Original Paper

Applying Regional Citrate Anticoagulation in Continuous Renal Replacement Therapy for Acute Kidney Injury Patients with Acute Liver Dysfunction: a Retrospective Observational Study

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Key Words

Citrate • CRRT • Anticoagulant • Liver dysfunction • AKI

Abstract

Background/Aims: Continuous renal replacement therapy (CRRT) is a treatment for acute kidney injury (AKI) patients. It has become a controversy about whether patients with liver dysfunction should perform CRRT with regional citrate anticoagulation (RCA). **Methods:** This retrospective observational study enrolled 145 AKI patients (275 CRRT sessions) who received CRRT with RCA and had no history of chronic liver disease. Circuit survival time, blood pressure, trans-membrane pressure (TMP), acid-base and electrolyte status were recorded and analyzed. The severity of liver dysfunction was determined by total bilirubin (TBil) and international normalized ratio (INR), while the accumulation degree of citrates was quantified by total/ionized calcium (tCa/iCa) ratio. **Results:** Our results showed that there was no correlation of tCa/iCa ratio with TBil or INR. And tCa/iCa ratio was not related to the disturbances of pH, lactates, sodium, magnesium, blood pressure or TMP despite that high tCa/iCa ratios might be related to the decrease of circuit survival time. TBil did not correlate with the above indexes, except for lactates levels. INR did not correlate with the above indexes except for lactates levels and blood pressure. In addition, neither was TBil, INR, nor tCa/iCa ratio, related with fatal outcomes (22.76% of the patients). **Conclusion:** The present study demonstrated that, with proper monitoring and adjustment of citrates and calcium infusion, applying RCA in CRRT is reasonably safe for AKI patients with acute liver dysfunction, as long as circuit time stays below roughly 50 hours.

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Introduction

Acute kidney injury (AKI) is a common disease in intensive care units (ICU) with a high mortality rate [1]. For severe AKI patients, renal replacement therapy (RRT) is often applied to compensate for their kidney function. RRT can be performed either in a continuous way (CRRT) or an intermittent way (IRRT). CRRT is optimal for hemodynamically unstable patients [2], with possible effects on long-term recovery of kidney function [3, 4]. Moreover, CRRT is proven cost-effective than IRRT [4-6]. Thus CRRT has become the predominant form of RRT for critically ill patients [7]. CRRT was designed to run continuously more than 24 hours in order to provide a slow and uninterrupted clearance of the endogenous and exogenous toxins, and a homeostasis of acid-base, electrolyte, and volume [8].

Anticoagulation is required for extracorporeal circulation in CRRT. Most widely used anticoagulant is unfractionated heparin (UFH) [9]. However, this kind of anticoagulant could increase the risk of bleeding due to antithrombin consumption, especially in critically ill patients [10-12]. Moreover, heparin could generate deleterious effects on microcirculation, inflammation pathways, and phagocytotic clearance of dead cells [10]. Whereas, applying regional citrate anticoagulation (RCA) could avoid these problems. Citrates are infused before blood enters CRRT circuit. Then citrates inactivates the ionized calcium (iCa), the key component of coagulation, by combining with it. In contrast with systemic heparin anticoagulation, RCA shows a benefit of less bleeding, longer filter lifespan, and lower transfusion rates [13-15].

As a matter of fact, in line with KDIGO (Kidney Disease: Improving Global Outcomes) guidelines, citrates should be used in CRRT for all patients without contraindications and heparin for other patients [2]. The contraindications referred to liver diseases or shock states as the metabolism is compromised in such conditions, which could lead to the accumulation of citrates [16]. The clearance of citrates is predominantly in the hepatic citric acid cycle and partly in the skeletal muscle, but almost completely independent of renal function and urinary excretion [17, 18]. Excessive amount of citrates could cause systemic ionized hypocalcemia, with a consequence of systemic hypocoagulability and decreased cardiac contractility, as well as hypotension induced by the decreased vascular tone [10]. Since available observational studies have shown different results [19-24], applying CRRT with RCA in patients with liver dysfunction remained controversial. Thus the present study was aimed to verify whether performing CRRT with RCA in AKI patients with acute liver dysfunction would lead to the assumed complications or adverse outcomes.

Materials and Methods

Study cohort and exclusion criteria

This retrospective observational study was approved by the Ethics Committee of Zhujiang Hospital (Southern Medical University, Guangzhou, China). Consents were obtained from the participants to participate and publish. All data were anonymized and de-identified before analysis. The medical records of AKI patients hospitalized in ICU of Zhujiang Hospital (Southern Medical University, Guangzhou, China), who were treated with CRRT using RCA during the time span from January 2014 to August 2015, were recorded. Any CRRT session with its duration less than 24 hours was excluded. We also excluded any cases with missing data regarding total bilirubin (TBil), international normalized ratio (INR), total calcium (tCa) or ionized calcium (iCa). In the study cohort, the liver dysfunction cases were all acute liver dysfunction, and mostly induced by septic shock.

Collections of clinical data

Clinical data were collected including age, gender, APACHE (acute physiology and chronic health evaluation) II score, diagnosis, fatal outcome as well as before and in the end of CRRT including TBil, INR,

blood urea nitrogen (BUN), the trans-membrane pressure (TMP), blood pressure, pH, lactates, sodium, magnesium, tCa and iCa levels.

Data categorization

All cases were categorized according to the liver function, accumulation degree of citrates and hospitalization outcome. According to their median levels, all cases were divided on a fifty-fifty basis. The accumulation degree of citrates was measured by tCa/iCa ratio. According to its cut-off value 2.1, all cases were divided into two groups as the low citrate group (tCa/iCa ratio <2.1) and the high citrate group (tCa/iCa ratio ≥2.1) [25]. Outcome was all-cause death.

CRRT protocol

The patients who developed AKI above stage II (mainly in stage III) according to KDIGO guidelines [2] were considered to receive CRRT. CRRT was performed in standard procedure, using Gambro Prismaflex, with the filter model AN69-M100. The effluent flow and mean blood flow rate were determined by the weight of the patient, respectively calculated as 35mL/(h · kg) and 3mL/(min · kg). The infusion rate of citrates was adjusted to maintain post-filter iCa levels in 0.25-0.45mmol/L. The infusion rate of 5% calcium chloride solution was adjusted according to the levels of iCa in blood (Supplemental Table 1), to maintain blood iCa levels in 1.0-1.2mmol/L. For all supplemental material see www.karger.com/doi/10.1159/000491057.

CRRT was stopped if the patient: 1) had an improvement on physical status; 2) died; 3) abandoned treatment; 4) was transferred to take exams; 5) had an obstruction in the effluent drainage; 6) showed a TMP higher than 300mmHg.

Data analysis

SPSS 20.0 statistics software was used to analyze the data. All data were nonparametric, presented as median (lower quartile value; upper quartile value). Mann-Whitney-Wilcoxon tests were applied for two independent variables, while Kruskal-Wallis H test for three or more independent variables. Spearman correlation analysis was applied to analyze the bivariate relations. Pearson Chi-square test was applied to analyze categorical variables. P<0.05 was considered statistically significant.

Results

Descriptive cohort information

A total of 145 patients were enrolled (providing 275 CRRT sessions), including 92 males and 53 females, aging from 13 to 88 years old, with a median of 59 (48;72) years old. The median APACHE II score was 28(23;35). 33 cases were categorized into the death group and 112 cases into the survival group (Table 1). The main reason for death was multiple organ dysfunction syndrome (MODS). And some other cases ended in abandonment of treatment because of economic pressure and poor prognosis.

There was no statistical difference in gender or age between the two levels of tCa/iCa ratio (both p>0.05). Also, there was no statistical difference in age between the two levels of TBil (p>0.05), and no statistical difference in gender between the two levels of INR (p>0.05). However, the high TBil group consisted of more male patients than the low TBil group (p=0.025), while the patients appeared generally older in the high INR group than the low INR group (p=0.037).

At the initiation of all CRRT sessions, the median level of blood creatinine was 241 (120;486) μmol/L; and the median level of BUN was 19.25 (10.73;32.50) mmol/L. Among all 275 CRRT sessions, there were 66 sessions that ended with their TMP higher than 300mmHg and 6 sessions ended because of the obstruction in the effluent drainage.

Table 1. Descriptive cohort information. *APACHE II score: Acute physiology and chronic health evaluation II score. *Low citrate group: Cases with tCa/iCa ratio<2.1. *High citrate group: Cases with tCa/iCa ratio≥2.1. *Low TBil group: Cases with total bilirubin level<13.20μmol/L. *High TBil group: Cases with total bilirubin level ≥13.20μmol/L. *Low INR group: Cases with international normalized ratio<1.29. *High INR group: Cases with international normalized ratio≥1.29. *P value: Mann-Whitney-Wilcoxon test was applied to compare age differences between the two groups. Pearson Chi-square test was applied to compare gender differences between the two groups. **P<0.05

Characteristics	Case number	Age [median(quartiles)]	Gender [male/female]	APACHE II score* [median(quartiles)]	Fatal outcome [death/survival]
All cases	145	59(48;72)	92/53	28(23;35)	33/112
Low citrate group*	85	58(48;71)	58/27	25(21;33)	16/69
High citrate group*	60	60(48;74)	34/26	25(21;36)	17/43
P value*		0.422	0.156	0.586	0.228
Low TBil group*	72	60(47;74)	39/33	25(20;35)	16/56
High TBil group*	73	57(48;69)	53/20	27(21;33)	17/56
P value		0.193	0.025**	0.536	1.000
Low INR group*	72	56(45;69)	41/31	24(20;33)	13/59
High INR group*	73	63(51;73)	51/22	29(22;36)	20/53
P value		0.037**	0.122	0.095	0.235

The correlation of tCa/iCa ratio with TBil and INR

The correlation analysis showed that the tCa/iCa ratio was not correlated with TBil level (p=0.122, correlation coefficient=-0.129), nor INR level (p=0.742, correlation coefficient=-0.028).

Comparing different variables in the end of CRRT between the two levels of tCa/iCa ratio

Using tCa/iCa ratio of 2.1 as the threshold [25], all cases were categorized into two groups. Different variables recorded in the end of CRRT were compared between these two groups (Table 2). Among them, no significant difference was found in the levels of blood pressure, TMP, pH, lactates, sodium or magnesium (all P>0.05), whereas the circuit survival time in the low citrate group was longer (P=0.026). In addition, there was no significant difference in death/survival numbers between the low citrate group and the high citrate group (p>0.05)(Table 1).

Comparing different variables recorded in the end of CRRT between the two levels of TBil

Different variables recorded in the end of CRRT were compared between the low TBil group and the high TBil group (Table 3). The variables included tCa/iCa ratio, circuit survival time, blood pressure, TMP, pH, lactates, sodium and magnesium. No significant difference was found in the above variables except for lactates. The lactates levels in the high TBil group were significantly higher than that in the low TBil group (p=0.018), with medians of 1.67 (1.10;2.26) mmol/L and 1.30 (0.93;1.80) mmol/L respectively. In addition, there was no significant difference in death/survival numbers between the low TBil group and the high TBil group (p>0.05) (Table 1).

Table 2. Comparing different variables recorded at the end of CRRT between the two levels of tCa/iCa ratio. *TMP: Trans-membrane pressure. *Low citrate group: Cases with tCa/iCa ratio<2.1. *High citrate group: Cases with tCa/iCa ratio≥2.1. *P value: Mann-Whitney-Wilcoxon test was applied to compare each variable between the two groups. **P<0.05

Parameter	Low citrate group* [median(quartiles)]	High citrate group* [median(quartiles)]	P value*
Circuit survival time (hour)	47.50(37.75;58.58)	40.25(31.01;53.81)	0.026**
pH	7.41(7.37;7.45)	7.41(7.38;7.47)	0.273
Lactate (mmol/L)	1.50(1.00;1.90)	1.40(1.00;2.18)	0.835
Sodium (mmol/L)	137(136;140)	138(136;140)	0.431
Magnesium (mmol/L)	0.77(0.69;0.87)	0.76(0.70;0.84)	0.774
Systolic pressure (mmHg)	130(114;144)	136(118;147)	0.240
Diastolic pressure (mmHg)	67(56;77)	65(56;78)	0.982
TMP* (mmHg)	246(194;292)	245(212;280)	0.823
Case number	85	60	

Table 3. Comparing different variables recorded at the end of CRRT between the two levels of TBil. TMP: Trans-membrane pressure. *Low TBil group: Cases with total bilirubin level<13.20μmol/L. *High TBil group: Cases with total bilirubin level ≥13.20μmol/L. *P value: Mann-Whitney-Wilcoxon test was applied to compare each variable between the two groups. **P<0.05

Parameter	Low TBil group* [median(quarters)]	High TBil group* [median(quarters)]	P value*
tCa/iCa ratio	2.08(1.95;2.22)	2.04(1.91;2.17)	0.274
Circuit survival time (hour)	44.53(34.75;58.16)	43.30(36.00;52.62)	0.809
pH	7.41(7.38;7.46)	7.41(7.37;7.46)	0.785
Lactate (mmol/L)	1.30(0.93;1.80)	1.67(1.10;2.26)	0.018**
Sodium (mmol/L)	137(136;140)	138(136;140)	0.956
Magnesium (mmol/L)	0.76(0.68;0.85)	0.77(0.71;0.87)	0.393
Systolic pressure (mmHg)	134(118;150)	129(113;140)	0.235
Diastolic pressure (mmHg)	67(56;77)	64(57;77)	0.738
TMP* (mmHg)	239(192;280)	258(218;291)	0.119
Case number	72	73	

Table 4. Comparing different variables recorded at the end of CRRT between the two levels of INR. *TMP: Trans-membrane pressure. *Low INR group: Cases with international normalized ratio<1.29. *High INR group: Cases with international normalized ratio≥1.29. *P value: Mann-Whitney-Wilcoxon test was applied to compare each variable between the two groups. **P<0.05

Parameter	Low INR group* [median(quarters)]	High INR group* [median(quarters)]	P value*
tCa/iCa ratio	2.06(1.92;2.22)	2.07(1.93;2.21)	0.611
Circuit survival time (hour)	44.96(35.04;53.60)	43.50(36.00;57.75)	0.907
pH	7.41(7.37;7.46)	7.41(7.37;7.45)	0.452
Lactate (mmol/L)	1.26(0.90;1.64)	1.80(1.23;2.43)	<0.001**
Sodium (mmol/L)	137(136;140)	138(136;140)	0.527
Magnesium (mmol/L)	0.79(0.70;0.87)	0.75(0.68;0.84)	0.150
Systolic pressure (mmHg)	135(121;150)	128(110;138)	0.013**
Diastolic pressure (mmHg)	69(57;79)	63(56;73)	0.043**
TMP* (mmHg)	252(218;284)	241(192;283)	0.305
Case number	72	73	

Comparing different variables recorded in the end of CRRT between the two levels of INR

Different variables recorded at the end of CRRT were compared between the low INR group and the high INR group (Table 4). The variables included tCa/iCa ratio, circuit survival time, blood pressure, TMP, pH, lactates, sodium and magnesium. No significant difference was found in the above variables except for lactates and blood pressure. The lactates levels in the high INR group were significantly higher than that in the low INR group ($p<0.001$), with medians of 1.80 (1.23;2.43) mmol/L and 1.26 (0.90;1.64) mmol/L respectively. The systolic pressure levels in the high INR group were significantly lower than that in the low INR group ($p=0.013$), with medians of 128 (110;138) mmHg and 135 (121;150) mmHg respectively. The diastolic pressure levels in the high INR group were also significantly lower than that in the low INR group ($p=0.043$), with medians of 63 (56;73) mmHg and 69 (57;79) mmHg respectively. In addition, there was no significant difference in death/survival numbers between the low INR group and the high INR group ($p>0.05$) (Table 1).

Discussion

We have shown in the present study that, with proper monitoring and adjustment of citrates and calcium infusion, applying RCA in CRRT is reasonably safe for AKI patients with acute liver dysfunction, as long as circuit time stays below roughly 50 hours.

In 2012, the use of citrates for the anticoagulation in CRRT has been recommended by KDIGO guidelines [2], mainly on the basis of a large randomized controlled trial involving 200 patients, which showed that citrate anticoagulation was associated with fewer complications (e.g. bleeding and thrombocytopenia) [14]. However, liver diseases were deemed as contraindications, according to the theory that the metabolism of citrates is impaired in patients with liver dysfunction, which could elevate the risk of citrates accumulation. Thus heparin was suggested to be applied as the anticoagulant for patients with liver disease.

Yet heparin could generate unpredictable effects by binding with nonspecific substances. By binding with antithrombin, it confers its anticoagulant effect. But by binding either with apoptotic cells, necrotic cells, or acute phase proteins, it may interfere with the microcirculation, inflammation pathways, and the phagocytotic clearance of dead cells. Especially under critical situations like sepsis or systemic inflammation, heparin could cause antithrombin consumption and degradation, as well as deleterious consequences due to the above reasons [10].

Patients with liver dysfunction may be accompanied by pathological changes like hyperfibrinolysis, accelerated intravascular coagulation, defected platelet (quantitatively and qualitatively), decreased synthesis of procoagulant and anticoagulant factors, as well as decreased clearance of activated factors [26, 27]. These pathological changes could contribute to developing hemorrhagic complications when using any type of extracorporeal support with systemic anticoagulation. In such situations, heparin is not an ideal anticoagulant. Thus the present study was designed to verify that whether applying RCA in CRRT for patients with acute liver dysfunction would result in the assumed complications or adverse outcomes.

In normal serum protein concentrations, total serum calcium is comprised of approximately 50% of ionized form (Ca^{2+}), 8%-10% of acid-complexed form (complexed to organic and inorganic acids as citrates, sulphates and phosphates), and the remaining 40% of protein-bound form (80% to albumins, 20% to globulins) [28]. To estimate the accumulation degree of citrates, iCa is a sensitive indicator, but not adequately specific and could be related to other causes [29]. Whereas, the increase of tCa/iCa ratio correlates best with plasma citrates level [30]. Therefore, tCa/iCa ratio was calculated to assess the accumulation degree of citrates in our study.

Some studies have reported or applied different cut-offs of tCa/iCa ratio to define citrates overdose, e.g. 2.1 [31, 32], 2.25 [33], 2.4 [34], 2.5 [23, 29, 35, 36]. Mostly the ratio of 2.1 and 2.5 are being used. However, the theory of using 2.5 as the cut-off ratio was simply based on a case report on one patient [29], while using 2.1 was based on a study enrolling 10 patients, and specifically with the definition of citrates overdose as citrates concentration $>1.0\text{mmol/L}$ [32]. Thus the ratio of 2.1 was set as the cut-off value in our study to divide the cases into the high citrate group and the low citrate group.

The study of Faybik P. et al. which involved 20 patients have demonstrated an increase of tCa/iCa ratios (2.04 ± 0.32 to 2.17 ± 0.35 ; $p=0.01$) in patients with liver failure [19]. However, our study showed that neither did TBil nor INR (indicating the residual liver function) interfere with the tCa/iCa ratio. And there was no correlation of the tCa/iCa ratio with TBil or INR. These could be explained by the sufficient and timely supplement of calcium. In addition, it's possible that the liver function was improved during CRRT. And some reports have indicated that the kidney musculature also appears to remove citrates in blood [20, 37].

The accumulation of citrates was reported to be associated with metabolic derangements like hypocalcemia, hypernatremia, hyponatremia, metabolic alkalosis and acidosis [10], as well as hypomagnesemia [33]. The molecule citrate itself is not toxic, but the accumulation of it could induce ionized hypocalcemia in the systemic circulation. Because in extracellular fluid, increases of anions such as citrates, phosphates, bicarbonates, or edetic acids, could chelate calcium and reduce the concentration of ionized calcium, but maintaining the concentration of total serum calcium [38]. Ionized calcium is the biologically active form. Ionized hypocalcemia may lead to decreased cardiac contractility and hypotension [39-41].

Yet, the results in our study showed that neither was the accumulation degree of citrates nor TBil associated with hypotension. However, the reason that INR was associated with hypotension might be the patients with lower blood pressure were likely to be in worse status of blood circulation, and more likely to develop disseminated intravascular coagulation (DIC), which could interfere with INR level.

Besides hypotension, acid-base derangements were also reported to be the results of citrates accumulation. Metabolic acidosis could be the result of large doses of citrates not being metabolized; metabolic alkalosis could be the result of mass delivering of sodium citrates (eg. accidentally rapid infusion or protocol violation); hypernatremia could be the result of the sodium not being reduced proportionally in the solution, leaving the unopposed sodium [42-44]; hypomagnesemia could be the result of citrates binding to Mg^{2+} [33].

However, the results of our study showed that neither did the accumulation degree of citrates nor the severity of liver dysfunction interfere with serum pH values, or concentrations of Na^+ or Mg^{2+} . This was consistent with the study led by Schultheiss C. et al. demonstrating 7 out of 43 runs of continuous venovenous hemodialysis (CVVHD) using CRA on liver failure

patients, with tCa/iCa ratios 10 times exceeding the threshold (the threshold was set as tCa/iCa ratio ≥ 2.5), yet have finished without major disturbances of acid-base or electrolyte status [23]. Kramer L. et al.'s study showed similar results by comparing 16 critically ill cirrhotic patients with 16 non-cirrhotic patients, demonstrating quantitatively similar net metabolic changes and noting no citrate-related side effects [22].

In addition, the tCa/iCa ratio did not interfere with serum lactates levels. However, patients with higher TBil and INR appeared higher lactates levels. This might be because that lactate is an index to indicate the status of systematic blood perfusion. And poor systematic blood perfusion could lead to poor residual liver function. Therefore, it's natural that TBil and INR showed an association with lactates levels.

Circuit survival time is another factor to consider when choosing anticoagulants for CRRT. The longer it lasts, the better consistency of therapy is gained, which means the better efficacy with less costs. The circuit survival time in our study appeared to be very low because many circuits were stopped for transferring patients to take image exams. Also, the cohort of this study consisted of patients with relatively high APACHE II scores. Thus the proportion of death or abandonment of treatment was relatively high. Although the circuit survival time in our study was affected by the accumulation degree of citrates, it was not affected by liver dysfunction levels. This was in accordance with the study led by Balogun R. A. et al., which enrolled 697 patients using RCA in CRRT and demonstrated no significant difference in circuit survival time among varying severities of liver dysfunction [21].

Moreover, our results indicated that neither were the accumulation degrees of citrates nor liver dysfunction levels related with fatal outcomes, which could be the result of the sufficient monitoring and adjustment of citrates and calcium infusion. In a way, it suggested that in clinical practice, even the assumed 'overdose' of citrates was not related with the fatal outcome. This further supported that using RCA in CRRT is reasonably safe for patients with acute liver dysfunction with proper monitoring and adjustment of citrates and calcium infusion.

Conclusion

In AKI patients with acute liver dysfunction who received CRRT with RCA, our study demonstrated that, with proper monitoring and adjustment of citrates and calcium infusion, using RCA in CRRT is reasonably safe for patients with liver dysfunction, as long as circuit time stays below roughly 50 hours.

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YY analyzed and interpreted the data, and was a major contributor in writing the manuscript. SP was a major contributor in collecting and interpreting the data. SP, ZC, JC, WW, YT, MD co-designed this study and collected the data. PC was a major contributor in designing and instructing this project. All authors read and approved the final manuscript.

Disclosure Statement

The authors declare that there is no conflict of interest associated with this manuscript.

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