



Anticoagulation strategies in continuous kidney replacement therapy — does one size fit all?

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Introduction

The field of critical care nephrology (CCN) in children has seen a number of advances in the last two decades — newer machines, membranes, solutions and in fact, there is no other subspeciality which has made so much progress as the field of CCN. One of the key elements which determine the successful running of the continuous kidney replacement therapy (CKRT) circuit in these sick children is the longevity of the circuit used, thus minimizing the downtime and increasing the efficacy of treatment. After optimising circuit and vascular access factors, we need to choose an anticoagulant which is selectively active in the circuit, yet having minimal effects on the child's systemic circulation.

In fact, systematic reviews on quality of CKRT programmes have listed filter life as one of the most important determinants of delivery of successful CKRT [1, 2]. The need for anticoagulation was demonstrated by Brophy et al. from the prospective pediatric CRRT (ppCRRT) Registry when it was shown that filter life was much better in patients in whom regional citrate anticoagulation (RCA) or regional unfractionated heparin (UFH) was used as an anticoagulant as compared to those patients in whom no anticoagulation was utilised [3].

There are numerous reasons why changing filters frequently can have adverse effects. It is the down time for the treatment which has the most deleterious effect on the efficacy of CKRT. It has been convincingly shown that the more downtime, the lower the prescribed dose delivered and the less efficacious the desired therapy. Changing the filters

and circuit frequently will add to the substantial financial burden. In addition, there is loss of blood when the circuit clots leading to more blood transfusion.

In this group of critically sick patients who require kidney replacement therapy in the intensive care setting, it can be quite tricky to have a balance between anticoagulation required to maintain the patency of the circuit versus preventing systemic bleeding. An ideal anticoagulant strategy should be readily available, selectively active in the extracorporeal circuit, with minimal effects on patient haemostasis. Anticoagulation of CKRT should ideally provide filter survival beyond 48 h. The monitoring should be rapid, simple, and in the case of complications, anticoagulation should be rapidly reversible. An important practical consideration is that the staff involved should be well trained in the use and recognition of side effects of the anticoagulant used.

There are various anticoagulants in use depending on the mechanism of action and which part of the coagulation system is affected (inhibitors of intrinsic, extrinsic or common coagulation cascade, inhibitors of platelet activation and aggregation or direct inhibitors of thrombin generation). Table 1 shows some commonly used anticoagulants along with their respective monitoring strategy. Each one has its advantages, disadvantages, ease of use and cost implications. Therefore, it is very important to understand the mechanism of action of each anticoagulant in order to understand the group of patients in which we would or would not use that particular anticoagulant and the anticipated complications.

Besides the standard RCA, UFH and low molecular weight heparin (LMWH), feasible options which can be potentially used are unfractionated heparin with protamine reversal, nafamostat mesilate, prostacyclin, argatroban and bivalirudin. It is extremely important to monitor the efficacy and side-effects of the anticoagulants we use. In centres, which use unfractionated heparin, there seems to be a lack of correlation between heparin dose and standard clinical monitoring tests like the activated partial thromboplastin time (aPTT) or activated clotting time (ACT), because of which some centres have attempted

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Table 1 Commonly used anticoagulants with suggested monitoring strategy

Anticoagulant	Monitoring
UFH	ACT aPTT Anti Xa levels
Regional UFH with protamine	Patient and circuit ACT and aPTT
LMWH	Anti Xa levels
RCA	Circuit and patient iCa
Direct thrombin inhibitors – argatroban, bivalirudin	ACT aPTT
Serine protease inhibitors – nafamostat mesilate, aprotinin	ACT aPTT
Combination of anticoagulants	
- Regional UFH plus regional prostacyclin	ACT/aPTT
- Subcutaneous LMWH plus RCA	Anti Xa plus circuit/patient iCa
- RCA plus systemic UFH	Circuit/Patient iCa, plus ACT/aPTT

ACT, activated clotting time; aPTT, activated partial thromboplastin time; iCa, ionised calcium; LMWH, low molecular weight heparin; RCA, regional citrate anticoagulation; UFH, unfractionated heparin

to use anti-Xa levels to accurately monitor the effect of UFH [4, 5]. Similarly, rigorous monitoring of ionised calcium whilst using RCA might not always be available in all centres. Depending on the availability of the drug and local expertise, clinicians tend to use other alternative anticoagulants, some of which are described below.

Epoprostenol is a prostaglandin that is a potent inhibitor of platelet aggregation, has an extremely short half-life and has been shown to be useful in patients with contraindications to UFH or heparin-induced thrombocytopenia and in patients with liver failure [6]. Side-effects include vasodilation leading to systemic hypotension and tendency to develop raised intracranial hypertension. No special monitoring is required and in case of side-effects, thromboelastogram (TEG) can be performed. Recommended dose for anticoagulation ranges between 2 and 8 ng per kg per minute administered regionally [7].

Argatroban is a direct thrombin inhibitor which is mainly metabolised in the liver and has a short half-life of 35 min. Therefore, it can be used in patients with bleeding tendencies and in patients with kidney failure without liver failure [8]. In case a patient has combined kidney and liver failure, bivalirudin, a hirudin analogue, can be used. It has a short half-life (25 min) and has extra-renal and extra-hepatic clearance. It reversibly binds to both the active and fibrin-binding sites of thrombin. aPTT is used to monitor the effect of thrombin inhibitors.

Study by Miyaji et al.

The study published by Miyaji et al. compares the safety and efficacy of two anticoagulation strategies (nafamosat mesilate (NM) versus RCA) in 2 different centres — one

in the USA and one in Japan. Though NM is not a new anticoagulant, its efficacy as an anticoagulant in CKRT in pediatrics had previously been tested only in those children who had a higher risk of bleeding, thus introducing an indication bias which could have rendered the efficacy claim speculative. In this study, the authors established that both strategies had similar filter lives with no major difference in bleeding rates [9]. The lack of difference in filter survival persisted even when controlled for filter surface area, catheter diameter and pre-CKRT platelet count. Studies like these are much needed to expand our horizon beyond our ‘norm’. NM is a synthetic protease inhibitor that works as an anticoagulant and anti-fibrinolytic by inactivating the action of thrombin and activated clotting factors XIIa and Xa. Centres in Japan and Korea have been using NM for many years now. Since NM is not used in many other centres, it was time that the efficacy and safety of NM be compared to an anticoagulation regimen which has established itself as standard of care in a number of centres. The authors have reassuringly found that the efficacy and safety of NM is comparable to RCA. Another important finding in the manuscript is the superiority of NM in patients with liver dysfunction in maintaining circuit patency (38.4 (21.7–76) vs. 22.3 (15.8–55.9) hours, $p = 0.02$) without increasing bleeding risk. Though this study was retrospective, it does add another choice to the armamentarium of a very limited number of anticoagulants used in liver failure. The authors very rightly conclude that NM can be used as an alternative to unfractionated heparin where there is a bleeding risk or an alternative to RCA where there is a risk of citrate accumulation/citrate toxicity, as in patients with liver failure. NM seems to be one-third the cost of RCA. There was heterogeneity in the study populations at the two centres (overall as well as the

liver sub-group); therefore, to establish the validity of the findings of this study, prospective comparison between the two drugs needs to be conducted.

This manuscript opens up a wider discussion on the choice of anticoagulant in CKRT and whether we need to be more diverse in our choice based on a patient's underlying disease process and the pros and cons of this strategy. There are patients with diverse underlying disease processes (patients at risk of bleeding or with bleeding diathesis, liver failure, patients undergoing extracorporeal membrane oxygenation (ECMO) or tandem therapies, neonatal population or more recently patients with COVID-19 who are hypercoagulable) which might affect the pharmacokinetics and pharmacodynamics of the administered anticoagulant. These critically ill children have specific changes which can make them prone to clotting — for example, they have a decrease in the concentration of natural anticoagulants (secondary to sepsis, multi-organ failure, transfusion of blood products) and an increase in the degradation of antithrombin by elastase making them more prone to being pro-coagulant. This has implications for the action of anticoagulants. Therefore, in an ideal world, the choice of the anticoagulant should be disease-specific to maximise efficacy and minimise side-effects. However, practically, can this be safely done in CKRT programmes where the staff have to use different drugs for different diseases? One would have to balance the risks and benefits

in making such a decision. Table 2 summarises common clinical conditions and suggested anti-coagulation regimen for those conditions.

How do we choose one anticoagulant over the other?

Choice of an anticoagulant for CKRT depends on the patient's underlying clinical condition, anticipated side-effects of the anti-coagulant being used, and very importantly availability of the drug and cost implications. Staff who would be running the CKRT machine should be familiar with its use, side-effect profile and trouble-shooting skills.

Anticoagulation strategy in specific disease states

Children at risk of bleeding/actively bleeding or who develop heparin-induced thrombocytopenia

Ranging from using no anticoagulation to the use of heparin-coated membranes has been advocated in this group of patients. Though surface-modified versions of the AN69 membranes have been developed, clinical data demonstrating acceptable circuit lives during CKRT performed with no

Table 2 Suggested anticoagulation strategy based on patient's clinical condition

Patient condition	Suggested anticoagulant
Active bleeding or at risk of bleeding patient or heparin-induced thrombocytopenia	No anticoagulation Saline flushes Regional citrate anticoagulation Prostacyclin (Regional) Nafamostat mesilate Argatroban
Liver failure	Prostacyclin Low dose heparin Nafamostat mesilate RCA (depending on the severity of liver failure) with close monitoring for citrate toxicity Bivalirudin
Neonatal population	UFH RCA Prostacyclin
CKRT with ECMO	Same systemic anticoagulation as used for ECMO
Tandem CKRT with TPE	Same anticoagulation for TPE as for CKRT
Anticoagulation during pandemic	Entirely resource based – UFH, RCA, prostacyclin In hypercoagulable state: <ul style="list-style-type: none"> • Combination of anticoagulants <ul style="list-style-type: none"> - Regional UFH plus regional prostacyclin - Subcutaneous LMWH plus RCA - RCA plus systemic UFH

CKRT, continuous kidney replacement therapy; ECMO, extracorporeal membrane oxygenation; LMWH, low molecular weight heparin; RCA, regional citrate anticoagulation; TPE, total plasma exchange; UFH, unfractionated heparin

anticoagulation are currently lacking. Intermittent flushing with saline can also prolong filter life. If CKRT is being applied through hemofiltration, using higher predilution to dilute the blood entering the filter can reduce haemoconcentration in the filter and prevent premature filter clotting. Whilst using post-dilution CKRT, filtration fraction should be below 20–25%. Catheter locks should be heparin-free to prevent leakage of heparin through the side holes. Citrate containing solutions can be used as a catheter lock. RCA is preferred in these patients in centres where this strategy is routinely used. Other anticoagulants which can be used in these patients include argatroban, or platelet aggregation inhibitors like prostacyclin. Other drugs which can be used as an anticoagulant in patients with heparin-induced thrombocytopenia are fondaparinux (synthetic heparin analogue) and lepirudin, or recombinant hirudin which is a direct thrombin inhibitor. In the absence of contraindications, alternate kidney replacement therapies like peritoneal dialysis (PD) or sustained low-efficiency dialysis (SLED) without anticoagulation can be used as an alternative KRT modality in patients at high risk for bleeding

Children with liver failure

A common myth about patients with liver failure is that these patients are coagulopathic and would not require any anticoagulant. In fact, patients with liver failure have a paradoxical coagulation status and are in fact prothrombotic [10]. Choices include low-dose heparin, RCA with close monitoring for citrate toxicity and prostacyclin. Depending on the severity of liver failure as measured by serum lactate and prothrombin time, RCA has been shown to be safe and effective in patients with liver failure [11]. However, one has to be extra-cautious in using RCA for intra-operative CKRT in patients undergoing liver transplantation as these patients have a huge citrate load due to the large requirements of administered FFP and packed cells. Use of RCA in this situation can precipitate citrate toxicity. Prostacyclin has been successfully used in a few paediatric liver centres in patients with liver failure with acceptable filter lives and good safety profile. The report by Miyaji et al. has added another choice of anticoagulant to the limited options available for these patients with liver failure undergoing CKRT.

Neonates and small children

Due to smaller vascular access and relatively small blood flows used in neonates, the risk of filter clotting is higher, therefore the need for anticoagulation is equally higher. Contrary to earlier beliefs, recent studies have demonstrated safety and efficacy of RCA in this population [12, 13]. In addition, depending on the local expertise and drug

availability, standard UFH, LMWH, RCA or argatroban can be safely used in this population.

Anticoagulation during a pandemic

The last 2 years have been extremely challenging for our community. COVID-19 is a hypercoagulable disease due to thrombo-inflammation and cytokine storm. Filter lives in patients who developed AKI and required CKRT was very short, circuits and filters clotted frequently. Provision of CKRT in a pandemic is entirely resource-based. Depending on the availability of resources, whatever anticoagulant was available and could be safely used, was used. Combination of UFH and RCA, prostacyclin alone or along with UFH, subcutaneous LMWH especially when infusion pumps were in short supply and LMWH along with RCA was used. In addition to combination of anticoagulants to prevent frequent filter-clotting, higher doses compared to traditional doses could be used to achieve better anticoagulation in this hypercoagulable state (higher ACT/APTT in UFH or lower ionised calcium within the circuit in RCA). As long as we understand the underlying disease physiology and the side-effect profile and mitigation measures, bespoke anticoagulation strategies can be safely applied [14].

ACT in specific extracorporeal therapy configurations

Patients on ECMO frequently require CKRT. Systemic anticoagulation required for ECMO can frequently be used for CKRT, or total plasma exchange (TPE) or CKRT and TPE plus ECMO, which obviates the need for individual local circuit anticoagulation. However, there is a theoretical small risk of clot embolization, which can potentially shorten oxygenator lifespan and increase a patient's risk.

Debate on the choice, monitoring, dosing and route of administration of an anticoagulant in CKRT is continuous and ongoing. There exists no perfect anticoagulant in the literature. It is very important to consider the complete clinical picture before choosing an anticoagulant for CKRT, including a patient's disease process which might affect the metabolism of the used anticoagulant, vascular access issues and blood product usage. Depending upon the availability of the chosen anticoagulant, local expertise, easy of monitoring and patient population, one needs to choose an anticoagulant, make easy-to-follow protocols and train staff to minimise adverse effects and maximise efficacy.

Considerations for the future include the use of CKRT machines which can provide fully automated RCA obviating the need for frequent monitoring and adjustment of the dose [15]. As shown with the study of Miyaji et al., novel anticoagulants need to be studied in prospective trials [9]. In parallel with advances in anticoagulants (including novel

agents that target Factor XII as demonstrated in pre-clinical trials), developing antithrombotic membranes that could either minimize or obviate the requirement for anticoagulation during CKRT seems to be an ideal alternative. This report aptly demonstrates that research collaboration has no boundaries and it is this international collaboration which is required in our community to minimise the current variation in practice to optimise outcomes in critically sick children undergoing CKRT. Academic collaborations amongst the research experts in paediatric CCN, as demonstrated by the organisation of the first pediatric-focussed 26th Acute Disease Quality Initiative (ADQI XXVI), is one such step in the right direction — the future is bright!

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Declarations

Conflict of interest The author declares no competing interests.

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