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Letters to the Editor – Comments on published articles

Comment to: Haemodialysis session: The perfect storm for vascular calcification☆

Comentario a: Sesión de hemodiálisis: la tormenta perfecta para la calcificación vascular

Dear Editor,

We read the article recently published in this journal by Seras et al.[1] with particular interest, and we would like to offer a few comments on it.

Regarding the variations in calcium concentration in the bath during dialysis, we believe that, effectively, it should be personalised. The main objective should be to create a calcium balance that is as neutral as possible during the session. The reason is that a positive balance will result in a greater risk of vascular calcification, and a negative balance will result in an increase in serum parathyroid hormone (PTH). To do this, we believe that predialysis serum calcium is the best indicator of the concentrations in the dialysis bath. It is not possible to extract from the intravascular space an amount of calcium equivalent to the amount physiologically eliminated through the urine in 48 h, in a period of 4 h, as that negative balance in such a short time increases PTH. A recent publication by our group[2] demonstrated that, in patients with a predialysis ionised calcium concentration of 0.96 mmol/l or 8.76 mg/dl of total calcium, the cut-off point for the calcium concentration in the bath is 1.25 mmol/l. Below these values, the patient creates a positive balance, and above them, the patient creates a negative balance. With baths of 1.5 mmol/l of calcium above 9.1 mg/dl of predialysis total calcium (Ca^{2+} of 1.01 mmol/l), a negative balance is created, and below, a positive balance is created. In a study by Seras et al.,[1] the cut-off point was 1.16 mmol/l or 10.4 mg/dl total calcium (estimating normal proteins of 7 mg/dl). This suggests that the group studied by the authors was very heterogeneous, and that there were patients above and below the cut-off point of 0.96 in both groups. In our view, the cut-off point of 1.16 mmol/l for ionised calcium is too high to establish it as a value to be used in one bath or another. In addition, we do not believe that using a bath of 1.25 mmol/l is generally suitable in all patients to prevent vascular calcification, as in patients with total calcium greater than 9.1 mg/dl (Ca^{2+} of 1.01 mmol/l) it could induce a sustained increase in PTH.

Like Professor O'Neill's group,[3] we have demonstrated[4] that the product of Ca × Pi is not a determinant of vascular calcification. In passive formation of calcium phosphate crystals in the vasculature, the serum calcium concentration is more determinant than the serum phosphate concentration. Moreover, calcification may be induced with elevated calcium concentrations even when the phosphate concentration is low.[4] Therefore, even if phosphorus were to be eliminated during a dialysis session, calcification could be induced in these patients provided that calcium is increased or maintained.[4] However, a few hours after completing the session, phosphorus levels rise again.

Regarding the alkalinisation of the blood of patients during a dialysis session, a distinction should be made between 2 matters. An increase in serum pH is not the same as an increase in bicarbonate in the blood. Blood pH is mostly governed by phosphate and bicarbonate, and this influences vascular calcification given that alkalosis shifts the balance between the 2 types of phosphate in the blood ($H_2PO_4^-$ and HPO_4^{2-}) towards the right. This increases the concentration of HPO_4^{2-}, which is a precursor of both brushite and hydroxyapatite,[4] 2 crystals detected in calcifications.

From a logical point of view, to reduce acidosis in these patients, adding bicarbonate to protocols was considered given its buffering capacity. For example, Seras et al.[1] observed that after dialysis there was a loss of approximately 2.5 mg/dl of phosphate, an increase of approximately 5 mmol/l of bicarbonate and a slight variation in blood pH (0.09 units). The

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result was slight alkalinisation of the blood at the end of the dialysis session. This modest change in blood pH suggested that this does not play a substantial role in vascular calcification. This was especially likely to be the case as this slight alkalinisation of the blood was lost after several hours.

Finally, without taking into account the fact that bicarbonate is responsible for the slight alkalinisation of the blood during dialysis, bicarbonate also plays a determinant role in the production of calcium crystals, including hydroxyapatite, as one of our studies has shown.[4]

Although it is a conceptual matter, it should be known that bicarbonate is responsible for the increase in the calcification process, whether directly by causing calcium crystals or indirectly by causing slight alkalinisation. Therefore, bicarbonate should be replaced with another buffering molecule or efforts should be made to reduce it during dialysis, like calcium, obviously within the available means.

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Haemodialysis session: The perfect storm for vascular calcification☆

Sesión de hemodiálisis: la tormenta perfecta para la calcificación vascular

Dear Editor:

We appreciate the interest shown and comments made by Villa-Bellosta et al. with respect to our recent publication.[1]

First, we agree that the dialysis bath should be personalised to generally achieve neutral calcium balances. As González-Parra et al.[2] effectively demonstrated in their article, the predialysis plasma calcium cut-off points that would allow one or another concentration of calcium in the dialysis bath to be decided on seem to be around 0.96 mmol/l and 1.01 mmol/l (8.75–9.15 mg/dl, respectively). However, the aim of our study was not to determine these cut-off points, but to analyse changes in calcaemia with randomly assigned calcium baths, and their relationship with phosphorus and bicarbonate, in pursuit of a parallel with studies *in vitro* by Lomashvili et al.[3] and De Solis et al.[4] Hence patients were classified as hypo- or normocalcaemic based on 1.16 mM, the lower limit of normal determined by our laboratory. When we analysed changes in calcaemia in our sample, based on the bath used, we observed that the 1.25 mM calcium bath scarcely induced hypercalcaemia (>1.3 mM), while all patients dialysed with the 1.5 mM bath completed the session with hypercalcaemia (all

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