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Risks and benefits of citrate anticoagulation for continuous renal replacement therapy

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ABSTRACT

Heparin, despite its significant side-effects, is the most commonly used anticoagulant for continuous renal replacement therapy in critical care setting. In recent years, citrate has gained much popularity by improving continuous renal replacement therapy circuit survival and decreasing blood transfusion requirements. However, its complex metabolic consequences warrant modification in the design of the citrate-based continuous renal replacement therapy protocol. With thorough understanding of the therapeutic mechanism of citrate, a simple and practicable protocol can be devised. Citrate-based continuous renal replacement therapy can

be safely and widely used in the clinical setting with appropriate clinical staff training.

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Introduction

Continuous renal replacement therapy (CRRT) is commonly used for the management of acute kidney injury in the intensive care unit (ICU) worldwide. Anticoagulation is necessary to prevent clotting of the extracorporeal circuit. Unfractionated heparin has the advantages of acceptable circuit life, low cost, easy monitoring and simple reversal, and hence, remains a popular choice.^{1,2} However, critically ill patients have various bleeding risks that may contraindicate the use of heparin. The contra-indications may include recent surgical procedures, multiple trauma, thrombocytopenia, and coagulation defects.³ Moreover, binding of heparin to endothelial antithrombin inhibits its anti-inflammatory actions and prevents local prostacyclin formation that, in turn, jeopardises micro-circulation.^{4,5} Hence, heparin use may be disadvantageous in patients with Gram-negative sepsis.⁴ Although implementation of an anticoagulation-free regimen is a safer alternative, circuit clotting occurs frequently, which not only increases treatment cost and downtime, but also increases the need of blood transfusion and the nursing workload. Among the various alternative anticoagulants like low-molecular-weight heparin, serine proteinase inhibitor nafamostat, prostacyclin, hirudin and direct thrombin inhibitor, citrate has gained popularity in recent years. This paper provides a general review on citrate use in CRRT and focuses on studies published in the past decade.

Mechanism of action

Citrate just mixes with the blood before it enters

the CRRT circuit as illustrated in the commonly used citrate-based CRRT regimens (Figures 1 to 3). Citrate chelates the ionised calcium, which is essential for the normal coagulation cascade and results in inhibition of thrombin generation. An extracorporeal, post-filter, ionised calcium concentration of 0.25 to 0.35 mmol/L is effective to achieve the anticoagulation effect. The majority of citrate is removed by either filtration or dialysis with a sieving coefficient of one in both processes.⁶ The removal fraction varies from 20% to 80%, depending on the blood flow rate, effluent flow rate, and CRRT modality.^{7,8} The remaining calcium-citrate product enters the systemic circulation and is metabolised in the liver, muscles, and kidneys to produce three molecules of bicarbonate for every molecule of citrate. Replacement infusion of calcium is commonly given to compensate the extracorporeal loss and to normalise a patient's systemic calcium level.^{8,9} The relative contra-indications for citrate-based CRRT include liver failure with or without cirrhosis, severe hypoxaemia, and after massive blood transfusion.

Circuit survival

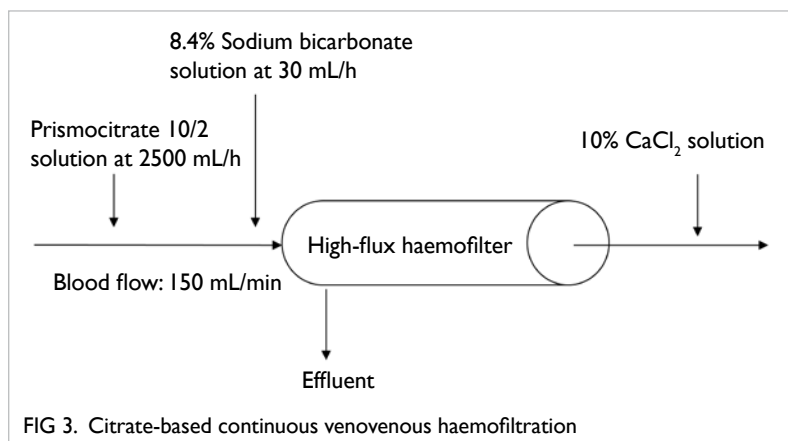
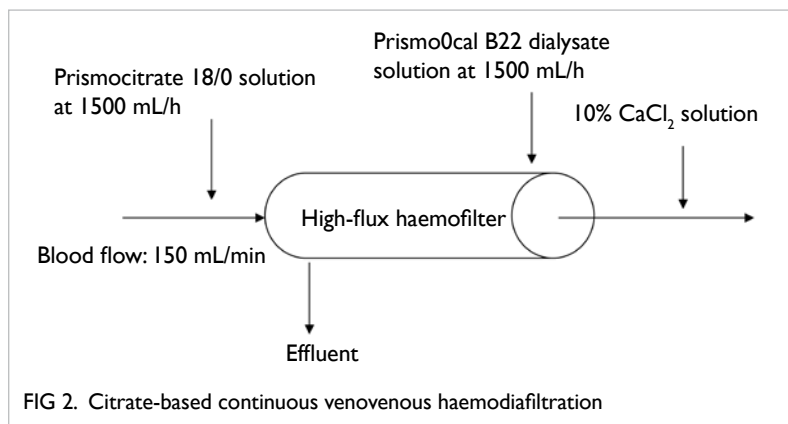
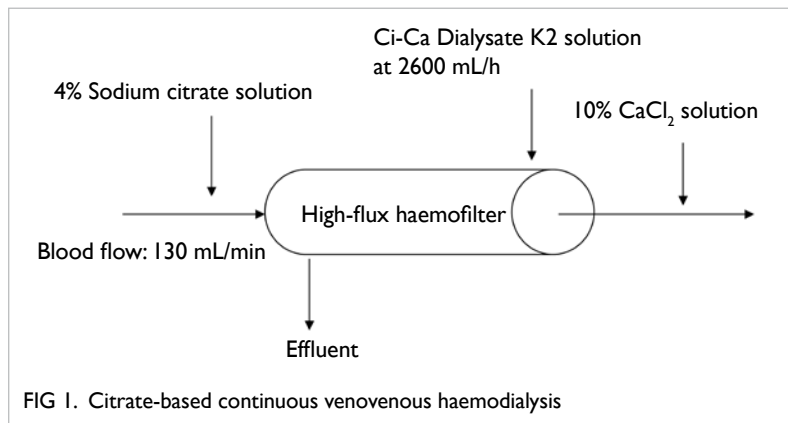
Factors affecting the circuit life include a patient's clinical condition and coagulation status, the position and patency of the vascular access, the choice of anticoagulant, modality of CRRT, and filtration fraction.^{10,11} Most of the published randomised controlled trials (RCTs) indicate improved circuit survival with citrate versus heparin (Table 1¹²⁻¹⁷). Three meta-analyses have been published recently that summarise this issue.¹⁸⁻²⁰ While Liao et al²⁰

枸橼酸抗凝作連續性腎臟替代治療的風險及效益

沈海平、殷榮華、陳德茂

肝素是連續性腎臟替代治療 (CRRT) 中最常用的抗凝劑，然而與其相關的副作用甚為顯著。枸橼酸抗凝可以改善CRRT使用壽命及降低輸血需求，因此枸橼酸近年來逐漸普及。設計枸橼酸CRRT方案時要多加注意其複雜的代謝後果。通過深入了解其治療機制，設計簡單可行的CRRT方案及適當培訓臨床人員，枸橼酸抗凝可安全及被廣泛應用。

only focused on RCTs that compare unfractionated heparin with citrate, Zhang and Hongying¹⁸ and Wu et al¹⁹ also included studies on low-molecular-weight heparin and regional heparin. They concluded that circuit life with citrate was comparable^{19,20} or better (by a mean difference of 23.03 hours; 95% confidence interval, 0.45-45.61 hours) than that with heparin.¹⁸ The main reason for the discrepancy between the findings by Zhang and Hongying¹⁸ (which showed more favourable circuit life for citrate group vs heparin group) and Wu et al¹⁹ (which showed comparable circuit life between citrate and heparin groups) was attributed to the study by Betjes et al,¹⁷ which did not report interquartile ranges of circuit survival. While Zhang and Hongying¹⁸ estimated the survival time in this study by Kaplan-Meier analysis, Wu et al¹⁹ excluded it from their circuit survival analysis. With the improved circuit life, citrate can decrease circuit downtime and minimise discrepancy between prescribed and delivered CRRT dose, achieve lower treatment cost, avoid unnecessary blood loss, and reduce nursing workload. In fact, the latest Kidney Disease Improving Global Outcomes Clinical Practice Guidelines recommended citrate as the anticoagulant of choice in patients requiring CRRT.²¹



Metabolic control

Concerning reversal of metabolic acidosis and control of uraemia, most RCTs^{12,13,17} reported similar efficacy when comparing citrate- with heparin-based CRRT, except one study¹⁶ which was in favour of citrate. This might be explained by the longer circuit lifetime, which offered better uraemic toxin clearance.

Bleeding events

All RCTs,^{12,13,15-17} except one,¹⁴ showed a higher bleeding risk with heparin-based CRRT when compared with citrate anticoagulation (Table 1). All the three meta-analyses¹⁸⁻²⁰ demonstrated a significantly lower incidence of bleeding in citrate-based CRRT compared with heparin, with a pooled risk ratio ranging from 0.25 to 0.34. However, the definition of bleeding events varied in all the included trials. Blood transfusion requirement was lower in the citrate group when compared with the unfractionated heparin group.²⁰

Mortality

Three studies provided outcome information on mortality (Table 1).^{12,13,15} The study by Kutsogiannis et al¹⁵ was relatively small (n=30, mortality rate of citrate group vs heparin group = 81% vs 71%; P=0.69) and was not powered to detect survival difference. The single-centre study by Oudemans-van Straaten et al¹³ showed a mortality benefit at 3 months (48%

TABLE I. Characteristics and major findings of randomised controlled trials comparing regional citrate- and heparin-based continuous renal replacement therapy¹²⁻¹⁷

	Hetzel et al ¹²	Oudemans-van Straaten et al ¹³	Fealy et al ¹⁴	Betjes et al ¹⁷	Kutsogiannis et al ¹⁵	Monchi et al ¹⁶
Year of publication	2011	2009	2007	2007	2005	2004
Centre	Multi	Single	Single	Single	Multi	Single
No. of patients	C: 87 H: 83	C: 97 H: 103	C: 10 H: 10	C: 21 H: 27	C: 16 H: 14	C: 8 H: 12
Age (years)	C: 62* H: 65*	C: 73† H: 73†	C & H: 71†	C: 58* H: 55*	C: 67* H: 64*	C: 67† H: 64†
Sepsis	C: 77% H: 74%	C: 43% H: 49%	C & H: 30%	C: 76% H: 59%	C: 31% H: 43%	C: 50% H: 42%
Treatment	Citrate vs UFH	Citrate vs LMWH	Citrate vs regional UFH	Citrate vs UFH	Citrate vs UFH	Citrate vs UFH
Circuit lifespan (hours)	C: 38 H: 26	C: 27 H: 26	C: 17 H: 13	C: 36 H: 38	C: 124 H: 38	C: 70 H: 40
Control of acidosis	Similar	Similar	NR	Similar	NR	Similar
Control of uraemia	Similar	Similar	NR	Similar	NR	In favour of citrate
Mortality	C: 47% H: 41%	C: 42% H: 57%	NR	NR	C: 81% H: 71%	NR
Renal recovery	NR	C: 69% H: 52%	NR	NR	NR	NR
Bleeding events	C: 6% H: 15%	C: 6% H: 16%	C: 0% H: 0%	C: 0% H: 33%	C: 6% H: 57%	C: 0% H: 8%
Metabolic alkalosis	Similar	C: 9% H: 19%	NR	C: 0% H: 7%	C: 6% H: 0%	C: 13% H: 0%
Hypocalcaemia	C: 1% H: 0%	C: 6% H: 2%	NR	C: 9% H: 0%	C: 6% H: 0%	C: 13% H: 0%

Abbreviations: C = regional citrate group; H = heparin group; LMWH = low-molecular-weight heparin; NR = not reported; UFH = unfractionated heparin

* Mean age

† Median age

vs 63% respectively; $P=0.03$) when comparing citrate with low-molecular-weight heparin. Mortality was mainly reduced in surgical patients, those with sepsis, those younger (<73 years), and in patients with higher Sepsis-related Organ Failure Assessment scores (>11 points). The study speculated that citrate, apart from being an excellent anticoagulant for CRRT, might have immunomodulatory actions that suppress inflammation, thus, leading to a survival benefit in critically ill patients.¹³ However, a subsequent multicentre study by Hetzel et al¹² failed to demonstrate such benefit. While Hetzel et al¹² used unfractionated heparin, Oudemans-van Straaten et al¹³ used a low-molecular-weight heparin preparation. Hetzel et al¹² also included subjects who were younger and more septic. The discrepancy in clinical background and the different mode of anticoagulation might explain the difference in the observed results. It was important to note that both studies were not sufficiently powered to ascertain survival benefit of regional citrate anticoagulation, and mortality rate was not the primary end-point. A properly powered, well-designed RCT is required to clarify this issue.

Side-effects

Citrate anticoagulation has complex metabolic consequences due to its physiochemical property. Apart from being an anticoagulant, it also serves as a pH buffer, chelating agent, and a source of energy and sodium.

Citrate toxicity

A recent pharmacokinetic study showed that citrate clearance is not impaired in critically ill patients.²² However, reduced metabolism of citrate occurs in patients with chronic liver disease, ischaemic hepatitis, hypoxia and impaired muscle perfusion, which are commonly found in the ICU setting. Citrate accumulation results in ionised hypocalcaemia and acidosis, which cause hypotension due to decreased myocardial contractility and vascular hypotonia. A paradoxical increase in total calcium concentration often occurs due to increased citrate-bound calcium, as well as the increased use of calcium replacement in response to ionised hypocalcaemia. The total-to-ionised calcium ratio is, therefore, an important marker to detect citrate accumulation.^{23,24} An

elevated ratio of >2.25 should alert the clinician to the possibility of citrate accumulation. Impaired citrate metabolism is an independent risk factor for mortality. A ratio of ≥ 2.4 independently predicted a 33.5-fold increase in 28-day mortality rate in critically ill patients.²⁵ There was also a significant correlation between total-to-ionised calcium ratio and the severity of critical illness. Citrate toxicity should be suspected, based on the presence of the following three observations, namely, elevated total-to-ionised calcium ratio of >2.25 , increased use of calcium replacement, and increasing metabolic acidosis. Clinically, patients may present with symptoms of hypocalcaemia like circumoral paraesthesia, carpopedal spasm, generalised tetany, and hyper-reflexia.²⁶ Prolonged QT interval may follow by the development of Torsades de pointes or ventricular arrhythmia in untreated patients.²⁶ Confirmation of citrate intoxication can only be done by checking citrate concentration in blood, which is not readily available in most hospital laboratories. Therefore, clinical symptoms and signs are suggestive but not diagnostic of citrate toxicity. In highly suspicious cases, citrate infusion should be stopped immediately, followed by intravenous calcium injection. Continuous renal replacement therapy could be resumed using citrate-free regimen after initial stabilisation. Despite the potential risks associated with citrate toxicity, CRRT with citrate anticoagulation is considered feasible in patients with liver impairment,²⁷ provided that careful monitoring of calcium level and meticulous titration are ensured. Citrate accumulation should be minimised with the reduction in citrate infusion, increase in effluent flow to promote citrate clearance, adequate calcium replacement to counteract hypocalcaemia, and supplementation with extra bicarbonate to correct acidosis.

Metabolic derangement

Recent meta-analyses showed no significant difference in the incidence of metabolic alkalosis in citrate groups compared with heparin groups in patients with normal metabolism.^{19,20} Hypernatraemia is a problem commonly associated with the use of concentrated citrate solution (4% trisodium citrate solution has 544 mmol/L sodium while Anticoagulant Citrate Dextrose Solution A [ACDA] has 224 mmol/L sodium). Adoption of a slightly hyponatraemic replacement or dialysate solution in the CRRT regimen may be a remedy to this problem. Alternatively, normonatremic citrate solution may be used, for instance, Prismocitrate 18/0 or Prismocitrate 10/2 (Gambro Hospal, Stockholm, Sweden), which serves as both an anticoagulant and a source of buffer for predilutional treatment.^{28,29} The drawback of this method is that it does not guarantee a fixed relationship between citrate and blood flow.

This is due to the fact that the amount of replacement fluid entering the circuit is dependent on filtrate flow and the desired amount of fluid removal, which are prone to variations. The varying citrate concentration may consequently exert a negative effect on the circuit survival time. This issue can be resolved by fixing the flow ratio between blood and the citrate-containing substitution fluid. Citrate binds to magnesium, resulting in excessive loss in filtrate and causing hypomagnesaemia, which in turn decreases the release of parathyroid hormone, promotes hypokalaemia, and induces tetany as well as cardiac arrhythmia. Monitoring and replacement of magnesium should be done regularly.

Energy gain

Citrate also serves as a source of energy with 0.59 kcal/mmol and can enter cells without insulin. The bioenergetic gain of citrate-anticoagulated CRRT is not limited to citrate itself, but is also contributed by glucose (in ACDA) and lactate (in replacement or dialysate solution). The energy delivered can differ substantially between modalities, even with comparable doses.³⁰ Such information should, therefore, be taken into account when nutritional needs are being calculated.

Treatment cost

The composition of commonly used fluid for CRRT is shown in Table 2. Using average filter life (citrate vs heparin = 52 hours vs 30 hours) calculated based on previously published RCTs (Table 1), the total treatment cost for citrate-based CRRT lasting for 72 hours is around HK\$10 000 (using continuous venovenous haemodiafiltration with 1250 mL/h pre-filter citrate containing replacement solution plus 1250 mL/h dialysate flow rate and two haemofilter/circuit changes within 72 hours of treatment). The cost is similar to that of heparin-based regimen (using continuous venovenous haemodiafiltration with 1250 mL/h post-filter replacement solution plus 1250 mL/h dialysate flow rate and three haemofilter/circuit changes within 72 hours of treatment).

Future development

Development of fluid for citrate-based continuous renal replacement therapy

The setup of regional citrate anticoagulant with conventional CRRT machines was more complicated compared with other anticoagulants. Since 1995, citrate in the form of ACDA had been the default anticoagulation method for CRRT in our unit, as described by Leung and Yan.³¹ The solutions for replacement are customised (with low bicarbonate and sodium level) as a concentrated citrate solution will provide extra sodium and bicarbonate load. Reconstitution of this customised replacement fluid

TABLE 2. Composition of fluids available in Hong Kong for continuous renal replacement therapy

	Na (mmol/ L)	K (mmol/ L)	Ca (mmol/ L)	Mg (mmol/ L)	Cl (mmol/L)	Lactate (mmol/L)	Acetate (mmol/ L)	Bicar- bonate (mmol/ L)	Citrate (mmol/ L)	Citric acid (mmol/ L)	Glucose (g/L)	HPO ₄ ²⁻ (mmol/L)	Osmol- arity (mOsm/L)
FMC multiBic (free K ⁺)	140	0	1.5	0.5	109	0	0	35	0	0	1	0	290
FMC multiBic (K ⁺ 2)	140	2	1.5	0.5	111	0	0	35	0	0	1	0	294
FMC multiBic (K ⁺ 3)	140	3	1.5	0.5	112	0	0	35	0	0	1	0	296
FMC multiBic (K ⁺ 4)	140	4	1.5	0.5	113	0	0	35	0	0	1	0	298
FMC multiPlus (K ⁺ 2)	140	2	1.5	0.75	109.7	0	0	35	0	0	1	1	295
FMC Ci-Ca Dialysate K2	133	2	0	0.75	116.5	0	0	20	0	0	1	0	278
FMC Ci-Ca Dialysate K4	133	4	0	0.75	118.5	0	0	20	0	0	1	0	282
FMC Ci-Ca Dialysate K2 Plus	133	2	0	1	115.75	0	0	20	0	0	1	1.25	278
FMC Ci-Ca Dialysate K4 Plus	133	4	0	1	117.75	0	0	20	0	0	1	1.25	282
Gambro Hemosol BO	140	0	1.75	0.5	109.5	3	0	32	0	0	0	0	287
Gambro Prismocal	140	0	0	0.5	106	3	0	32	0	0	0	0	282
Gambro Prismocal B22	140	4	0	0.75	120.5	3	0	22	0	0	6.1	0	296
Gambro Phoxilium	140	4	1.25	0.6	115.9	0	0	30	0	0	0	1.2	293
Haemofiltration solution 1	140	1	1.62	0.75	100.75	45	0	0	0	0	2	0	300
Haemofiltration solution 2	135	2	1.87	0.75	108.5	33.75	0	0	0	0	1.5	0	290
Haemofiltration solution 3	135	0	1.87	0.75	106.5	33.75	0	0	0	0	1.5	0	286
Haemofiltration solution 4	135	3	1.87	0.75	109.5	33.75	0	0	0	0	1.5	0	292
Haemofiltration solution 5	140	0	2	1	111	0	35	0	0	0	1.5	0	292
ACDA	225	0	0	0	0	0	0	0	75	38	22.3	0	462
ACDB	135	0	0	0	0	0	0	0	45	23	13.4	0	277
FMC Trisodium citrate 4%	408	0	0	0	0	0	0	0	136	0	0	0	544
Gambro Prismocitrate 10/2	136	0	0	0	106	0	0	0	10	2	0	0	254
Gambro Prismocitrate 18/0	140	0	0	0	86	0	0	0	18	0	0	0	244

Abbreviations: ACDA = Acid Citrate Dextrose Solution A; ACDB = Acid Citrate Dextrose Solution B; Ca = calcium; Cl = chloride; FMC = Fresenius Medical Care; Mg = magnesium; Na = sodium; K = potassium

was tedious, time-consuming, and error-prone. The next evolution was to use online replacement fluid generated from Gambro AK200 Ultra S (Gambro Hospital, Stockholm, Sweden) together with post-dilution continuous venovenous haemofiltration with citrate anticoagulation using ACDA. The advantage of this system was the flexibility of adjusting sodium and bicarbonate concentrations with the replacement solution generated online. It also came at a lower treatment cost due to generation of sterile replacement fluid via the online system.³² However, generation of ultra-pure water is a prerequisite for implementation, and ICUs without pre-installed water delivery and treatment systems will be precluded from this treatment technology. In the recent 10 years, commercially prepared citrate-containing replacement solution and tailor-made dialysate have become widely available (Table 2), and citrate-based CRRT has been widely adopted in different ICUs.

Machine and protocol development

Previous CRRT machines were not specifically

designed for citrate-based treatment. Additional infusion pumps for continuous citrate administration were required during treatment, and posed major safety problems. When the CRRT machine alarm sounds for bag exchange or for other mechanical problems, all CRRT infusion pumps will stop except for the pump used to infuse the citrate solution, which may result in the direct infusion of citrate solution into the patient. Nowadays, the new CRRT machines have incorporated integrated citrate modules and specific protocols. Continuous monitoring of citrate and ionised calcium levels together with computerised algorithms may further improve patient safety and minimise potential side-effects.^{33,34} Yet, successful implementation of the protocol requires focused and continuous training for the involved clinical staff.

Conclusion

Citrate is a safe and effective anticoagulant for CRRT. Its advantages can be fully appreciated with a simple, well-devised and practicable protocol, and appropriate clinical staff training.

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