



# Calcium Repletion and Regional Citrate Anticoagulation in Hemodialysis and Hemodiafiltration: Using Dialysate Calcium to Modify Hypocalcemia

J. R. Dorie, C. W. McIntyre, S. Lemoine

## ► To cite this version:

J. R. Dorie, C. W. McIntyre, S. Lemoine. Calcium Repletion and Regional Citrate Anticoagulation in Hemodialysis and Hemodiafiltration: Using Dialysate Calcium to Modify Hypocalcemia. *Kidney medicine*, 2021, 3 (6), pp.1100-1101. 10.1016/j.xkme.2021.05.003 . inserm-03587212

**HAL Id: inserm-03587212**

**<https://inserm.hal.science/inserm-03587212>**

Submitted on 24 Feb 2022

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

## RESEARCH LETTER

**Calcium Repletion and Regional Citrate Anticoagulation in Hemodialysis and Hemodiafiltration: Using Dialysate Calcium to Modify Hypocalcemia**

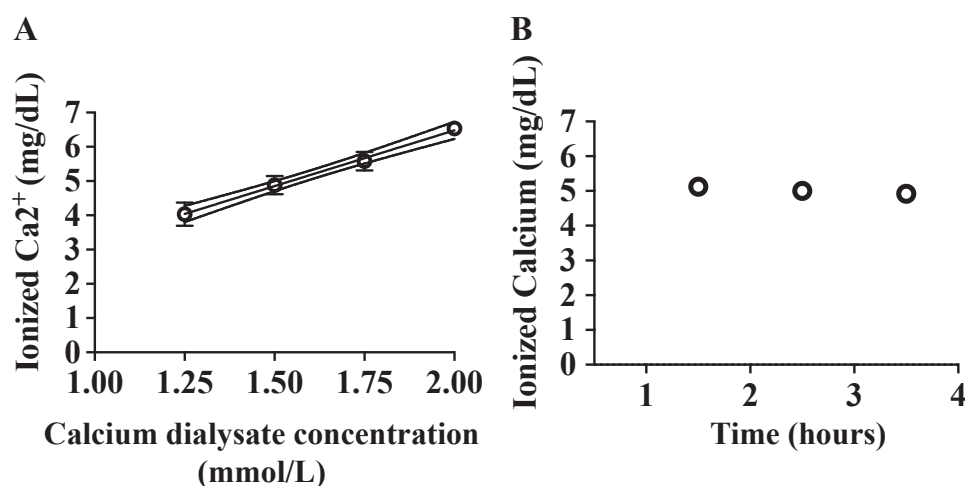
To the Editor:

The ideal extracorporeal circuit for kidney replacement therapy (CKRT) would have no systemic anticoagulation. However, this approach runs the risk of extracorporeal circuit loss or partial loss of dialyzer fibers. Regional citrate anticoagulation provides anticoagulation of the circuit owing to citrate chelating calcium<sup>1,2</sup> but is not usually used with hemodialysis (HD) because of difficulties in implementing it in clinical practice. Regional citrate anticoagulation requires rigorous monitoring of ionized calcium levels,<sup>3</sup> which leads to increased workload for nurses (frequent modulation of calcium infusion rate is needed to ensure the patient is not exposed to dangerous hypocalcemia) and increases costs significantly related to calcium measurement and replacement infusion supply.

Recent pandemic conditions have posed additional challenges to the use of CKRT in intensive care units. Hypercoagulability, filter loss, nursing workload, and personal protective equipment needs associated with CKRT have all rendered intermittent therapy increasingly preferable. HD is widely considered to be comparable to CKRT.<sup>4</sup> Accessible HD equipment with easily modifiable dialysate generated from treated tap water requires considerably fewer resources and offers freedom from consumable components. Because regional citrate anticoagulation is not commonly used with HD, we propose the use of a standard HD monitor to provide a hybrid therapy combined with a substantially simplified utilization of regional citrate anticoagulation to address current challenges.

An ex vivo dialysis circuit was set up using donated whole human blood. Ethics committee approval was not required because we used expired donated blood. Dialysis was performed using a Fresenius 5008 machine (Fresenius Medical Care) with online-generated ultrapure dialysate in hemodiafiltration post-dilution mode. A conventional and affordable high-flux synthetic polymer dialyzer (FX 600, Fresenius) was used. Dialysate flow was 500 mL/min, blood pump speed 150 mL/min, and substitutive rate 25 mL/min. Calcium dialysate concentration was increased in increments of 0.25 mmol/L using a standard hemodialysis additive (Baxter Corporation). Anticoagulation was obtained using citrate dextrose solution. Citrate was infused into the heparin infusion port at 200 mL/h and ultrafiltration rate was set at 180 mL/h to account for citrate infusion. Blood samples were obtained pre-dialyzer ( $n = 4$ ) and post-dialyzer ( $n = 16$ ) and were analyzed using an i-STAT 1 Analyzer (Abbott Point of Care Inc.). We assessed the following: (1) ionized calcium stability with a fixed calcium dialysate concentration of 1.5 mmol/L. Ionized calcium was tested every hour at 1.5, 2.5, and 3.5 hours. (2) Ionized calcium changes after every 0.25 mmol/L change of calcium dialysate concentration with initial calcium dialysate concentration from 1.25 mmol/L to 2.0 mmol/L ( $n = 4$ ). Samples were collected every hour ( $n = 4$ ) and/or 10 minutes after every calcium dialysate concentration change ( $n = 8$ ).

The mean  $\pm$  standard deviation (SD) pre-dialyzer ionized calcium was  $0.26 \pm 0.02$  mmol/L. The mean  $\pm$  SD post-dialyzer ionized calcium was  $1.01 \pm 0.09$ ,  $1.22 \pm 0.07$ ,  $1.39 \pm 0.07$ , and  $1.55 \pm 0.15$  mmol/L for calcium dialysate concentration at 1.25, 1.5, 1.75, and 2 mmol/L, respectively. Ionized calcium was tightly correlated to dialysate calcium concentration,  $r = 0.99$ ,  $P = 0.001$  (Fig 1A). No clotting was observed in any component of the circuit at any time. By using low exchange volume post dilution



**Figure 1.** (A) Correlation between mean  $\pm$  SD ionized calcium levels (mg/dL) and calcium dialysate concentrations (1.25, 1.50, 1.75, and 2.00 mmol/L). (B) Ionized calcium levels (mg/dL) sampled at 1.5, 2.5, and 3.5 hours of simulation using 1.50 mmol/L calcium dialysate concentration in only 1 experiment.

hemodiafiltration, we were able to further reduce the risk of venous bubble trap clotting by adding additional flow/dilution and vortexing of the blood within the bubble trap, which otherwise could be prone to clotting.

When calcium dialysate concentration was changed by 0.25 mmol/L, the mean  $\pm$  SD ionized calcium level was  $0.20 \pm 0.04$  mmol/L. When calcium dialysate concentration was modulated, ionized calcium levels were not different when blood was sampled every hour ( $0.19 \pm 0.07$  mmol/L,  $n = 3$ ) compared to every 10 minutes ( $0.20 \pm 0.03$  mmol/L,  $n = 7$ ),  $P = 0.98$ . For a fixed calcium dialysate concentration of 1.5 mmol/L, ionized calcium was 1.28 mmol/L, 1.25 mmol/L, and 1.23 mmol/L, after 1.5, 2.5, and 3.5 hours, respectively (Fig 1B).

These experiments demonstrate that ionized calcium levels can be managed by modulating calcium dialysate concentrations without the need to administer additional calcium intravenously. We report stable ionized calcium over time to ensure a pre-dialyzer ionized calcium  $<0.3$  mmol/L. We also demonstrated that calcium dialysate concentration changes lead to an immediate modification of ionized calcium levels, since these values were achieved after only 10 minutes, with mass transfer of calcium from dialysate to blood self-regulating as product of the changing relative concentrations within the 2 compartments.

Recent studies have shown patients infected with COVID-19 are severely hypercoagulable,<sup>5</sup> which can pose a significant risk to maintaining patency of the extracorporeal circuit and may also require a combination of anticoagulants, with heparin-based approaches being inadequate alone.<sup>6</sup>

We present an alternative option to maintain a calcium level target by modulating calcium dialysate concentration, in combination with limited replacement derived from the administration of online-generated dialysate in hemodiafiltration mode, without the need of additional venous calcium infusion. Such an approach is globally available, and is feasible from both a financial and workload perspective. This new protocol could be easily implemented in all HD patients at high risk of bleeding or with heparin contraindications.

Justin R. Dorie, RPN, Christopher W. McIntyre, MD, PhD,  
Sandrine Lemoine, MD, PhD

## ARTICLE INFORMATION

**Authors' Affiliations:** Lilibeth Caberto Kidney Clinical Research Unit (JRD, CWM, SL) and Department of Medical Biophysics (CWM),

University of Western Ontario, London, Ontario, Canada; Lawson Health Research Institute, London, Ontario, Canada (JRD, CWM, SL); and Division of Nephrology, London Health Sciences Centre, London, Ontario, Canada (CWM).

**Address for Correspondence:** Christopher W. McIntyre, MD, PhD, The Lilibeth Caberto Kidney Clinical Research Unit (KCRU), Kidney Clinical Research Unit Rm ELL-101, London Health Sciences Centre, 800 Commissioners Rd E, London, Ontario, Canada N6A 5W9. Email: [cmcint48@uwo.ca](mailto:cmcint48@uwo.ca)

**Authors' Contributions:** Research idea and study design: CM, SL, JD; data acquisition: JD; data analysis/interpretation: JD, SL; statistical analysis: JD, SL; supervision or mentorship: CM, SL. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

**Support:** None

**Financial Disclosure:** The authors declare that they have no relevant financial interests.

**Acknowledgements:** The authors would like to thank Ms Jarrin Penny and Mr Sal Treesh for their support in this study.

**Disclaimer:** The data presented in this article have not been published previously.

**Peer Review:** Received January 21, 2021. Evaluated by 1 external peer reviewer, with direct editorial input by an Associate Editor and the Editor-in-Chief. Accepted in revised form May 2, 2021.

**Publication Information:** © 2021 The Authors. Published by Elsevier Inc. on behalf of the National Kidney Foundation, Inc. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>). Published online July 15, 2021 with doi [10.1016/j.xkme.2021.05.003](https://doi.org/10.1016/j.xkme.2021.05.003)

## REFERENCES

1. Monchi M. Citrate pathophysiology and metabolism. *Transfus Apher Sci*. 2017;56(1):28-30.
2. Kasiske BL, Wheeler DC. Kidney disease: improving global outcomes—an update. *Nephrol Dial Transplant*. 2014;29(4):763-769.
3. Fiaccadori E, Regolisti G, Cademartiri C, et al. Efficacy and safety of a citrate-based protocol for sustained low-efficiency dialysis in AKI using standard dialysis equipment. *Clin J Am Soc Nephrol*. 2013;8(10):1670-1678.
4. Zarbock A, Küllmar M, Kindgen-Milles D, 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.
5. Yuriditsky E, Horowitz JM, Merchan C, et al. Thromboelastography profiles of critically ill patients with coronavirus disease 2019. *Crit Care Med*. 2020;48(9):1319-1326.
6. Volbeda M, Londema M, van Meurs M, et al. A method to improve continuous renal replacement therapy circuit survival time in critically ill coronavirus disease 2019 patients with acute kidney injury. *Crit Care Explor*. 2020;2(10):e0258.