Magnesium sulphate for treatment of severe tetanus: a randomised controlled trial

C L Thwaites, L M Yen, H T Loan, T T D Thuy, G E Thwaites, K Stepniewska, N Soni, N J White, J J Farrar

Summary

Oxford University Clinical
Research Unit
(C L Thwaites MRCP,
G E Thwaites MRCP,
K Stepniewska PhD,
Prof N J White FRCP,
Prof J J Farrar FRCP); Hospital for
Tropical Diseases, Ho Chi Minh
City, Vietnam (L M Yen MD,
H T Loan MD, T T D Thuy); Centre
for Tropical Medicine, Nuffield
Department of Clinical
Medicine, John Radcliffe
Hospital, Oxford, UK
(C L Thwaites, G E Thwaites,
K Stepniewska, N J White,
J J Farrar); and Magill
Department of Anaesthesia,
Chelsea and Westminster
Hospital, London, UK
(N Soni FRCA)

Correspondence to:
Dr C Louise Thwaites, Oxford
University Clinical Research Unit,
Hospital for Tropical Diseases,
190 Ben Ham Tu, District 5,
Ho Chi Minh City, Vietnam
louise.thwaites@btinternet.
com

Background The most common cause of death in individuals with severe tetanus in the absence of mechanical ventilation is spasm-related respiratory failure, whereas in ventilated patients it is tetanus-associated autonomic dysfunction. Our aim was to determine whether continuous magnesium sulphate infusion reduces the need for mechanical ventilation and improves control of muscle spasms and autonomic instability.

Methods We did a randomised, double blind, placebo controlled trial in 256 Vietnamese patients over age 15 years with severe tetanus admitted to the Hospital for Tropical Medicine, Ho Chi Minh City, Vietnam. Participants were randomly assigned magnesium sulphate (n=97) or placebo solution (n=98) intravenously for 7 days. The primary outcomes were requirement of assisted ventilation and of drugs to control muscle spasms and cardiovascular instability within the 7-day study period. Analyses were done by intention to treat. This trial is registered as an International Standard Randomised Clinical Trial, number ISRCTN74651862.

Findings No patients were lost to follow-up. There was no difference in requirement for mechanical ventilation between individuals treated with magnesium and those receiving placebo (odds ratio 0·71, 95% CI 0·36–1·40; p=0·324); survival was also much the same in the two groups. However, compared with the placebo group, patients receiving magnesium required significantly less midazolam (7·1 mg/kg per day [0·1–47·9] *vs* 1·4 mg/kg per day [0·0–17·3]; p=0·026) and pipecuronium (2·3 mg/kg per day [0·0–33·0] *vs* 0·0 mg/kg per day [0·0–14·8]; p=0·005) to control muscle spasms and associated tachycardia. Individuals receiving magnesium were 4·7 (1·4–15·9) times less likely to require verapamil to treat cardiovascular instability than those in the placebo group. The incidence of adverse events was not different between the groups.

Interpretation Magnesium infusion does not reduce the need for mechanical ventilation in adults with severe tetanus but does reduce the requirement for other drugs to control muscle spasms and cardiovascular instability.

Introduction

Tetanus is an important cause of hospital admission and death in parts of the world with limited vaccination programmes. At least 1 million cases require hospital treatment worldwide every year and there are about 400 000 deaths.[1,2] The disease is caused by a neurotoxin released from wounds infected with *Clostridium tetani*, a bacterium transmitted as spores and present in soil throughout the world.

Tetanus is a painful and protracted disease characterised by increased muscle tone, muscle spasm, and, in severe cases, cardiovascular instability secondary to autonomic dysfunction. The toxin blocks neurotransmitter release from the inhibitory pathways of the motor and autonomic nervous systems, which can result in unrestrained neuronal activity of both pathways.[3] Data from a limited number of controlled trials suggest that antitoxin and antibiotics—penicillin or metronidazole—improve outcome.[4,5] However, beyond these disease-specific therapies, the optimum management of the respiratory compromise and cardiovascular instability that characterise the severe form of the disease remains uncertain.[6] Supportive management is focused on controlling muscle spasms, maintaining and protecting the upper airway and providing adequate ventilation, and limiting the consequences of autonomic dysfunction.

Benzodiazepines, often in very high doses, have been the mainstay of controlling muscle spasms, although there is little evidence to support their use over alternative sedatives such as phenobarbital and chlorpromazine.[7–9] Severe spasms might necessitate the use of non-depolarising neuromuscular blocking agents,[10,11] although the use of such drugs requires ready access to mechanical ventilation. However, such facilities are often absent in settings where tetanus is common.

Autonomic dysfunction with labile blood pressure, heart rate, and temperature is difficult to treat irrespective of the setting,[2,12] and occurs in those with severe disease, usually in the second week of illness. Where there is access to mechanical ventilation, and respiratory muscle spasm can be controlled, autonomic dysfunction is the most common cause of death.[13] A range of treatments have been advocated, including the use of morphine, clonidine, beta-adrenergic receptor blockade, and epidural bupivacaine, but none is supported by evidence from controlled trials.[9,10,14–18]

Magnesium sulphate was first used in the treatment of tetanus more than 100 years ago[19] and has several attractive therapeutic properties including muscle relaxation, which could control spasms, and cardiovascular effects (eg, vasodilatation, lowering of heart rate, and a reduction of systemic catecholamine release), all of which

could ameliorate the effects of autonomic dysfuntion.[20,21] Whether magnesium improves the outcome of tetanus remains uncertain. In 1985, James and Manson[22] did an open label, uncontrolled study of ten patients with severe tetanus in Zimbabwe that suggested that a continuous magnesium infusion (1–3 g/h) might help control blood pressure and heart rate. In Sri Lanka, Attygalle and Rodrigo[23] reported treating eight patients with severe tetanus with continuous magnesium infusion, titrating against patella reflex (serum concentrations 2–4 mmol/L), and noted that spasms were reduced within 2–3 h of starting the infusion and were abolished within 24 h. The same protocol was used to treat a further 40 patients and magnesium was seen to reduce not only the use of neuromuscular blocking agents to control severe spasms but also the requirement for mechanical ventilation when compared with historical controls.[24] The authors concluded that magnesium should be used as a first-line agent for treatment of tetanus.[25]

However, Thwaites and Farrar[26] were not so enthusiastic, and suggested that this conclusion seemed premature without any data from an adequately powered controlled study. There was concern about the potential adverse effects of magnesium. In particular, muscle weakness induced by magnesium could paradoxically increase the requirement for mechanical respiratory support, which could be dangerous in settings without access to such facilities.

To address these issues we did a randomised, double blind, placebo controlled study of magnesium sulphate in patients with severe tetanus. Our aim was to determine whether magnesium can control muscle spasm and autonomic activity and reduce the need for mechanical ventilation in such individuals.

Methods

Participants

The study was done in the tetanus unit at the Hospital for Tropical Diseases in Ho Chi Minh City, Vietnam. The unit consists of a 14 bed intensive care ward reserved for the care of patients with tetanus, and serves the local community as well as acting as a tertiary referral centre for the whole of southern Vietnam (population about 35 million). The unit admits about 300 patients with tetanus every year, 75% of whom have severe tetanus and require mechanical ventilation.

Only patients over 15 years of age with a clinical diagnosis of tetanus were eligible to enter the study. Patients also had to have a tracheostomy in situ for at least 4 h and be breathing spontaneously without mechanical assistance. Unlike some other centres, tracheostomies were not done routinely on all patients with tetanus but were reserved for those with severe (Ablett grade III or IV[6,27]) disease. The indications for a tracheostomy were patients having acute airway obstruction due to laryngeal spasm or frequent spasms that interfered with respiration, or to facilitate mechanical ventilation.

Patients were excluded from entry if they had the following contraindications to magnesium therapy: serum creatinine concentration greater than 2 mg/dL, urine output of less than 1 mL/kg every hour, electrocardiogram evidence of conduction abnormality or arrhythmia, systolic blood pressure under 80 mm Hg unresponsive to 500 mL fluid challenge, or if they required inotropic support.

The study was approved by the Scientific and Ethical Committee of the Hospital for Tropical Diseases and the Oxford University Tropical Review Ethics Committee. Written informed consent to participate in the study was obtained from all patients or from their relatives if the patient could not provide consent.

Procedures

Patients entering the study were randomly assigned either placebo (glucose anhydrous 5% in water) or magnesium sulphate (magnesium sulphate heptahydrate in water, Torbay Pharmaceutical Manufacturing Unit, Torbay, UK) for 7 days in addition to normal tetanus management. An intravenous loading dose of 40 mg/kg over 30 min was given, followed by intravenous infusion of 2 g/h for patients over 45 kg and 1·5 g/h for patients 45 kg or under. To maintain blinding, study drug infusions were prescribed in mL per h with a 2 g/h infusion corresponding to a 4 mL/h infusion rate.

Treatment was allocated by a computer-generated sequence of random numbers in blocks of 30. Vials of placebo and magnesium were identical in appearance and were prepared in numbered individual 7-day treatment packs. Packs were distributed for sequential administration to patients fulfilling the entry criteria. The attending physicians were responsible for enrolling the participants, ensuring the study drug was given from the correct treatment pack, and recording clinical data in individual study notes.

Daily tidal volume, respiratory rate, and serum magnesium measurements were recorded to monitor magnesium toxicity. Serum concentrations were measured by a technician, independent of the study, and the results reported to an independent physician who then advised on changes to the infusion rate to maintain serum concentrations of 2–4 mmol/L. The independent physician also instructed sham infusion rate changes in the placebo group. All participants, enrolling physicians, and investigators remained blinded to the treatment allocation until the last patient completed follow-up.

All patients received standard management for tetanus as detailed previously.[2] Briefly, this consisted of wound cleaning and debridement, antibiotics (usually metronidazole), equine antitoxin, and intermittent boluses of intravenous diazepam to control muscle spasms. If diazepam was insufficient to control spasms, intermittent boluses of pipecuronium were used, followed by intravenous infusion if necessary. Intravenous midazolam infusions were used in place of diazepam in those

requiring higher doses of diazepam (usually >100 mg/day) or with those judged clinically to have the most severe spasms.[2] Tachycardia associated with autonomic disturbance (excessive sweating and labile blood pressure) was treated with verapamil as a first-line agent, followed by morphine or digoxin if necessary. All patients had continuous cardiac monitoring with electrocardiograms done if clinically indicated. Hypotension was treated with fluid bolus or inotropes (noradrenaline and dopamine as first-line agents) as clinically indicated.

The primary outcome was requirement for assisted ventilation within the 7-day study period. Indications for ventilation were defined a priori as respiratory failure caused by uncontrolled spasms (lasting >10 s or more than four spontaneous spasms per hour), incipient respiratory failure (defined as p_aO_2/F_iO_2 <300, or S_aO_2 <90%, or p_aO_2 <60 mm Hg or p_aCO_2 >50 mm Hg), or respiratory rate of 8 breaths per minute or less. However, the final decision to ventilate a patient rested with the attending physician on duty and all reasons to ventilate were recorded prospectively.

Secondary outcome measures were chosen to assess the effect of magnesium on both spasm control and autonomic instability. Surrogate markers of spasm control were chosen because continuous 24-h direct observation of spasm frequency, severity, and duration was impossible. The markers chosen were requirement for mechanical ventilation during hospital stay, anti-spasm drug requirements (total diazepam, midazolam, and pipecuronium used), and serum creatine kinase (area under the serum total creatine kinase-time curve). Control of autonomic dysfunction was assessed by heart rate, systolic and diastolic blood pressure (mean, minimum, maximum, and area under blood pressure/heart rate-time curve), and total dose of verapamil prescribed. Verapamil is the first-line agent used to treat tachycardia associated with autonomic dysfunction in this unit.[2] Other secondary outcome measures included in-hospital mortality and duration of intensive care unit and total hospital stay. A daily estimate of tidal volume was obtained for spontaneously breathing patients, and serum calcium concentrations (adjusted for albumin concentration) were monitored daily.

An independent data monitoring and safety committee was established to oversee the trial. They reviewed the results of the study after 50 patients had been enrolled and after 100 had been enrolled. The trial was not stopped early.

Statistical analysis

75% of adults with severe tetanus admitted to our unit before the start of the study required mechanical ventilation. We estimated effect size with data from Attygalle and Rodrigo[23] and an uncontrolled pilot study done in our unit before the controlled study began. We calculated that 180 patients (90 in both groups) would be required to provide at least 80% power to identify a

reduction in ventilation rate in adults with tracheostomies in situ, from 75% to 55%, with a two-sided significance level of 5%.

The outcomes were assessed by intention-to-treat analyses and prespecified subgroup analysis. The primary outcome measure, requirement for mechanical ventilation, was compared between the treatment groups by χ^2 tests and odds ratios (OR) calculated by logistic regression. The prespecified subgroup analysis compared the primary outcome in subgroups defined according to age less than, or greater than, 60 years.

We compared cardiovascular parameters (heart rate, systolic and diastolic blood pressure) between treatment groups as mean values calculated for the 7-day study period or until death, if it occurred sooner; or as area-under-the-curve values calculated per day to allow for patients dying before the end of the period. Drug requirements were compared between treatment groups as mean daily dose (mg/kg per day). Serum creatine kinase values were compared as mean daily values (IU/day). We used the Student's t test to compare
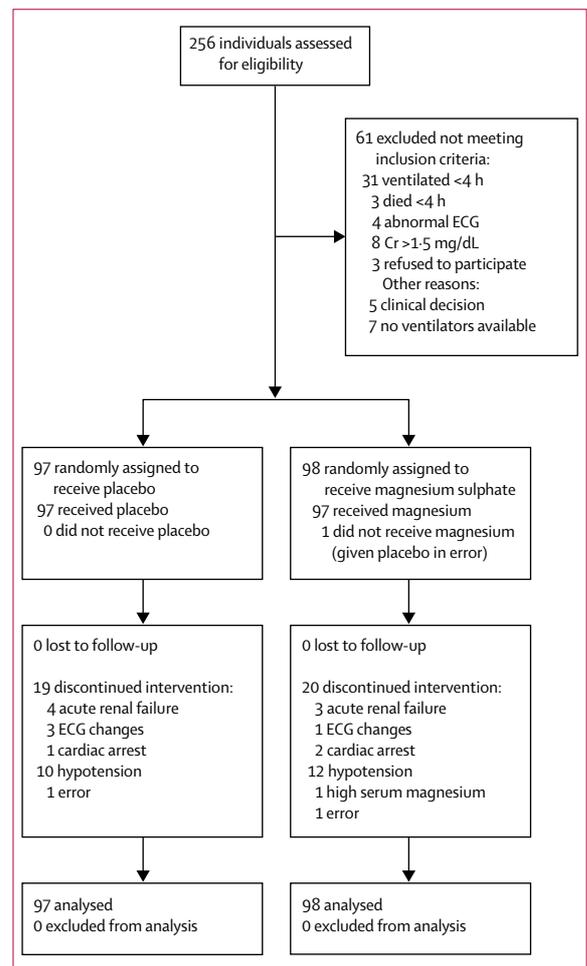
Figure 1: Trial profile
Cr=serum creatinine. ECG=electrocardiogram.

variables if the data were normally distributed and the Mann Whitney U test if they were not.

We used Kaplan-Meier estimates to display the duration of intensive care unit admission, duration of hospital stay, and in-hospital survival experiences of the two treatment groups. Data on patients transferred to another hospital were censored at the time of transfer. Multivariate logistic regression was used to identify independent risk factors for mechanical ventilation and death. This trial is registered as an International Standard Randomised Clinical Trial, number ISRCTN74651862.

Role of the funding source

The study sponsors had no role in the study design, the collection, analysis, or interpretation of the data, the writing of the report, or the decision to submit the paper for publication. All authors had full access to all the data in the study and approved the final version of the paper.

Results

Of 256 patients initially assessed for eligibility, 195 patients with severe tetanus were randomly assigned either magnesium or placebo from May, 2002, to April, 2005 (figure 1). One patient in the magnesium group was given placebo in error. Although no patients were lost to follow-up, a number in both groups discontinued treatment early (figure 1). Primary outcome data were available from all patients entered into the study.

Baseline serum concentrations of magnesium were 0·76 mmol/L (IQR 0·66–0·87) in the placebo group and 0·75 mmol/L (0·64–0·84) in the magnesium group. Median steady state concentrations were 0·76 mmol/L (0·70–0·81) in the placebo group and 2·30 mmol/L (2·09–2·52) in the magnesium group. The infusion rate was adjusted 14 times in the magnesium arm and 14 times in the placebo arm.

The baseline characteristics at randomisation were much the same in the placebo and magnesium groups (table 1). Individuals in both groups entered the study after a median of 5 days of symptoms. Disease severity was assessed by three different tetanus prognostic scores—the Dakar,[28] Phillips,[29] and Ho Chi Minh City Tetanus Severity[30] scores—and was much the same for both treatment groups with all three scores.

The proportion of patients who required mechanical ventilation during the 7 days of study drug intervention was not significantly different between the treatment groups (table 2; OR 0·71, 95% CI 0·36–1·40). Extending the observation period to the entire hospital stay did not alter this result (table 2).

There was no difference in the requirement for diazepam between the two groups; however, there was a significantly reduced requirement for midazolam and pipecuronium in those receiving magnesium (p=0·026 and p=0·005, respectively; table 2). Pipecuronium was required by 55 (57%) patients in the placebo group versus 44 (45%) of those in the magnesium group

|	Placebo group (n=97)	Magnesium group (n=98)
Age (years)	47·0 (31·0–66·5)	49·0 (34·0–64·0)
Male	67 (69%)	73 (74%)
Weight (kg)	50·0 (45·5–55·5)	52·0 (46·8–55·3)
Incubation period (day)*	7·0 (6·0–10·0)	7·0 (5·0–10·0)
Period of onset (h)†	24·0 (24·0–48·0)	24·0 (24·0–48·0)
Time from first symptom to study entry (day)	5·0 (4·0–7·0)	5·0 (4·0–7·0)
Dakar score‡	2·0 (1·0–3·0)	2·0 (1·0–3·0)
Phillips score§	15·0 (14·0–17·0)	15·0 (13·0–17·0)
Tetanus severity score¶	3·0 (0·0–9·0)	3·0 (0·0–6·0)

Data are median (IQR) or number (%). *Time between the wound and the onset of the first symptom of tetanus. Data were available for 76 individuals given placebo and 69 given magnesium; in the remaining patients no wound was apparent and therefore no period calculated. †Time between the first symptom and the first muscle spasm. ‡Assesses tetanus severity using six variables: incubation period <7 days, period of onset <48 h, high-risk entry site, and presence of fever, spasms, and tachycardia on admission. Variables are scored either 0 (absent) or 1 (present), giving a maximum score of 6 for disease with the worst prognosis. §Uses four variables: incubation period, site of infection, state of immune protection, and complicating factors. The first two categories assign scores of 1–5 and the second two scores of 0–10. Thus a final score with a maximum value of 30 is given, with higher scores associated with worse outcome. ¶Uses age, time from first symptom to admission, difficulty breathing, co-existing medical problems, entry site, and highest systolic blood pressure, heart rate, and temperature during the first day of admission and lowest heart rate, with higher scores associated with worse outcome. Maximum score is 46, minimum is –6.

Table 1: Baseline characteristics of study population

	Placebo group (n=97)	Magnesium group (n=98)	p value
Primary outcome			
Ventilation during study	78 (80%)	73 (74%)	0·392
Secondary outcomes			
Ventilation during hospital stay	80 (82%)	74 (76%)	0·292
In hospital mortality	16 (16%)	13·0 (13%)	0·645
Duration in intensive care unit (day)	23·0 (17·0–29·5)	22·5 (16·0–28·0)	0·299
Duration of hospital stay (day)	35·0 (26·5–43·0)	33·0 (27·0–40·3)	0·262
Measures of spasm control			
Diazepam (mg/kg per day)	40·0 (5·8–68·6)	47·1 (9·1–80·0)	0·169
Midazolam (mg/kg per day)	7·1 (0·1–47·9)	1·4 (0·0–17·3)	0·026
Pipecuronium (mg/kg per day)	2·3 (0·0–33·0)	0·0 (0·0–14·8)	0·005
Mean creatine kinase AUC (IV days)	1255·6 (655·8–2600·2)	2134·5 (1077·5–4276·6)	0·001
Mean daily total creatine kinase concentration (IV/day)	1499·0 (813·0–3257·4)	2487·8 (1277·0–4681·5)	0·003
Measures of cardiovascular stability and autonomic control			
Mean systolic blood pressure (mmHg)	120·8 (114·6–131·0)	122·4 (116·2–130·2)	0·768
Mean systolic blood pressure AUC (mm Hg days)	2843·6 (2694·6–3087·6)	2877·5 (2735·9–3070·7)	0·705
Mean diastolic blood pressure (mm Hg)	75·1 (70·7–78·3)	74·4 (70·8–77·5)	0·711
Mean diastolic blood pressure AUC (mm Hg days)	1757·1 (1658·7–1846·1)	1755·0 (1668·2–1828·4)	0·853
Mean arterial blood pressure (mm Hg)	90·4 (85·6–95·6)	90·7 (86·6–94·9)	0·977
Mean arterial blood pressure AUC (mm Hg days)	2130·0 (2012·2–2253·2)	2132·9 (2017·9–2228·9)	0·976
Mean heart rate (bpm)	116·1 (108·9–123·6)	104·3 (98·2–112·0)	<0·0001
Mean heart rate AUC (bpm days)	2745·0 (2548·1–2893·9)	2450·4 (2312·4–2623·3)	<0·0001
Mean temperature (°C)	38·1 (37·8–38·3)	37·9 (37·7–38·2)	0·087
Mean temperature AUC (°C days)	896·5 (888·5–901·5)	893·3 (887·1–900·0)	0·177
Mean tidal volume (mL)	342·5 (289·3–405·0)	333·8 (274·4–385·0)	0·296
Mean serum calcium concentration (mmol/L)	2·2 (2·1–2·5)	1·9 (1·8–2·1)	<0·0001

Data are number (%), median (IQR), or mean (IQR). AUC=area under curve.

Table 2: Primary and secondary outcomes
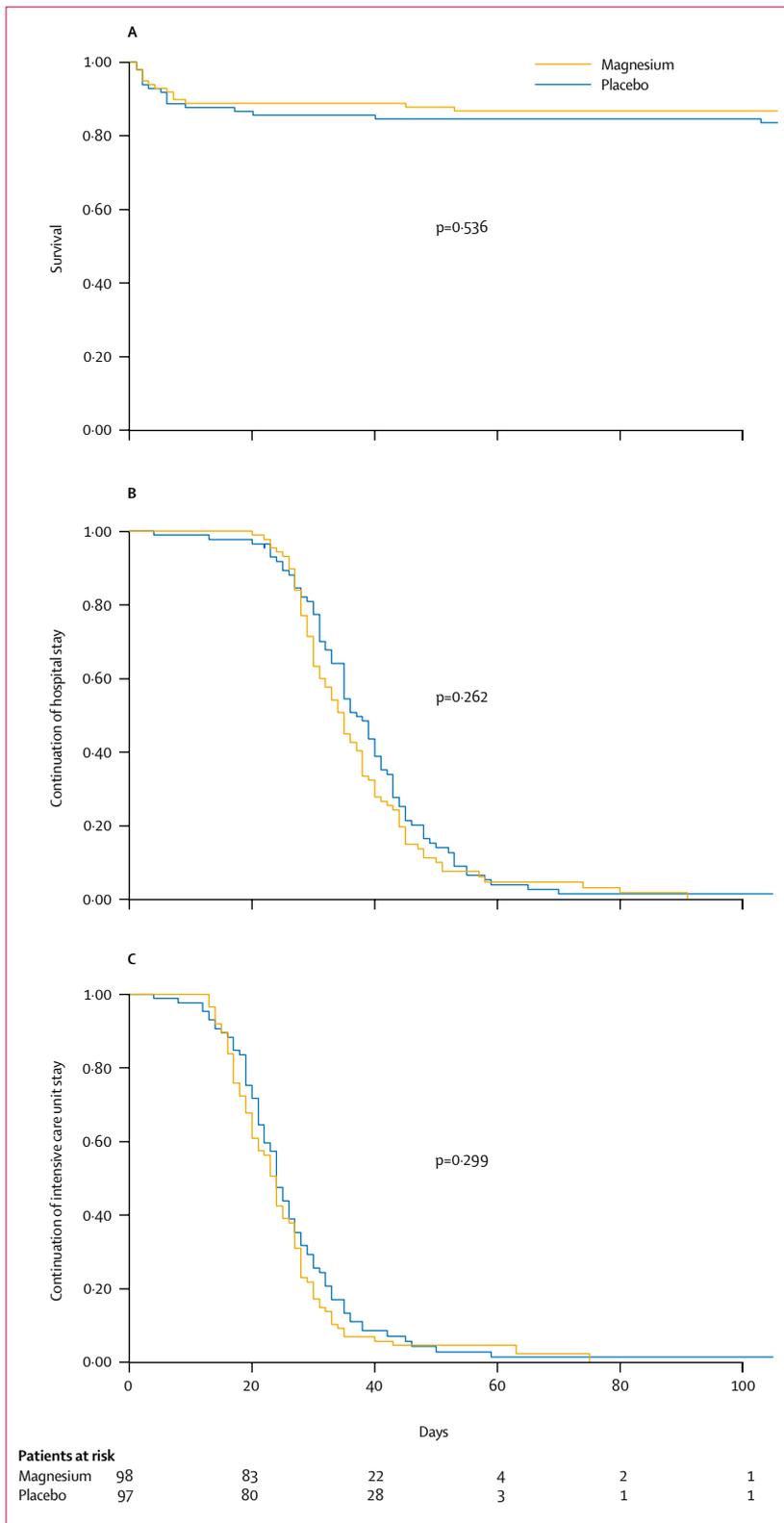
Figure 2: Kaplan-Meier curves of secondary outcomes
(A) Cumulative probability of survival; (B) cumulative probability of continuation of the hospital stay; (C) cumulative probability of continuation of the intensive care unit stay.[2]

(p=0·116). The daily pipecuronium requirements in those prescribed the drug were significantly less in those receiving magnesium (median 17·89 mg/day, IQR 0·75–29·51) than those receiving placebo (31·66 mg/day, 10·63–39·43; p=0·001). Despite the apparent effect of magnesium on spasm control, it was associated with higher mean daily concentrations of serum creatine kinase and greater area under the creatine kinase time-curve than placebo for the study period (table 2).

There was no difference in systolic, diastolic, or mean arterial blood pressure in patients receiving magnesium compared with those on placebo; likewise, change in body temperature was much the same in both groups (table 2). However, exploratory post-hoc analysis showed that very low (minimum daily) diastolic blood pressures (<40 mm Hg) occurred in a greater proportion of patients in the placebo group than in the magnesium group (nine individuals [9%] vs one person [1%]; p=0·009). Both the mean heart rate and the mean area under the heart rate time-curve were significantly lower in those on magnesium than in those receiving placebo (table 2). In support of a cardiovascular stabilising effect of magnesium was a lower requirement for verapamil in the magnesium group: 14 (14%) individuals in the placebo group were treated with verapamil compared with three (3%) in the magnesium group (relative risk 4·7, 95% CI 1·4–15·9; p=0·005). The mean daily doses of the drug did not differ between the two groups when it was used (data not shown).

There was no difference in survival between individuals in the magnesium group and those in the placebo group, either during the study or throughout the hospital admission (figure 2). In the magnesium group, nine (9%) individuals died during the study and 13 (13%) died in hospital, compared with 11 (11%) and 16 (16%) individuals in the placebo group, respectively (p=0·645 during the study and p=0·552 in hospital). There was no difference between length of stay in hospital or intensive care unit between the two treatment groups (p=0·262 and 0·299, respectively; figure 2).

The influence of magnesium on outcome was examined in subsets defined by age. In the placebo group, 52 (78%) of 67 patients aged less than 60 years required mechanical ventilation, compared with 47 (68%) of 69 patients in the magnesium group (p=0·250). 26 (87%) of 30 patients aged 60 years or more given placebo were ventilated compared with 26 (90%) of 29 individuals who received magnesium (p=1·000). Overall, the effect of magnesium on requirement for mechanical ventilation was homogeneous across the age groups (test of heterogeneity p=0·209) with a Mantel-Haenszel combined OR of 0·75 (95% CI 0·38–1·51; p=0·425).

Age 60 years or more was shown by multivariate logistic regression to be an independent risk factor for mechanical ventilation (OR 7·05, 2·22–22·35; p=0·001). Other independent risk factors for ventilation during the study period were time to first symptom of tetanus (OR 0·88,

0·78–0·99; p=0·035) and Dakar score (OR 1·83, 1·29–2·61; p=0·001).

Hypocalcaemia and muscle weakness with respiratory depression were expected to be the most common complications of magnesium therapy. Mean daily serum calcium (albumin adjusted) was significantly lower in the magnesium group than the placebo group (p<0·0001; table 2), but no clinical consequences of hypocalcaemia were seen in either group. In individuals able to breathe without assistance, mean daily tidal volume was not significantly different in those receiving magnesium treatment compared with those on placebo (table 2). Other adverse events are shown in table 3. Eight (73%) of the 11 patients in the placebo group whose infusion was stopped because of sudden cardiac arrest or hypotension died, compared with ten (71%) of 14 patients in the magnesium group. Severe autonomic instability was observed in 11 of these deaths (six in the placebo group; five in the magnesium group).

Discussion

Our results show that magnesium infusions for the treatment of severe tetanus in adults did not affect the requirement for mechanical ventilation, either during the 7 days of infusion or for the rest of the hospital stay. However, such infusions did improve both muscle spasm control and cardiovascular stability, as shown by a significant reduction in the daily requirement of both sedation (midazolam) and neuromuscular blockade (pipecuronium). There was no effect on survival.

The primary outcome measure chosen in this trial was the need for ventilation. Although a smaller proportion of adults required ventilation in the magnesium group than in the placebo group, this difference was not significant. Indeed, if the difference seen was to be a trend that continued, the magnitude of this difference would necessitate a trial with at least 820 people in both treatment arms to achieve adequate power. The clinical significance of such a difference would be questionable.

Placing our results into the context of previous research is difficult given that there are no previous randomised controlled trials in this area. Published uncontrolled studies suggest magnesium controls spasms, reduces the requirement for neuromuscular blocking agents, and reduces the requirement for mechanical ventilation.[22–24] However, differences in study design and magnesium administration between these studies and our trial could account for the conflicting data. Previous investigators were able to titrate the rate of magnesium infusion to treatment effect; blinding made this impossible during our trial. Also, we studied only patients with a tracheostomy in situ because of concern that magnesium might increase the need for mechanical ventilation by causing sufficient muscle weakness to induce acute respiratory failure. Therefore, for safety reasons, only those with a tracheostomy and immediate

	Placebo group	Magnesium group	p value
Sepsis*	10 (10%)	4 (4%)	0·103
Urinary tract infection†	25 (26%)	24 (24%)	1·000
Pneumonia‡	46 (47%)	48 (49%)	0·886
Acute renal failure§	4 (4%)	3 (3%)	0·721
Arrythmia¶	3 (3%)	1 (1%)	0·369
Cardiac arrest	1 (1%)	2 (2%)	1·000
Hypotension‖	10 (10%)	12 (12%)	0·822
Pressure sore**	21 (22%)	14 (14%)	0·262

*White blood cell count ≤4×10⁹/L or ≥12×10⁹/L and pathogenic microorganism in blood. †Pathogenic microorganism in urine and either fever ≥38°C or white blood cell count ≤4×10⁹/L or ≥12×10⁹/L. ‡Presence of new and persistent infiltrates on chest radiograph plus two of the following three criteria: fever ≥38°C, white blood cell count ≤4×10⁹/L or ≥12×10⁹/L, or purulent tracheal secretions; pathogenic microorganism in blood or pleural fluid or in non-directed bronchial lavage at ≥105 colony forming units per mL. §Urine output < 1 mL/kg per h for more than 4 h or serum creatinine >2 mg/dL. ¶Electrocardiogram evidence of heart block or other conduction abnormality or bradycardia <50 bpm. ‖Systolic blood pressure <80 mm Hg unresponsive to 500 mL fluid challenge, or requiring inotropic support. **Diagnosed according to local protocol by skilled senior nursing staff.

Table 3: **Adverse events reported throughout hospital admission**

access to a mechanical ventilator entered our study. Our results suggest that these precautions were unnecessary and that future investigations could safely include patients either before a tracheostomy is done or in those patients in whom the disease is less severe. Indeed, as previous investigations have suggested, magnesium might have a greater benefit in these groups.[24] We also chose to limit the administration of magnesium to the first 7 days of therapy because previous data from our hospital suggested that the requirement for ventilation and mortality was greatest in this period.[2] Most patients entered the study with established disease (median 5 days of illness). Therefore, magnesium was given predominantly in the second week of illness, the time when autonomic dysfunction and muscle spasms are greatest. Prolonged treatment into the third week of disease, as reported by Attygalle and Rodrigo,[24] could have additional benefits. Further controlled trials are required to explore these possibilities.

Like previous reports,[22–24] our results show that magnesium had a significant effect on muscle spasm control and on cardiovascular stability. The control of muscle spasm is central to the management of all patients with tetanus. In this study, conventional first-line treatment was high-dose diazepam followed by a non-depolarising neuromuscular blocking agent—pipe-curonium—for more severe disease. If these agents failed to control spasm, diazepam was replaced with midazolam. Therefore, the observed reduction in pipecuronium and midazolam use in the magnesium group is a significant clinical result and suggests that magnesium could be an effective and inexpensive alternative to these drugs. This assessment is strongly supported by the trial's double blind design, whereby the attending doctors used diazepam, pipecuronium, and midazolam without bias to the potential effect of magnesium.

An unexpected finding was the higher serum concentration of creatine kinase in those given magnesium.

Creatine kinase is released from damaged or active muscle and so higher concentrations would be expected in those with more severe spasms rather than in those in whom the spasms had been lessened. The most plausible explanation for this finding is that pipecuronium reduces the release of creatine kinase by causing complete muscle paralysis. Because the placebo group had to be given more pipecuronium than the magnesium group to control the spasms they paradoxically have lower serum concentrations of creatine kinase.

Autonomic dysfunction is a life-threatening complication of tetanus that manifests as fluctuating heart rate, blood pressure, and temperature. This complication is very difficult to manage, especially if intensive care support is not available. In the unit where the study took place, verapamil is the first-line treatment for these complications and was therefore assessed as a means of assessing the extent of autonomic dysfunction. The requirement for verapamil was significantly reduced in those individuals who received magnesium. The predominant effect of magnesium was a significant reduction in tachycardia (both mean daily heart rate and area under the heart rate time-curve), presumably as a result of attenuation of sympathetic overactivity, since magnesium does not reduce heart rate in healthy individuals.[31] Although there was no obvious effect on mean daily systolic or diastolic blood pressures, there was a lower incidence of very low blood diastolic pressure readings in patients on magnesium.

A major objective of this study was to characterise the safety profile of magnesium in severe tetanus. In other conditions—eg, eclampsia—magnesium has been shown to be safe, but extrapolating to a very different disease state and in different populations—eg, elderly patients—would be unwise. Our study provides a reassuring safety profile of magnesium in severe tetanus. There were no obvious problems using magnesium in conjunction with either benzodiazepines or muscle relaxants or indeed both, in elderly patients, and over long periods. The infusion protocol was satisfactory and produced consistent serum concentrations within the target range. Magnesium infusions did not induce substantial respiratory depression, and had few cardiovascular effects.

Thus, although magnesium treatment alone does not reduce the need for mechanical ventilation in adults with severe tetanus in whom a tracheostomy had been done, its use reduces the requirement for other muscle relaxants and improves cardiovascular instability. Magnesium is safe, inexpensive, and suitable for use in the developing world. Benefits could be greater in settings with little or no intensive care support. Magnesium is thus an important therapeutic advance in treating a major cause of morbidity and mortality in the developing world. Further work is needed to define its role in the less severely ill and in settings with limited facilities.

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