Magnesium flux during continuous venovenous haemodiafiltration with heparin and citrate anticoagulation

Matthew Brain, Mike Anderson, Scott Parkes and Peter Fowler

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 Prism0cal) 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. Magnesium loss was calculated from an equation for conservation of mass, and arterial magnesium concentration was described by an equation for exponential decay.

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.

Crit Care Resusc 2012; 14: 274–282

Hypomagnesaemia is common in critical care patients[1] generally and particularly in patients receiving continuous renal replacement therapy (CRRT).[2,3] Low magnesium concentration ([Mg]) has been associated with adverse outcomes including increased mortality.[4-6] 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%.[7] Magnesium supplementation for arrhythmia prevention has been most studied in cardiac surgical patients,[8-10] with a meta-analysis suggesting an overall reduction in the incidence of atrial fibrillation.[11]

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,[3] commensurate with its pivotal role coordinating inorganic phosphate transfer in ATP synthesis.[12] 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.[3,13]

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.[13] As a consequence, some commonly used dialysis fluids have relatively low [Mg] relative to serum concentrations.[13]

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[14] 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.[14] 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.

Table 1. Electrolyte composition of fluids used in this study and magnesium concentrations of other fluids commonly used in continuous renal replacement therapy (CCRT)*

CCRT fluid	Electrolyte	Concentration (mmol/L)
Used in this study		
Prismocitrate 10/2	Trisodium citrate	10
	Citric acid	2
	Sodium	136
	Chloride	106
Prism0cal	Magnesium	0.5
	Sodium	140
	Chloride	106
	Lactate	3
	Bicarbonate	32
Hemosol B0	Calcium	1.75
	Magnesium	0.5
	Sodium	140
	Chloride	109
	Lactate	3
	Bicarbonate	32
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.

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 $y = B + C.e^{(-k.t)}$, 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 ($T_{1/2} = \ln(2)/k$).

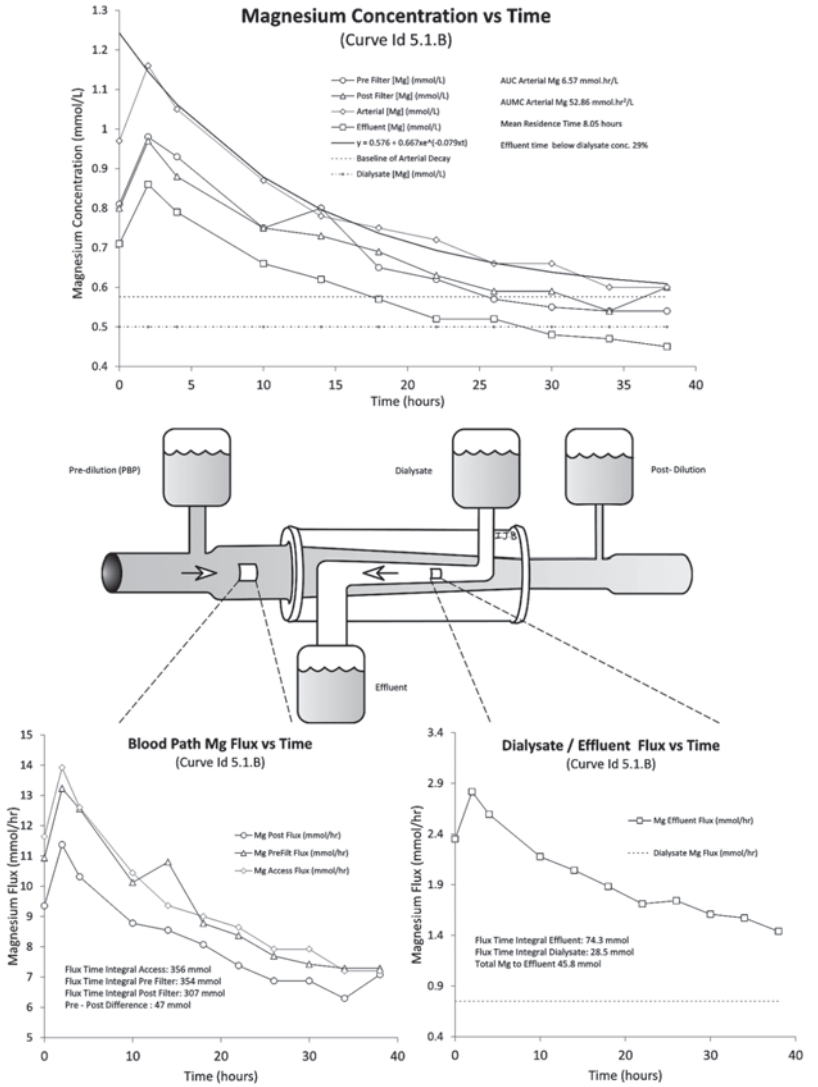
Figure 1 is a circuit schematic demonstrating volumetric flow, with sample measurements and calculations from one curve studied.

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). δ-AUC and δ-AUMC were determined as area above the calculated baseline ($AUC_{observations} - AUC_{baseline}$) and ($AUMC_{observations} - AUMC_{baseline}$), respectively.[15] Mean residence time (MRT) and mean k was determined from the ratio of δ-AUC/δ-AUMC.[16,17] 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.

Figure 1. Schematic of circuit with sample measurements from one curve studied



[Mg] = magnesium concentration. The diameter of the large tube reflects the blood compartment volumetric flow (L/h) with variations in diameter reflecting volume shifts from predilution, ultrafiltration and postdilution. The increasing tube diameter from dialysate to effluent reflects the addition of ultrafiltrate to the dialysate path. Typically, blood enters the circuit at 200 mL/min (12 L/h) and is further expanded by the addition of about 1.5–2 L of predilution before entering the haemofilter. Manipulation of transmembrane pressure within the filter forces fluid from the blood path to the dialysate–effluent path and is controlled to remove all pre- and postdilution and any additional fluid removal. Example measurements and derived fluxes after a 20 mmol magnesium infusion in a patient receiving citrate anticoagulation are included and are presented as raw measurements in the top graph, magnesium flux in the blood path (bottom left), and magnesium flux in the effluent path (bottom right). Note magnesium concentration falls from arterial to prefilter but is similar between pre- and postfilter sites, whereas magnesium flux is unchanged (in citrate) between arterial and prefilter sites and falls before the postfilter site. Note also that effluent [Mg] falls below the dialysate concentration, implying net absorption when arterial concentrations are low.

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:

$$Mg_{loss} = [Mg_{eff}] \times Q_{eff} - \{[Mg_{PBP}] \times Q_{PBP} + [Mg_{dial}] \times Q_{dial} + [Mg_{post}] \times Q_{post}\}$$

where Mg_{loss} is in mmol/h, Q = volumetric flow rate (L/h), eff = effluent, dial = dialysate, PBP = pre blood pump fluid, and post = 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:

$$Mg_{loss} = FTI_{pre} - FTI_{post} + FTI_{PBP} + FTI_{rep}$$

where FTI_{pre} and FTI_{post} are integrals of the pre- and postfilter flux–time curves, and FTI_{PBP} and FTI_{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 (CV_{RMSE} = 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 $P < 0.05$.

Table 2. Patient characteristics, continuous renal replacement therapy (CRRT) duration and number of filters

Patient no.*	Anticoagulation	Duration/filters†	Age, years	Sex	Diagnosis	Indication for CRRT	APACHE II/III score	Outcome
5	Citrate	101/3	75	Male	Intra-abdominal sepsis	MOD/AKI	22/96	Died
6	Citrate	125/7	58	Male	Necrotising pancreatitis	MOD	17/71	Survived
7	Citrate	76/3	50	Male	Sepsis	AKI/CKD	29/89	Survived
12	Citrate	46/2	66	Male	GI loss, acidosis	AKI, acidosis	27/96	Survived
13	Citrate	14/1	55	Female	Cardiac failure, sepsis	Fluid removal	22/88	Survived
8	LDH, citrate‡	13/2, 142/5§	74	Female	Ruptured AAA	AKI	30/113	Survived
9	LDH, citrate‡	20/1, 15/1§	60	Male	Sepsis	AKI	29/126	Survived
1	LDH, nil¶	197/5	47	Male	Intra-abdominal sepsis	MOD/AKI	46/176	Survived
2	LDH	12/1	60	Male	Overdose	MOD/AKI	23/64	Died
3	LDH	23/1	71	Male	Cardiac failure	Fluid removal/AKI	29/62	Survived
4	WBH, LDH	161/5	72	Male	AMI, APO	CKD, fluid removal	32/103	Survived
10	LDH, nil¶	140/10	30	Male	Overdose	MOD	45/152	Died
11	LDH	22/1	59	Male	Hepatic failure, CCF	Fluid removal	31/149	Died

AAA = abdominal aortic aneurysm. AKI = acute kidney injury. AMI = acute myocardial infarction. APACHE = Acute Physiology, Age and Chronic Health Evaluation. APO = acute pulmonary oedema. CCF = congestive cardiac failure. CKD = chronic kidney disease. GI = gastrointestinal. LDH = low-dose heparin. MOD = multiorgan dysfunction. WBH = weight-based heparin. * Patient number refers to the sequential order of enrolment in the study. † Duration refers to total time in hours of venovenous haemodiafiltration; filters refers to the total number of haemofilters consumed over therapy course. ‡ Patients 8 and 9 received low-dose heparin initially and were later changed to citrate; their data have been divided and analysed in each group. § Two anticoagulation methods were performed sequentially and filter hours are divided respectively. ¶ Patients 1 and 10 had periods without any circuit anticoagulation due to coagulopathy; during this time, their continuous venovenous haemodiafiltration treatment otherwise continued as per our LDH protocols with Hemosol B0.

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,

Figure 2. Range and median magnesium concentrations by patient and sampling site for 13 patients

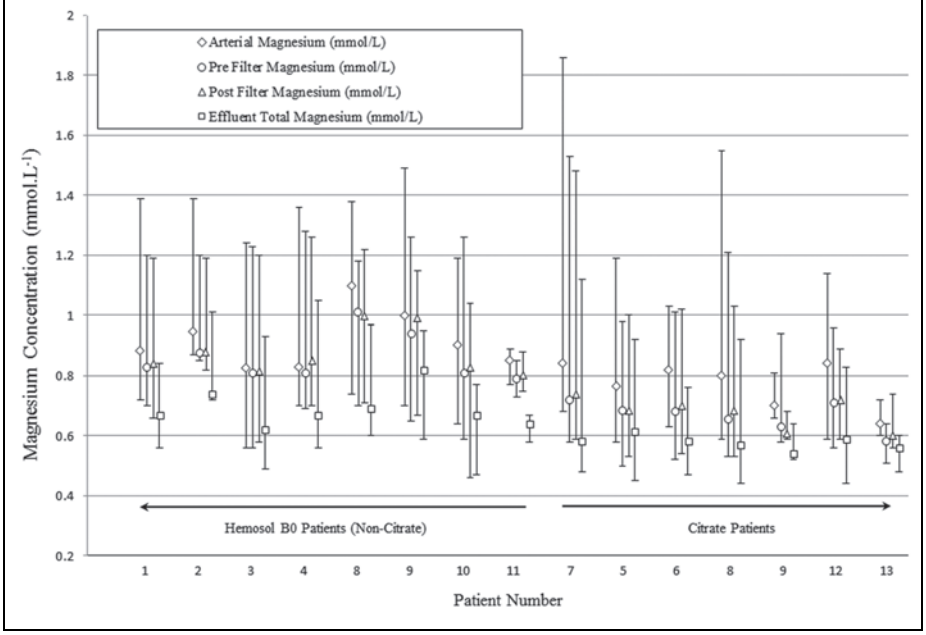
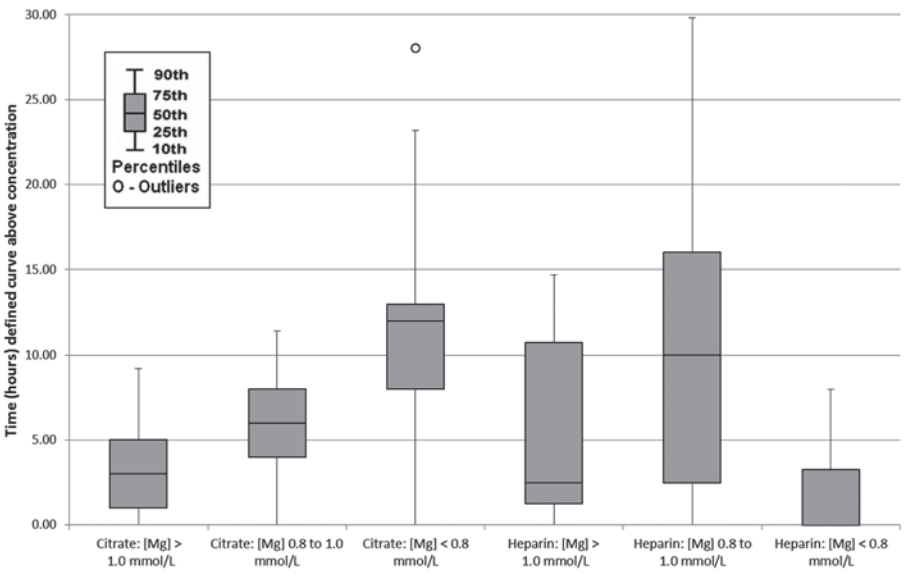


Figure 3. Time after a magnesium infusion at stratified arterial magnesium concentration ([Mg])



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 (R^2 = 0.048; P = 0.24).

Median residence time (MRT) was calculated from δ-AUC and δ-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 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]; R^2 = 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; R^2 =0.43, and for citrate, y = 2.265x – 0.716; R^2 = 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_{pre} – FTI_{post}; Table 4) correlated well with magnesium appearing in effluent (FTI_{eff} – FTI_{dial}; R^2 = 0.946; P < 0.001).

Table 3. Arterial magnesium concentrations and parameters of exponential decay curves of arterial magnesium concentration in venovenous haemodiafiltration

Curve Description		Magnesium (mmol)			Observed Magensium			Mean Circuit Flow			Curve Characteristics				Curve Fit			
Curve Name	Anti-coagulation	Mg - infusion	Mg via TPN (total)	Total Mg over curve (infusion + TPN)	Max Arterial Mg	Arterial [Mg] Median	Min Arterial Mg	Mean Q_B (L/hr)	Mean Q_B ml/hr	Effluent Flow (ml/hr)	Equation for Curve of Best Fit	Observations	Total Time (hours)	T1/2 of decay curve	NRMSE	CV (RMSE)	R^2	p (F distribution)
Id 7.2.B	C	40	12.32	52.32	1.86	0.99	0.84	12.0	2000	4129	y= 0.793 + 1.778e^(- 0.169.t)	6	24	4.097	0.48%	0.43%	0.999	<0.001
Id 6.5.E	C	20	21.75	41.75	0.86	0.68	0.63	11.1	1846	3918	y= 0.589 + 0.473e^(- 0.108.t)	6	25	6.407	1.38%	0.45%	0.992	<0.001
Id 6.3.B	C	20	9.58	29.58	1	0.82	0.71	13.4	2000	4274	y= 0.760 + 0.794e^(- 0.254.t)	9	22	2.729	3.81%	1.31%	0.784	0.001
Id 6.4.C	C	20	7.75	27.75	1.03	0.77	0.68	12.0	2000	4317	y= 0.669 + 0.489e^(- 0.157.t)	5	23	4.423	1.93%	0.83%	0.984	<0.001
Id 5.1.B	C	20	7.71	27.71	1.16	0.75	0.6	12.0	1500	3296	y= 0.576 + 0.667e^(- 0.079.t)	10	41	8.792	0.91%	0.64%	0.992	<0.001
Id 6.5.D	C	20	7.00	27.00	0.93	0.79	0.68	12.0	2000	4254	y= 0.669 + 0.472e^(- 0.148.t)	5	23	4.678	3.43%	1.09%	0.952	0.002
Id 8.4.E	C	20	4.38	24.38	1.17	0.73	0.68	12.0	1500	3464	y= 0.700 + 1.326e^(- 0.346.t)	5	20	2.006	1.28%	0.76%	0.977	<0.001
Id 8.6.H	C	20	4.25	24.25	1.55	0.88	0.64	10.2	1500	3140	y= 0.645 + 1.223e^(- 0.161.t)	6	22	4.317	2.01%	1.93%	0.978	<0.001
Id 8.2.B	C	20	0.00	20.00	1.01	0.83	0.72	9.0	1500	2877	y= 0.594 + 0.556e^(- 0.098.t)	4	18	7.092	0.70%	0.24%	0.999	<0.001
Id 8.2.C	C	20	0.00	20.00	1.14	0.89	0.7	11.0	1500	3370	y= 0.640 + 0.523e^(- 0.078.t)	6	21	8.911	2.46%	1.20%	0.902	<0.001
Id 8.6.I	C	20	0.00	20.00	1.24	0.78	0.62	10.2	1500	3067	y= 0.605 + 0.968e^(- 0.145.t)	6	23	4.789	1.15%	0.85%	0.993	<0.001
Id 9.1.I	C	20	0.00	20.00	0.81	0.7	0.66	12.0	2000	3819	y= 0.640 + 0.178e^(- 0.150.t)	7	13	4.612	6.21%	1.29%	0.869	0.007
Id 12.1.A	C	20	0.00	20.00	1.14	0.83	0.59	12.0	2000	3748	y= 0.520 + 0.746e^(- 0.085.t)	11	31	8.166	2.14%	1.45%	0.955	<0.001
Id 7.1.A	C	0	15.66	15.66	1.2	0.75	0.68	12.0	2000	4152	y= 0.699 + 0.491e^(- 0.154.t)	15	44	4.504	0.75%	0.48%	0.990	<0.001
Id 8.6.G	C	0	9.92	9.92	0.87	0.78	0.64	10.3	1500	3415	y= 0.670 + 0.215e^(- 0.182.t)	4	13	3.805	11.54%	3.47%	0.610	0.201
Id 5.2.D	C	0	8.33	8.33	0.8	0.65	0.58	12.0	1000	2631	y= 0.555 + 0.305e^(- 0.064.t)	9	39	10.809	1.84%	0.61%	0.968	<0.001
Id 6.1.A	C	0	4.17	4.17	0.97	0.86	0.82	12.0	2000	4294	y= 0.635 + 0.363e^(- 0.079.t)	4	10	8.774	3.09%	0.53%	0.975	0.004
Id 5.1.A	C	0	0.00	0.00	1.19	0.94	0.69	12.0	1688	3864	y= 0.669 + 0.486e^(- 0.114.t)	8	15	6.075	5.47%	2.97%	0.730	0.01
Id 8.2.A	C	0	0.00	0.00	0.89	0.7	0.66	9.0	1500	3350	y= 0.616 + 0.337e^(- 0.186.t)	7	13	3.725	1.86%	0.58%	0.982	<0.001
Id 1.3.F	nil	30	19.38	49.38	1.16	1.01	0.89	12.0	1500	3376	y= 0.887 + 0.300e^(- 0.092.t)	8	30	7.510	6.21%	1.67%	0.910	0.004
Id 1.5.H	LDH	20	18.63	38.63	0.9	0.86	0.72	12.0	1500	3294	y= 0.820 + 0.110e^(- 0.060.t)	11	45	11.552	7.14%	1.52%	0.309	0.164
Id 1.3.E	nil	20	10.67	30.67	1.39	0.85	0.83	12.0	2938	6152	y= 0.824 + 0.563e^(- 0.269.t)	9	23	2.572	5.87%	3.48%	0.702	0.008
Id 3.1.B	LDH	20	0.00	20.00	1.24	0.86	0.76	12.0	1000	2245	y= 0.743 + 0.731e^(- 0.195.t)	5	20	3.555	0.72%	0.37%	0.998	<0.001
Id 11.1.A	LDH	20	0.00	20.00	0.89	0.85	0.77	12.0	2000	4375	y= 0.760 + 0.198e^(- 0.120.t)	7	22	5.787	10.68%	1.54%	0.635	0.105
Id 8.1.A	nil	20	0.00	20.00	1.38	1.1	0.74	12.0	2000	4225	y= 0.754 + 0.642e^(- 0.154.t)	4	6	4.512	1.65%	0.96%	0.947	0.003
Id 4.1.C	WBH	20	0.00	20.00	1.36	1.02	0.93	12.0	1000	2320	y= 0.915 + 0.488e^(- 0.100.t)	8	31	6.943	1.09%	0.43%	0.991	<0.001
Id 1.2.C	nil	10	1.26	11.26	1.08	0.91	0.84	12.0	3000	6363	y= 0.849 + 0.202e^(- 0.079.t)	19	38	8.798	2.84%	0.75%	0.752	<0.001
Id 1.1.A	LDH	10	0.00	10.00	1.08	0.87	0.81	12.0	3000	6319	y= 0.818 + 0.341e^(- 0.262.t)	8	14	2.645	1.56%	0.47%	0.980	<0.001
Id 10.1.B	nil	10	0.00	10.00	1.19	0.88	0.75	11.2	1933	4147	y= 0.692 + 0.487e^(- 0.205.t)	6	14	3.376	1.25%	0.60%	0.922	<0.001
Id 1.4.G	LDH	0	15.00	15.00	0.96	0.92	0.86	12.0	1500	3327	y= 0.881 + 0.124e^(- 0.140.t)	6	23	4.961	7.49%	0.82%	0.678	0.059
Id 1.3.D	nil	0	4.10	4.10	0.91	0.83	0.82	12.0	3000	6260	y= 0.834 + 0.003.t	7	12	#N/A	14.36%	1.52%	0.124	0.304
Id 4.2.E	LDH	0	0.00	0.00	1.25	1.02	0.9	12.0	100	2400	y= 0.879 + 0.369e^(- 0.144.t)	4	21	4.799	1.37%	0.46%	0.995	<0.001
Id 4.4.F	LDH	0	0.00	0.00	0.87	0.82	0.79	12.0	0	2301	y= 0.814 + 0.168e^(- 0.239.t)	10	46	2.900	6.38%	0.62%	0.475	0.055
Id 10.7.E	LDH	0	0.00	0.00	1	0.93	0.88	10.0	1900	4033	y= 0.848 + 0.200e^(- 0.096.t)	5	19	7.251	2.84%	0.37%	0.968	0.001
Id 10.11.I	LDH	0	0.00	0.00	0.91	0.87	0.8	11.5	1909	4177	y= 0.790 + 0.141e^(- 0.081.t)	4	21	8.544	7.77%	0.99%	0.764	0.088
Id 10.13.K	LDH	0	0.00	0.00	0.86	0.83	0.81	12.0	2000	4419	y= 0.807 + 0.142e^(- 0.199.t)	5	21	3.487	1.25%	0.08%	0.994	<0.001
Id 1.2.B	nil	0	0.00	0.00	0.89	0.88	0.87	12.0	3000	6438	y= 0.892 + - 0.004.t	4	6	#N/A	11.18%	0.25%	0.800	0.011
Id 2.1.A	nil	0	0.00	0.00	0.98	0.95	0.87	12.0	1357	3058	y= 0.989 + - 0.018.t	4	6	#N/A	4.66%	0.55%	0.939	<0.001
Id 4.1.A	WBH	0	0.00	0.00	0.79	0.73	0.7	12.0	1813	4115	y= 0.754 + - 0.002.t	5	15	#N/A	14.70%	1.78%	0.065	0.704
Id 4.2.D	WBH	0	0.00	0.00	0.89	0.83	0.8	12.0	1138	2604	y= 0.804 + 0.209e^(- 0.186.t)	6	28	3.734	4.68%	0.51%	0.882	0.005

Data are organised by anticoagulation type then by magnesium infusion amount. Curve Name = patient number. filter number. curve letter. Mg infusion = total mmol of magnesium infused. Mg via TPN = total amount given over the time period of that curve (hourly rate may vary). CV = coefficient of variation. NRMSE = normalised root mean square error. Q_B = volumetric blood flow rate. Q_D = volumetric flow of dialysate. TPN = total parenteral nutrition *Curves marked with an asterix contain a single extreme outlier. Ignoring these outliers significantly improves the numerical parameters of curve fit as follows: Curve ID/NRMSE/CV(RMSE)/R^2; ID 11.1.A/4.09%/0.59%/0.852; ID 4.4.F/7.93%/0.77%/0.620; ID 4.1.A/2.98%/0.36%/0.900. † RMSE linear equation: 0.013, RMSE exponential equation: 0.088. F-ratio negative. †† RMSE linear equation: 0.002; RMSE exponential equation: 0.009. F-ratio negative. ††† RMSE linear equation: 0.005; RMSE exponential equation: 0.029. F-ratio negative. ‡ RMSE linear equation: 0.013; RMSE exponential equation: 0.055. F-ratio negative.

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; Wilcoxon W = 20 151.5; $P < 0.001$), 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 v heparin < 0.0001; W = 347).

Table 4 and Figure 2 reveal the postfilter [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 v heparin = 0.174; W = 148.5]), confirming a net loss of magnesium from the blood path. Further, in citrate where no magne-

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

Curve Name	Anti-coagulation	Mg infusion	Pre-filter [Mg] Median (Range) mmol/L	Post Filter [Mg] Median (Range) mmol/L	Effluent [Mg] Median (Range) mmol/L	Effluent [Mg] <0.5 mmol/L % curve time	ΔAUC Arterial [Mg] mmol.hr/L	ΔAUMC Arterial [Mg] mmol.hr²/L	MRT Arterial [Mg] hrs	Mg-FTI Access (mmol)	Mg-FTI PBP (mmol)	Mg-FTI Pre-Filter (mmol)	Mg-FTI Post Filter (mmol)	Mg from Blood: Pre-Post (mmol)	Patient Loss: Pre-Post+PBP+Rep (mmol)	Indexed Loss / 24 hours	Mg-FTI Effluent (mmol)	Mg-FTI Dialysate (mmol)	Mg To Effluent (mmol)	Effluent : Prefilter Flux Ratio
Id 7.2.B	C	40	0.88 (0.7 - 1.53)	0.87 (0.7 - 1.48)	0.73 (0.58 - 1.12)	0%	6.34	49.37	7.78	266.4	0.0	261.0	215.5	45.5	43.52	45.41	63.3	20.0	43.3	16.6%
Id 6.5.E	C	20	0.59 (0.52 - 0.75)	0.62 (0.54 - 0.73)	0.51 (0.47 - 0.62)	32.0%	2.29	25.99	11.36	168.7	0.0	167.7	145.9	21.8	19.80	19.01	43.6	20.0	23.6	14.1%
Id 6.3.B	C	20	0.66 (0.62 - 0.82)	0.72 (0.61 - 0.82)	0.56 (0.52 - 0.68)	0%	2.46	11.43	4.65	228.3	0.0	216.0	188.6	27.4	25.41	29.04	50.3	20.0	30.3	14.0%
Id 6.4.C	C	20	0.67 (0.58 - 1.01)	0.66 (0.59 - 1.02)	0.59 (0.53 - 0.76)	0%	2.16	14.21	6.56	154.8	0.0	156.5	132.5	24.0	22.42	29.90	41.8	16.0	25.8	16.5%
Id 5.1.B	C	20	0.65 (0.54 - 0.98)	0.69 (0.54 - 0.97)	0.57 (0.45 - 0.86)	29.3%	6.57	52.86	8.05	356.6	0.0	354.2	307.5	46.7	42.90	27.10	74.3	28.5	45.8	12.9%
Id 6.5.D	C	20	0.63 (0.57 - 0.73)	0.68 (0.59 - 0.76)	0.55 (0.51 - 0.64)	0%	3.11	16.42	5.28	189.6	0.0	179.5	158.0	21.5	19.53	23.44	47.9	20.0	27.9	15.5%
Id 8.4.E	C	20	0.66 (0.53 - 1.21)	0.65 (0.58 - 0.98)	0.58 (0.5 - 0.92)	0%	1.56	7.88	5.05	144.7	0.0	141.4	118.1	23.2	21.74	28.99	30.9	11.3	19.6	13.9%
Id 8.6.H	C	20	0.69 (0.57 - 1.06)	0.76 (0.59 - 1.03)	0.6 (0.49 - 0.92)	18.2%	5.48	38.27	6.98	187.9	0.0	166.0	148.5	17.5	15.54	16.95	38.7	15.0	23.7	14.3%
Id 8.2.B	C	20	0.76 (0.58 - 0.84)	0.75 (0.63 - 0.79)	0.58 (0.52 - 0.63)	0%	2.97	22.53	7.60	90.9	0.0	89.2	76.6	12.6	11.44	18.30	20.2	9.0	11.2	12.6%
Id 8.2.C	C	20	0.76 (0.55 - 1.01)	0.75 (0.6 - 0.95)	0.66 (0.47 - 0.85)	19.0%	4.56	29.97	6.57	206.8	0.0	201.6	171.9	29.7	27.56	31.50	46.7	15.8	30.9	15.3%
Id 8.6.I	C	20	0.65 (0.55 - 0.95)	0.69 (0.56 - 0.94)	0.55 (0.47 - 0.8)	17.4%	4.21	35.20	8.37	95.7	0.0	157.1	142.7	14.4	12.38	12.92	35.2	15.0	20.2	12.9%
Id 9.1.I	C	20	0.63 (0.58 - 0.94)	0.61 (0.59 - 0.68)	0.54 (0.52 - 0.64)	0%	1.03	4.52	4.40	112.2	0.0	116.6	92.1	24.5	23.24	42.91	27.7	13.0	14.7	12.6%
Id 12.1.A	C	20	0.68 (0.56 - 0.96)	0.71 (0.59 - 0.89)	0.58 (0.44 - 0.8)	38.7%	6.76	73.16	10.83	255.0	0.0	261.1	229.7	31.4	28.59	22.87	59.3	28.0	31.3	12.0%
Id 7.1.A	C	0	0.64 (0.58 - 1.02)	0.67 (0.59 - 0.98)	0.53 (0.48 - 0.86)	27.3%	3.23	20.46	6.34	407.9	0.0	401.6	351.1	50.6	46.15	25.17	100.8	44.0	56.8	14.1%
Id 8.6.G	C	0	0.66 (0.6 - 0.75)	0.71 (0.64 - 0.76)	0.58 (0.54 - 0.61)	0%	1.09	3.84	3.51	166.5	0.0	96.0	86.8	9.2	8.00	16.00	23.5	9.0	14.5	15.1%
Id 5.2.D	C	0	0.56 (0.5 - 0.68)	0.59 (0.53 - 0.68)	0.51 (0.45 - 0.64)	41.0%	2.14	25.52	11.90	252.0	0.0	241.8	220.4	21.4	18.20	12.14	43.6	16.0	27.6	11.4%
Id 6.1.A	C	0	0.8 (0.69 - 0.84)	0.78 (0.7 - 0.81)	0.59 (0.58 - 0.59)	0%	2.00	8.88	4.43	85.1	0.0	87.1	71.1	16.0	15.18	40.48	20.1	8.0	12.1	13.9%
Id 5.1.A	C	0	0.82 (0.69 - 0.97)	0.8 (0.67 - 1)	0.73 (0.6 - 0.87)	0%	3.41	17.53	5.14	152.6	0.0	157.2	133.7	23.5	22.09	37.87	40.6	11.8	28.9	18.4%
Id 8.2.A	C	0	0.61 (0.56 - 0.73)	0.62 (0.57 - 0.69)	0.53 (0.49 - 0.65)	30.8%	1.36	6.54	4.81	78.8	0.0	78.0	65.0	13.0	11.78	21.75	21.6	9.0	12.6	16.2%
Id 1.3.F	nil	30	0.95 (0.91 - 1)	0.97 (0.89 - 1.03)	0.77 (0.73 - 0.84)	0%	3.09	26.23	8.48	363.7	22.5	388.8	339.8	49.0	23.49	18.79	78.3	22.5	55.8	14.3%
Id 1.5.H	LDH	20	0.82 (0.74 - 0.88)	0.84 (0.66 - 0.86)	0.67 (0.56 - 0.71)	0%	1.39	21.33	15.35	398.2	29.3	425.9	377.3	48.7	15.50	8.86	85.1	29.3	55.8	13.1%
Id 1.3.E	nil	20	0.78 (0.76 - 1.2)	0.8 (0.76 - 1.19)	0.67 (0.62 - 0.73)	0%	1.65	7.32	4.44	226.8	31.5	259.4	206.0	53.4	19.81	21.62	87.9	31.5	56.4	21.8%
Id 3.1.B	LDH	20	0.83 (0.77 - 1.23)	0.83 (0.75 - 1.2)	0.63 (0.58 - 0.93)	0%	2.55	15.05	5.90	173.3	8.0	189.8	165.7	24.1	14.45	19.27	23.9	8.0	15.9	8.4%
Id 11.1.A	LDH	20	0.79 (0.73 - 0.85)	0.81 (0.75 - 0.88)	0.64 (0.58 - 0.67)	0%	1.01	7.82	7.75	179.4	18.0	196.3	167.2	29.1	9.32	11.18	49.6	18.0	31.6	16.1%
Id 8.1.A	nil	20	1.01 (0.88 - 1.03)	1 (0.96 - 1.02)	0.69 (0.65 - 0.69)	0%	1.42	5.26	3.70	53.4	4.0	55.3	46.9	8.4	3.96	15.83	11.6	4.0	7.6	13.7%
Id 4.1.C	WBH	20	1.01 (0.88 - 1.28)	0.99 (0.89 - 1.26)	0.79 (0.7 - 1.05)	0%	4.21	37.63	8.93	358.3	14.0	371.3	334.9	36.4	19.61	16.23	53.0	14.0	39.0	10.5%
Id 1.2.C	nil	10	0.84 (0.78 - 0.95)	0.83 (0.75 - 0.97)	0.68 (0.62 - 0.74)	0%	2.23	25.46	11.40	393.4	54.0	450.8	356.1	94.7	37.09	24.06	153.3	54.0	99.3	22.0%
Id 1.1.A	LDH	10	0.78 (0.7 - 0.88)	0.81 (0.75 - 0.96)	0.65 (0.61 - 0.72)	0%	0.98	4.03	4.11	130.0	18.0	141.0	117.4	23.6	4.36	8.06	49.2	18.0	31.2	22.1%
Id 10.1.B	nil	10	0.8 (0.68 - 0.98)	0.8 (0.71 - 0.99)	0.66 (0.58 - 0.75)	0%	2.10	6.84	3.26	107.5	10.5	114.9	95.4	19.6	8.07	19.37	29.8	10.5	19.3	16.8%
Id 1.4.G	LDH	0	0.87 (0.86 - 0.88)	0.86 (0.84 - 0.92)	0.73 (0.68 - 0.74)	0%	0.56	4.79	8.49	217.9	15.0	234.9	204.9	30.0	12.37	13.53	48.5	15.0	33.5	14.2%
Id 1.3.D	nil	0	0.78 (0.74 - 0.86)	0.78 (0.77 - 1.13)	0.64 (0.62 - 0.65)	0%	0.23	1.88	8.11	123.4	18.0	142.2	122.7	19.5	0.31	0.61	47.9	18.0	29.9	21.0%
Id 4.2.E	LDH	0	0.92 (0.81 - 1.09)	0.98 (0.87 - 1.09)	0.74 (0.68 - 0.86)	0%	2.51	11.23	4.47	209.9	17.0	220.6	194.7	25.9	7.20	10.17	32.8	2.0	30.8	13.9%
Id 4.4.F	LDH	0	0.79 (0.74 - 0.86)	0.83 (0.79 - 0.86)	0.64 (0.61 - 0.67)	0%	0.35	4.07	11.57	354.2	36.0	400.7	348.9	51.8	12.17	7.12	53.4	0.0	53.4	13.3%
Id 10.7.E	LDH	0	0.85 (0.77 - 0.91)	0.84 (0.8 - 0.92)	0.69 (0.58 - 0.73)	0%	1.24	10.92	8.79	151.0	16.0	163.0	135.2	27.8	10.22	12.91	45.6	16.0	29.6	18.2%
Id 10.11.I	LDH	0	0.8 (0.8 - 0.83)	0.82 (0.8 - 0.85)	0.63 (0.61 - 0.64)	0%	1.09	8.56	7.82	165.6	16.0	181.7	154.3	27.4	9.80	13.07	44.2	16.0	28.2	15.5%
Id 10.13.K	LDH	0	0.78 (0.75 - 0.82)	0.79 (0.79 - 0.84)	0.6 (0.59 - 0.66)	0%	0.61	3.13	5.15	193.4	20.0	218.1	186.4	31.7	9.73	11.12	54.1	20.0	34.1	15.6%
Id 1.2.B	nil	0	0.82 (0.8 - 0.83)	0.82 (0.79 - 0.87)	0.62 (0.6 - 0.65)	0%	0.12	0.27	2.27	63.4	9.0	73.5	58.1	15.4	5.82	23.27	24.4	9.0	15.4	20.9%
Id 2.1.A	nil	0	0.87 (0.85 - 0.9)	0.88 (0.82 - 0.91)	0.74 (0.72 - 0.77)	0%	0.33	0.59	1.80	67.6	4.5	70.2	61.6	8.6	3.51	14.03	13.5	4.0	9.5	13.5%
Id 4.1.A	WBH	0	0.69 (0.69 - 0.71)	0.72 (0.7 - 0.77)	0.57 (0.56 - 0.62)	0%	0.23	0.91	4.00	106.9	12.0	117.0	102.4	14.6	1.44	2.89	29.0	11.0	18.0	15.4%
Id 4.2.D	WBH	0	0.8 (0.77 - 0.87)	0.81 (0.76 - 0.86)	0.66 (0.61 - 1.03)	0%	0.96	5.44	5.64	240.2	13.0	253.2	226.2	27.0	11.61	11.14	42.8	13.0	29.8	11.8%

ΔAUC = change in the area under the concentration time curve. ΔAUMC = change in the area under the first moment curve. C = citrate. L DH = low-dose heparin. WBH = weight-based heparin. FTI = flux-time integral. [Mg] = magnesium concentration. Mg from Blood = the amount in mmol that left the haemofilter blood path over curve duration and is calculated from Mg-FTI Prefilter − Mg-FTI Postfilter. Postdilution flux used in Patient Loss is not shown but can be calculated as 0.2 L/h × 0.5 mmol/L × curve duration. Mg To Effluent = the amount of Mg entering the effluent above the dialysate concentration. Effluent: Prefilter Flux Ratio = (Mg To Effluent)/(Mg-FTI Prefilter).

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 homoeostasis 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[18] 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[3] 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.

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[19] 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 multicompartment model with two to three extra plasma pools has been described in healthy subjects[20] 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 multicompartment 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.[21,22] 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 supplementation 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.

Author details

Matthew J Brain, Post Fellowship Registrar in Intensive Care[1,2]
Mike Anderson, Senior Intensive Care Specialist[3]
Scott Parkes, Intensive Care and Respiratory Physician[1]
Peter Fowler, Clinical Pharmacist[1]

1 Launceston General Hospital, Launceston, TAS, Australia.
2 The Alfred Hospital, Melbourne, VIC, Australia.
3 Royal Adelaide Hospital, Adelaide, SA, Australia.
Correspondence: matthew.brain@monash.edu

References

1 Reinhart RA, Desbiens NA. Hypomagnesemia in patients entering the ICU. *Crit Care Med* 1985; 13: 506-7.

2 Morimatsu H, Uchino S, Bellomo R, Ronco C. Continuous veno-venous hemodiafiltration or hemofiltration: impact on calcium, phosphate and magnesium concentrations. *Int J Artif Organs* 2002; 25: 512-9.
3 Vaporean ML, Van Stone JC. Dialysate magnesium. *Semin Dial* 1993; 6: 46-51.
4 Ru GJ, Thi M, Hardie D, Carlson RW. Association of hypomagnesemia and mortality in acutely ill medical patients. *Crit Care Med* 1993; 21: 203-9.
5 Soliman HM, Mercan D, Lobo SSM, et al. Development of ionized hypomagnesemia is associated with higher mortality rates. *Crit Care Med* 2003; 31: 1082-7.
6 Safavi M, Honarmand A. Admission hypomagnesemia — impact on mortality or morbidity in critically ill patients. *Middle East J Anesthesiol* 2007; 19: 645-60.
7 RENAL Replacement Therapy Study Investigators. Intensity of continuous renal-replacement therapy in critically Ill patients. *N Engl J Med* 2009; 361: 1627-38.
8 Najafi M, Hamidian R, Haghighat B, et al. Magnesium infusion and postoperative atrial fibrillation: a randomized clinical trial. *Acta Anaesthesiol Taiwan* 2007; 45: 89-94.
9 Toraman F, Karabulut EH, Alhan HC, et al. Magnesium infusion dramatically decreases the incidence of atrial fibrillation after coronary artery bypass grafting. *Ann Thorac Surg* 2001; 72: 1256-61; discussion 1261-2.
10 Tiryakioglu O, Demirtas S, Ari H, et al. Magnesium sulphate and amiodarone prophylaxis for prevention of postoperative arrhythmia in coronary by-pass operations. *J Cardiothorac Surg* 2009; 4: 8.
11 Burgess DC, Kilborn MJ, Keech AC. Interventions for prevention of post-operative atrial fibrillation and its complications after cardiac surgery: a meta-analysis. *Eur Heart J* 2006; 27: 2846.
12 Blum DJ, Ko YH, Pedersen PL. Mitochondrial ATP synthase catalytic mechanism: a novel visual comparative structural approach emphasizes pivotal roles for Mg^{2+} and P-loop residues in making ATP. *Biochemistry* 2012; 51: 1532-46.
13 Llach F. Renal osteodystrophy. In: Jacobs C, Kjellstrand C, Koch K, Winchester J, editors. Replacement of renal function by dialysis. Dordrecht: Kluwer Academic Publishers, 1996.
14 Brain M, Parkes S, Fowler P, et al. Calcium flux in continuous venovenous haemodiafiltration with heparin and citrate anticoagulation. *Crit Care Resusc* 2011; 13: 72-81.
15 White J, Massey L, Gales SK, et al. Blood and urinary magnesium kinetics after oral magnesium supplements. *Clin Ther* 1992; 14: 678-87.
16 Bourne D. Basic pharmacokinetics. Chapter 20. http://www.boomer.org/c/p4/c20/c2001.html (accessed Jun 2012).
17 Gunaratna C. Drug metabolism and pharmacokinetics in drug discovery: a primer for bioanalytical chemists, part I. *Curr Sep* 2000; 19: 17-23.
18 Kozik-Jaromin J, Nier V, et al. Citrate pharmacokinetics and calcium levels during high-flux dialysis with regional citrate anticoagulation. *Nephrol Dial Transplant* 2009; 24: 2244-51.
19 Davey MJ, Teubner D. A randomized controlled trial of magnesium sulfate, in addition to usual care, for rate control in atrial fibrillation. *Ann Emerg Med* 2005; 45: 347-53.
20 Sabatier M, Pont F, Arnaud MJ, Turnlund JR. A compartmental model of magnesium metabolism in healthy men based on two stable isotope tracers. *Am J Physiol Regul Integr Comp Physiol* 2003; 285: R656-63.
21 Huijgen HJ, Soesan M, Sanders R, et al. Magnesium levels in critically ill patients. *Am J Clin Pathol* 2000; 114: 688-95.
22 Mazzaferro S, Barberi S, Scarda A, et al. Ionised and total serum magnesium in renal transplant patients. *J Nephrol* 2002; 15: 275-80.❑