

Anticoagulation and Continuous Renal Replacement Therapy

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ABSTRACT

More than half of patients with acute renal failure in the intensive care unit require dialysis, and the majority of them have significant hemodynamic instability. Continuous renal replacement therapy (CRRT) is often the preferred dialysis modality in these patients. One requirement for CRRT is anticoagulation, which can expose patients to the risk of bleeding. However, absence of effective anticoagulation may result in clotting of

the CRRT circuit and subsequently less effective treatment. While heparins are widely used for anticoagulation, because of potential side effects such as bleeding and heparin-induced thrombocytopenia, alternative anticoagulation protocols should be considered. Citrate anticoagulation, regional heparin/protamine, predilution, r-hirudin, prostacyclin, and nafamostat are among these methods.

The development of acute renal failure (ARF) in critically ill patients is a significant determinant of survival. Despite recent advances in the management of ARF patients, prognosis has not significantly improved. This is partly related to its occurrence in patients with an increasing number and complexity of comorbid conditions. Data from the Program to Improve Care in Acute Renal Disease (PICARD) study suggest that more than half of patients with ARF in intensive care units require dialysis, and a large number of these have significant hemodynamic instability (1). Continuous renal replacement therapy (CRRT) is often the procedure of choice in these patients.

One requirement for CRRT that has potential deleterious consequences is anticoagulation. While anticoagulation exposes patients to the risk of bleeding, the absence of it may result in clotting of the CRRT circuit. This prolongs the downtime of CRRT, results in less effective treatment, and increases the cost of care. In a randomized clinical trial of continuous versus intermittent hemodialysis for ARF, the mean duration of CRRT treatment was 16.1 hr/day, indicating almost 8 hours of downtime per day (2). In another study, the mean downtime was more than 5 hours, and this affected azotemic control (3). These findings underline the importance of a safe and effective anticoagulation strategy.

An optimal anticoagulation method is easy to implement and monitor, has few side effects, and is cost effective (4). In this article we review different methods of anticoagulation employed during CRRT and discuss the most recent data regarding the safety and efficacy of these protocols.

Predisposing Factors for Clotting in CRRT

Blood flow, dialyzer type, coagulation pathway activation, and convective mass transfer are among the factors that contribute to filter clotting. Undetected blood flow reductions may occur during CRRT, and they may be correlated with filter life span (5). However, in one study, increasing blood flow from 125 to 250 ml/min failed to decrease filter clotting (6). Dialyzer type is another factor that may affect clotting. In one study, the mean survival of polyacrylonitrile filters was significantly lower compared with polyamide filters (7). However, Martin et al. (8) reported no differences in heparin requirement between these two membranes. While intrinsic coagulation pathway activation is seen in the majority of critically ill patients receiving CRRT, activation of tissue factor (extrinsic pathway) may also occur. In one study, levels of factor VIIa initially decreased and tissue factor pathway inhibitor (TFPI) increased, but during the course of hemofiltration, levels of TFPI decreased and factor VIIa increased (9). Subnormal levels of antithrombin III and heparin cofactor II seen in critically ill patients with sepsis may also be an important factor in determining filter longevity (10,11). Finally, a higher convective mass transfer during hemofiltration and hemodiafiltration is associated with increased procoagulant activity in the extracorporeal circuit and may promote filter clotting (12).

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Seminars in Dialysis—Vol 19, No 4 (July–August) 2006 pp. 311–316

TABLE 1. CRRT nomogram for heparin

aPTT (seconds)	Bolus dose	Rate change	Repeat aPTT
< 40	1000 U	+200 U/hr	In 6 hours
40.1–45.0	Nothing	+100 U/hr	In 4 hours
45.1–55.0	Nothing	No change	In 6 hours
55.1–65.0	Nothing	Stop $\frac{1}{2}$ hour and –100 U/hr	In 4 hours
> 65.0	Nothing	Stop 1 hour and –200 U/hr	In 4 hours

Heparin solution is made by mixing 1 ml of 10,000 U/ml of heparin in 19 ml of normal saline for a heparin concentration of 500 U/ml. Initial bolus is 25 U/kg followed by an infusion of 5 U/kg/hr. The goal of treatment is to maintain systemic prefilter aPTT between 45 and 55 seconds (1.5 times control).

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Regional Citrate

Calcium is a necessary element in blood coagulation. Regional citrate use in the extracorporeal circuit provides anticoagulation by chelating calcium. This effect is reversed by calcium infusion into the systemic circulation. Citrate metabolism in liver and skeletal muscle generates bicarbonate. In one published protocol, citrate solution is made by mixing 40 g of trisodium citrate in 1000 ml D5W for a final concentration of 40 mg/ml. The infusion is started at 180 ml/hr proximal to the dialyzer. In patients with suspected liver failure or cirrhosis, the infusion is started at 90 ml/hr. The goal is to maintain postfilter ionized calcium concentration between 0.25 and 0.35 mmol/L. Calcium chloride (80 ml of 10% calcium chloride in 1000 ml of normal saline, for a final concentration of 0.056 mmol/L) is infused via central venous catheter to maintain a systemic ionized calcium concentration of 1.00–1.35 mmol/L. The infusion is initiated at 40 ml/hr (2.2 mmol/hr). Tables 1–3 illustrate nomograms for heparin, citrate, and calcium chloride in this protocol (13). Hyponatremia, metabolic alkalosis, hypocalcemia, and hypercalcemia are potential complications of this anticoagulation method (14). Base and calcium-free dialysate solution with a sodium chloride concentration of 110–117 mEq/L is employed to avoid metabolic alkalosis and hyponatremia.

In one study, morphologic analysis of hemodialysis membrane-associated coagulation activation was performed with scanning electron microscopy. Three methods

TABLE 2. CRRT nomogram for citrate

Postfilter ionized Ca ⁺ (mmol/L)	Rate change	Repeat postfilter ionized Ca ⁺ (mmol/L)
< 0.25	–20 ml/hr	In 1 hour
0.25–0.35	No change	In 4 hours
0.36–0.40	+10 ml/hr	In 1 hour
0.41–0.45	+20 ml/hr	In 1 hour
> 0.45	+30 ml/hr	In 1 hour

Citrate solution is made by mixing trisodium citrate 40 g in 1000 ml D5W for a final concentration of 40 mg/ml. The infusion is started at 180 ml/hr. If the patient has suspected liver failure or cirrhosis, the infusion is started at 90 ml/hr. The goal of treatment is to maintain postfilter ionized calcium between 0.25 and 0.35 mmol/L.

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of anticoagulation (heparin, citrate, and low molecular weight heparin [LMWH] [dalteparin]) were studied in single-use polysulfone capillary dialyzers. A dialyzer clotting score was used for a quantitative description of coagulation activation on membrane segments. Citrate use was associated with the least cell adhesion and thrombus formation in comparison to dalteparin and unfractionated heparin (UFH) (15). In a prospective randomized clinical trial, the efficacy and safety of UFH versus regional citrate anticoagulation was evaluated in 20 patients treated with continuous venovenous hemofiltration (CVVH). Forty-nine dialyzers were analyzed: 23 with heparin and 26 with citrate. The median hemofilter life span was 70 hours (interquartile range 44–140 hours) with citrate and 40 hours (17–48 hours) with heparin ($p = 0.0007$). One major bleeding episode occurred with heparin anticoagulation, and one case each of metabolic alkalosis and hypocalcemia (0.90 mmol/L) were noted with citrate. Transfusion rates (units of packed red cells per day of CVVH) were 0.2 (0.0–0.4) with citrate and 1.0 (0.0–2.0) with heparin ($p = 0.0008$) (16).

Three additional studies compared the efficacy and safety of citrate and heparin anticoagulation. In the first, three anticoagulation protocols including citrate only, citrate plus low-dose heparin, and heparin only were compared in a prospective observational study. Filter life span was significantly longer with citrate compared to heparin (80.2 ± 60 hours versus 30.2 ± 32 hours; $p < 0.001$). No difference was observed between the citrate and citrate plus heparin groups. In patients on citrate, metabolic alkalosis and hypercalcemia were observed in 50% and 12% of patients, respectively. Citrate anticoagulation was well tolerated hemodynamically, and the longer filter life span resulted in lower cost compared to heparin. Alkalosis can be reversed in almost all cases by increasing the dialysate flow rate (14). However, sufficient citrate clearance, preventing toxic accumulation, may be achieved by convective clearance (CVVH) alone, and diffusive clearance (continuous venovenous hemodiafiltration [CVVHDF]) may not be necessary (17).

In the second study, citrate and heparin were used in 66% and 30% of filters for 8776 and 2651 hours of CRRT, respectively. Overall, median filter life span with citrate was significantly greater than with heparin (40 versus 20 hours, $p < 0.001$) (13). Finally, patients

TABLE 3. CRRT nomogram for calcium chloride

Systemic ionized Ca ⁺ (mmol/L)	Rate change	Repeat systemic ionized Ca ⁺ (mmol/L)
< 0.75	+40 ml/hr (2.2 mmol/hr)	In 2 hours
0.75–0.85	+30 ml/hr (1.65 mmol/hr)	In 2 hours
0.86–0.90	+20 ml/hr (1.1 mmol/hr)	In 4 hours
0.91–0.99	+10 ml/hr (0.5 mmol/hr)	In 6 hours
1.00–1.35	No change	In 6 hours
> 1.35	–20 ml/hr (1.1 mmol/hr)	In 4 hours

Calcium chloride solution is made by mixing 80 ml of 10% calcium chloride in 1000 ml of normal saline for a concentration of 0.056 mmol/L. Systemic calcium homeostasis is maintained by infusion for a targeted systemic ionized calcium of 1.00–1.35 mmol/L. The infusion is initiated at 40 ml/hr (2.2 mmol/hr).

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from seven U.S. pediatric centers receiving CRRT were studied to assess filter life span and complications related to anticoagulation with heparin, citrate, and no anticoagulation. Clotting rates were similar for heparin (25%) and citrate (27%), but were significantly higher (50%) with no anticoagulation ($p < 0.001$). Life-threatening bleeding complications attributable to anticoagulation were noted in nine patients in the heparin group, but were absent in the citrate group (4).

One can conclude from these studies that citrate anticoagulation is at least as effective as heparin, and that it can be safely used as an alternative to heparin in CRRT patients, especially those at high risk for bleeding.

Heparin

Heparin is a heterogeneous mixture of branched glycosaminoglycans and in humans is found in the secretory granules of mast cells. It is extracted from porcine intestinal mucosa or bovine lung. Heparin increases the thrombin-antithrombin reaction rate. Antithrombin inhibits activated coagulation factors of the intrinsic and common pathways, including thrombin, Xa, and IXa. High-dose heparin interferes with platelet aggregation and thereby prolongs the bleeding time. Acquired antithrombin deficiency may occur in patients with cirrhosis, nephrotic syndrome, or disseminated intravascular coagulation. Larger heparin doses may not prolong the activated partial thromboplastin time (aPTT) in these patients. Bleeding, heparin-induced thrombocytopenia (HIT) (in 3–5% of patients with standard heparin), mild transaminase elevation, and hyperkalemia are other side effects of heparin. The anticoagulant effect usually dissipates within hours of discontinuation. The effect of heparin can be reversed quickly by slow intravenous infusion of protamine sulfate. However, anaphylactic reactions occur in about 1% of patients with diabetes mellitus who have received protamine-containing insulin (neutral protamine Hagedorn [NPH] or protamine zinc insulin), but are not limited to this group (18).

The recommended initial bolus and continuous infusion rate for UFH in CRRT in one published protocol was an initial bolus of 25 U/kg followed by an infusion rate of 5 U/kg/hr (13); this may vary between different protocols. While using UFH is an effective strategy in increasing extracorporeal circuit longevity, it is associated with an increased risk of bleeding and HIT. In one study, the crude incidence of hemorrhage was 2.9 ± 1.0 per 1000 hours at an aPTT of 15–35 seconds, and increased almost threefold to 7.4 ± 2.4 per 1000 hours when the aPTT was 45–55 seconds ($p = 0.009$). After adjustment for filter type, mean arterial pressure, and platelet count, the risk for filter clotting decreased 23% (relative risk 0.77; 95% confidence interval [CI] 0.62–0.96) for every 10 second increase in aPTT. At the same time, the risk of patient hemorrhage increased 57% (relative risk 1.57; 95% CI 1.43–1.72) (7). It was suggested that the risk of hemorrhage or clotting of the extracorporeal circuit is a function of aPTT rather than heparin dose. An aPTT of 35–45 seconds may offer the best degree of safety and efficacy (7,8). However, variability in aPTT reagents neces-

sitates site-specific validation of the aPTT therapeutic range in order to properly monitor CRRT therapy (19).

Low molecular weight heparins (1000–10,000 Da) are derived from UFH. Because of their insufficient length to catalyze inhibition of thrombin, LMWH preparations produce an anticoagulant effect predominantly through antifactor X activity. As a result of lower nonspecific binding, LMWH may have a more favorable profile of bleeding complications compared to UFH. LMWHs have a longer half-life and are cleared by the kidneys. As a result, their half-life is prolonged in patients with renal failure.

A review of prospective studies comparing pharmacokinetic differences of LMWHs in nondialyzed patients with varying degrees of renal dysfunction concluded that there is an increased antifactor Xa activity in patients with diminished renal function, and this effect may differ among LMWHs. Also there was no single creatinine clearance cutoff value that correlated with an increased risk of bleeding for all LMWH preparations (20). Despite their small size, neither UFHs nor LMWHs cross the dialyzer membrane in any measurable quantity (11). However, one study of high-flux membranes showed reduced antifactor Xa levels immediately (predialyzer, $p = 0.028$; postdialyzer, $p = 0.027$) and 4 hours after ($p = 0.001$) administration of enoxaparin compared with low-flux membranes. This indicated that high-flux membranes may require greater doses of enoxaparin to ensure adequate anticoagulation during dialysis (21).

Protamine is unable to completely reverse the anticoagulant effect of LMWH. Reduced protamine binding to LMWH and reduced sulfate charges in LMWH are among proposed mechanisms of incomplete reversal by protamine (22,23). However, in clinical conditions where the antithrombotic effects of LMWH require neutralization, protamine can be used. If LMWH was administered within 8 hours, protamine can be given at a dose of 1 mg per 100 antifactor Xa units LMWH (1 mg enoxaparin equals approximately 100 antifactor Xa units). A second dose of 0.5 mg protamine per 100 antifactor Xa units may be administered if needed. Smaller doses can be considered if LMWH was administered more than 8 hours before (19). In a case report, recombinant factor VIIa was used to stop postoperative bleeding in an end-stage renal disease (ESRD) patient after LMWH (24).

In a meta-analysis of 11 randomized trials, the safety and efficacy of LMWH was compared to UFH in ESRD patients who required chronic intermittent hemodialysis or hemofiltration. It was found that LMWH did not significantly affect the number of bleeding events assessed by vascular access compression time or extracorporeal circuit thrombosis as compared with UFH (25). A prospective randomized controlled clinical trial compared the efficacy, safety, and cost of fixed-dose LMWH (dalteparin) with adjusted-dose UFH as an anticoagulant for continuous hemofiltration in adult intensive care unit patients requiring continuous hemofiltration for ARF or systemic inflammatory response syndrome (SIRS). Dalteparin-treated patients received a bolus of 20 U/kg and a maintenance infusion of 10 U/kg/hr. Heparin-treated patients received a bolus of 2000–5000 units and a maintenance infusion of 10 U/kg/hr, titrated to achieve an

aPTT of 70–80 seconds. Fixed-dose dalteparin provided identical filter life, comparable safety in terms of bleeding, but increased total daily cost, including coagulation assays (approximately 10% higher), compared with adjusted-dose heparin (26).

In summary, UFH and LMWH appear to be effective methods of anticoagulation in CRRT. However, given the potential deleterious effects, such as bleeding and HIT, alternative anticoagulation methods should be considered in patients who have developed or are at risk for these complications.

No Anticoagulation

The efficacy of CVVH without anticoagulation was compared with heparin or regional heparin/protamine. Of 300 consecutive circuits, 143 (47.6%) received no anticoagulation. Platelet count was significantly lower in the no-anticoagulation group (73,000/ μ l) compared with the low-dose heparin group (119,000/ μ l) and the protamine group (104,000/ μ l) ($p < 0.01$ for both comparisons). There was no significant difference in mean extracorporeal circuit life among the three groups and no patient experienced bleeding complications (27).

In another study, patients at high bleeding risk were compared with those treated with prefilter low-dose heparin during CVVH. Mean extracorporeal circuit life was significantly longer in the no-anticoagulation group. The coagulation profile in the no-anticoagulation group differed from the control group in that the International Normalized Ratio (INR) was longer and the platelet count lower. However, hemofilter life span was not significantly correlated with INR, aPTT, or platelet count in either group (28). Bellomo et al. reported that in patients at high risk of bleeding, continuous venovenous hemodialysis (CVVHD) without anticoagulation provided an adequate mean filter survival of 40.9 hours (95% CI 27–54.8) (29).

In conclusion, for a group of so-called autoanticoagulated patients deemed to be at risk of bleeding, CRRT with no anticoagulation seems to be safe and provides an acceptable filter life span.

Regional Heparin

Another alternative for patients at high bleeding risk is regional anticoagulation with heparin and protamine. The efficacy and safety of this method was compared to no anticoagulation in a group of high-risk patients. The regional anticoagulation regimen used a continuous infusion of a UFH solution (500 IU/ml) into the arterial line. The infusion rate (in IU/hr) was determined using the following formula: $9 \times \text{blood flow (in ml/min)}$. A continuous and simultaneous infusion of protamine hydrochloride (5 mg/ml) into the venous line starting at a 1:100 ratio (protamine 1 mg/heparin 100 IU) was used. Heparin and protamine infusion rates were adjusted ($\pm 20\%$) according to the circuit aPTT (arterial line postheparin) and patient aPTT (arterial line preheparin) values, aiming to achieve a circuit aPTT greater than 55 seconds

and a patient aPTT of less than 45 seconds or closer to the starting value. Patients with a filter life span of less than 24 hours were shifted to regional heparin/protamine. This study concluded that in high-risk patients, when no anticoagulation is ineffective, regional heparin/protamine provided a safe and effective alternative (30). In liver transplant patients requiring CVVH, regional anticoagulation with heparin/protamine also provided a filter life span that was comparable to systemic anticoagulation with heparin (31). However, in another study, regional anticoagulation with heparin/protamine resulted in a significantly shorter filter life span (32).

In conclusion, regional heparin/protamine anticoagulation in CRRT may be considered in patients at high risk of bleeding who fail to have an acceptable filter life span with no anticoagulation.

Hirudin

Hirudin, a 65-residue peptide from the salivary gland of the European leech *Hirudo medicinalis*, is a highly specific and effective thrombin inhibitor that can be used in patients that develop HIT after heparin. Since it is renally excreted, it has a longer half-life in patients with chronic kidney disease and can result in bleeding. Close monitoring is performed by measuring r-hirudin blood levels by ecarin clotting time (ECT) or chromogenic assays, in addition to aPTT (18,33,34). There is no effective antidote for hirudin and its recombinant derivatives (r-hirudin). In an animal study, activated prothrombin complex (APC) concentrate was able to decrease the anticoagulation effect of r-hirudin (35). Recombinant factor VIIa was also used in postoperative hirudin-induced bleeding (36). High-volume hemofiltration with r-hirudin-permeable hemodialyzers such as high-flux polysulfone may be used to reduce r-hirudin blood concentrations in case of overdose or bleeding (34,37,38).

In a prospective controlled study, the safety and efficacy of intermittent hirudin was compared with continuous heparin in patients receiving CRRT. The hirudin group received an initial bolus of 2–5 μ g/kg. The dose was adjusted in 2 μ g/kg bolus steps with a targeted ECT greater than 80 seconds, and in the heparin group continuous administration of 250 IU/hr heparin. The dose was adjusted in 125 IU/hr steps with a targeted ACT of 180–210 seconds. Over 96 hours of observation, filter life span was longer in the heparin group compared to hirudin. One of 12 patients on hirudin and 2 of 14 on heparin had bleeding (39). In another study, there was no difference in filter life span, but the risk of bleeding was higher in the hirudin group compared to heparin (40). In conclusion, r-hirudin can be used for CRRT; however, more studies are needed to fully evaluate appropriate dosing and safety.

Argatroban

Argatroban is a direct thrombin inhibitor synthesized to bind the catalytic site of thrombin. It binds rapidly and reversibly to both clot-bound and soluble thrombin. The relatively short elimination half-life (39–51 minutes)

and reversible binding allow rapid achievement of therapeutic effect on initiation of therapy and rapid restoration of normal hemostasis upon cessation (41). Argatroban is hepatically metabolized, but not cleared by the kidneys. Dose reduction should be considered in patients with liver failure. The recommended initial dose is 2 µg/kg/min (0.5 µg/kg/min in hepatic impairment) adjusted to achieve aPTT values 1.5–3.0 times baseline (42). It can be used in patients on renal replacement therapy who develop HIT. Since it is a direct thrombin inhibitor, it can also be considered in patients that have congenital or acquired antithrombin deficiency, and consequently are resistant to heparin (43).

Published data about the safety and efficacy of argatroban during CRRT is scant. However, the available data suggest that it may provide effective alternative anticoagulation with an acceptably low risk of bleeding in patients with or at risk for HIT during renal replacement therapy. In one of the largest reported studies on renal replacement therapy and argatroban, safety and efficacy were evaluated in 47 patients, including 14 on CRRT. Major bleeding occurred in 3 of 50 treatment courses (6%) (42). Argatroban clearance by high-flux membranes during hemodialysis and CVVH is clinically insignificant, necessitating no dose adjustment (44).

Prostacyclin

Drugs such as prostacyclin and prostaglandin E1 that inhibit interaction between platelets and artificial membranes were introduced as an alternative anticoagulant strategy for CRRT (45). Prostacyclin as a substitute for heparin in chronic dialysis patients has been reported to be safe and also associated with increased efficiency of hemodialysis (46). Hemodialysis activates both platelets and leukocytes, which might play a role in the development of multiple organ dysfunction in critically ill patients. Prostacyclin reversibly inhibits platelet function by diminishing the expression of platelet fibrinogen receptors and P-selectin and reduces heterotypic platelet-leukocyte aggregation, but not leukocyte activation during hemofiltration (47).

In one study, the safety and efficacy of a synthetic prostacyclin analog (epoprostenol) as a sole anticoagulant during CVVH in patients with ARF was evaluated. Four patients out of 51 (7.8%) experienced major bleeding (1.0 episode per 1000 patient-hours of treatment; 95% CI 0.4–2.6), and a therapeutic intervention for hypotension (fluids or vasopressors) was required in 15.5% of CVVH sessions monitored. The median life span of the extracorporeal circuit was 15.0 hours (95% CI 13.0–16.5) (48). In another study, citrate anticoagulation offered longer filter survival during continuous hemofiltration compared to the combination of prostacyclin (PGI₂) and heparin and was less expensive (49). However, comparative studies suggest that prostaglandins may be more effective in decreasing hemofilter failure and are also associated with less bleeding risk than UFH during CRRT in patients at high risk of bleeding (50,51). The combination of heparin and prostacyclin during

CVVH may provide a better hemodynamic profile and enhanced hemofilter duration compared with either agent alone (52).

Patients with fulminant hepatic failure and ARF are at risk of dying from cerebral edema. The direct administration of prostacyclin, used for extracorporeal anticoagulation, may cause a further increase in intracranial pressure and reduce cerebral perfusion, thus resulting in patient morbidity and mortality (53,54). In patients with respiratory and renal failure who require inotropic support, prostacyclin may result in reductions in systemic and pulmonary vascular resistances and mean arterial pressure. The subsequent increase in pulmonary ventilation/perfusion mismatch can result in decreased tissue oxygen delivery and uptake, and ultimately worsening of acidosis and lactate production (52,55). In summary, it appears that the current available data support the combination of heparin and prostacyclin as a more effective method if prostacyclin is used. However, given the possible adverse hemodynamic consequences of prostacyclin, other effective anticoagulation methods such as citrate may need to be considered in patients with significant hemodynamic compromise.

Predilution and Nafamostat

Predilution CVVH by decreasing the viscosity of blood in the circuit may decrease dialyzer clotting risk. In one study, predilution CVVH resulted in the greatest filter run time, but a lower creatinine clearance compared to postdilution (32). Nafamostat is a synthetic serine protease inhibitor that is mainly used in Japan. It has been suggested that it is safer than anticoagulation with regional or low-dose heparin. However, because it is adsorbed by negatively charged membranes, it cannot be used as an anticoagulant with polyacrylonitrile membranes (56,57).

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