Anticoagulation for Continuous Renal Replacement Therapy

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ABSTRACT

Continuous renal replacement therapy (CRRT) has emerged as the preferred dialysis modality for critically ill patients with acute kidney injury, particularly those with hemodynamic instability. Anticoagulation is necessary for effective delivery of CRRT, but this requirement can also present challenges, as many critically ill patients with sepsis and inflammation already have a higher risk of bleeding as well as clotting. Without anticoagulation, CRRT filter and circuit survival are diminished, and therapy becomes less helpful. Heparins are presently the most commonly used anticoagulants worldwide for CRRT. They are widely available and can be easily monitored, but disadvantages include risks of hemorrhage, heparin resistance, and heparin-induced thrombocytopenia (HIT). Because of the potential side effects of heparin, alternative methods of anticoagulation have been investigated, including regional heparin/protamine, low molecular weight heparins, heparinoids, thrombin antagonists (hirudin and argatroban), regional citrate, and platelet inhibiting agents (prostacyclin and nafamostat). Each of these techniques has unique advantages and disadvantages, and anticoagulation for CRRT should be adapted to the patient's characteristics and institution's experience. Of the alternative methods, citrate anticoagulation is gaining wider acceptance with the development of simplified and safer protocols.

The primary disadvantage of continuous renal replacement therapy (CRRT) is the need for anticoagulation to prevent clotting of the extracorporeal circuit. Although nonrandomized studies have shown that CRRT without anticoagulation is feasible in patients with coagulopathy, most patients require some form of anticoagulation. The ideal anticoagulant should provide optimal anti-thrombotic activity with minimal bleeding complications and negligible systemic effects. It should be inexpensive, have a short half-life, and be easily reversed. Moreover, monitoring methods of the anticoagulant effect should be simple and readily available. The advantages and disadvantages of various reported methods of systemic and regional anticoagulation for CRRT are reviewed in this manuscript.

Unfractionated Heparin

Unfractionated heparin (UFH), the most commonly used anticoagulant for CRRT, potentiates antithrombin III by a 1000-fold, resulting in inhibition of factors IIa (thrombin) and Xa. UFH is made up of heparin molecules of varied sizes (5–30 kDa). The larger fragments have predominantly anti-IIa activity and are cleared more rapidly than the smaller fragments. Anti-IIa activity is measured by the activated partial thromoboplastin time (APTT). The smaller fragments principally inhibit Xa and may result in an anticoagulant effect in the setting of a normal APTT because of its delayed clearance (1–3). UFH metabolites are eliminated by the kidneys. Plasma half-life is approximately 90 minutes but can increase up to 3 hours in the presence of renal insufficiency.

The advantages of UFH are that it is inexpensive, widely available and familiar to physicians, easy to administer, simple to monitor, and reversible with protamine. Disadvantages include the unpredictable and complex pharmacokinetics of UFH (resulting in dosing variability), the development of heparin-induced thrombocytopenia (HIT), heparin resistance because of low patient antithrombin levels, and the increased risk of hemorrhage (1). Van de Wetering et al. (4) demonstrated that the efficacy of UFH for prolonging filter life was proportional to the APTT and not to the heparin dose. Hemofilter clotting occurred less frequently when the PTT was increased by 10 seconds, but coincided with a 50% increase in the incidence of intracranial or retroperitoneal bleeding. Considering all the administration methods of heparin, the incidence of bleeding episodes ranges from 10–50%, with mortality because of bleeding as high as 15% (4–6).

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Most of the publications using UFH in CRRT are small, nonrandomized studies that used variable doses of heparin and variable APTT targets (1,5–9). Circuit survival times ranging from 20 to 40 hours have been reported. UFH is generally administered as a bolus of 2000–5000 IU (30 IU/kg), followed by a continuous infusion of 5–10 IU/kg/hour into the arterial limb of the dialysis circuit. APTT is maintained between 34–45 seconds, or an APTT of 1.5–2.0 times normal.

Regional Unfractionated Heparin–Protamine

Regional anticoagulation of the circuit is achieved by constant infusion of UFH into the hemofilter arterial line along with a constant infusion of protamine administered postfilter on the return line of the extracorporeal circuit. This approach requires measurement of both circuit and patient APTT. The advantage of this method is that the anticoagulant effects of UFH are restricted to the extracorporeal circuit, thereby lowering the risk of systemic patient bleeding.

Regional heparinization, however, is technically complicated because of the difficulty in estimating the amount of protamine required to antagonize postfilter heparin. For CRRT, an initial ratio of 100 between prefilter heparin (in units) and postfilter protamine (in mg) has been recommended, with subsequent adjustment according to the APTT. However, the amount of protamine needed to neutralize 100 IU of heparin varies substantially. The heparin–protamine complex is taken up by the reticuloendothelial system and broken down, but then heparin and protamine are released back into the circulation. Thus, protocols are cumbersome and difficult to standardize (7,10–14). In practice, UFH at 1000–1500 U/hour is infused prefilter and neutralized with postfilter protamine at 10–12 mg/hour. Protamine infusion is also associated with hypotension, anaphylaxis, cardiac depression, leukopenia, and thrombocytopenia (15). Although several small studies have demonstrated that regional heparinization with protamine is feasible and safe, its efficacy in prolonging filter lifespan has been variable (10,11,14).

Low Molecular Weight Heparins

Because of their reduced chain length, low molecular weight heparins (LMWHs) have higher anti-Xa/anti-IIa activity than UFH (1). The pharmacokinetics of LMWHs is more predictable than that of UFH because of less plasma protein binding. The advantages include a more reliable anticoagulant response and a lower incidence of HIT. However, because of the stronger anti-Xa effect, reversal with protamine is less effective. Dalteparin, enoxaprin, and nadroparin have been studied in CRRT; these LMWHs differ in size, half-life, and activity. Since LMWHs are excreted renally, their effects are prolonged in renal failure. Special coagulation assays are required to monitor anti-Xa activity. Furthermore, LMWHs are more expensive than standard heparin.

Controlled studies of LMWHs in CRRT have utilized either fixed doses or doses based on anti-Xa levels (16–19). Studies have demonstrated mixed results as to whether anti-Xa levels correlate with circuit survival (16–19). Loading doses of 15–25 IU/kg of nadroparin and dalteparin have been used, with maintenance doses of 5 IU/kg/hour. Although some studies use LMWHs in a fixed dose, for safety reasons, monitoring of anti-Xa (target level 0.25–0.35 U/ml) is recommended with prolonged use. Levels of anti-Xa between 0.45 and 0.8 U/ml have been associated with bleeding complications (20).

Three small randomized trials have shown fixed-dose LMWHs to be as effective as, but not superior to, standard heparin in prolonging circuit life (14,17,18). One small randomized study by Joannidis et al. (19) showed that enoxaprin (loading dose 0.15 mg/kg; maintenance dose 0.05 mg/kg/hour) extended circuit life, correlated with anti-Xa activity, and demonstrated less bleeding when compared with UFH.

Heparinoids

Danaparoid is a synthetic glycosaminoglycuron derived from pig intestine. It has a low-grade sulfation that reduces the incidence of platelet cross-reactivity with heparin-induced antibodies. It primarily has an anti-Xa, rather than anti-IIa, effect. While danaparoid has been used for HIT, it has several disadvantages: cross-reactivity with heparin/platelet factor 4 (PF4) antibodies in 5–10% of patients; a prolonged half-life (up to 48 hours) in renal failure; and notably, no antidote.

For CRRT anticoagulation, danaparoid is administered as a bolus dose between 750–2500 U followed by a maintenance dose of 1–2 U/kg/hour. The dose is adjusted to achieve an anti-Xa level of between 0.25 and 0.35 IU/ml. One observational study of danaparoid in 13 patients on CRRT found a high rate of bleeding (46%) despite lower mean anti-Xa activity (0.4 ± 0.2 U/ml) (21). Monitoring of anti-Xa activity is therefore critical with prolonged use.

Thrombin Antagonists

Recombinant (r) hirudin irreversibly inhibits bound and unbound thrombin independent of cofactors and PF4. The advantage is that it can be used in patients with or suspected HIT. However, the half-life of r-hirudin (normally 1–2 hours) is prolonged in patients with renal insufficiency since it is almost exclusively eliminated by the kidneys. Moreover, because it has a molecular weight of 6980 Da, it is negligibly removed by diffusion and variably removed with convection. No antidote exists. Since the anticoagulation effect at higher doses of r-hirudin is not linearly related to the APTT, the ecarin clotting time (ECT) is a more reliable test employed but not yet easily available (22,23). ECT uses the prothrombin-activating enzyme ecarin to monitor the concentration of r-hirudin plasma levels. Several authors have reported successful use of r-hirudin as an anticoagulant

for CRRT in critically ill patients diagnosed with HIT (24–27). For CRRT, it is administered either as a continuous infusion (0.005–0.01 mg/kg/hour) or delivered in bolus doses (0.002 g/kg) (28). The ECT is targeted for 80–100 seconds. In patients without HIT, two studies have demonstrated increased bleeding with continuous infusion, and less bleeding but a shorter circuit life with bolus doses (26,27). The use of hirudin as an anticoagulant in CRRT has been associated with hemorrhagic complications in up to 38% of patients (25,26).

Argatroban is a second generation direct thrombin inhibitor used in patients with HIT. Unlike hirudin, it is metabolized by the liver and has a 35 minute half-life in chronic dialysis (29). Furthermore, anticoagulation can be effectively measured by APTT levels. Similar to hirudin, no antidote exists. Studies are limited but describe a loading dose of 250 μg/kg and a maintenance dose of 0.5–2 μg/kg/minute with an APTT 1–1.4 times normal (30,31). Dose reduction is required in hepatic failure. It is the preferred CRRT anticoagulant in patient with HIT and acute kidney injury.

Recombinant human activated protein C (rhAPC) is a potent thrombin antagonist shown to reduce patient mortality in severe sepsis (32). It inhibits thrombin formation by degrading coagulation factors Va and VIIIa. Few studies exist, and experience is limited. However, one study reported a mean circuit life of 55 $\pm$ 14 hours with rhAPC as compared with 66 $\pm$ 19 hours with UFH (33).

Regional Citrate

Citrate is infused into the blood at the beginning of the extracorporeal circuit and provides anticoagulation by chelating ionized calcium (iCa^{++}). Optimal regional anticoagulation occurs when the iCa^{++} concentration in the extracorporeal circuit is below 0.35 mmol/l (measured as the postfilter iCa^{++} level). Since citrate is a small molecule, majority of the calcium–citrate complex is freely filtered and lost in the effluent. Therefore, a systemic calcium infusion is necessary to replace the calcium lost with citrate. Any calcium–citrate complex remaining then returns to the patient and is metabolized to bicarbonate by the liver, kidney and skeletal muscle. Each citrate molecule potentially yields three bicarbonate molecules. Calcium released from the calcium–citrate complex helps restore normal iCa^{++} levels. Advantages of citrate anticoagulation include the avoidance of systemic anticoagulation and HIT. The disadvantage is that citrate adds complexity and labor intensity to CRRT because of requirements for customized dialysate or replacement solutions. Frequent monitoring of electrolytes, iCa^{++}, and acid–base status is required, as a result of the potential for hypernatremia, metabolic alkalosis, and systemic ionized hypocalcemia. Patients with severe liver failure and lactic acidosis may have difficulty with citrate metabolism and develop citrate toxicity, which is characterized by low systemic iCa^{++}, elevated total serum calcium, metabolic acidosis, and an increased anion gap (34–37). If properly monitored, complications associated with regional citrate are uncommon.

A variety of methods of regional citrate anticoagulation are described in the literature (38–58). Citrate is administered either as a separate citrate solution or added to a calcium-free predilution replacement fluid. We have reported a simple citrate anticoagulation protocol with continuous veno-venous hemodiafiltration (CVVHDF) (58). By using an isotonic dilute-citrate based replacement solution and a commercially available physiologic calcium-free bicarbonate-based dialysate, the incidence of metabolic abnormalities is reduced.

Overall, studies of regional citrate anticoagulation, as compared to UFH, report better filter survival times and less bleeding (38–58). There is also some evidence for improved biocompatibility by decreased activation of coagulation and leukocytes (59,60). In a prospective, randomized trial, Monchi et al. (43) compared the safety and efficacy of UFH with regional citrate anticoagulation in 20 patients treated with continuous veno-venous hemofiltration (CVVH). Median circuit lifetime was longer with citrate (adjusted to maintain iCa^{++} in the circuit below 0.3 mmol/l) than with UFH (adjusted to maintain APTT 60–80 seconds), 70 hours vs. 40 hours, $p < 0.001$. In a randomized study of 30 patients by Kutsogiannis et al. (45), median hemofilter survival time was 124.5 hours in the citrate group and 38.3 hours in the heparin group ($p < 0.001$).

In a multicenter study involving 138 patients and 442 CRRT circuits, no difference was observed in the mean circuit life between citrate and UFH (44.7 $\pm$ 35.9 hours vs. 42.1 $\pm$ 27.1 hours, respectively) (46). The UFH group experienced more life-threatening bleeding episodes requiring transfusion of blood. In another study of 87 patients undergoing CRRT from the Calgary Health Region, Canada, 54 were initially treated with citrate (212 filters), 29 with heparin (97 filters), and 4 with saline flushes (42). Median filter lifespan was significantly higher with citrate than with UFH (40 hours vs. 30 hours, $p < 0.001$). In addition, citrate anticoagulation was well tolerated, with no treatment discontinued because of bleeding or metabolic complications.

Platelet-Inhibiting Agents

Prostacyclin (PGI_2) and its synthetic derivative epoprostenol inhibit platelet aggregation and adhesion. Prostacyclin can cause hypotension from vasodilation at doses of 20 ng/kg/minute. While the vasodilator half-life is 2 minutes, the antiplatelet effect remains for 2 hours. Prostacyclin has been investigated alone or in combination with UFH (5, 61-66). The usual dose is 2 to 8 ng/kg/minute infused prefilter. Monitoring is not required unless UFH is used. Its main drawbacks include the risk of hypotension and expense of the drug.

Most authors have reported only limited clinical experience with prostacyclin, and published reports on its safety and efficacy are scant (5,61–66). Langenecker et al. (61) compared the efficacy and safety of PGI_2 as an alternative to and combined with UFH in a randomized-controlled trial. While PGI_2 increased circuit life, it was associated with more hemodynamic instability

compared with heparin alone or heparin combined with PGI_2. The median filter life with prostacyclin as a sole agent is about 15–19 hours and extends to 20–22 hours when combined with low-dose UFH at 5–6 IU/kg/hour (65).

Nafamostat mesilate, a synthetic serine protease inhibitor, is a prostacyclin analog without the hypotensive activity. It is not available in the United States but typically administered at a dose of 0.1 mg/kg/hour. However, studies have demonstrated that levels of thrombin–antithrombin III complex and prothrombin activation fragment 1 + 2 increase, while protein C activity decreases, leading to circuit clotting (67,68). Several side effects (anaphylaxis, agranulocytosis, hyperkalemia) have been reported with use of nafamostat (69–71).

Conclusion

The choice of anticoagulant for CRRT should be determined by patient characteristics, local expertise, nursing comfort, ease of monitoring and pharmacy issues. There is no consensus on which anticoagulant should be first choice for all CRRT patients. However, citrate anticoagulation is gaining wide acceptance with the development of simpler and safer protocols. Monitoring should include evaluation of anticoagulant effect, filter efficacy, and circuit life and complications.

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