

LETTER

Open Access



Response to “Adjuvant vitamin C in cardiac arrest patients undergoing renal replacement therapy: an appeal for a higher high-dose”

Angelique M. E. Spoelstra – de Man* , Harm-Jan de Groot, Paul W. G. Elbers and Heleen M. Oudemans – van Straaten

Keywords: Vitamin C, Cardiac arrest, Pharmacokinetics, Continuous renal replacement therapy

We thank Honore et al. [1] for raising the issue of the optimal dose of vitamin C in cardiac arrest patients, especially those requiring continuous renal replacement therapy (CRRT). They propose to treat patients post-cardiac arrest with 6 g daily. However, the efficacy of vitamin C after cardiac arrest has not been settled yet, let alone the optimal dose. Up to now, only one small trial in septic patients compared two different doses: 200 mg/kg/day (~ 16 g/day) seemed superior to 50 mg/kg/day (~ 4 g/day) [2]. All other studies in varying populations (but not after cardiac arrest) investigated a single dose (3 g up to 125 g/day). So, clinical studies on efficacy and dose in the cardiac arrest population are crucial before recommending an optimal dose. We are starting such a study (NCT03509662).

Honore et al. propose to double this dose to 12 g during CRRT based on three studies. Two of these studies included patients on intermittent chronic hemodialysis/diafiltration. One found a mean loss of 66 mg vitamin C per day (200 mg/week) [3], the other did not report total loss. The only study in patients on CRRT (continuous venovenous hemofiltration (CVVH)) reported a median loss of 93 (0–372) mg vitamin C per day. Furthermore, the mean plasma concentration in the CRRT patients was not

lower than in the contemporary ICU population (43 (23–57) $\mu\text{mol/L}$ vs 37 (28–108) $\mu\text{mol/L}$) [4]. This suggests that not the CRRT but the critical illness is the cause of the low vitamin C concentrations.

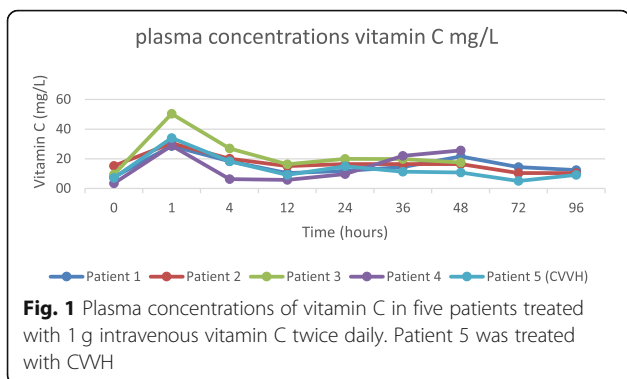
We calculated vitamin C loss by CVVH in a patient from our pharmacokinetic study treated with 1 g intravenous vitamin C twice daily [5]. He had an average vitamin C plasma concentration of 17.3 mg/L (98.6 $\mu\text{mol/L}$) during the 48-h treatment period (AUC 832 mg/L·48 h). Simultaneous plasma and post-filter measurements confirmed a sieving coefficient of about 1. At an effluent CVVH flow of 2 L/h, this amounts to a total loss by CVVH of 830 mg per day (17.3 mg/L·2 L/h·24 h), 41% of the administered dose. Removal by CRRT is therefore lower than removal by the native kidney (1476 mg/day; 74% of administered dose) in the four other patients not on CVVH treated with 2 g/day bolus infusions. The reason is that a CVVH dose of 2 L/h corresponds to a clearance of 33 ml/min, much lower than a native kidney clearance. The plasma vitamin C concentrations of this patient (patient 5; Fig. 1) were all within the normal range, suggesting that a dose of 1 g vitamin C twice a day may be sufficient to maintain normal plasma concentrations during CVVH.

In conclusion, vitamin C loss by CVVH does not seem to be higher than loss by the native kidney. So based on the scarce available data, it is not

* Correspondence: am.spoelstra@vumc.nl

Department of Intensive Care Medicine, Amsterdam UMC, Vrije Universiteit Amsterdam, De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands





2. Fowler AA III, Syed AA, Knowlson S, Sculthorpe R, Farthing D, DeWilde C, et al. Phase I safety trial of intravenous ascorbic acid in patients with severe sepsis. *J Transl Med.* 2014;12:32.
3. Morena M, Cristol JP, Bosc JY, Tetta C, Forret G, Leger CL, et al. Convective and diffusive losses of vitamin C during haemodiafiltration session: a contributive factor to oxidative stress in haemodialysis patients. *Nephrol Dial Transplant.* 2002;17(3):422–7.
4. Story DA, Ronco C, Bellomo R. Trace element and vitamin concentrations and losses in critically ill patients treated with continuous venovenous hemofiltration. *Crit Care Med.* 1999;27(1):220–3.
5. de Grooth HJ, Manubulu-Choo WP, Zandvliet AS, Spoelstra-de Man AME, Girbes AR, Swart EL, et al. Vitamin C pharmacokinetics in critically ill patients: a randomized trial of four IV regimens. *Chest.* 2018;153(6):1368–77.

necessary to increase the vitamin C dose during CVVH above 2 g/day when normal plasma concentrations are targeted. Whether higher concentrations are beneficial needs to be shown. In our RCT in cardiac arrest patients more pharmacokinetic data will be collected.

Abbreviations

CRRT: Continuous renal replacement therapy; CVVH: Continuous venovenous hemofiltration

Acknowledgements

None.

Funding

We have received a grant from the Netherlands Organisation for Health Research and Development to perform an RCT with intravenous vitamin C in post-cardiac arrest patients.

Availability of data and materials

Available on request.

Authors' contributions

ASM drafted the original version of the manuscript. HJG, PWE, and HMO reviewed and revised the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Consent for publication

All authors have reviewed the final version of the manuscript and approve the manuscript for publication.

Competing interests

The authors declare that they have no competing interests.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Received: 8 September 2018 Accepted: 24 September 2018

Published online: 19 December 2018

References

1. Honore PM, De Bels D, Preseau T, Redant S, Attou R, Spapen HD. Adjuvant vitamin C in cardiac arrest patients undergoing renal replacement therapy: an appeal for a higher high-dose. *Crit Care.* 2018;22(1):207.