

## COMMENTARY

# Regional citrate anticoagulation in patients with liver failure - time for a rethink?

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See related research by Schultheiss et al., <http://ccforum.com/content/16/4/R162>

### Abstract

Regional citrate anticoagulation (RCA) for continuous renal replacement therapy (CRRT) has become increasingly attractive in recent years due to its favourable low bleeding risk profile. Its use in liver failure, however, has been limited due to the risk of citrate accumulation and toxicity. In the previous issue of *Critical Care*, Schultheiss and colleagues look at CRRT using RCA in liver failure patients. They demonstrate that citrate accumulation can be predicted using the total calcium ( $Ca_{tot}$ ) to ionised calcium ( $Ca_{ion}$ ) ratio ( $Ca_{tot}/Ca_{ion}$ ), and determine that despite the occurrence of significant citrate accumulation, the effects of citrate accumulation are not as severe as might have been expected. This study raises interesting prospects with regard to RCA use in liver failure, and we postulate that citrate may have a role as a prognostic marker of metabolic capacity much as in the way of lactate and methacetin. However, further studies are warranted, in particular examining its application in subgroups of liver failure (chronic, acute, hyperacute and subacute), before its use becomes commonplace.

Continuous renal replacement therapy (CRRT) frequently requires anticoagulation to prevent clotting of the extracorporeal circuits. In recent years regional citrate anticoagulation (RCA) has become a favourable alternative to heparin in patients at risk from excessive bleeding. Its use in liver failure patients, however, has been minimal due to the perceived risk of citrate accumulation and toxicity. In the previous issue of *Critical Care*, Schultheiss and colleagues [1] look at CRRT using RCA in liver failure patients, to determine whether citrate accumulation can

be predicted using the total calcium ( $Ca_{tot}$ ) to ionised calcium ( $Ca_{ion}$ ) ratio ( $Ca_{tot}/Ca_{ion}$ ), and whether RCA is feasible in such patients. They demonstrate that, as expected, significant citrate accumulation does occur, that it can be predicted using the  $Ca_{tot}/Ca_{ion}$  ratio, but more interestingly that the effects of citrate accumulation are not as severe as might have been expected. They, therefore, conclude that CRRT in such patients is possible, an altogether interesting prospect in the management of liver patients.

Traditional concerns regarding RCA in liver failure have focused on the perceived risk of citrate toxicity. Reduced metabolism and subsequent systemic accumulation lead to potentially significant metabolic derangements, with patients frequently exhibiting either metabolic alkalosis or acidosis [2], hypocalcaemia and other electrolyte disturbances, and notably a raised  $Ca_{tot}/Ca_{ion}$  ratio [3].

These concerns have recently been somewhat tempered by several studies involving use of RCA during extracorporeal liver support using the molecular adsorbent recirculation system. Faybik and colleagues [4] found that RCA was well tolerated despite raised  $Ca_{tot}/Ca_{ion}$  ratios, and that there were no adverse effects secondary to electrolyte disturbances, notably hypocalcaemia. They suggest that citrate anticoagulation is possible and that the perceived benefits of fewer bleeding complications and longer filter circuit lifespans were realised. Meijers and colleagues [5] performed an open labelled crossover study - RCA versus anticoagulation-free liver dialysis using the molecular adsorbent recirculation system - and similarly demonstrated that use of citrate in such patients is safe and feasible, with no significant adverse outcomes. Neither study demonstrated significant metabolic or electrolyte disturbances, largely as a result of clearly defined and applied treatment protocols, reflecting learning from general critically ill patients [6].

Of interest, the recent study by Link and colleagues [7] determined that the  $Ca_{tot}/Ca_{ion}$  ratio was an independent predictor of 28 day mortality. Patients who had a ratio >2.4 had higher mortality rates, 33.5 times greater than those with a ratio <2.4. It might be that this reflects

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limited metabolic capacity in the liver and as such is a marker of degree of hepatocyte injury. One of the difficulties in studying patients with liver failure is the breadth of disease this generic term covers. Patients with decompensated chronic liver disease are highly likely to have the metabolic capacity to cope with citrate anticoagulation whilst those with hyperacute liver failure may not. Various measures of metabolic capacity have the potential to be highly sensitive and specific clinical prognostic markers. Lactate [8], methacetin [9] and lignocaine [10] have all previously been shown to be useful, and citrate has such potential also. It would, however, need any clinician considering the use of citrate in patients with liver metabolic failure to be cognisant of the complications and identify such patients as carrying significant mortality. In some, the use of citrate may be contraindicated, but the potential to introduce citrate metabolism into prognostic models may prove a further development [11]. Interestingly, such groups are not at particular risk of bleeding, having balanced disturbances in coagulation [12]. This is of concern to clinicians, as one would expect those patients in fulminant liver failure to potentially fall into this category, contraindicating the use of citrate anticoagulation.

Schultheiss and colleagues looked at potential predictors of citrate accumulation in an attempt to identify those patients who might develop a  $Ca_{tot}/Ca_{ion}$  ratio  $>2.5$  [1]. They found that baseline liver function tests did not have any predictive capabilities, but that a baseline serum lactate level  $\geq 3.4$  mmol/L and a prothrombin time  $\leq 26\%$  were useful markers. However, such findings may lead to inappropriate preclusion of citrate use, especially as several factors other than liver failure can lead to raised lactate levels, particularly low cardiac output states secondary to hypovolaemia or circulatory failure, findings commonly encountered in intensive care patients; therefore, one should temper these findings by stating that only baseline levels after appropriate fluid resuscitation has occurred should potentially be used as a guide when considering the use of RCA.

This study raises interesting prospects with regard to RCA use in liver failure. However, it did not look at mortality, and based on the findings of Link and colleagues [7], future investigations should certainly do so. In addition, none of these studies have looked at the effects of ultra-high continuous venovenous haemofiltration, frequently employed in the management of fulminant liver failure patients with septic shock to reduce vasopressor requirements, and for hyperammonaemia and associated raised intracranial pressure [13]. Despite this, recent studies have served to somewhat dispel the notions that RCA is contraindicated in liver

failure patients, but further studies are warranted before its use becomes commonplace.

#### Abbreviations

CRRT, continuous renal replacement therapy; RCA, regional citrate anticoagulation.

#### Competing interests

The authors declare that they have no competing interests.

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