ORIGINAL ARTICLE

Protocolized Regional Citrate Anticoagulation during Continuous Renal Replacement Therapy: A Single Center Experience

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Abstract

Background: Regional citrate anticoagulation (RCA) has emerged as a treatment modality that reduces bleeding risk and filter clotting. With initial experience of using RCA with continuous renal replacement therapy (CRRT), we have formulated a working protocol based on published literature.

Objective: The study aimed to evaluate the protocol for routine use of RCA during CRRT requiring anticoagulation and evaluation of filter life.

Methodology: It is a single-center, open-label, prospective, non-randomized, non-interventional, single-arm, observational study conducted at a tertiary care hospital between September 2022 and July 2023. All adult patients with acute kidney injury (AKI) or hyperammonemia requiring CRRT and necessitating the use of anticoagulation were enrolled in the study. The study used Prisma Flex M100 AN 69 dialyzer on Prisma Flex (Baxter) CRRT machines during continuous venovenous hemodiafiltration (CVVHDF). The targeted CRRT dose in all the study patients was 25–30 mL/kg/hour. Based on the published literature, we have developed a working protocol (Appendix 1) for managing patients on CRRT using RCA.

Results: A total of 159 patients were analyzed for the study. The median [interquartile range (IQR)] filter life using RCA was 30 (12–55) hours. Filter clotting was observed in 33.3% of patients. Citrate accumulation was present in 52.25% of patients, but no CRRT was discontinued as citrate accumulation resolved after following the corrective steps in the protocol. None of the patients had citrate toxicity. Chronic liver disease (CLD) ($p \leq 0.001$) and those who were post-living donor liver transplant recipients ($p = 0.004$) had a statistically significant increase in citrate accumulation. Also, patients who had higher lactate at baseline (6 hours post-CRRT initiation), had a higher chance of citrate accumulation.

Conclusion: Our RCA protocol provides a safe approach to regional anticoagulation during CRRT in critically ill patients.

Keywords: Acute kidney injury, Acute liver failure, Chronic liver disease, Continuous renal replacement therapy, Hyperammonemia, Regional citrate anticoagulation.

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Highlights

- Protocol-based regional citrate anticoagulation (RCA) in continuous renal replacement therapy (CRRT) was assessed during the study.
- We found that RCA to be safe and effective. Citrate accumulation did not affect the outcome of the patients and can be easily resolved with corrective steps mentioned in the protocol.

Introduction

Continuous renal replacement therapy is increasingly being utilized as a treatment modality in intensive care units (ICUs). Despite numerous advancements, achieving appropriate anticoagulation to prevent circuit clotting without elevating the risk of bleeding remains a challenge. Circuit clotting leads to treatment interruptions, which significantly contributes to sub-optimal dosing. Interruptions from clotting have been shown to reduce the time on CRRT from 24 to 16 hours a day.[1] The main disadvantage of systemic anticoagulation is the risk of bleeding, which could be as high as 30–50%, with bleeding mortality as high as 15%.[2–4] Regional citrate anticoagulation has emerged as a treatment modality that prevents filter clotting and reduces bleeding manifestations. When citrate mixes with blood, it binds to ionized calcium (iCa), which is crucial for the normal coagulation process, thereby preventing the generation of thrombin. An extracorporeal, postfilter, iCa concentration of less than 0.35 mmol/L effectively prevents the filter's clotting and prolongs filter life.[5] Most of the citrate which is infused is removed by either diffusion or convection. The clearance of citrate can range from 20 to 80%, depending on the blood flow

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rate, dialysate flow rate, and the CRRT modality used.[6] The citrate that remains in the blood, enters the patient where the concentration gets diluted in the patient's blood where it is metabolized in the liver, kidney, and muscle, and thus calcium is released from the calcium citrate complex. This limits the anticoagulant properties of citrate to the circuit. A patient's iCa levels of more than 0.9 mmol/L are always required to prevent hypocalcemia-induced systemic complications.[7,8] Commercially prepared citrate solutions with predetermined citrate concentrations (Prismocitrate 10/2) have been successfully used in various studies.[9,10] Regiocit (Baxter), a commercially prepared citrate-containing fluid which can be combined with calcium-free dialysate and replacement fluids [Biphozyl (Baxter)] for CRRT, were launched in our country a few years ago. There is limited experience in the use of RCA during CRRT in India. With initial experience of using the above-mentioned CRRT fluids, we have formulated a working protocol based on published literature.

Objectives

The study aimed to assess the protocol for the routine use of RCA during CRRT that requires anticoagulation and to evaluate the lifespan of the filter.

Methodology

It is a single-center, open-label, prospective, non-randomized, non-interventional, single-arm, observational study conducted at a tertiary care hospital between September 2022 and July 2023. The initial plan was to enrol patients until at least 100 evaluable patients were included in the study. All adult patients with acute kidney injury (AKI) or hyperammonemia requiring CRRT and necessitating the use of anticoagulation were enrolled in the study. The EC/IRB approval was sought before initiating the recruitment of patients. The study was registered with the Clinical Trials Registry India (CTRI): CTRI/2022/08/045125 and approved by the Institutional Ethics Committee, Medanta – The Medicity, Gurugram, Haryana [Ref no: 866/2018(Academic)]. Written informed consent was taken before initiating CRRT, either from the patient or next of kin. The study used Prisma Flex M100 AN 69 dialyzer on Prisma Flex (Baxter) CRRT machines during continuous venovenous hemodiafiltration (CVVHDF). The targeted CRRT dose in all the study patients was 25–35 mL/kg/hour. The filtration fraction was always targeted at less than 25%. The patient and circuit ionized calcium were checked first after 1 hour of initiation of RCA-based CRRT. For the study and protocol validation, total serum calcium (mmol/L) to patient's ionized calcium (mmol/L) was calculated after 6 hours of initiation of RCA-based CRRT and repeated after every 6 hours. Based on the published literature, we have developed a working protocol (Fig. 1) for managing patients on CRRT using RCA. A detailed protocol is available in Annexure 1. This study will help us formalize our protocol and highlight any critical differences observed with Indian patients.

Patients and Outcome Measures

Patients of age 18 years or older, with AKI, diagnosed using RIFLE, AKIN classification or hyperammonemia requiring CRRT and anticoagulation were included in the study. Patients with hyperkalemia, i.e., potassium ≥5.5 meq/L and pregnant females were excluded from the study. All patient data entered were in a case report form (CRF) which was analyzed without naming the patients.

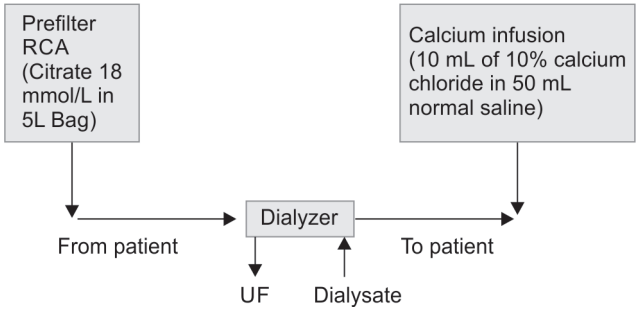

Fig. 1: Schematic diagram of RCA-based CRRT circuit

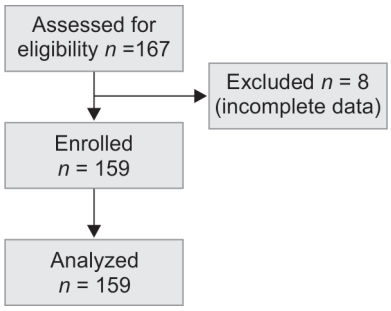

Fig. 2: Consort diagram of patients included in the study

The study's primary outcome was the average filter life with RCA during CRRT. The secondary outcomes include the incidence of citrate accumulation defined as "total serum calcium (mmol/L) to patient's ionized calcium ratio (mmol/L) >2.4"(during the therapy with RCA), citrate accumulation in patients with liver diseases and the relationship between lactate levels and citrate accumulation.

Statistical Analysis

The analysis included descriptive analysis of quantitative parameters expressed as means along with standard deviation as well as median along with interquartile range (IQR). Categorical data were expressed as absolute numbers and percentages. Fisher's *F*-test was used for testing of mean difference between independent groups whereas Kruskal–Wallis Chi-square was used for nonparametric comparisons of quantitative parameters. Cross tables were generated, and the Chi-square test was used for testing associations. A significant association on univariate analysis *p*-value ≤ 0.05 was considered statistically significant. All analyses were done using SAS 9.4.

Results

All adult ICU patients treated with CRRT using the study protocol during the above-mentioned period were screened for inclusion in the study. Initially, 167 consecutive patients meeting the inclusion criteria were evaluated for the study, but 8 patients were excluded in view of incomplete data (Fig. 2). A total of 159 patients were enrolled in the study and analyzed. Demographic data are presented in Table 1.

Primary Objective

The median (IQR) filter life using RCA was 30 (12–55) hours, with a maximum filter life of 108 hours (Table 2). Filter clotting was

Table 1: Demographic profile of patients included in the study

Demographic profile	*Frequency (n = 159)*	*Percentage (%)*
Gender		
Male	116	72.95
Female	43	27.04
Age (years)		
≤20	8	5.03
21–40	54	33.96
41–60	60	37.73
>60	37	23.27
Indication for CRRT		
Hyperammonemia	22	13.83
AKI + Metabolic acidosis + Septic shock	123	77.35
AKI + Metabolic acidosis + Septic shock + Hyperammonemia	7	4.4
AKI + Metabolic acidosis + Septic shock + Fluid overload	7	4.4
Patients with liver diseases		
Chronic liver disease	42	26.41
Acute liver failure	23	14.46
Post LDLT	6	3.77

AKI, acute kidney injury; LDLT, living donor liver transplant

Table 2: CRRT filter life

CRRT filter life	*Filter life (hours)*
Median filter life	30
Minimum filter life	2
Maximum filter life	108
75th percentile filter life	55
25th percentile filter life	12

Table 3: Comparison of citrate accumulation with patient outcome

Patient outcome	*Number of patients (%) with citrate accumulation absent*	*Number of patients (%) with citrate accumulation present*	*Chi-square*	*p-value*
Discharged	21 (55.3%)	17 (44.7%)	1.51	0.469
Expired	50 (44.6%)	62 (55.4%)		
LAMA	5 (55.6%)	4 (44.4%)		

LAMA, leave against medical advice; $p \leq 0.05$ is significant

observed in 53 (33.3%) patients with a median (IQR) filter life of 43 (28–64) hours, while CRRT treatment was terminated [patients who expired or left against medical advice (LAMA)] without filter clotting in 75 (47.2%) patients. Also, in 31 (19.5%) patients CRRT treatment was completed (CRRT was discontinued without filter clotting). The median (IQR) filter life in these patients was 66 (36–84) hours.

Secondary Objectives

Citrate accumulation was present in 82 (52.25%) patients. Citrate accumulation was not significantly different when compared with the outcome of the patients, i.e., between patients who expired, were discharged or LAMA ($p = 0.469$; Table 3). Citrate toxicity was not observed in any patient. In subgroup analysis of patients with liver diseases, acute liver failure (ALF) patients did not have a significant increase in citrate accumulation ($p = 0.367$) but patients with chronic liver disease (CLD) ($p \leq 0.001$) and those who were post living donor liver transplant recipients ($p = 0.004$) had statistically significant increase in citrate accumulation (Table 4).

Table 4: Citrate accumulation in patients with liver disease

	Citrate accumulation			
	Absent n (%)	*Present n (%)*	*Chi-square*	*p-value*
In ALF when compared with patients without liver disease				
ALF (*n* = 23)	12 (52.2%)	11 (47.8%)	0.8126	0.367
Others (*n* = 88)	55 (62.5%)	33 (37.5%)		
In CLD when compared with patients without liver disease				
CLD (*n* = 42)	8 (19.1%)	34 (81%)	21.493	<0.001*
Others (*n* = 88)	55 (62.5%)	33 (37.5%)		
In post-LDLT when compared with patients without liver disease				
PLDLT (*n* = 6)	0 (0.0%)	6 (100.0%)	–	0.004*
Others (*n* = 88)	55 (62.5%)	33 (37.5%)		

ALF, acute liver failure; CLD, chronic liver disease; LDLT, living donor liver transplant. $p \leq 0.05$ is significant

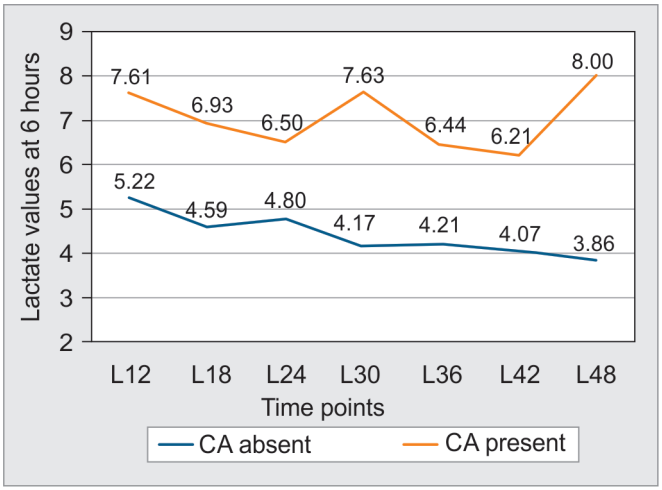

Fig. 3: Lactate values with citrate accumulation at different time points

It was also observed that patients in whom the lactate values were greater than 6 at the baseline (i.e., 6 hours post-CRRT initiation) then, for the next 36 hours, these patients were more likely to have citrate accumulation (Fig. 3). However, RCA for CRRT was not required to be discontinued in any patient with citrate accumulation. We also looked at citrate accumulation among patients who had an indication for CRRT as AKI or hyperammonemia ($n = 152$). There were 22 patients for whom CRRT was initiated only for hyperammonemia, while patients with AKI and no hyperammonemia requiring CRRT were 130. Citrate accumulation when compared between the two groups was not significant ($p = 0.291$, Table 5).

Discussion

This prospective observational study on the use of RCA during CRRT in patients with AKI or hyperammonemia requiring anticoagulation found that a median (IQR) filter life of 30 (12–55) hours. Zarbock et al. in their randomized control trial (RCT) of 596 patients, comparing RCA and heparin had a median (IQR) filter life of 47 (19–70) hours with RCA. The median filter life in the heparin group was

Table 5: Comparison of citrate accumulation in patients having hyperammonemia or AKI

	Citrate accumulation				
Groups	*Absent*	*Present*	*Total*	*Chi-square*	*p-value*
Hyperammonemia ($n = 22$)	13 (59.1%)	9 (40.9%)	22 (14.5%)	1.15	0.291
AKI ($n = 130$)	61 (46.9%)	69 (53.1%)	130 (85.5%)		

$p \leq 0.05$ is significant

26 (12–51) hours.[11] Gattas et al. in their RCT comparing RCA with regional heparin anticoagulation found median (IQR) filter life with RCA 39.2 (32.1–48) hours while that with regional heparin anticoagulation was 22.8 (13.3–34) hours.[12] Zarbock and Gattas both had a filter life more than our study.[11,12] This was probably because Zarbock et al. excluded patients with persistent and severe lactic acidosis [pH < 7.2 in two consecutive measurements for more than 2 hours and lactate level >72.1 mg/dL (8 mmol/L)], whereas our study included these patients.[11] Gattas et al. excluded patients who were anticipated to stay in the ICU for less than 24 hours.[12] These patients were included in the present study. The median circuit life in our study was also higher than the heparin group in the above-mentioned studies. A subsequent meta-analysis by Li et al. found that the heparin group had a significantly shorter filter life when compared with the RCA group ($p < 0.0001$).[13]

Palsson and Niles in an early study on RCA in CRRT found that 75.2% of patients had filter clotting with RCA.[14] Leroy et al. in their propensity score-matched cohort study found that circuit clotting was more with RCA (12.9 vs 2.4%; $p = 0.02$) when compared with the heparin.[15] This was, however, much less when compared with the study done by Palsson et al. In our study, filter clotting was observed in 33.3% of patients with RCA with a median (IQR) filter life of 43 (28–64) hours.

In our study, citrate accumulation was defined as "total serum calcium to patient's ionized calcium ratio >2.4." It is used as a surrogate marker for citrate accumulation. The present study found citrate accumulation in 52.25% of patients, however, citrate accumulation did not affect the filter life. Also, citrate accumulation did not make any difference to the patient outcome. Our RCA protocol mandates that in any patient having a total calcium to ionized calcium ratio >2.4, citrate needs to be stopped for 20 minutes and subsequently restarted afterwards with a citrate dose of 0.5 mmol/L less than the previous citrate dose. These corrective measures helped in resolving citrate accumulation in all the patients and thus allowed us to continue RCA without any citrate toxicity or any significant difference to the outcome. Increasing the CRRT dose by increasing dialysate where citrate accumulation is present will also help in the early clearance of citrate. Khadzhynov et al. of 1,070 patients found citrate accumulation in 2.99% of patients.[16] Meier–Kriesche et al. in their study had citrate accumulation in 12% of total patients undergoing continuous venovenous hemodialysis (CVVHD) and 33% in patients with liver disease.[17] The increased citrate accumulation observed in our study compared with earlier studies can be attributed to the fact that 44.64% of patients in our study had liver disease or were post-liver transplant patients. In our study, in a subgroup analysis, citrate accumulation was statistically significant in CLD ($p < 0.001$) and post-liver transplant patients ($p = 0.004$) when compared with non-liver disease patients, however, citrate accumulation was not statistically significant in acute liver failure patients (0.367). Again, RCA was not required to be discontinued in this subset also using our RCA protocol despite citrate accumulation episodes. In the L-CAT study by Slowinski et al., 133 individuals who were managed with RCA and CVVHD were included.[18] Severe acidosis or alkalosis (pH ≤ 7.2 or ≥ 7.55) and severe hypo- or hypercalcemia (ionised calcium ≤0.9 or ≥1.5 mmol/L, respectively) of any cause were the safety endpoints. Using their initial serum bilirubin level as a guide, the patients were divided into three predetermined groups based on their liver function (normal liver function ≤2 mg/dL, mild liver function >2–≤7 mg/dL, severe LF >7 mg/dL). It was discovered that there was no difference in the safety endpoints between the three patient strata: severe acidosis (normal liver function 13%, mild LF 16%, severe LF 14%; $p = 0.95$), severe hypocalcemia (normal liver function 8%, mild LF 14%, severe LF 12%; $p = 0.70$), and severe hypercalcemia (0% in all strata). Only three patients showed signs of impaired citrate metabolism. They concluded that people with liver illness can safely utilize RCA.[18] Peng et al. in their meta-analysis of 1,026 patients also found RCA to be safe and effective in liver failure patients.[19] In research by Saner et al. on liver transplant recipients who needed CRRT in the post-operative phase, no significant time trend of serum pH, bicarbonate, sodium, potassium, or calcium was discovered during CRRT. They came to the conclusion that RCA is both secure and useful for liver transplant recipients.[20]

In our study, it was observed that patients in whom the lactate values were greater than 6 at the baseline (i.e., 6 hours post-CRRT initiation) then, for the next 36 hours, these patients were more likely to have citrate accumulation. In their retrospective research, Khadzhynov et al. discovered that patients with starting lactate levels greater than 4 mmol/L had the highest citrate buildup (6.33%).[21] Khadzhynov et al. in their earlier study found that all patients who had citrate accumulation had severe lactic acidosis (pH 7.20 ± 0.11, lactate 136 ± 61 mg/dL).[16] In a prospective observational trial, Schultheiß et al. discovered that a rise in the total calcium to ionized calcium ratio ≥ 2.5 was predicted by serum lactate ≥ 3.4 mmol/L and prothrombin time ≤ 26%. These predictions had high sensitivity (86% for both lactate and prothrombin time), as well as specificity (86% for lactate and 92% for prothrombin time).[22] The present evidence available in the literature concurs with our findings.

Indian Society of Critical Care Medicine (ISCCM) guidelines on AKI and renal replacement therapy suggest that RCA should be the preferred choice over heparin at centers which have adequate expertise.[23] Sodhi et al. in their survey have found that the use of RCA was low (11%) across India.[24] Our study findings and RCA protocol will help various centers with limited exposure to enhance their expertise in using RCA during CRRT.

There are certain limitations to our study. Firstly, it is an observational study, with a significant number of patients having liver disease. Secondly, the study did not consider some other factors like the need for blood transfusion, baseline patient parameters and sequential organ failure assessment (SOFA) score which could have shed more light on the results of the study.

Conclusion

The RCA is a safe and effective way of prolonging filter life when tailored to a protocol, more so in patients at high risk of bleeding.

Our RCA protocol has demonstrated the feasibility of RCA in ICU patients. Citrate accumulation doesn't affect the patient outcome and can be resolved by following the RCA protocol used in the study. Patient selection and monitoring become paramount, especially in patients with high lactate levels. There is no absolute contraindication to RCA.

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References

1. Venkataraman R, Kellum JA, Palevsky P. Dosing patterns for continuous renal replacement therapy at a large academic medical centre in the United States. J Crit Care 2002;17(4):246. DOI: 10.1053/jcrc.2002.36757.
2. Davenport A, Will EJ, Davison AM. Comparison of the use of standard heparin and prostacyclin anticoagulation in spontaneous and pump-driven extracorporeal circuits in patients with combined acute renal and hepatic failure. Nephron 1994;66(4):431–437. DOI: 10.1159/000187859.
3. Martin PY, Chevrolet JC, Suter P, Favre H. Anticoagulation in patients treated by continuous venovenous hemofiltration: A retrospective study. Am J Kidney Dis 1994;24(5):806–812. DOI: 10.1016/s0272-6386(12)80675-5.
4. van de Wetering J, Westendorp RG, van der Hoeven JG, Stolk B, Feuth JD, Chang PC. Heparin use in continuous renal replacement procedures: The struggle between filter coagulation and patient hemorrhage. J Am Soc Nephrol 1996;7(1):145–150. DOI: 10.1681/ASN.V71145.
5. Calatzis A, Toepfer M, Schramm W, Spannagl M, Schiffl H. Citrate anticoagulation for extracorporeal circuits: Effects on whole blood coagulation activation and clot formation. Nephron 2001;89(2):233–236. DOI: 10.1159/000046075.
6. Hartmann J, Strobl K, Fichtinger U, Schildbock C, Falkenhagen D. In vitro investigations of citrate clearance with different dialysis filters. Int J Artif Organs 2012; 35(5):352–359. DOI: 10.5301/ijao.5000098.
7. Egi M, Kim I, Nichol A, Stachowski E, French CJ, Hart GK, et al. Ionized calcium concentration and outcome in critical illness. Crit Care Med 2011;39(2):314–321. DOI: 10.1097/CCM.0b013e3181ffe23e.
8. Zaloga GP1. Hypocalcemia in critically ill patients. Crit Care Med 1992;20(2):251–262. DOI: 10.1097/00003246-199202000-00014.
9. Ooi EL, Lim TW, Lim N. Comparison of the efficacy and safety of two regional citrate anticoagulation protocols using acid citrate dextrose A or Prismocitrate 10/2, in patients with acute renal failure undergoing continuous venovenous haemodiafiltration. Crit Care 2010;14(Suppl 1):P515. DOI: 10.1186/cc8747.
10. Shum H-P, Chan K-C, Yan W-W. Regional citrate anticoagulation in predilution continuous venovenous hemofiltration using prismocitrate 10/2 solution. Ther Apher Dialysis 2012;16(1):81–86. DOI: 10.1111/j.1744-9987.2011.01001.x.
11. Zarbock A, Küllmar M, Kindgen-Milles D, Wempe C, Gerss J, Brandenburger T, et al. Effect of regional citrate anticoagulation vs systemic heparin anticoagulation during continuous kidney replacement therapy on dialysis filter life span and mortality among critically ill patients with acute kidney injury: A randomized clinical trial. JAMA 2020;324(16):1629–1639. DOI: 10.1001/jama.2020.18618.
12. Gattas DJ, Rajbhandari D, Bradford C, Buhr H, Lo S, Bellomo R. A randomized controlled trial of regional citrate versus regional heparin anticoagulation for continuous renal replacement therapy in critically ill adults. Crit Care Med 2015;43(8):1622–1629. DOI: 10.1097/CCM.0000000000001004.
13. Li R, Gao X, Zhou T, Li Y, Wang J, Zhang P. Regional citrate versus heparin anticoagulation for continuous renal replacement therapy in critically ill patients: A meta-analysis of randomized controlled trials. Ther Apher Dial 2022;26(6):1086–1097. DOI: 10.1111/1744-9987.13850.
14. Palsson R, Niles JL. Regional citrate anticoagulation in continuous venovenous hemofiltration in critically ill patients with a high risk of bleeding. Kidney Int 1999;55(5):1991–1997. DOI: 10.1046/j.1523-1755.1999.00444.x.
15. Leroy C, Pereira B, Soum E, Bachelier C, Coupez E, Calvet L, et al. Comparison between regional citrate anticoagulation and heparin for intermittent hemodialysis in ICU patients: A propensity score-matched cohort study. Ann Intensive Care 2021;11(1):13. DOI: 10.1186/s13613-021-00803-x.
16. Khadzhynov D, Schelter C, Lieker I, Mika A, Staeck O, Neumayer HH, et al. Incidence and outcome of metabolic disarrangements consistent with citrate accumulation in critically ill patients undergoing continuous venovenous hemodialysis with regional citrate anticoagulation. J Crit Care 2014;29(2):265–271. DOI: 10.1016/j.jcrc.2013.10.015.
17. Meier–Kriesche HU, Gitomer J, Finkel K, DuBose T. Increased total to ionized calcium ratio during continuous venovenous hemodialysis with regional citrate anticoagulation. Crit Care Med 2001;29(4):748–752. DOI: 10.1097/00003246-200104000-00010.
18. Slowinski T, Morgera S, Joannidis M, Henneberg T, Stocker R, Helset E, et al. Safety and efficacy of regional citrate anticoagulation in continuous venovenous hemodialysis in the presence of liver failure: The liver citrate anticoagulation threshold (L-CAT) observational study. Crit Care 2015;19:349. DOI: 10.1186/s13054-015-1066-7.
19. Peng B, Lu J, Guo H, Liu J, Li A. Regional citrate anticoagulation for replacement therapy in patients with liver failure: A systematic review and meta-analysis. Front Nutr 2023;10:1031796. DOI: 10.3389/fnut.2023.1031796.
20. Saner FH, Treckmann JW, Geis A, Lösch C, Witzke O, Canbay A, et al. Efficacy and safety of regional citrate anticoagulation in liver transplant patients requiring postoperative renal replacement therapy. Nephrol Dial Transplant 2012;27(4):1651–1657. DOI: 10.1093/ndt/gfr510.
21. Khadzhynov D, Dahlinger A, Schelter C, Peters H, Kindgen-Milles D, Budde K, et al. Hyperlactatemia, lactate kinetics and prediction of citrate accumulation in critically ill patients undergoing continuous renal replacement therapy with regional citrate anticoagulation. Crit Care Med 2017;45(9):e941–e946. DOI: 10.1097/CCM.0000000000002501.
22. Schultheiß C, Saugel B, Phillip V, Thies P, Noe S, Mayr U, et al. Continuous venovenous hemodialysis with regional citrate anticoagulation in patients with liver failure: A prospective observational study. Crit Care 2012;16(4):R162. DOI: 10.1186/cc11485.
23. Mishra RC, Sodhi K, Prakash KC, Tyagi N, Chanchalani G, Annigeri RA, et al. ISCCM guidelines on acute kidney injury and renal replacement therapy. Indian J Crit Care Med 2022;26(Suppl 2):S13–S42. DOI: 10.5005/jp-journals-10071-24109.
24. Sodhi K, Philips A, Mishra RC, Tyagi N, Dixit SB, Chaudhary D, et al. Renal replacement therapy practices in India: A nationwide survey. Indian J Crit Care Med 2020;24(9):823–831. DOI: 10.5005/jp-journals-10071-23554.

Appendix

Medanta, the Medicity Institute of Critical Care & Anesthesiology
Division of Gastro, GI Surgery and Liver Critical Care
Protocol for Continuous Renal Replacement Therapy Using Citrate
(Regiocit, Citrate Concentration 18 mmol/L)

Starting Parameters

Effluent dose: Always less than 35 mL/kg/hr unless specifically mentioned (reduce dialysate and replacement fluid accordingly).

Filtration fraction: Target less than 25%.

Citrate dose: 3 mmol/L.

Calcium compensation: Its by 10% calcium chloride depending on initial patient ionized calcium level (see Table A1).

Table A1: Initial calcium compensation

Patient ionized calcium	*Starting calcium compensation*
Less than 0.8 mmol/L	15 mL/hr and give 1 gm calcium chloride 10% over 30 minutes before starting
0.8–1.0 mmol/L	12.5 mL/hr
Greater than 1.0 mmol/L	10 mL/hr

Treatment Monitoring

Low patient ionized calcium values should ALWAYS be attended to as a priority, as they will have the biggest impact on patient physiology and stability.

If at any time during treatment the patient's ionized calcium is less than 0.8 mmol/L, administer 1 gm calcium chloride 10% through central line.

A patient with ionized Ca of 0.8–1.0 mmol/L is required to keep the patient safe from the effects of hypocalcemia. A filter ionized calcium concentration of 0.25–0.35 mmol/L is required to prevent filter clotting.

So, once treatment is initiated and blood flow is established, wait for 60 minutes, then do the below checks:

Patient ionized calcium: Check this from the patient's arterial line.

Filter ionized calcium: Check this from the blue port on Prisma flex.

The table below gives the timings of the filter ionized calcium and patient ionized calcium checks (as well as other blood tests that will be needed).

Parameter	*Initial check*	*And then*
Filter Ionized Ca – ABG from blue port on circuit target 0.25–0.35 mmol/L	2nd hourly until stable (no further correction needed)	6 Hourly
Patient ionized Ca – ABG from arterial line target 0.8–1.0 mmol/L	2nd hourly until stable (no further correction needed)	6 Hourly
Serum Ca	After 6 hours	Daily
Total calcium to patient Ca ratio target ratio <2.4	After 6 hours	Daily

Adjust the calcium compensation and citrate dose based on the table below. Adjustments are made through the anticoagulation screen of the CRRT machine.

Parameter	*Filter ionized Ca > 0.35*	*Filter ionized Ca 0.25–0.35*	*Filter ionized Ca < 0.25*
Patient ionized Ca < 0.8	Citrate dose increased by 0.5 mmol/L blood and Calcium compensation increased by 2.5 mL/hr	Calcium compensation increased by 2.5 mL/hr	Citrate dose decreased by 0.5 mmol/L blood
Patient ionized Ca 0.8–1.0	Citrate dose increased by 0.5 mmol/L blood	'Normal' ideal values	Citrate dose decreased by 0.5 mmol/L blood
Patient ionized Ca > 1.0	Calcium compensation decreased by 2.5 mL/hr	Calcium compensation decreased by 2.5 mL/hr	Calcium compensation decreased by 2.5 mL/hr and citrate dose decreased by 0.5 mmol/L blood
Recheck 2nd hourly after any change			
If at any time during treatment the patient's ionized calcium is less than 0.8 mmol/L, administer 1 gm calcium chloride 10%.			
Always target an effluent dose of less than 35 mL/kg/hr and filtration fraction less than 25% (unless specifically indicated otherwise)			

Total Calcium to Ionized Calcium Ratio Monitoring

A high "total calcium to ionized calcium ratio" is a surrogate marker of citrate toxicity. To obtain the value, perform the following calculation manually – Patient total calcium ÷ Patient ionized calcium. Note that it is the total calcium and not the "corrected calcium" that is used in the equation.

After 6 hours of treatment commencing, request a total calcium from the lab. However, increasing calcium compensation in the preceding hours could indicate citrate accumulation. In these circumstances, a total calcium level may be checked before the 6-hour mark.

Ratio	*Action*
<2.4	Check ratio daily
>2.4	Stop citrate for 20 minutes and restart afterwards with 0.5 mmol/L less than the previous citrate dose.
	Leave calcium compensation unchanged. This would result in a slightly higher filter ionized calcium. (0.35–0.45 acceptable).
	If ratio remains above 2.4 despite filter Ionized calcium of 0.35–0.45 mmol/L then consider:
	• Doubling baseline dialysate flow (will increase citrate clearance).
	• Reducing blood pump speed (will reduce total administered citrate dose).
	• Stopping citrate and using an alternative anticoagulant (or no anticoagulant).