Hypomagnesaemia is common in critical care patients generally and particularly in patients receiving continuous renal replacement therapy (CRRT). Low magnesium concentration ([Mg]) has been associated with adverse outcomes including increased mortality. Maintaining the serum [Mg] in the high normal range is considered desirable for cardiovascular stability and may be important in CRRT given the arrhythmia incidence in one large study approached 45%. Magnesium supplementation for arrhythmia prevention has been most studied in cardiac surgical patients, with a meta-analysis suggesting an overall reduction in the incidence of atrial fibrillation.

Adult humans contain about 24 g (1000 mmol) of magnesium, of which 60% is in bone and available to support plasma levels. Around 40% (400 mmol) is intracellular, of which half is contained in skeletal muscle, commensurate with its pivotal role coordinating inorganic phosphate transfer in ATP synthesis. The extracellular compartment contains only 1%–1.9% of total body magnesium (about 12 mmol). About 30% of plasma magnesium is protein bound and not readily removed by dialysis, 5%–10% is complexed with other anions (citrate, bicarbonate, phosphate and sulfates), and 60% is present as free magnesium ions.

Plasma magnesium levels are frequently elevated in chronic kidney disease when the creatinine clearance rate is below 30 mL/min. Most studies of total magnesium balance in renal failure have been in this context as it may, in combination with calcium, contribute to renal osteodystrophy. As a consequence, some commonly used dialysis fluids have relatively low [Mg] relative to serum concentrations.

The effect of CRRT on magnesium in acute kidney injury has been less well studied. The capacity for magnesium loss during continuous venovenous haemodiafiltration (CVVHDF) is significant, and may potentially be exacerbated by additional chelation when citrate is used for anticoagulation. We recently described calcium ion flux in CVVHDF using citrate or heparin for anticoagulation and here present an analysis of concurrently studied magnesium.

**Methods**

Protocols for CVVHDF with citrate and heparin anticoagulation, calcium replacement, blood and circuit sampling, data collection and calculation of electrolyte loss in the effluent have been described previously. Sampling sites were patient arterial line, prefilter (after addition of predilution), postfilter (before postdilution), and the effluent line. [Mg] in blood and effluent was measured by spectrophotometric dye binding (Abbott Architect c8000; dye for magnesium was xylidyl blue; analysed at 660 nm). The laboratory reference range for total serum [Mg] is 0.7–1.16 mmol/L.

**ABSTRACT**

**Objective:** To describe magnesium flux and serum concentrations in ICU patients receiving continuous venovenous haemodiafiltration (CVVHDF).

**Design:** Samples were collected from 22 CVVHDF circuits using citrate anticoagulation solutions (Prismocitrate 10/2 and PrismOcal) and from 26 circuits using Hemosol B0 and heparin anticoagulation. CVVHDF prescription, magnesium supplementation and anticoagulation choice was by the treating intensivist. We analysed 334 sample sets consisting of arterial, prefilter and postfilter blood and effluent.

**Results:** Using flow rates typical of adults receiving CVVHDF, we determined a median half-life for arterial magnesium concentration to decay to a new steady state of 4.73 hours (interquartile range [IQR], 3.73–7.32 hours). Median arterial magnesium concentration was 0.88 mmol/L (IQR, 0.83–0.97 mmol/L) in the heparin group and 0.79 mmol/L (IQR, 0.69–0.91 mmol/L) in the citrate group. Arterial magnesium concentrations fell below the reference range regularly in the citrate group and, when low, there was magnesium flux from dialysate to patient. Magnesium loss was greater in patients receiving citrate.

**Conclusions:** Exponential decline in magnesium concentrations was sufficiently rapid that subtherapeutic serum magnesium concentrations may occur well before detection when once-daily sampling was used. Measurements should be interpreted with regard to timing of magnesium infusions. We suggest that continuous renal replacement therapy fluids with higher magnesium concentrations be introduced in the critical care setting.

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Citrate anticoagulation used Prismocitrate 10/2 (Gambro) as the predilution fluid and Prism0cal (Gambro) as the dialysate. Those not anticoagulated with citrate received Hemosol B0 (Gambro) with or without heparin anticoagulation (for simplicity in reporting results this group is described as heparin). Compositions of fluids are shown in Table 1.

This observational study was approved by the Human Research Ethics Committee (Tasmania) Network. Treating physicians had access to all results; however, a different laboratory code meant results did not appear with routine blood tests.

Magnesium replacement
In our institution, total [Mg] is routinely measured once daily and the target concentration is 0.9–1.0 mmol/L. Magnesium is typically administered as an intravenous infusion in doses of 20 mmol (occasionally up to 40 mmol) over a period of 2 hours to avoid hypotension associated with faster infusion rates.

If administered, parenteral nutrition (PN) provided 5–15 mmol of magnesium per day according to an estimate of patient requirements. No attempt was made to quantify enteric magnesium intake or loss.

Exponential decay analysis
After infusion, the arterial [Mg] rises to a peak followed by a curve demonstrating exponential decay to a baseline. A similar decay is observed after starting a new CRRT circuit with a high–normal arterial [Mg].

This exponential decay is described by the general equation $y = B + C \cdot e^{-k \cdot t}$, where $y$ is the concentration at time $t$ (hours), $B$ is the baseline concentration that the curve trends to (an asymptote), $C$ is the $y$-intercept (relative to the baseline), $e$ is Euler's number, and $k$ is the rate constant of the decay. Half-life is the natural logarithm of 2 divided by $k$ ($T_{1/2} = \ln(2)/k$).

Figure 1 is a circuit schematic demonstrating volumetric flow, with sample measurements and calculations from one curve studied.

We segmented the data into concentration–time curves where the start of a curve is defined as the start of a new haemofilter or the start of a magnesium infusion and the end of a curve is defined as the end of a haemofilter (filter failure or scheduled cessation) or the start of the next magnesium infusion. We excluded curves in which less than four data points after the peak concentration were obtained. Observed data were summarised as time above specific [Mg] cut offs. We then analysed the individual decay curves from the peak recorded concentration after a magnesium infusion to the end of the curve.

Non-compartmental analysis
Area under the concentration–time curve (AUC) and area under the first moment curve (AUMC) were calculated from time zero (not peak concentration as for decay curves) to last observation, using PK Functions for Microsoft Excel (Usansky J et al, Department of Pharmacokinetics and Drug Metabolism, Allergan, Irvine, Cal, US). $\delta$-AUC and $\delta$-AUMC were determined as area above the calculated baseline ($AUC_{\text{observations}} - AUC_{\text{baseline}}$) and ($AUMC_{\text{observations}} - AUMC_{\text{baseline}}$), respectively. $\delta$ Mean residence time (MRT) and mean $k$ was determined from the ratio of $\delta$-AUC/$\delta$-AUMC. The area under the solute flux (point concentration in mmol/L × flow in L/h) versus time curve (flux–time integral [FTI]) yields the total amount (mmol) of magnesium that passed the sampling point over the analysed time period.

<table>
<thead>
<tr>
<th>CCRT fluid</th>
<th>Electrolyte</th>
<th>Concentration (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Used in this study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prismocitrate 10/2</td>
<td>Trisodium citrate</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Citric acid</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Sodium</td>
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<tr>
<td></td>
<td>Chloride</td>
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</tr>
<tr>
<td>Prism0cal</td>
<td>Magnesium</td>
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</tr>
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</tr>
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<tr>
<td></td>
<td>Bicarbonate</td>
<td>32</td>
</tr>
<tr>
<td>Hemosol B0</td>
<td>Calcium</td>
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</tr>
<tr>
<td></td>
<td>Magnesium</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>Sodium</td>
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<tr>
<td></td>
<td>Chloride</td>
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<td></td>
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<td>3</td>
</tr>
<tr>
<td></td>
<td>Bicarbonate</td>
<td>32</td>
</tr>
</tbody>
</table>

In widespread use (not used in this study) [Mg] (mmol/L)

- Fresenius multiPlus (1.0 mmol HPO$_4^{2-}$) 0.75
- Fresenius multiBic 0.5
- Fresenius Ci-Ca K2/K4 0.75
- Gambro Phoxilium (1.2 mmol HPO$_4^{2-}$) 0.6
- Hospal Prism0cal B22 0.75
- Hospal Hemosol L0/LG2/LG4 0.75
- Baxter Monosol haemofiltration solution 0.75

* Data from manufacturers’ product information.
Calculation of magnesium loss

Total magnesium flux from the patient to the effluent was calculated in two ways. Method 1 takes the median (across all measurements) result of an equation for conservation of mass from each sample set:

\[ \text{Mg}_{\text{loss}} = \text{Mg}_{\text{eff}} \times Q_{\text{eff}} - \left( \text{Mg}_{\text{PBP}} \times Q_{\text{PBP}} + \text{Mg}_{\text{dial}} \times Q_{\text{dial}} + \text{Mg}_{\text{post}} \times Q_{\text{post}} \right) \]

where \( \text{Mg}_{\text{loss}} \) is in mmol/h, \( Q \) = volumetric flow rate (L/h), \( \text{eff} = \text{effluent}, \text{dial} = \text{dialysate}, \text{PBP} = \text{pre blood pump fluid}, \) and \( \text{post} = \text{postfilter replacement} \).

Method 2 uses the FTI at each sampling site to determine the total amount of magnesium to transit that point in the circuit. Conservation of mass then dictates loss over the total time of the circuit calculated as:

\[ \text{Mg}_{\text{loss}} = \text{FTI}_{\text{pre}} - \text{FTI}_{\text{post}} + \text{FTI}_{\text{PBP}} + \text{FTI}_{\text{rep}} \]

where \( \text{FTI}_{\text{pre}} \) and \( \text{FTI}_{\text{post}} \) are integrals of the pre- and postfilter flux-time curves, and \( \text{FTI}_{\text{PBP}} \) and \( \text{FTI}_{\text{rep}} \) are integrals of magnesium added via predilution (none in citrate) and postdilution over curve life. The result is the amount of magnesium lost over the curve’s duration and can be indexed to 24 hours to roughly estimate mean daily loss (assuming a similar sampling and replacement frequency).

Statistical analysis

The curve of best fit for exponential decay from the observed peak concentration was found using the Solver generalised reduced gradient nonlinear module (Frontline Systems) contained in Excel 2010 (Microsoft Corporation) to solve for the smallest root mean square error (RMSE) by varying the constants of the exponential decay equation \( B, C, \) and \( k \). The normalised RMSE (NRMSE = RMSE/range of observed concentrations), coefficient of variation (CVRMSE = RMSE/mean concentration), coefficient of determination \( (R^2) \), and significance (F-distribution) are reported. Four curves that did not follow a magnesium infusion demonstrated decay better described by a linear equation. Effluent dose and half-life were compared using linear regression. Statistical comparisons were made in Intercooled Stata, version 9 (StataCorp) and R, version 2.15.1 (R Foundation for Statistical Computing) by two sample Wilcoxon rank-sum tests with continuity correction for ties, and Wilcoxon signed-rank test with continuity correction where appropriate. Significance was set at \( P<0.05 \).
Results

Patient characteristics and data

Patient parameters, outcomes and filter life are described in Table 2. In total, 334 sample sets each comprising an arterial, prefilter, and postfilter blood and an effluent sample were collected from 13 consecutive ICU patients treated with CVVHDF as part of their ICU stay. Hemosol B0 was used in 26 circuits with or without heparin anticoagulation. Citrate anticoagulation was used in 22 circuits using Prismocitrate 10/2 and Prism0cal fluids.

Raw magnesium concentrations

Figure 2 demonstrates range and median concentrations from each sample site across all patients studied. The median arterial [Mg] in the heparin group was 0.88 mmol/L (interquartile range [IQR], 0.83–0.97 mmol/L; n = 180) and in the citrate group, 0.79 mmol/L (IQR, 0.69–0.91 mmol/L; n = 151; Wilcoxon W=8351; P v heparin < 0.0001; two-tailed).

Arterial magnesium concentration–time decay curve analysis

Forty curves with four or more arterial magnesium samples in the decay phase (time zero defined as peak [Mg] after starting a new filter or administration of a magnesium infusion) were identified for decay curve analysis. Of these, 19 were from patients receiving citrate anticoagulation and 21 from patients using Hemosol B0 with or without heparin anticoagulation. Concentration–time curve parameters are described in Table 3 and an example from one patient is provided in Figure 1. Four curves did not demonstrate exponential decay over the sampling period but demonstrated a smaller RMSE when described with a linear equation. Inspection of the range and slope (Table 3) of these curves suggest that concentrations at time zero were too near steady state in three cases, limiting decay definition. In the fourth case, a rising slope is observed in association with PN administration however this may be explained by noise in the data. Of 26 magnesium infusions administered to the patients, four were excluded due to insufficient sample points after the infusion. PN was administered to 12 patients in the citrate group and to five in the heparin group. The total quantity (mmol) of magnesium provided in PN over the course of the curve is shown in Table 3. Thirteen curves sampled a magnesium infusion in the citrate group and nine in the heparin group. Figure 3 displays the time the arterial [Mg] remained between stratified ranges after a magnesium infusion. Thirty-eight observations were < 0.7 mmol/L in the citrate group but only two < 0.7 mmol/L were recorded in the heparin group. In the citrate group,
the median time that the arterial [Mg] spent below 0.7 mmol/L was 4 hours (IQR, 0–8 hours).

Elimination half-life and mean residence time
The median half-life for decay to baseline for all derived magnesium curves was 4.73 hours (IQR, 3.73–7.32 hours). When confined only to the curves where a magnesium infusion was administered, the result was not significantly different between citrate (median, 4.68 hours; IQR, 4.32–7.09 hours) and heparin (median, 5.14 hours; IQR, 3.42–7.37 hours; W = 67; P = 0.9274). There was no relationship between the effluent flow rate and half-life (R² = 0.048; P = 0.24).

Median residence time (MRT) was calculated from \( \delta \)-AUC and \( \delta \)-AUMC for arterial [Mg] (Table 4). There was no significant difference between the two groups, with a median heparin MRT of 5.90 hours (IQR, 4.11–8.49 hours) and a median citrate MRT of 6.56 hours (IQR, 4.93–7.91 hours; \( P \text{v heparin} = 0.84; W = 206 \)). From the MRT, an estimated elimination half-life can be derived; for citrate, the half-life is 4.09 hours and for heparin, 4.54 hours.

Baseline of the magnesium concentration–time decay curve
Table 3 reports the minimum arterial [Mg] for each curve and the first constant of the corresponding equation is the calculated baseline. The calculated baselines of the derived decay curves correlated well with the minimum arterial [Mg] from each curve (\( B = 1.0262C - 0.03 \), where \( C \) is the minimum arterial [Mg]; \( R² = 0.8335 \)). The median of the minimum arterial [Mg] was significantly lower in the citrate group (0.68 mmol/L; IQR, 0.63–0.71 mmol/L) compared with the heparin group (0.82 mmol/L; IQR, 0.78–0.88 mmol/L; \( W = 216.5; P < 0.0001, \) two-tailed).

Magnesium flux proportional to the arterial [Mg]. For heparin, \( y = 1.644x - 0.724; R² = 0.43 \), and for citrate, \( y = 2.265x - 0.716; R² = 0.71 \), where \( y \) is magnesium lost to the patient in mmol/h and \( x \) is the arterial [Mg]. As a marker of model validation, using flux–time integrals to calculate magnesium leaving the filter blood compartment (FTI\(_{\text{pre}}\) − FTI\(_{\text{post}}\); Table 4) correlated well with magnesium appearing in effluent (FTI\(_{\text{eff}}\) − FTI\(_{\text{dial}}\); \( R² = 0.946; P < 0.001 \)).
Magnesium loss was greater in patients receiving citrate than heparin. When calculated by conservation of mass for each sample set, the median loss from heparin circuits was 0.72 mmol/h (IQR, 0.53–0.97 mmol/h) or 17.28 mmol/day. Median loss from citrate circuits was 1.09 mmol/h (IQR, 0.80–1.41 mmol/h; \( P < 0.001 \)), or 26.2 mmol/day. When calculated using flux–time integrals (indexed to 24 hours), the values for heparin were 13.07 mmol/day (IQR, 10.17–18.79 mmol/day) and for citrate, 25.17 mmol/day (IQR, 18.65–30.70 mmol/day; \( P < 0.001 \); \( V = 18 474 \)).

Table 4 and Figure 2 reveal the postfilter \([\text{Mg}]\) frequently to be greater than the prefilter concentration. The effect is small but significant (citrate: median postfilter [Mg], 0.03 mmol/L greater than prefilter [Mg] [\( P = 0.004 \); Wilcoxon \( W = 5722.5 \)]; heparin: median postfilter [Mg], 0.01 mmol/L greater than prefilter [Mg] [\( P = 0.001 \); \( V = 17 847 \)]) and probably results from bloodstream concentration after ultrafiltration to remove the predilution volume. In contrast, the flux–time integral is universally greater prefilter compared with postfilter (heparin: median prefilter minus postfilter difference, 27.4 mmol [IQR, 19.6–36.4 mmol]; citrate: median prefilter minus postfilter difference, 23.2 mmol [IQR, 16.8–28.5 mmol]; \( P < 0.001 \); \( V = 148.5 \)), confirming a net loss of magnesium from the blood path. Further, in citrate where no magne-
sium is added in predilution, the flux–time integrals are not significantly different between the arterial sampling site (surrogate for access line) (median, 168.7 mmol) and the prefilter flux (median, 166.0 mmol; V = 135; P = 0.1134).

To summarise, with magnesium-free predilution, there is a concentration drop between the access line and the filter due to dilution; after the filter, the concentration rises slightly. This rise in concentration occurs despite magnesium flux across the filter and is due to haemoconcentration from ultrafiltration. This is shown in the example in Figure 1.

In nine curves in the citrate group (magnesium-free predilution), the effluent [Mg] fell below the dialysate concentration of 0.5 mmol/L for part of the time (Table 4 and Figure 1). This suggests that sufficiently low [Mg] occurred within the filter to drive net flux of magnesium from the dialysate to the blood path.

**Discussion**

Attention to magnesium homeostasis is recognised as an important component of critical care.

Using typical fluid flow rates for adult patients receiving CVVHDF, our findings suggest that responding to once-daily measurement of serum magnesium results in substantial time periods near or below the lower reference range value. This effect was greatest in those receiving citrate and is likely due both to loss of magnesium chelated to citrate in the effluent and the lack of magnesium in the predilution used with this method.

We determined a half-life for magnesium to decay to a new baseline after starting CVVHDF or receiving a magnesium bolus. It should be noted that this baseline only implies a steady concentration (slope negligible) and does not necessarily imply a state where net intake equals loss. As magnesium exists in multiple compartments, mobilisation from bone as well as enteric and intravenous magnesium administration will contribute to maintenance of a steady plasma concentration. Magnesium supplementation practices vary between units and non-CRRT losses will vary between patients making approximating net balance in a patient difficult.

<table>
<thead>
<tr>
<th>Curve Name</th>
<th>Concentration</th>
<th>Predilution</th>
<th>Postdilution</th>
<th>Effluent</th>
<th>Patient Loss</th>
<th>Induced Loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mg-To-Effluent</td>
<td>Mg-To-Filter</td>
<td>Mg-To-Blood</td>
<td>Mg-To-Dialysate</td>
<td>Mg-To-Filter</td>
<td>Mg-To-Blood</td>
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<td>Mg-To-Dialysate</td>
</tr>
</tbody>
</table>

**Table 4. Non-compartmental analysis of magnesium (Mg) concentration and flux**

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Our results highlight that the driving concentration gradient for diffusive clearance will be the mean of the pre- and postfilter diffusible magnesium after the addition of predilution to the bloodstream. Assuming a bound fraction approximating 30% and an approximate 15% dilution effect of the predilution, it can be appreciated that the bloodstream diffusible [Mg] will be close to (and sometimes below) the 0.5 mmol/L dialysate concentration. We demonstrated that ultrafiltration of water must offset the mass transfer of magnesium to the effluent to maintain or slightly raise the blood compartment concentration over the filter.

The results are subject to several limitations due to the observational nature of the study and the small number of patients. A limitation of our sampling frequency is that we may have underestimated peak concentrations; however, administration over 2 hours would have decreased the magnitude of this error. Where magnesium is given at faster rates, higher peak levels than we sampled may be achieved and may have therapeutic or adverse effects depending on the clinical scenario. Decay curve analysis is subject to a risk of overfitting; however, visual inspection of the data and derived curves, and the parameters of curve fit suggest this was not the case. In four cases where a magnesium bolus was not given, we found that a linear model best described the data. We do not suggest alternative kinetics in these cases but rather sampling limitations obscuring detection of exponential decay.

A multicomartment model with two to three extra plasma pools has been described in healthy subjects using radiolabelled magnesium; however, to our knowledge magnesium compartments in CRRT have not been described. It is possible that the model we have used is not the best approximation and that more frequent sampling under controlled conditions would reveal kinetics consistent with a multicomartment model. As our data were generally well described by monoexponential decay and gave similar results with a non-compartmental analysis, an alternative is that the effect of CRRT on the system masks detection of relatively smaller shifts between compartments.

Imprecision in concentration measurement and recorded sample timing may have compounded errors in constructing the true decay curve. These sources of error may account for us not detecting a half-life difference between lower and higher effluent flow rates. We have studied total [Mg]; however, newer generation blood gas analysers can report ionised magnesium. Ionised hypomagnesaemia is less frequent than total hypomagnesaemia and may be more clinically relevant. Access to the ionised magnesium result on blood gas analysis may have improved detection and response to low concentrations in the citrate group, where blood gas analysis was frequently performed as part of protocol-driven ionised calcium monitoring. Future studies incorporating ionised magnesium may better define the effects of citrate and protein binding and with more frequent sampling could describe other factors influencing magnesium kinetics in CRRT such as body weight, gastrointestinal losses, filter age and effluent dose.

Although many of our findings can be predicted from an understanding of CRRT, these data quantify the time for magnesium to fall with two widely used CRRT fluids and reinforce the need to monitor [Mg] frequently or increase the frequency of supplementation if a high-normal arterial concentration is to be maintained consistently. The demonstration of significant exponential decay makes determining the timing of magnesium sampling in relation to dosing important when interpreting results. We would suggest at least twice-daily magnesium sampling for patients receiving CRRT, with measurement of trough concentrations to guide dosage or further increases in frequency. It may potentially be advantageous to administer magnesium supplementation over longer time periods to attenuate peaks and promote steady concentrations.

Our findings should hopefully encourage a shift towards the supply of CRRT fluids with a higher [Mg], just as a trend towards avoiding hypophosphataemia has led to the production of CRRT fluids with higher phosphate ion concentration. We suggest that dialysate [Mg] of 0.8 mmol/L may be more suited to the critically ill population. In those receiving magnesium free predilution fluids with concomitant citrate anticoagulation, a dialysate concentration of 1.0 mmol/L may be required and should be the subject of further study.

Acknowledgements
We thank Dr David Pilcher for assisting with statistical analysis, Isaac Brain for vector art, and the staff of the Launceston General Hospital intensive care unit and pathology service for (unfunded) sample collection and analysis.

Competing interests
No relevant disclosures.

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