Haemodynamic stability is maintained during extended daily diafiltration in critically ill septic patients

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ABSTRACT

Background: Extended daily diafiltration (EDDf) is a prolonged intermittent dialysis technique introduced as an alternative to continuous renal replacement therapy in critically ill patients. Although EDDf has the advantages of ease of use, low cost and patient tolerability, there is concern that the high blood and dialysate flow rates used with EDDf may precipitate haemodynamic instability.

Objective: To identify whether haemodynamic changes occur during the course of EDDf therapy in adult patients who are admitted to the intensive care unit with sepsis and require dialysis.

Design, setting and participants: A prospective observational study of patients fitting the inclusion criteria who were admitted to the ICU of the Gold Coast Hospital, Queensland, during the period 1 January 2002 to 31 December 2005.

Main outcome measures: Mean arterial pressure (MAP) and heart rate (HR) before, during and after EDDf treatment.

Results: 178 EDDf treatments were administered to 44 patients. Haemodynamic parameters remained stable during EDDf, despite median blood flow rates of 265 mL/min and dialysate flow rates of 300 mL/min: MAP was 81.2 mmHg before EDDf v 82.7 mmHg after EDDf (P = 0.13); HR was 100.4 beats/min before EDDf v 98.9 beats/min after EDDf (P = 0.23). For treatments in which vasopressive support was required (n = 75), no increase in dose requirement was observed. Patient mortality at the time of hospital discharge (41%) was less than the rate predicted by APACHE III scores (52%).

Conclusion: EDDf did not significantly worsen haemodynamic stability in patients with sepsis during their treatment.

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Acute renal failure, a serious condition that is common among patients with sepsis, has been established as an independent risk factor for poor survival,[1] with mortality rates of about 50% reported in Australian intensive care units.[1,2] Intermittent haemodialysis (IHD) and continuous renal replacement therapy (CRRT) have previously been the only available options for renal replacement therapy in these patients. In most ICUs across Australia, CRRT is favoured over IHD, as it allows slower, more controlled fluid and electrolyte shifts (due to lower blood and dialysate flows), thereby providing increased cardiovascular stability[3] in critically ill patients.

In the past 5 years, extended daily diafiltration (EDDf), a hybrid modality of CRRT and IHD (also known as sustained low-efficiency daily dialysis [SLEDD]) has been developed, although there have been reports of slow intermittent haemodialysis over the past 20 years.[4,5] EDDf aims to combine the favourable characteristics of both IHD and CRRT — notably, sustained treatment to maximise haemodialysis dose, a reduced ultrafiltration rate to improve haemodynamic stability, and slower solute removal to minimise solute disequilibrium. An additional benefit of EDDf is that treatment lasts up to 12 hours a day (as opposed to 24 hours a day with continuous therapies). This allows for increased patient mobility to perform other activities such as medical procedures,[6-12] and less demand on nursing time. In addition, with less time spent on dialysis, the patient requires less anticoagulation treatment. This is an advantage, given that administering anticoagulation therapy to patients with a critical illness such as renal failure can predispose them to gastrointestinal bleeding.[13] EDDf can also be delivered by intensive care trained nurses with no input required from renal physicians.

Theoretical concerns have been raised that the higher blood and dialysate flow rates of EDDf may reduce haemodynamic stability. However, several studies have shown excellent cardiovascular stability across all ICU dialysis patients receiving EDDf treatment.[6-8,14,15] A few studies comparing continuous with sustained dialysis have shown that both methods offer comparable small solute control and haemodynamic stability.[6,8,16]

In the ICU of the Gold Coast Hospital, Queensland, EDDf has been the treatment of choice for acute renal failure since 2002, replacing the prior use of CRRT. Our study investigated patients with sepsis undergoing EDDf. Our objective was to show that EDDf is safe in terms of haemodynamic stability for patients with suspected sepsis in the ICU.

Methods

The Gold Coast Hospital is a tertiary level referral centre in Southport, Queensland, Australia. The hospital's ICU has about 950 admissions annually, servicing (mostly adult) medical and surgical populations. We conducted a prospective observational study at the Gold Coast Hospital ICU. Data were extracted from the medical records of 44 patients who fit the inclusion criteria: (i) aged 18 years and over; (ii) admitted to the ICU between 1 January 2002 and 31 December 2005; (iii) had an admission diagnosis of suspected sepsis; and (iv) received EDDf during their ICU stay. Patients were excluded if they: (i) required inodilators, such as dobutamine, as an adjunct to their primary vasopressor; (ii) received haemodiafiltration (HDF) treatment of 4 hours or less; or (iii) received more than one form of dialysis. Data extracted included age, sex, number of treatments, diagnosis, APACHE III (Acute Physiology and Chronic Health Evaluation III) score, indication for treatment, length of treatment in hours, inotropic drug infusion rates during treatments, blood flow rates, ultrafiltrate volumes, fluid removal volumes, reason for EDDf discontinuation, mean arterial pressure (MAP) and heart rate (HR) components related to the EDDf treatment episode. The Gold Coast Health Service District Human Research Ethics Committee approved the research.

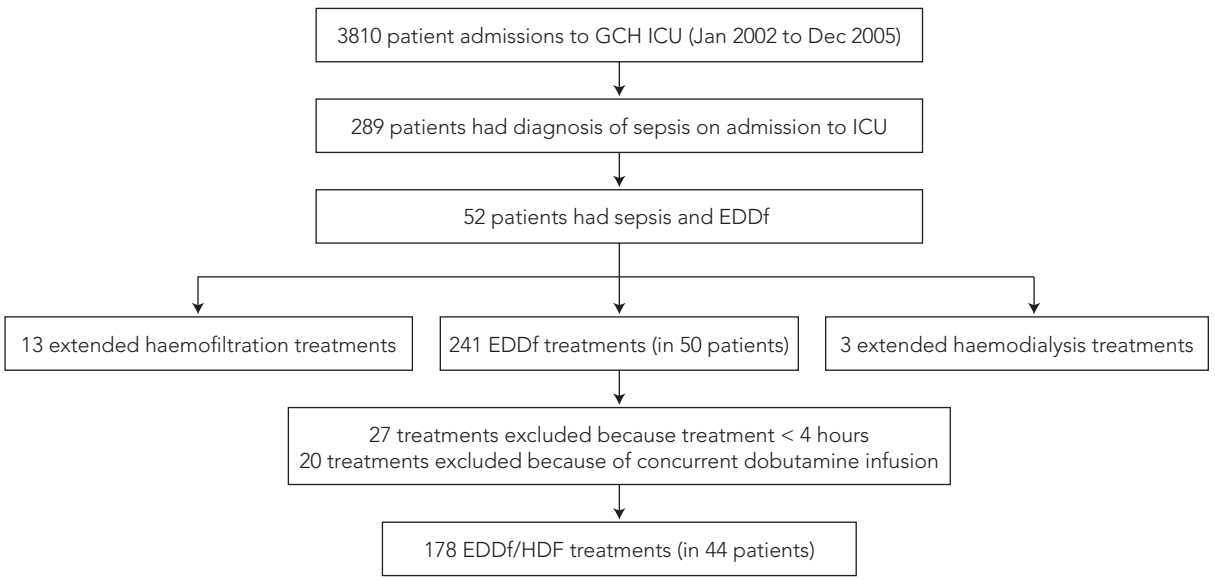
All dialysis sessions were prescribed by intensivists and managed by intensive care nurses, and each patient's treatment was counted as a separate entity. MAP and HR were recorded from arterial invasive blood pressure monitoring devices. Dialysis was performed on the Fresenius Medical Care 4008S ArRT-Plus machine. Ultraflux AV600 polysulfone membrane filters were used. These have an effective surface area of 1.4 m^2 and a urea sieving coefficient of 1. Dialysate composition varied according to patient need, with default settings of potassium 2 mmol, bicarbonate 26 mmol and sodium 140 mmol. Dialysis flow rates were prescribed at about 300 mL/min, and blood flow rates varied according to vascular access function and required ultrafiltration rate. Generally, substitution fluid (ultrafiltration replacement) was prescribed at 20 mL/min. Replacement fluids and dialysis were generated on-line from tap water treated by a reverse osmosis unit. The use of heparin for anticoagulation was prescribed on a case-by-case basis. Temperature of the dialysate was at a constant 37° C for every treatment.

All data were collected by tertiary-trained personnel with ICU and data collection experience. To avoid entry bias, data collection personnel had no prior involvement with the clinical cases. Every 10 entries were counter-checked by an independent nurse researcher to ensure accuracy of data entry. Demographic data were also entered into the Australian and New Zealand Intensive Care Society aortic database, with every 10 entries counter-checked by an independent nurse researcher.

The APACHE III score was used to calculate predicted hospital mortality for critically ill hospitalised patients.[17]

The primary aim of our study was to measure MAP and HR directly before the commencement of an EDDf treat-

Figure 1. Flowchart of sample consistency



EDDf = extended daily diafiltration. GCH = Gold Coast Hospital. HDF = haemodiafiltration. ICU = intensive care unit.

ment and observe changes in those variables across the course of treatment, to determine whether there was significant change in those variables. Changes in infusion rates of vasopressors were also measured for patients receiving vasopressor support. Management of patients during the course of their treatment was at the sole discretion of the intensive care treating team. Sample size was predetermined by the number of patients who fit the inclusion criteria over the 4-year study period.

Descriptive statistics are presented as mean (SD) or median (interquartile range [IQR]). Inferential statistics used to compare MAP and HR before and after treatment were the paired sample *t*-test or, for comparison of vasopressor infusion rates before and after treatment, the Wilcoxon signed rank test. SPSS version 12 (SPSS, Inc, Chicago, Ill, USA) was used for data analysis.

Results

Among 3810 admissions to the ICU during the 4-year study period, 44 patients required 178 EDDf treatments. For seven of the 178 EDDf treatment episodes (4%), data were missing or incomplete. These were excluded from the final analysis (Figure 1). The median age of patients in our study was 64.9 (IQR, 44.7–77.3) years. Twenty-five (57%) were male. The median APACHE III score was 101.5 (IQR, 86.0–110.5). Patient mortality at time of hospital discharge (41%) was less than the predicted mortality based on APACHE III score (52%) but the difference was not statistically significant ($P = 0.41$). Each EDDf episode lasted a mean of 7.5 (SD, 2.05) hours. The most common indication for EDDf therapy was fluid overload and clearance of toxins accumulated because of acute renal impairment. Other indications are outlined in Table 1.

Reasons for discontinuing EDDf therapy were recorded. Among the treatments that were included in our analysis, the most common reason for discontinuation was completion of planned treatment ($n = 119$ [66.8%]). Other reasons, such as clotting ($n = 49$ [27.5%]) and poor blood flows from failing venous access ($n = 3$ [1.7%]) were also identified. In only three cases (1.7%) was the treatment discontinued due to the patient's condition being unstable. For treatments that were excluded from our analysis, reasons for discontinuation of treatment are summarised in Table 2.

Physical characteristics of dialysis treatments, including dialysis flow rates, blood flow rates, ultrafiltrate volume and fluid removal, are summarised in Table 3.

Hourly HR and MAP recordings were collected for each of the treatment episodes (Figures 2 and 3). During EDDf therapy, mean HR remained stable over time at around 100 beats/min and MAP stayed at $\geqslant 60$ mmHg for the majority of the treatment episodes. MAP increased by $\geqslant 10$ mmHg in 93/178 treatment episodes (52%), from the time EDDf commenced up to and including the 7th hour of treatment. In 10/178 treatments (6%), MAP fell below 60 mmHg.

Further data analysis was conducted to identify whether there were any significant changes in the haemodynamic

Table 1. Indications for EDDf therapy

Indication for EDDf therapy	Number of episodes (%)
Fluid overload and clearance of toxins	64 (36%)
Fluid overload	26 (15%)
Clearance of toxins	26 (15%)
Clearance of toxins and electrolyte imbalance	11 (6%)
Fluid overload and electrolyte imbalance	8 (5%)
Fluid overload, clearance of toxins and electrolyte imbalance	8 (5%)
Acidosis	7 (4%)
Acidosis and clearance of toxins	6 (3%)
Acidosis, clearance of toxins and electrolyte imbalance	6 (3%)
Electrolyte imbalance	5 (3%)
Acidosis and electrolyte imbalance	4 (2%)
Fluid overload, acidosis and clearance of toxins	4 (2%)
Fluid overload and acidosis	3 (2%)
Total	*178 (100%)*

EDDf = extended daily diafiltration.

Table 2. Reasons for discontinuation of EDDf at less than 4 hours

Reason for treatment end at < 4 h	Number of treatments (%)
Clotted lines	17 (63.0)
Treatment completed	5 (18.5)
Poor access	3 (11.1)
Unstable condition	1 (3.7)
Death of patient	1 (3.7)

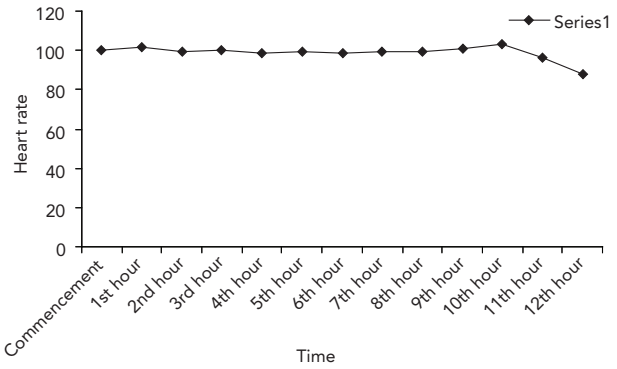
EDDf = extended daily diafiltration.

Table 3. Characteristics of treatments

Treatment characteristic	Median (IQR)
Dialysis flow (mL/min)	300 (300–300)
Blood flow (mL/min)	265 (222–300)
Ultrafiltrate volume (mL/h)*	2700 (1200–3000)
Fluid removed (total)*	1776 (500–2900)

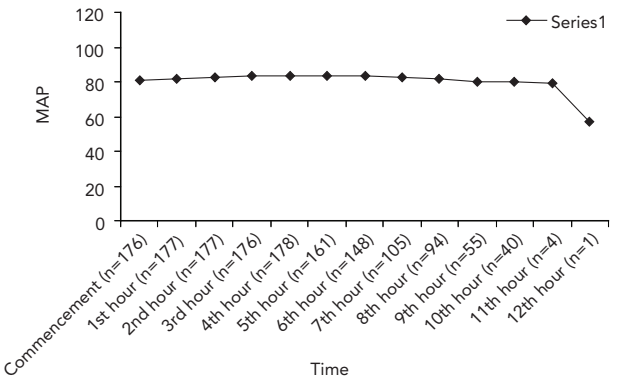
IQR = interquartile range. * There were missing data for some treatment episodes (ultrafiltrate volume [1], fluid removed [2]).

Figure 2. Mean heart rate over time during EDDf treatments*



EDDf = extended daily diafiltration. * Mean time of EDDf therapy was 7 hours.

Figure 3. MAP over time during EDDf therapy



EDDf = extended daily diafiltration. MAP = mean arterial pressure.

stability (HR and MAP) from before to after EDDf treatment (Table 4). Neither HR nor MAP varied significantly.

Seventy-five of the 178 EDDf treatment episodes (42%) involved patients receiving vasopressor support: 61 required noradrenaline infusion and 14 required adrenaline. The rates of vasopressor administration at commencement and completion of EDDf treatment are shown in Table 5. The median duration of noradrenaline therapy while undergoing EDDf was 7.0 (IQR, 4.5–8.0) hours. There was a statistically significant difference in the median rate of noradrenaline administration at commencement of EDDf treatment (0.84 μg/min) compared with the rate at completion (0.60 μg/min) ($P = 0.03$). The median duration of adrenaline therapy while undergoing EDDf was 9.0 (IQR, 8.0–10.0) hours. There was no statistically significant difference in the median rate of adrenaline administration at commencement of EDDf treatment (1.38 μg/min) compared with the rate at completion (0.60 μg/min) ($P = 0.11$). This may be due to the small sample size of patients receiving adrenaline during treatment.

Table 4. Heart rate (HR) and mean arterial pressure (MAP) before and after EDDf treatment

Observation	Before EDDf	After EDDf	P*
Mean HR (SD), beats/min ($n = 171$)	100.4 (20.3)	98.9 (20.0)	0.23
MAP (SD), mmHg ($n = 176$)	81.2 (15.8)	82.7 (14.1)	0.13

EDDf = extended daily diafiltration. * Based on paired sample *t*-test.

Table 5. Differences between commencement and completion rates of vasopressor agent administration during EDDf treatment

	Median rate (IQR) (μg/min)		
Vasopressor agent	At commencement	At completion	P*
Noradrenaline ($n = 61$)	0.84 (0.32–1.64)	0.60 (0.24–1.53)	0.03
Adrenaline ($n = 14$)	1.38 (0.60–1.88)	0.60 (0.24–1.89)	0.11

EDDf = extended daily diafiltration. IQR = interquartile range.
* Based on Wilcoxon signed rank test.

Discussion

Our results show that haemodynamic stability was maintained, with HR and MAP varying little over the duration of EDDf. Vasopressor administration showed no significant rise in dose requirements. In fact, noradrenaline infusion rates fell significantly during the course of the treatment, a finding consistent with previous research.[14,15] However, this may simply reflect improvements in patients' clinical condition. In this patient population, dialysis and blood flow rates were comparable to or higher than rates reported previously in studies involving EDDf as a dialysis modality.[14,15,18]

Death in patients undergoing EDDf treatment has not been extensively studied. Among patients in our study, mortality rates at time of discharge from hospital were lower than rates predicted on the basis of APACHE III scores (41% v 52%). Marshall and colleagues,[15] studying 56 EDDf–HDF treatments in 24 critically ill patients, also showed that the observed hospital mortality rate of 46% did not vary significantly from predicted mortality rates based on APACHE criteria.

HDF, when used in continuous veno-venous haemodiafiltration (CVVHDF), may have a role in clearing inflammatory

mediators such as tumour necrosis factor,[19-23] activated complement fractions[21,24] and interleukins 1β[20-23] and 6,[21,22] which are commonly elevated in patients with sepsis. If inflammatory marker clearance is an attribute of CVVHDF, the same may occur in EDDf, although this finding has not been specifically reported in the literature. The impact on patient survival rates of clearance with HDF in CVVHDF has not been reported.

Several limitations of our research are acknowledged. Patients were selected on the basis of suspected sepsis at the time of ICU admission. It may be that some of these patients were found to have a different diagnosis during their stay. Also, some potentially eligible patients may have been excluded because they became septic after their ICU admission diagnosis had been made. In addition, the size of our sample ($n = 44$) may be considered small and limiting to interpretation. However, to our knowledge, it is the largest study of its kind to date, especially involving dialysis in patients with sepsis. Previous EDDf studies have involved sample sizes ranging from 14 to 37 patients.[9,14,15,18]

Limitations also apply to the exclusion of treatments not used in final calculations. Exclusion criteria were set primarily for data interpretation purposes, with the aim of having a sample that was as similar as possible in terms of length of time receiving EDDf treatment and also vasopressor support. On further examination of the data excluded when therapy lasted less than 4 hours, it was evident that only one treatment was stopped due to haemo-dynamic instability. We also excluded 20 treatments in which patients were receiving an inodilator plus adrenaline infusion, an inodilator plus noradrenaline infusion, or solely inodilator while undergoing dialysis. This may have affected the statistical significance of results, but it was felt that ensuring clinically meaningful interpretation of data pertaining to the infusion of both vasopressor and inodilators would be difficult. Additionally, other premorbid patient medical conditions were not examined or analysed in our study. This may have had an impact on tolerance of EDDf. Finally, as this was an observational study, we did not account for other interventions that may have been put in place by treating intensivists during the course of the treatments that may have influenced haemodynamic stability.

Future recommendations for research include investigating the possible use of EDDf in children. Children are not immune to renal complications, and some require dialysis. There is a need to identify the most effective and safe dialysis therapy for that particular subsection of the population. Given the intermittent nature of EDDf, it may have some benefits for children.

Conclusion

The use of EDDf did not significantly worsen haemodynamic stability (as measured by mean arterial pressure and heart rate) in patients with sepsis during the course of their treatments. Furthermore, observed mortality was lower than mortality predicted by APACHE III scores for this group of patients. Vasopressor drug administration showed no significant rise in dose requirements during EDDf treatment.

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