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How to Prolong Filter Life During Continuous Renal Replacement Therapy?

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Abstract

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Introduction

Renal replacement therapy (RRT), now also called kidney replacement therapy [1], is an essential intervention in critical care. Epidemiological studies have reported around 40% of patients in the intensive care unit (ICU) have acute kidney injury (AKI) [2–4]. However, effective strategies to prevent or treat AKI have yet to be established. Thus, RRT remains the mainstay of supportive measures for critically ill patients with AKI. It has been reported that 17–24% of critically ill patients with AKI receive some form of RRT during the ICU stay [2–4]. Continuous renal replacement therapy (CRRT), which runs slowly but continuously over 24 h, is more likely to be used than intermittent RRT in the ICU. Its mild impact on hemodynamics and solute clearance rate is preferred for critically ill patients. However, CRRT requires some measure(s) to prevent the filter from clotting due to the nature of the extracorporeal circuit. Filter clotting causes downtime of the therapy, leading to undertreatment, which may not be sufficiently recognized in clinical settings. A recent randomized controlled trial (RCT) [5] added evidence on the choice of anticoagulation strategies to prolong filter life in critically ill patients with AKI. The trial compared regional citrate administration with

systemic heparin administration to find that regional citrate could increase filter life span by 11 h. Attempts that are made in the ICU to prevent filters from clotting are not limited to anticoagulation therapies. Choices of the modality, blood flow, filter, and catheters potentially affect filter life [6, 7]. Clinical research related to AKI or RRT in the ICU has revealed variations across countries or facilities in the prescription of RRT [3, 4, 8–10]. The variations imply much uncertainty in the prescription of RRT to improve clinical practice. This state-of-the-art chapter summarizes the latest best available evidence for pharmacological and non-pharmacological interventions to prevent filters from clotting during CRRT in the ICU, focusing on recent clinical trials and observational studies.

Pharmacological Interventions to Prolong Filter Life

Pharmacological approaches include intravenous anticoagulants, oral anticoagulants, and antiplatelet agents. Regional citrate anticoagulation and systemic heparin are commonly used to maintain adequate patency of the extracorporeal circuit during CRRT. A major downside of the pharmacological approach is bleeding. Critically ill patients are commonly at high risk of bleeding due to coagulation abnormalities, including thrombocytopenia, prolonged prothrombin time (PT), and activated partial thromboplastin time (APTT). For such patients, clinicians may prescribe CRRT without anticoagulants

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Table 1 Pharmacological interventions investigated in randomized clinical trials for preventing clotting during continuous renal replacement therapy. Adapted from a Cochrane systematic review [6] and the RICH trial [5]

Intervention	Number of trials	Total number of participants in the trials
<i>Anticoagulants</i>		
Regional citrate anticoagulation	14	1697
Systemic heparin infusion	24	1837
Low molecular weight heparin	11	584
Regional heparin with protamine reversal	6	441
Nafamostat mesylate	2	133
Direct thrombin inhibitors (hirudin and bivalirudin)	3	53
<i>Antiplatelet agents</i>		
Prostaglandin I2 inhibitors (epoprostenol and iloprost)	5	154
Prostaglandin E1 inhibitors (Alprostadil)	1	54
Glycoprotein IIb/IIIa antagonists (tirofiban)	1	40
<i>Placebo or no pharmacological intervention</i>	3	177

for filter clotting prevention, concerned that the bleeding risk exceeds the benefits of the drug in providing an extended circuit life. In fact, a recent large multinational clinical trial of CRRT reported that 24% of patients did not receive any anticoagulants during CRRT [9].

However, the evidence to support the practice, i.e., no anticoagulation for CRRT in patients at high risk of bleeding, is scarce. Only small and inconclusive trials have examined the effects of pharmacological interventions, including systemic heparin, regional heparin with protamine reversal, and nafamostat mesylate, on filter life and bleeding events compared with no anticoagulation (Table 1) [11–13].

Regional Citrate Anticoagulation Versus Systemic Heparin, Low Molecular Weight Heparin, or Regional Heparin with Protamine Reversal

The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines suggest using regional citrate anticoagulation for CRRT based on a low certainty of evidence [14]. The mechanism of action of regional anticoagulation with citrate is that citrate chelates calcium and acts as a local anticoagulant when administered prefilter, reducing the risk of bleeding compared to systemic anticoagulation. However, citrate poses a risk of hypocalcemia, metabolic acidosis, or metabolic alkalosis if partially metabolized and accumulated.

An observational study from Germany (n=1059) reported that citrate accumulated in 2% of patients in the first 48 h of continuous venovenous hemodialysis (CVVHD) in the ICU [15]. In addition, the study explored the predictability of lactate clearance for citrate accumulation and reported a threshold of 24.3% at 12 h of CRRT.

The finding suggested regional citrate anticoagulation can be used safely with close monitoring of lactate clearance. A Cochrane review published in 2020 summarized the evidence from RCTs. Regional citrate anticoagulation probably decreases major bleeding events with no difference in successful prevention of clotting compared with systemic heparin [6].

The RICH trial was the largest so far, enrolling 596 patients, to compare the effects of regional citrate anticoagulation with those of systemic heparin anticoagulation on filter life and mortality [5]. The trial was terminated after the first interim analysis for the early proof of the superiority of regional citrate anticoagulation on filter life and futility in effects on mortality at 90 days. With the available data, anticoagulation with regional citrate significantly prolonged filter life (mean difference, 11.2 h [95% CI 8.2–14.3]) and reduced bleeding complications (odds ratio, 0.27 [95% CI 0.15–0.49]).

Regional citrate anticoagulation was compared with systemic low molecular weight heparin (LMWH) in two trials (n=268 in total) [6]. The larger trial (n=215) using nadroparin reported similar filter life in the two groups (median, 27 h vs. 26 h); however, adverse events that required discontinuation of study anticoagulant occurred more frequently with nadroparin (2% vs. 19%) [16]. Three trials compared regional anticoagulation with regional heparin accompanied by protamine reversal (n=252 in total) [6]. The largest trial (n=212) found longer filter life with regional citrate anticoagulation (median, 39.2 h vs. 22.8 h) [17]. The two largest RCTs in these two comparisons showed superiority of regional citrate anticoagulation over the comparator in terms of filter life and adverse events. Unfortunately, no trial has been conducted to

compare regional citrate anticoagulation with other anticoagulation strategies [6].

Systemic Heparin Versus Regional Heparin with Protamine Reversal, Low Molecular Weight Heparin, Thrombin Antagonists, or Antiplatelet Agents

KDIGO guidelines recommend using either unfractionated or low molecular weight heparin, rather than other anticoagulants during CRRT in patients with contraindications for citrate, such as liver failure or shock representing a risk of citrate accumulation [14]. Alternatives include nafamostat mesylate, thrombin antagonists (e.g., hirudin or bivalirudin), and antiplatelet agents (e.g., epo-prostenol, iloprost, alprostadil, or tirofiban).

A recent large multinational RCT showed that less than 3% of patients undergoing CRRT received such alternative anticoagulation strategies [9]. In addition, the recent Cochrane systematic review found no convincing evidence to indicate the superiority or inferiority of systemic heparin, regional heparin with protamine reversal, LMWH, or other alternative anticoagulants [6].

Implications for Clinicians and Future Research on Pharmacological Interventions

- Benefits from any pharmacological intervention compared to no pharmacological intervention are uncertain, particularly in patients at high risk of bleeding.
- If there is no contraindication, regional citrate anticoagulation is the first choice as a pharmacological strategy to maintain filter patency.
- Clinical research is needed to investigate which/whether anticoagulants should be used for patients at high risk of bleeding or patients with contraindication/s to regional citrate anticoagulation.

Non-pharmacological Interventions to Prolong Filter Life

Non-pharmacological interventions to prolong filter life during CRRT include the strategic selection of modalities, blood flow rates, catheter sites and types, and filters. However, the effects of those non-pharmacological interventions in patients undergoing CRRT have not been well studied compared with pharmacological interventions. Only a few randomized trials have been conducted so far (Table 2); furthermore, most studies were conducted more than a decade ago [7]. The clinical practice in this field has changed dramatically, as exemplified by the widespread use of regional citrate. However, some evidence, including “no evidence of effect”, may inform clinicians in decisions on the use of non-pharmacological

Table 2 Non-pharmacological interventions investigated in randomized clinical trials for preventing clotting during continuous renal replacement therapy. Adapted from a Cochrane systematic review [7]

Interventions	Number of trials	Number of participants in the trials
<i>Modes</i>		
CVVH, CVVHD, or CVVHDF	10	520
Pre-dilution or post-dilution	2	48
<i>Blood flow</i>		
Higher blood flow or standard blood flow	2	134
<i>Catheter types</i>		
Long or short catheter	1	100
Surface-modified double-lumen catheter	1	236
<i>Filter types</i>		
AN69ST	3	76
More and shorter hollow fiber	1	6
Flat plate fiber ^a	1	38
Filter with a larger membrane surface area ^a	1	38
<i>Others</i>		
Single- or double-site infusion anticoagulation ^a	1	38

^a From one study embedding three comparisons. *CVVH* continuous venovenous hemofiltration, *CVVHD* continuous venovenous hemodialysis, *CVVHDF* continuous venovenous hemodiafiltration, *AN69ST* polyethylenimine-treated AN69 membrane

interventions and is, therefore, summarized here with some recent observational findings.

Modes of Continuous Renal Replacement Therapy

Standard modes of CRRT include continuous venovenous hemofiltration (CVVH), CVVHD, and continuous venovenous hemodiafiltration (CVVHDF). Theoretically, CVVH has a better clearance of medium-sized solutes than CVVHD, but in practice it has been suggested that CVVHD provides equivalent clearance [18].

Although many studies have compared different modes of CRRT to each other for solute clearance or mortality, filter life was seldom measured as an outcome [7]. Limited available evidence (n=77 in total) shows that CVVHD or CVVHDF might prolong filter life compared with CVVH [18, 19]. However, a single-center observational study published in 2021 (n=284) reported no difference in filter life between CVVHD and CVVHDF (median, 16.4 h vs. 16.8 h) [20].

When CVVH or CVVHDF is used, replacement fluid can be infused before and/ or after the filter: pre-dilution and/or post-dilution. The effect of pre-dilution on filter life was compared with post-dilution in two very small RCTs (n=47 in total) [7]. The pooled effect reported in

the recent Cochrane systematic review implied that pre-dilution filtration might improve filter lifespan compared with the post dilution technique [7]. Pre-dilution CRRT aims to decrease hemoconcentration; however, excessive hemodilution reduces solute clearance. To this end, replacement fluid may be split between pre- and post-filter, or blood flow rate may be kept high at at least 200 ml/min [21].

Blood Flow Rate

The blood flow rate of CRRT is variably prescribed from 80 to >300 ml/min worldwide [22, 23]. Expert consensus recommends a blood flow rate of >200 ml/min [24]. However, evidence from two RCTs (n = 499 in total) found that a higher blood flow rate may make little or no difference to circuit lifespan compared with a standard blood flow rate [7]. In addition, a recent observational study suggested that low blood flow did not independently affect filter life [20].

Vascular Access and Catheter Types

KDIGO guidelines [14] recommend using uncuffed, non-tunneled dialysis catheters, rather than tunneled catheters for initiating CRRT, based on a small RCT [25]. The RCT (n = 34) showed less dysfunction, fewer infectious or thrombotic complications, and more prolonged catheter survival with tunneled catheters [25]. However, tunneled catheters required increased insertion time and resulted in more femoral hematomas. The uncertainty of the findings due to the small sample size and uncommon catheter insertion procedure for CRRT settings precluded the recommendation of tunneled catheters [14]. A RCT comparing the functionalities of tunneled and non-tunneled catheters as the initial catheter for CRRT was registered (ClinicalTrials.gov Identifier: NCT03496935); however, the trial status is unclear. The guidelines recommend using the right jugular vein, then the femoral vein, the left jugular vein, and the subclavian vein in this order when inserting catheters [14], based on observational studies. Catheters in the right jugular vein have fewer complication of stenosis or thrombosis as they have a straight course into the superior vena cava and the least contact with the vessel wall. By contrast, a catheter inserted through the subclavian or the left jugular vein has one or more angulations, which increases the risk of contact with blood vessels. An RCT (n = 750) that included patients having CRRT or intermittent hemodialysis showed little difference between femoral or jugular catheter placement in catheter survival and complications except in patients with a high body mass index [26].

Several types of catheters have also been studied [7]. Compared with short catheters targeting tip placement in the superior vena cava, long catheters arriving in the

right atrium may prolong the filter life [27]. A surface-modified double-lumen 177 catheter compared with a standard double-lumen catheter may also extend filter life [28].

Types of Filters

Many filters have been examined for effects on clinical outcomes; however, most evidence is of very low certainty [7]. Polyethylenimine-coated AN69 membranes (AN69ST), in which unfractionated heparin is bound onto the polymers, have been suggested to reduce the need for anticoagulation during CRRT [29, 30]. However, the AN69ST membrane has yet to be proven to provide longer filter life than other membranes in randomized studies (n = 56 in total) [7]. Furthermore, a small RCT suggested that citrate would provide better regional anticoagulation than AN69ST membranes in patients at high risk of bleeding [31]. As such, AN69ST should not be used to extend filter life at this stage. Two RCTs are currently underway to determine the impact of AN69ST on filter life (ClinicalTrials.gov Identifiers: NCT03426943 and NCT01779635).

For the other types of filter, including filters with more and shorter fibers, hollow fibers, or flat plate fibers, and filters with large membrane areas, there is no reliable evidence regarding their impact on filter life [7].

Implications for Clinicians and Future Research on Non-pharmacological Interventions

- Convection predominant modes may shorten the filter life; however, the evidence is uncertain.
- Keeping blood flow rates greater than 200 ml/min appears not to prolong filter life.
- Jugular access does not have evident superiority over femoral access in terms of filter life.
- There is insufficient evidence on the effects of non-pharmacological interventions on preventing filter clotting during CRRT to be able to make recommendations for routine practice. In particular, up-to-date evidence is lacking.

Conclusion

The recent RICH trial [5] confirmed evidence that regional citrate anticoagulation provides longer filter life than systemic heparin anticoagulation during CRRT in critically ill patients. The effects of other anticoagulants, even compared with no anticoagulation, are uncertain. Non-pharmacological interventions have not been investigated sufficiently. With the widespread use of regional citrate anticoagulation over the last decade, high quality

pragmatic trials investigating second line anticoagulation and non-pharmacological interventions in current ICU settings are warranted.

Acknowledgements

This work was supported by Grant-in-Aid for Early-Career Scientists (JSPS 214KAKENHI 21K16580) to TF. We appreciate all staff in the critical care field for their support and contribution to the clinical research.

Authors' contributions

YT and TF had conceived the review article, written the manuscript, and read and approved the final manuscript.

Funding

The publication costs were funded by Grant-in-Aid for Early-Career Scientists (JSPS KAKENHI 21K16580) to TF. The funding source had no role in the design of this study and did not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

Availability of data and material

Not applicable.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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