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ORIGINAL

Early acid–base and blood pressure effects of continuous renal replacement therapy intensity in patients with metabolic acidosis

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Abstract *Purpose:* In acute kidney injury patients, metabolic acidosis is common. Its severity, duration, and associated changes in mean arterial pressure (MAP) and vasopressor therapy may be affected by the intensity of continuous renal replacement therapy (CRRT). We aimed to compare key aspects of acidosis and MAP and vasopressor therapy in patients treated with two different CRRT intensities. *Methods:* We studied a nested cohort of 115 patients from two tertiary intensive care units (ICUs) within a large multicenter randomized controlled trial treated with lower intensity (LI) or higher intensity (HI) CRRT. *Results:* Levels of metabolic acidosis at randomization were similar [base excess (BE) of -8 ± 8 vs. -8 ± 7 mEq/l; $p = 0.76$]. Speed of BE correction did not differ between the two groups. However, the HI group had a greater increase in MAP from baseline to 24 h (7 ± 3 vs. 0 ± 3 mmHg; $p < 0.01$) and a greater decrease in norepinephrine dose (from 12.5 to 3.5 vs. 5 to 2.5 μg/min; $p < 0.05$). The correlation (r) coefficients between absolute change in MAP and norepinephrine (NE) dose versus change in BE were 0.05 and −0.37, respectively. *Conclusions:* Overall, LI and HI CRRT have similar acid–base effects in patients with acidosis. However, HI was associated with greater improvements in MAP and vasopressor requirements (clinical trial no. NCT00221013).

Keywords Acidosis · Acid–base · Acidemia · Norepinephrine · Alkalosis · Base excess · Bicarbonate · pH · Continuous renal replacement therapy · Hemodialysis · Strong ion difference

Introduction

Acid–base homeostasis is a key therapeutic target in critically ill patients [1, 2]. However, acidosis is common in the critically ill [3]. Such acidosis is an independent predictor of unfavorable outcome in this population [4, 5]. In patients with acute kidney injury (AKI), metabolic acidosis is especially common [6]. Although the exact

mechanisms of metabolic acidosis in AKI are complex, excess of retained metabolic acids is likely to contribute, together with other general acid–base disorders of critical illness (hyperlactatemia and/or hyperchloremia) [7, 8]. Depending on its severity, correction may require different levels of intervention including renal replacement therapy (RRT) [9].

Despite the logical expectation that RRT should improve metabolic acidosis, studies have reported that its effect on acid–base status is likely dependent on the nature of acidosis (anion gap positive vs. non-anion gap acidosis), its intensity, choice of buffer, ability of the body to metabolize buffer to bicarbonate, site of delivery of the buffer, and quantity of buffer delivered [10–12]. In addition, the plasma concentration of solutes available for ultrafiltration, and the rate of ultrafiltration also appear to determine the effect of RRT on acid–base status [13, 14]. In this regard, although under most circumstances other buffers are adequate, bicarbonate-based replacement or dialysis solutions more predictably and consistently reverse metabolic acidosis [11]. However, once bicarbonate is used as replacement fluid and dialysate fluid, little is known about the impact of CRRT intensity on the speed and extent of correction of metabolic acidosis in advanced AKI. In particular, it is unknown whether applying more intensive CRRT would lead to faster and/or greater resolution of acidosis in the early (first 24 h) treatment period. Also, given concerns that acidosis and/or acidemia might lower MAP and increase vasopressor requirements, it is unknown whether such correction would be accompanied by an effect on mean arterial pressure.

We hypothesized that, in the first 24 h, higher intensity (HI) CRRT would reverse metabolic acidosis at a faster rate and to a greater degree than lower intensity (LI) CRRT, and thus had correction of acidosis in the first 24 h as our primary endpoint. We also hypothesized that such changes would be accompanied by a greater increase in MAP, and therefore had improved MAP at 24 h as our secondary endpoint. We tested these hypotheses by conducting a nested cohort study within the randomized evaluation of normal versus augmented level (RENAL) Replacement Therapy Study, a multicenter randomized controlled study comparing two levels of CRRT intensity [15].

Methods

The study involved a nested cohort of patients from two centers within the RENAL study in whom detailed data on acid–base status were obtained during the first 24 h of CRRT treatment. The RENAL study was a multicenter, prospective, randomized trial of two levels of intensity of continuous renal replacement therapy (CRRT) originally in 1,508 critically ill patients with acute kidney injury conducted in 35 ICUs in Australia and New Zealand [15]. The study was approved by the Human Research Ethics Committees of the University of Sydney and all participating institutions.

The methodological details of the RENAL study were recently reported [15]. In brief, patients were eligible for enrollment if they were critically ill adults who had AKI, were deemed to require RRT by the treating clinician, and fulfilled predefined criteria [15]. Eligible patients were randomly assigned to continuous venovenous hemodiafiltration (CVVHDF) with effluent flow at 25 ml/kg/h (lower intensity, LI) or 40 ml/kg/h (higher intensity, HI). Replacement fluid was delivered into the extracorporeal circuit after the filter (i.e., postdilution), with a ratio of dialysate to replacement fluid of 1:1. Blood flow was kept above 150 ml/min. Fluid was removed by decreasing the flow of the replacement fluid and of the dialysate in equal proportion, so that effluent exceeded them by any amount prescribed by the clinician.

Filters with the AN69 membrane (Gambro) were used. Hemosol BO fluid (Gambro) was used as the dialysate and replacement fluid. Hemosol contains sodium ion (Na^+, 140 mmol/l), chloride ion (Cl^-, 109.5 mmol/l), bicarbonate (HCO_3^-, 32 mmol/l), lactate (3 mmol/l), calcium ion (Ca^{2+}, 1.75 mmol/l), and magnesium ion (Mg^{2+}, 0.5 mmol/l).

All patients were anticoagulated with unfractionated heparin with target at the attending clinician's discretion.

The intensive care management of the patients including CO_2 tension in arterial blood ($PaCO_2$) and MAP aims were set by the treating physicians. Study treatment was discontinued on death, discharge from ICU, or recovery of renal function.

Measurements

In all patients arterial blood pH, plasma lactate, $PaCO_2$, K, Na, Mg, ionized Ca (iCa), Cl, phosphate (Phos), albumin (alb), creatinine, and urea levels, MAP, and dose of norepinephrine in μg/min were recorded 2-hourly for 24 h.

Calculations

Plasma standard HCO_3^- levels and BE values were calculated by blood gas machines.

The strong ion gap (SIG) [16] was calculated as the difference between the apparent (SIDa) and effective (SIDe) strong ion difference [17, 18], where

$$\mathrm{SIDa} = [\mathrm{Na}^+] + [\mathrm{K}^+] + 2 \times [\mathrm{iCa}^{2+}] + 2 \times [\mathrm{Mg}^{2+}] - [\mathrm{Cl}^-] - [\text{L-lactate}]$$

and [16]

$$\mathrm{SIDe} = 1000 \times 2.46 \times 10^{-11} \times \mathrm{PaCO_2}/10^{-\mathrm{pH}} + \mathrm{Alb} \times (0.123 \times \mathrm{pH} - 0.631) + \mathrm{Phos} \times (0.309 \times \mathrm{pH} - 0.469).$$

Statistical analysis

Data are expressed as mean with standard deviation (SD) for normally distributed variables and as median and interquartile range (IQR) for non-normally distributed variables.

To adjust for the effect of any missing data, calculations were made with and without imputations for missing data. Imputations were done by calculating the mean of the value immediately before and after the missing value. If a value was missing at the end of the observational period, the "last value carry forward" method was used. The calculations with the two datasets corresponded well to one another, thus only analysis based on original data without imputations is reported, unless otherwise stated.

Comparisons were made using the *z*-test for dichotomous variables, *t* test or analysis of variance (ANOVA) as appropriate for repeated measurements for variables with normal distribution and the Mann–Whitney test or Wilcoxon matched-pairs test for variables with non-normal distribution. Spearman's rank test was used for calculating correlation coefficients. $p < 0.05$ was considered significant. Statistical analyses were performed by STATISTICA™ software, version 10 (StatSoft, Tulsa, OK, USA).

Results

Patient characteristics

We studied 115 patients, of whom 59 (51 %) were randomized into the lower intensity (LI) group and 56 (49 %) into the higher intensity (HI) group. The two groups were comparable in terms of age, mortality, severity of illness and organ failure, and delivered CRRT time (Table 1). All but one patient had an abnormal anion gap, and 28 of the 115 patients (24 %) had plasma lactate over 4 mmol/l. Discharge diagnosis groups are provided in Table 2.

At 28 days, 45 (39 %) patients were dead: 24 (41 %) in the LI group and 21 (38 %) in the HI group. The most common ICU admission diagnosis was sepsis with AKI ($n = 43$, 37 % of total), followed by postoperative AKI ($n = 21$, 18 % of total), AKI due to primary renal disease ($n = 19$, 17 % of total), and AKI secondary to other medical conditions ($n = 32$, 28 % of total).

Acid–base effects

Biochemical, acid–base, and MAP values at baseline and 24 h are given in Table 3. Overall, acidosis improved similarly in both groups. In particular, BE increased similarly from 0 to 24 h in both groups (Fig. 1).

Normal BE between −2 to +2 mmol/l at 24 h was achieved in 29 (49 %) LI patients and 29 (52 %) HI patients.

Table 2 ICU discharge diagnosis groups for cohort ($n = 115$)

	n	Percentage of total
Medical diagnoses	89	77
Infectious conditions	34	30
Cardiac conditions	6	5
Respiratory conditions	2	2
Genitourinary conditions	25	22
Hepatic conditions	8	7
Other medical conditions	14	12
Surgical diagnoses	26	23
General surgical conditions	13	11
Cardiac surgical conditions	9	8
Vascular surgical conditions	3	3
Trauma	1	1

Table 1 Characteristics of the study population according to treatment allocation

	Overall population	LI group	HI group	*p*-Value
Sex (% male)	83/115 (72 %)	41/59 (70 %)	42/56 (75 %)	0.51
Day 28 mortality (% dead)	45/115 (39 %)	24/59 (41 %)	21/56 (38 %)	0.70
Age (IQR), years	67 (19)	66 (18)	69 (19)	0.24
APACHE III (IQR)	103 (30)	100 (35)	107 (33)	0.09
SOFA (IQR)	11 (6)	11 (6)	11 (6)	0.43
Hours on CRRT (IQR)	21 (6)	21 (7)	22 (6)	0.46

p-Values refer to intergroup differences

LI lower intensity, *HI* high intensity, *APACHE* Acute Physiology and Chronic Health Evaluation score, *CRRT* continuous renal replacement therapy, *SOFA* Sequential Organ Failure Assessment score

Table 3 Change in biochemical and physiologic data in the two study groups from baseline to 24 h

Change from baseline to 24 h of CRRT	Lower intensity CRRT			Higher intensity CRRT		
	0	24	*p*-Value	0	24	*p*-Value
pH	7.30 ± 0.12	7.36 ± 0.12	<0.001	7.29 ± 0.11	7.38 ± 0.07	<0.001
HCO_3^- (mmol/l)	18 ± 6	22 ± 4	<0.001	18 ± 6	23 ± 6	<0.001
BE (mEq/l)	−8 ± 8	−3 ± 6	<0.001	−8 ± 7	−2 ± 4	<0.001
SIDa (mmol/l)	38 ± 6	38 ± 5	0.38	38 ± 6	37 ± 4	0.17
SIG (mmol/l)	10 ± 4	8 ± 14	0.30	10 ± 5	5 ± 4	<0.001
Lactate (mmol/l)	2.4 (1.3–4.6)	1.8 (1.4–2.9)	0.83	2.2 (1.6–3.8)	1.4 (1.1–2.5)	<0.01
Chloride (mmol/l)	104 ± 7	103 ± 4	0.24	103 ± 8	103 ± 3	0.97
MAP (mmHg)	78 ± 11	78 ± 12	0.93	73 ± 11	81 ± 15	<0.001
Norepinephrine dose (μg/min)	5 (0–14)	3 (0–11)	0.53	13 (0–22)	4 (0–14)	<0.001

Values are given at 0 h (at the start of CRRT) and at 24 h of CRRT
Data are given as mean ± standard deviation or median (interquartile range)
p-Values refer to intragroup difference from 0 to 24 h

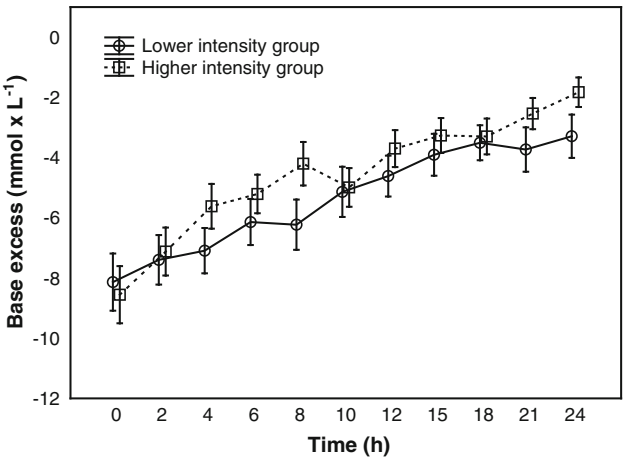

Fig. 1 Changes in base excess (BE) levels in the first 24 h of treatment in patients receiving lower intensity and higher intensity CRRT (mean ± standard error, SE)

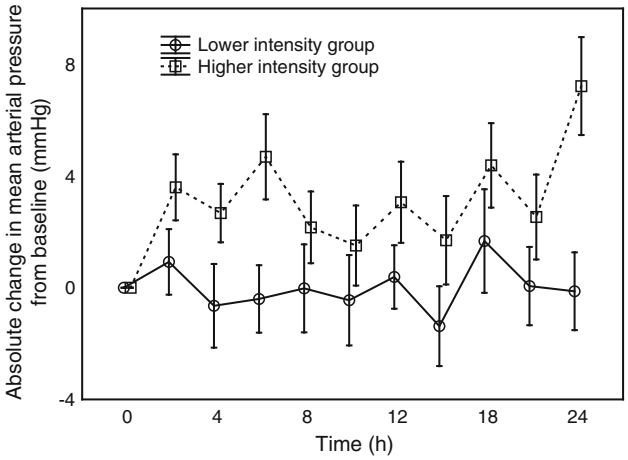

Fig. 2 Absolute changes in mean arterial pressure (MAP) from baseline in the first 24 h of treatment in patients receiving lower intensity and higher intensity CRRT (mean ± SE)

Effect on mean arterial pressure and norepinephrine dose

MAP was higher in the LI group at baseline compared with the HI group (78 ± 12 vs. 73 ± 11 mmHg; $p < 0.05$) in the overall population. However, the absolute change in MAP from baseline to 24 h was greater in the HI group ($p < 0.001$) (Fig. 2). The absolute change in MAP did not correlate with the absolute change in BE ($r = 0.05$).

The dose of norepinephrine differed between the groups at baseline ($p < 0.05$; Table 3). The absolute change in norepinephrine dose from baseline to 24 h (Fig. 3) was greater in the HI group (−7 ± 5 vs. 0 ± 5 μg/min; $p < 0.05$) than in the LI group. This difference in dose remained significant even when patients without baseline norepinephrine treatment were excluded (25 out of 59 patients in the LI group and 15 out of 52 patients in the HI group). The correlation between

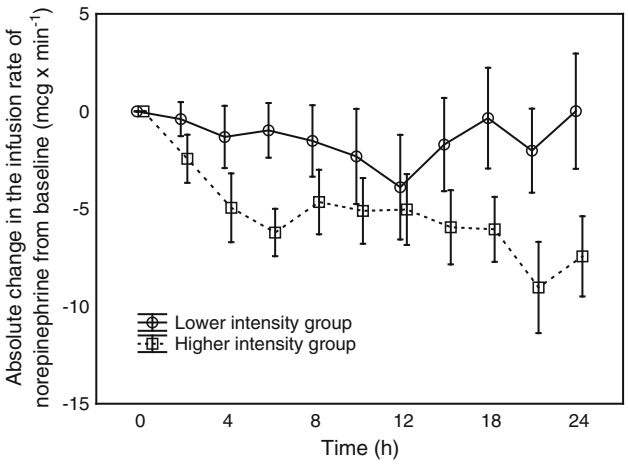

Fig. 3 Absolute changes in the infusion rate of norepinephrine from baseline in the first 24 h of treatment in patients receiving lower intensity and higher intensity CRRT (mean ± SE)

absolute change in norepinephrine dose and the absolute change in BE was weak ($r = -0.37$).

Discussion

Key findings

We conducted a nested cohort study within the RENAL trial to test whether HI CRRT would result in faster and/or greater early correction of acidosis and whether it would also affect MAP and NE treatment. Overall, we found that HI CRRT achieved a similar rate and magnitude of acidosis correction compared with LI CRRT. However, HI CRRT resulted in a greater increase in blood pressure and a greater decrease in norepinephrine requirements. These changes did not correlate with changes in pH or BE.

Relationship to previous studies

The effect of CRRT on acid–base balance appears determined by the plasma concentration of solutes available for ultrafiltration, the composition of the dialysis or replacement fluid, the intensity of ultrafiltration, and body weight [13, 14]. Our study showed, as expected, that bicarbonate-based CRRT attenuates metabolic acidosis [10–12]. Although the effects of bicarbonate-based CRRT on acid–base disorders have been investigated previously [19], our study is the largest study of the acid–base effect of CRRT intensity within a randomized trial.

The overall reversal of acidosis was similar in the LI and HI groups in terms of pH change and change in HCO_3^- levels and BE.

Despite the similar effects on BE, HI and LI had a different effect on SIG, which decreased more in the HI group. This effect could be consistent with the view that the removal of unmeasured organic anions by CRRT is increased with greater intensity [7, 20]. However, since SIG decreased similarly in both HI and LI groups in the severe acidosis subgroup, this effect may not entirely be related to CRRT intensity or only operate at less severe acid–base disturbances. In contrast, there were no or minimal effects of CRRT on the SID, a major determinant of acid–base status [16]. However, one ion (potassium) was affected by CRRT intensity. Such decrease in plasma potassium levels appears due to direct clearance by CRRT rather than a pH effect [21].

CRRT has been previously associated with improved MAP in animal models of sepsis and in humans [22–25]. However, no controlled studies have compared two intensities of CRRT in terms of their effect on MAP and vasopressor requirements [26]. We found that MAP increased and vasopressor requirements decreased with HI CRRT. Although decreased norepinephrine requirements could be attributed to normalization of pH, this was not different between the two groups and cannot be logically used to explain our findings [27, 28]. Cooling by CRRT at higher intensity may also explain changes in MAP. However, in all cases fluids were warmed to 37 °C or more, making this mechanism somewhat unlikely. A potential alternative mechanism could be more efficient removal of biologic mediators responsible for hypotension and/or vasodilatation [23, 29–31]. Some of these mediators may have contributed to the changes in SIG as well as inducing hypotension. Our study, however, cannot provide a mechanistic analysis of the physiological effects observed.

Implications

Our study suggests that acidemia is generally effectively reversed during CRRT after 24 h of therapy. This information could be of interest to clinicians wishing to correct metabolic acidosis in patients with severe AKI, but it is not clear if it would actually change the management of these patients. Additionally, the findings that higher intensity CRRT improves MAP and reduces vasopressor doses may assist clinicians dealing with patients with the combination of acidosis, severe hypotension, and vasopressor requirements during early CRRT. Although bicarbonate buffer was used in this study, other buffers may have similar effects on acid–base balance.

Strengths and limitations

This study is the largest investigating the effect of CRRT dialysate and replacement fluid flow on acid–base status within a randomized controlled trial (RCT); data collection was extensive, numerical, and based on blood gas machine output or independently recorded by the bedside nurse. These aspects of the study make bias unlikely. As this is a nested cohort study of the RENAL trial, thus a substudy, selection bias introduced by studying a subpopulation can influence results. However, patients included in this study were recruited by including all patients from two centers of the RENAL study, their age and illness severity are similar to those reported for the whole population of RENAL trial patients [15], and the cohort represents a mixture of patients typically seen in general intensive care units. Others have reported that nested cohort studies have a design that preserves the validity of the original population when selection bias can be avoided [32].

Another consequence of our methodology is that our patients were not recruited and randomized to test the specific hypothesis of this study. However, since a majority of study patients had metabolic acidosis, this population was particularly useful to investigate the acid–base effects of CRRT in this setting. This study investigated a specific CRRT setup (bicarbonate-based continuous venovenous hemodiafiltration, with fixed blood flow and

postfilter replacement); conclusions from this study, therefore, may not apply to other CRRT techniques.

Finally, our study was only conducted for 24 h, thus we cannot comment on the later effects associated with CRRT [33]. However, most acid–base disturbances are reversed within this time period, and if CRRT fails to restore acid–base homeostasis by 24 h, clinicians may choose additional therapies [34].

Future research

Further studies of CRRT intensity with other buffers (e.g., citrate) may be of interest given the evolution of therapy toward greater use of citrate as anticoagulant [35]. In addition, investigation of the mechanism by which HI CRRT improves MAP might provide insights into future therapeutic interventions.

Conclusions

In this nested cohort study within a large RCT, HI CRRT did not affect acid–base differently from LI CRRT overall. In addition, HI CRRT increased MAP and decreased norepinephrine requirements compared with LI CRRT. These physiological observations may be helpful to clinicians faced with the treatment of patients with combined AKI, metabolic acidosis, hypotension, and vasopressor therapy.

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