysis treatment as per the daily requirements. Ultrafiltration was done at 50 mL/h to 250 mL/h and adjusted according to the alteration in hemodynamic parameters and fluid status of individual patients. Unfractionated heparin was used as the anticoagulant, given as a bolus dose of 5000 U at the start of therapy, and then, 1000 U/h in the IHD group and 500 U/h in the EDD group, in order to maintain an activated partial thromboplastin time at least 50% above the reference value. Anticoagulation was stopped 1 hour before completion of dialysis.

Hourly blood pressure monitoring was done during the procedures. Hypotension was defined as a single systolic blood pressure less than 90 mm Hg or a mean arterial pressure (MAP) less than 60 mm Hg. Blood urea, arterial blood pH, and serum levels of bicarbonate, calcium, and phosphate were recorded daily. The urea reduction ratio (URR) was also calculated. The postdialysis blood samples were collected 1 hour after dialysis (to allow time for equilibration).[7] The patients were followed up till death or recovery up to a minimum period of 3 months. Recovery was defined as stabilization of kidney function without further need for dialysis as suggested by serial serum creatinine levels or creatinine clearance rates. The primary measure was the all-cause inpatient mortality.

Statistical Analyses

All data were summarized and expressed as mean ± standard deviation, median (25th to 75th percentiles), or percentages, as appropriate. The Mann-Whitney test was used to analyze nonparametric data. Pretest and posttest values within a single group were analyzed by the Wilcoxon signed rank test. The chi-square test was used to analyze categorical variables, while the *t* test was used to analyze normally distributed data. Statistical significance was considered at a *P* value less than .05.

RESULTS

Characteristics at Initiation of Dialysis

The characteristics of the patients in the EDD and IHD groups are summarized in Table 1. The patients of the two groups were comparable in terms of age, sex distribution, primary cause of ARF, number of organ failures, and indication for initiation of dialysis. Obstetric sepsis was the most important cause of ARF and comprised at least 40% of the patients in each group. None of the patients was on ventilatory support.

Table 1. Characteristics of Patients With Acute Renal Failure at Presentation Assigned Into Each Treatment Group*

Characteristics	Treatment Groups		*P*
	EDD	IHD	
Number of patients	15	15	
Age, y	37.3 ± 15.0	38.2 ± 12.2	.93
Sex			.67
Male	3 (25.0)	4 (26.7)	
Female	12 (75.0)	11 (73.3)	
Primary diagnosis			.48
Hypovolemia	5 (33.3)	6 (40.0)	
Toxicity	0	1 (6.7)	
Obstetric sepsis	6 (40.0)	7 (46.7)	
Sepsis (others)	2 (13.3)	0	
Malaria falciparum	2 (13.3)	1 (6.7)	
Failing Organs			.71
1	8 (53.3)	9 (60.0)	
2	7 (46.7)	6 (40.0)	
Oliguria	11 (73.3)	9 (60.0)	.44
Primary indication for dialysis			.19
Uremia	6 (40.0)	5 (33.3)	
Acidosis	1 (6.7)	1 (6.7)	
Hyperkalemia	2 (13.3)	8 (53.3)	
Encephalopathy	1 (6.7)	0	
Fluid overload	1 (6.7)	0	
Multiple indications	4 (26.7)	1 (6.7)	

*Values in parentheses are rounded percents. EDD indicates extended daily dialysis and IHD, intermittent hemodialysis.

Table 2 outlines the initial metabolic and hemodynamic parameters in the two groups. The MAP at presentation was comparable in the two groups. Patients who underwent EDD had significantly lower levels of arterial blood pH and serum bicarbonate at the time of dialysis initiation as compared to patients with IHD. Three patients in each group were on inotropic support. None of the patients was on more than 1 inotropic drug at the time of initiating dialysis.

Dialysis Therapy

During the study period, a total of 140 EDD sessions and 82 IHD sessions were administered to the 15 patients in each group. The mean duration of dialysis received by a patient in the EDD group was 74.67 ± 29.70 hours which was significantly higher than that received by a patient in the IHD group (21.73 ± 5.99 hours; $P < .001$). The mean number

Table 2. Initial Metabolic and Hemodynamic Parameters in Patients With Acute Renal Failure Assigned Into Each Treatment Group*

Parameters	Treatment Groups		*P*
	EDD	IHD	
MAP, mm Hg	101.9 (99.9 to 109)	103.3 (89.9 to 109.9)	.23
Blood urea, mg/dL	240.0 (215 to 269)	236.0 (207 to 277)	.96
Serum creatinine, mg/dL	10.1 (8.1 to 11.7)	7.8 (6.7 to 1.2)	.15
Sodium, mEq/L	137.0 (133 to 138)	137.0 (133 to 139)	.75
Potassium, mEq/L	6.4 (4.8 to 7.1)	5.9 (5.85 to 6.8)	.92
Calcium, mEq/L	7.6 (6.6 to 8.2)	6.8 (5.7 to 9.2)	.97
Phosphate, mEq/L	6.3 (4.9 to 7.1)	6.8 (6.1 to 8.2)	.37
pH	7.21 (7.13 to 7.30)	7.38 (7.28 to 7.40)	.003
Bicarbonate, mEq/L	9.7 (4.2 to 12.8)	13.3 (12.5 to 17.4)	.01

*Values in parentheses are the minimum and maximum ones. EDD indicates extended daily dialysis; IHD, intermittent hemodialysis; and MAP, mean arterial pressure.

of dialysis sessions received by a single patient in the EDD group was 9.33 ± 6.37 as compared to 5.47 ± 1.55 in the IHD group ($P < .001$).

Hemodynamic Parameters

Table 3 depicts the mean pre-dialysis and post-dialysis mean arterial pressures (MAP) in the two groups. There was a significant intradialytic decrease in the MAP with both modalities of treatment, but the magnitude of change was greater in the IHD group (Table 3). None of the patients on EDD developed any episode of hypotension, whereas in the IHD group, there were 6 hypotensive episodes during the 82 dialysis sessions ($P = .10$). Occasionally, during the EDD, blood flow rates were reduced to 200 mL/min or less due to the changes in vital signs that occurred during dialysis. However, a conscious attempt was made to maintain the blood flow rate over 250 mL/min during the entire procedure.

Table 3. Median MAP in Patients on EDD and IHD

Treatment	MAP, mm Hg		*P*
	Predialysis	Postdialysis	
EDD	103.3 (99 to 106)	78.6 (75 to 83)	< .001
IHD	100 (95 to 103)	73 (70 to 79)	< .001

*Values in parentheses are the minimum and maximum ones. EDD indicates extended daily dialysis; IHD, intermittent hemodialysis; and MAP, mean arterial pressure.

Figure 1 depicts the progressive change in the mean MAP over a single day of dialysis with each modality of therapy. Blood pressure followed a similar trend in the subsequent dialysis sessions.

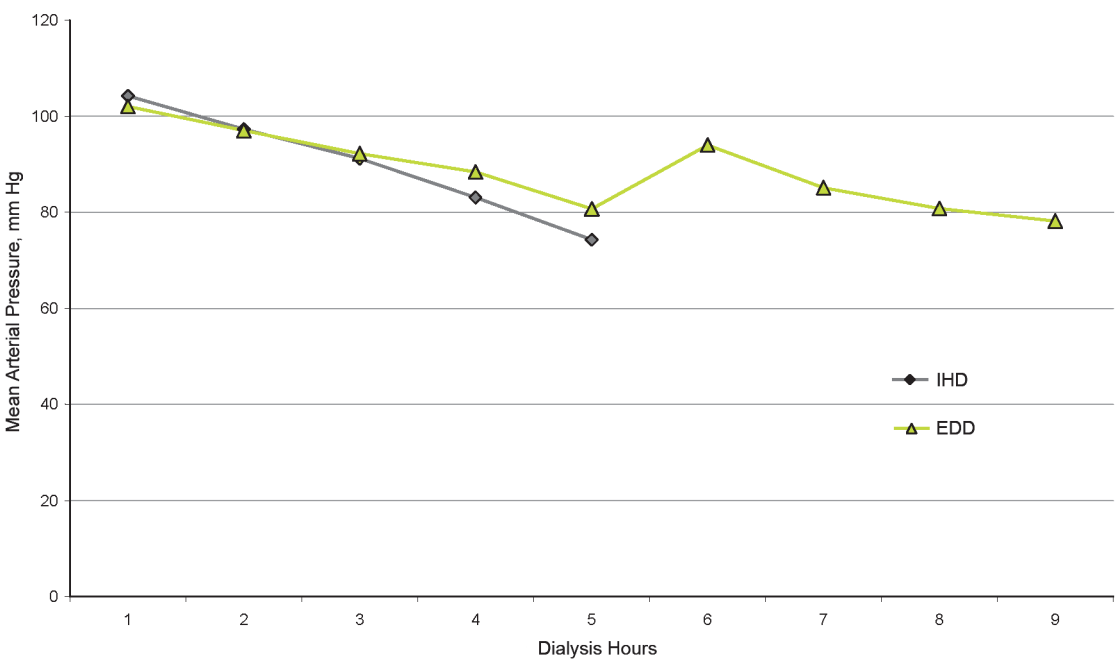

Figure 1. Trends in the intradialytic mean arterial pressure (MAP) on day 1 of therapy.

Figures 2 and 3 show the average magnitude of change in the MAP (before and after therapy) occurring over consecutive dialysis days.

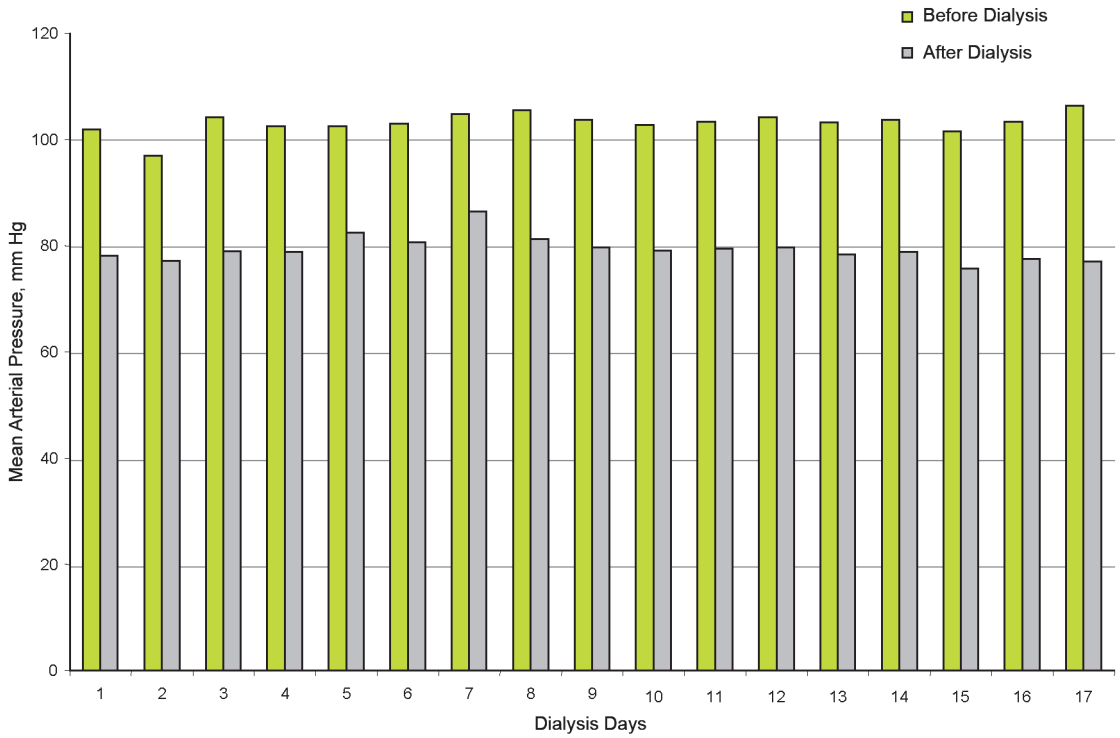

Figure 2. The mean predialysis and postdialysis MAP in the EDD group. EDD indicates extended daily dialysis and MAP, mean arterial pressure.

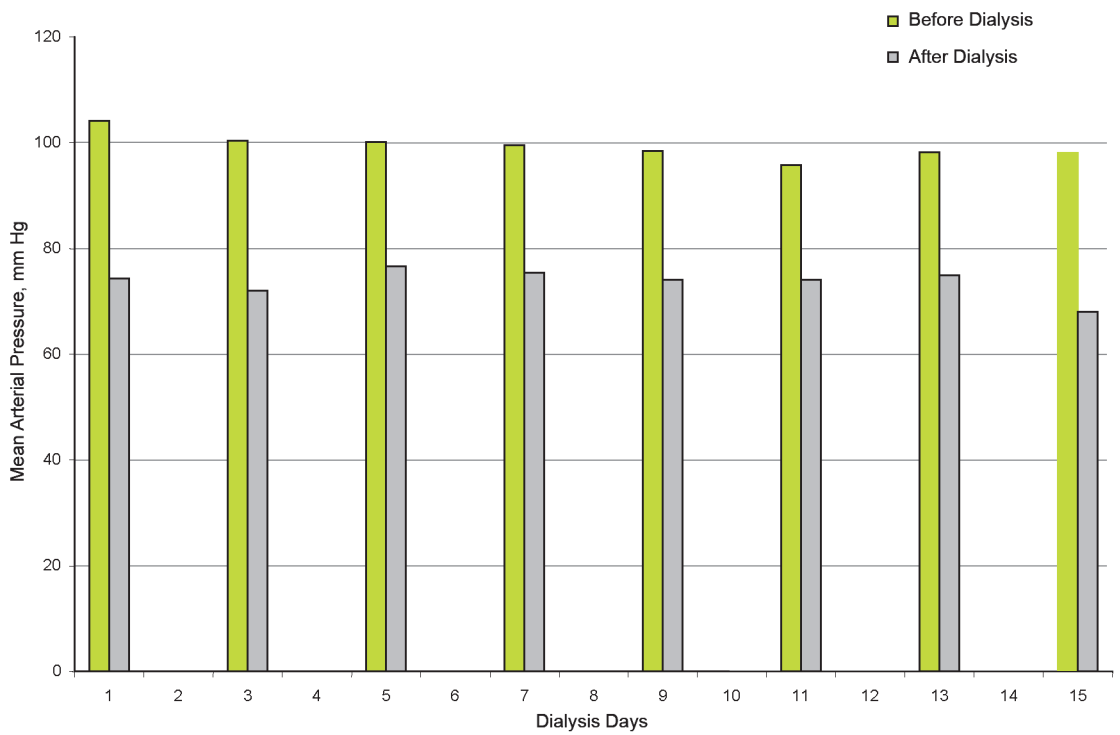

Figure 3. The mean predialysis and postdialysis MAP in the IHD group. IHD indicates intermittent hemodialysis and MAP, mean arterial pressure.

Trends in Metabolic Parameters

The daily trends in predialysis blood urea, potassium, and pH are depicted in Figures 4 to 6. The deranged parameters improved much faster in the EDD group compared to the IHD group (as is seen clearly in Figures 4 to 6). Subjective

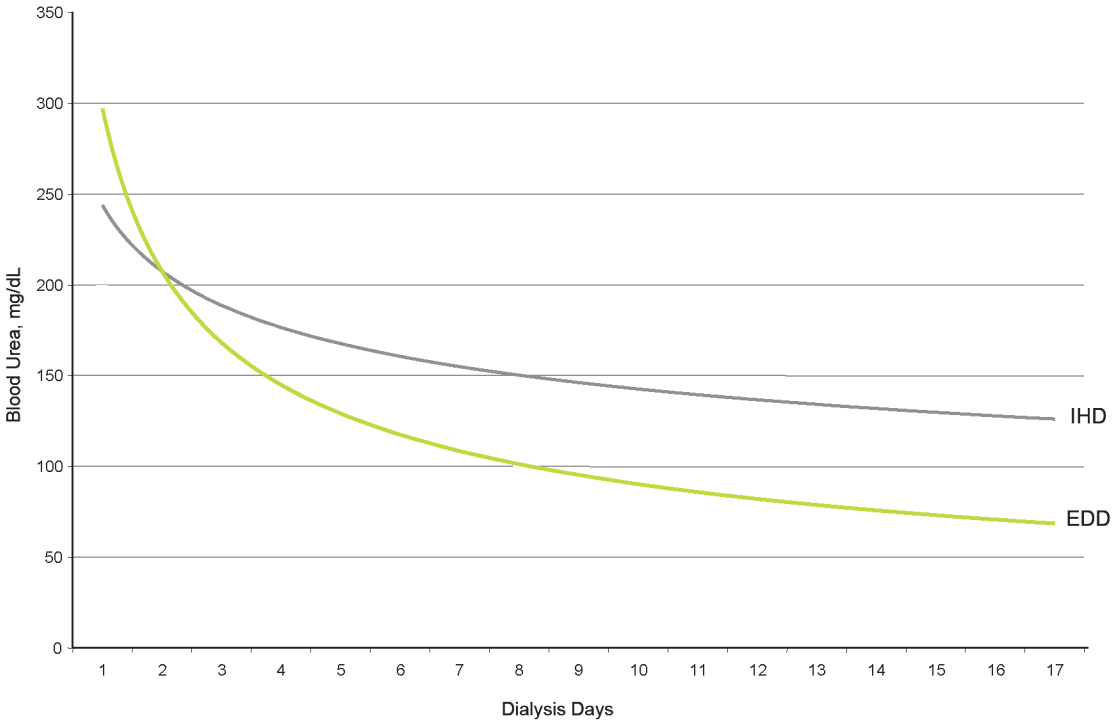

Figure 4. Trends in the levels of daily predialysis blood urea levels in the EDD and IHD groups. EDD indicates extended daily dialysis and IHD, intermittent hemodialysis.

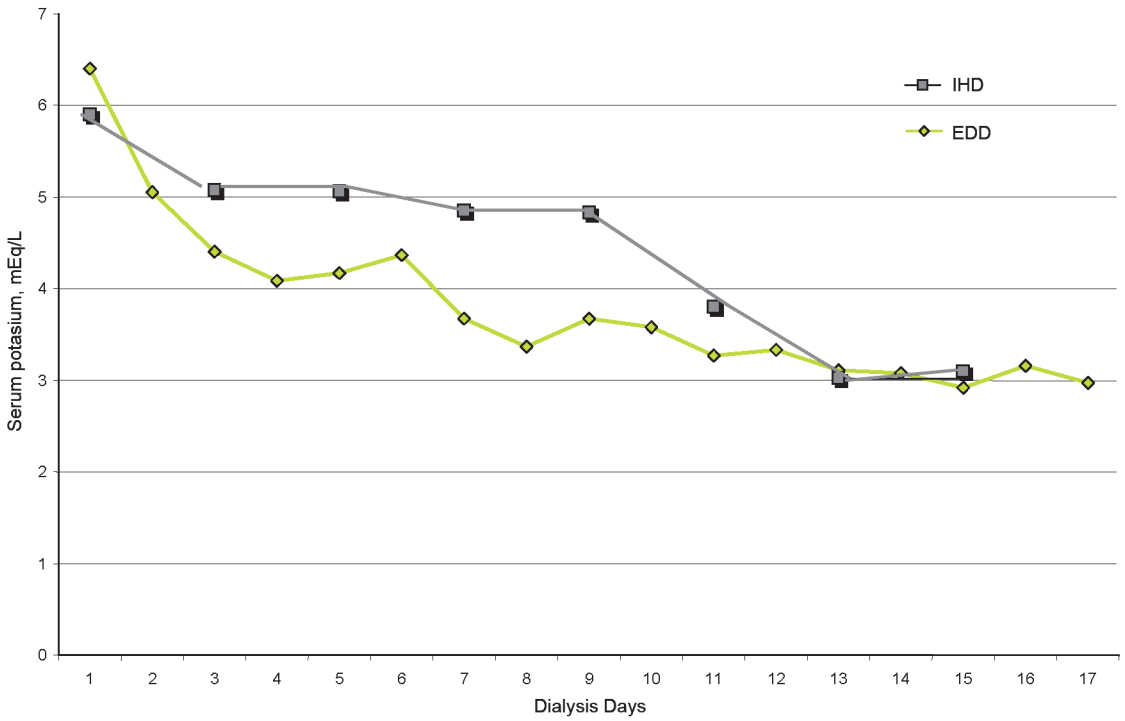

Figure 5. Trends in the levels of daily predialysis serum potassium levels in the EDD and IHD groups. EDD indicates extended daily dialysis and IHD, intermittent hemodialysis.

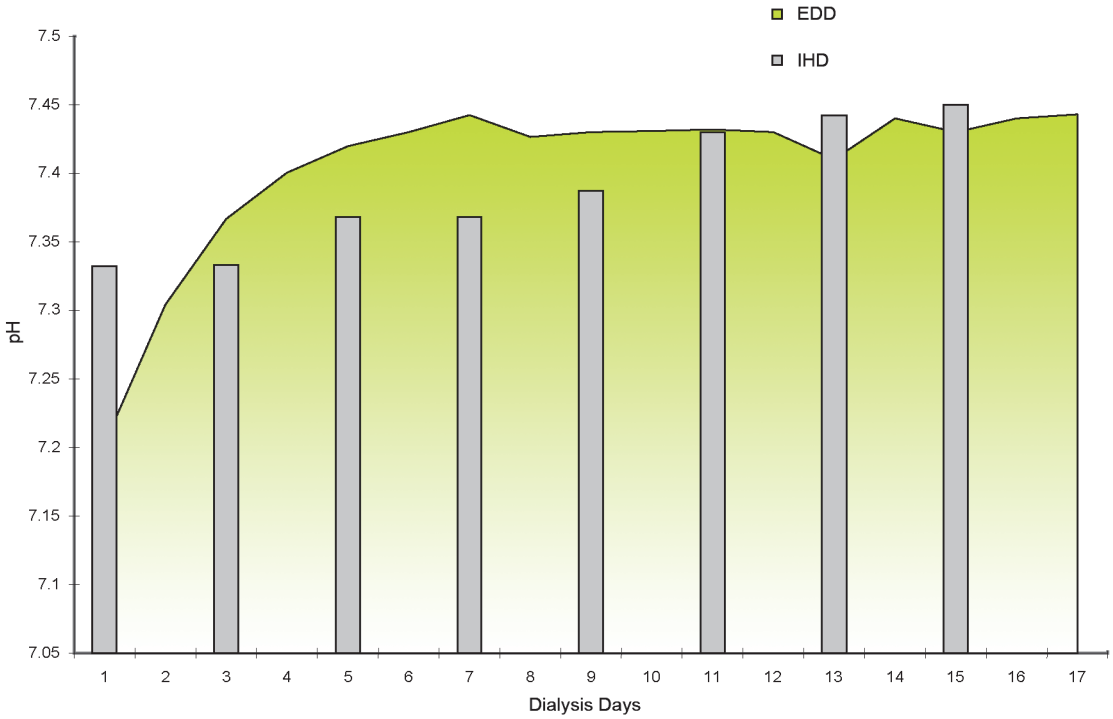

Figure 6. Trends in the levels of daily predialysis pHs in the EDD and IHD groups. EDD indicates extended daily dialysis and IHD, intermittent hemodialysis.

improvement in uremic symptoms occurred earlier in the patients on EDD than in those on IHD. The median URR in the EDD group (for all dialysis sessions) was 83.82% (80.9% to 86.4%), while the same figure for the IHD group was 64.66% (61.3% to 67.8) ($P < .001$).

Fluid Removal

Fluid removal by ultrafiltration was dictated by the clinical assessment of fluid status of the individual patients. The mean quantity of fluid removed in a single dialysis session by ultrafiltration in the EDD group was 2426 ± 1230 mL, while the corresponding value for the IHD group was 1112 ± 309 mL ($P < .001$).

Outcome and Complications

All of the patients initiated on dialysis could be successfully salvaged and none of the patients died. During the follow-up, 2 patients in the EDD group had persistently deranged kidney function tests, but they were managed conservatively without the need for long-term dialytic support. One patient in the EDD group developed seizures on the first day of dialysis, approximately 6 hours after the end of the procedure. The patient was found to have hyponatremia and improved after administration of intravenous hypertonic saline. Also, 1 patient in the IHD group developed upper gastrointestinal bleeding after dialysis, in view of a raised partial thromboplastin time. The patient was successfully treated with protamine and blood transfusions. No structural gastrointestinal lesions were detected on endoscopy.

DISCUSSION

During the course of this study, EDD and IHD were performed on 2 groups of 15 patients with ARF. The most common cause of ARF in both groups was obstetric sepsis (about 40% in each group) due to abortions and mismanaged deliveries. This is still the usual spectrum of ARF seen in low-income and middle-income populations in India (as our hospital mainly caters to this segment of the population) and is similar to that reported in previous studies.[8] Although our experience with EDD is limited, yet the procedure was well tolerated by all of the patients and had the added benefit of requiring only the existing dialysis machines and work force.

All of our patients on EDD showed excellent hemodynamic stability. Although the postprocedure MAP in both the groups was significantly lower compared to the preprocedure values, the magnitude of fall in the MAP was significantly

greater in the IHD group. This may be due to rapid removal of water and solutes during the IHD. The fluid and solute removal in the IHD occurs over a short period of time (4 hours every alternate day) as compared to that in a patient on the EDD which occurs over a much longer period (8 hours daily). The greater degree of decline in blood pressure is explained by this rapid removal of solutes and fluid over a short period of time in the IHD as compared to the EDD.[9,10] Extended daily dialysis is well tolerated by patients even though the procedure runs for a period of 8 hours, double that of conventional dialysis.

Vital signs of the patients were monitored meticulously through the course of dialysis. Most of the patients on EDD had a significant decrease in blood pressure, especially towards the end of the long 8-hour dialysis sessions; however, none of them developed frank hypotension (defined as an MAP less than 60 mm Hg or a systolic BP less than 90 mm Hg). In contrast, among the patients on IHD, there were 6 hypotensive episodes. The difference in the occurrence of hypotension in the two groups was not statistically significant. This might be because of the small sample size of the two groups. A study on a larger sample size would be required to assess whether hypotensive episodes are indeed significantly more common with IHD as compared to the EDD. Repeated episodes of hypotension during dialysis may aggravate injury to the kidney and delay recovery from ARF.[11] It is pertinent to note that in some previous studies, the EDD was found to be hemodynamically well tolerated even by critically ill patients on inotropic support, and its effect on hemodynamic variables was found to be comparable with continuous venovenous hemofiltration.[12-14]

We measured metabolic changes in terms of reduction in the levels of blood urea and serum creatinine as well as normalization of serum bicarbonate, pH, sodium, potassium, calcium, and phosphate. As depicted in the Figures, with EDD, there was a rapid correction in urea, creatinine, phosphate, and potassium levels and faster normalization of pH and bicarbonate. Faster removal of uremic solutes provided earlier amelioration of uremic symptoms, which is important as one of the most common indications for initiating dialysis in our study was the uremic syndrome.

Figure 7 shows the plot of the predialysis and

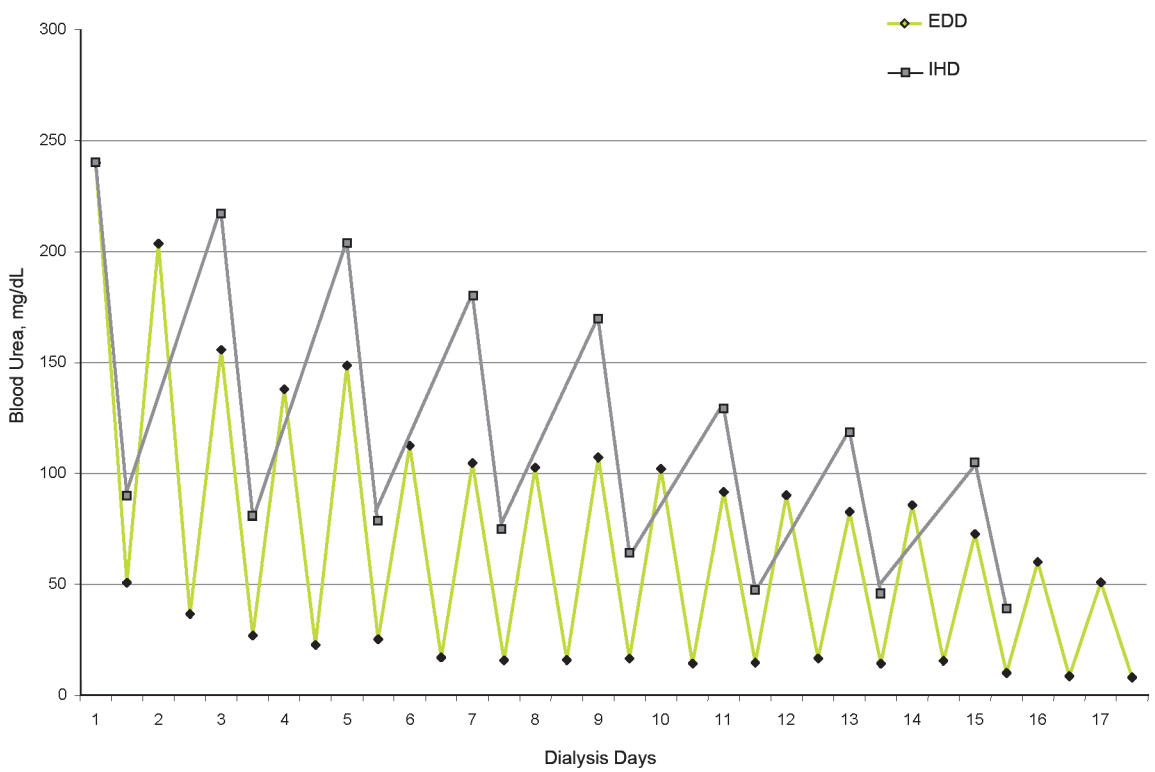

Figure 7. Daily predialysis and postdialysis blood urea levels. EDD indicates extended daily dialysis and IHD, intermittent hemodialysis.

postdialysis blood urea levels against the dialysis days in our patients. It has been hypothesized that the peak urea concentration immediately before the next dialysis treatment may be a better indicator of uremic toxicity than the calculated time-averaged urea concentration.[15] The characteristic saw-tooth pattern of urea clearance classically seen with the IHD persists with the EDD. Nonetheless, the peaks attained with the latter are much lower, which might be beneficial and cause lesser degrees of uremic toxicity.

The median URR for the EDD group of our patients (83.82%) was significantly higher as compared to that in the IHD group (64.66%). This was as expected since these patients had been subjected to longer duration of dialysis as compared to the IHD. However, the magnitude of difference in the URR between the two groups is lower than expected (even though the patients had been dialyzed for almost twice as long as the IHD controls). The possible explanation might be that since the EDD is performed more frequently, compared to IHD, blood urea removal tends to spread out over several sessions. As depicted in Figures 4, correction of hyperkalemia and normalization of arterial blood pH and bicarbonate levels was much faster with the EDD. Since a potassium-free dialysate was used in the dialysis procedure, many patients on EDD had to be administered potassium supplements in the later sessions of dialysis to prevent hypokalemia. Addition of potassium to the dialysate (used in the EDD group, especially for later sessions of dialysis) is recommended in order to minimize the occurrence of hypokalemia. Overall, the EDD offers excellent metabolic control that appears to be far superior to the IHD.

Extended daily dialysis was able to achieve satisfactory fluid balance in the patients with ARF without the fear of inducing hypotension. Previous studies with the EDD have reported similar findings and this modality has been shown to be comparable to continuous therapies in allowing large volumes of fluid to be removed by ultrafiltration.[12-14]

In our study, no significant difference was observed in the final outcome of the patients between the treatment of ARF with EDD and IHD. The nil mortality is because we had excluded very sick patients (with more than 2 organ failures). Further studies using larger sample size and including patients with multiple-organ failure may bring out differences in the outcome between the two therapies.

CONCLUSIONS

Extended daily dialysis appears to be a promising technique for renal replacement therapy in patients with ARF, offering several advantages over the IHD in moderately ill patients having up to 2 organ failures. It might be appropriate to consider it as a reasonable compromise between the IHD and CRRT and could be utilized in centers where access to continuous therapies is lacking.

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CONFLICT OF INTEREST

None declared.

APPENDIX

Criteria for Determining Organ Failure

Circulatory failure

- Bradycardia (heart rate < 60 bpm)
- Hypotension (systolic blood pressure < 90 mm Hg or mean arterial pressure < 60 mm Hg).
- Ventricular tachycardia or fibrillation

Respiratory failure

- Hypercapnia (PCO_2 > 46 mm Hg)
- Hypoxemia (PO_2 < 60 mm Hg)

Acute renal failure

- Serum creatinine > 2.0 mg/dL

Hematological failure

- Thrombocytopenia (platelet < 20×10^9/L)

Hepatic failure

- Hyperbilirubinemia (serum bilirubin > 3 mg/dL)

Neurological failure

- Depressed level of consciousness (Glasgow coma score ≤ 6)

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