Magnesium sulfate therapy after cardiac surgery: a before-and-after study comparing strategies involving bolus and continuous infusion

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ABSTRACT

Background: Magnesium therapy may reduce the risk of atrial fibrillation after cardiac surgery. However, studies are heterogeneous in relation to dosage and method of delivery and no studies have directly compared the biochemical effect of different delivery strategies.

Aims: We conducted a before-and-after study to compare the effects of two strategies of magnesium delivery after cardiac surgery.

Methods: We conducted a prospective interventional before-and-after study. We enrolled patients admitted to the intensive care unit (ICU) after cardiac surgery and with no history of renal failure. The before period consisted of a single 20 mmol of magnesium sulfate bolus administered over one hour. The after period comprised a 10 mmol magnesium loading dose over one hour followed by a continuous infusion at 3 mmol/h for 12 hours. We measured serum and urine magnesium levels at baseline (T0), at the end of loading dose (T1), 6 (T2) and 12 hours after the intervention (T3).

Results: We enrolled 60 patients (30 in each group) with similar baseline characteristics. In the before period, patients had a higher peak serum magnesium level at T1 (1.88 ± 0.06 *v* 1.59 ± 0.04 mmo/L; $P < 0.001$) compared with the after period. However, at 6 hours, patients in the after period had a significantly higher magnesium level (1.61 ± 0.04 *v* 1.29 ± 0.26 mmol/L; $P < 0.001$) and this level remained higher at 12 hours (1.70 ± 0.05 *v* 1.17 ± 0.02; $P < 0.001$), leading to increased time-weighted magnesaemia ($P < 0.001$). These changes occurred despite a significantly increased urinary magnesium concentration, fractional excretion of magnesium, and magnesium clearance, which paralleled changes in magnesaemia ($P < 0.001$).

Conclusions: The strategy of a 10 mmol magnesium bolus followed by a continuous infusion over 12 hours achieved a more sustained and moderately elevated magnesium concentration in comparison to a single 20 mmol bolus, despite increased urinary losses of magnesium. Further studies are required to assess a more extended continuous infusion.

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Atrial fibrillation (AF) is the most common arrhythmia after cardiac surgery, with an incidence ranging from 20% to 50%.[1,2] Several possible triggers have been proposed as responsible for the development of AF after cardiac surgery, including pericardial inflammation, increased levels of catecholamines, autonomic imbalance, and changes in neurohumoral environment.[2] Its prevention is an important therapeutic target.

Magnesium regulates important cardiac enzymatic and metabolic pathways and stabilises cellular membranes.[3] Reductions in its concentration are associated with formation of free radicals and changes in membrane permeability.[3,4] In this regard, after cardiothoracic surgery, hypomagnesaemia is frequent, possibly due to haemodilution and urinary excretion.[5] These observations have led to the view that magnesium administration in this setting may decrease the risk of arrhythmias in general and AF in particular.[6]

Despite the above considerations, the role of magnesium administration after cardiac surgery remains controversial. Although meta-analyses reported a possible effect on the rate of atrial fibrillation,[7-9] studies of magnesium therapy in cardiac surgery are heterogeneous in relation to dosage, method, timing and duration. They also highlight the potential importance of understanding magnesium pharmacokinetics in this setting and the limited knowledge in relation to it.[10] In particular, no direct comparisons of different approaches to magnesium therapy have yet been performed.

Accordingly, we conducted a before-and-after study to compare the effects of these two strategies of delivery of magnesium after cardiac surgery. We hypothesised that, compared with bolus administration, a strategy of limited bolus followed by continuous infusion of magnesium would deliver greater time-weighted magnesium plasma levels despite increased fractional excretion, clearance, and urinary losses.

Methods

Study design

We conducted a prospective interventional before-and-after study from December 2016 to April 2017 in the

intensive care unit (ICU) of the Austin Hospital, Melbourne, Vic, Australia. The protocol was approved by the Human Research Ethics Committee of the Austin Hospital (HREC No. LNR/15/Austin/306). Written informed consent was obtained from all participants or their legal representatives.

Participants

We enrolled adult elective cardiac surgery patients (age ≥18 years) with a serum magnesium level at ICU admission lower than 1.6 mmol/L. We excluded patients with pre-operative estimated creatinine clearance lower than 60 ml/mL, lack of a dedicated line for intravenous magnesium therapy, and refusal to participate in the study.

Magnesium therapy

Before period

We administered a bolus of 20 mmol of magnesium sulfate (Hospira, Melbourne, Vic, Australia) diluted in 100 mL of normal saline over one hour. No additional boluses were given during the study period of 12 hours.

After period

We administered a loading dose of 10 mmol of magnesium sulfate diluted in 100 mL of normal saline over one hour. After the end of the loading dose, we started a continuous infusion of magnesium sulfate at 3 mmol/h and continued it for 12 hours. For the continuous infusion, we diluted 50 mmol of magnesium sulfate in 50 mL of normal saline. If the serum magnesium concentration was greater than 2 mmol/L at one or 6 hours, during the intervention period, the continuous infusion rate was decreased by 50%.

Measurement of magnesium

In all patients, levels of total magnesium were measured in blood and urine spot samples before the intervention (T0), at the end of the loading dose (T1), 6 hours after the onset of the intervention (T2) and 12 hours after the intervention (T3). Magnesium concentrations were determined photometrically by a colorimetric endpoint method (Roche Cobas 8000 C702 system; Roche Diagnostics, Rotkreuz, Switzerland).

Data collection

We recorded the following variables for all the patients enrolled in the study: age, gender, weight, comorbidities, type of surgery, physiologic variables during the intervention period (urine output and fluid balance), incidence of atrial fibrillation, incidence of other arrhythmias, duration of mechanical ventilation, length of ICU stay, and length of hospital stay. For the pharmacokinetics analysis, we measured the concentration of magnesium, creatinine, sodium and potassium in both serum and urine samples at the four time points.

Renal clearance of magnesium was calculated based on the standard formula (K [clearance] = urinary concentration x urine flow ÷ plasma concentration).[11] Fractional excretion of magnesium (FEMg) was defined as the percentage of filtered magnesium that was excreted in the urine. We calculated it by using the formula: FEMg = 100 x (Urine Mg x Serum Cr) ÷ (Serum Mg x Urine Cr).

The volume of distribution (VD) was estimated as follows: VD = dose of drug ÷ increase in plasma concentration over one hour. We calculated the time-weighted average of serum magnesium concentration by adjusting each measurement by the length of time contributed until the subsequent measurement.

Statistical analyses

Categorical variables were reported as count (percentage). For continuous variables, we used the Shapiro–Wilks test to verify normal distribution, and reported study variables as mean ± standard deviation (SD) or median with interquartile ranges (IQR) accordingly. Two-way repeated measures analysis of variance (ANOVA) was used to compare measures of serum and urinary concentrations of magnesium and creatinine, fractional excretion of magnesium and magnesium clearance at different time points (T0, T1, T2 and T3) between before and after periods. The interaction between period and time was introduced in the ANOVA model to compare the change over time between the two periods. A two-sided $P < 0.05$ was considered statistically significant. Statistical analyses were performed using Stata version 14.2 (StataCorp, College Station, TX, USA).

Results

We studied a convenience sample of 60 patients, with 30 patients in the before period and 30 patients in the after period. Baseline characteristics were similar between both groups (Table 1). The majority of patients underwent coronary artery bypass surgery, with similar duration of cardiopulmonary bypass. Two patients from each group had a pre-existing diagnosis of atrial fibrillation. The groups did not differ regarding the time from ICU admission to enrolment.

Data on the pharmacokinetics of magnesium are reported in Table 2, Figure 1 and Figure 2. Despite an equivalent baseline magnesium concentration, there were significant differences in magnesaemia when comparing patients in the before and after periods ($P < 0.001$). In particular, patients in the before period had higher peak levels at one hour, which were about 20% higher but still within the desired range of between 1.5 to 2.0 mmol/L. However, at 6 hours, their levels were only just above baseline, while patients in the after period maintained

Table 1. Baseline characteristics of study patients

Demographic characteristics	Before period (*n* = 30)	After period (*n* = 30)	*P*
Age, mean (SD)	66.03 ± 1.96	61.22 ± 1.94	0.087
Female gender	6 (20.0%)	6 (20.0%)	1.000
Body weight, mean (SD)	86.02 ± 3.12	86.15 ± 2.80	0.976
Comorbidities			
Hypertension	21 (70.0%)	16 (53.3%)	0.184
Ischaemic heart disease	23 (76.7%)	20 (66.7%)	0.390
Hyperlipidaemia	19 (63.3%)	14 (46.7%)	0.194
Diabetes mellitus	11 (36.7%)	9 (30.0%)	0.584
Chronic liver disease	2 (6.7%)	2 (6.7%)	1.000
Atrial fibrillation	2 (6.7%)	2 (6.7%)	1.000
Type of surgery			0.181
Coronary artery bypass surgery	20 (66.7%)	18 (60.0%)	
Valve replacement	4 (13.3%)	6 (20.0%)	
CABG + valve surgery	4 (13.3%)	2 (6.7%)	
Aorta surgery	0 (0.0%)	4 (13.3%)	
Myectomy	1 (3.3%)	0 (0.0%)	
Other	1 (3.3%)	0 (0.0%)	
Surgery characteristics			
CPB time (min), mean (SD)	130.07 ± 13.40	124.4 ± 8.28	0.4746
Cross-clamping time (min), mean (SD)	94.73 ± 7.52	92.48 ± 7.04	0.6637
Characteristics at enrolment			
Cardiac index, mean (SD)	2.74 ± 0.10	2.76 ± 0.13	0.8629
Inotropic support			
▸ Noradrenaline	11 (36.7%)	7 (23.4%)	0.260
▸ Adrenaline	3 (10.0%)	0 (0.0%)	0.237
▸ Milrinone	3 (10.0%)	8 (26.7%)	0.090
Cardiac rhythm			0.593
▸ Sinus	18 (0.6%)	18 (0.6%)	
▸ Paced	11 (36.7%)	12 (0.4%)	
▸ Atrial fibrillation	1 (3.3%)	0 (0.0%)	
Ventilation			0.403
▸ Spontaneous breathing	7 (23.3%)	4 (13.3%)	
▸ Assisted ventilation	3 (10%)	6 (20%)	
▸ Controlled ventilation	20 (66.7%)	20 (66.7%)	
Time from ICU admission to enrolment (hours), median (IQR)	3.08 (1.92–5.62)	2.92 (2.27–4.07)	0.750

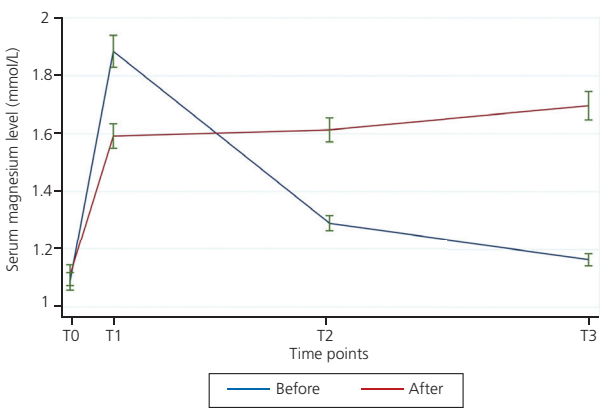
CABG = coronary artery bypass graft. CI = confidence interval. CPB = cardiopulmonary bypass. ICU = intensive care unit. IQR = interquartile range. SD = standard deviation.

Table 2. Pharmacokinetic measurements during bolus or continuous infusion magnesium therapy

		T0	T1	T2	T3	*P*
Serum magnesium (mmol/L), mean (SD)	Before	1.08 ± 0.03	1.88 ± 0.06	1.29 ± 0.26	1.17 ± 0.02	< 0.001
	After	1.10 ± 0.04	1.59 ± 0.04	1.61 ± 0.04	1.70 ± 0.05	
Serum creatinine (µmol/L), mean (SD)	Before	73.43 ± 4.53	75.66 ± 4.57	80.77 ± 4.62	83.17 ± 5.31	0.998
	After	72.77 ± 2.82	74.67 ± 3.01	80.43 ± 3.19	83.47 ± 3.18	
Urinary magnesium (mmol/L), mean (SD)	Before	11.49 ± 1.77	27.36 ± 4.19	25.16 ± 2.26	16.82 ± 2.07	< 0.001
	After	10.75 ± 1.62	18.84 ± 2.08	40.27 ± 3.08	50.17 ± 3.55	
Urinary creatinine (mmol/L), mean (SD)	Before	7.05 ± 1.00	7.74 ± 1.00	10.74 ± 0.97	12.31 ± 0.80	0.864
	After	6.14 ± 0.85	7.82 ± 0.86	10.16 ± 0.93	11.79 ± 0.87	
Fractional excretion of magnesium (%), mean (SD)	Before	13.51% ± 1.69%	16.16% ± 2.01%	15.75% ± 1.49%	10.52% ± 1.68%	< 0.001
	After	13.14% ± 1.52%	14.42% ± 1.66%	20.95% ± 1.30%	21.87% ± 1.27%	
Magnesium clearance (mL/min), mean (SD)	Before	17.78 ± 2.95	19.66 ± 3.21	22.53 ± 2.60	15.98 ± 4.08	0.006
	After	13.34 ± 2.43	14.33 ± 1.32	28.07 ± 3.48	27.32 ± 2.40	
Time-weighted average of serum magnesium level (mmol/L), mean (SD)	Before	1.38 ± 0.03				< 0.001
	After	1.61 ± 0.04				
Magnesium given per kg (mmol/kg), median (IQR)	Before	0.29 (0.27–0.34)				< 0.001
	After	0.78 (0.66–0.86)				
Volume distribution (L), median (IQR)	Before	26.31 (20.83–31.25)				0.404
	After	26.81 (23.21–30.23)				
Volume distribution per kg (L/kg), median (IQR)	Before	0.30 (0.24–0.33)				0.243
	After	0.32 (0.29–0.38)				

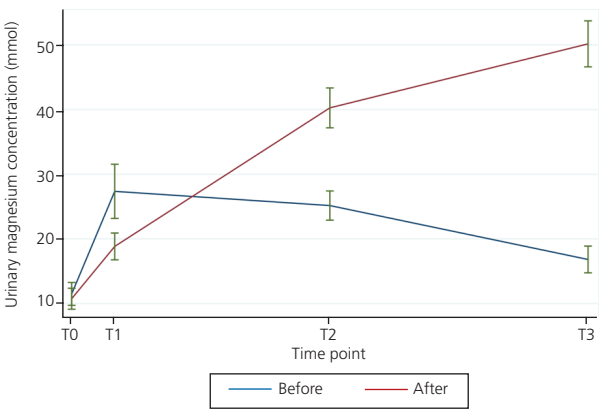
CI = confidence interval. IQR = interquartile range. SD = standard deviation. T0 = baseline. T1 = end of loading dose. T2 = 6 hours after the intervention. T3 = 12 hours after the intervention.

Figure 1. Serum magnesium concentration in mmol/L during the period of 12 hours



T0 = baseline. T1 = end of loading dose. T2 = 6 hours after the intervention. T3 = 12 hours after the intervention.

Figure 2. Urinary magnesium concentration in mmol/L during the period of 12 hours



T0 = baseline. T1 = end of loading dose. T2 = 6 hours after the intervention. T3 = 12 hours after the intervention.

magnesium levels, which were almost identical to those seen at one hour and which remained stable at 12 hours. In contrast, by 12 hours, patients in the before period had magnesium levels that were indistinguishable from baseline. Accordingly, the time-weighted average of serum magnesium concentration in patients in the after period was greater in comparison to the patients in the before period (1.61 ± 0.04 *v* 1.38 ± 0.03, $P < 0.001$).

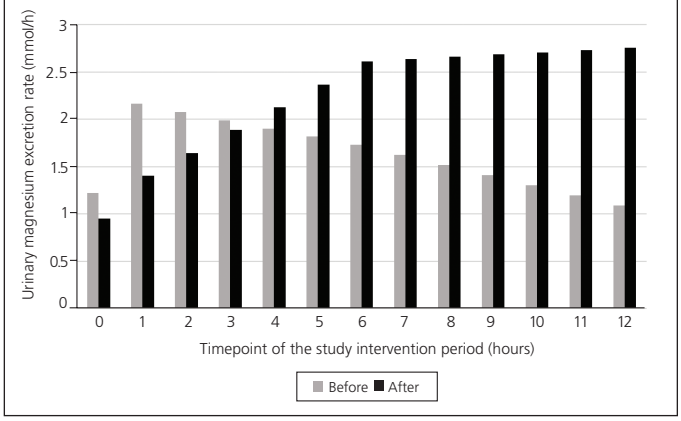
The urinary magnesium concentrations (mmol/L) increased over time in both groups ($P < 0.001$) (Figure 3). However, patients in the after period had a lower fractional excretion of magnesium and lower magnesium clearance at T1 compared with patients in the before period. In contrast, T2 and T3, urinary losses, fractional excretion and clearance of magnesium were greater and more sustained with the onset of continuous infusion. By 12 hours, in the before period, total estimated magnesium losses represented 99.1% of the 20 mmol given. In the after period, they represented 65.7% of the 43 mmol of magnesium given.

The changes in key haemodynamic variables for a period of 12 hours after the commencement of the intervention are shown in Table 3. The groups had similar measurements of mean arterial pressure and heart rate at all time points; however, patients in the before period received a higher dose of noradrenaline in comparison to patients in the after period ($P = 0.03$). We found no side effects or complications associated with the intervention in both groups.

Associated clinical outcomes

The duration of pacemaker dependency, mechanical ventilation, ICU length of stay and hospital length of stay were similar (Table 4). Atrial fibrillation was newly diagnosed in the ICU in five patients (16.7%) in the bolus group and three patients (10%) in the continuous infusion group.

Figure 3. Time-weighted average of urinary magnesium excretion rate in mmol/h



Discussion

Key findings

We conducted a prospective interventional before-and-after study in adult elective cardiac surgery patients to compare the effects of a single 20 mmol bolus of magnesium sulfate with a 10 mmol bolus followed by a continuous infusion of 3 mmol/h for 12 hours. We found that patients in the bolus group had a greater serum magnesium level at the end of the loading dose; however, such levels rapidly decreased while patients

Table 3. Haemodynamic variables and noradrenaline requirement during magnesium therapy*

		T0	T1	T2	T3	*P*
Mean arterial pressure (mmHg)	Before	74.77 (72.42–77.12)	72.83 (69.63–76.04)	75.6 (72.70–78.50)	78.7 (75.37–82.03)	0.689
	After	77.4 (73.07–81.73)	74.77 (71.53–78.01)	77.9 (74.12–81.68)	78.4 (74.90–81.90)	
Heart rate (bpm)	Before	83.5 (79.91–87.09)	82.93 (79.95–85.92)	83.33 (79.80–86.87)	85.3 (81.50–89.10)	0.099
	After	86.67 (82.44–90.90)	85.7 (81.70–89.70)	87.53 (83.45–91.61)	84.03 (80.71–87.36)	
Noradrenaline dose (µg/kg/min)	Before	0.017 (0.007–0.026)	0.017 (0.007–0.026)	0.015 (0.005–0.024)	0.013 (0.001–0.024)	0.027
	After	0.009 (0.002–0.016)	0.009 (0.002–0.016)	0.007 (0.000–0.015)	0.004 (0.001–0.009)	

bpm = beats per minute. T0 = baseline. T1 = end of loading dose. T2 = 6 hours after the intervention. T3 = 12 hours after the intervention. * Before refers to the period when bolus therapy was administered. After refers to the period after the introduction of half-dose bolus therapy followed by continuous infusion. Data are expressed as means with 95% confidence intervals.

Table 4. Incidence of clinical outcomes

Outcomes	Before (*n* = 30)	After (*n* = 30)	*P*
Newly diagnosed AF in the ICU	5 (16.7%)	3 (10.0%)	0.448
Newly diagnosed AF in 72 hours	9 (30.0%)	8 (26.7%)	0.774
Newly diagnosed AF in 96 hours	13 (43.3%)	9 (30.0%)	0.284
Newly diagnosed AF in hospital	16 (53.3%)	14 (46.7%)	0.606
Other arrhythmias*	3 (10.0%)	4 (13.3%)	0.688
Pacemaker dependency (hours), median (IQR)	3.5 (0–25)	2.5 (0–16)	0.595
Duration of mechanical ventilation, (hours), median (IQR)	8.6 (6–13)	7.5 (6.0–11.2)	0.673
ICU length of stay (hours), median (IQR)	42.9 (22–70)	25.5 (22.3–47.5)	0.387
Hospital length of stay (days), median (IQR)	6.0 (5.0–8.0)	6.2 (5.8–10.0)	0.487

AF = atrial fibrillation. ICU = intensive care unit. IQR = interquartile range. * Episode of ventricular tachycardia or junctional rhythm.

with continuous infusion achieved sustained moderate hypermagnesaemia and greater time-weighted magnesium plasma levels during the entire observation period, despite increased urinary losses.

Relationship to previous studies

No previous studies have directly compared different strategies of magnesium administration in terms of their pharmacokinetic profile after cardiothoracic surgery.[12] A meta-analysis of pooled studies evaluated methods of magnesium delivery after cardiac surgery and suggested different effects on the rate of AF for continuous versus bolus delivery. However, protocols were heterogeneous for dose, timing and duration, and all investigations were at high risk of type I error.[13]

In paediatric patients with status asthmaticus, a small cohort study investigated the pharmacokinetics of a bolus of magnesium followed by a continuous infusion for 4 hours.[14] This strategy resulted in a similar distribution of serum magnesium levels to the after period in our study. In addition, no major safety issues were reported. However, despite such observations, surveys report that physicians tend to express safety concerns over the prolonged administration of magnesium therapy.[15,16]

In patients with pre-eclampsia or eclampsia, magnesium sulfate has been used for decades for the prevention and treatment of convulsion, but there are scarce pharmacokinetic data. A meta-analysis showed that maintenance infusions of magnesium were associated with fewer fluctuations during the period of administration, while intermittent bolus therapy produced a spike in magnesium concentration that fell very rapidly after 2 hours.[17] These findings are consistent with the pharmacokinetic profile of our patients. Our population had no renal impairment and their serum and urinary magnesium concentrations followed a similar pattern, which is consistent with previous reports.[18,19] Also in keeping with our findings, another study reported that an abrupt rise in the serum magnesium levels resulted in much of the infused magnesium being eliminated in the urine.[20]

Implications of study findings

Our study implies that the strategy of a smaller bolus followed by a continuous infusion of magnesium, leads to a more sustained and stable target total magnesium level in comparison to a single larger bolus. It also suggests that a greater time-weighted average in the moderate hypermagnesaemia can be achieved with continuous infusion in patients who had cardiac surgery. Finally, it indicates that, despite the inevitable increase in urinary losses, it is feasible to achieve and maintain a stable serum magnesium concentration within a moderate supranormal range, but far below from the levels associated with neuromuscular weakness.

Strengths of the study

To our knowledge, this is the first study directly comparing the pharmacokinetics of two different strategies of

magnesium administration after cardiothoracic surgery. Our findings are robust, as demonstrated by the small standard deviations of the measurements, and could be potentially relevant to magnesium administration for all patients with normal renal function undergoing cardiac surgery. Finally, our study represents an initial step toward understanding the pharmacokinetic properties of magnesium sulfate in cardiac surgery and toward enabling trials aimed at optimising magnesium therapy and achieving a possible decrease in atrial fibrillation.

Our study also carries some limitations. It is only a pharmacokinetic study and is not powered to detect differences in clinical outcomes (eg, arrhythmias). However, it provides a comprehensive comparative assessment of two relevant approaches to magnesium therapy and delivers information, which is essential to optimising the design of future randomised controlled trials. Second, our study was conducted in a single centre, with the inherent limitations of such studies. Nevertheless, our laboratory measurements were according to standard methodology and the patients were typical patients of elective cardiac surgery in high income countries, which lends a degree of external validity of our findings. Third, we did not measure ionised magnesium concentration in our population. However, a previous report showed poor agreement between serum and ionised magnesium measurements in critically ill patients,[21] and a systematic review found that almost all studies so far have used total magnesium levels to guide therapy. Fourth, we only studied a 12-hour period. However, our unit protocol calls for 20 mmol of intravenous magnesium twice daily after cardiac surgery, and the next 20 mmol administration would have likely replicated the findings of the first 12 hours. Finally, we excluded patients with renal failure because of concerns about magnesium accumulation. Thus, our findings cannot apply to such patients.

Conclusion

Our study showed that, in patients who had cardiothoracic surgery, the strategy of a 10 mmol bolus of magnesium followed by a continuous infusion over 12 hours delivered a sustained and moderately elevated magnesium concentration as targeted and greater time-weighted magnesium plasma levels than a single 20 mmol bolus. Further prospective studies are now required to assess whether an extended duration of the continuous infusion strategy can continue to deliver high but stable magnesium levels, remain safe and reduce the risk of AF during ICU stay.

Competing interests

None declared.

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