A randomised trial to investigate the efficacy of magnesium sulphate for refractory ventricular fibrillation

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Background: Ventricular fibrillation (VF) remains the most salvageable rhythm in patients suffering a cardiopulmonary arrest (CA). However, outcome remains poor if there is no response to initial defibrillation. Some evidence suggests that intravenous magnesium may prove to be an effective antiarrhythmic agent in such circumstances.
Study hypothesis: Intravenous magnesium sulphate given early in the resuscitation phase for patients in refractory VF (VF after 3 DC shocks) or recurring VF will significantly improve their outcome, defined as a return of spontaneous circulation (ROSC) and discharge from hospital alive.
Design: A randomised, double blind, placebo controlled trial. Pre-defined primary and secondary endpoints were ROSC at the scene or in accident and emergency (A&E) and discharge from hospital alive respectively.
Setting, participants, and intervention: Patients in CA with refractory or recurrent VF treated in the prehospital phase by the county emergency medical services and/or in the A&E department. One hundred and five patients with refractory VF were recruited over a 15 month period and randomised to receive either 2–4 g of magnesium sulphate or placebo intravenously.
Results: Fifty two patients received magnesium treatment and 53 received placebo. The two groups were matched for most parameters including sex, response time for arrival at scene and airway interventions. There were no significant differences between magnesium and placebo for ROSC at the scene or A&E (17% v 13%). The 4% difference had 95% confidence intervals (CI) ranging from –10% to +18%. For patients being alive to discharge from hospital (4% v 2%) the difference was 2% (95% CI –7% to +11%). After adjustment for potential confounding variables (age, witnessed arrest, bystander cardiopulmonary resuscitation and system response time), the odds ratio (95% CI) for ROSC in patients treated with magnesium as compared with placebo was 1.69 (0.54 to 5.30).
Conclusion: Intravenous magnesium given early in patients suffering CA with refractory or recurrent VF did not significantly improve the proportion with a ROSC or who were discharged from hospital alive.

V entricular fibrillation (VF) is the most salvageable rhythm in patients suffering a prehospital cardiopulmonary arrest (CA).[1] Early defibrillation is the best treatment, but its success is dependent upon whether the arrest was witnessed, if bystander cardiopulmonary resuscitation (CPR) took place before defibrillation and most importantly, the time from collapse to applying the first shock.[2]

There is conflicting evidence about the role of ALS measures other than defibrillation.[3] Debate surrounds the additional benefit in terms of outcome for those patients who do not respond to the first cycle of three defibrillatory shocks.[4] Antiarrhythmic agents such as lignocaine (lidocaine), bretylium and amiodarone are recommended for use at this late stage in the resuscitation algorithm although no convincing evidence exists that they are efficacious in treating VF.[5] These agents have significant negative inotropic actions as well as some pro-rhythmic effects. This potentially negates any benefit gained from their antiarrhythmic role. A novel therapeutic approach in the management of refractory or recurrent VF is therefore required.

Magnesium has been shown to act favourably against a number of ventricular arrhythmias including intractable tachycardia and fibrillation as well as a variety of supraventricular arrhythmias.[6] It has also been proved to be a simple and safe agent with minimal side effects in a large cohort of patients suffering acute myocardial infarction in whom it is thought to minimise reperfusion injury.[7] It does not cause negative inotropism as compared with other antiarrhythmic

agents. In addition, its ability to suppress automaticity and inhibit calcium flux into myocytes may be cardioprotective.[8]

Magnesium's role as a primary antiarrhythmic agent remains poorly studied. A number of case reports have suggested a beneficial outcome in treating patients with prolonged refractory VF.[9] [10] Three randomised studies have been published to date, all suggesting no beneficial outcome.[11–13] However, each study suffered from significant limitations, making the conclusions drawn open to question and leaving magnesium's exact role as an antiarrhythmic agent unanswered.[14]

The aim of this study was to assess the efficacy of empirical magnesium treatment as compared with placebo in patients suffering refractory or recurrent ventricular fibrillation during CA. Return of spontaneous circulation and discharge from hospital alive were used as the primary and secondary endpoints respectively.

METHODS
Study design
This study was a randomised, placebo controlled, double blinded trial. It was approved by the Leicestershire Ethics Committee. The committee accepted that informed consent

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was not possible as the patients were in a life threatening situation for which existing treatment protocols had been shown to have no significantly beneficial effect.

Study setting and population

The Leicestershire Ambulance and Paramedic Service (LAPS) provided prehospital care to approximately 900 000 people in the county of Leicestershire during the study period. Critically ill patients were predominantly taken to the accident and emergency (A&E) department at the Leicester Royal Infirmary, a 1100 bedded university teaching hospital. A small number of patients were transferred to other hospitals at the edges of the county.

All adult patients (age greater than 18) with confirmed prehospital CA treated by the LAPS or in CA on arrival in the A&E department at the Leicester Royal Infirmary were eligible for entry into the study. Inclusion into the study protocol required the patient to have either VF resistant to three defibrillatory shocks (refractory VF) or a second episode of VF during a resuscitation cycle for none-VF treatment. Exclusion criteria were age less than 18 years and mechanism of CA being related to trauma, hanging or drowning.

Study protocol

CA was defined as per the ERC guidelines.[15] All patients were treated according to these guidelines by the paramedics in LAPS and senior staff in the A&E department. The study intervention consisted of either magnesium sulphate (2 g or 8 mmol) repeated with a further 2 g if the patient remained in VF after six defibrillatory shocks, or a matched normal saline placebo. All other therapeutic interventions adhered to the ERC guidelines.

Each patient treatment pack consisted of two pre-filled syringes marked with identical randomisation labels and three spare randomisation labels for the documentation. Codes for the study were kept by the pharmacy department at the Leicester Royal Infirmary and the statistician (CJ). The randomisation schedule was produced from a computer generated list using block randomisation with block sizes of six. The packs were distributed to each of the 11 ambulance stations in Leicestershire and also to the A&E department.

Primary and secondary outcome measures

The predefined primary outcome measure was a stable return of spontaneous circulation (ROSC) that has an association with discharge from hospital.[1] This was defined as one being present on arrival in the A&E department or on discharge from the resuscitation room if the patient had suffered a CA in the A&E department. Secondary outcome measures included admission to the intensive care unit (ICU), duration of stay on the ICU, duration of stay in hospital, neurological outcome as measured by the Glasgow-Pittsburgh Outcome Score and discharge from hospital alive.

Study size

Previous work from the same prehospital care system had shown that the mortality in patients with refractory VF was 100%.[16] This was consistent with other studies suggesting a mortality in excess of 80% in the same group of patients.[4] The trial was designed to detect an improvement of 15% in the primary end point. We estimated that a total of 50 patients per arm of the study would have over 80% power to detect this difference with a 5% level of significance.

Data collection and statistical analysis

There was no facility for prospectively recording the timing of therapeutic interventions. These were therefore noted retrospectively by the emergency medical services (EMS) personnel. In the A&E department all interventions were documented by a member of the resuscitation team. For the purposes of the study, serum magnesium levels were measured in the A&E department if the patient had suffered a prehospital CA. The data collection adhered to the Utstein template for patients suffering a prehospital CA.[17]

All patients suffering a prehospital CA during the study period, regardless of inclusion in the study, were entered onto a dedicated Microsoft Access database by an audit assistant based in the A&E department. Accuracy of the data entry was confirmed by review of each patient record by one of the study investigators (TBH). All follow up data from inhospital notes were collected and inputted onto the database by TBH.

Analysis was performed on an intention to treat basis. Dichotomous variables were analysed using the χ^2 test. Analysis for identifying significant differences of survival to discharge from hospital alive was carried out using the Mann-Whitney U test. Multivariate logistic regression modelling was used to analyse the primary and secondary end points. The covariates in the analysis were: age, whether the CA was witnessed or not, presence of bystander CPR, a shorter response time, treatment with the magnesium or not and the amount of magnesium received.

RESULTS

During the 15 month study period, a total of 356 patients suffered a prehospital CA. A further 27 suffered a CA soon after arrival in the A&E department and were also eligible for entry into the study. Of these patients, 108 met the protocol requirements and were recruited.

Three patients were excluded from analysis because the randomisation labels were lost before arrival at the hospital. It was therefore impossible to ascertain whether the patient had received magnesium or placebo. In all three patients, there was no ROSC at the scene and all were certified dead in the resuscitation room. The trial profile (fig 1) describes the outcomes of the remaining 105 patients all of whom were followed up to death or discharge alive from hospital. The study population consisted of 52 patients who received magnesium and 53 who received placebo.

The characteristics of the study population are described in table 1. The baseline characteristics were generally well matched although the placebo group tended to be older on average. In addition, there was a greater incidence of the CA occurring at home in the magnesium group (65% versus 39%). There was also a greater proportion of professional CPR in the placebo group as compared with the magnesium group (19% versus 39%). Although professional CPR was arbitarily defined, it was generally consistent with the CA occurring in the presence of the ambulance crew or the patient's general practitioner (GP). The median response time for the LAPS in both study groups was eight minutes, the arrival time recorded being that for arrival at the scene and not arrival at the patient's side. Overall, the majority of patients entered into the study had VF as an initial and persisting rhythm (77 of 105). A smaller group (28 of 105) had non-VF rhythms initially, which interchanged with VF on at least two occasions after therapy was commenced. They were recruited per the study protocol as being patients with recurrent VF.

Of the 105 patients entered, 16 (15%) achieved a ROSC. Fifteen patients had refractory VF as their initial rhythm (table 2). Most patients who were admitted to hospital had a witnessed CA (84%). All three of the survivors to discharge from hospital alive had collapsed in front of the EMS. There were no significant differences between those patients who died soon after the CA either at the scene or in A&E versus those admitted to ICU in terms of the response times, number of defibrillatory shocks and the amount of adrenaline (epinephrine) given.

Eight patients received lignocaine (lidocaine) therapy as an adjunct to treatment for refractory VF after nine DC shocks. This was in keeping with the study protocol. The only protocol deviation was one patient who was given lignocaine with
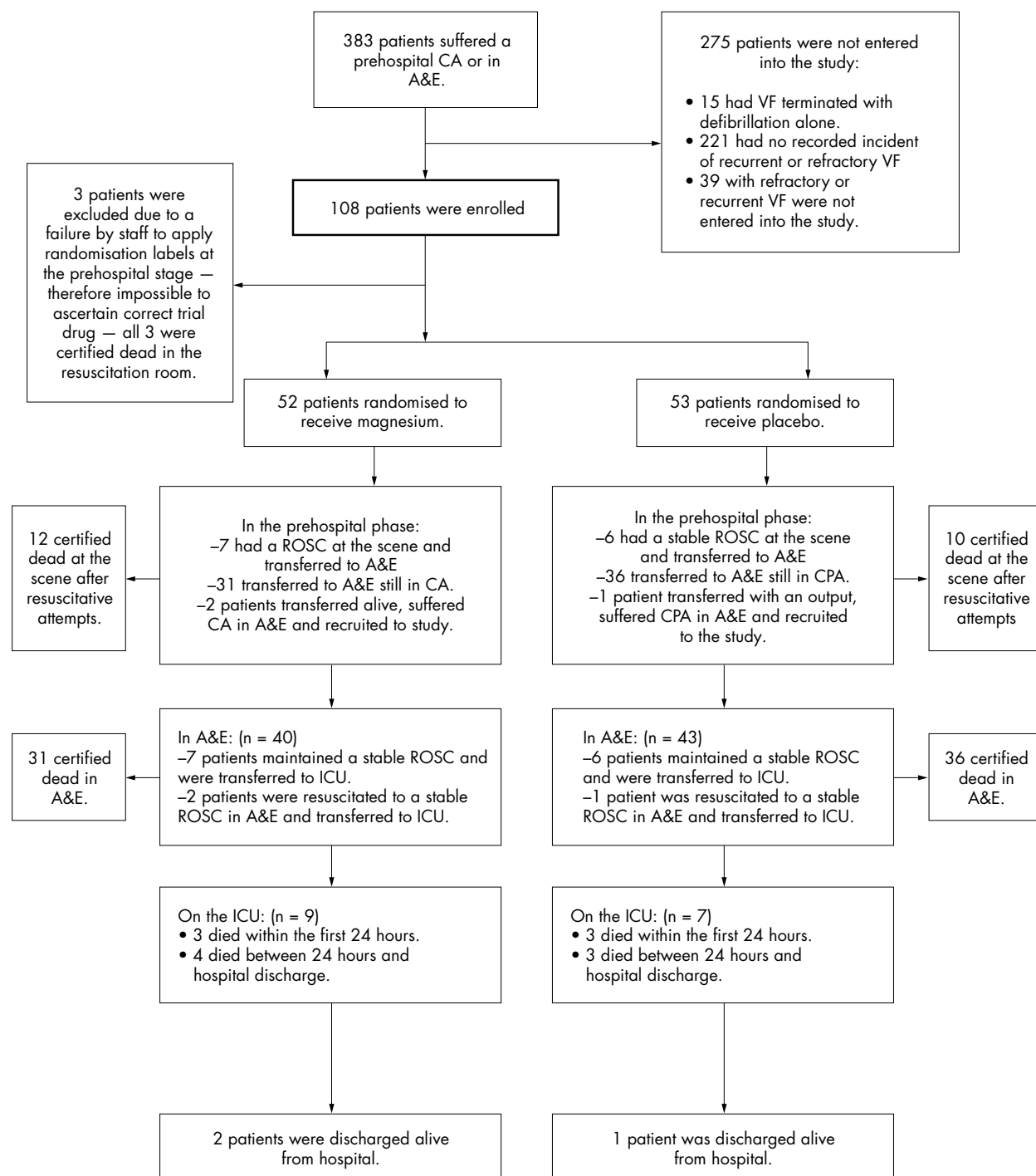
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┌──────────────────────────┐                    ┌────────────────────────────────┐
│ 383 patients suffered a  │                    │ 275 patients were not entered  │
│ prehospital CA or in     │                    │ into the study:                │
│ A&E.                     │                    │                                │
└──────────────────────────┘                    │ • 15 had VF terminated with    │
            │                                    │   defibrillation alone.        │
            │          ─────────────────────────▶│ • 221 had no recorded incident │
            ▼                                    │   of recurrent or refractory VF│
┌──────────────────────────┐                    │ • 39 with refractory or        │
│ 108 patients were enrolled│                   │   recurrent VF were not        │
└──────────────────────────┘                    │   entered into the study.      │
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3 patients were excluded due to a failure by staff to apply randomisation labels at the prehospital stage — therefore impossible to ascertain correct trial drug — all 3 were certified dead in the resuscitation room.

52 patients randomised to receive magnesium.

53 patients randomised to receive placebo.

12 certified dead at the scene after resuscitative attempts.

In the prehospital phase:
–7 had a ROSC at the scene and transferred to A&E
–31 transferred to A&E still in CA.
–2 patients transferred alive, suffered CA in A&E and recruited to study.

In the prehospital phase:
–6 had a stable ROSC at the scene and transferred to A&E
–36 transferred to A&E still in CPA.
–1 patient transferred with an output, suffered CPA in A&E and recruited to the study.

10 certified dead at the scene after resuscitative attempts

31 certified dead in A&E.

In A&E: (n = 40)
–7 patients maintained a stable ROSC and were transferred to ICU.
–2 patients were resuscitated to a stable ROSC in A&E and transferred to ICU.

In A&E: (n = 43)
–6 patients maintained a stable ROSC and were transferred to ICU.
–1 patient was resuscitated to a stable ROSC in A&E and transferred to ICU.

36 certified dead in A&E.

On the ICU: (n = 9)
• 3 died within the first 24 hours.
• 4 died between 24 hours and hospital discharge.

On the ICU: (n = 7)
• 3 died within the first 24 hours.
• 3 died between 24 hours and hospital discharge.

2 patients were discharged alive from hospital.

1 patient was discharged alive from hospital.

Figure 1 Trial profile for the magnesium in cardiac arrest (CA) study.

adrenaline and the study drug after the third DC shock. He had received placebo and went on to be discharged from hospital neurologically intact. In patients who had a stable ROSC in the A&E department, the mean serum magnesium level was 1.35 mmol/l in those given magnesium and 0.89 mmol/l in the placebo group.

No significant differences were identified between the magnesium and placebo groups in the proportion of patients who died at the scene or in A&E versus those who achieved a stable ROSC with admission to the ICU (χ^2 test: p=0.56). However, two of the three survivors had received magnesium. Similarly there were no significant differences in survival to discharge from hospital alive between the two groups (Mann-

Whitney U test, p=0.99). All three patients discharged from hospital alive were alert, orientated, self caring and independent in activities of daily living. On the Glasgow Pittsburgh Outcome score ratings they each had an Overall Performance Score and Cerebral Performance Score of 1.

In order to account for potential differences in confounding variables between the groups, a logistic regression model was fitted with ROSC as the dependent variables. Confounding variables included the age, the arrest being witnessed, presence of bystander CPR, the response time of the system, whether magnesium was given and the amount given (2 g or 4 g) (table 3). There were no definite univariate predictors of a ROSC. However, the response time had a statistical trend

Table 1 Demographic data for the MICA study

	Magnesium	Placebo
Number	52	53
Male (%)	37 (71)	37 (70)
Median age in years (IQR)	65 (15)	67 (12)
Site of CPA (%)		
At home	34 (65)	21 (39)
In public place	11 (21)	16 (30)
At work	3 (6)	6 (11)
In ambulance	3 (6)	6 (11)
In A&E	1 (2)	2 (4)
At GP surgery	0	2 (4)
Witnessed arrest (%)	42/47 (93)	43/49 (88)
Unrecorded data	5/52 (10)	4/53 (8)
Bystander CPR (%)		
Professional CPR*	9/48 (19)	19/49 (39)
Lay CPR†	13/48 (28)	10/49 (20)
No CPR	26/48 (54)	20/49 (41)
Unrecorded data	4/52 (8)	4/53 (7)
Median response time interval in minutes (range)	8 (1–25)	8 (1–18)
Initial rhythm (%)		
VF	38 (73)	39 (74)
EMD	11 (21)	12 (23)
Asystole	3 (6)	2 (4)

*CPR given by medical, nursing, paramedical or trained first aid responders; †CPR given by the lay public.

Table 3 Logistic regression analysis of possible factors contributing to the primary end point: (ROSC at the scene or in A&E)

	Odds ratio (95% CI)	p
Age		0.56
An increase of 1 year	1.01 (0.97 to 1.07)	
Witnessed arrest		0.87
Witnessed	1.00	
Unwitnessed	0.56 (0.06 to 4.97)	
Unknown	0.93 (0.09 to 9.77)	
Bystander CPR		0.23
Good	1.00	
Poor/none	0.48 (0.14 to 1.61)	
Unknown	0.56 (0.23 to 1.72)	
Response time		0.10
An increase of 1 minute	0.89 (0.77 to 1.02)	
Received magnesium		0.37
Placebo	1.00	
Magnesium	1.69 (0.54 to 5.30)	
Amount of magnesium given		0.51
2 g (8 mmol)	1.00	
4 g (16 mmol)	1.74 (0.37 to 8.14)	
Placebo	0.77 (0.19 to 3.11)	

towards significance (p=0.10). Regression analysis was not possible using the discharge alive from hospital as the dependent variable because of the relative lack of number of survivors. Using multivariate logistic regression the odds ratios (95% confidence intervals) for ROSC in patients treated with magnesium as compared with placebo was 1.69 (0.54 to 5.30).

DISCUSSION
Principal findings
Coronary artery disease is the leading cause of prehospital sudden death in the UK.[18] Approximately 25% of patients with acute myocardial infarction will die in the prehospital phase and up to 84% of these will have a ventricular arrhythmia as their initial arrest rhythm.[19] In excess of 80% of patients with refractory or recurrent VF who do not respond successfully to the first cycle of three defibrillatory shocks will die.[4]

This study was specifically designed to evaluate the primary role of intravenous magnesium sulphate as an adjunct to defi-

brillation in treating refractory or recurrent VF. It was performed in the difficult and challenging environment of prehospital care medicine and is the first study of its kind to be reported. Although some small improvement occurred, this was not statistically significant for stable ROSC or discharge from hospital alive for a group of patients with recurrent or refractory VF treated with magnesium as compared with placebo.

Existing evidence
Laboratory studies suggest that magnesium has a number of cellular actions that could result in acute suppression or treatment of arrhythmias. These include, suppression of automaticity in partially depolarised cells, inhibition of calcium flux, suppression of early and late after-depolarisations and interactions with potassium to stabilise cell membranes.[20] The exact mechanism particularly in circumstances where there is a coexisting loss of cardiac output, remains unknown.[13]

Clinical evidence of magnesium's role in preventing serious arrhythmias is predominantly restricted to patients having suffered an acute myocardial infarction. A meta-analysis of

Table 2 Characteristics of patient subgroups

	Died at the scene or in A&E	Died on ICU	Alive to discharge
Number	89	13	3
Initial rhythm (%)			
VF	62 (70)	12 (92)	3
EMD	22 (24)	1 (8)	0
Asystole	5 (6)	0	0
Witnessed CA	71/89 (78)	11/13 (84)	3/3 (100)
Bystander CPR (%)			
Professional CPR	22 (25)	3 (23)	3 (100)
Lay person CPR	22 (25)	1 (8)	0
No CPR	40 (44)	6 (46)	0
Unrecorded data	5 (6)	3 (23)	0
Median response time in minutes (range)	9.5 (2–20)	8 (1–14)	10 (7–12)
Median number of defibrillatory shocks (range)	5 (2–17)	3 (1–12)	8 (4–9)
Median amount of adrenaline given in mg (range)	5 (2–10)	3 (1–8)	3 (1–8)
Proportion of patients given lignocaine (%)	7/89 (9)	1/13 (8)	1/3 (33)
GCS on admission to ICU	–	3	3
Number of days on ICU: median (range)	–	2 (1–6)	1 (1–2)
Number of days in hospital: median (range)	–	2 (2–6)	6 (6–8)

randomised trials of patients with acute myocardial infarction found a reduction of ventricular arrhythmias by 49% in those treated with magnesium.[21] This was supported by the ISIS-4 study, which showed a reduction in the incidence of VF post infarction.[22] In contrast, the largest single centre study to specifically evaluate the role of magnesium did not show any evidence of suppressive antiarrhythmic action.[23]

In the setting of CA, there have been three randomised studies, all of which failed to identify an improvement in outcome.[11–13] However, each trial suffered from a number of methodological limitations. In the first, with 62 patients being recruited, a trend towards improved ROSC and survival to hospital discharge was found.[11] However, the trial drugs were not blinded, given late in the resuscitation phase and 42 patients were excluded from the study for a variety of reasons. In an Australian study of prehospital CA patients, no difference in outcome was identified with only one survivor to discharge from hospital alive.[12] Unfortunately, the study was carried out in an EMS system with no prehospital ALS. As a result, the intervention was not given until after arrival in the emergency department, an average of some 30 minutes after the collapse.

Thel *et al* recruited patients who had suffered an inhospital CA and had not necessarily been admitted with a primary cardiac event.[13] Thirty five per cent were from the ICU. A significant proportion had malignant disorders as their primary diagnosis and 55% of those who regained a stable ROSC were later assigned do not resuscitate status. However, although the study did not show magnesium to have any beneficial effect on the ROSC or discharge from hospital there was a surprising and significant improvement in the neurological status of the survivors who had received magnesium as opposed to the placebo (p=0.04). This potential cerebro-protective effect has been attributed to the part magnesium possibly plays in regulating cerebral vascular tone and its action as a calcium channel blocker preventing increase in the concentration of intraneuronal calcium during cerebral hypoperfusion.[24] In our study there were no differences in the GCS of patients on the ICU who had received magnesium or placebo. All three patients who survived to hospital discharge were neurologically intact. Quality of life was not chosen as a secondary end point.

This study was designed to test the benefit of empirical intravenous magnesium given at an early stage in the resuscitation process. Unlike previous studies, only patients who were defined by the study protocol as being in refractory or recurrent VF were recruited. Patients suffering a prehospital CA with asystole or pulseless electrical activity as their initial rhythms have a mortality approaching 100% in most EMS systems.[25] Inclusion of these patients into a study is likely to produce a dilution of the beneficial effect of the agent being tested as most will be unsalvageable. In addition, there is no mechanistic or clinical evidence for giving magnesium in such circumstances. Of the 28 patients who had an initial arrest rhythm other than VF but who developed VF on at least two occasions during the resuscitation process, there was only one who achieved a stable ROSC. He was admitted to the ICU where he subsequently died. In contrast, 15 of the 16 patients who achieved a stable ROSC to be admitted to the ICU, had VF as their initial rhythm.

Multivariate modelling did not identify any factor that significantly contributed to survival, although the shorter response time showed a trend towards a stable ROSC (p=0.10). Nine of these 16 patients had received at least 2 g of magnesium at an early stage in their resuscitation. After multivariate adjustment of all other factors, magnesium did not have a beneficial effect on the ROSC.

Reliability
This failure to identify any beneficial outcome could be due to magnesium truly having no effect. It is also possible that a type II error occurred. From previous work within the same EMS system and available literature on the effects of magnesium in reducing ventricular arrhythmias, the study was designed to detect an improvement of 15% in the primary endpoint. However, in the study, the observed ROSC rates were 17% and 13% in the magnesium and placebo groups respectively. Assuming this to be true, it would require in excess of 1500 patients with refractory or recurrent VF to be recruited to prove magnesium to have a small effect of 5%.

A second potential limitation is that the dose of magnesium given during CA may have been inadequate. Previous studies have used dose regimens from 8 mmol (2 g)[13] to 20 mmol as a bolus.[12] Although it has been shown that 8 mmol will increase the serum concentration twofold, this is not the case in CA especially if the drug is being given via a peripheral intravenous line. A higher bolus dose of magnesium may however cause side effects. In a dog model,[26] high dose magnesium of 0.14 g/kg (equivalent to 40 mmol in a 75 kg man) produced a reduction in the aortic diastolic and coronary perfusion pressures. This dosing regimen was probably too high to be clinically applicable. We chose to use 8 mmol as a bolus with a second similar dose if the patient remained in VF after six defibrillatory shocks. Serum measurements of magnesium in patients with a stable ROSC post cardiac arrest in the A&E department and given magnesium, had mean levels of 1.35 mmol/l compared with placebo. Future studies may need to give consideration to a higher dosing regimen.

Prehospital CA is a difficult field in which to carry out randomised studies. Individual factors such as the incidence of bystander CPR, the response time to the first defibrillatory shock, protocol violations and even the aggressiveness of care provided in hospital both within the A&E department and particularly on the ICU can have major influences.[13] These factors can have a marked effect particularly if the study population is small. They cannot always be controlled for by a single EMS study even if it is robustly designed. For example, we chose to include only patients with refractory or recurrent VF, a well recognised group in whom ALS interventions are more likely to have a beneficial effect. The one patient in the placebo group who survived to hospital discharge was a significant protocol violation in that he received lignocaine at the same time as the trial drug after the third defibrillatory shock. This may have been the main contributory factor to his survival.

A multicentre trial would tackle a number of these issues and increase the precision and external validity of the trial although recruiting from different EMS systems would carry other significant problems. This study took place in a system with average response times and incidence of bystander CPR compared with others in the UK. The response time is obviously critical to success in prehospital CA. A high performance EMS with faster response times, approaching eight minutes in 90% of cases is likely to produce more survivors. There are also likely to be an increase in the proportion that might benefit from other therapeutic interventions. Response time could have been a significant factor in magnesium's seeming lack of efficacy in treating refractory VF in this study population.

CONCLUSION AND FUTURE WORK
This study has shown that for patients in CA with refractory or recurrent VF, empirical intravenous magnesium did not significantly increase the proportion of patients with a stable ROSC or the number who were discharged home. A smaller beneficial effect cannot be excluded, but would require a much larger study group.

Future work on magnesium's possible role as a primary antiarrhythmic agent in prehospital CA should be carried out in high performance systems. The dose of magnesium to give in these circumstances also merits further investigation.

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