Efficacy and safety of regional citrate anticoagulation in liver transplant patients requiring post-operative renal replacement therapy

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Abstract

Background. Liver transplant patients with acute kidney injury (AKI) requiring continuous renal replacement therapy (CRRT) early post-operatively are at high risk for bleeding. Using heparin for anticoagulation during CRRT may contribute to the increased bleeding risk. Regional anticoagulation with citrate may decrease the risk of bleeding. However, citrate anticoagulation may be associated with metabolic complications in patients with liver impairment. The aim of the study was to evaluate the safety and efficacy of citrate anticoagulation in liver transplant patients.

Methods. All liver transplant recipients transplanted between November 2004 and August 2007, requiring CRRT and using citrate as the anticoagulant were included in this retrospective study. Demographic data, CRRT specific and metabolic data were collected and analysed.

Results. Sixty-eight patients (40 male/28 female) with a mean age of 47.1 ± 11.8 years and a Model of End-stage Liver Disease score of 23 ± 9 developed post-operative AKI requiring CRRT using citrate as the anticoagulant. The median duration on CRRT was 8 days (range 1–39 days) with a mean circuit life of 22.7 ± 14.6 h. There was no relevant time trend of serum sodium, potassium, calcium, bicarbonate and pH values during CRRT. Bleeding occurred in 8 of 68 (11.7%) patients during CRRT.

Conclusion. Regional citrate anticoagulation for CRRT in the early post-operative period after liver transplantation is effective and safe. Therefore, the general exclusion of citrate anticoagulation during CRRT in patients after liver transplantation is not justified.

Keywords: citrate anticoagulation; intensive care; liver transplantation; renal replacement therapy

Introduction

Patients following liver transplantation are at major risk of developing acute kidney injury (AKI) requiring continuous renal replacement therapy (CRRT). The reported incidence of AKI requiring CRRT after liver transplantation ranges from 10 to 30% [1, 2]. CRRT requires anticoagulation in order to prevent clotting of the extracorporeal circuit. Heparin, the most frequently used anticoagulant is associated with bleeding complications [3], particularly in patients with an impaired coagulation profile and thrombocytopenia such as liver transplant patients. Although a number of non-randomized studies have shown that CRRT without anticoagulation is feasible in patients with coagulopathy, most patients require some form of anticoagulation [4]. Prostacyclin, another alternative, is a potent inhibitor of platelet aggregation and has been shown to be an effective anticoagulant for CRRT [5, 6]. However, its use is limited due to vasodilatation-induced hypotension, particularly among patients with systemic inflammation such as liver transplant patients [7]. Regional citrate anticoagulation is recognized as an alternative [8]. Citrate chelates ionized calcium, which is a cofactor in the coagulation cascade. While thrombin and fibrin generation is inhibited, the blood is prevented from clotting in the extracorporeal circulation. The infused citrate is rapidly cleared by CRRT and the tricarboxylic acid cycle in the liver [9]. The levels of citrate and ionized calcium return to normal values within 30–120 min after discontinuing citrate infusion [10–12]. However, citrate anticoagulation can lead to severe hypocalcaemia and metabolic disorders, especially when citrate cannot be cleared in the liver [13, 14]. Therefore, the use of citrate as an anticoagulant in patients following liver transplantation is regarded as hazardous because of the potential risk of liver dysfunction/failure. However, very recently, a group from Austria showed that citrate anticoagulation was safe and feasible in 20 cirrhotic patients treated with molecular adsorbent recirculating system (MARS) [15].
Many different protocols have been developed in recent years in order to reduce the frequency and severity of electrolyte and metabolic derangements during citrate anticoagulation [16–18]. Data concerning citrate anticoagulation in liver transplant patients are lacking. The aim of this study was to assess the safety and efficacy of citrate anticoagulation in liver transplant patients in the early post-operative phase [16].

Materials and methods
The study was conducted in accordance with the Declaration of Helsinki from 2002 and appropriate data protection was followed. All consecutive liver transplant patients between November 2004 and August 2007, who were admitted to the intensive care unit (ICU), developed AKI requiring CRRT and were treated with citrate as the anticoagulant, were included in the analysis. Exclusion criteria were paediatric patients (age < 18 years) and incomplete patient records. All transplantations were performed using standard surgical techniques and a standardized anaesthesia protocol was applied to all patients. Patients were treated post-operatively in a single ICU applying standardized care consisting of triple immune suppression (corticosteroids, mycophenolatmofetil and tacrolimus or cyclosporine A) [19]. Patients with an activated partial thromboplastin time (aPTT) < 45 s received 210 U/h heparin for thrombosis prophylaxis, if there were no signs of bleeding. Low-molecular-weight heparin was not used in any patient. CRRT was initiated during the course of AKI [20, 21] if potassium levels increased to > 5.5 mmol/L or patients were significantly volume overloaded. CRRT was performed primarily as continuous venovenous haemodialysis (CVVHD) using citrate as the anticoagulant (see related paragraph in the Materials and methods section). Blood samples were collected for electrolytes and acid–base balance every 4 h. Creatinine, blood urea nitrogen and total calcium were measured at least once daily. Circuit lifetime and bleeding episodes were recorded. Bleeding was defined when a site of gross bleeding had been identified and at least one of the following criteria was met:

1. Drop of mean arterial pressure ≥ 10 mmHg
2. Transfusion of greater than or equal to two red packed cells (RPC) within 24 h
3. Decrease in haemoglobin of ≥ 2 g/dL
4. Failure of haemoglobin increase after RPC transfusion

Sepsis and systemic inflammatory response syndrome (SIRS) was defined according to the American College of Chest Physicians and the Society of Critical Care Medicine [22]. SIRS was assumed, if the patient met two or more of the following four criteria:

1. Body temperature < 36°C or > 38°C (hypothermia or fever).
2. Heart rate > 90 beats/min.
3. Respiratory rate > 20 breaths/min or a PaCO₂ < 32 mmHg (4.3 kPa) (tachypnoea or hypopcapnia due to hyperventilation).
4. White blood cell count < 4 or > 12 cells/μL.

Sepsis was defined as SIRS in response to a confirmed or probable infectious process.

Methods of CVVHD and monitoring
CVVHD with regional citrate anticoagulation was performed using Fresenius ADM 68 machine (Fresenius Medical Care, Bad Homburg, Germany) with a F605 polysulphon membrane high-flux dialyser with a 1.3 m² surface area (Fresenius Medical Care). Venous access for dialysis was obtained via 13.5 F double-lumen catheters (model Niagam™; Bard Access Systems, Salt Lake City, UT) inserted mainly in the internal jugular or subclavian vein. Haemodialysers were primed with 2000 mL 0.9% saline. Blood flow was maintained at 75–100 mL/min and dialysate flow was started with 1000 mL/h and adjusted as needed (see below and Figure 1). Circuits were changed on a routine basis every 48 hours as specified by the manufacturer.

Citrate anticoagulation was performed using a solution containing trisodium citrate 743 mmol/L and calcium acit 381 mmol/L (solution prepared by the hospital’s pharmacy), which was infused pre-dialysis with a flow rate of 35–45 mL/h. Citrate dose was adjusted depending on the post-ionized calcium concentration. Post-dialyzer-ionized calcium concentration was supposed to be < 0.3 mmol/L, whereas pre-dialyzer calcium concentration was maintained > 0.95 mmol/L (normal range: 1.15–1.29 mmol/L). In cases of calcium concentration < 0.95 mmol/L, calcium was substituted with 10% calcium gluconate solution (BBraun Avitum AG, Melsungen, Germany). Pre- and post-dialysis Ca concentrations were checked 10 min after citrate infusion had been started and then every 4 h thereafter. At the same time, sodium, potassium and the acid–base balance were also determined. Episodes of significant hypocalcaemia (ionized calcium < 0.8 mmol/L) were recorded.

Dialysate fluid was either SH 44 HEP or SH 35 HEP (BBraun Avitum AG) containing 2 mmol potassium or no potassium, respectively. The dialysate fluid contained 1.75 mmol/L calcium, which was deliberately chosen to decrease the risk of severe hypocalcaemia. This choice was made for logistical reasons because we apply this mode of citrate anticoagulation on several different ICUs with various nursing teams having different experience and training with citrate anticoagulation. Therefore, it was critical for us to design a mode of citrate anticoagulation, which most efficiently prevents hypocalcaemia the most feared complication of citrate infusion. Sodium bicarbonate (8.4%; BBraun Avitum AG) was added to the dialysate in variable quantities (60–160 mL) immediately before use to achieve a final concentration of 13.2–34.3 mmol/L bicarbonate in the dialysate fluid (Table 1). The patients’ base excess (BE) guided the added amount of sodium bicarbonate. Patients with higher BE (> 3 mmol/L) received lower bicarbonate concentration in order to avoid citrate associated alkalosis. If alkalosis could not be controlled by the low bicarbonate concentration, dialysis flow was increased to enhance bicarbonate and citrate removal. The variable sodium bicarbonate addition was determined as shown in Figure 3.

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Critera for stopping citrate anticoagulation were severe and uncontrolled alkalosis (BE > 10 mmol/L) and non-lactic metabolic acidosis indicating citrate accumulation.

Statistical analysis
Categorical variables were analysed by the Chi-squared test with Yates correction. Continuous variables were analysed by t-test when normal distribution was given. Non-normally distributed continuous variables were analysed by the Mann–Whitney rank-sum test. Survival times were analysed with the log-rank test and mortality rates at specific time points were determined according to the Kaplan–Meier method. A test was considered significant when P < 0.05. To assess the trend of the parameters under investigation, mixed models were fitted to the data. To be precise, we calculated a mixed linear model for each of the mentioned parameters as dependent and day of measurement as independent variable, using SAS 9.2 (SAS Institute Inc., Cary, NC). To account for the variability between patients, the heterogeneous time points and duration/number of measurement a model with random coefficients was used to estimate an overall time trend based on the individual trends of all patients. The distribution of aspartat aminotransferase (AST) is strongly skewed so that a linear model for AST is not appropriate. We therefore transformed AST with the decadic logarithm and fitted a mixed model to the transformed data. Data are presented as mean ± SD.

Results
Patients’ characteristics
From 274 consecutive patients, who received a liver transplantation between November 2004 till August 2007 in our department, 74 (27.0%) developed AKI-requiring CRRT. In six of those patients, heparin was used as the anticoagulant and in 68 patients, citrate was used as the anticoagulant. Patients receiving citrate were included in
the study. Demographical data and study population are presented in Table 2. All patients were critically ill and were on vasopressor treatment (norepinephrine) with a median dose of 0.2 l/g/kg/min (range 0–1 l/g/kg/min). The aetiology of AKI is shown in Table 2. There may be several possible mechanisms that contribute to the development of AKI in the early post-operative setting after liver transplantation in a single patient. In Table 2, we have indicated the aetiology that was most likely the primary mechanism for the development of AKI. The median time for starting dialysis after transplantation was 7.5 days (range 0–47 days). The mortality rates are presented in Table 2. One-year mortality rate in the non-septic patients was significantly better as compared with septic patients (55 versus 82.1%, log rank P = 0.002). Since there was no other significant difference between septic and non-septic patients during CRRT, both groups were analysed together, except where indicated.

**Laboratory data**

Laboratory data prior and at the end of treatment are given in Table 3. There was a significant time trend in creatinine, partial thromboplastin time, total and direct bilirubin, total protein, albumin, international normalized ratio (INR), platelets, aspartate and alanine aminotransferase (Table 3) Total calcium, ionized calcium, the ratio of total calcium/ionized calcium and all other determined values did not show a statistically significant time trend during CRRT treatment (Table 3).

**Acid–base status**

The pH remained stable during the whole treatment period (Figure 2, Table 3). The BE increased from \(-0.89 \pm 4.88\) to \(1.93 \pm 4.62\) on the seventh day of treatment; however, this
The pH value at Day 0 represents the value before the start of CRRT treatment and the other values were taken on the indicated consecutive days at 7 am in the morning. Based on the calculation of the mixed model (see Table 3), where all treatment days were included, there was no significant change of BE during CRRT treatment with citrate anticoagulation (P = 0.248).

Fig. 3. BE in patients after liver transplantation from before until the seventh day of CRRT treatment (values are mean ± SD, n = 27–66). The BE value at Day 0 represents the value before the start of CRRT treatment and the other values were taken on the indicated consecutive days at 7 am in the morning. Based on the calculation of the mixed model (see Table 3), where all treatment days were included, there was no significant change of BE during CRRT treatment with citrate anticoagulation (P = 0.248).

Treatment duration and circuit lifetime
The median duration for CRRT with citrate anticoagulation was 8 days (range 1–39) with a total of 729 treatment days. Mean circuit lifetime was 22.7 ± 14.6 h. The circuit life was not different in septic and non-septic patients (non-septic: 23.3 ± 13.9 h versus septic patients: 22.4 ± 14.5 h, t-test, P = 0.470).

Transfusion required bleeding episodes
Bleeding occurred in 11.8% (8 of 68) of patients (exact 95% confidence interval 5.22–21.87%). Two of these eight

<table>
<thead>
<tr>
<th>Laboratory parameter</th>
<th>Base line</th>
<th>End of treatment</th>
<th>P-value for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>BUN (mg/dL)</td>
<td>60.6 ± 31.5</td>
<td>56.8 ± 29.8</td>
<td>0.488</td>
</tr>
<tr>
<td>*Creatinine (mg/dL)</td>
<td>2.35 ± 1.01</td>
<td>2.27 ± 1.17</td>
<td>0.002</td>
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<tr>
<td>Haematocrit (%)</td>
<td>28.8 ± 5.3</td>
<td>27.5 ± 4.4</td>
<td>0.149</td>
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<tr>
<td>*Platelets (n/L)</td>
<td>73 ± 60</td>
<td>71 ± 38</td>
<td>0.027</td>
</tr>
<tr>
<td>*aPTT (s)</td>
<td>53.9 ± 20.0</td>
<td>42.8 ± 23.9</td>
<td>0.002</td>
</tr>
<tr>
<td>INR</td>
<td>1.8 ± 0.8</td>
<td>1.4 ± 0.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>*AST (U/L)</td>
<td>2046 ± 3795</td>
<td>706 ± 1710</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>*ALT (U/L)</td>
<td>1220 ± 1693</td>
<td>660 ± 1107</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>*Albumin (g/dL)</td>
<td>2.11 ± 0.60</td>
<td>2.05 ± 0.49</td>
<td>0.008</td>
</tr>
<tr>
<td>*Total protein (g/dL)</td>
<td>42.5 ± 1.04</td>
<td>41.2 ± 0.74</td>
<td>0.009</td>
</tr>
<tr>
<td>*Total bilirubin (mg/dL)</td>
<td>8.7 ± 8.1</td>
<td>6.9 ± 5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>*Direct bilirubin (mg/dL)</td>
<td>6.4 ± 6.5</td>
<td>5.7 ± 4.9</td>
<td>0.015</td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>142 ± 6</td>
<td>142 ± 6</td>
<td>0.160</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>4.5 ± 0.8</td>
<td>4.5 ± 0.8</td>
<td>0.553</td>
</tr>
<tr>
<td>Ionized calcium (mmol/L)</td>
<td>1.08 ± 0.13</td>
<td>1.04 ± 0.13</td>
<td>0.696</td>
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<tr>
<td>Total calcium (mmol/L)</td>
<td>2.01 ± 0.31</td>
<td>2.21 ± 0.40</td>
<td>0.756</td>
</tr>
<tr>
<td>Ratio total/ionized calcium</td>
<td>1.87 ± 0.29</td>
<td>2.18 ± 0.87</td>
<td>0.563</td>
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<tr>
<td>Lactate (mmol/L)</td>
<td>3.67 ± 2.96</td>
<td>3.26 ± 4.23</td>
<td>0.971</td>
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<tr>
<td>Bicarbonate (mmol/L)</td>
<td>24.2 ± 5.35</td>
<td>26.9 ± 4.14</td>
<td>0.616</td>
</tr>
<tr>
<td>BE (mmol/L)</td>
<td>−0.89 ± 4.88</td>
<td>1.93 ± 4.62</td>
<td>0.248</td>
</tr>
<tr>
<td>pH</td>
<td>7.37 ± 0.08</td>
<td>7.41 ± 0.06</td>
<td>0.295</td>
</tr>
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</table>

*tValues are mean ± SD, *indicates significant time trend, P-value pertains to the time variable in a random coefficient mixed model for repeated measures. The parameters, creatinine, AST, ALT, total and direct bilirubin, aPTT, INR, total protein and albumin, show a significant decrease over time, whereas the parameter platelets increases significantly over time. ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Systemic and post-dialyser-ionized calcium values
Calcium gluconate 10% infusion rate during CRRT with citrate anticoagulation is shown in Figure 4. Calcium substitution was not required at all in 11 of 68 patients (16.2%). In the course of citrate anticoagulation, the variability of the systemic ionized calcium declined, keeping ionized calcium well controlled within the normal range (see Figure 5). The incidence of hypocalcaemia was 2.3% (95 of 4079 obtained calcium values were <0.8 mmol/L, exact 95% confidence interval 1.8–2.8%). All episodes of hypocalcaemia were asymptomatic and resolved after increasing calcium substitution. The incidence of hypercalcemia was 4.2% (34 of 810 obtained total calcium values were >2.75 mmol/L, exact 95% confidence interval 2.9–5.8%). No episode of hypercalcemia was symptomatic and no CRRT treatment had to be stopped because of hypercalcemia. The mean post-dialysis calcium at 4 h after initiation of citrate anticoagulation was 0.18 ± 0.06 mmol/L. The dose of citrate solution and the corresponding ratio of citrate dose per litre blood are depicted in Figure 6.
anticoagulation were reported for various patient cohorts [24]. The most life-threatening complication of citrate infusion is the induction of hypocalcaemia [25, 26], which may lead to weakness, myocardial dysfunction and death. To prevent hypocalcaemia and to achieve a stable calcium level, we deliberately used calcium in the dialysis solution. Protocols for regional citrate anticoagulation in CRRT proposed so far have used calcium-free dialysis solution, which considerably increases the risk of hypocalcaemia. Using our protocol, 16% of the patients did not require calcium replacement. The prevalence of hypocalcaemia in critically ill patients is reported to be up to 88% [26, 27], but consensus has never been achieved regarding the threshold for calcium replacement of ionized calcium level (recommended threshold in the literature ranges from 0.65 to 1.12 mmol/L) [27]. We used a concentration of 0.95 mmol/L for ionized calcium as the threshold for starting calcium replacement and defined significant hypocalcaemia as an ionized calcium concentration < 0.8 mmol/L. Most critically ill patients with an ionized calcium concentration > 0.8 mmol/L are asymptomatic. In a study with > 200 patients, no relationship between ionized calcium concentrations and haemodynamic variables were seen in patients with mild hypocalcaemia (ionized calcium > 0.8 mmol/L). These patients had normal cardiovascular function and responded normally to inotropes and vasoressor agents [26]. Significant hypocalcaemia (< 0.8 mmol/L) in our study was seen in 2.3% of the cases (95 of 4079) without symptoms of hypocalcaemia.

Hypercalcaemia has also been described as a complication during citrate infusion [14]. Meier-Kriesche et al. [14] and Morgera et al. [28] indicated in their studies that the incidence of hypercalcaemia was ~ 12% in all patients. In a subgroup cohort with severe liver failure hypercalcaemia occurred in 33% of the cases [8]. Hepatic failure, which impairs citrate metabolism, can lead to profound reductions in ionized calcium, whereas the total calcium concentration will increase [13]. The increase of total calcium is the result of the accumulation of calcium citrate complexes, caused by the impaired citrate metabolism. Therefore, hypercalcaemia in the context of reduced ionized calcium is an indication of citrate accumulation and mandates withdrawal of citrate infusion. In our study, citrate anticoagulation did not need to be stopped due to hypercalcaemia.

Citrate administration during CRRT may induce different acid–base derangements. First of all, citrate can induce metabolic alkalosis. Citrate is rapidly cleared by the citric acid cycle (tricarboxylic acid cycle), primarily in the liver. However, the citrate used for anticoagulation is mostly trisodium citrate, which has to be converted to citric acid before it can be metabolized in the citric acid cycle. The conversion of 1 mmol/L trisodium citrate to citric acid yields 3 mmol sodium bicarbonate according to the following reaction [9].

$$\text{Na}_3\text{citrate} + 3\text{H}_2\text{CO}_3 \rightarrow \text{citric acid} + 3\text{NaHCO}_3.$$  

Alkalosis indicates citrate metabolism by the liver. Morgera et al. [25] reported a 55% incidence of severe alkalosis (pH > 7.5) and Mehta et al. indicated an alkalosis rate of 23% (6 of 23 patients) in patients with citrate anticoagulation [29]. Our data also indicated a trend towards metabolic
alkalosis, which was not significant (Figure 2). There are different possibilities to treat metabolic alkalosis; first of all, alkalosis could be reversed by increased citrate removal during dialysis by increasing dialysis flow rate. Another possibility is the use of hydrochloric acid to reverse alkalosis, but this can lead to significant side effects and complications. Our approach is the use of variable concentrations of bicarbonate in the dialysis solution, so that the concentration of bicarbonate could be adjusted according to the acid–base status of the individual patient. Based on this protocol, neither a treatment with hydrochloric acid was required nor had citrate infusion to be stopped due to uncontrolled metabolic alkalosis. Therefore, our approach of individual bicarbonate concentrations in the dialysis solution ensured a stable acid–base balance. On the other hand, citrate infusion can also lead to significant uncontrolled acidosis. Citrate used for anticoagulation contains a small but significant amount of citric acid, which would lead to rapid metabolic acidosis, if citrate is not metabolized. Patients with liver insufficiency are at major risk of developing acidosis during citrate infusion [9]. This is the main reason why citrate anticoagulation is regarded as problematic in liver transplant patients. In our study, no patient experienced uncontrolled acidosis. However, the potential risk of citrate accumulation and uncontrolled acidosis in patients after liver transplantation, particularly with poor graft function, demands tight control of acid-base status.

The mean circuit lifetime in our study was 23 h, which is comparable to data of Palsson and Niles [17]. They described 17 patients with regional citrate anticoagulation during continuous veno-venous haemofiltration (CVVH). The mean circuit lifetime in their study was 26 h. Mehta et al. [23] indicated a mean circuit lifetime of 48 h for continuous arteriovenous haemofiltration and Oudemans-van Straaten [30] reported a mean circuit lifetime of 27 h during CVVH with citrate anticoagulation. Another study showed a mean circuit lifetime of 37 h in 87 patients using CVVH [31]. Several factors may contribute to these variable circuit survival: different treatment modes (filtration versus dialysis), variations in the venous access and in the size of catheters used, differences in blood flow and different patient cohorts [32]. We used 13.5 F Shaldon catheters, whereas Mehta et al. [23] and Palsson and Niles [17] used 14 F catheters. The slightly lower circuit survival in our study could be related to the lower diameter of our catheter. The main venous access in our study was internal jugular and subclavian vein. Baldwin and Bellomo [33] reported on superior blood flows, if the femoral venous access was chosen, in contrast to internal jugular or subclavian approach. The use of only jugular and subclavian venous approach in our study may have contributed to the shorter circuit survival as compared with other studies. Morgera et al. [28] reported a circuit half-life of up to 80 h in his study. The lower circuit half-life in the above mentioned and our studies compared to Morgera may be attributed to the different severity of illness of the studied patients. This is supported by a recent study by Mariano et al. [34], who showed a circuit half-life with citrate anticoagulation of septic shock burn patients of 28.5 h. Critically ill patients typically have cytokine-mediated activation of the coagulation cascade due to both increased tissue factor release and also endothelial injury, with local inhibition of fibrinolysis, resulting in a procoagulant state. Thus, although these patients may have laboratory tests of disseminated intravascular coagulation, CRRT circuits often clot prematurely [35]. Especially in patients with both acute and chronic liver disease, coagulopathy is a cardinal manifestation. Coagulopathy in liver disease is characterized by thrombocytopenia with impaired platelet function, defective synthesis of both procoagulant and anticoagulant factors, fibrinolysis and disseminated intravascular coagulation [36]. This results in a variable clinical picture of active bleeding and increased risk of thrombus formation. In the context of impaired coagulation profile in patients with liver disease, reduced anticoagulation requirement during CRRT would be expected. However, Agarwell et al. [37] indicated that quite the opposite is true, showing that circuit life in patients after liver transplantation is severely limited. Moreover, the correction of impaired coagulation with coagulation factors like fibrinogen, prothrombin concentration complex and platelets transfusion may further contribute to a lower circuit half-life. In contrast to the other mentioned studies, our cohort consists exclusively of patients with liver disease after transplantation, which may explain the shorter circuit half-life.

In our study, bleeding episodes occurred in 8 of 68 patients (11.8%). Some authors indicated lower bleeding episodes with citrate anticoagulation. Oudemans-van Straaten [30] reported about bleeding events of only 6% in their patients (6 of 97 patients), which were anticoagulated with citrate. Kutsogiannis et al. [38] demonstrated in CRRT with citrate 0% bleeding episodes (0 of 14 patients). However, in contrast to both studies, the present study evaluates patients in the early post-operative phase after liver transplantation, which might have a higher risk for bleeding. The authors wish to stress that all bleeding episodes correlated with impaired coagulation. Several studies with heparin anticoagulation described bleeding episodes with up to 19% [38, 39]. These studies evaluated ICU patients with lower risk for bleeding. Compared with these data, bleeding events in our study seem to be low.

In conclusion, the data show that our protocol for citrate anticoagulation with the use of a dialysis solution containing calcium and variable concentrations of bicarbonate is safe and effective in the early post-operative period after liver transplantation. The general exclusion of citrate anticoagulation in patients during the early post-operative phase after liver transplantation does not seem to be justified.

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References

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