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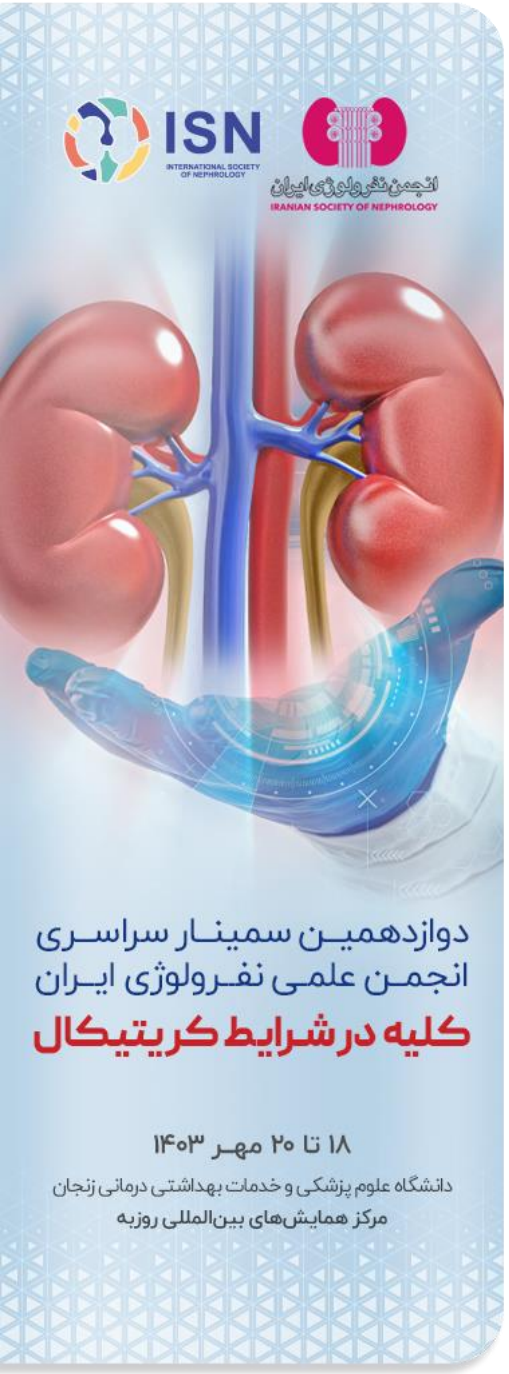

Anticoagulation

In CRRT

- **INDICATIONS AND RATIONALE**

- **Anticoagulation is used to prevent clotting of the extracorporeal system. Clotting of the circuit may be minor,leading to clotting in the capillary fibers and reduced solute clearances, or major, leading to loss of the hemofilter,tubing, and blood in the circuit. Replacing the hemofilter and tubing interrupts continuous kidney replacement therapy (CKRT) and reduces the total therapy time. Studies have shown that interruptions from clotting may reduce the total time on CKRT from 24 to 16 hours per day. Such reductions reduce the effectiveness of CKRT. A sufficient operating time is required to ensure that an adequate kidney replacement therapy (KRT) dose is delivered.**

- **However, anticoagulation increases the complexity and cost of the procedure. Some centers, perform CKRT without anticoagulation, providing filter life can be maintained for >24 hours. We use anticoagulation if the filter life cannot be maintained for >24 hours. However, some centers routinely use anticoagulation from the start to prevent clotting,and the Kidney Disease Improving Global Outcomes (KDIGO) guidelines suggest the use of anticoagulation.However, a Cochrane systematic review concluded that the most effective anticlotting options for CKRT remain to be determined.**

- **AVAILABLE ANTICOAGULANT THERAPIES**

The most commonly used options for continuous kidney replacement therapy (CKRT) anticoagulation include regional citrate (RCA) and unfractionated heparin (UFH).

Low-molecular-weight heparin (LMWH), thrombin antagonists (argatroban and bivalirudin), UFH with protamine reversal, heparinoids, nafamostat mesylate, platelet-inhibiting agents, and heparin surface-coated hemofilters are less common options.

- **Regional citrate anticoagulation**

RCA decreases the rate of clotting and may be used in all CKRT modalities. Compared with systemic heparin, RCA reduces the risks of bleeding.

During RCA, sodium citrate is infused into the inflow ("arterial") limb of the extracorporeal circuit, chelating calcium and inhibiting clotting. The majority of the calcium citrate complex is removed across the hemofilter. Any calcium citrate complex that remains postfilter is returned to the patient and indirectly metabolized to bicarbonate by the liver,kidney, and skeletal muscle. Regional anticoagulation is reversed by dilution of citrate in the extracellular compartment and by its rapid metabolic clearance. A systemic calcium infusion is required to replace the calcium that is lost in the effluent to maintain a normal ionized serum calcium concentration.

- The use of RCA may require modification of the composition of dialysate or replacement fluid.

  The concentration of buffers (eg, bicarbonate, lactate) should be reduced to prevent alkalosis since citrate provides alkali.

  In addition,citrate can also bind magnesium and, therefore, we prefer dialysates or replacement fluid solutions that have 0.75 mmol/L rather than 0.5 mmol/L of magnesium.

- Ideally, the dialysate and replacement fluids should also be calcium free to prevent reversal of the citrate effect in the extracorporeal circuit, although this is not absolutely necessary. If calcium-containing replacement fluid is used, moe citrate is required to chelate calcium in both the blood and replacement fluid, but a separate calcium reinfusion may not be required.

- RCA use for CKRT is not approved by the US Food and Drug Administration (FDA). The absence of an FDA-approved citrate regimen has been a barrier to use of citrate regimens in the United States. Some institutional pharmacies have been unwilling to permit off-label use of citrate. However, worldwide the use of citrate continues to increase following the availability of replacement fluids and dialysates designed to be used with citrate regional anticoagulation.

- *Principles of RCA*

It is recommended to set initial citrate dose based on blood flow rate, and the citrate dose should be appropriately adjusted according to the monitoring value of filter ionized calcium (iCa).

Citrate is widely found in various tissues and fluids in the human body. It is not only an important component of the skeletal system but also an intermediate product of the metabolism of glucose, lipids, and some amino acids.

It plays an important role in energy metabolism. In normal circumstances, the serum concentration of citrate is extremely low, about 0.1 mmol/L, mainly in a form of stable soluble calcium citrate.

Citrate contains three carboxyl groups that can dissociate into the trivalent anion of Citrate3−.
Because of the characteristics of its structure, two negatively charged carboxyl groups in Citrate3−

can chelate with divalent cations such as iCa or magnesium in blood and form monovalent anions like calcium citrate or magnesium citrate. The chelation reaction is rapid and the chelate does not dissociate spontaneously in the circulation.

The space distance between the two positive charges of iCa matches better with the distance between the two negative charges of the citrate 3- carboxyl groups, resulting in stronger citrate-calcium complexes (CCC).

When citrate is infused into the blood, it rapidly chelates the iCa in the blood to form CCC (equivalent to changing the iCa to binding calcium), thus reducing the level of iCa in the blood. iCa also called coagulation factor IV which is vital for multiple steps of coagulation process and platelet interactions.

In the endogenous coagulation pathway, iCa can assist in activating factor XI, and activate factor X together with factor VIII and activated factor IX. In the exogenous coagulation pathway,factor X is activated by iCa, factors III and VII. In the common pathway, fibrinogen can be converted into fibrin monomers by assistance of iCa, factor V and activated factor X. In addition, it can also assist in activating factor XIII and continue to assist factor XIII in transforming soluble fibrin monomers into stable fibrin polymers. The exogenous and endogenous coagulation pathway steps would be blocked if the blood level of iCa decreases obviously.

Under physiological conditions, the concentration of serum iCa is 1.0–1.2 mmol/L. The blood coagulation will not occur if the blood level of iCa is reduced to below 0.35–0.4 mmol/L.

- During CRRT, when citrate is infused at the access end of the extracorporeal circulation, the concentration of calcium in the extracorporeal circulation is rapidly reduced to below 0.4 mmol/L, thus preventing clotting. The negative univalent CCC formed by the chelation reaction is a small molecule (298 Dalton) with good water solubility and a sieving coefficient of about 1, which can be rapidly removed by the filter through its semi-permeable membrane .Due to different CRRT modes and therapeutic doses, about 30–60% of CCC molecules will enter the effluent through the permeable membrane. The CCC molecules which are not removed via the hemofilter enter the systemic circulation and are first metabolized into citric acid rapidly in body cells. Citric acid is metabolized through the tricarboxylic acid cycle, which is oxygen dependent and mainly occurs in organs with high mitochondrial content.

In physiological conditions, it is mainly metabolized in liver and a small portion is metabolized in skeletal muscles. The half-life of CCC under physiological conditions is only 5 min. CCC is eventually decomposed into bicarbonate through the tricarboxylic acid oxidation cycle (one molecule of citrate yields three molecules bicarbonate), and the iCa is released back into the blood. Meanwhile, the unchelated calcium ions are also partially removed from the circuit blood into the effluent. As a result,severe hypocalcemia can occur if ongoing supplementation of iCa is not provided. Therefore, adequate amounts of iCa must be supplied directly to the patient intravenously(via central vein) or through the return end of extracorporeal circulation circuit to maintain physiological iCa level. RCA anticoagulation is thus achieved only in the CRRT circuit (i.e., regional anticoagulation) with little interference with in vivo coagulation processes.

When RCA is used, citrate is added at the access end of extracorporeal circuit to ensure a citrate concentration of 3–4 mmol/L (i.e., 3–4 mmol citrate per 1 L of whole blood). The flow rate of citrate is then adjusted by monitoring the concentration of iCa in the filter (hereinafter referred to as iCa in the filter, with the sampling site residing behind the filter, so as to ensure the effectiveness of anticoagulation with the concentration of iCa in the filter ranging from 0.2 to 0.4 mmol/L. It is very important to monitor the concentration of iCa in patients' systemic circulation (hereinafter referred to as iCa in the body ,sampled from the patient's artery or vein)

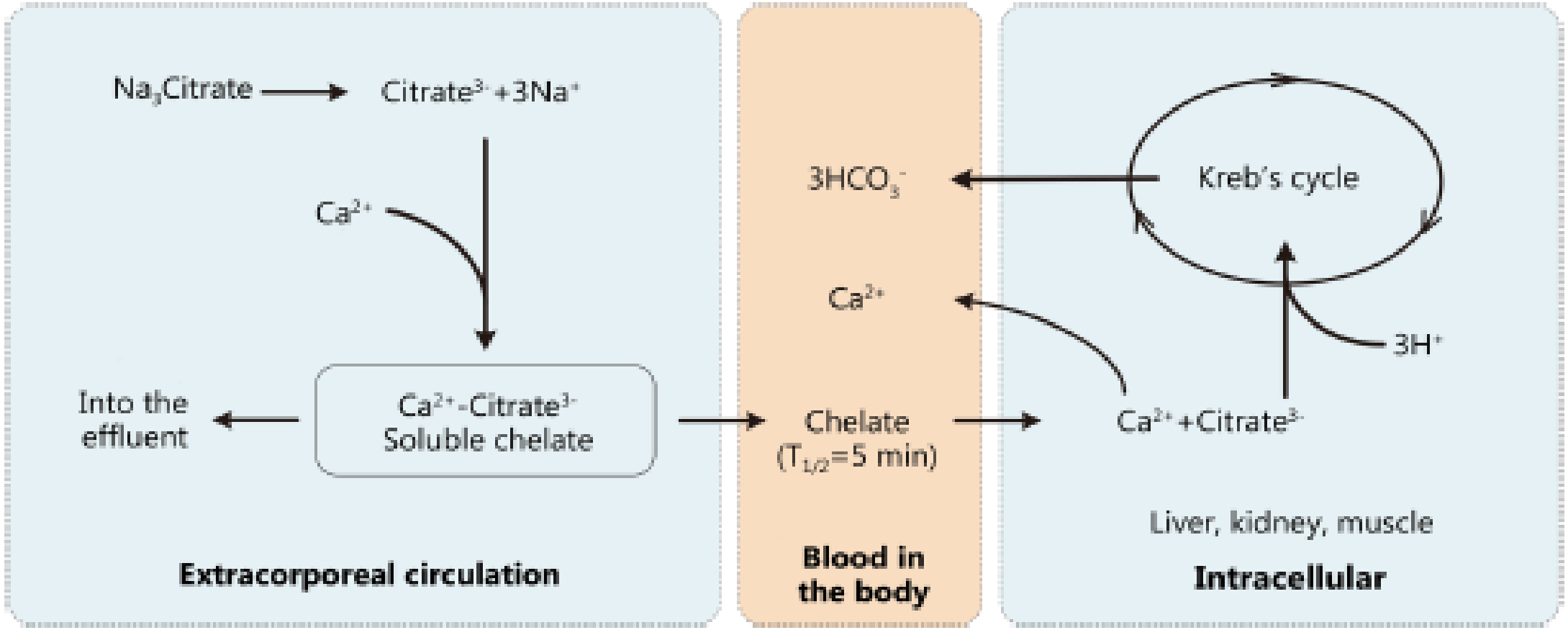

Fig. 2 Schematic diagram of citrate metabolism. When trisodium citrate is infused into the extracorporeal circulation, citrate-calcium complexes (CCC) is formed by the chelation reaction of ionized calcium (iCa) and $Citrate^{3-}$. iCa is rapidly reduced to prevent clotting. About 30–60% of CCC molecules enter the effluent through the permeable membrane depending on different continuous renal replacement therapy (CRRT) modes and therapeutic doses. The residual CCC molecules return to the systemic circulation and are metabolized rapidly in body cells. The half-life of CCC under physiological conditions is only 5 min. CCC is eventually decomposed into bicarbonate through the tricarboxylic acid oxidation cycle (one molecule of citrate yields three molecules bicarbonate), and the iCa is released back into the blood

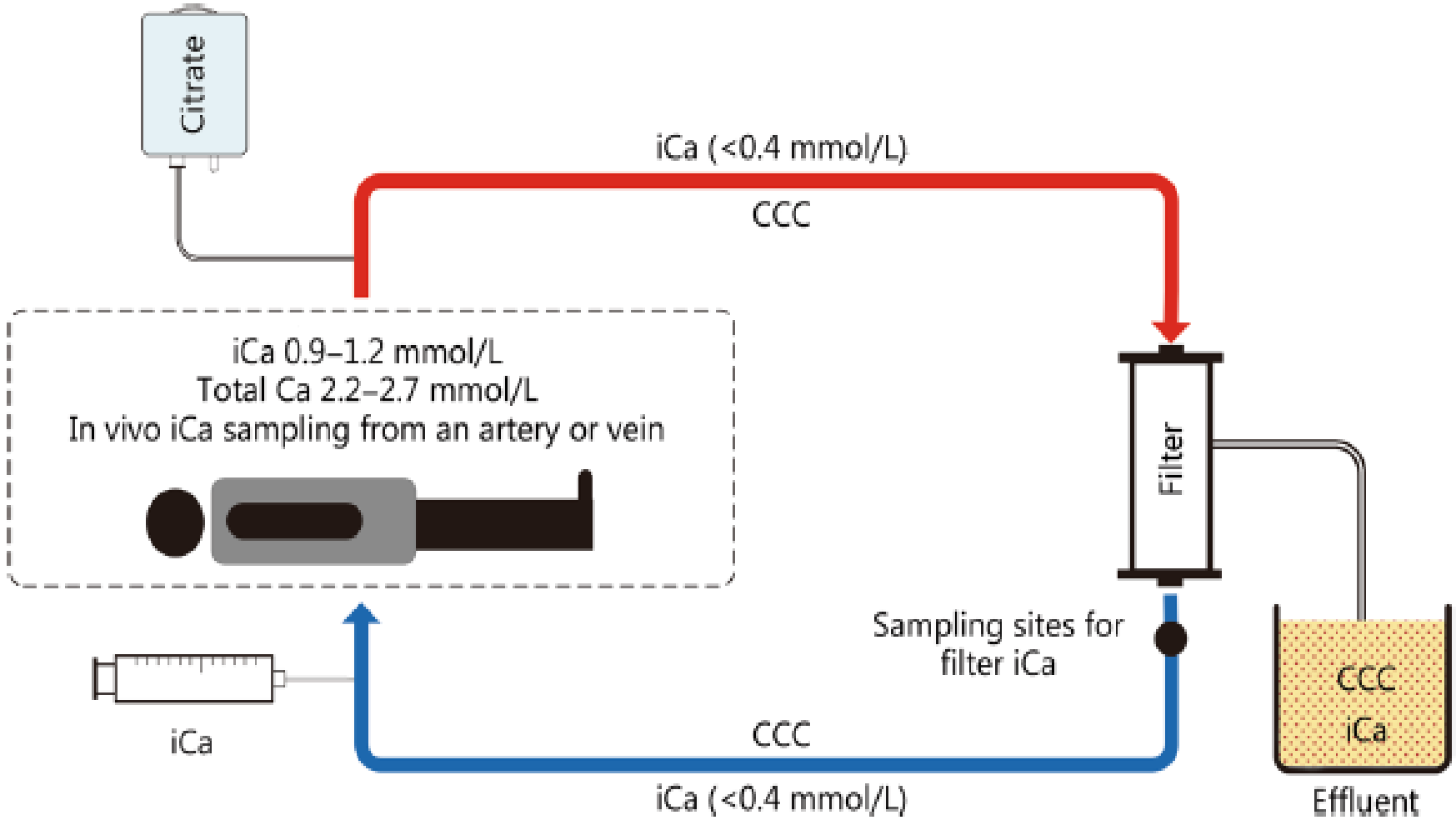

Fig. 3 Schematic diagram of RCA in the CRRT system. Citrate is infused into the extracorporeal circulation before filter. Citrate-calcium complexes (CCC) is formed by the chelation reaction of ionized calcium (iCa) and $Citrate^{3-}$. Partial CCC and iCa are removed by the filter. As a result, iCa in the filter is rapidly reduced to below 0.4 mmol/L, thus preventing clotting. The concentration of iCa in the filter is routinely monitored at the site behind the filter. Before the blood is returned to the body, additional iCa is infused to the blood in order to replenish the calcium removed to effluent by the filter. RCA regional citrate anticoagulation, CRRT continuous renal replacement therapy

Customized Citrate Anticoagulation versus No Anticoagulant in Continuous Venovenous Hemofiltration in Critically Ill Patients with Acute Kidney Injury: A Prospective Randomized Controlled Trial

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Keywords
Continuous venovenous hemofiltration · Regional citrate anticoagulation · Customized citrate-based replacement fluid · Citrate accumulation · Bleeding

Abstract
Introduction: The use of anticoagulants during continuous renal replacement therapy (CRRT) is essential. Regional citrate anticoagulation (RCA) is recommended rather than systemic heparinization to prolong the filter's lifespan in patients at high risk of bleeding. However, commercial citrate is expensive and may not be available in resource-limited areas. The objective of this study is comparing filter life between our locally made customized RCA and no anticoagulation. The primary outcomes were the first circuit life in hours and the number of filters used within the first 72 h of therapy. ***Methods:*** We conducted a single-center prospective randomized controlled trial in critically ill patients requiring CRRT. The participants were randomized to receive continuous venovenous hemofiltration (CVVH) with either customized RCA or no anticoagulant. ***Results:*** Of 76 patients, 38 were randomized to receive customized RCA and 38 to receive CVVH without anticoagulant. There was no significant difference in baseline characteristics between the two groups. Compared to anticoagulant-free group, the median circuit life of customized RCA group was significantly longer [44.9 (20.0, 72.0) vs. 14.3 (7.0, 22.0) hours; $p < 0.001$]. The number of filters used within 72 h was significant lower [2.0 (1.0, 2.0) vs. 2.5 (1.0, 3.0); $p < 0.015$]. RCA was prematurely discontinued in 5 patients due to citrate accumulation (2 cases) and severe metabolic acidosis requiring higher dose of CVVH (3 cases). No differences in bleeding complications were observed ($p = 0.99$). ***Conclusion:*** Customized citrate-based replacement solution improved filter survival in CVVH compared to anticoagulant-free strategy. This regimen is safe, feasible, and suitable for low- to middle-income countries.

Trial registration: TCTR20210924001.

- **Unfractionated heparin**

UFH is widely used for CKRT, particularly in the many institutions that do not have the ability to use RCA.

UFH is effective, inexpensive, and widely available.

However, there are disadvantages associated with the use of UFH, including unpredictable and complex pharmacokinetics that result in dosing variability, the development of heparin-induced thrombocytopenia (HIT),heparin resistance due to low patient antithrombin levels, and an increased risk of bleeding .The reported incidence of bleeding ranges from 10 to 50 percent and is related to the degree of prolongation of the activated partial thromboplastin time (aPTT).

If the patient requires anticoagulation and we cannot use RCA, we use UFH. We start with a loading dose of 500 to 1000 international units followed by infusion of 500 units per hour. We adjust the heparin infusion according to activated partial thromboplastin time (aPTT) or ratio (aPTTr).

We target an aPTT of 45 seconds or aPTTr 1.5 times normal .

The heparin dose should be reduced in patients with disseminated intravascular coagulation or thrombocytopenia.

Using a heparin-coated dialyzer membrane has not shown a benefit compared with standard no-anticoagulation protocols .

- **Other**

- **Other approaches include, UFH with protamine reversal low-molecular-weight heparins, thrombin antagonists,danaparoid, nafamostat mesylate , prostacyclin and other prostanoids, and platelet-inhibiting agents .**

- **We do not routinely use these agents, because there are insufficient data demonstrating benefit and safety among patients on CKRT. However, some centers have developed expertise in using epoprostenol and nafamostat as alternative regional anticoagulants .**

Initial approach

- **For most patients, we attempt continuous kidney replacement therapy (CKRT) without anticoagulation. We usually can achieve adequate CKRT filter survival without anticoagulation, providing the patient has a well-functioning vascular access .**

RESEARCH Open Access

Nafamostat mesylate versus regional citrate anticoagulation for continuous renal replacement therapy in patients at high risk of bleeding: a retrospective single-center study

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Abstract

Purpose The choice of continuous renal replacement therapy (CRRT) anticoagulation program for patients at high risk of bleeding has always been a complex problem in clinical practice. Clinical regimens include regional citrate anticoagulation (RCA) and nafamostat mesylate (NM). This study aimed to evaluate the efficacy and safety of these two anticoagulants for CRRT in patients at high risk of bleeding to guide their clinical use better.

Patients and methods Between January 2021 and December 2022, 307 patients were screened for this study. Forty-six patients were finally enrolled: 22 in the regional citrate anticoagulation group and 24 in the nafamostat mesylate group. We collected patients' baseline characteristics, laboratory indicators before CRRT, and CRRT-related data. We then performed a statistical analysis of the data from both groups of patients.

Results In our study, the baseline characteristics did not differ significantly between the two groups; the baseline laboratory indicators before CRRT of patients in the two groups were not significantly different. The duration of CRRT was 600 min in the regional citrate anticoagulation (RCA) group, 615 min in the nafamostat mesylate (NM) group; the success rate was 90.7% in the RCA group, and 85.6% in the NM group, the anticoagulant efficacy between the two groups was comparable. There was no significant difference in the safety of anticoagulation between the two groups. We used Generalized Estimating Equations (GEE) to test whether different anticoagulation methods significantly affected the success rate of CRRT and found no statistical difference between RCA and NM.

Conclusion Our study suggests that nafamostat mesylate's anticoagulant efficacy and safety are not inferior to regional citrate anticoagulation for continuous renal replacement therapy in patients at high risk of bleeding.

Keywords Nafamostat mesylate, Regional citrate anticoagulation, Anticoagulation, Continuous renal replacement therapy, High risk of bleeding

- The following strategies may prolong hemofilter survival in the absence of anticoagulation.
- Maintain adequate blood flow .
- Minimize hemoconcentration within the hemofilter
- React promptly to alarms
- Reduce the blood-air contact in the drip chamber
- Avoiding overheating dialysate and replacement solutions
- Avoiding mechanical obstruction of blood lines

- **Maintain adequate blood flow**

We try to maintain blood flow between 100 to 300 mL/min.

Very low blood flows are a common cause of circuit clotting because they increase the risk of stasis and increase the filtration fraction, which causes hemoconcentration across the hemofilter. However a higher blood flow (ie, >300 mL/min) may also cause clotting by triggering pressure alarms that stop the blood flow and cause stasis. Even in the absence of clotting, very high blood flows limit the lifespan of the extracorporeal circuit tubing and hemofilter because they can only process a finite volume of blood before the tubing starts to degrade.

- **Minimize hemoconcentration within the hemofilter**

Hemoconcentration refers to the increasing concentration of red blood cells, platelets, and coagulation factors in blood. The risk of clotting may be increased by hemoconcentration within the hemofilter, which occurs as a result of ultrafiltration (ie, the removal of water across the hemofilter).

We minimize hemoconcentration with the hemofilter by the following approach:
We administer predilution rather than postdilution replacement fluid. For convective therapies, such as continuous venovenous hemofiltration (CVVH), giving fluid before the hemofilter (ie, predilution replacement) decreases hemoconcentration within the hemofilter.

We keep the filtration fraction <20 to 25 percent. Filtration fraction is the fraction of plasma water that is removed from blood during ultrafiltration. Higher filtration fractions are associated with increased circuit clotting, presumably from hemoconcentration and blood protein-membrane interactions.

- **Hemoconcentration may also be decreased by the use of diffusive therapies (such as continuous venovenous hemodialysis [CVVHD]) and continuous venovenous hemodiafiltration (CVVHDF) rather than postdilutional convective therapies (such as CVVH.)**

Some studies have suggested that CVVH is associated with increased hemofilter clotting, believed to be related to the high ultrafiltration rate required for adequate CVVH.

In addition to clotting within the hemofilter,clotting also occurs with blood-air interfaces. As such, careful priming of the extracorporeal circuit and adding saline to the drip chamber such that there is a layer of saline above the blood level may minimize blood-air contact.

- **React promptly to alarms** – Alarms are triggered by increases in pressure, which are generally associated with blood stasis. Slow reaction allows the stasis to persist longer and leads to clotting .

- **Reduce the blood-air contact in the drip chamber** – Contact between blood and air increases platelet activation, which may cause clotting . Blood-air contact can be minimized by adding saline to the drip chamber such that there is a layer of saline above the blood level.

- **Avoiding overheating dialysate and replacement solutions** – Cooling of replacement solution below normothermia has been shown to improve patency in animal studies. While it is not clinically feasible to lower the temperature of replacement fluid below normal, we are careful not to overheat the solution.

- **Avoiding mechanical obstruction of blood lines** – When moving patients, care should be taken not to kink lines and to ensure that lines are clearly visible.

If there is repeated clotting, the first step is **to ensure that the vascular access is functioning adequately**.

Crit Care. 2023; 27: 222.
Published online 2023 Jun 7. doi: 10.1186/s13054-023-04519-1
PMCID: PMC10249230
PMID: 37287084

Anticoagulation options for continuous renal replacement therapy in critically ill patients: a systematic review and network meta-analysis of randomized controlled trials

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Associated Data

- **Supplementary Materials**
- **Data Availability Statement**

Abstract

Go to:

Background

Continuous renal replacement therapy (CRRT) is a widely used standard therapy for critically ill patients with acute kidney injury (AKI). Despite its effectiveness, treatment is often interrupted due to clot formation in the extracorporeal circuits. Anticoagulation is a crucial strategy for preventing extracorporeal circuit clotting during CRRT. While various anticoagulation options are available, there were still no studies synthetically comparing the efficacy and safety of these anticoagulation options.

Methods

Electronic databases (PubMed, Embase, Web of Science, and the Cochrane database) were searched from inception to October 31, 2022. All randomized controlled trials (RCTs) that examined the following outcomes were included: filter lifespan, all-cause mortality, length of stay, duration of CRRT, recovery of kidney function, adverse events and costs.

Results

Thirty-seven RCTs from 38 articles, comprising 2648 participants with 14 comparisons, were included in this network meta-analysis (NMA). Unfractionated heparin (UFH) and regional citrate anticoagulation (RCA) are the most frequently used anticoagulants. Compared to UFH, RCA was found to be more effective in prolonging filter lifespan (MD 12.0, 95% CI 3.8 to 20.2) and reducing the risk of bleeding. Regional-UFH plus Prostaglandin I2 (Regional-UFH + PGI2) appeared to outperform RCA (MD 37.0, 95% CI 12.0 to 62.0), LMWH (MD 41.3, 95% CI 15.6 to 67.0), and other evaluated anticoagulation options in prolonging filter lifespan. However, only a single included RCT with 46 participants had evaluated Regional-UFH + PGI2. No statistically significant difference was observed in terms of length of ICU stay, all-cause mortality, duration of CRRT, recovery of kidney function, and adverse events among most evaluated anticoagulation options.

Conclusions

Compared to UFH, RCA is the preferred anticoagulant for critically ill patients requiring CRRT. The SUCRA analysis and forest plot of Regional-UFH + PGI2 are limited, as only a single study was included. Additional high-quality studies are necessary before any recommendation of Regional-UFH + PGI2. Further larger high-quality RCTs are desirable to strengthen the evidence on the best choice of anticoagulation options to reduce all-cause mortality and adverse events and promote the recovery of kidney function.

Trial registration The protocol of this network meta-analysis was registered on PROSPERO (CRD42022360263). Registered 26 September 2022.

• Preferential use of regional citrate anticoagulation

We use a blood flow rate of 80 to 200 mL/min. In contrast to patients who are not receiving any anticoagulation,higher blood flows are not required to prevent clotting. In addition, higher blood flows are counterproductive since the amount of required citrate increases with higher blood flows.

A variety of methods of RCA have been described. In all, citrate solution is infused into the blood at the beginning of the extracorporeal circuit.

Commercially available replacement and dialysate solutions that have been specifically designed for CKRT include **Prismocitrate 10/2**, which contains 10 mmol/L citrate,2 mmol/L citric acid, and 136 mmol/L sodium; **Prismocitrate 18/0**, which contains 18 mmol/L citrate; and **calcium-free dialysates (Ci-Ca dialysate)**.

Some centers may use commercially available citrate solutions that were not designed for CKRT and have high concentrations of citrate and sodium.

Depending upon the concentration of citrate solution used and the corresponding sodium load, compensatory hyponatremic replacement and/or dialysate solutions with either no or reduced bicarbonate concentrations may be required to prevent the development of electrolyte abnormalities.

- A separate calcium infusion is delivered to the patient and titrated to keep the systemic ionized calcium concentration in normal range. The citrate infusion rate is adjusted to keep the ionized calcium concentration in the extracorporeal circuit <0.4 mmol/L (measured as the postfilter ionized calcium concentration), which correlates with citrate blood concentration of 4 to 6 mmol/L. Calcium chloride or calcium gluconate is infused into the venous return line at an initial rate of 2 to 3 mmol/hour to replace calcium lost in the effluent when using calcium-free dialysate and replacement fluids. The rate is adjusted according to measurements of plasma calcium concentration to prevent hypocalcemia or hypercalcemia.
- Citrate-based anticoagulation can also be used among patients receiving CVVHD.

- Filter calcium levels should be closely monitored during the first 24 h of treatment (usually measured with a blood gas analyzer). It is recommended to conduct the first detection 30 min after the start of treatment, and then monitor iCa every 2 h for 4 consecutive times.

- Adjust the flow of citrate according to the level of iCa in the filter, and then monitor it once every 4 h for 4 consecutive times after it is deemed stable. If the treatment goes well, monitoring can be changed to once every 6 h after 24 h, i.e., (30 min) → (q2 h × 4) → (q4 h × 4) → (q 6 h × 4).

- From the perspective of the principles of using RCA, factors determining the dose of citrate include: 1) Blood flow rate. The citrate flow rate must match the blood flow rate to ensure a stable anticoagulant concentration in the extracorporeal circulation and should be adjusted accordingly after a change in the blood flow rate. 2) The site where replacement fluid is added. If a calcium-free replacement fluid is used in predilution mode, the blood entering the filter will be diluted, so that the iCa concentration in the filter will decrease, and the demand for citrate will decrease accordingly. 3) Composition of replacement fluid. Whether the replacement fluid contains calcium and magnesium also affects the flow rate of citrate. If calcium-containing replacement fluid is used in predilution mode, the amount of iCa entering the filter will increase, requiring more citrate to chelate them. If calcium-containing replacement fluid is used in postdilution mode, the impact on the amount of citrate will be small, but may increase the risk of coagulation in the post-filter air trap chamber. The blood sampling location of the iCa in the filter is usually before the infusion site of the postdilution replacement fluid, and the post-filter air trap chamber is usually located behind the input point of the postdilution replacement fluid,therefore the actual iCa concentration in the post-filter air trap chamber is higher than the measured value.4)Individual anticoagulation intensity target.

Table 4 Flow of citrate infusion and adjustment scheme

iCa in the filter (mmol/L)	Flow of 4% TSC Infusion	Flow of ACD-A Infusion
≤ 0.20	Reduce 10 ml/h	Reduce 12 ml/h
0.20–0.40	Unchanged	Unchanged
0.40–0.50	Increase 10 ml/h	Increase 12 ml/h
> 0.50	Increase 20 ml/h	Increase 24 ml/h

iCa ionized calcium, *ACD-A* citrate-glucose anticoagulant A, *TSC* trisodium citrate

Table 6 Adjustment scheme for the iCa supplemental Infusion

In vivo iCa (mmol/L)	5% calcium chloride	10% calcium gluconate
≥ 1.2	Reduce 2 ml/h	Reduce 3 ml/h
≥ 1.0	Reduce 1 ml/h	Reduce 1.5 ml/h
≥ 0.9	Unchanged	Unchanged
≥ 0.8	Increase 1 ml/h	Increase 1.5 ml/h
< 0.8	After 0.1 ml/kg IV, increase 2 ml/h	After 0.15 ml/kg IV, increase 3 ml/h

iCa should be measured in vivo (sampling from artery or vein) or at the access end of the extracorporeal circulation circuit. *IV* intravenous injection, *iCa* ionized calcium

- **Contraindications of RCA**

We generally do not use RCA, at least initially, in patients who are likely to have minimal metabolic clearance of citrate :

- **Hyperacute liver failure with elevated serum liver transaminase values >1000 international unit/L: Hyperacute liver failure (ie, within seven days) is usually from severe ischemia (ie, shock liver) or toxin exposure (eg, acetaminophen poisoning). Patients with severe hyperacute liver failure are unlikely to metabolize citrate,resulting in decreased ionized calcium and severe acidosis. However, RCA may be used once liver function starts to improve.**

By contrast, many patients with markedly elevated transaminases who have liver failure that is acute (ie, 7 to 21days), subacute (ie, >21 days and <26 weeks), or acute on chronic (eg, alcoholic hepatitis or cirrhosis) may metabolize enough citrate to tolerate RCA. However, the risk of citrate accumulation and hypocalcemia in such patients is increased.

- **Cardiogenic shock with blood lactate values >8 mmol/L :Similar to patients with hyperacute liver failure,such patients typically do not metabolize citrate. RCA may be used if there is clinical improvement and a decrease in lactate to ≤8 mmol/L.**
- **However, some centers have developed RCA protocols designed for use in patients with reduced or minimal clearance of citrate, by reducing citrate flow rate or increasing dialysis clearance.**

- **Monitoring**

We check blood electrolytes at least every six hours and include sodium, potassium, chloride, ionized calcium,magnesium, and blood gas analysis, along with calculation of the anion gap. At least once daily, total blood calcium concentration should be monitored to calculate the calcium ratio (total calcium/ionized calcium) or calcium gap (total calcium minus ionized calcium), which, if abnormal, may indicate citrate accumulation.

Once steady state is reached after 48 to 72 hours and the patient remains clinically stable, monitoring of electrolytes can be decreased to every 12 hours.

The need for monitoring anticoagulation efficacy in the circuit depends on the method of citrate delivery. If the dose of citrate is fixed in relation to the blood flow, monitoring is not necessary as long as blood flow is constant. If the citrate dose is not fixed to a constant blood flow rate, postfilter ionized calcium levels should be measured at least every six hours and the infusion of citrate titrated for an ionized calcium between 0.3 and 0.4 mmol/L. However,some centers monitor postfilter ionized calcium levels less frequently.

• Citrate accumulation and indications to stop RCA

Regional citrate anticoagulation (RCA) should be stopped if there is citrate accumulation.

It is difficult to predict which patients will develop citrate accumulation. Patients at very high risk are those with hyperacute liver failure who have serum liver transaminases >1000 international unit/L and also those with cardiogenic shock and lactate concentrations >8 mmol/L, although other causes of hyperlactatemia do not necessarily preclude the use of citrate. As noted above, we generally do not use RCA in such patients.

Citrate accumulation is suggested by the following :

- Worsening metabolic acidosis with increasing anion gap
- Decreasing ionized calcium requiring escalating calcium infusion rates
- Increasing total calcium
- A ratio of total calcium to ionized calcium >2.5

- There is no absolute value or threshold that is used to stop RCA. We generally look at trends of all those criteria and stop RCA only when all criteria are met.
  Prior to stopping RCA, certain measures to reduce citrate accumulation can be tried, such as reducing the citrate infusion rate for patients on hemofiltration or increasing the dialysate infusion rate for patients on hemodialysis or hemodiafiltration.

• Other complications of RCA

The potential complications associated with regional citrate include hypocalcemia (ie, in absence of other evidence of citrate toxicity), hypercalcemia, hypernatremia, hypomagnesemia, and acid-base disorders. Either alkalosis or acidosis can occur. These are rarely indications to stop CKRT, providing acidosis is not accompanied by other evidence of citrate accumulation. The rate of specific complications depends on the specific protocol used and on patient comorbidities.

Alkalosis is less common when replacement solutions and dialysate solutions contain reduced bicarbonate concentrations. Solutions commonly used for patients who are not on RCA contain bicarbonate solution of 32 to 35 mEq/L, whereas solutions for patients treated with RCA contain bicarbonate concentration of 22 to 25 mEq/L. As noted above, severe acidosis may develop if citrate is not metabolized by the liver or muscle. However, acidosis may also develop in the absence of citrate accumulation.

Original Article

Clinical efficacy of regional citrate anticoagulation in continuous renal replacement therapy: systematic review and meta-analysis

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Background: A systematic review and meta-analysis were conducted to explore the clinical efficacy and coagulation function of regional citrate anticoagulation (RCA) in continuous renal replacement therapy (CRRT) in critically ill patients, to provide an effective treatment options for CRRT in severe patients.

Methods: The English databases Embase, Medline, PubMed, Ovid, Springer, and Web of Science were searched to screen for randomized controlled trials (RCTs) on RCA in the CRRT treatment of critically ill patients published before June 1, 2020. Meta analysis using the RevMan5.3 provided by the Cochrane collaboration network. The search terms included "citrate anticoagulation", "patient in severe condition", "CRRT", "clinical effect", and "coagulation function".

Results: ten articles meeting requirements were included, comprising 1,411 subjects. Meta-analysis results showed that after treatment, total calcium/ionized calcium (totCa/ionCa) [mean difference (MD) =0.05; 95% confidence interval (CI): (−0.02 to 0.12); Z=1.31; P=0.19], prothrombin time [MD =4.51; 95% CI: (2.77, 6.24); Z=5.10; P<0.00001], activated partial thromboplastin time [MD =2.56; 95% CI: (1.17, 3.95); Z=3.61; P=0.0003], and thrombin time [MD =4.22; 95% CI: (2.07, 6.36); Z=3.85; P=0.0001] all increased. However, platelet count [MD =−5.75; 95% CI: (−8.85, −2.64); Z=3.63; P=0.0003], cystatin [MD =−0.39; 95% CI: (−0.63, −0.15); Z=3.22; P=0.001], alanine aminotransferase [MD =−17.63; 95% CI: (−20.09, −15.16); Z=14.02; P<0.00001], aspartate aminotransferase [MD =−6.49; 95% CI: (−11.94, −1.04); Z=2.33; P=0.02], creatinine [MD =−3.70; 95% CI: (−5.08, −2.32); Z=5.24; P<0.00001], and total bilirubin [MD =−3.65; 95% CI: (−5.91, −1.40); Z=3.18; P=0.001] all decreased. Except for totCa/ionCa, the differences in other indicators were not statistically significant compared with the control group.

Discussion: RCA can significantly improve the clinical efficacy and blood coagulation indicators of CRRT for severely ill patients.

Keywords: Citrate; critically ill patients; continuous renal replacement therapy (CRRT); clinical efficacy; coagulation function

Submitted Jun 09, 2021. Accepted for publication Jul 23, 2021.

doi: 10.21037/apm-21-1693

View this article at: https://dx.doi.org/10.21037/apm-21-1693

- **Combined RCA and unfractionated heparin**

Regional citrate anticoagulation (RCA) has not been shown to reduce platelet activation or thrombin generation in critically ill patients undergoing CKRT . As such, circuit clotting was increased with the first wave of coronavirus disease 2019 (COVID-19) infections, and therefore, many centers combined systemic heparin with RCA without observing an increase in bleeding complications.

- **SUMMARY AND RECOMMENDATIONS**
- **Indications – Continuous kidney replacement therapy (CKRT) may require anticoagulation to prevent clotting in the extracorporeal system and loss of the hemofilter. Clotting decreases the total therapy time and efficacy.**
- **A sufficient time on CKRT is necessary to ensure an adequate kidney replacement therapy (KRT) dose is delivered.**
- **Initial approach – For most patients, we attempt CKRT without anticoagulation, although many clinicians use anticoagulation from the outset. We usually can achieve adequate CKRT filter survival if the patient has a wellfunctioning vascular access.**
- **Regional citrate anticoagulation (RCA) preferred – If the hemofilter cannot be maintained without anticoagulation for at least 24 hours, we use anticoagulation. If RCA is available and the patient has no contraindications, we use RCA rather than unfractionated heparin (UFH).**

RCA is better than heparin at preserving filter patency and is less likely to cause adverse events, including bleeding. However, RCA has not been shown to provide a survival benefit compared with heparin.

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