Review article

ANTICOAGULATION DURING CONTINUOUS RENAL REPLACEMENT THERAPY: AN UPDATE.

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Abstract

Renal replacement therapy in Intensive Care Units is a daily practice worldwide. Ensuring blood flow continuum within extracorporeal circuit is one of the basic tasks during therapy. Unfractionated heparin remains the most popular anticoagulant used. Alternatives, such as low molecular weight heparins, prostacyclin, fondaparinux, or regional use of citrate or nafomostate mesilate are also gaining ground, mainly due to their safety profile. Still, there is no worldwide consensus about their use. Systemic, regional, combined or no coagulation at all; the final choice depends on the patients' characteristics and co-morbidities, as well as institutional and organizational protocols, equipment availability and staff education. This article presents a review of the current modalities for anticoagulation during continuous renal replacement therapy.

Keywords: anticoagulation; continuous renal replacement therapy

Introduction

Acute renal dysfunction is substantially contributing to morbidity and mortality among critically ill patients¹. In the intensive care unit (ICU) renal replacement therapy (RRT) has proven its role in the management of patients with – acute and chronic- renal failure; although reports about long-term outcome of these patients are controversial^{2,3}.

RRTs include intermittent hemodialysis, peritoneal dialysis, continuous renal replacement therapies (CRRTs), and hybrid therapies such as prolonged intermittent renal replacement therapies (PIRRTs), which provide prolonged but still intermittent dialysis. Narrower terms used to describe PIRRT include sustained low-efficiency (daily) dialysis (SLEDD), sustained low-efficiency (daily) diafiltration (SLEDD-f), extended daily dialysis (EDD), slow continuous dialysis (SCD), go slow dialysis, and accelerated venovenous hemofiltration (AVVH)^{4,5}.

In general, RRT therapy is chosen based upon the patients' characteristics and institutional avail-

ability. In the dynamic ICU environment, CRRTs are the most popular type of RRT, as it is related to fewer episodes of hemodynamic instability and better control of fluid balance⁶.

One of the most essential issues during CRRT is ensuring continuous extracorporeal blood flow without clotting, both within the circuit (especially in central venous catheter for RRT) and the artificial filter. However, anticoagulation strategy during CRRT needs special attention and balancing between the life of the artificial extracorporeal circuit and the danger for patient bleeding^{7,8}.

The current article provides a review of the literature about the methods of anticoagulation during CRRT.

Unfractionated Heparin

Unfractionated heparin (UFH) is a heterogeneous mixture of glycosaminoglycans with molecular weight 5000–30000 Daltons kiloDaltons. It acts by forming a complex with antithrombin III (ATIII), catalyzing the inhibition of several activated (a) blood coagulation factors: thrombin (factor IIa),

Christmas factor (FIXa), Stuart factor (FXa), plasma thromboplastin antecedent (factor XIa) and Hageman factor (FXIIa)⁷. UFH is metabolized by the liver and metabolites are excreted by the kidneys. Heparin is heterogeneous in regard not only to its molecular weight but also to its anticoagulant effects and its pharmacokinetics. Its half life is dose-dependent ranging from 30 to 180 minutes⁹. However, it is considered as the classic choice for anticoagulation during CRRT, mainly because of its low cost, high availability and ease of administration^{10,11}.

Dosing of UFH during CRRT is usually based on measured activated partial thromboplastin time (APPT) or activated clotting time (ACT). The target treatment for APPT ratio is between 1.2–1.5 and 120–180 sec for ACT^{6,7}.

In practice, development of local (bedside) protocols should be used. Each protocol includes every aspect of UFH anticoagulation during CRRT and incorporates possible local characteristics (institutional, organizational). Key points in every protocol: 1) the need or not for priming the circuit before initiation of therapy, 2) starting dose, 3) monitoring parameters, measuring interval and target, 4) modification of dose, 5) other (e.g. handling complications and emergencies). A parallel quality assurance strategy (staff education, assessment meetings, etc.) should also be in place. In general, a filter life of 20–24 h is common when a UFH anticoagulation protocol is „working”.

A simple example of such protocol is displayed table 1.

Despite its popularity, UFH should be administered with caution during CRRT. First of all, be-

cause the basic assay for monitoring UFH therapy (APPT) is just a surrogate marker for estimation of heparin concentration, which is susceptible to several confounding factors¹¹. In other conditions, like deep venous thrombosis, weight-based nomograms have been suggested in order to overcome difficulties delivering UFH¹². Yet, in CRRT several authors claim that Anti-Factor Xa (anti-FXa) levels may provide better and more reliable monitoring; however, even these levels show considerable inter-laboratory variation, and there are insufficient clinical studies proving improved clinical efficacy^{14–16}.

The above creates additional problems in a seemingly simple problem: UFH reversal. Protamine dosing is generally 1–1.5 mg per 100 UI of Heparin, yet time elapsed from heparin administration modifies the regiment to 0.5–0.75 mg / 100 units UFH if 30–120 min has passed, or 0.2–0.375 mg/100 UI UFH, if time elapsed is > 2 h. APPT should be monitored 5–15 min after dose and then every 2–8 h¹⁷. Some authors suggest an alternative to sole UFH protocol, with Heparin administration (at 1000 UI/h) prefilter and protamine administration (at 10 mg/h or 1:100 ratio) postfilter into venous chamber or directly into the return limb of the access catheter (via a suitable Y piece, but not a three-way tap)¹⁸. In any case, attention is needed because protamine can trigger serious adverse effects, such as anaphylactoid reactions, hypotension and catastrophic pulmonary vasoconstriction¹⁹.

Along with that, UFH use is not without complications. Bleeding, defined as a decrease in hemoglobin ≥ 1.5 gr/dl, below the level at initiation of CRRT often leads to transfusion of one or more units of red

Table 1. An example of UFH CRRT protocol (authors' protocol).

APTT (seconds)	Bolus dose	Rate change
<40	1000-2000 UI*	+200 UI/h (do not exceed 20UI/kg/h)
40.1-45	Nothing	+100UI/h (do not exceed 20UI/kg/h)
45.1-55	Nothing	No change
55.1-65	Nothing	Stop 30 min and -100 UI/h
>65	Nothing	Stop 1h and -200UI/h

*UI: International Units

Heparin solution: 1ml of 10000 U/ml of UFH in 19 ml of NaCl 0.9% (500U/ml)

Initial bolus 20 UI/kg, followed by infusion of 5 UI/kg/h

Monitoring APTT/ 4h

blood cells²⁰. In case of increased (bleeding) risk, higher circuit blood flow is recommended²¹.

Heparin-induced thrombocytopenia (HIT) is heparin's most clinically relevant non hemorrhagic complication. HIT Type I caused direct effect of heparin on platelets and HIT II is caused by antibodies to complexes of platelet factor 4 (PF4) and heparin²². In patients in CRRT, HIT II is usually observed²³. Clinically, thrombocytopenia with both arterial and venous thrombosis is the main feature of HIT II²⁰. Additionally, recent reports suggest that CRRT *per se* may also be a thrombocytopenia-related factor²⁴. Regardless of the latter, HIT probability should be calculated in all patients before CRRT, either via 4Ts Score or by newer HIT Expert Probability (HEP) score. While the 4Ts score system calculates the risk for HIT after considering selected parameters (Table 2), the HEP score uses more variables such as skin necrosis, acute skin reaction and the presence of bleeding²⁵.

In general, patients with a baseline APPT > 55 sec, platelet count < 40000/mm³, allergy in heparin, prior history of heparin induced thrombocytopenia or high 4Ts or HEP score, incident of intracranial or gastrointestinal hemorrhage within the previous three months, active bleeding or significant trauma within 3 days and evidence of

irreversible coagulopathy because of liver failure should not receive heparin during CRRT²⁶.

Other side effects of UFH are hypertriglyceridemia (releases and depletes endothelium-bound lipoprotein lipase), osteoporosis and hypoaldosteronism¹⁰. Furthermore, it should be kept in mind that conditions, like sepsis or systemic inflammation, require special caution due to reduction of ATIII concentration as a result of its consumption or proteolytic degradation²⁷. In the latter, an ATIII supplementation protocol has been suggested. The supplementation protocol aims to achieve a plasma ATIII level greater than 110 to 120%. Each time that ATIII activity drops below 70% (measurement before CRRT), 50 UI/kg ATIII is administered intravenously. The fixed daily 50 UI/kg dose regimen of ATIII supplementation is chosen because of the 1.7% per UI/kg AT response and a mean half-life of 18.9 hours are expected in these patients, as reported^{28,29}.

Low Molecular Weight Heparins

During the last decades, low molecular weight heparin (LMWHs) are replacing UFH as anticoagulants in CRRT. This increasing tendency, despite

Table 2. HIT score. Applying the scoring system to suspected patients produces a totalled score between 0 and 8. Scores of 0 to 3, 4 to 5, and 6 to 8 are respectively classified as low, moderate, and high probability for HIT.

Points	2	1	0
Thrombocytopenia	>50% fall or PLT nadir >20 × 10 ⁹ L ⁻¹	30-50% fall or PLT nadir 10- 19 × 10 ⁹ L ⁻¹	<30% fall or PLT nadir 10 × 10 ⁹ L ⁻¹
Timing of PLT fall	Clear onset between days 5 and 10 or platelet fall ≤ 1 day (prior heparin exposure within 30 days)	Consistent with days 5–10 fall, but not clear (e.g. missing platelet counts) or onset after day 10 or fall ≤ 1 day (prior heparin exposure 30–100 days ago)	Platelet count fall < 4 days without recent heparin exposure
Thrombosis or other sequelae	New thrombosis (confirmed) or skin necrosis at heparin injection sites or acute systemic reaction after intravenous heparin bolus	Progressive or recurrent thrombosis or nonnecrotizing (erythematous) skin lesions or suspected thrombosis (not proven)	None
Other causes of thrombocytopenia	None apparent	Possible	Definite

the higher cost, could be attributed to the clinical benefits of LMWHs over UFH (Table 3).

Their longer half-time, low affinity to endothelial cells, plasma proteins, macrophages and ab-

Table 3. Comparative statements between UFH and LMWHs^{9,10,30,31}.

Characteristic	UFH	LMWHs
Availability for antithrombin reaction	30%	>85%
AntiXa/AntiIIa ratio	1:1	>2-9.7:1
Molecular weight-(MW) (kDa)	15 (4-30)	4.5 (2-10)
Half-time ($T_{1/2}$)	Short (~1h, dose-dependent)	Longer, more predictable
Bioavailability	Low	Higher than UFH
Dosage regiment	Frequent	Less frequent
Clearance	Hepatic	Renal
Bleeding tendency	High	Lower than UFH
Thrombocytopenia	High	Lower than UFH
Osteoporosis propensity	High	Lower than UFH
Therapeutic response	Variable	Predictable
Reversal	Fully with protamine	Partially with protamine
Laboratory monitoring	Essential	See text for monitoring*

LMWHs are produced by depolymerization of the long oligosaccharide chains of UFH into smaller chains. The different depolymerization methods (chemical or enzymatic β -elimination, oxidative cleavage or nitrous depolymerization) result in LMWHs with distinct characteristics (Table 4).

Tests for monitoring LMWH's include anti-factor Xa (anti-FXa), activated partial thromboplastin time (APTT) and thrombin generation. Since they have predominantly anti-FXa activity, it is appropriate to monitor their levels by an anti-FXa chromogenic assay³⁹ (detection limit of 0.01 UI/ml). Therapeutic levels are defined as 0.5–1 UI/ml and levels below 0.5 UI/ml are considered insufficient, while above 1 UI/ml are considered excessive anticoagulation^{39–41}. Thrombin generation with tissue factor-rich activator is an alternative promising method for monitoring LMWHs⁴².

Heparin complications (Bleeding, HIT) can also be triggered by LMWHs, although less often and in milder forms¹⁰. In case of hemorrhage due to overdose, protamine is not as efficient as in UFH overdose and fresh frozen plasma (FFP) or recombined activated factor VII (rFVIIa) may be needed⁴³.

sence of clearance by the different modes of RRT, allow for one single bolus dose at start of therapy, in case of intermittent hemodialysis or PIRRT⁸. For CRRT, the most adopted strategy most is either an initial bolus followed by a continuous infusion or intermittent boluses every 6 hours⁴⁶. An alternative regimen is to omit the loading dose and simply start with a continuous intravenous infusion (civ) (Table 5).

Dermatan sulfate

Dermatan sulfate is a natural heparinoid that also has been used for CRRT anticoagulation. It acts by selectively inhibiting thrombin and it does not inhibit factor Xa and does not interfere with platelets. Dosing include a bolus loading of 150 mg followed by an infusion of 12–13 mg/h⁵². Measuring APPT is suggested as monitoring method.

Table 4. Comparative table of LMWHs³²⁻³⁹.

	MW (kDa)	T _{1/2} (h)	Bioavailability (%)	AntiXa/AntiIIa ratio	AntiXa activity (UI/mg)
Nadroparin	4.3	3.7	89	3.5	100
Enoxaparin	4.5	4.5	90-92	3.8	100
Dalteparin	6	3-5	87	2.7	156
Bemiparin	3.6	5.1	96	8.1	110
Certoparin	5.4	6	>90	2.4	
Parnaparin	5	4	~100	2.3	
Reviparin	4.4	3	95	4.2	124
Tinzaparin	6.5	3.4	87	2.8	100
Ardeparin	5.5-6.5	3.3	92	1.7-2.4	

Table 5. Examples of LMWHs used for CRRT.

LMWH used	Initial bolus	Maintenance dose	Anti FXa –level activity (UI/ml)	Monitoring interval
Enoxaparin [44]	0.15 mg/kg	0.05 mg/kg/h	0.25-0.3	6h
Enoxaparin [45]		0.5-0.7 mg/kg/12h	0.5-1	12h
Enoxaparin [46]		1.5mg/kg per 24h	0.07-1.26	6h
Enoxaparin [47]	0.5 mg/kg	1mg/kg/day	0.29	
Tinzaparin [48]		400-800 UI/h	*	*
Nadroparin [49]	0.6 ml	0.3 ml/4h	*	*
Dalteparin [50]		600 UI/h	0.3-08	*
Dalterparin [51]	2000 UI	320 UI/h	0.5-1	*

* not available

Danaparoid

Danaparoid is a low molecular weight (5 kDa) heparinoid glycosaminoglycuronan antithrombotic agent that contains a mixture of heparan sulfate (84%), dermatan sulfate (12%) and chondroitin sulfate (4%). It acts mainly via ATIII and on factor IIa (Anti-Xa / Anti-IIa activity ration > 20:1)⁵³. In CRRT, it has been used in patients with high risk of HIT in the following dosing regiments: 1) 750UI loading bolus followed by 50-150UI/h civ or 2) 3500 UI bolus followed by 100 U/h civ, aiming at anti-Xa levels of 0.5–0.7 U/ml^{54,55}.

Fondaparinux

Fondaparinux is the only synthetic pentasaccharide factor Xa inhibitor (Table 5) that has been used in CRRT.

Yet, data are limited to case reports or case series. In such a case (patient with HIT type II), dosing regimen of 2.5 mg instilled directly into the dialysis circuit was chosen⁵⁷; while in case of RRT (Intermittent Hemodialysis), fondaparinux 0.05 mg/kg actual body weight was administered on days of dialysis. Dosing was increased to a maximum dose of 0.08 mg/kg actual body weight based on anti-factor Xa levels⁵⁸. Still, the optimal fondaparinux dosage remains unknown. Thus, peak

Table 6. Comparative table of synthetic Factor Xa inhibitors⁵⁶.

	Fondaparinux	Idraparinux	Idrabiotaparinux
Bioavailability	100	100	100
Half-life	17-21 hours	80-130 hours*	60 days
Dose	2.5-10 mg	2.0 mg	3.0mg
Elimination	Renal	Renal	Renal
Antidote	No	No	Avidin

*can be increased to 600 hours in subsequent dosing

anti-factor Xa concentrations may be essential for guiding therapy⁵⁹.

Hirudin, Lepirudin and Bivalirudin

Hirudin and its analogs, lepirudin (recombinant hirudin) and bivalirudin, act independently of PF4 and cofactors; thus has been used as an alternative in patients with HIT^{60–66}. For CRRT, lepirudin is administered either as a continuous infusion (0.005–0.01 mg/kg/h) or delivered in bolus doses (0.2 mg/kg); while bivalirudin is administered pre-filter in 0.009–0.023 mg/kg/h (1–2.5mg/h)^{62–66}. Although, APPT can be used as monitoring tool (aiming at 1.5–2.5 times baseline), there is no linear correlation with anticoagulation activity. Instead specialized tests such as ecarin clotting time (ECT) or hirudin ELISA have been suggested. Target for ECT during CRRT is 80–100 sec⁶⁴. In case of bleeding, no antidote exists and rFVIIa or FFP may be needed. Yet, in general, results from its use in CRRT are comparable with UFH protocols^{67–69}.

Argatroban

Argatroban is a monovalent direct thrombin inhibitor (DTI) with hepatic metabolism and a short half time (35 min). Although it does not require a dosage adjustment in patients with renal dysfunction or in patients undergoing RRT, up to 22% of the drug is renally excreted; thus, caution is needed⁷⁰. Half time may increase to 2.7 in cardiac surgical critical ill patients with HIT⁷¹. Monitoring is usually achieved via APTT or activated clotting time (ACT) measurements; although recent studies suggest thrombin time (TT) and rotational thromboelastometry (ROTEM)

as better alternatives⁷². Data about dosing vary: 1) initiation at 0.2 µg/kg/min at up to 3.1 µg/kg/min in accordance to APTT⁷³ 2) start at 0.5 µg/kg/minute, and adjustment in 0.1–0.25 µg/kg/minute increments⁷¹ or 3) a loading dose of 100 µg/kg followed by a maintenance infusion rate (µg/kg/min), which can be calculated from the scores as follows: for Acute Physiology and Chronic Health Evaluation (APACHE)-II: $2.15 - 0.06 \times \text{APACHE II}$; for Simplified Acute Physiology Score (SAPS) II: $2.06 - 0.03 \times \text{SAPS II}$; and for indocyanine green plasma disappearance rate (ICG-PDR): $-0.35 + 0.08 \times \text{ICG-PDR}$ ⁷⁴.

Oral Direct thrombin inhibitors, Direct factor X inhibitors and Warfarin

This group includes the oral DTI dabigatran and the factor X inhibitors apixaban, rivaroxaban and edoxaban. Given the need for oral access without the current ability to assess adequate absorption and level of anticoagulation with these drugs, this is likely to limit their use in CRRT⁷⁵. Although vitamin K antagonist warfarin has been studied in intermittent hemodialysis, there are no data for use in CRRT^{76–78}.

Tirofiban

Tirofiban, an antiplatelet agent, is the only glycoprotein IIB/IIA inhibitor (the group includes also abciximab and eptifibatide) used in RRT. Tirofiban in dose regiment 0.2 µg/kg/min bolus over 30 min followed by 0.05 µg/kg/min civ. has been used in conjunction with UFH (APTT target 2–3 times normal range) in patients with cardiogenic shock and acute kidney injury requiring CRRT⁷⁷.

In polymixina-B hemoperfusion a loading dose of 250 µg/kg has also demonstrated good results⁸⁰.

Prostacyclin

Prostacyclin (PGI₂) and other prostanoids have been used alone or in combination with UFH and LMWHs in CRRT⁸¹. Whereas their vasodilating effect lasts for 2 minutes, their antiplatelet effect continues for over 2 hours. Dosing in CRRT is 4–10 ng/kg/min *civ*. Limiting hypotension is achieved either by titrating to 0.5 ng/kg/min at the initiation of therapy or by restricting infusion at extracorporeal circuit only⁸¹. Other side effects include minimal increase in intracranial pressure (especially in hepatic failure), nausea, vomiting, chest pain, anxiety, bradycardia, tachycardia, dyspnoea, abdominal pain and ventilation perfusion mismatch (clinically significant in those with reflex hypoxic pulmonary vasoconstriction). ROTEM can be used in monitoring of anticoagulant effect⁸². Apart from hypotension and difficulty of monitoring, PGI₂ cost is another drawback for its wider application.

Nafomostate mesilate

Nafomostate mesilate (NM) is a synthetic proteinase inhibitor with short half life (5–8 min). It acts on plasmin, trypsin, kalikrein, thrombin, factor Xa and XIIa and tissue factor-factor VIIa complex. It has no antidote and serious side effects include agranulocytosis, hyperkalemia and anaphylactoid reactions⁸³. Yet, the use of NM as an anticoagulant during CRRT is associated with decreased incidence of bleeding complications compared with the use of UFH⁸⁴. Data about its use in CRRT comes mainly from Japan, where it is the most frequent CRRT anticoagulant⁸⁵. Filter is primed with 500 solution of NaCl 0.9% with 20 mg NM and then a maintenance infusion of 10–30 mg/h is administered⁸⁶. Monitoring is performed via APTT or ACT⁸⁷.

Citrate anticoagulation

Citrate is a small (191 Da) negative charged molecule that acts by forming citrate-calcium (ionized-iCa) complexes, thus depleting an essential co-factor of the coagulation process. Citrate-iCa

molecules are freely filtered and lost in effluent. The rest is metabolized in liver⁸⁰. Each molecule complex releases 3 molecules carbonate and 5 molecules calcium to circulation. The above create several difficulties during CRRT. For achieving anticoagulant effect citrate infusion is adjusted to blood flow in targeting a concentration of 3–6 mmol/l or aiming at a postfilter concentration of iCa of less than 0.35 mmol/l or postfilter ACT 200–250 sec⁸⁷. Since calcium is removed from the circulation, calcium infusion is added in order to maintain normal concentration range. Monitoring about metabolic derangements (hyponatremia, hypercalcemia, hypocalcemia, metabolic acidosis or alkalosis) and appropriate adjustments in citrate and calcium infusions are also essential during RRT. For example, accumulation of citrate due to decreased metabolism can be detected accurately by the symptoms of metabolic acidosis, increasing anion gap, ionized hypocalcemia, and most specifically by an increased total/iCa concentration (a ratio > 2.1 has 89% sensitivity and 100% specificity in predicting citrate concentrations)⁸⁸. In recent years, regional citrate anticoagulation (RCA) in CRRT has become increasingly attractive due to its beneficial low bleeding risk problem. Bai's meta-analysis study demonstrated that regional citrate anticoagulation for CRRT could prolong the filter lifespan and decrease the bleeding risk, compared with heparin anticoagulation⁸⁹. And the KDIGO guideline for AKI recommended RCA rather than heparin in patients who do not have contraindications for citrate. Even in liver failure (LF) patients considering the accumulation of citrate, a recent systematic review and meta-analysis pooled ten observational studies and demonstrated that the RCA might be safe and effective for LF patients underwent CRRT⁹⁰.

No anticoagulation, managing contributing factors and other alternatives

No matter how important anticoagulation strategy is, filter life and efficiency is depending on other numerous factors. A recent meta-analysis favors higher blood flow rates and continuous veno-venous hemodiafiltration (CVVHDF) over continuous veno-venous hemofiltration (CVVH)⁹¹. CRRT has also been performed without anticoagulation with 100–150 ml NaCl 0.9% circuit flush

/ hour⁹². Along with that, technology membranes' progresses over the last years are moving towards limiting anticoagulation needs. Future research might enable use of other intravenous anticoagulant or antiplatelet agents during CRRT (e.g. the adenosine diphosphate receptor inhibitor cangrelor, the thromboxane receptor antagonist terutroban, the phosphodiesterase inhibitor cilostazol or the adenosine reuptake inhibitor dipyridamole).

Conclusion

There are several choices for anticoagulation during CRRT. Yet, the decision to use one over another is a complex task. On one hand, the patient's condition, comorbidities and special characteristics; on the other hand, organizational/ institutional factors, staffing and level of education/experience, type/modes of RRT used, availability of agents chosen and application of a quality assurance program are determinants of the decision about both the anticoagulant and the protocol to be followed.

Author Disclosures:

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