To the Editorial Office of the World Journal of Nephrology

Please find attached our manuscript entitled 'SEVERE HYPERKALEMIA FOLLOWING BLOOD TRANSFUSIONS: IS THERE A LINK?' revised according to the reviewers' comments. All changes are highlighted in yellow in the revised text. At this point we would like to thank the reviewers for their kind comments.

Specifically,

According to Reviewer 00503002 comments:

1. The authors describe hyperkalaemia secondary to old PRBC in a patient predisposed to hyperkalaemia (ACE inhibitor and volume depletion). Although this clinical scenario is not uncommon, it would be of interest for the readership of this journal. The discussion on pathophysiological mechanisms for hyperkalaemia including subjective analysis of the various contributing factors is written well.

   We thank reviewer 00503002 for the kind comments.

According to Reviewer 00503254 comments:

1. In this manuscript, the authors report on a case of hyperkalemia after packed red blood cells transfusion for hematemesis due to gastric ulcer. They also review the pathogenesis and treatment of hyperkalemia. Although this case report is not so rare, it is clinically useful. However, there is one point that

needs to be addressed. Minor comment: In the Discussion, they described the physiology of volume depletion as follows: “In fact, volume depletion is associated with a decreased glomerular filtration rate and increased proximal sodium and water reabsorption.” Is this sentence correct?

We have rephrased the sentence (page 7; line 13)

According to Reviewer 00503313 comments:

1. Dear Authors, this is a good case, well managed, well written, and discussed. however, this complication is not uncommon, in particular in a patient like yours, with multi underlying risk factors for hyperkalemia, including hyperkalemia upon admission

   We thank reviewer 00503313 for the kind comments.

According to Reviewer 00503321 comments:

1. Very good case report of a rather common problem that merits attention widely. The discussion is clinically relevant and appropriate. My only point is that I would not necessarily think the treatment with Insulin/dextrose in a patient with previous potassium retention really works (other than as a short and transient measure). Frequently other measures like the use of loop diuretics and/or of cationic exchange resins (calcium resonium) or even dialysis might be necessary to remove the excess potassium especially in CKD patients.

   Indeed, we used treatment with insulin/dextrose as a short and transient measure to decrease potassium levels. The patient after the initial massive transfusion and the following aggravation of baseline hyperkalemia became

hemodynamically stable and quickly restored renal function resulting in a decrease of potassium levels. Indeed, if hyperkalemia persisted then additional measures to reduce potassium levels would have been required (page 6; lines 15-16)

According to Reviewer 00503255 comments:

1. The authors described a patient receiving ACE inhibitor who developed gastric bleeding and severe hyperkalemia after large volume transfusion of packed RBC. 1. ACE inhibitor hypovolemia and large volume transfusion are well-known contributing factors for hyperkalemia (Vraets A, et al, Transfus Med Rev 2011). Is severe hyperkalemia in this patient merely due to hypovolemia and a receiving ACE inhibitor before large volume stored RBC transfusions?

   Indeed, as discussed in the manuscript baseline hyperkalemia was due to the coexistent prerenal azotemia associated with oliguria and subsequently decreased potassium excretion. Moreover, the simultaneous administration of benazepril further aggravated baseline hyperkalemia. However, despite the restoration of circulating volume, diuresis and the discontinuation of benazepril, a further increase of potassium levels was observed which can be attributed to the initial massive transfusion (page 7; lines 11-28 and page 8; lines 1-15).

2. Recently, Raza et al. reported a prospective study on RBC transfusion related hyperkalemia in critically ill patients and showed that rise in serum K+ level

was more pronounced in patients who received stored blood (> 12 days) (Raza S, et al. J Clin Med Res 2015). It is better to cite in the paper.

The suggested reference has been added (page 8; lines 17-18; reference 10)

We do hope that the revised manuscript now meets your requirements.

Yours sincerely,

Moses Elisaf MD FASA FRSH

Professor of Internal Medicine

Department of Internal Medicine

Medical School, University of Ioannina

Ioannina 45 110, Greece

Tel: +30-26510-07509

Fax: +30-26510-07016

E-mail: egepi@cc.uoi.gr;