A pilot randomised controlled comparison of continuous veno–venous haemofiltration and extended daily dialysis with filtration: effect on small solutes and acid–base balance

Abstract  Background and aims: Continuous veno–venous haemofiltration (CVVH) is an established treatment for acute renal failure (ARF). Recently, extended intermittent dialytic techniques have been proposed for the treatment of ARF. The aim of this study was to compare these two approaches. Setting: Intensive care unit of tertiary hospital. Subjects: Sixteen critically ill patients with ARF. Design: Randomised controlled trial. Intervention: We randomised sixteen patients to three consecutive days of treatment with either CVVH (8) or extended daily dialysis with filtration (EDDf) (8) and compared small-solute, electrolyte and acid–base control. Results: There was no significant difference between the two therapies for urea or creatinine levels over 3 days. Of 80 electrolyte measurements taken before treatment, 19 were abnormal. All values were corrected as a result of treatment, except for one patient in the CVVH group who developed hypophosphataemia (0.54 mmol/l) at 72 h. After 3 days of treatment, there was a mild but persistent metabolic acidosis in the EDDf group compared to the CVVH group (median bicarbonate: 20 mmol/l vs. 29 mmol/l: p = 0.039; median base deficit: –4 mEq/l vs. –2.1 mEq/l, p = 0.033). Conclusions: CVVH and EDDf as prescribed achieved similar control of urea, creatinine and electrolytes. Acidosis was better controlled with CVVH.

Keywords  CRRT · Daily dialysis · Intensive care · ARF · Haemofiltration · SLEDD

Introduction

Acute renal failure (ARF) is associated with a high mortality in the intensive care unit (ICU) [1–4]. Intermittent haemodialysis (IHD) and continuous renal replacement therapy (CRRT) techniques such as continuous veno–venous haemofiltration (CVVH) are widely used for its treatment [5–7]. CVVH has been associated with frequent clotting, is technically demanding and expensive [8, 9]. If IHD is used for 3–4 h every second day, costs are lower, clotting not a problem, but solute control is limited [10]. Recently, small clinical studies have reported a new “hybrid” technique of intermittent daily dialysis treatment applied for an extended time in the ICU [11–14], and uses dialysate fluid similar to that used in IHD [14, 15]. The approach has been called slow low-efficiency daily dialysis (SLEDD) when only diffusion is applied [15] or extended daily diafiltration (EDDf) and SLEDD-f when convection is added [16]. We hypothesised that use of such a therapy would be no less effective in control of small solutes and acid–base balance in critically ill patients than a continuous technique. Accordingly, we conducted a pilot randomised controlled study to compare EDDf with CVVH in ICU patients.
**Methods**

Human Research Ethics Committee approval and informed consent for each patient was obtained. The study was conducted in a single centre and patients were randomised to either continuous veno–venous haemofiltration (CVVH) continuously or to 8 h of EDDf each day. Any patient over 18 years of age with ARF according to consensus definitions [17] was eligible for inclusion. Exclusion criteria were: recent neurosurgery, known or suspected raised intracranial pressure, and pregnancy.

Continuous veno–venous haemofiltration

CVVH was performed with the Kimal Hygieia CRRT machine (Kimal, Uxbridge, United Kingdom) with blood flow set at 200 ml/min and fluid replacement at 2000 ml/h. Ultrafiltrate was also set at 2000 ml/h for isovolaemic therapy with additional fluid removal to achieve necessary fluid loss or negative fluid balance where needed. Replacement fluid (Gambro, HF1, Sydney, Australia) was in 5-l bags with a set electrolyte composition and administered pre-filter. Potassium was prepared to 4.0 mmol/l.

Extended daily dialfiltration

We set EDDf to be a combined convective and diffusive therapy using the Fresenius 4008S ARrT plus machine, (Fresenius Medical Care, Homburg, Germany). We set blood flow at 100 ml/min and fluid replacement at 21 ml/min pre-filter. Dialysate flow was set at 280 ml/min with effluent flow being the sum of fluid replacement, dialysate and any negative fluid loss required. The fluid replacement and dialysate flow rates were set at the lowest possible settings for the machine to perform EDDf. Additional fluid removal was then set to achieve necessary negative fluid balance as prescribed. Replacement and dialysate fluids were manufactured from tap water at the bedside. Potassium was set to 2.0 mmol/l.

Treatment followed a protocol providing a similar prescribed calculated daily dose of urea clearance for each therapy in adult patients of similar weight.

Polysulfone membranes were used in both therapies, the APS 650 1.3 m² (Asahi Medical Company, Tokyo, Japan) for CVVH and the Fresenius AV600S 1.4 m² (Fresenius Medical Care, Bad Homburg, Germany) for EDDf. Anticoagulation was achieved with low-dose heparin (5–10 IU/kg/h) in both therapies.

Treatments were studied over a 3-day period after randomisation. Serum values for small solutes (urea and creatinine), electrolytes, pH, bicarbonate and base excess were assessed before the start of each treatment, at 10 h and daily at 0500 hours thereafter.

Clearance calculation

Daily solute clearance estimation (based on complete equilibration of urea from blood to effluent) was determined for each therapy. This calculation considered the effect of pre-filter haemodilution by replacement solutions and the actual treatment time performed each day.

For acid–base balance, the mean daily apparent strong ion difference (SIDa), the effective strong ion difference (SIDe) and the strong ion gap (SIG) were calculated for each group and compared using the following conceptual framework as described by Stewart [18] and modified by Figge et al. [19]. This method involves first calculating the SIDa:

\[
\text{SIDa} = [\text{Na}^+] + [\text{K}^+] + [\text{Mg}^{2+}] + [\text{Ca}^{2+}] - [\text{Cl}^-] - [\text{Lactate}],
\]

where all values are mEq/l.

To account for weak acids (CO₂, albumin, and phosphate) in the balance of electrical charges in plasma water, the SIDe is calculated:

\[
\text{SIDe} = 1000 \times 2.46 \times 10^{-11} \times \text{pCO}_2/(10^{-\text{pH}}) + [\text{Alb}] \times ((0.12 \times \text{pH} - 0.631) + [\text{Phos}] \times (0.309 \times \text{pH} - 0.469),
\]

where pCO₂ is expressed in mmHg, albumin in g/l and phosphate in mmol/l.

Once weak acids are quantitatively taken into account, the difference between SIDa and SIDe should equal zero unless there are unmeasured charges. Such charges are described by the SIG:

\[
\text{SIG} = \text{SIDa} - \text{SIDe}.
\]

Data analysis

Descriptive statistical analysis was used to present the data. Due to lack of normal distribution, comparisons of data from each group were done using the Mann–Whitney U-test. We also compared baseline data with end of treatment data within each group (paired comparison) with the Wilcoxon signed rank test. A *p* value of <0.05 was taken to indicate statistical significance. Statview software program (Abacus, Berkeley, CA) was used for analysis.

**Main results**

The CVVH and EDDf patients were similar in age, APACHE II score, pre-treatment urea, pre-treatment creatinine, and use of mechanical ventilation (Table 1).

Five patients in the EDDf group completed the full 3-day protocol, with a total of 20 treatment days and 146 h
of EDDf; three filters were required for each patient. Six patients completed the full 3-day protocol in the CVVH group, with 22 treatment days and a total of 405 h with 4.5 filters required for each patient. The time off or “down-time” for the CVVH group was a median of 5.4 (4.6–6.2) h per day. Using actual treatment time for each patient, daily urea clearance for CVVH was estimated at 27.4 l and for EDDf at 24.9 l ($p = 0.04$).

Urea and creatinine levels were different at 10 h on day 1, reflecting the greater short-term clearance achieved with EDDf (urea, $p = 0.03$; creatinine, $p = 0.09$). Such differences, however, were corrected after 24 h and solute control remained similar thereafter (Figs. 1, 2).

Of the 80 electrolyte measurements taken before treatment, 19 were abnormal (see ESM S.T1). All values were corrected as a result of treatment, except for one patient in the CVVH group who developed hypophosphataemia (0.54 mmol/l) at 72 h (see ESM S.T2).

Metabolic acid–base balance at randomisation as assessed by lactate, pH, bicarbonate, and base excess values was similar for both groups.

The median lactate concentration was lower in the EDDf than in the CVVH group after 10 h (1.3 mmol/l vs. 3.6 mmol/l; $p = 0.04$), and remained non-significantly lower throughout treatment with a peak difference at 72 h (1.2 mmol/l vs. 2.3 mmol/l, $p = 0.054$). Despite these changes in lactate, pH was similar at randomization and throughout both treatments (Fig. 3). Bicarbonate concent-

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**Table 1** Patient characteristics at study enrolment

<table>
<thead>
<tr>
<th></th>
<th>CVVH</th>
<th>EDDf</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>8</td>
<td>8</td>
<td>0.563</td>
</tr>
<tr>
<td>Age</td>
<td>71 (66–77)</td>
<td>68 (59–75)</td>
<td>&gt; 0.99</td>
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<tr>
<td>Sex (M:F)</td>
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<td>5:3</td>
<td></td>
</tr>
<tr>
<td>APACHE II score</td>
<td>22 (15–23)</td>
<td>23 (20–27)</td>
<td>0.372</td>
</tr>
<tr>
<td>Urea (mmol/l)</td>
<td>16.3 (14.0–22.7)</td>
<td>15.4 (12.7–24.1)</td>
<td>0.674</td>
</tr>
<tr>
<td>Creatinine (mmol/l)</td>
<td>354 (173–425)</td>
<td>205 (160–321)</td>
<td>0.248</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>75% (6/8)</td>
<td>75% (6/8)</td>
<td>&gt; 0.99</td>
</tr>
</tbody>
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![Fig. 1](https://example.com/fig1.png)

**Fig. 1** Boxplot diagram for urea (mmol/l) levels at baseline, 10 h ($p = 0.03$), 24 h, 48 h and 72 h, in patients treated with EDDf ($n = 8$) or CVVH ($n = 8$).

![Fig. 2](https://example.com/fig2.png)

**Fig. 2** Boxplot diagram for creatinine (mmol/dl) levels at baseline, 10 h ($p = 0.09$), 24 h, 48 h and 72 h, in patients treated with EDDf ($n = 8$) or CVVH ($n = 8$).

![Fig. 3](https://example.com/fig3.png)

**Fig. 3** Boxplot diagram of pH in arterial blood: before treatment (pre), at 10 h after treatment on day 1, and on days 2, 3 and 4 using EDDf ($n = 8$) or CVVH ($n = 8$). No significant differences.
tration was similar at randomization, but became lower in the EDDf group at 48 h ($p = 0.019$) and remained lower at 72 h ($p = 0.039$) (Fig. 4).

Similarly to bicarbonate, base excess became lower at 24 h ($p = 0.089$) and remained so at 48 h ($p = 0.019$) and 72 h ($p = 0.039$) (Fig. 5).

For CVVH the mean SIDa during treatment was 42.2 mEq/l (41.7–45.4), and for EDDf it was 39.7 mEq/l (36.8–40.8; $p = 0.01$). For SIG there was no difference, with a mean value of 6.4 mEq/l (5.1–7.2) during CVVH and of 7.2 mmol/l (6.2–7.4; $p = 0.46$) during EDDf.

**Discussion**

We conducted a pilot randomised controlled trial comparing CVVH with EDDf in critically ill patients with ARF. We found equivalent small-solute and electrolyte control over a 3-day period but different acid–base control, with EDDf being associated with a greater degree of hyperchloremic metabolic acidosis.

A more detailed analysis (day 1) shows, as expected, greater urea and creatinine reduction after completion of the first EDDf treatment. It also shows the expected “rebound” or increase for these solutes during the 16 h without treatment. Solute clearance during CVVH demonstrated a slower and more linear decline.

Treatment clearance calculation for each group indicated a greater estimated solute clearance in the CVVH group despite an associated downtime of 5.4 h per day.

A study by Kielstein et al. [20] provides the only other published randomised comparative analysis of CVVH and extended daily dialysis. This “batch fluids” technique with no convective therapy was a form of slow dialysis, rather than combined dialysis and filtration, and therapies were compared after 12 h. To compensate for these differences in the daily application of these two treatments, we designed a study comparing them over a continuous, 3-day cycle. As might be expected, this clinically relevant approach showed that the initial better solute control achieved with EDDf was not sustained over a 24-h cycle. Findings were similar for bicarbonate and pH values.

We found that both techniques achieved correction of several electrolyte abnormalities present before intervention. This is in keeping with published uncontrolled observations [21, 22]. Hypophosphataemia in one CVVH patient suggests the need for vigilance and frequent serum phosphate monitoring [23, 24]. Importantly, in all patients, hypo- or hyperkalaemia/magnesaemia were avoided with the prescriptions used.

Although the serum sodium was maintained within the normal range and was similar in both groups, there were significant differences in the chloride concentration. The relative hyperchloremia in the EDDf patients was almost certainly due to the greater concentration of chloride in the fluids used for EDDf (111.8 mmol/l) than in the fluids used for CVVH (100.75 mmol/l).
We found the two therapies affected metabolic acid–base variables differently. First, the concentration of lactate was lower with EDDf throughout the study period. This difference is likely explained by the use of lactate as buffer during CVVH, compared to bicarbonate during EDDf [25]. Secondly, despite the increase in lactate with CVVH, median pH, bicarbonate and base excess values were all less acidic with continuous treatment. These findings are consistent with both the lower amount of buffer in EDDf fluids (26 mEq/l) than in CVVH (45 mEq/l) and the relative hyperchloremia of these fluids. The effect of hyperchloremia is also likely to explain the difference in mean SIDa between the two groups. A decrease in CO₂ in response to this metabolic acidosis accounted for the lower SIDe values observed during EDDf. Conversely, the SIG was similar for both treatments, in keeping with likely equivalent clearance of unmeasured acids. Although the clinical significance of these differences is uncertain, a higher bicarbonate concentration in EDDf fluids may be desirable. The maximum bicarbonate concentration in EDDf fluids with the Fresenius 2008s machine is 32 mmol/l.

This study has several strengths and limitations. Its strengths include the fact that it is randomised and controlled in design, and that it compared therapies over several days of treatment and analysed their affect on several relevant biochemical variables. Its limitations include the relatively small number of patients studied, the single-centre nature of the investigation and the fact that our findings can apply only to the specific EDDf and CVVH doses used in this study. The small size of the study means that it carries a high chance of a type II statistical error. However, despite such lack of statistical power, several clinically relevant differences emerged and achieved statistical significance. A cross-over design might have increased the statistical power of the study. In addition, this is a pilot investigation with the aim of assessing the feasibility and solute control effect of prolonged EDDf in critically ill patients when compared to our standard approach to CVVH. For such studies, power is typically limited and only major differences are detected. Despite this limitation, several differences emerged in acid–base control, which support our stepwise approach to investigating EDDf and indicate the need to adjust dose and buffer concentration in future studies of this technique.

In conclusion, EDDf at a conservative intensity of solute clearance is comparable to CVVH for the overall control of small solutes, and electrolytes in critically ill patients with ARF. If a physiologic concentration of bicarbonate is used during EDDf, acid–base control is less complete than during CVVH. Further comparative studies of EDDf at higher intensity and with greater buffer administration appear desirable.

References