Ionized Magnesium and Regional Citrate Anticoagulation for Continuous Renal Replacement Therapy

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Key Words

Magnesium · Ionized magnesium · Magnesium deficiency · Calcium · Renal replacement therapy · Regional citrate anticoagulation

Abstract

Background: The regional citrate anticoagulation (RCA) induces changes in total (Ca^{tot}) and ionized (Ca^{2+}) calcium. As of now, we do not have much information about parallel changes of total (Mg^{tot}) and ionized (Mg^{2+}) magnesium. **Methods:** The authors compared changes of Mg^{2+} and Mg^{tot} with changes of Ca^{2+} and Ca^{tot} in 32 critically ill patients on 4% trisodium citrate (4% TSC) with calcium-free fluids. **Results:** The median continuous venovenous hemodiafiltration balance of Mg^{tot} was -0.91 (-1.18 to -0.53) mmol/h compared to the median balance of Ca^{tot} 0.86 (0.08 – 1.55) mmol/h. Postfilter Mg^{2+} decreased by 68.3% (70.8 – 65.6) in parallel ($r = 0.41$, $p = 0.03$) to decrease of postfilter Ca^{2+} (by 70.2% (73.0 – 66.1)) and was significantly related to the postfilter Ca^{2+} ($r = 0.50$, $p < 0.001$). The decrease of prefilter to postfilter Ca^{2+} correlated to a dosage of 4% TSC per blood flow ($r = 0.37$, $p = 0.04$). **Conclusions:** The loss of Mg^{tot} during RCA is not covered by magnesium concentration in ordinary dialysis/sub-

stitution fluid and may lead to the depletion of total body magnesium. The postfilter Mg^{2+} is significantly related to the postfilter Ca^{2+} .

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Introduction

The efficacy and safety of regional citrate anticoagulation (RCA) have been reflected in guidelines, suggesting the use of citrate for prevention of filter clotting in preference to standard heparin even in patients without an increased bleeding risk [1–6]. Citrate inhibits coagulation through the chelation of ionized calcium (Ca^{2+}), which is the principle of all citrate modes of regional anticoagulation. The postfilter changes of Ca^{2+} are used to guide the dose of citrate, and substitution of calcium is required to maintain the systemic level of Ca^{2+} .

Various citrate protocols have shown mild accumulation, deficit or even balance of total calcium (Ca^{tot}), mostly depending on the intensity of calcium substitution [7–10]. Another bivalent cation likely to be chelated in a sim-

Fig. 1. Configuration of the CVVHDF circuit under citrate anticoagulation. UF = Ultrafiltration, that is, net fluid removal (l/h); Qb = blood flow (l/h); Qc = 4% TSC flow (l/h); Qd = dialysis flow (l/h); Qeff = effluent flow (l/h) = UF + Qc + Qd + postdilution.

ilar fashion as calcium is magnesium. The balance of total magnesium (Mg^{tot}) is not well explored under various modalities and solutions used with citrate anticoagulation [11]. Brain found a significantly negative magnesium balance using dialysis/replacement fluids containing 0.5 mmol Mg^{tot} per liter [12]. While balances in total cations (Ca^{tot} and Mg^{tot}) have implications for total body pools and substitutions during RCA, the changes in ionized forms (Ca^{2+} and Mg^{2+}) represent changes of physiologic function (anticoagulation) and are included in the balances of the total ions. In contrast to Ca^{2+} , the ionized magnesium (Mg^{2+}) is not monitored as part of citrate modality of continuous renal replacement therapy (CRRT); yet, its decrease is directly related to patient's prognosis [13]. Besides a single paper on Mg^{2+} changes during platelet apheresis [14], the exact relationship of Ca^{2+} to changes of Mg^{2+} under citrate anticoagulation that are not monitored in renal failure patients is not known. The aims of the study were to determine whether the postfilter Mg^{2+} is related to postfilter Ca^{2+} and whether the decrease in postfilter Mg^{2+} is related to the decrease in postfilter Ca^{2+} . RCA might cause a magnesium loss on filter similar to loss of calcium. Magnesium depletion potentiated by citrate may not be compensated by current levels of magnesium in dialysis and substitution fluid.

Methods

This prospective observational study was carried out in a 20-bed ICU of the university hospital. The study was approved by the university hospital ethical board and informed consent was obtained from the next of kin. All patients were critically ill and mechanically ventilated.

The fluxes of magnesium and calcium, changes of their ionized forms and possible relationships to citrate dosage and citratemias were studied during postdilution continuous venovenous hemo-

diafiltration (CVVHDF) performed on Aquarius device (Baxter®, Irvine, Calif., USA) with 1.9 m² polysulfone filter (Aquamax®, Bellco, Mirandola, Italy). The commercially available trisodium citrate (4% TSC) and dialysis/substitution fluid were used. The bicarbonate buffered solution was calcium-free and had reduced levels of sodium and bicarbonate. The fluid was used as dialysis and replacement fluid (Citralsate®, GML, Czech Republic, Na 133 mmol/l, K 2.0 mmol/l, Mg 0.75 mmol/l, Cl 116.5 mmol/l, glucose 5.6 mmol/l, HCO_3^- 20 mmol/l).

Indications for RRT were renal failure with elevated levels of uremic toxins and loss of response to diuretics. Prescribed CVVHDF dose was 20–25 ml/kg/h [15, 16]. The dialysis flow (Qd) was set at 1,500 ml/h and postdilution at 500 ml/h. The blood flow (Qb) was set at 100 ml/min. Reason to use a lower Qb was to allow for a lower citrate flow, which prevents metabolic alkalosis and hypernatremia [17, 18]. A Qb of 100 ml/min is sufficient to saturate dialysate at a flow rate of 2 l/h [19]. Four percent TSC infusion was initiated at 200 ml/h and titrated in increments to maintain the postfilter Ca^{2+} under 0.4 mmol/l. Ca^{2+} was checked every hour until its level became stable and thereafter once in every 3 hours. Calcium chloride (10%) was infused into a port distal from the venous bubble trap to maintain arterial Ca^{2+} within a normal range (0.8–1.3 mmol/l). Arterial Ca^{2+} was monitored every 6 h. A routine substitution of intravenous 20–30 ml of 20% magnesium sulfate (16.2–24.3 mmol) per day was part of the RCA protocol.

The study commenced at least 24 h after the start of CRRT. Samples were drawn from the arterial blood, the effluent, the pre-filter and postfilter ports of the circuit (fig. 1). To improve accuracy, the second sampling took place 60 min later. During this hour, the configuration of CRRT including anticoagulation did not change. Ca^{2+} and Mg^{2+} were measured using the STAT profile analyzer (Nova Biomedical) at the bedside. Besides measuring citrate levels (measured by capillary zone electrophoresis, P/ACE 5100, Beckman), the laboratory analysis also included the measuring of Ca^{tot} and Mg^{tot} .

Calculation of Magnesium and Calcium Fluxes from Patient's CVVHDF Circuit to the Effluent

The amount of magnesium removed on filter was deducted from magnesium delivered as part of dialysis fluid and postdilution. Effluent removal of magnesium was calculated from the effluent flow (Qeff) multiplied by the magnesium concentration in the effluent ($[Mg]_{eff}$). Magnesium input was calculated as Qd

Table 1. Levels of citrate, total and ionized cations in arterial blood, prefilter, postfilter and effluent samples

Parameter, mmol/l	Arterial	Prefilter	Postfilter	Change, mmol/l	Change, %	Effluent
Citrataemia	0.55 (0.41 to 0.75)	0.61 (0.41 to 0.92)	3.99 (3.47 to 5.11)	3.54 (2.6 to 4.5)	684 (284.6 to 1,140.5)	5.9 (5.31 to 6.51)
Ca ^{tot}	2.27 (2.07 to 2.47)	2.27 (2.1 to 2.41)	1.55 (1.44 to 1.79)	-0.63 (-0.8 to -0.52)	-43.6 (-52.9 to -29.7)	1.59 (1.52 to 1.71)
Ca ²⁺	1.07 (0.99 to 1.15)	1.02 (0.96 to 1.11)	0.32 (0.27 to 0.37)	-0.75 (-0.78 to -0.65)	-70.2 (-73.0 to -66.1)	0.30 (0.25 to 0.34)
Mg ^{tot}	1.08 (0.88 to 1.26)	1.07 (0.94 to 1.23)	0.9 (0.84 to 1.09)	-0.12 (-0.19 to -0.06)	-11.0 (-19.9 to -7.9)	1.0 (0.76 to 1.18)
Mg ²⁺	0.51 (0.43 to 0.61)	0.46 (0.40 to 0.58)	0.15 (0.13 to 0.18)	-0.31 (-0.4 to -0.26)	-68.3 (-70.8 to -65.6)	0.14 (0.12 to 0.17)

The changes are differences in concentrations during passage through blood circuit without including postfilter calcium substitution.

times magnesium concentration in the dialysis fluid ([Mg]d) plus postdilution flow times postdilution magnesium concentration ([Mg]d). The same fluid was used for dialysis and postdilution.

$$\text{Magnesium flux} = (Q_d \times [\text{Mg}]_d + \text{post-dilution} \times [\text{Mg}]_d) - Q_{\text{eff}} \times [\text{Mg}]_{\text{eff}}$$

The calcium flux was calculated similarly, that is, by deducting the calcium amount eliminated in the effluent from the calcium input. The effluent amount of calcium was calculated as Q_{eff} multiplied by the effluent calcium concentration ([Ca]eff). Due to the fact that dialysate and postdilution calcium concentration ([Ca]d) equals zero, the calcium input was calculated as calcium replacement flow ($Q[\text{Ca}]$) times 10% calcium chloride concentration ([Ca]in = 0.456 mmol/ml). For better comparison to magnesium flux, the results were recorded as calcium balance without postfilter calcium substitution and overall calcium flux including postfilter CaCl_2 infusion.

$$\text{Calcium flux} = Q[\text{Ca}] \times [\text{Ca}]_{\text{in}} - Q_{\text{eff}} \times [\text{Ca}]_{\text{eff}}$$

The postfilter Mg^{2+} and postfilter Ca^{2+} were tested for correlations to prefilter levels. The postfilter Mg^{2+} levels were also tested for a relationship to postfilter Ca^{2+} levels. Changes of ionized cations in blood during passage through filter (i.e. absolute value of difference between prefilter and postfilter levels and the decrease of post to prefilter values in percent of prefilter values) were tested for correlations between Mg^{2+} and Ca^{2+} . The decreases of both cations were tested for correlations with dosages of citrate, dosage of citrate per Q_b and with changes of circuit citratemias (i.e. absolute value of difference between prefilter and postfilter levels of citrate).

The statistical analysis was performed using Statistica version 9 software. Data sets were checked for distribution, and the differences between groups were evaluated using the Mann-Whitney U test. Correlations between various parameters were tested using the Pearson's test. The level of significance was set at $p = 0.05$.

Results

A sequential sample of 32 patients was analyzed (age 67 (54.5–72.3), admission APACHE II 31 (27.5–37.3), SOFA 14 (10–15)).

Fig. 2. The relationship of postfilter Mg^{2+} to prefilter Mg^{2+} ($r = 0.86$, $p < 0.001$).

The median total Q_{eff} was 2,370 (2,290–2,420) ml/h, citrate dose 200 (180–230) ml/h, that is, 26.5 (24.5–32.6) mmol/h, citrate dose per Q_b 4.4 (4.1–5.4) mmol/l·h. The median dosage of 10% postfilter calcium chloride was 9.5 (8–12) ml/h, that is, 4.3 (3.7–5.5) mmol/h. Ultrafiltration (net fluid loss) was titrated according to the hemodynamic needs. Median circuit survival time was 67 (44.5–108) h.

The levels of citrate, total and ionized cations in arterial blood, prefilter, postfilter and effluent samples are shown in table 1. The median balance of Mg^{tot} was -0.91 (-1.18 to -0.53) mmol/h compared to the median balance of Ca^{tot} -3.80 (-4.03 to -3.5) mmol/h without inclusion of postfilter CaCl_2 substitution. The Ca^{tot} balance with input of postfilter calcium substitution was 0.86 (0.08–1.55) mmol/h. The postfilter Mg^{2+} correlated to prefilter Mg^{2+} ($r = 0.86$, $p < 0.001$; fig. 2) similarly as did postfilter

Fig. 3. The relationship of postfilter Ca^{2+} to prefilter Ca^{2+} ($r = 0.60$, $p < 0.001$).

Fig. 4. The postfilter Mg^{2+} was significantly correlated to postfilter Ca^{2+} ($r = 0.50$, $p < 0.001$). Postfilter $\text{Mg}^{2+} = 0.08 + 0.22 \cdot \text{postfilter } \text{Ca}^{2+}$.

Ca^{2+} to prefilter Ca^{2+} ($r = 0.60$, $p < 0.001$; fig. 3). In contrast to lack of significant relationship between prefilter Mg^{2+} to prefilter Ca^{2+} ($r = 0.30$, $p = 0.13$) the postfilter Mg^{2+} significantly correlated to postfilter Ca^{2+} ($r = 0.50$, $p < 0.001$; fig. 4). The percentual decrease of Mg^{2+} (-68.3% (-70.8 to -65.6)) was significantly related to the percentual decrease of Ca^{2+} (-70.2% (-73.0 to -66.1); $r = 0.41$, $p = 0.03$; table 1; fig. 5). The relationships between absolute and percentual decreases of cations to dosages of citrate and circuit citratemias are summarized in table 2. The absolute and percentual decreases of prefilter to postfilter Mg^{2+} did not significantly correlate to absolute dose of citrate prefilter, dose of citrate per Qb or change of citrate levels. The absolute and percentual decreases of prefilter to postfilter Ca^{2+} did not significantly correlate to the absolute dose of citrate prefilter and to the change of citrataemia. The absolute decrease of Ca^{2+} correlated to the dose of citrate per Qb ($r = 0.37$, $p = 0.04$) as well as the percentual decrease of Ca^{2+} did ($r = 0.36$, $p = 0.04$; table 2).

Discussion

The present prospective observational cohort study, comparing the flux of magnesium with the flux of calcium during citrate-anticoagulated CVVHDF shows that the RCA associates with changes of magnesium

Fig. 5. The scatterplot of correlation between percentual decreases of Mg^{2+} and Ca^{2+} during passage through blood circuit under RCA ($r = 0.41$, $p = 0.03$).

similar to changes of calcium. Mg^{2+} decreases to about one third during passage through citrate anticoagulated circuit, which is almost the same proportional decrease as for Ca^{2+} . The effects of citrate upon ionized cations can also be seen by their correlation postfilter compared to relationship prefilter that is not significant. The measurement of Mg^{2+} is mostly unavailable; how-

Table 2. The relationships (Pearson's correlation, the significant ones are in bold) between changes (absolute and percentual) in Ca^{2+} , Mg^{2+} and dose of citrate prefilter, dose of citrate prefilter in relation to blood flow and increase of circuit citratemia during RCA

Parameter		Dose of 4% TSC, ml/h 200 (180–230)	Dose of 4% TSC/Qb, mmol/l·h 4.4 (4.1–5.4)	Increase of citratemia, mmol/l 3.54 (2.6–4.5)
Ca^{2+} change, mmol/l	–0.75 (–0.78 to –0.65)	p = 0.95	p = 0.04, r = 0.37	p = 0.53
Ca^{2+} change, %	–70.2 (–73.0 to –66.1)	p = 0.67	p = 0.04, r = 0.36	p = 0.79
Mg^{2+} change, mmol/l	–0.31 (–0.4 to –0.26)	p = 0.67	p = 0.62	p = 0.63
Mg^{2+} change, %	–68.3 (–70.8 to –65.6)	p = 0.43	p = 0.08	p = 0.83

ever, the postfilter Mg^{2+} significantly correlates with routinely taken postfilter Ca^{2+} . In contrast to Mg^{2+} , the absolute and percentual decreases of Ca^{2+} correlated to the dose of citrate per Qb. This could be partially due to the confounding effect of magnesium in the dialysate/substitution fluid, which was calcium free. This study including normomagnesemic patients (table 1) also shows very similar relationship between Mg^{tot} and Mg^{2+} in systemic blood when using citrate anticoagulation compared to this relationship in non-renal failure patients [20, 21]. The losses of Mg^{tot} were in contrast to mild gain of Ca^{tot} , which is caused by the routine postfilter calcium infusion during RCA compared to the absence of postfilter magnesium substitution. On the other hand, the losses of Mg^{tot} were limited by Mg levels in dialysis and substitution fluid, which was calcium free and were balanced by the routine parenteral magnesium sulfate replenishment included in the institutional RCA protocol. The presence of magnesium in dialysis/substitution fluid in citrate anticoagulated CRRT is a matter of debate [8, 22] because Mg is also chelated by citrate, which may neutralize a portion of citrate and increase the demand for its infusion to lower Ca^{2+} postfilter into a desired range. The importance of removing magnesium for reduction of filter clotting is questionable [23], and the eventual reduction of citrate dosage for calcium chelation does not outweigh the risk of hypomagnesemia [13, 20, 24, 25] if Mg is not replenished properly [9, 17].

The study shows that the decreases of Mg^{tot} are not sufficiently compensated by the amount of magnesium in dialysis/substitution fluid even with the level of 0.75 mmol/l. The estimated median loss of magnesium of 22 mmol/day (–0.91 mmol/h) may represent a depletion of about 15–20% of total body pool of magnesium during 1 week of CRRT with RCA. The loss is similar to the Brain's study reporting a median of –1.09 mmol/h with 0.5 mmol/l of magnesium in dialysis/substitution fluid

and mildly higher Qeffs [12]. Considering the limited body pool of magnesium, the citrate anticoagulated CRRT may put critically ill patients at risk of hypomagnesemia [13, 24]. A deficit of Mg^{tot} and Mg^{2+} is related to cardiovascular stability, pulmonary hypertension, resistance to insulin, neuromuscular function as well as to non-recovery of renal function and mortality of patients [13, 20, 24–30]. It is very likely that increasing the amount of magnesium in current dialysis/substitution fluids for RCA may eliminate a need for parenteral magnesium replenishment and contribute to the cost effectiveness of RCA modalities.

Our study suffers from several limitations. First, it is limited to only 1 hour of observations. The calculated daily loss of Mg^{tot} is therefore only an estimate, because continuous is not always continuous [31]. We did not correct for filter-down time, which differs between centers and modalities. Estimates of total loss of Mg^{tot} may therefore be 10–20% lower. However, this does not apply much to the RCA, because circuit life with citrate is longer and thus the downtime might be shorter. Second, Qb was limited as part of the RCA protocol, limiting the dosage of 4% TSC and its side effects [18]. Therefore, the magnesium and calcium losses on filter could be even more significant in higher Qbs and higher citrate dosage. Third, our conclusion should also be tested for CVVH, although clearance of magnesium is similar with diffusive transport (dialysis) as with a convective (filtration) mode if a similar dose (Qeff) is applied, because the sieving coefficient of the molecule is about one in both modalities. Fourth, the calcium fluxes and balances would be different if calcium containing fluid would have been used. There are still units where this modality is applied [32, 33] leading to a high dosage of citrate and higher amount of calcium-citrate complexes in effluent. Fifth, the changes of calcium and magnesium might relate to citrate dosages and levels of citrate when analyzing larger cohort of patients.

Conclusion

This study shows that postfilter Mg^{2+} decreases similarly as does Ca^{2+} under RCA. The postfilter Mg^{2+} can be predicted from postfilter levels of Ca^{2+} . While calcium is routinely replenished as part of the protocol, the loss of Mg^{tot} in citrate CVVHDF is not balanced by the insufficient levels in commercially available dialysis/substitution fluids. Mg^{2+} is related to Mg^{tot} similarly as in non-

dialysis patients. Citrate anticoagulation of CRRT may lead to the inapparent depletion of magnesium body pool with resulting organ disorders.

Disclosure Statement

The research was supported by the ESICM Stoutenbeek Award 2012.

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