

Role of citrate and other methods of anticoagulation in patients with severe liver failure requiring continuous renal replacement therapy

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Abstract

Anticoagulation is required during continuous renal replacement therapy to prevent filter clotting and optimize filter performance. However, anticoagulation may also be associated with serious bleeding complications. Patients with liver failure often suffer from underlying coagulopathy and are especially prone to anticoagulation complications. The aim of this review is to present the unique features of patients with hepatic injury in terms of anticoagulation disorders and to analyze data on safety and efficacy of the different anticoagulation methods for liver failure patients undergoing continuous renal replacement therapy.

Keywords: anticoagulation; citrate; continuous renal replacement therapy; liver failure

Introduction

During continuous renal replacement therapy (CRRT), anticoagulation is required to preserve filter performance, avoid filter clotting and prevent blood loss due to circuit clotting. As anticoagulation is optimized, the risk of haemorrhage is also heightened [1]. No optimal strategy has been established to prevent filter clotting while minimizing related adverse events. Some populations at risk for acute kidney injury (AKI) are especially prone to anticoagulation complications. Liver failure patients often present with AKI and bleeding thus presenting therapeutic challenges for CRRT anticoagulation. The aim of this review is to present the unique features of patients with hepatic injury in terms of anticoagulation disorders and to analyse data on safety and efficacy of the different anticoagulation methods for liver failure patients undergoing CRRT.

Unique coagulation characteristics of liver failure patients

Liver failure patients are prone to bleeding complications, variceal haemorrhage occurring in one-third of all cirrhotic patients [2]. Although thrombotic events are less well characterized, portal vein thrombosis can be diagnosed in up to 20% of cirrhotic patients [3]. Hence, patients with liver failure have concurrent bleeding and thrombotic diatheses, the resulting clinical state usually being determined by the predominant mechanism involved [4]. A thrombotic event can occur at one site, for example the dialysis filter, even if a systemic bleeding tendency is present [4].

Bleeding diathesis

In chronic liver disease, bleeding tendency has commonly been attributed to decreased production and dysfunction of platelets, reduced synthesis of clotting factors and vitamin K deficiency [4,5]. Quantitative and qualitative abnormalities of fibrinogen have also been documented [3,5]. In acute and fulminant hepatic failure (FHF), there is respectively a partially reversible deficit in vitamin K and reduced platelet aggregation, although adhesion to glass beads is increased [5]. Disseminated intravascular coagulation (DIC) can contribute to bleeding in cirrhosis and FHF [5–7]. Several characteristics contributing to enhance risk of bleeding are often present in patients with liver failure. These include advanced age, poor general condition, recent bleeding and variceal haemorrhage, hepatic dysfunction itself, sepsis, coagulopathy and low platelets [5,8]. In patients undergoing CRRT, other risk factors include heparin dose [8] and dialysis-induced platelet damage and loss [9].

Thrombotic tendency

Mechanisms underlying hypercoagulability in these patients are less clearly defined. In acute and chronic diseases, elevated levels of factor VIII and von Willebrand factor, DIC, and reduced synthesis of the natural anticoagulants (protein C, S and antithrombin III) have been suggested as contributing factors [4,5]. Abnormal platelet adhesion and decreased levels of plasminogen commonly

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occur in chronic liver failure, while hypofibrinolysis is usually present in acute liver failure. Patients with cholestatic liver disease may be more prone to thrombosis, but this has not been adequately assessed [5]. There are limited data on diagnostic tests able to predict hypercoagulability. In one study, only a low albumin level was shown to be predictor of venous thrombotic events [10]. Low antithrombin levels have also been associated with filter clotting but are rarely measured [11,12].

Methods of anticoagulation

Although there is increasing use of renal replacement therapy (RRT) in a liver failure population, no study has primarily looked at the frequency of thrombosis of extra-corporeal circuits in these patients [4]. Recent review articles and one case report suggest a significant incidence of circuit and filter clotting without the use of anticoagulation [4,8,13]. The different methods of anticoagulation in this population are reviewed and summarized in Table 1.

No anticoagulation, saline flushes and pre-dilution

No anticoagulation. CRRT without anticoagulation is performed in patients judged to be at high risk for bleeding. Bellomo and colleagues have defined this population with the following criteria: platelet count $<60 \times 10^9/l$, activated partial thromboplastin time (aPTT) >60 s, INR >2 , DIC and spontaneous bleeding [14].

In patients without liver failure undergoing CRRT, one trial compared no anticoagulation to low-dose heparin or regional heparin–protamine. Filter life was not statistically different between the groups [14]. Another similar study including 48 patients assessed the efficacy of no anticoagulation versus regional anticoagulation with heparin–protamine (1000 IU/h + protamine 10 mg/h) versus low-dose heparin (5 IU/kg/h) on bleeding complications and filter survival. No bleeding complications and no significant difference in filter life were observed, although patients without anticoagulation showed a trend towards thrombocytopenia and higher INR [15].

A prospective cohort study of 24 patients at high risk of bleeding reported that the mean circuit life was significantly higher in patients without anticoagulation compared to controls with low-dose pre-filter heparin infusion (5–10 IU/kg/h) (32 h versus 19.5 h; $P = 0.017$) [16]. Interestingly, the former group had statistically higher INR and lower platelet counts. However, the largest retrospective study available reported that filter life was similar with no anticoagulation or different doses of heparin, including doses superior to 700 IU/h [17]. Platelet count seemed to correlate with clot formation. Thus, in patients without liver failure, CRRT without anticoagulation seems mostly appropriate for severely thrombopaenic patients [17].

There are scant data on dialysis without anticoagulation in liver failure. A retrospective study of 66 patients including 26 transplants showed that no anticoagulation is the predominant method used, being prescribed in 58% and 73% of transplanted and non-transplanted patients, respectively [18]. Unfortunately, no data on filter survival or bleeding

complications were presented. A retrospective study of 11 liver transplanted patients undergoing CRRT without anticoagulation did not include information related to filter life [19].

Saline flushes and pre-dilution. Saline flushes can be infused every 30–60 min in the circuit in an attempt to decrease filter clotting. This method is simple and relatively safe but has not been studied extensively. Pre-dilution has been postulated to decrease filter clotting by reducing blood viscosity with the infusion of substitution fluid before the filter [20]. In patients without liver failure, two studies have evaluated the effect of pre-dilution on filter life during CRRT. Both studies have demonstrated a significant increase in filter life with pre-dilution compared to post-dilution [21,22].

In one randomized study of 34 patients, including 21 patients with pre-existing liver disease, saline flushing every 30 min compared to every hour did not prevent filter clotting [23]. Hence, very limited data are available on the efficacy of saline flushes and pre-dilution in patients with liver failure.

Citrate

Regional citrate anticoagulation (RCA) has been advocated to be the preferred method of anticoagulation in patients at risk of bleeding [12,24]. However, it is more hazardous in patients with liver failure and important precautions must be taken before its use is considered safe in this population. We will briefly review the mechanisms, advantages and potential complications of RCA, and its use in patients with liver impairment.

Method of anticoagulation, advantages and complications. Several different protocols and modalities (haemofiltration and/or haemodialysis) can be used for citrate anticoagulation [12,25,26]. More commonly, 4% tri-sodium citrate (TSC) is used and is delivered pre-filter. Less frequently, citrate can be administered in the dialysate. Citrate exerts its anticoagulation effect by chelating ionized calcium, an essential component in the clotting cascade. The target post-filter ionized calcium concentration is usually <0.4 mmol/l [27,28]. Citrate–calcium complexes are normally partly removed by the filter, and the remaining are metabolized in bicarbonate by the liver [29]. The chelated calcium is then liberated and returned to the total calcium body pool [30]. There is risk of hypocalcaemia and hypomagnesaemia due to the binding of citrate to ionized calcium and magnesium and possibly due to freely filtered calcium and magnesium citrate complexes [24,31,32]. Calcium losses are usually proportional to the effluent dose [33]. Additional calcium is infused into the systemic circulation to compensate for the loss of calcium through the filter [28]. Most protocols use either calcium-free or calcium-reduced dialysate or replacement fluid and thus enhance calcium losses [27,33,34]. Moreover, since citrate provides a sodium load, the dialysate and/or the substitution fluid need to be hypotonic to avoid hypernatraemia. Due to citrate metabolism into bicarbonate, metabolic alkalosis can also occur. To avoid metabolic disorders, many centres use customized solutions with

Table 1. Summary of anticoagulation methods in liver failure

Method	Advantages	Disadvantages	Comments
No anticoagulation	No risk	Limited efficacy in preventing filter clotting	
Pre-dilution	No risk	Decrease solute clearance	
Saline flushes	No risk	Limited efficacy in preventing filter clotting	
Citrate	No systemic anticoagulation	Risk of citrate accumulation with hypocalcaemia and metabolic acidosis	Close monitoring of citrate accumulation with total to ionized calcium ratio; monitor serum and ionized calcium 2 h after a modification of calcium or citrate administration and every 4 h if stable
Unfractionated heparin	Anticoagulation effect easily monitored with aPTT; complete reversal with protamine	Limited data on its safety in liver failure	Use only if needed by another indication and target aPTT 1–1.4 × baseline if possible; monitor aPTT every 6 h; close monitoring of bleeding
Heparin–protamine		Limited data on safety and efficacy	
Low-molecular-weight heparin		Increased risk of bleeding in AKI; incomplete reversal with protamine; no data in AKI and liver failure	Should be avoided until further data available; if used, close monitoring with anti-Xa is recommended (target 0.25–0.35 IU/ml and monitor daily)
Prostacyclin		Limited data on efficacy and safety	
Nafamostat mesilate		Limited data on efficacy and safety	

reduced sodium and buffer content [26]. These complications are more frequent at the beginning of a new citrate anticoagulation program due to a lack of training [34].

In patients without liver failure, three randomized trials have compared citrate to unfractionated heparin (UFH), including a total of 98 patients and 270 filters [12,35,36]. In two of these studies, citrate increased filter life [12,35] and reduced the number of blood transfusions [35,36]. Citrate also decreased bleeding complications in patients both at high [12] and low risk of bleeding [36]. Non-randomized studies have reported prolonged filter life with citrate compared to UFH [27,37]. When compared to nadroparin in a cohort of patients at high risk for bleeding, citrate also significantly reduced the incidence of bleeding complications during CRRT (14.8% versus 25%; $P = 0.04$). However, there was no difference in the number of transfusions and the nadroparin group had a longer filter run time (31.5 h versus 22.5 h, $P = 0.0001$) [38]. The authors did not mention the targeted post-filter calcium values. Higher values could shorten filter lifetime. One observational study compared citrate to prostacyclin-heparin and showed superior filter survival, reduced risk of hypotension, more stable platelet count and lower cost with citrate [39].

Possible adverse events of citrate in liver failure. In liver failure, the two major complications related to RCA are hypocalcaemia and metabolic acidosis [8,25,30,31,40,41]. Hypocalcaemia occurs due to the reduced liver function that leads to the accumulation of citrate–calcium complexes. Consequently, there is a reduction in ionized calcium and a possible rise in total calcium levels [28,30]. In liver failure,

an associated decrease in muscle perfusion can also contribute to impaired citrate metabolism. The increase in total calcium and decrease in ionized calcium (total to ionized calcium ratio) are directly proportional to the concentration of citrate in systemic blood [30]. Hence, total to ionized calcium ratio values >2.5 are suggestive of citrate accumulation. However, in two different studies, a ratio >2.5 could only identify 17.6% (3/17) and 75% (3/4) of patients with citrate concentrations >1.5 mmol/l [28,42]. In the former study, calcium supplementation was remarkably high and could have contributed to normalize ionized calcium [42].

Impairment in citrate metabolism can also lead to high anion gap metabolic acidosis. Acidosis is explained by the incapacity of the liver to metabolize citrate into 3 moles of bicarbonate, and the anion gap is caused by the accumulation of citrate. As expected, metabolic acidosis mainly occurs when citrate is the principal buffer and is lessened when bicarbonate is included in the dialysate and/or the replacement fluid solution. Patients with acute liver failure may also suffer from significant respiratory alkalosis due to hyperventilation, and this may need to be considered when using citrate.

Once excess citrate is metabolized, potential complications include hypercalcaemia and hypermagnesaemia, due to the release of these electrolytes from their complexes with citrate [28,43]. Therefore, calcium and magnesium should be monitored for a few days after citrate metabolism is returned to normal [28].

Management of citrate in liver failure. Until recently, most caregivers considered citrate to be contraindicated

Table 2. Citrate anticoagulation: risk factors, suggested monitoring and strategies for the prevention and treatment of citrate accumulation

Risk factors for citrate accumulation
Severity of liver failure
Hypoxaemia
Citrate-containing blood products (blood transfusions, fresh frozen plasma)
Suggested monitoring ^a
pH, bicarbonate and anion gap
Total and ionized calcium
Total to ionized calcium ratio (abnormal >2.5)
Prevention and treatment strategies ^a
Decrease citrate administration
Decrease blood flow rate
Target higher post-filter calcium value
Avoid citrate-containing blood products
Increase citrate clearance
Increase convective dialysis dose
Increase diffusive dialysis dose
Treat hypoxaemia if present
For hypocalcaemia
Increase calcium delivery before correcting metabolic acidosis and supplement hypomagnesaemia
For metabolic acidosis
Increase bicarbonate administration in replacement and dialysis solutions if required and check sodium levels if sodium bicarbonate is administered
Consider alternatives to citrate if metabolic complications remain despite the above measures

^aTo be adapted according to the degree of hepatic insufficiency.

in patients with liver failure [35,36,44]. However, recent studies suggest that RCA may be used safely in patients with liver injury undergoing CRRT [27,42,45,46]. Nevertheless, several precautions should be taken when considering citrate as an anticoagulant in this population. We will review the risk factors, suggested monitoring and precautions regarding prevention of hypocalcaemia and metabolic acidosis.

Several factors may contribute to citrate-induced hypocalcaemia and metabolic acidosis (Table 2). First, since these complications occur because of impaired citrate metabolism due to liver failure, the severity of liver dysfunction may correlate with the risk of complications. In a recent report, however, several patients with advanced cirrhosis treated with RCA showed no sign of citrate toxicity [47]. In addition, a retrospective study of 161 patients undergoing citrate-based CRRT failed to identify features of hepatic failure able to predict reduced citrate metabolism [30]. Another factor that may contribute to citrate-induced hypocalcaemia and metabolic acidosis is hypoxaemia. Oxygen seems essential for citrate metabolism by the tricarboxylic pathway. Thus, hypoxaemia may favour citrate accumulation and hence hypocalcaemia and acidosis [45]. Finally, the administration of blood products that contain citrate, such as packed red cells and fresh frozen plasma, may increase citrate loading. Since these products are often used in large quantities in patients with liver failure, the total amount of citrate administered can become significant.

To detect and prevent hypocalcaemia, close monitoring of total and ionized calcium levels is required. Both tests should be obtained as early as 2 h after the initiation of CRRT [30] and every 2–4 h subsequently. Both tests can also be used to compute the total to ionized calcium ratio, in

order to uncover citrate accumulation. To detect and prevent acidosis, pH, bicarbonate levels and anion gap should be measured every 4–6 h in high-risk patients, especially at the beginning of the therapy.

To prevent the occurrence or the worsening of complications associated with impaired citrate metabolism, several strategies may be implemented (Table 2). First, the amount of citrate administered can be decreased [20,27,42]. For example, the infusion of 4% TSC can be started at 90 ml/h instead of 180 ml/h [27]. Other protocols target higher post-filter ionized calcium values, such as 0.38–0.45 mmol/l [48]. However, some centres have experienced increased filter clotting with this strategy [30]. Although the following recommendation has not been formerly validated, reducing the blood flow rate to 100 ml/min can also theoretically decrease the amount of citrate required without compromising clearance. In addition, citrate-containing blood products should be avoided.

A second strategy to prevent the occurrence or worsening of complications associated with impaired citrate metabolism is to increase citrate clearance through increased convective or diffusive dialysis dose [29]. One publication reported a diffusive citrate clearance ranging from 28 to 54 ml/min with dialysate flow rates of 2000 and 4000 ml/h, respectively [29]. The sieving coefficient for citrate was 0.87 ± 0.06 , and the total citrate clearance was almost equal to the sum of diffusive and convective clearances [29]. In this study, haemodiafiltration could remove 35–50% of the citrate–calcium chelate.

At some point, when citrate cannot be sufficiently metabolized into bicarbonate because of severe liver impairment, the only available strategy to prevent and treat metabolic acidosis is to administer bicarbonate [8,25,41]. The sodium content of the dialysate and replacement fluids needs to be adjusted when sodium bicarbonate is added to prevent a total sodium delivery higher than the normal concentration range. When commercial solutions are used, the sodium content cannot be easily customized. However, the use of pharmacy-made solutions can avoid this pitfall. Ultimately, if acidosis remains a problem despite adequate treatment, alternatives to citrate should be considered.

Similarly, when citrate–calcium complexes cannot be sufficiently metabolized to normalize ionized calcium, calcium supplementation should be provided by increasing calcium infusion and if necessary, by intravenous bolus [40]. When hypocalcaemia and acidosis are present concomitantly in a patient, it is recommended to correct hypocalcaemia before acidaemia, because rapid administration of bicarbonate may enhance calcium deficit. In addition, hypomagnesaemia [28] should also be corrected.

Unfractionated heparin

Despite bleeding complications reported in 10–50% of patients [8], UFH remains the most commonly used method of anticoagulation in acute RRT [49]. Heparin is easily monitored with aPTT. However, during UFH administration, partial anticoagulation can occur with normal aPTT values [24]. This finding is particularly important for liver failure patients for whom a normal aPTT should not be automatically considered as a low risk of bleeding. In one study,

maintaining aPTT between 35 and 45 s seemed to be the best compromise between bleeding and clotting [1]. However, variation in aPTT results occurs due to the different reagents used in practice [50]. Therefore, a target aPTT 1–1.4 times normal has been suggested to minimize the risk of bleeding [24]. The use of activated clotting times cannot be recommended due to their inaccuracy in critically ill patients [51].

There are limited data regarding the safety of heparin in patients with liver failure. Liver failure itself is not a formal contraindication to UFH. Common reported contraindications are platelet count $<20\text{--}60 \times 10^9/l$, heparin-induced thrombocytopenia (HIT), acute bleeding, gastro-intestinal or intracranial haemorrhage (<3 months), significant trauma (<3 days), first 24 h post-surgery, coagulopathy (aPTT $> 65\text{--}80$ s, INR $>2.5\text{--}3.0$) or other conditions judged at high risk of bleeding [12,18,36,52,53]. Due to the perceived risk of bleeding, there is a restricted use of heparin in liver failure patients undergoing RRT. A retrospective study of 66 patients with liver failure has shown a rate of utilization of only 12% for transplanted and 20% for non-transplanted patients [18]. No data on filter survival or bleeding complications were available. In 24 patients with FHF treated with intermittent dialysis, Langley and colleagues used heparin with a target ACT of 200–250 s, and nine minor and three major bleeding complications occurred [9].

In summary, no large studies have assessed the safety of UFH during acute RRT in patients with liver failure. Since these patients are at high risk of bleeding, careful evaluation must be made before starting UFH and close monitoring of bleeding complications should be assessed.

Heparin–protamine. The continuous infusion of heparin pre-filter and protamine post-filter allows regional anticoagulation, since protamine will counteract the systemic effect of UFH. These medications can be initiated at a 1:100 ratio (protamine 1 mg:heparin 100 IU), and the circuit aPTT and the systemic aPTT should be 1.5–2 times baseline and in the normal range, respectively [54].

In general populations undergoing CRRT, when heparin–protamine was compared to no anticoagulation and low-dose heparin (500 IU/h), heparin–protamine did not offer any significant benefit on filter survival [14,15]. The side effects of protamine include hypotension, pulmonary hypertension, haemorrhage and allergic reactions [22]. Moreover, this method is time and resource consuming [13]. A recent evidence-based review did not recommend its use due to better alternatives [24], whereas another supported its use in patients at high risk of bleeding who do not have acceptable filter life without anticoagulation [20].

There is only one study on the use of heparin–protamine in liver failure patients, all of them being liver transplant recipients [55]. Heparin–protamine was compared to low-dose heparin (5–10 IU/kg/h) in 27 patients, and no difference in circuit life and no pathologic bleeding were observed. Adverse events related to protamine were not reported [55].

Hence, there are very limited data related to the use of heparin–protamine in liver failure and formal recommendations cannot be made. There is a possible influence of

liver on the clearance of heparin–protamine from plasma, and therefore, careful monitoring is advised if these medications are used.

Low-molecular-weight heparin

In critically ill patients with AKI, low-molecular-weight heparins (LMWH) have major drawbacks: an increased half-life and risk of bleeding and an incomplete reversal of their anticoagulation effect by protamine [50]. Therefore, the American College of Chest Physicians support the use of UFH rather than LMWH in severe AKI [50]. If LMWH are used, anti-Xa should be closely monitored [24,50].

In patients without liver failure, two randomized studies comparing LMWH and UFH in CRRT have appeared in full paper [56,57]. The first study included 46 patients and did not show any difference between filter life and incidence of haemorrhages between dalteparin and UFH. Thirty-seven patients completed the second study. Similar numbers of bleeding and a superior filter lifetime were reported with the use of enoxaparin adjusted to the anti-Xa level at 0.25–0.3 IU/ml (30.6 h versus 21.7 h; $P = 0.017$). One cohort study including 55 patients found that nadroparin significantly increased filter life (31.5 h versus 22.5 h; $P = 0.0001$) and risk of bleeding complications compared to citrate (25% versus 14.8%; $P = 0.04$), even though patients at high risk for haemorrhage received citrate [38].

Hence, there are no data available on the safety and efficacy of LMWH in patients with liver failure undergoing CRRT. Due to their prolonged half-life and incomplete reversal with protamine, we do not recommend the use of LMWH in patients with severe liver failure undergoing CRRT.

Minimal systemic anticoagulation

Prostacyclin. Prostacyclin is an arachidonic metabolite that inhibits interaction between platelets and artificial membranes [8,20]. Prostacyclin use has been limited by hypotension, possible bleeding, difficulty in dose adjustment and absence of antagonist [8,14,17,58]. The haemodynamic complications can be reduced by priming the circuit with human albumin solutions and increasing vasoconstrictors prior to starting the perfusion.

More importantly, in patients with fulminant liver failure, the direct (intravenous) administration of prostacyclin has been shown to increase intracranial pressure and reduce cerebral perfusion, being hazardous in this population at risk for cerebral oedema [59,60]. However, the same authors have reported that infusion of prostacyclin pre-filter is safe [61]. Prostacyclin has been reported to be associated with a significant longer filter life (60 h versus 8 h; $P < 0.01$) and a reduction in bleeding complications compared to heparin (3 versus 8 major haemorrhages) [61].

Nafamostat mesilate. Nafamostat is a synthetic serine protease inhibitor mainly used in Japan in patients at high risk of bleeding [8,20,62,63]. There are limited data on its use in patients with liver failure undergoing CRRT [64].

Table 3. Summary of anticoagulation methods in HIT and liver failure

Method	Advantages	Disadvantages	Recommended dosage	Comments
Argatroban	Data available in kidney and liver failure	Prolonged half-life; no antagonist	Start at 0.5 µg/kg/min [78]; adjust for aPTT 1.5-(3×) baseline and monitor 4–5 h after a dose change	Increasing safety in liver failure and AKI; close monitoring for bleeding
Hirudin	May be reversed by recombinant factor VII and/or haemofiltration with high-flux polysulfone membrane	No data in liver and kidney failure; risk of antibodies preventing removal; monitoring with aPTT unreliable	Start at 0.005 mg/kg/h; adjust for aPTT 1.5-(2×) baseline [78] or ecarin clotting time (ECT) assay 80–100 s or hirudin 0.6–1.4 mg/l (both two not widely available), monitor ECT every 2 h × 2 and every 4 h [76]	Close monitoring for bleeding if used; should probably be avoided in patients with liver and renal failure
Bivalirudin	Preliminary data suggest good safety	Not yet approved for HIT	Start at 0.03–0.04 mg/kg/h; adjust for aPTT 2 × baseline and monitor aPTT frequently (usually every 6 h) [81,82]; careful anticoagulant monitoring if antilepirudin antibodies because they may influence pharmacokinetics [82]	May be promising; no specific antidote; haemodialysis, haemofiltration and plasmapheresis may reduce levels [82]
Danaparoid		Prolonged half-life; no antagonist	Bolus 750 IU and start infusion at 1–2 IU/kg/h; adjusted for anti-Xa 0.2–<0.35 IU/ml and monitor daily	Close monitoring for bleeding; could be used as a possible alternative to argatroban

Anticoagulation agents for HIT

HIT type 2 is a potential life-threatening condition caused by antibodies against the platelet factor 4-heparin complex [65] and must be considered when platelet count decreases by 50% or $<100 \times 10^9/l$. HIT causes paradoxical hypercoagulability and requires immediate cessation of all forms of heparins [65]. Systemic anticoagulation with selected molecules should be provided if not contraindicated to avoid thromboses. In most cases, the prescribed anticoagulant is argatroban, hirudin or danaparoid. Table 3 summarizes the various agents that may be used for HIT.

Argatroban. Argatroban is a direct thrombin inhibitor mainly metabolized by the liver available in North America and Europe [66]. This drug significantly prolongs INR. A retrospective study of 82 patients, including 43 with both liver and kidney dysfunctions, showed that this medication may be used safely and effectively with adequate dosing and monitoring [66]. In this study, hepatic dysfunction was defined as bilirubin $>25.5 \mu\text{mol/l}$, aspartate aminotransferase $>100 \text{ IU/l}$ and/or alanine aminotransferase $>100 \text{ IU/l}$. However, all four major bleeding occurred in patients with both liver and kidney injury. Another retrospective study showed three major bleeding episodes in 14 patients with renal and liver failures requiring RRT, but dose adjustments were not correctly performed [67]. No bleeding occurred in the 16 patients without liver failure.

For patients with hepatic impairment, it is recommended to start argatroban with a reduced dosage [66]. CRRT procedures do not significantly modify argatroban clearance [68]. Patients with liver failure should reach steady-state levels more slowly, and argatroban should be stopped sev-

eral hours to days before a procedure requiring temporary reversal of anticoagulation [66,69]. Monitoring for bleeding complications should be emphasized and targeting the lower range of therapeutic aPTT values must be considered [69,70]. Activated factor VII has been reported to reverse its anticoagulation effect [71].

Hirudin. Hirudin is also a direct thrombin inhibitor. The commercially available drug, lepirudin, has an increased half-life in severe renal failure (50 h), and the risk of haemorrhage is related to creatinine levels [72]. In addition, antibodies preventing lepirudin removal in RRT occur in up to 60% of patients [65]. Monitoring with aPTT is difficult due to the absence of linear relationship between aPTT and hirudin concentrations [65]. As an alternative, monitoring with ecarin clotting time assay or hirudin concentrations has been recommended [53,65,73]. Rare cases of anaphylaxis have been reported [65,72]. In the case of bleeding, recombinant factor VIIa [74], and in the absence of antibodies, haemofiltration with high-flux polysulfone membrane, have been used [75]. Two small randomized studies have compared its use to UFH and found confounding results regarding bleeding complications and filter life [53,76]. No specific data were reported on hepatic status. We have found only one case report on the successful use of lepirudin in a patient with liver failure undergoing CRRT, and in this case, a high-flux polysulfone membrane was used [77].

Bivalirudin. Bivalirudin is a direct thrombin inhibitor that has a prolonged half-life (3.5 h) in patients on dialysis [78]. A retrospective study has shown its successful use in patients with hepatic impairment on CRRT [79].

Danaparoid. Danaparoid is a heparinoid that has a prolonged half-life in renal failure (36–48 h versus 25 h) and no antagonist [24]. Only one retrospective study of 13 patients has assessed its use in CRRT [80]. Major bleeding was observed in 46.2% of patients even if anti-Xa levels were in the prophylactic or low therapeutic range. No data are available for patients with liver impairment.

Summary and recommendations

Patients with both renal and hepatic impairments present unique coagulation characteristics that complicate the choice of anticoagulation therapies for CRRT. In addition, there are limited data regarding the safety and efficacy of different methods of anticoagulation in these patients.

In liver failure patients, to minimize bleeding and other complications, we suggest (1) to use pre-dilution rather than post-dilution CRRT; (2) to attempt CRRT without anticoagulation as a first step and (3) to use RCA as a second step for repeated filter coagulation in centres with previous experience with citrate anticoagulation. Centres without experience with RCA should avoid using citrate in patients with liver failure. Strict monitoring of acid base status and total to ionized calcium ratio is required to rapidly detect citrate accumulation and its related complications. There is no definite cut-off level of total to ionized calcium ratio that should prompt discontinuation of citrate anticoagulation, although a ratio >2.5 is typically reported to be associated with citrate accumulation. Citrate serum levels can also be measured directly (when available) when the risk of accumulation is believed to be very high. Citrate accumulation can be prevented by lowering the amount of citrate administered and enhancing its clearance. In the setting of hypocalcaemia, calcium delivery should be optimized. If citrate-induced metabolic acidosis occurs, the amount of bicarbonate administered should be optimized in the dialysate and the replacement fluid. Serum sodium should be closely monitored if an increase in sodium delivery (through the use of sodium bicarbonate) occurs concomitantly. The use of citrate should be reassessed if any or little improvement in the acid base status is not quickly noticed.

UFH may be used when required by other conditions, such as Budd-Chiari syndrome, and when clinical risk of bleeding is felt to be low to moderate. In our opinion, the use of LMWH should be avoided in this population due to its prolonged half-life and incomplete reversal by transitory use of protamine. In patients with HIT and combined liver and renal failure, there is no optimal anticoagulation method. We tend to use argatroban as a first choice due its shorter half-life, availability and increasing clinical experience in liver failure. Danaparoid can be used as an alternative. Prospective studies are needed to assess the required level of anticoagulation during RRT and to determine the optimal method of anticoagulation in this population.

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