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Does the prophylactic administration of magnesium sulphate to patients undergoing thoracotomy prevent postoperative supraventricular arrhythmias? A randomized controlled trial

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Editor's key points

- Supraventricular arrhythmias (SVA) are common after thoracic surgery and magnesium may be of use in prevention.
- Randomized controlled trial (magnesium/placebo) of 200 patients undergoing a variety of thoracic surgery.
- Overall, magnesium did not reduce the incidence of SVA.
- Magnesium was effective in the subgroup undergoing pneumonectomy.

Background. Supraventricular arrhythmias (SVA) are common after thoracic surgery and are associated with increased morbidity and mortality. This prospective, randomized, double-blind, placebo-controlled trial examined the effects of perioperative magnesium on the development of postoperative SVA.

Methods. Two hundred patients undergoing thoracotomy for lobectomy, bi-lobectomy, pneumonectomy, or oesophagectomy were recruited and randomly allocated into two groups. The treatment group received magnesium (5 g daily) intraoperatively, and on days 1 and 2 after operation, the control group received placebo. The primary outcome of the study was the development of SVA within the first 5 days after operation.

Results. There were 100 patients in each arm of the study, with one withdrawal and three lost to follow-up in the treatment group and four withdrawals in the control group. Ninety-six patients received magnesium and 96 received placebo. There was no difference in the incidence of SVA between the treatment and control groups, 16.7% (16/96) *vs* 25% (24/96), $P=0.16$. In the predefined subgroup analysis, patients at highest risk of arrhythmias (those undergoing pneumonectomy) had a significant reduction in the frequency of SVA, 11.1% (2/18) *vs* 52.9% (9/17), $P=0.008$. There were no differences in hospital length of stay or mortality. Patients receiving i.v. magnesium experienced a higher frequency of minor side-effects (stinging at injection site). The treatment was otherwise well tolerated.

Conclusions. Overall, prophylactic magnesium did not reduce the incidence of SVA in patients undergoing thoracotomy. However, it reduced the incidence of SVA in the high-risk cohort of patients undergoing pneumonectomy. (ISRCTN22028180.)

Keywords: complications, arrhythmia; ions, magnesium; prevention; surgery, non-cardiac; surgery, thoracic

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Cardiac arrhythmia is a common complication associated with lung resection and can lead to significant morbidity, including the increased risk of thrombo-embolism, stroke, myocardial infarction, and heart failure. Currently, the emphasis is on treatment after an arrhythmia has become established. The most common arrhythmias that occur in patients who have undergone lung resection are supraventricular arrhythmias (SVA) and ~90% of these are atrial fibrillation (AF). The incidence of SVA varies and is dependent on the degree of lung resection.[1–9] With a wedge resection, the incidence is <5%, which increases to 12–20% with a lobectomy and increases up to 37% with a pneumonectomy. However, thoracotomy without lung resection, as in oesophagectomy, the incidence varies between 13% and 32% and this may be due to pericardial disruption. This is supported by the observation that intrapericardial pneumonectomies can have an incidence as high as 43%.[3 10 11] Postoperative stay is longer and the occurrence of other complications is higher for patients who develop SVA.[2 5 12] The risk of death is increased from 3% in those without SVA to 8–17% in patients who develop recurrent or persistent SVA after operation.[2 4 5]

Right heart dilatation has traditionally been regarded as a risk factor for the development of postoperative SVA. However, echocardiographic studies in patients undergoing lung resection suggest an association between tricuspid regurgitation velocity and postoperative SVA development rather than right atrial or ventricular enlargement.[2] During thoracic resection, right-sided heart pressures increase due to a reduction in pulmonary vascular bed volume and

reactive pulmonary vasoconstriction.[13] Therefore, the reduction in right heart afterload may have important prognostic significance in the reduction in SVA development after operation.

Magnesium sulphate is often used as an anti-arrhythmic agent in the critical care setting and during cardiac surgery. It reduces the rate of the sino-atrial node impulses and increases the refractory period of the atrioventricular node.[14] It may also reduce the afterload of the right heart through vasodilation. These properties of magnesium sulphate form the basis for its potential use as a prophylactic agent in reducing the incidence of SVA post-thoracotomy.

This study was a prospective, randomized, double-blind, placebo-controlled, single-centre trial to test the hypothesis that the prophylactic administration of a total of 15 g (in three divided doses of 5 g daily) of magnesium sulphate during the perioperative period would reduce the incidence of SVA in patients undergoing thoracotomies for lung resection or oesophagectomy. The primary outcome was the incidence of SVA based on Holter monitoring/ECG recordings in the first 5 days after operation or before discharge if earlier. Secondary outcomes were the incidence of SVA according to the type of operation, length of hospital stay (days), inpatient and 30 day mortality, frequency of adverse events, and compliance with the intervention.

Methods

The study was approved by the South Birmingham Research Ethics Committee (reference 05/Q2707/1), the Research and Development Department at the Heart of England NHS Foundation Trust and MHRA. The study was registered with the international standard randomized controlled trial register, ISRCTN22028180.

Consecutive patients undergoing thoracotomy for lung resection or oesophagectomy were screened between June 2006 and 2008, against the set inclusion/exclusion criteria and invited to take part in the study. The inclusion criteria were adult ($\geq$18 yr of age) patients who were to undergo elective thoracotomy for lobectomy, bi-lobectomy, pneumonectomy, or oesophagectomy. The risk of magnesium toxicity through accumulation in renal failure influenced the exclusion criteria. The exclusion criteria include a serum creatinine of $>$130 μmol litre^{-1}, liver failure (alkaline phosphatase $>$180 IU litre^{-1}, aspartate transaminase $>$35 IU litre^{-1}, and bilirubin $>$25 μmol litre^{-1}), pre-existing cardiac arrhythmia, long-term treatment for an arrhythmia, long-term treatment with nifedipine or aminoglycosides, known hypersensitivity to magnesium sulphate, and preoperative magnesium level $\geq$1.2 mmol litre^{-1}.

After obtaining written, informed consent, participants were randomly allocated to numbered treatment packs. The randomization sequence was generated in 10 blocks of 20 in a 1:1 ratio of active drug or placebo (www.randomization.com). Identical packs were prepared by the trial pharmacist and contained either 5 g i.v. magnesium sulphate suspended in 100 ml of 0.9% saline or placebo (100 ml of 0.9% saline) for 3 days. The first dose was administered intraoperatively with the second and third doses given on days 1 and 2 after operation. The study would be stopped if there were any reasons to indicate serious adverse effects related to a trial infusion.

During the course of the study, stinging during peripheral i.v. administration of the trial infusion was observed. In some cases, the participants found it to be intolerable and declined further intervention. Half-way through the study, approval for a substantial amendment was sought and gained from the ethics committee and the MHRA, for the trial infusion to be diluted in 250 ml of 0.9% saline rather than the 100 ml. The first 100 participants received trial infusion volume of 100 ml daily and the second 100 participants received 250 ml volume daily.

All patients were anaesthetized by one of the thoracic consultant anaesthetists. A portable, battery-powered, three-lead Holter monitor (Del Mar Reynolds, Hertford, UK) was attached to patients post-induction of anaesthesia which would remain so for 5 days or patient discharge (whichever was earlier). Patients in the interventional arm received 5 g of magnesium sulphate i.v. during the intraoperative period and then 5 g daily on days 1 and 2 after operation. Patients in the placebo arm of the study received equal volume of 0.9% saline intraoperatively, days 1 and 2 after operation. Both groups of patients had their blood urea, creatinine, sodium, potassium, calcium, and magnesium levels measured before operation and on days 1, 2, and 3 after operation. If the plasma level of magnesium was $>$1.2 mmol litre^{-1}, then the infusion (placebo or magnesium sulphate) was not administered. Magnesium sulphate was a possible treatment choice for the clinical staff for SVA development if indicated, provided the serum magnesium level was $<$1.2 mmol litre^{-1}. Patients, clinical staff, the investigators, and the cardiac physiologist reporting the Holter data were blinded to the treatment allocation.

Ambulatory two-channel electrocardiography was carried out using a portable, battery-operated, 7 day digital ECG recorder (Del Mar Reynolds). Three disposable Ag/Ag–Cl electrodes were positioned at midsternum, right and left anterior auxiliary lines over seventh intercostal spaces (advised standard positions) to maximize the visibility of P-wave signals. Electrode positions were modified pre- and post-thoracotomy.

Data were analysed by using Del Mar Reynolds Life screen analysing software. Data were reviewed to eliminate any artifacts. SVA was defined as AF, atrial flutter, and junctional tachycardia (atrioventricular nodal re-entrant tachycardia and atrioventricular re-entrant tachycardia) and event duration was measured with digital calliper. Episodes of 30 min duration or longer were marked as significant.

A prospective, observational study was conducted (n=98) between August and December 2003 to evaluate the local incidence of dysrhythmias in this patient population. This found an incidence in SVA of 25.5%. Sample size estimation showed that to detect a 15% reduction in the incidence of SVA (from a baseline incidence of 25%) with 80% power at a significance level of 0.05 would require 100 patients in each arm.

Data were tested for normality using Shapiro–Wilk's *W*-test. The quantitative variables were analysed using an unpaired *t*-test and the Mann–Whitney *U*-test for normally and non-normally distributed data, respectively. The categorical data were analysed by the χ^2 test, Fisher's exact test, and the Mann–Whitney *U*-test. Data were presented as median (inter-quartile range), mean (SD), or as number (%). A *P*-value of <0.05 was considered statistically significant. Analyses were performed using SPSS Statistics version 17.0 software (SPSS Inc., Chicago, IL, USA).

Results

There were 100 participants recruited to each group (Fig. 1). One was consented but met the exclusion criteria before surgery and three participants withdrew from the study in the interventional arm (one transferred to another hospital on day 1, one participant found the Holter monitor uncomfortable, and the third participant did not want to take part any further). Four participants in the placebo arm of the study did not undergo thoracotomy and were excluded. There were no mini-thoracotomy or video-assisted thoracoscopy procedures included within the study. There were 96 participants in each of the treatment and control groups for analyses (Tables 1 and 2).

There was no significant difference in the development of SVA between the magnesium-treated and placebo arms; 16 of 96 (16.7%) and 24 of 96 (25.0%), respectively, $P=0.16$ [odds ratio 0.6, 95% confidence interval (CI) 0.30–1.22].

The incidences of SVA by surgical procedure (Table 3) show that patients undergoing pneumonectomy had a reduced incidence of SVA in the magnesium arm compared with the placebo arm, nine of 17 (52.9%) and two of 18 (11.1%), respectively, $P=0.008$. There were five and six intrapericardial pneumonectomies in the treatment and control groups, respectively. The most common day for arrhythmia occurrence was the second day after operation for both groups and was predominately AF.

There was no significant difference between the control and treatment group patients with regard to the duration of hospital stay; 9.1 (SD 8.5) and 8.0 (5.5) days, respectively, $P=0.28$. No difference was observed between the two arms of the study in respect to inpatient mortality [one patient in the placebo group *vs* four in the magnesium group with pneumonia, acute respiratory distress syndrome (ARDS) as causes of death, $P=0.21$] and 30 day mortality (two in the control group *vs* five in the treatment group, $P=0.44$).

Compliance was defined as all three infusions given in accordance with the study protocol (Table 4). All patients had their intraoperative dose; however, problems were encountered with the administration of the second and third infusions resulting in significant protocol non-compliance in the treatment group. The compliance rates for the control and treatment groups were 89 of 96 (92.7%) *vs* 69 of 96 (71.9%), respectively, $P<0.001$. In the treatment group, 20 patients reported stinging/ache at the peripheral site; however, no major side-effects were observed with the i.v. magnesium sulphate intervention (Table 4).

There was an amendment to the protocol at the 100th patient resulting in the magnesium sulphate being diluted into 250 ml of 0.9% saline. This reduced the non-compliance rate secondary to stinging, ache, or nausea from nine of 12 in the first 100 patients to five of 10 in the second 100 patients. Out of the protocol non-compliant participants, three of 27 in the interventional arm and one of seven participants in the control group developed SVA after operation.

Magnesium sulphate for the treatment of SVA was given in nine and 12 patients in the control group. Eight of these 12 patients received magnesium sulphate for the treatment of SVA and four had low plasma magnesium levels which were corrected. The mean total dose of magnesium sulphate given in the interventional arm of the study was 13.4 (3.2) g compared with 0.9 (3.2) g in the placebo arm.

There was no difference in the plasma levels of magnesium, potassium and calcium between the interventional and placebo arms of the study before operation. There was a difference in the magnesium plasma levels on each of the 3 postoperative days, $P<0.001$, and calcium levels on days 1 and 2 after operation, $P<0.001$. No difference was observed in the plasma potassium levels after operation (Fig. 2).

Discussion

The two groups of participants were well matched; however, there were more wedge resections and oesophagectomies in the control group than in the treatment group. There was no significant difference in the primary outcome between the treatment and control groups. However, a significant reduction in the incidence of SVA was seen in the high-risk cohort group undergoing pneumonectomy in the interventional arm of the study.

Given the frequency and significance of SVA after thoracic surgery, a number of different strategies have been investigated in an attempt to prevent SVA in this patient population. Digoxin is commonly used for rate control in patients with AF. However, in five prospective, open, controlled trials, prophylactic treatment with digoxin was associated with a trend towards increased SVA in the digoxin treated arm in four of the studies.[11 15–18] The prophylactic use of amiodarone during lung resection surgery was abandoned due to the significant development of ARDS in patients in the amiodarone arm.[19] A systematic review of pharmacological prophylaxis for postoperative SVA in thoracic surgery identified that both β-adrenergic antagonists (relative risk 0.4, 95% CI 0.17–0.95) and calcium channel antagonists (relative risk 0.5, 95% CI 0.34–0.73) were effective in preventing SVA.[13 20–24] However, β-adrenergic antagonists were poorly tolerated with an increased risk of severe pulmonary complications (relative risk 2.15, 95% CI 0.74–6.23) and calcium channel antagonists were associated with increased risk of hypotension and bradycardia.[21] In this study, there were no reported serious adverse events associated with the i.v.

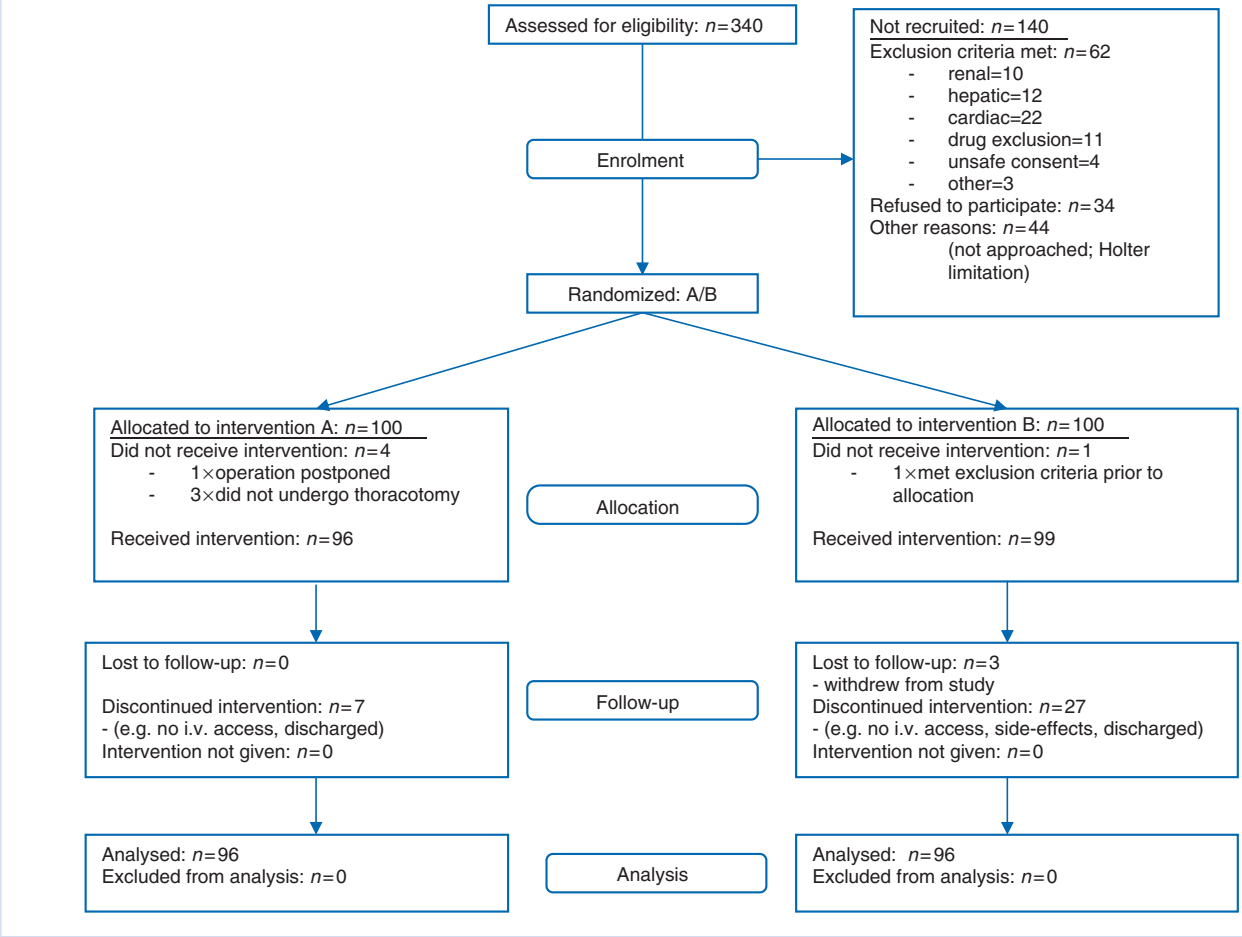

Fig 1 The consort flow diagram.

administration of magnesium sulphate in this study. However, the minor and intermediate side-effects proved to be intolerable in 16 of 24 cases in the interventional arm. These may be reduced by dilution or rate reduction in i.v. magnesium sulphate administration.

To date, there has only been one prospective study investigating the preventative effect of magnesium on post-thoracotomy SVA when compared with a control group. This demonstrated a significant reduction in the incidence of SVA after operation in patients who underwent thoracotomy and received prophylactic administration of magnesium compared with the control group.[9] The study was a prospective, randomized, open, placebo controlled trial. The results showed a statistically significant reduction in the incidence of SVA from 26.7% in the control group to 10.7% in the magnesium group.

However, there were differences between this trial and our study. The dosing regimen differed and used 2 g magnesium sulphate i.v. in 100 ml of 5% dextrose over 20 min at thoracotomy, followed by a further 2 g after 6 h.[9] Both continuous ECG monitoring (for up to 48 h) and 12-lead ECG recordings were used as a means of detecting SVA as opposed to 5 day continuous Holter monitoring. It was an open study as opposed to being double-blinded. One hundred and ninety-four patients were studied with 101 in the control group and 93 in the magnesium group, and there were more pneumonectomies in the control group than in the magnesium group (23 of 18), more lobectomies in the control group (51/40), and fewer wedge resections in the control group (10/15).[9]

There are a number of possible reasons for the contrasting primary outcome results between the two studies. There may be no biological effect of magnesium sulphate in reducing the incidence of SVA post-thoracotomy or there is the possibility of a type II error in this trial. Also, for consideration is the significant under compliance in the interventional arm of this study. However, the positive result observed by Terzi and colleagues may have been a chance finding in view of the dose of magnesium sulphate administered was much lower when compared with this.

There were limitations with this study. Although there were no major side-effects of magnesium sulphate observed, full protocol compliance was significantly less in the treatment group than in the control group due to predominantly stinging during administration. Despite designing the study as double blinded, the presence of stinging resulted in

Table 1 Patient characteristics. Values are shown as median (inter-quartile range), mean (SD), or as number (%)

	Control group ($n=96$)	Treatment group ($n=96$)	*P*-value
Age (yr) (median)	64.0 (56–71)	65.5 (58–70)	0.70
Male (*n*)	52 (54.2)	57 (59.4)	0.47
ASA (*n*)			
I	3 (3.1)	4 (4.2)	0.11
II	66 (68.8)	53 (55.2)	
III	27 (28.1)	39 (40.6)	
Co-morbidities (*n*)			
Hypertension	38 (39.6)	35 (36.5)	0.66
IHD	15 (15.6)	17 (17.7)	0.70
COPD	21 (21.9)	18 (18.8)	0.59
Diabetes mellitus	7 (7.3)	8 (8.3)	0.79
Thyroid disorder	8 (8.3)	5 (5.2)	0.39
Drug treatment (*n*)			
β-Receptor block	10 (10.4)	11 (11.5)	0.82
Ca channel block	14 (14.6)	11 (11.5)	0.52
ACE-inhibitors	14 (14.6)	16 (16.7)	0.69
Angiotensin receptor antagonist	4 (4.2)	8 (8.3)	0.23
Diuretics	19 (19.8)	15 (15.6)	0.45
Statins	31 (32.3)	31 (32.3)	1.00
Preop oxygen saturations (%) (mean)	97.1 (1.3)	97.1 (1.5)	0.86
FEV1 (mean)	2.10 (0.7)	2.24 (0.7)	0.13
FVC (mean)	3.19 (0.9)	3.26 (0.9)	0.64
BMI (mean)	25.9 (5.2)	26.8 (5.0)	0.28
Preop magnesium (mmol $litre^{-1}$) (mean)	0.86 (0.1)	0.88 (0.1)	0.10
Preop potassium (mmol $litre^{-1}$) (mean)	4.5 (0.4)	4.5 (0.4)	0.66
Preop calcium (mmol $litre^{-1}$) (mean)	2.28 (0.1)	2.27 (0.1)	0.48
Duration of surgery (h:min) (mean)	2:41 (1:07)	2:25 (0:54)	0.06
Epidural analgesia (*n*)	46 (47.9)	38 (39.6)	0.31
Surgical intervention (*n*)			
Right	54 (56.3)	50 (52.1)	
Left	42 (43.8)	46 (47.9)	0.56
Pneumonectomy	17 (17.7)	18 (18.8)	0.85
Right	4 (23.5)	7 (38.9)	
Left	13 (76.5)	11 (61.1)	0.33
Bi-lobectomy	8 (8.3)	5 (5.2)	0.39
Lobectomy	49 (51.0)	46 (47.9)	0.67
Wedge/segmentectomy/partial lobe resection	11 (11.5)	18 (18.8)	0.16
Oesophagectomy	5 (5.2)	0 (0)	
Inoperable	4 (4.2)	6 (6.3)	0.52
Other (chest wall, bronchial resection)	2 (2.1)	3 (3.1)	1.00

Table 2 Patient characteristics for pneumonectomy subgroup. Values are shown as median (inter-quartile range), mean (SD) or as number (%)

	Control group ($n=17$)	Treatment group ($n=18$)	*P*-value
Age (yr) (median)	61 (52–67)	65.5 (57–69)	0.34
Male (*n*)	14 (82.4)	13 (72.2)	0.69
ASA (*n*)			
I	0 (0)	0 (0)	0.20
II	11 (64.7)	7 (38.9)	
III	6 (35.3)	11 (61.1)	
Co-morbidities (*n*)			
Hypertension	5 (29.4)	8 (44.4)	0.36
IHD	2 (11.8)	5 (27.8)	0.40
COPD	7 (41.2)	3 (16.7)	0.15
Diabetes mellitus	2 (11.8)	2 (11.1)	1.00
Thyroid disorder	1 (5.9)	0 (0)	
Drug treatment (*n*)			
β-Receptor block	1 (5.9)	2 (11.1)	1.00
Ca channel block	2 (11.8)	3 (16.7)	1.00
ACE-inhibitors	2 (11.8)	5 (27.8)	0.40
Angiotensin receptor antagonist	2 (11.8)	2 (11.1)	1.00
Diuretics	1 (5.9)	2 (11.1)	1.00
Statins	6 (35.3)	8 (44.4)	0.58
Preop oxygen saturations (%) (mean)	97.4 (1.1)	96.9 (1.0)	0.10
FEV1 (mean)	2.30 (0.65)	2.23 (0.46)	0.94
FVC (mean)	3.56 (0.85)	3.32 (0.68)	0.38
BMI (mean)	27.2 (4.86)	27.9 (4.44)	0.68
Preop magnesium (mmol $litre^{-1}$) (mean)	0.86 (0.08)	0.87 (0.10)	0.70
Preop potassium (mmol $litre^{-1}$) (mean)	4.52 (0.36)	4.46 (0.48)	0.67
Preop calcium (mmol $litre^{-1}$) (mean)	2.31 (0.13)	2.28 (0.09)	0.45
Duration of surgery (h:min) (mean)	2:57 (0:43)	2:55 (1:00)	0.92
Epidural analgesia (*n*)	5 (29.4)	5 (27.8)	1.00

insufficient blinding of the observing research staff. However, the primary outcome was assessed by staff blinded to knowledge of side-effects. There were a higher number of wedge resection (lower risk of SVA) in the treatment group and of oesophagectomy (greater risk of SVA) in the control group. However, three of the five oesophagectomy patients were cared for on the general high dependency unit (HDU) rather than the thoracic HDU where the protocol was to monitor and correct magnesium levels. During the trial, the researchers were unaware of group allocation and continued to follow the study protocol. However, since the analysis was

Table 3 SVA incidences with different surgical procedures; values are shown as numbers (%)

	SVA/total		*P*-value
	Control group	Treatment group	
Pneumonectomy	9/17 (52.9)	2/18 (11.1)	0.008
Intrapericardial	3/6 (50.0)	1/5 (20.0)	0.55
Bi-lobectomy	2/8 (25.0)	1/5 (20.0)	1.00
Lobectomy	10/49 (20.4)	11/46 (23.9)	0.68
Wedge/segmentectomy/ partial lobe resection	2/11 (18.2)	1/18 (5.6)	0.54
Oesophagectomy	0/5 (0.0)	0/0 (0.0)	
Inoperable	1/4 (25.0)	0/6 (0.0)	0.40
Other	0/2 (0.0)	1/3 (33.3)	1.00

Table 4 Protocol compliance and side-effects observed; values are shown as numbers (%)

	Control group (*n*=96)	Treatment group (*n*=96)
Protocol compliance (*n*)		
Compliance	89 (92.7)	69 (71.9)
15 g/three infusions fully completed		
Non-compliance	7	27
5–9 g/only one infusion fully completed	1 (1.0)	10 (10.4)
10–14 g/only two infusions fully completed	6 (6.3)	17 (17.7)
Side-effects (*n*)		
None reported	96 (100.0)	72 (75.0)
Minor (stinging, nausea, abnormal taste)	0	22 (22.9)
Intermediate (vomiting, flushing)	0	2 (2.1)
Major (respiratory depression, cardiac arrhythmia, central depression)	0	0

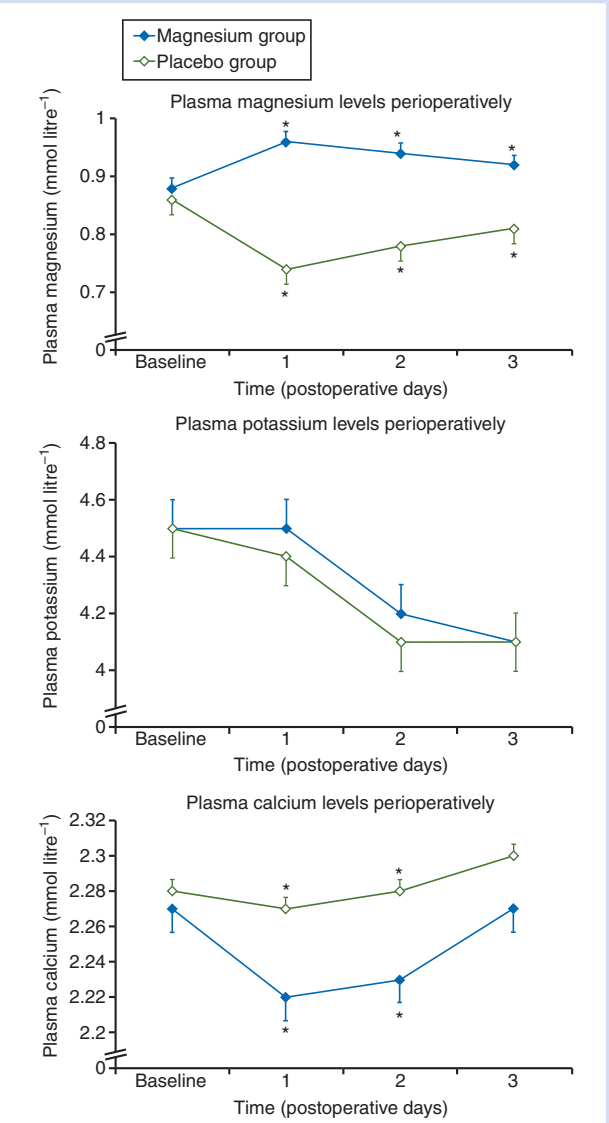

Fig 2 Plasma magnesium, potassium, and calcium levels perioperatively. *$P<0.05$.

intention to treat, the three remained in the control group despite having received magnesium after operation. Further studies are needed to control for these factors and may have added to the limitations of this study. The definition of SVA of 30 min duration or greater in this study was more rigid than in previous studies which may have led to the under-estimation of SVA incidence compared with other studies.

Although the primary result of this study was negative, magnesium warrants further investigation given the limitations of the study. Currently, another study is in progress investigating the effect of prophylactic administration of magnesium sulphate in patients undergoing thoracotomy (ISRCTN01500324). In addition, further work is required to see whether the difference observed, which may have been a false-positive, in the pneumonectomy subgroup is reproducible before recommending prophylactic treatment with magnesium sulphate.

Conflict of interest

None declared.

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