Survival benefit with regional anticoagulation with citrate in CRRT: the end of a myth?

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Efficient anticoagulation of the extracorporeal blood is a precondition for any renal replacement therapy. Heparin is the most frequently used anticoagulant in this regard. However, heparin is associated with a number of serious risks including life-threatening haemorrhages and the induction of a heparin-induced thrombocytopenia (HIT). In recent years, great efforts have been made towards the development of alternative anticoagulation strategies. Regional anticoagulation with citrate has been shown to be a valuable and efficient option. Its anticoagulatory effect is exclusively restricted to the extracorporeal circuit without any systemic bleeding risk, and it can be safely applied in HIT type II. This makes citrate an excellent anticoagulant for continuous renal replacement therapy (CRRT) devices in an intensive care unit.

Regional anticoagulation with citrate was proposed in 1983 for haemodialysis of patients with acute renal failure but was not widely accepted due to the occurrence of severe side effects including alkalosis [1], hypernatraemia and severe hypocalcaemia. A better understanding of the metabolic effects of citrate as well as technical progress in the bedside monitoring of the acid–base status and the systemic ionized calcium has helped to better control and overcome these threats. The development of metabolic alkalosis during citrate anticoagulation results from the metabolic conversion of citrate to bicarbonate. It usually occurs when CRRT replacement fluids with high buffer content are used. In these circumstances, citrate provides additional buffer equivalents on top of the bicarbonate or lactate buffer provided by the CRRT replacement fluid thus leading to metabolic alkalosis. Hypernatraemia is also an iatrogenic complication. Citrate is usually applied in the form of tri-sodium citrate which as a consequence can lead to an unphysiological high sodium load. Many citrate anticoagulation protocols therefore apply renal replacement fluids with a reduced sodium and buffer content to avoid the occurrence of hypernatraemia and metabolic alkalosis [2–5]. However, the most threatening side effect of citrate still remains the induction of hypocalcaemia. During citrate anticoagulation, calcium-free renal replacement fluids are commonly used in order to avoid a clotting of the haemofilter due to the calcium ions from the renal replacement fluids (either by calcium backfiltration during dialysate or calcium infusion during dialysis or haemofiltration). If the systemic ionized calcium is not adequately monitored and substituted, a negative calcium balance occurs which inevitably results in systemic hypocalcaemia, a phenomenon that often occurred in the early years of citrate anticoagulation when a bedside monitoring of the systemic ionized calcium was technically not available. The widespread

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availability of bedside monitoring devices for ionized calcium has significantly improved the safety and feasibility of regional citrate anticoagulation.

In CRRT, regional anticoagulation with citrate was first introduced by Mehta and Ward [2] in the early 1990s. Since then, numerous protocols for the use of regional anticoagulation with citrate have been introduced into clinical routine. Based on the preferences of the clinicians in charge, protocols for CVVH, CVVHDF or CVVHDF were developed [3–6]. Today, it is well accepted that citrate significantly improves filter lifetime and reduces the risk of bleeding complications [7,8]. For effective anticoagulation of the extracorporeal circuit, a citrate-blood concentration of ~4 mmol/L within the extracorporeal circuit is necessary correlating to ionized calcium value in the extracorporeal circuit of ~0.25–0.35 mmol/L [3,4,9].

In this edition of Nephrology Dialysis Transplantation, Hetzel and co-workers published a protocol for regional citrate anticoagulation in pre-dilution CVVH. In this protocol, citrate serves as an anticoagulant and a buffer in one. A fixed blood flow to HF-citrate solution flow rate of 3:1 provides an equivalent of ~4 mmol citrate per 1 L blood for an effective anticoagulation. The primary objective of the study was to evaluate the efficacy of the citrate-based replacement fluid in comparison with a commercially available bicarbonate-based replacement fluid on acid–base status. As secondary objectives, a variety of clinical important aspects of CRRT performance such as control of uraemia, filter patency, incidence of HIT and bleeding as well as mortality were included. The citrate anticoagulation protocol is based on works done by Palsson and Nils in 1999 [6] but adds a few new features for better performance and metabolic control. At first glance, the paper simply seems to be one further protocol for regional citrate anticoagulation. However, to date, this is the largest multicentre, prospective randomized controlled trial on regional citrate anticoagulation. One hundred and seventy-four critically ill, ventilated patients were randomized to receive either citrate- or bicarbonate-based replacement fluid. Heparin was allowed for systemic anticoagulation in both treatment arms. Not surprisingly, the applied cumulative heparin dose was significantly lower during citrate anticoagulation.

Citrate proved to be as potent as bicarbonate to achieve an equilibrated acid–base status. The use of citrate resulted in less systemic anticoagulation, a lower risk of bleeding and a longer haemofilter patency. Although episodes of hypercalcemia, hypocalcaemia and the need for additional bicarbonate infusions occurred more often under citrate anticoagulation, the metabolic risks of citrate anticoagulation were very well controlled without serious side effects. The most striking observation of this study, however, was the fact that the patients' high mortality was not influenced by the mode of anticoagulation. This is quite interesting and exciting since a recent discussion has sparked off on whether regional citrate anticoagulation may improve the outcome of our ICU patients. Very recently, Oudemans-van Straaten and colleagues conducted a single-centre study comparing regional anticoagulation with citrate to a systemic anticoagulation with the low-molecular-weight heparin nadroparin in 200 critically ill acute kidney injury patients [10]. A remarkable finding of the Oudemans-van Straaten trial was that the use or regional anticoagulation with citrate resulted in a survival benefit. Three-month mortality on intention-to-treat was 48% for citrate and 63% for nadroparin anticoagulation (P < 0.03). Surgical patients, patients with sepsis or severe organ failure, and relatively younger patients particularly profited from regional anticoagulation with citrate. Based on these findings, it has been speculated that citrate—apart from being an excellent anticoagulant for CRRT—may exert immunomodulatory effects that attenuate or even block inflammation, thus leading to a survival benefit in critically ill patients on renal replacement therapy. This notion was supported by experimental data showing that dialysis-induced polymorphonuclear cell (PMC) degranulation and thrombocyte activation are significantly hampered during regional citrate anticoagulation. PMC degradation as well as thrombocyte activation is primarily ionized calcium-dependent and can effectively be blocked by the administration of citrate [11,12]. Although interesting, this hypothesis has its limitations. During CRRT, citrate is given directly into the extracorporeal circuit of the patient which leads to a dramatic drop of the ionized calcium within the extracorporeal circuit. However, this effect is restricted to the extracorporeal circuit. The effects of citrate on the systemic calcium homeostasis are low (and this is intended and mandatory!). Large parts of the infused citrate (at least 50%) get eliminated with the haemofilter. Citrate that enters the systemic circulations gets rapidly metabolized to bicarbonate mainly in the liver and to a lower extent also in the kidney, muscles and other tissues. In addition, during citrate anticoagulation, calcium is infused systemically in order to keep a normal systemic ionized calcium level. Thus, the calcium-induced effects of citrate are mainly restricted to the extracorporeal circuit. It would be very speculative to assume a ‘take over effect’ of citrate that leads to a cooling down of the systemic inflammation which in the end would exert a survival benefit during CRRT. In fact, the data published by Hetzel and co-workers do not support the ‘survival effect’ of citrate anticoagulation. Are the data published by Oudemans-van Straaten and colleagues comparable with the work done by Hetzel and co-workers? Hetzel included more septic patients (~78%), and patients tended to be younger compared with the Oudemans-van Straaten trial. Both trials were not primarily designed to look into patient outcome but included more or less the same number of patients. The main difference may be the mode of systemic anticoagulation. While Hetzel and co-workers used unfractionated heparin, Oudemans-van Straaten and colleagues used the low-molecular-weight heparin (LMWH) nadroparin. Nadroparin was applied as a fixed dose of 2850 IU at initiation of CVVH, or 3800 IU when body weight exceeded 100 kg, followed by a continuous infusion in the extracorporeal circuit of 380 or 456 IU/h, respectively. Monitoring of the anti-Xa activity was not done. Although not statistically significant, more bleedings occurred during nadroparin anticoagulation (16 patients versus 6 patients in the citrate group). In recent years, LMWHs have seen a renaissance in the ICU due to a less critical side effect profile compared with unfractionated heparin (lower incidence of allergic reactions, lower side effects on thrombocytes, skin, the liver, etc.) [13]. However, the use of LMWHs remains a challenge. The monitoring can only be done by measuring...
anti-Xa activity, unfortunately not yet available as a bedside test. Half-life time during renal failure is prolonged and varies significantly depending on the type of LMWH used [14,15]. Although a substantial amount of the infused LMWH gets eliminated with the haemofilter during CRRT [16], LMWH may accumulate when LMWH with a predominantly renal excretion mode is used or when the LMWH infusion is not disrupted in case of a breakdown/dismantling of the CRRT device. A regular control of the anti-Xa activity during LMWH anticoagulation in CRRT is therefore strongly recommended in order to provide both an efficient and safe anticoagulation.

The data published by Hetzel and co-workers cool down the speculation of a survival benefit of citrate anticoagulation. Regional citrate anticoagulation remains what it was aimed for, an excellent anticoagulant for CRRT in critically ill patients with a high bleeding risk.

Conflict of interest statement. None declared.

(See related article by Hetzel et al. Regional citrate versus systemic heparin for anticoagulation in critically ill patients on continuous venovenous haemofiltration: a prospective randomized multicentre trial. Nephrol Dial Transplant 2011; 26: 232–239.)

References


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