Optimizing continuous renal replacement therapy in the ICU

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Chapter 7

How do I use citrate-based CVVH in predilution?

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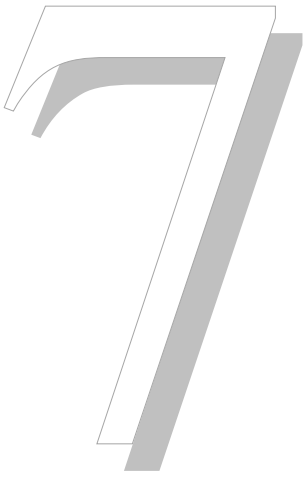

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Abstract

The necessity of anticoagulating the extracorporal circuit (ECC) when applying continuous venovenous hemofiltration (CVVH) in critically ill patients, implicates an increased risk for bleeding complications, when using unfractionated heparin or low molecular weight heparins, especially in patients at high risk for bleeding. Regional anticoagulation of the ECC using citrate-based solutions has emerged as the most suitable method to avoid this increased risk for bleeding. There are several protocols described in the literature how to apply this method. The most frequently used method, including in The Netherlands, makes use of a hypertonic trisodiumcitrate solution, infused prior to the hemofilter, combined with a postdilution replacement fluid. In this article we focus on an alternative method for citrate-based CVVH, using a citrate-containing predilution replacement fluid, combined with calcium-supplementation separated from the ECC. Potential advantages and limitations of this method are discussed.

Introduction

Continuous venovenous hemofiltration (CVVH) is the most frequently used modality of renal replacement therapy (RRT) for intensive care patients in the Netherlands.[1] The advantages of this modality compared to conventional intermittent hemodialysis (IHD) appear logical. The high level of metabolic control in terms of Kt/V_{urea}, the flexibility in manipulating fluid balance, and the continuous nature of the technique of CVVH are intuitively desirable features. It is important to keep in mind that up to date no controlled trial of this technique has proven its superiority over IHD in terms of patient outcome.[2-7] However, probably due to multifactorial threats to ICU patients in general,[8] one might argue that it is not realistic to expect evident improved survival from a change in RRT-modality. Even more important, comparative studies between these modalities excluded patients with hemodynamic instability, because of the widespread experience that in these patients the continuous techniques are tolerated better than conventional hemodialysis. For that reason, authorities in the field propagate the continuous technique,[9] partly based on the abovementioned arguments. Indeed, most clinicians, at least in Europe, feel more comfortable with the continuous and "smooth" technique administered by CVVH as compared to intermittent hemodialysis in critically ill patients.

When applying CVVH, one faces the need of anticoagulating the extracorporal circuit (ECC) for extended periods of time. Heparin, either unfractionated or low molecular weight heparin (LMWH), is associated with an increased risk for bleeding and the development of heparin induced thrombocytopenia and thrombosis (HITT).[10] Regional anticoagulation using citrate has been proposed as an alternative to overcome these problems, since both systemic anticoagulation is avoided and the development of HITT is prevented. The aim of the present paper is to describe our citrate-based CVVH protocol, since it differs in several fundamental aspects, as compared to the majority of published protocols, as will be pointed out. We intend to highlight an alternative way for citrate-based CVVH. The issue of all possible anticoagulation strategies in CRRT was recently reviewed,[11] and is beyond the scope of the present paper.

The principle of citrate-based anticoagulation in CVVH

Depending on the protocol used, a variable concentration of trisodiumcitrate is dissolved in a solution (saline, water or dextrose). Due to its high dissociation constant, nearly all TSC will be dissociated from the accompanying sodium. As the solution enters the

bloodstream, upstream from the hemofilter, the trivalent citrate meets ionized bivalent calcium (iCa) and magnesium and due to the lower dissociation constant of calciumcitrate, a substantial portion of calcium will be bound. This will lower free calcium levels, down to a level where it interrupts several steps in the coagulation cascade. Calcium has an essential role in activation of several coagulation factors (II,V,VII,VIII,IX,X and XIII) and the conversion of fibrinogen to fibrin. So, TSC is an anticoagulant by virtue of its ability to chelate calcium. Upon entering the hemofilter, roughly one third to one fourth of it (depending on hematocrit and ultrafiltration fraction) will be cleared by convection as either calciumcitrate complex or as free citrate. The remainder will enter the systemic circulation. Here, the citrate will be metabolized, mostly by the liver and skeletal muscle. The metabolism of citrate, either gluconeogenesis or its utilisation as an intermediate in the tricarboxylic (Krebs) cycle, consumes $^{H+}$, and as such has an alkalemic effect. This is explained by the following formula:

$$3\ Na^+ + \ citrate^{3-} + H_2CO_3 \leftrightarrow \text{citric acid} + 3\ Na^+ + 3\ HCO_3^-$$

The disappearance of citric acid by metabolism shifts this reaction to the right, thereby generating bicarbonate. Although the exact metabolic fate of citrate is unknown a part may require ATP.[12] The metabolism of calcium-citrate complex liberates the bound calcium from the complex, thereby in part attenuating the tendency to a low iCa. The calcium lost with the ultrafiltrate, either as free calcium or complexed with citrate, has to be replenished.

Citrate-based protocols

There is a substantial number of citrate-based protocols described in the literature,[13-28] and the potential variations on these protocols are numerous. This issue has been reviewed in the Netherlands Journal of Critical Care recently.[13] There are differences in modality, like CAVH,[14] CVVHDF,[15-22] CVVHD,[23] and CVVH.[24-26,28] They differ in citrate-concentration (varying from 0,4% [15,20] to 30% [25] for TSC), the solution in which the citrate is dissolved (usually TSC of varying tonicity in water, or anticoagulant dextrose A [ACD-A]), the way the calcium loss is supplemented (calciumchloride infusion via the ECC,[2,15,17,20,24] via a separate central line [16,18,19] or calcium as a component of the dialysate solution [21,22]), pre- or postdilution modality, not to speak of different protocols for metabolic monitoring. A more fundamental difference is that in the minority of protocols,[15,19,24] citrate is dissolved in the replacement fluid itself, while in the majority of published protocols [13,14,16-18,20-23,25-28] citrate comes in a separate solution.

Only two of these studies were designed as prospective randomized controlled trials showing superiority of their citrate protocol, compared to unfractionated heparin in terms of filter survival or bleeding tendency.[19,25] The other cited studies were designed as prospective observational cohorts (vide supra). These studies report low or absent bleeding complications while the ECC was being anticoagulated with some citrate formula and filter life span ranged from 25 hours [23] up to 124 hours.[19] It is not surprising that the study showing the lower filter survival,[23] supplemented calcium via the dialysate solution, thereby attenuating the anticoagulant effect of citrate in the ECC. One controlled study showed inferior filter survival for TSC compared to heparin.[15] However, this study was not randomized, had a vague crossover design, and was highly biased by confounding by indication. Other observational data also failed to demonstrate superior filter survival for regional citrate anticoagulation compared to heparin,[29,30] but due to the non-randomized design, baseline characteristics of the two treatment groups differed might have differed, influencing outcome (selection bias). The question whether or not regional citrate anticoagulation improves filter survival, or even patient outcome, when compared to heparin is not definitely settled in unselected critically ill patients. This question is the primary end point of our current randomized controlled multicentre trial (www.clinicaltrial.gov; NCT 00209378). The advantages of citrate-based CVVH are more evident in patients with manifest bleeding or at high risk for bleeding. For this reason The Nederlandse Vereniging voor Intensive Care (NVIC) has published a guideline when to use citrate anticoagulation, namely in case of active bleeding or high-risk for bleeding, or in the presence of HITT.[13] The latter indications (HITT) may be challenged in the near future by synthetic pentasaccharides.[31]

How do I use citrate-based CVVH in predilution?

Our citrate-based CVVH protocol, schematically depicted in figure 1, is a modification of the scheme by Palsson and Niles.[24] It is obligate that citrate is administered prefilter. In our protocol, citrate is an integral component of the replacement fluid, and therefore, we exclusively perform predilution CVVH, when using citrate-CVVH. The composition of this replacement fluid is commercially prepared (Dirinco®, Rosmalen, The Netherlands) and is shown in table 1. The replacement fluid does not contain bicarbonate or lactate, because citrate, apart from being an anticoagulant, is an alkaline when dissolves as trisodiumcitrate. Obviously, the solution also lacks calcium, since it would complex with citrate and abrogate its anticoagulant properties. The amounts of sodiumchloride,

potassiumchloride and glucose are chosen in order to yield an isotonic solution. The infusion rate of the predilution replacement fluid (Quf) is coupled to blood flow rate (Qb) according to an algorithm as shown in table 2. Replenishment of lost calcium is performed by infusing calciumglubionate (Calcium Sandoz ®, Novartis), via a separate venous line, either peripheral or central. Calciumglubionate instead of calciumchloride is used because in can be administered peripherally and does not contain chloride. It is not administered in the downstream portion of the ECC, in order to prevent coagulation in the venous line. Metabolic monitoring comprises of determination of blood gas analysis, electrolytes including chloride and magnesium, total and iCa levels and the calculations of aniongap, and calcium-ratio. The calcium ratio is defined by [total Ca]/[iCa]. This ratio should not exceed 2.5. These laboratory tests are performed prior to the start of treatment, one hour after its start and at least every 6 hours thereafter. After an initial infusion rate of calciumglubionate, dictated by an algorithm, coupled to Quf, its infusion rate is adapted to the results of iCa, aiming at 1.0-1.1 mmol/l. When signs of citrate accumulation occur (a rise of calcium ratio above 2.5, the development of an otherwise unexplained high-aniongap acidosis) citrate-CVVH is stopped and predilution CVVH using bicarbonate-based replacement fluid without anticoagulation is started, unless contra-indications for systemic anticoagulation does not exist anymore. The iCa concentration in the ECC is not routinely determined since efficacy without making adaptations the iCa in the ECC has been shown,[24] it adds to simplicity, and prevents unnecessary adaptations of the coupling of Qb to flow rate of replacement fluid (Qrf).

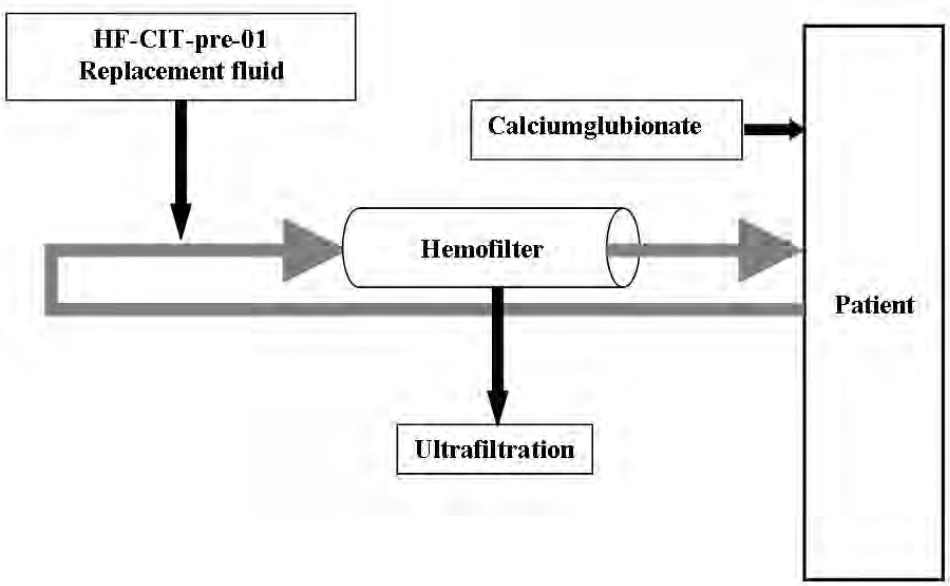

Fig. 1. Schematic representation of predilution citrate-CVVH

Table 1. Formulation of HF-CIT-pre01.

Sodium	140	mmol/l	
Potassium	3	mmol/l	
Citrate	13.3	mmol/l	39.9 mEq/l
Chloride	104	mmol/l	
Magnesium	0.5	mmol/l	1.0 mEq/l
Glucose	5	mmol/l	

Table 2. Algorithm for blood flow, substitution flow and calcium-supplementation;
For calcium infusion, calciumglubionate (0.225 mmol/ml) is used.

Blood flow (ml/min)	Substitution flow (ml/h)	Calcium-infusion (ml/h)
140	1900	9.5
160	2100	10.5
180	2400	12
200	2700	13.5

Metabolic implications of citrate as an anticoagulant

As was pointed out in the previous section the aim citrate-infusion is to accomplish a regional anticoagulated ECC, without a chance of the development of HITT. However, these advantages are partly annulled by increased complexity, which is caused by the fact that regional anticoagulation with trisodiumcitrate (TSC) simultaneously influences at least 5 different metabolic phenomena:

1. Ionized calcium level in the ECC is lowered, which is the virtue of TSC as a local anticoagulant
2. Systemic iCa levels may also be lowered, as an unintended event
3. Acid-base balance, since dissolved TSC has an affinity for protons
4. Sodium-balance, since three moles of sodium are the cationic counterpart for one mole trivalent citrate
5. Magnesium homeostasis, since there will also be binding of magnesium to citrate.

This means that when titrating TSC administration on one of these parameters, homeostasis in the other four will inevitably be influenced. Therefore, it is mandatory to be aware of the fact that the risks of bleeding and HITT, associated with heparin use, are substituted for the complex and potentially dangerous [32] metabolic derangements, associated with the use of TSC. Another feature of using citrate-based regional anticoagulant for RRT is the fact that thrombosis prophylaxis is not supplied, different from the situation when unfractionated heparin, LMWH or fondaparinux is used.

Impact on calcium balance. Due to its intended effect on iCa level in the ECC, one has to anticipate that on occasions dysregulation of systemic calcium homeostasis might occur.[33-35] The infusion rate of citrate in all protocols, including ours, averages 30-35 mmol citrate/hour (roughly 100 mEq/hour). With a bloodflow rate in the ECC of 200 ml/min, this amount of citrate mixes with approximately 19 mmol/hour total calcium (38 mEq/hour). It follows that a substantial portion of infused citrate will remain unbound to calcium when it enters the systemic circulation. When it is not metabolized quickly, as was pointed out, calcium chelating will continue and the iCa will decrease, making an increment in the dose of calcium supplementation necessary. By its very nature, possible derangements of calcium homeostasis are inherent to every citrate-based protocol, and should be checked at a regular basis.

Impact on acid-base balance. It is helpful to make distinction between metabolic derangements that are due to insufficient metabolism of citrate on the one hand, and derangement caused by the citrate-containing solution itself, in the absence of diminished metabolism of citrate, on the other. The former is a consequence of organ dysfunction, usually the liver, the latter is iatrogenic.

When considering the potential impact of the citrate-solution itself on acid-base balance it is important to realize the differences in citrate-concentrations of these solutions, ranging from 500 mmol/l [28] to 13,3 mmol/l.[24,36] When using a more concentrated citrate-formula this has to be corrected by selecting an appropriate replacement fluid in postdilution setting, containing no or low buffer [13,28] to prevent development of metabolic alkalosis.[37] Accidental bolus-infusion of hypertonic citrate-solution will inevitably lead to severe metabolic alkalosis.[32,38]

As was pointed out, metabolic acidosis will occur whenever citrate metabolism retards. The bicarbonate loss with the ultrafiltrate is not replenished from citrate metabolism. A high-aniongap metabolic acidosis, with citrate itself as the added anion, will develop. Especially in patients with liver failure this requires attention,[39] although the technique might be feasible.[33,34]

Impact on sodium balance. Severe derangements in sodium levels are infrequently reported in patients using trisodium citrate. When using 15% TSC with a sodium concentration of 1500 mmol/l, this complication is prevented because the hypertonic TSC mixes with a larger volume of isotonic blood, and by using a slightly hypotonic replacement fluid or dialysate in postdilution setting.[13,28] Whether these fluctuations in tonicity in the ECC are of importance

for biocompatibility is unknown. Also, when using isotonic citrate-containing replacement fluid as in the currently described protocol, derangements in sodium concentrations and tonicity are not to be expected from a theoretical point of view, and indeed have not been described.[15,20,24]

Limitations of the method applying citrate as component of replacement fluid

Since citrate infusion rate is coupled to Qb, CVVH dose is dependent on Qb. The predilution method might negatively impact CVVH-dose,[40] although others did not found this impact of predilution.[41] Since Qb frequently is limited due to catheter performance, it might be difficult to obtain higher CVVH-doses. In our protocol an average patient of 70 kg with a bloodpump flow of 180 ml/min and a hematocrit of 0.28 will receive a theoretical dose of 26 ml/kg/hour, after correction for the predilution effect of plasma-water. Although this is substantially higher than the lower dose (20 ml/kg/h) in the Lancet-trial by Ronco [42] it is below the dose associated with improved patient outcome (35 ml/kg/h). Higher dose can be achieved by increasing blood flow, or by the addition of a postdilution replacement fluid, but the latter implies a concession to simplicity. However, the issue of dose is not settled,[43-48] and two large multi-centre trial are currently recruiting patients, addressing the question.[48]

As was pointed out in the previous section, the separation of (concentrated) citrate and the postdilution replacement fluid implies that these fluids have to be balanced in terms of buffer and sodium content. This is not necessary when citrate is a component of the replacement fluid itself, due to its composition. However, this limits the ability to correct severe acidemia quickly, and extreme metabolic acidosis has to be corrected be using sodiumbicarbonate apart from the CVVH.[49] When using concentrated citrate, one can use postdilution replacement fluids of differing composition, including higher buffer content.

As with all protocols using citrate as an anticoagulant, the system can only be used safe when stringently adhering to the protocol. Not connecting the calcium supplementation will inevitably lead to hypocalcemia and loosely performing metabolic monitoring might jeopardize our patients. Like many other interventions applied in intensive care medicine, citrate-based CVVH is no different, but its ease of use and potentially improved filter survival might induce nonchalance.

A final potential limitation of the technique described is the fact that iCa concentration is not measured routinely, for reasons as describes above. This may impact filter survival

when insufficient amounts of calcium are chelated in the ECC. This of course can be done in case of repeated unexpected filter clotting, and modifications on the Qb to Qrf can be made.

Conclusion

Citrate-based anticoagulant regimes for CRRT overcome the major drawback of systemic anticoagulation by, for instance, unfractionated heparin or LMWH, namely the increased bleeding tendency. There is sufficient evidence to support the use of regional anticoagulation in critically ill patients at high risk for bleeding or with manifest bleeding, as acknowledges by the recently published guidelines of the NVIC. Potential advantages for using citrate in all patients include cost savings due to extended filter survival [36] or improved biocompatibility.[50] However, up to date there are no conclusive data to advocate the use of citrate-based CVVH in all patients, and this question is addressed in a currently recruiting multicentre randomized trial. The advantage of a citrate-based regime in patients at risk for bleeding, comes with increased complexity and potentially severe metabolic derangements. There are no studies comparing the different citrate-based protocols for CRRT, and there is no evidence showing the superiority of one protocol over another. The most safe anticoagulation regime is the one with which the clinician is most familiair. When deciding which protocol to adopt, several arguments as has been described can be weighed. The citrate-based protocol described in this paper uses an isotonic predilution replacement fluid of which citrate is an integral component. This regime appears to be safe and feasible. It might be considered more simple to use, since TSC and replacement fluid are combined in one solution, when compared with a protocol using citrate and replacement fluid seperately. Both systems require separate calcium supplementation. The potentially improved simplicity comes with the drawback of decreased flexibility of metabolic manipulations, especially in acid-base balance, and dependency on Qb for higher dose of CVVH since it is an obligate predilution technique

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