Anticoagulation for continuous renal replacement therapy

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Anticoagulation during continuous renal replacement therapy should aim for an optimal filter performance allowing the delivery of an adequate dose of renal replacement therapy. On the other hand, the patient's safety should not be endangered. Although numerous options have been proposed, none of them appears to be ideal. Unfractionated heparin is still the most widely used anticoagulant. Reported experience with low-molecular-weight heparin is limited and does not confirm the anticipated increased safety. Regional citrate anticoagulation has been shown to reduce bleeding complications during continuous haemodialysis. A recent report demonstrates the feasibility and safety of citrate anticoagulation during continuous predilution haemofiltration. However, its use is labour intensive and the prevention of side-effects requires meticulous monitoring. Hirudin, a selective thrombin inhibitor, appears to be a suitable, although not completely safe, alternative in patients with heparin-induced thrombocytopenia. Continuous renal replacement therapy without anticoagulation may result in acceptable filter lives in patients with reduced coagulatory potential or an increased risk of bleeding. Although receiving little attention in the literature, the adequate selection of treatment characteristics may also contribute to an improved filter performance. Curr Opin Anaesthesiol 14:143–149.

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Current Opinion in Anaesthesiology 2001, 14:143–149

Abbreviations

ACT	activated clotting time
APTT	activated partial thromboplastin time
CHD	continuous haemodialysis
CHF	continuous haemofiltration
CRRT	continuous renal replacement therapy
CVVHF	continuous venovenous haemofiltration
HIT	heparin-induced thrombocytopenia
LMWH	low-molecular-weight heparins

0952-7907

Introduction

Critically ill patients with acute renal failure are increasingly treated with continuous renal replacement therapy (CRRT) [1,2]. One of the major drawbacks of CRRT is frequent filter thrombosis. Reported filter lives vary between a few hours and a few days, and filter clotting has been held responsible for the majority of circuit terminations. Frequent filter clotting not only increases the cost of the treatment and the workload and frustrations of the nursing staff, but more importantly, the numerous treatment interruptions reduce the efficiency of the therapy and may thus affect patient outcome [3••]. The continuous nature of the required anticoagulation results in prolonged exposure of the patient, increasing the risk of haemorrhagic and other side-effects.

The haemostatic system of the patient with acute renal failure

The requirement for anticoagulation depends on the condition of the haemostatic system, which in critically ill acute renal failure patients may show a reduced procoagulatory potential, an activated coagulation and often even a combination of both [4]. A reduced procoagulatory potential can be detected with routine coagulation assays. However, the diagnosis of an activated coagulation requires more sensitive assays, which, unfortunately, are not yet routinely available. Studies reporting baseline haemostatic parameters of patients requiring CRRT show prolonged clotting times [5–9], decreased platelet count [5–8,10], decreased platelet function [6,11,12], activated coagulation [8,10–13], and decreased natural anticoagulants [8,9,12,14,15].

Treatment characteristics affecting filter life

The selection of treatment characteristics may have a considerable effect on circuit life or anticoagulant requirement, but the effect of extracorporeal clearance on patient outcome should also be considered. Although not evaluated in a prospective randomized trial, reported circuit lives tend to be shorter with venovenous compared with arteriovenous treatment [16–18], possibly related to a difference in circuit length, a different design of the catheter, the use of a blood pump resulting in more turbulence, or the use of a bubble trap with blood–air contact. On the other hand, the extracorporeal clearances achieved with arteriovenous treatment are too limited. In a recent review, Davenport [19] pointed to the importance of using a large-bore catheter with a

smooth surface and atraumatic insertion in order to avoid vessel damage and turbulence. In our own experience, treatment interruption is frequently provoked by access problems. No prospective studies have evaluated the effect of access location on filter life. Compared with continuous haemodialysis (CHD), continuous haemofiltration (CHF) might result in more haemostatic activation as a result of the concentration of coagulation factors along the filter and increased blood–membrane contact. A retrospective study by van de Wetering *et al.* [20] did not establish a difference in filter life between continuous arteriovenous haemofiltration and CAVHDF (continuous arteriovenous haemofiltration). Prospective comparisons of filter life with CHD and CHF are, however, lacking. Predilution is expected to result in an increased effective filter life or a decreased anticoagulant requirement by the dilution of prefilter haematocrit, clotting factors, and platelet count [21]. A prospective study showing prolonged filter life with pre- compared with post-dilution is, however, lacking. Viscosity in the extracorporeal circuit can also be reduced by frequent saline flushes. A recent study [22•] did not establish a benefit of more intense flushing. The same study also did not establish a difference in filter life between a blood flow of 125 and 250 ml/min. The high workload of intensive care unit nurses may result in delayed reaction to circuit alarms. This results in frequent cessations of circuit flow and subsequent clotting [23].

Flat-plate geometry has been shown to prolong filter life during continuous arteriovenous haemodialysis, probably related to a reduced blood–dialysate flow mismatch [24]. Baldwin *et al.* [25], on the other hand, did not find a difference in circuit life between flat plate and hollow fibre filters during continuous venovenous haemofiltration (CVVH). Whereas a retrospective analysis [20] suggested longer filter lives with a polyamide membrane compared with an AN69 membrane, a prospective study [26] did not establish a different filter life between AN69 and polysulfone.

Mechanisms of filter thrombosis

The critical activation steps that take place in blood–material interaction are currently not completely understood. For many years the rapid adsorption of plasma proteins followed by activation of platelets and contact activation of the intrinsic coagulation cascade were considered to be the major mechanisms involved in thrombogenesis on artificial surfaces [27]. Platelet activation results from their interaction with adsorbed fibrinogen [28], exposure to high shear stress [29] and thrombin, the latter being considered the key agonist [30]. Although an inverse correlation between platelet count and filter life is by no means a universal finding [8,10,11,23,31•], the feasibility of CRRT without anticoagulation in patients with thrombocytopenia [16,32] and an inverse correlation between platelet count and heparin requirement [7,11] could point to an important contribution of platelet activation to filter thrombosis. Thrombin generation on artificial surfaces has traditionally been attributed to contact activation of the intrinsic pathway of coagulation. In-vitro experiments [33] have shown that dialysis membranes can activate the contact system, an activation that is most pronounced with negatively charged hydrophilic membranes such as the AN69 membrane [34]. However, whether contact activation contributes to thrombin generation is increasingly being questioned in normal in-vivo haemostasis [35] as well as during intermittent haemodialysis and cardiopulmonary bypass [36–38]. A contribution of the extrinsic pathway to thrombin generation on artificial surfaces is at first sight unexpected because, in normal circumstances, tissue factor is only found on the surface of cells outside the vasculature. However monocytes can express tissue factor under certain pathophysiological conditions, mostly associated with increased endotoxin or cytokine levels, and thus frequently encountered in critically ill patients [39,40]. The expression of tissue factor and procoagulant activity on circulating and even more on adherent monocytes has also been demonstrated in an in-vitro model of extracorporeal circulation [41]. Cardigan *et al.* [10] recently demonstrated that the extrinsic pathway is activated during CVVH with an AN69 membrane. However, their conclusion, although probably correct, is based on disputable arguments. Low levels of natural anticoagulants have been suggested to contribute to early filter clotting [14]. An inverse correlation between filter life and the antithrombin level has been demonstrated in patients receiving heparin [42], which can be explained by the antithrombin dependence of the anticoagulant effect of heparin. However, in the absence of heparin, antithrombin as well as protein C require an endothelial counterpart, glycosaminoglycans and thrombomodulin, respectively, to exert an anticoagulant effect. In an extracorporeal system without endothelium, their level can therefore not be expected to influence filter life.

Currently used anticoagulants

The ideal anticoagulant for CRRT should prevent filter clotting without inducing haemorrhage, and should have a short half-life with action limited to the extracorporeal circuit. Monitoring should be easy, systemic side-effects should be absent, and an antagonist should be available [43]. None of the currently available anticoagulants can come up to these expectations, explaining why no single approach is widely accepted or generally utilized. Reviewing the literature on anticoagulation during CRRT is rather frustrating because prospective trials are rare, operational characteristics differ widely, and there are no standardized definitions of filter life, bleeding complications or bleeding risk.

Unfractionated heparin

Unfractionated heparin is still the most commonly used anticoagulant in CRRT. It catalyses the inactivation of thrombin, fXa and fIXa by antithrombin. The main advantage of unfractionated heparin is the large experience, the short biological half-life, the availability of an efficient inhibitor, and the possibility to monitor its effect with routine laboratory tests. On the other hand, unfractionated heparin also has a number of important drawbacks. The pharmacokinetics are not only time- and dose-dependent but also unpredictable with considerable inter- and intrapatient variability, which is related to an interaction with a variety of proteins and cells. Some of these proteins are acute phase reactants, the level of which will be elevated in critically ill patients. The anticoagulant response to heparin depends on the level of antithrombin and the presence of activated platelets. Meticulous monitoring is therefore required. Heparin is an incomplete anticoagulant because it has no effect on bound thrombin or fXa. Unfractionated heparin has a complex effect on platelets causing direct activation or an immune-mediated thrombocytopenia (heparin-induced thrombocytopenia or HIT), which is a life-threatening complication. The most frequent complication of unfractionated heparin is bleeding [44].

Clinical studies mentioning or studying the use of unfractionated heparin during CRRT use a wide variety of doses. Mostly 5000–20 000 U of unfractionated heparin are added to the priming solution, followed by a continuous infusion of 3–15 U/kg per hour. Some centres also administer a bolus of 1000–5000 U before the initiation of the treatment. Depending on the bleeding risk, a 50–100% prolongation of the activated partial thromboplastin time (APTT) or activated clotting time (ACT) is mostly aimed at. The APTT is probably better suited to monitor the level of anticoagulation required in CRRT. Its increased sensitivity should be weighed against the bedside availability of the ACT, which can speed up clinical decision making. Bedside APTT measurements are probably ideal. The incidence of reported bleeding complications during CRRT with unfractionated heparin varies widely between 0 and 50% [7,20,32,45–47,48••]. However, not all of these bleeding episodes can be attributed to the anticoagulant, e.g. a retrospective study by Martin *et al.* [7] reported that 10% of the deaths in the 'high heparin' (>700 U/h) group were caused by haemorrhagic shock; however, 15% of the deaths in the group that did not receive heparin were also related to haemorrhage. Several case reports on HIT during CRRT have been published [7,49,50•,51•].

Regional heparinization

An infusion of protamine on the return line has been used to produce regional anticoagulation in the extracorporeal circuit [16,52]. However, in our experience as well as that of others, this procedure is very complex, not very successful and is associated with the risk of both products. Compared with low-dose unfractionated heparin, it has not been shown to prolong filter life nor to reduce bleeding complications in continuous veno-venous haemodialysis [16]. Another approach to restrict the anticoagulant effect of unfractionated heparin to the extracorporeal circuit is to incorporate devices containing immobilized protamine [53,54], immobilized heparinase [55,56•], or a heparin removal device [57] in the venous return line. However, the clinical efficacy and safety of these devices remains to be established.

Low-molecular-weight heparins

In the last decennium low-molecular-weight heparins (LMWH) have increasingly replaced unfractionated heparin in many indications for antithrombotic therapy. Their mechanism of action is comparable with unfractionated heparin. However, because of a reduced chain length, LMWH do not bind thrombin, resulting in a reduced antithrombin effect and a high anti-Xa : anti-IIa ratio. Compared with unfractionated heparin, LMWH bind considerably less to proteins and cells, resulting in a more predictable pharmacokinetic and anticoagulant response, in an increased half-life that is more dependent on renal function, and in a decreased likelihood of inducing HIT. LMWH are only partly antagonized by protamine. They differ substantially in molecular weight and anti-Xa : anti-IIa ratio and are considered to be different drugs by the Food and Drug Administration. Optimal doses should therefore be determined for each of them [44]. In contrast to the majority of the indications for LMWH, monitoring of the plasma level is required during CRRT because accumulation may occur in patients with renal failure [44], and extracorporeal elimination has been shown to be limited [14,58]. This monitoring requires an anti-Xa level that, unfortunately, is not routinely performed. An anti-Xa level of 0.25 U/ml appears to be necessary for an acceptable filter life [13,59], whereas doses resulting in anti-Xa levels of 0.45–0.8 U/ml have been shown to be associated with bleeding complications [13]. Other authors question the relationship between the anti-Xa level and the antithrombotic effect [5,31•]. A recent randomized trial [48••] comparing fixed dose LMWH and adjusted dose unfractionated heparin found comparable filter lives and bleeding complications. Daily costs were, however, 10% higher with LMWH.

Prostacyclin and analogues

Platelet inhibitors, such as prostacyclin and analogues, have been used in CRRT, often in combination with unfractionated heparin or LMWH [5,9,18,26,47,60,61]. Their anti-platelet action has a heparin-sparing effect as a result of the reduced inhibition of unfractionated

heparin by platelet factor 4. Compared with heparin, the risk of bleeding is reduced [18,26], an advantage that must, however, be paid for with a shorter filter life [26,61]. The combination with unfractionated heparin or LMWH results in a better preservation of membrane permeability than heparin alone [5,26]. Systemic side-effects (hypotension, and an increase of intracranial pressure) can be prevented or limited by infusion into the extracorporeal circuit, reducing the systemic levels due to extracorporeal elimination [18]. An important drawback of prostacyclin is its cost price, a daily dose costing almost as much as a haemofilter.

Citrate

Sodium citrate is increasingly being used during CHD, especially in the USA [45,62,63,64••,65•]. The anticoagulant effect of citrate relies on the chelation of calcium, thus depleting a necessary co-factor of several steps of the coagulation process. This effect is antagonized through dilution of citrated blood on return to the central venous compartment, through the release of calcium when citrate is metabolized to bicarbonate in the liver (each citrate ion produces three bicarbonate ions) and through the systemic infusion of calcium, compensating for the loss of citrate–calcium complexes in the dialysate. The resulting anticoagulation is thus restricted to the extracorporeal system. The citrate flow rate is adjusted to obtain a post-filter ACT of 200–250 s [45]. Unfortunately, this seemingly attractive procedure is very labour intensive. In order to compensate for the sodium and alkali load associated with the infusion of sodium citrate, a hyponatremic dialysate without buffer should be used. Dialysate should also be free of calcium. This results in supplementary costs for the customized production of this solution. pH, electrolytes and clotting times should be monitored meticulously. The possible side-effects are hypernatremia, metabolic alkalosis and citrate intoxication with ionized hypocalcemia (with normal or elevated total calcium), and high anion gap metabolic acidosis [45,66–68]. The amount of citrate required to maintain a low enough ionized calcium level depends on the blood flow. Blood flow should therefore be kept low in order to avoid a citrate load that exceeds the metabolization capacity, and this may conflict with the requirement for higher clearances in critically ill patients [3••]. Liver insufficiency, limiting citrate metabolization, is a contraindication. Although convective clearance alone has been thought insufficient to remove the citrate load, limiting its use to CHD or CHF, a recent report [64••] also evaluated the use of citrate in predilution CVVH, decreasing the complexity of the method. Two clinical studies [45,63] reported a longer circuit life with citrate compared with unfractionated heparin. However, patients were not prospectively randomly assigned, which may have introduced selection bias. Reported mean filter lives vary between 66 h in continuous arteriovenous haemodialysis and 29.5 h in predilution CVVHF. The incidence of bleeding complications is low, despite non-randomized selection favouring citrate in patients with a high risk of bleeding [45,46,62,64••].

Hirudin

Hirudin is a highly selective and specific thrombin inhibitor that has been used in HIT patients requiring CRRT [50•,51•]. Non-renal clearance is negligible, resulting in a marked increase of the half-life in anuric patients [69], which, together with the absence of a specific antagonist, represents a considerable drawback to the use of hirudin in CRRT. Doses of 0.006–0.025 mg/kg per hour have been used during CVVHF [50•,51•]. The drug has a high molecular mass (6 980 M_r), resulting in negligible diffusive elimination. However, protein binding is low requiring dosage adaptation for convective elimination, which differs according to the membrane with sieving coefficients of 0.6 and 0.44 for polysulfone and AN69, respectively [70]. Bucha *et al.* [71] reported higher sieving coefficients for all high-flux membranes. Although the ecarin clotting time has been deemed necessary to monitor hirudin anticoagulation [51•], other authors [72] reported a linear relationship between hirudin levels and the APTT, at least in the range of anticoagulation required during CRRT. Fischer *et al.* [50•] did not report bleeding complications in seven medical patients, whereas Kern *et al.* [51•] reported major bleeding in postoperative patients, despite similar doses.

Nafamostate mesilate

Nafamostate mesilate is a synthetic proteinase inhibitor that acts on several serine proteases, including thrombin, fXa and fXIIa [73]. The tissue factor–fVIIa complex is also inhibited [74]. Nafamostate mesilate has a low molecular mass of 540 M_r, resulting in extracorporeal elimination, which, together with the short half-life of 20 min, limits systemic anticoagulation. Unfortunately, the drug has no antidote and several side-effects (agranulocytosis, hyperkalemia and anaphylactoid reactions) have been described [75–77]. Data on the use of nafamostate during CRRT are limited, and the drug is not available in the USA and Europe. A few Japanese studies [78,79] showed a lower incidence of bleeding complications compared with unfractionated heparin.

Non-thrombogenic surfaces

Arakawa *et al.* [80] used an antithrombogenic membrane consisting of a polyacrylonitrile-polyethyleneoxide polymer combined with heparin-coated lines and catheters and, without using anticoagulation, obtained a filter life of 7.6 h in animal experiments and 25.7 h (5–216 h) in clinical application. Heparin-coated membranes have been shown to prevent thrombus formation and prolong

filter life in an animal model [81]. Published clinical results are limited to two abstracts [82,83], showing a reduced heparin requirement, a tendency towards longer filter lives and a better preservation of platelet numbers. Why further studies on this membrane have failed to appear is not clear.

No anticoagulation

CRRT has been performed without anticoagulation, often combined with saline flushes of 50–100 ml every hour [7,16,32,45,46]. In most of the studies, patients were selected for anticoagulant-free treatment because of an already disturbed haemostatic system or because of an increased risk of bleeding, which is seldom clearly defined. Whether CRRT without anticoagulation results in the consumption of clotting factors, inhibitor or platelets or in platelet dysfunction has not been investigated.

Conclusion

Anticoagulation during CRRT should be individualized. The first goal should be the safety of the patient. If the haemostatic system is disturbed to the extent that 'spontaneous' anticoagulation results, the administration of an anticoagulant will not be required. Patients who can not tolerate anticoagulation because of active bleeding or very recent surgery or trauma, can be treated without anticoagulation or, in the case of frequent filter clotting, with regional anticoagulation with citrate. Attention should be paid to treatment characteristics and non-pharmacological means of prolonging filter life. In patients with normal or moderately disturbed haemostasis and a moderate or absent risk of bleeding, an antithrombotic drug can be administered. Unfractionated heparin is still the most widely used anticoagulant. In patients with HIT, citrate or hirudin can be considered. In the case of frequent filter clotting prostacyclin can be added. However, the high costs should be weighed against the gain in filter life. The experience with LMWH (at least as far as reflected in the literature) is too limited yet. Research on the molecular and cellular biology of haemostasis progresses steadily and has led to new (and maybe safer) drugs with antithrombotic properties, such as active-site blocked fVIIa, activated protein C, thrombomodulin, dermatan sulphate, fXa inhibitors, etc. In addition, important interactions between coagulation and inflammation have recently been established [84–87]. Some antithrombotic drugs have been shown to have anti-inflammatory activities and to improve the outcome of animals in experimental sepsis and ischaemia–reperfusion [88–95]. Limited clinical data also suggest an anti-inflammatory effect of antithrombin and activated protein C [87,96]. In addition to the prevention of filter clotting, some antithrombotic drugs might thus have a beneficial effect on the underlying disease of CRRT patients, and could become the future anticoagulant of choice in these patients.

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