How do I use citrate-based CVVH in predilution?

M.G. Vervloet, S.A. Nurmohamed

Introduction

Continuous venovenous haemofiltration (CVVH) is the most frequently used modality in renal replacement therapy (RRT) for intensive care patients in the Netherlands [1]. The advantages of this modality compared to conventional intermittent haemodialysis (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 to date, no controlled trial has proven the superiority of this technique over IHD in terms of patient outcome [2, 3, 4, 5, 6, 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 importantly, comparative studies between these modalities excluded patients with haemodynamic instability, because of widespread experience in these patients that continuous techniques are tolerated better than conventional haemodialysis. For this reason, authorities in the field propagate the continuous technique [9], partly based on the above-mentioned arguments. Indeed, most clinicians, at least in Europe, feel more comfortable with the continuous and "smooth" technique administered by CVVH as compared to intermittent haemodialysis in critically ill patients.

When applying CVVH, the extracorporeal circuit (ECC) needs to be anticoagulated for extended periods of time. Heparin, either unfractionated or low molecular weight heparin (LMWH), is associated with an increased risk of 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, as it both avoids systemic anticoagulation and prevents the development of HITT. The aim of this paper is to describe our citrate-based CVVH protocol, since it differs in several fundamental aspects to the majority of published protocols. We intend to highlight an alternative way for citrate-based CVVH. The issue of all possible anticoagulation strategies in CRRT was recently reviewed [11], but is beyond the scope of this paper.

The principle of citrate-based anticoagulation in CVVH

Depending on the protocol used, a variable concentration of trisodium citrate (TSC) 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 haemofilter, the trivalent citrate meets ionized bivalent calcium (iCa) and magnesium and due to the lower dissociation constant of calcium citrate, a substantial portion of calcium will be bound. This will lower free calcium levels to a level where several steps in the coagulation cascade are interrupted. Calcium has an essential role in the activation of several coagulation factors (II, VII, VIII, IX, X and XIII) and the conversion of fibrinogen to fibrin. This means TSC is an anticoagulant by virtue of its ability to chelate calcium. Upon entering the haemofilter, roughly one-third to one-quarter of it (depending on haematocrit and ultrafiltration fraction) will be cleared by convection as either calcium citrate 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 utilization as an intermediate in the tricarboxylic (Krebs) cycle, consumes H⁺, and as such has an alkalaeamic effect. This is explained by the following formula: 3 Na⁺ + citrate³⁻ + H₂CO₃ ↔ citric acid + 3 Na⁺ + 3 HCO₃⁻.

The metabolic removal 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.

Abstract. The necessity of anticoagulating the extracorporeal circuit (ECC) when applying continuous venovenous haemofiltration (CVVH) in critically ill patients, implicates an increased risk of bleeding complications when using unfractionated heparin or low molecular weight heparins, especially in patients at high risk of bleeding. Regional anticoagulation of the ECC using citrate-based solutions has emerged as the most suitable method to avoid this increased risk of bleeding. There are several protocols described in the literature on how to apply this method. The most frequently used method, also in the Netherlands, makes use of a hypertonic trisodium citrate solution, infused prior to the haemofilter, 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 given separately from the ECC. Potential advantages and limitations of this method are discussed.
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 obligatory that citrate be 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®, Kosmalen, 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 dissolved as trisodium citrate. Obviously, the solution also lacks calcium, since it would complex with citrate and abrogate its anticoagulant properties. The amounts of sodium chloride, potassium chloride 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 shown in Table 2. Replenishment of lost calcium is performed by infusing calcium gluconate (Calcium Sandoz ®, Novartis) via a separate venous line, either peripherally or centrally. Calcium gluconate is used instead of calcium chloride because it 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 determination of blood gas analysis and electrolytes including chloride and magnesium, total and iCa levels and the calculations of anion gap, 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 calcium gluconate, 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 other-
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 unintentionally.
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 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, unlike the situation where 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, 34, 35]. The infusion rate of citrate in all protocols, including ours, averages 30-35 mmol citrate/hour (roughly 100 mEq/hour). With an ECC blood flow rate 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. If it is not metabolized quickly, 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 a distinction between metabolic derangements due to insufficient metabolism of citrate, and derangement caused by the citrate-containing solution itself in the absence of diminished metabolism of citrate. 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 containing no or low buffer [13,28] in the postdilution setting, 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-anion gap metabolic acidosis, with citrate itself as the added anion, will develop. This requires particular attention in patients with liver failure [39], since these patients are at high risk for insufficient citrate metabolism, 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 the 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 this 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 find this impact of predilution [41]. Since Qb frequency 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 blood flow of 180 ml/min and a haematocrit of 0.28 will receive a theoretical dose of 28 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 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 trials are currently recruiting patients [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 by using sodium bicarbonate 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 safely when stringently adhering to the protocol. Not giving calcium supplementation will inevitably lead to hypocalcaemia and loosely performed metabolic monitoring might jeopardize our patients. However, the ease of use of citrate based CVVH and its potentially improved filter survival might induce noncompliance.

A final potential limitation of the technique described is the fact that iCa concentration is not measured routinely, for reasons described above. This may impact filter survival if 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 namely the increased bleeding tendency, caused by for instance heparin or LMWH. 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 acknowledged by the recently published guidelines of the NVIC. The potential advantages of using citrate in all patients include cost savings due to extended filter survival [36] and improved biocompatibility [50]. However, to date there are no conclusive data to advocate the use of citrate-based CVVH in all patients. This question is being 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 familiar. When deciding which protocol to adopt, several arguments 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 simpler to use when TSC and replacement fluid are combined in one solution, compared with a protocol using citrate and replacement fluid separately. Both systems require separate calcium supplementation. The potential 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.

**Disclosure**

Research support has been provided by Dirinco® b.v., Rosmalen, The Netherlands to both authors.

**References**


30 Sproonke PE, Steenbergen H, ten Kleij M, Rommes JH. 2006. Regional citrate anticoagulation does not prolong filter survival during CVVH. J Crit Care. 21:239-244


48 Bellomo R. 2006. Do we know the optimal dose for renal replacement therapy in the intensive care unit? Kidney Int. 70:1202-1204
