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Anticoagulation in Continuous Renal Replacement Therapy

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• **Anticoagulation is necessary for continuous renal replacement therapy (CRRT) as it prevents clotting of the circuit and helps deliver an adequate dialysis dose.**

• **Unfractionated heparin is the main anticoagulant used, although regional citrate anticoagulation is gaining wider acceptance.**

Introduction

Continuous renal replacement therapy (CRRT) is the favoured modality of renal replacement therapy for haemodynamically unstable patients with acute kidney injury (AKI) in the intensive care unit (ICU). Its main disadvantage is clotting of the extracorporeal circuit, leading to decreased solute clearance and inadequate metabolic, acid-base, and volume control (Tolwani and Wille 2009). To combat this problem, anticoagulation is typically used with CRRT. The perfect anticoagulant should provide optimum anticoagulation, be easily reversible, have a short half-life, and have negligible systemic effects.

There are various anticoagulants that can be used for CRRT, including systemic unfractionated heparin, regional heparin (in conjunction with protamine sulphate), low molecular weight heparin, regional citrate, thrombin antagonists, and platelet inhibiting agents. Of these, unfractionated heparin and regional citrate are more commonly used and will primarily be discussed here. For the other methods of anticoagulation, larger prospective studies and standardised protocols are needed to determine the best application of these agents.

Heparin

Unfractionated heparin is the most common anticoagulant used worldwide. Reasons for its mainstream use include relatively lower cost, wider availability, and easy reversibility with protamine sulphate. Unfractionated heparin inhibits factors IIa and Xa by potentiating antithrombin III. The anticoagulant effect is monitored by measuring activated plasma prothrombin time (aPTT), with typical protocols targeting the aPTT in the extracorporeal circuit 1.5 to 2 times control. However, heparin use in sepsis may be limited by the fact that the very substrate it acts upon, antithrombin III, may be depleted. Furthermore, heparin can result in several undesired effects, such as bleeding and heparin induced thrombocytopenia (HIT) (Hirsh et al. 2001). Thrombocytopenia is common in critically ill patients, and this may preclude use of systemic

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heparin as well.

The major complication of heparin is an increased risk of bleeding due to systemic anticoagulation. Erratic heparin pharmacokinetics in the setting of renal failure can predispose to bleeding despite normal aPTT levels, and the mortality from anticoagulation-related bleeding may be as high as 15% (Greaves 2002; van de Wetering et al. 1996). Low molecular weight heparins such as nadroparin and enoxaparin have been used in conjunction with CRRT to provide a more reliable anticoagulation response (van der Voort et al. 2005; Journois et al. 1990). Typical protocols for CRRT recommend target anti-Xa levels of 0.25 to 0.35 units/mL. These agents have less plasma protein binding, and so pharmacokinetic parameters are more predictable. Nevertheless, low molecular weight heparins are more expensive, require anti-Xa measurements for titration of anticoagulation, accumulate in renal failure, and can lead to systemic bleeding.

To minimise the systemic effects of heparin, regional anticoagulation can be delivered using unfractionated heparin and protamine sulphate by administering heparin pre-haemofilter and protamine sulphate post-haemofilter, thus restricting anticoagulation to only the circuit. However, protamine sulphate may have negative systemic effects, such as hypotension and anaphylaxis, and the protocols that use regional heparin anticoagulation are difficult to standardise (Horror 1985).

Regional Citrate Anticoagulation

Given the challenges with heparin, use of regional citrate anticoagulation (RCA) for CRRT has increased. Regional citrate limits anticoagulation to the extracorporeal circuit and serves as a substrate for metabolism to bicarbonate by mainly the liver.

Citrate is delivered into the blood at the beginning of the CRRT extracorporeal circuit. It binds ionised calcium and prevents clotting by making free calcium unavailable to the coagulation cascade. A post-haemofilter ionised calcium level less than 0.35 mmol/l in the extracorporeal circuit, which correlates with a citrate blood concentration of 4-6 mmol/l, has been shown to adequately inhibit anticoagulation (Calatzis et al. 2001). As some of the calcium-citrate complex is filtered across the haemofilter and lost in the effluent or ultrafiltrate during CRRT, a systemic calcium infusion is necessary. The remainder of the calcium-citrate complex enters the systemic circulation of the patient, where it is diluted and metabolised by the liver to bicarbonate, releasing ionised calcium back to the circulation. By maintaining normal levels of ionised calcium in the systemic circulation, anticoagulation is limited only to the circuit.

While RCA has several advantages, disadvantages include metabolic alkalosis, hypernatraemia from the use of commercially available hypertonic citrate solutions (such as 4% Trisodium Citrate, and 2.2% Anticoagulant Citrate Dextrose Solution), and hypocalcaemia. It is therefore necessary to frequently monitor acid-base status, electrolytes, and ionised calcium in the systemic circulation. Citrate accumulation may occur in patients who cannot metabolise citrate, such as those with liver failure or severe lactic acidosis, leading to severe hypocalcaemia and metabolic disorders (Meier-Kriesche et al. 2001). The use of citrate as an anticoagulant in these patients may be contraindicated. Predictive models using citrate kinetic parameters have been developed to assess the risk of citrate accumulation in patients with AKI undergoing CRRT (Zheng et al. 2013).

The use of citrate as a regional anticoagulant for CRRT was first reported in 1990 (Mehta et al. 1990). Despite its introduction over two decades ago and the experience gained since then, citrate is yet to become the mainstream anticoagulant used with CRRT. Obstacles to wider citrate use include a lack of safe citrate formulations for CRRT (commercially available CRRT solutions have high concentrations of sodium and citrate, which increase the risk of metabolic complications), cumbersome protocols, and lack of Food and Drug Administration approval in the United States (Tolwani and Wille 2012).

Comparing Heparin to Regional Citrate Anticoagulation

To date, there have been six randomised controlled trials comparing low molecular weight heparin or unfractionated heparin to citrate during CRRT. In the largest trial, by Oudemans-van Straaten et al., 200 patients on continuous venovenous haemofiltration (CVVH) were randomised to citrate or the low molecular weight heparin nadroparin (Oudemans-van Straaten et al. 2009). Citrate was administered at a dose of 3 mmol/l blood flow, without monitoring of post-haemofilter ionised calcium. Safety was significantly better in the citrate group with only two patients requiring a change in anticoagulation regimen versus 20 patients in the nadroparin group. Patients in the nadroparin group developed more metabolic alkalosis, hyponatraemia, and lactic acidosis. In the citrate arm, fewer patients developed chronic dialysis dependence, and 3-month mortality was lower. To explain the beneficial effects of citrate on patient and kidney survival, the authors theorised that, by binding calcium, citrate reduces calcium-induced release of pro-inflammatory mediators. In another large trial, by Hetzel et al., 174 patients with AKI on mechanical ventilation were randomised to systemic heparin or RCA (Hetzel et al. 2011). Enrolled patients received pre-dilution CVVH, and while citrate use did not improve survival, it did lead to longer filter patency and a lower risk of bleeding.

Wu et al. conducted a meta-analysis that included all six randomised controlled trials of citrate anticoagulation (Wu et al. 2012). They found no significant difference in circuit life, incidence of metabolic complications, or incidence of HIT between heparin and regional citrate for CRRT. Fewer bleeding events occurred in the citrate arm. The authors concluded that RCA was safe and effective, provided that proper protocols for citrate with CRRT were in place. In a separate meta-analysis that included the same six randomised trials, Zhang et al. found that circuit life was prolonged by 23 hours with citrate, as compared to heparin (Zhang and Hongying 2012). They also reported fewer bleeding events in the citrate group.

Conclusion

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While studies have demonstrated that fewer bleeding events occur with citrate use, there is conflicting data about its efficacy in terms of circuit survival time, frequency of metabolic complications, and patient and kidney survival. Unfractionated heparin is currently the most common anticoagulant used with CRRT; however, RCA is gaining acceptance. Future work involving citrate should include standardisation of citrate protocols and solutions to lessen the incidence of bleeding and metabolic complications.

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