Journal of Critical Care 30 (2015) 1096–1100

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.jccjournal.org

Sustained low-efficiency dialysis with regional citrate anticoagulation in medical intensive care unit patients with liver failure: A prospective study☆,☆☆

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ARTICLE INFO

Keywords:
SLED
Citrate anticoagulation
Liver failure
Critical care

SUMMARY

Purpose: Patients with liver failure requiring dialysis are at increased risk for citrate accumulation during sustained low-efficiency dialysis (SLED). The aim of this study was to evaluate the feasibilty of citrate SLED in critical ill patients with liver failure and investigate predictive parameters regarding citrate accumulation.
Materials and methods: This is a prospective study in 24 medical intensive care unit patients with liver failure and a total of 43 SLED runs (maximum of 3 runs per patient) using citrate anticoagulation. Liver function was characterized before SLED using not only laboratory parameters but also determination of the plasma disappearance rate of indocyanine green. In addition, blood gas parameters as well total calcium and citrate in serum were measured at baseline and defined time points during SLED.
Results: Accumulation of citrate could be observed in all SLED runs, which were nearly normalized until the end of SLED and 24 hours after SLED, respectively. However, the critical threshold of total calcium/ionized calcium on ratio of greater than 2.5 was exceeded in only 1 patient. Equalization of initial metabolic acidosis was possible without major disturbances of acid base and electrolyte status. Liver function parameters showed poor predicitve capabilities regarding citrate accumulation.
Conclusions: Despite substantial accumulation of citrate in serum, SLED is save and feasible in patients with liver failure using a citrate anticoagulation. Careful monitoring of electrolytes and acid base status is mandatory to ensure patient safety.

1. Introduction

One of the most often complications in hospitalized patients is still an acute kidney injury (AKI), which significantly affects morbidity and mortality of intensive care unit (ICU) patients if renal replacement therapy (RRT) is required [1,2]. In most cases, continuous RRT is used in ICUs, which is often seen as the preferable RRT in critically ill AKI patients [3-5].

However, intermittent RRTs, so-called sustained low-efficiency dialysis (SLED), are more and more used in critically ill patients with AKI [6]. Sustained low-efficiency dialysis, with a running time of 8 to 12 hours, shares the advantages of a conventional intermittent (4 hours) and a continuous RRT (up to 72 hours) [7].

Moreover, over the last years, citrate has emerged as a safe and efficacious alternative to heparin for extracorporeal circuit anticoagulation [8]. Citrate chelates ionized calcium (Caion), the most important cofactor of the coagulation cascade. Thus, regional anticoagulation with citrate is a very effective anticoagulation method for hemodialysis. Some studies on continuous venovenous hemodialysis (CVVHD) detected a reduction of bleeding complications, a longer filter lifetime, and a possible reduction of mortality in ICU patients with a citrate anticoagulation [9].

Therefore, regional citrate anticoagulation has also been recommended by the recent Kidney Disease Improving Global Outcomes guidelines. However, some intensivists are still reluctant to adopt this technique. Reasons may be the complexity; need of customized citrate solutions/replacement fluids; fear of metabolic complications (eg, hypocalcemia and metabolic alkalosis); and difficulties in predicting and preventing citrate accumulation, especially in patients with impaired liver function [10].

Around 50% of citrate is removed as a complex bound with Caion through the dialyzer by diffusion/convection. However, citrate can partly

☆ Competing interests: The author(s) declare that they have no competing interests. Declaration of interest: None of the authors have any potential financial conflict of interest related to this manuscript. None of the authors have got any funding or financial support regarding this manuscript. The manuscript has not been submitted or accepted elsewhere. All authors fulfill the criteria given in the authorship paragraph. No writing assistance other than copy editing was provided in the preparation of the manuscript.

☆☆ Authors' contribution: TL, MM, SR, AB, CS, RMS, and WH. Study design: TL, MM, SR, CS, RMS, and WH. Collected data: TL, MM, SR, AB, CS, RMS, and WH. Analyzed data: TL, MM, AB, SR, and WH. Wrote manuscript: TL, MM, AB, SR, CS, RMS, and WH. Study is approved by the Institutional Review Board of the Technical University of Munich, Munich, Germany. Written informed consent was obtained.

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http://dx.doi.org/10.1016/j.jcrc.2015.06.006
0883-9441/

enter the systemic circulation [11]. The hepatic citric acid cycle is the major site of citrate metabolization, which leads to the release of Caion into the systemic circulation. This is almost independent of renal function and urinary excretion [11,12]. However, in cases of impaired liver function with an also impaired citrate metabolism, the risk of citrate accumulation is rising. Drop of Caion due to complex binding between citrate and Caion requiring more calcium chloride substitution at the venous line of the extracorporeal circuit can result [12]. Moreover, this leads to an increase of total calcium (Catot) concentration, which is the sum of Caion, protein, and citrate-bound calcium, and an increased Catot/Caion ratio might be observed. After former studies, a serum Catot/Caion ratio greater than or equal to 2.5 might be a critical threshold of potential citrate accumulation [11,12]. Other side effects could be metabolic acidosis combined with an enlarged anion gap caused by reduced citric acid cycle production of bicarbonate out of citrate and accumulation of negative loaded citrate ions [8,9]. These possible side effects may be the reason why data on the feasibility of citrate CVVHD in liver failure patients are scarce. Moreover, there are only small data in critically ill patients with liver impairment using SLED [13,14]. Therefore, the aim of our study was to determine predictors for citrate accumulation and to investigate the feasibility of citrate anticoagulation in patients with impaired liver function.

2. Materials and methods

2.1. Patients

Twenty-four ICU patients between aged 29 and 73 years with decompensated liver cirrhosis (18 patients) or acute liver failure (6 patients) who needed RRT were included in this study. A total of 43 SLED runs (maximum, 3 per patient) were analyzed in this study cohort.

Liver cirrhosis was diagnosed either by histologic specimen, by ultrasound and/or computed tomography, and by clinical criteria for instance ascites or esophageal varices. We defined an acute liver failure as an abrupt loss of liver function without preexisting liver disease.

Before SLED treatment, we used the model of end-stage liver disease score (MELD score), the Child-Pugh score in case of cirrhosis, and laboratory liver function parameters (aspartate aminotransferase [ASAT], alanine aminotransferase [ALAT], bilirubin, and prothrombin time) to characterize baseline liver function. In addition, plasma disappearance rate of indocyanine green was performed. Sequential Organ Failure Assessment (SOFA) score as well the Acute Physiology and Chronic Health Evaluation (APACHE) II score was calculated in accordance to demonstrate the severity of the underlying disease (Table 1). Patients with severe alkalosis (pH >7.55) or acidosis (pH <7.1) and deficiency of Caion (<0.9 mmol/L) were excluded from our study.

In accordance to our Institutional Review Board of the Technical University of Munich, Germany, this study was approved, and written informed consent was obtained.

Table 1
Overview of baseline liver function parameters

	Mean/range/SD	Reference range
MELD score (points)	35/25-40/6.5	Maximum, 40 points
Child-Pugh score	all C	
APACHE II score	33/24-40/3.5	Maximum, 71 points
SOFA score	16/8-19/2.5	Maximum, 24 points
ICG-PDR	5.1/1.5-24/4.3	18-25
Prothrombin time (%)	38/16-66/13	70-120
INR	2.2/1.3-4.3/0.9	
Bilirubin (mg/dL)	18.4/2.1-46.5/14.5	<1.2
ASAT (U/L)	331/25-1261/331	10-50
ALAT (U/L)	157/15-1047/157	10-35
Lactate (mmol/L)	2.1/0.8-9.7/1.7	<2.4

ICG-PDR indicates indocyanine green-plasma disappearance rate; INR, international normalized ratio.
To characterize baseline liver function, the MELD score and the plasma disappearance rate of indocyanine green (ICG-PDR) were calculated in each patient, and the Child-Pugh score only in patients with cirrhosis. The APACHE II score and the SOFA score as well as the laboratory parameters were determined immediately before the start of SLED treatment. Data were expressed as mean (highlighted), range, and SD.

2.1.1. Sustained low-efficiency dialysis treatment

We used the commercially available hemodialysis Genius single-pass batch dialysis system (Fresenius Medical Care, Bad Homburg, Germany) for SLED treatment. It provides 90 L of bicarbonate dialysate per dialysis session. The dialysis system uses a double-sided roller pump that generates equal blood, and dialysate flows up to a maximum of 350 mL/min. Moreover, the Genius system contents a closed dialysate tank of 90 L, in which fresh and spent dialysate are stored together without any mixing of both compounds. The ultrafiltered water out of the patient plasma is collected in an ultrafiltrate recipient. High-flux FX60 dialyzers (Fresenius Medical Care) were used in all sessions.

For all SLED treatments, a blood flow of 150 mL/min, which is equal to dialysate flow, was used. The dialysate solution is a compound of an instant (HC-90; Fresenius Medical Care) and liquid (DS-90; Fresenius Medical Care) component. The instant component contains sodium chloride,sodium bicarbonate, and glucose. The liquid component contains potassium chloride, calcium chloride, and magnesium chloride.

In all patients, the HC-90 concentration HC 31-90, which contains 40 mmol/L sodium, 3 mmol/L potassium, 1 mmol/L calcium, 0.5 mmol/L magnesium, 48 mmol/L chloride, 0.067 mmol/L citrate, and 2 mmol/L HCL, and the DS-90 concentration DS 135/35-90, which contains 95 mmol/L sodium, 35 mmol/L bicarbonate, 60 mmol/L chloride, and 5.5 mmol/L glucose, were used.

Citrate solution was produced in the local hospital pharmacy (100 mL consists of 22 g tri natriumcitrate dihydrate and 8 g citrate monohydrate in aqua destillata).

Calcium chloride solution was produced in the local hospital pharmacy (500 mmol/L, 73.5 g calcium chloride dihydrate in 1000 mL aqua destillata).

Sodium citrate flow was started with 60 mL/h, and calcium chloride flow was started with 10 mL/h, respectively, and adapted according to the required limits of calcium between 0.35 and 0.45 mmol/L postfilter and 1.00 and 1.10 mmol/L in the patient's circulation.

According to the study protocol, citrate and Catot in serum were measured at baseline just before the beginning of SLED treatment, after 45 L, 90-L dialysate turnover, and 24 hours. Blood gas analyses of the patient's circulation and Caion postfilter were measured at baseline, after 1 hour, after 3 hours, 45 L, 9 hours, 90 L, and after 24 hours. The total run time of SLED was approximatley 10.5 hours.

Citrate levels were measured enzymatically by the citrate-lyase method (MVZ Labor Limbach, Heidelberg, Germany). In this method, citrate is metabolized to oxalacetate, and acetate is catalyzed by the enzyme citrate lyase. Oxalacetate is reduced to malate and lactate by the enzymes L-malate-dehydrogenase and L-lactate-dehydrogenase in a nicotinamide adenine nucleotide hydrogen-dependent manner. Nicotinamide adenine nucleotide hydrogen is the measured variable and is equivalent to the amount of citrate.

2.2. Statistical analysis

In our study, we used for statistical analyses the IBM SPSS Statistics 21 (SPSS Inc, Chicago, IL). Descriptive statistics were expressed with mean ± SD and range for normally distributed continuous data. The *t* test was performed for paired samples. Wilcoxon signed rank test was performed for paired samples for normally distributed data and not normally distributed data, respectively. A *P* value below a significance level of 5% ($P < .05$) indicates statistical significance.