MHRA Final Study Report

The 3Mg Trial: A randomised trial of intravenous or nebulised magnesium sulphate versus placebo for acute severe asthma.

EudraCT Number	2007-001187-78
ISRCTN Number	00441706
Sponsor's name and address	STH NHS Foundation Trust 1st Floor 11 Broomfield Road Sheffield S10 2SE UK
Sponsor Protocol Number	STH14731
Investigational Drugs	Magnesium Sulphate Heptahydrate ($MgSO_4.7H_2O$)
Date of Report	03/01/2017

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Medicinal product

The active substance was given to the patient in one of two forms:
a. Magnesium sulphate, intravenous: This product was provided as a solution for infusion, 8 mmol (millimoles) and was administered via Intravenous bolus use (Noncurrent).
b. Magnesium sulphate, nebulised: This product was provided as nebuliser solution, 6 mmol (3 doses of 2mmol in 7.5ml) and is administered via Inhalation use.

Placebos were also used in this trial, both forms (IV and nebuliser) were sterile solutions containing 0.9%w/v Sodium Chloride in Water for Injections

Worldwide Marketing Approval Status

The IMP used in this clinical trial does not have a marketing authorisation for this indication (acute severe asthma).

Magnesium chloride is an inorganic salt with a long history of usage as a pharmaceutical material and is non-proprietary. Presentations of magnesium sulphate for oral or topical use are available for sale to the public. Other preparations containing magnesium sulphate are used for a variety of purposes including the treatment of hypomagnesaemia, arrhythmias, as an anticonvulsant for eclampsia and pre-eclampsia, and for the prevention of premature labour. There are a number of licensed injectable preparations suitable for intravenous or intramuscular use, which are formulated as simple solutions in water for injections and sterilised by autoclaving. Magnesium sulphate and magnesium sulphate injection are subject to monographs in the European Pharmacopoeia.

Table 1. Cumulative exposure of participants

1109 patients were randomised to the trial. Allocation to the treatment arms was by randomisation in a 1:1:1 ratio, stratified by recruiting site. The actual exposure (patients receiving treatment once randomised) are displayed in the table below. A full explanation of actual exposure and those included or excluded from the main trial analyses is reported in the results section on page 7.

Treatment Arm	Number randomised	Number of patients exposed
IMP: Magnesium Sulphate - route IV	406	396
IMP: Magnesium Sulphate - route nebulised	339	333
Placebo: Saline	364	358

Safety Data

Reference Information

The Sponsor's Standard Operating Procedure for SAE reporting was followed.

The 3Mg Investigator's Brochure, Version 2, 05JAN09, was the latest version of the Reference Safety Information and included details of expectedness. Patients were followed up for 30 days following exposure to the IMP as per the trial protocol.

Cumulative summary tabulations of SAEs have been assessed as being either related to the underlying patient disease (respiratory), related to the study drug received, or unrelated to either the underlying disease or study drug.

Line listings of SARs during report period

No SARs reported

Cumulative Summary Tabulations of SAEs

Cumulative SAEs reported for all participants during the duration of the trial recruitment and follow-up (30/07/2008 – 31/07/2012). None were assessed as being related to the medicinal product.

There were very few adverse events in the pre-specified categories: seven patients required intubation, seven required non-invasive ventilation, two patients suffered an arrhythmia, one patient suffered a cardiac arrest and two died. However, the definition of an adverse event used in the trial included any subsequent hospitalisation. A substantial number of patients were therefore recorded as having an adverse event by virtue of subsequent admission to hospital, either due to worsening of their asthma or other unrelated problems.

Cumulative SAEs are detailed in the table 2, categorised by treatment received, and type of event.

The total number of patients included in the cumulative SAE data (N=1085, table 2) differs from the numbers in cumulative exposure (N=1087, table 1). One patient in the nebulised arm was subsequently found to be ineligible as they were a prisoner. Two patients in the IV magnesium arm had been included previously and recruited in error during a subsequent Emergency Department attendance. One of the ineligible patients in the IV arm experienced an SAE, so they are included in the summary SAE results table, but the other two ineligible patients are not.

Table 2 – Cumulative Summary Tabulations of SAEs

Serious adverse events

Study allocation: received and analysed	Nebulised magnesium sulphate (N=332)	IV magnesium sulphate (N=395)	Placebo (N=358)	Overall (N=1085)
Any serious adverse event	35 (10.5%)	45 (11.4%)	28 (7.8%)	108 (10.0%)
Arrhythmia	0	1 (0.3%)	0	1 (0.1%)
Cardiac arrest	0	1 (0.3%)	0	1 (0.1%)
Death	1 (0.3%)	1 (0.3%)	0	2 (0.2%)
Intubation	2 (0.6%)	4 (1.0%)	1 (0.3%)	7 (0.6%)
Non-invasive ventilation	0	1 (0.3%)	3 (0.8%)	4 (0.4%)
Other asthma related	24 (7.2%)	23 (5.8%)	21 (5.9%)	68 (6.3%)
Other non-asthma related	8 (2.4%)	14 (3.6%)	5 (1.4%)	27 (2.5%)

Numbers refer to patients experiencing an event of each type.
Total number of events will not equal the sum of individual events if a patient experiences multiple events.

Summary of overall safety assessment:
Magnesium Sulphate has been used in standard practice for many years and has an excellent safety profile. No significant new information has been identified during this clinical trial.

Summary of important risks:
No new information regarding the risk of using Magnesium Sulphate in the study population has been identified.

Study Design / Executive Summary

Objectives

We aimed to measure the effectiveness and cost-effectiveness of IV and nebulised magnesium sulphate in acute severe asthma. Our specific objectives were to determine whether: (1) IV or nebulised magnesium sulphate reduces the proportion of patients who require admission at initial presentation or during the following week; and (2) IV or nebulised magnesium sulphate improves patient assessment of their breathlessness over two hours after initiation of treatment. We also measured the effect of IV or nebulised magnesium sulphate on: length of hospital stay; use of the intensive care unit (ICU) or high dependency unit (HDU); mortality; adverse events and use of respiratory support; change in peak expiratory flow rate (PEFR) and physiological variables after initial treatment; health utility; patient satisfaction with care; use of health and social services over the following month; time taken off work; health and social care costs.

Methods

We undertook a multi-centre, double blind, placebo controlled, three-arm, randomised trial in 34 emergency departments in the United Kingdom. Adults (age>16) attending the emergency department (ED) with acute severe asthma were eligible for recruitment (i.e. acute asthma with either PEFR < 50% of best or predicted, respiratory rate > 25/min, heart rate > 110/min, or inability to complete sentences in one breath). We excluded patients who had life threatening features, a contraindication to either nebulised or IV magnesium sulphate (pregnancy, hepatic or renal failure, heart block or known hypermagnesaemia), those unable to provide written or oral consent, and previous participants in the 3Mg trial. We amended the protocol during the trial to also exclude those who had received magnesium sulphate in the 24 hours prior to recruitment. Written or verbal consent was sought from all participants.

Consented participants were randomised to either: (1) IV magnesium sulphate, 8 mmol (2g) in 100ml normal saline given over 20 minutes, and three 7.5ml vials of 0.9% saline nebulised at 20 minute intervals; or (2) IV normal saline, 100ml given over 20 minutes, and three 7.5ml vials of 2 mmol (500mg) magnesium sulphate nebulised at 20 minute intervals; or (3) IV normal saline, 100ml given over 20 minutes, and three 7.5ml vials of 0.9% saline nebulised at 20 minute intervals.

Standard therapy was provided in accordance with guidelines from the British Thoracic Society (BTS) and Scottish Intercollegiate Guidelines Network (SIGN) and consisted of oxygen, nebulised salbutamol, nebulised ipratropium and oral prednisolone administered during recruitment, followed by up to 5mg salbutamol added to each trial nebuliser. Other treatments were given at the discretion of the clinician.

Two primary outcomes were specified: (1) Admission to hospital, either after ED treatment or at any time over the subsequent week; (2) Visual analogue scale (VAS) for breathlessness over two hours after initiation of treatment. Secondary outcomes included: mortality; adverse events; use of ventilation or respiratory support; length of hospital stay; use of ICU or HDU; change in PEFR and physiological variables (oxygen saturation, heart rate, respiratory rate, blood pressure) over two hours; quality of life at baseline and one month; number of unscheduled health care contacts over the subsequent month; satisfaction with care.

We planned to recruit 1200 participants divided equally between the three trial arms (400 per arm) to provide the following statistical power: (1) Assuming that 80% of patients with acute severe asthma were admitted to hospital the study would have 90% power to detect a 10% absolute reduction in the proportion admitted (i.e. to 70%) for any pair of treatment groups compared (two-sided alpha=0.05); (2) Assuming that 80% of participants have their VAS measured then the study would have 90% power to detect a 0.8cm difference in a 10cm VAS at two hours after treatment initiation (two-sided alpha=0.05). Based on the pre-existing evidence we selected two primary comparisons for analysis: (1) Active treatment (IV and nebulised combined) versus placebo, and (2) IV versus nebulised treatment. Secondary comparisons were undertaken between IV treatment and placebo, and between nebulised treatment and placebo.

Economic evaluation took an approach consistent with the National Institute for Health and Clinical Excellence (NICE) reference case analysis and the perspective of the NHS and personal social services. Health benefits were measured in two ways using trial data: (1) Quality adjusted life years (QALYs) using the EQ-5D over a 30 day time horizon; (2) Breathlessness on a 100mm VAS at one and two hours after the initiation of study treatment. Resource use relating to hospital care, community health and social services and medications were collected using either the hospital records or patient questionnaire. Productivity loss as a consequence of the number of days patients took off work during the study was collected using the patient

questionnaire and separate analyses were conducted excluding and including productivity loss. The primary economic analysis was a cost-effectiveness analysis using the QALYs associated with treatment, focussing on the probability that the intervention arms would be cost-effective at funding thresholds of £20,000 and £30,000 per QALY. Additionally, the change from baseline in breathlessness 2-hours after the initiation of study treatment was used as a secondary cost-effectiveness analysis.

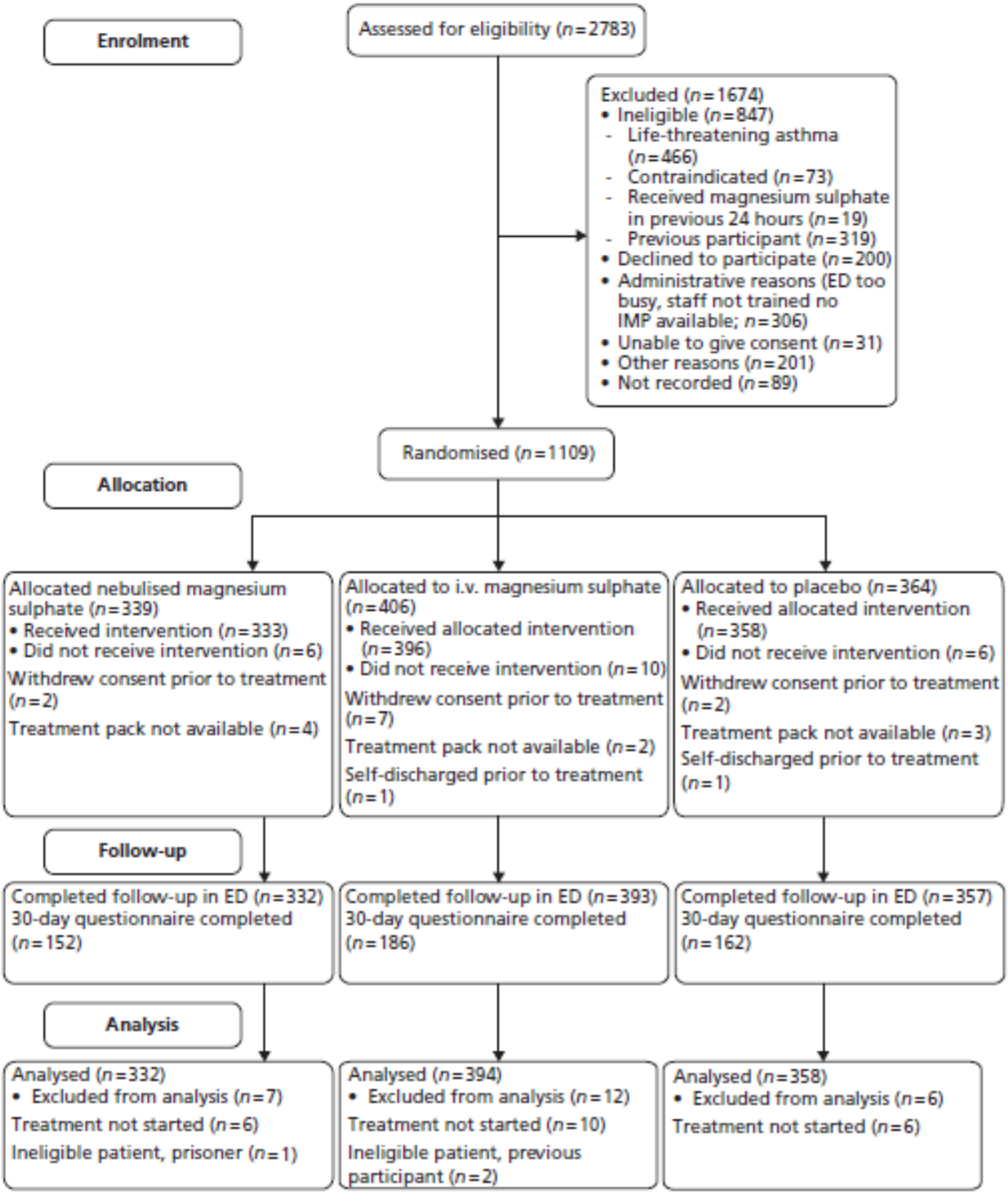
We also planned to undertake an additional analysis of trial data to identify factors that predict unsuccessful treatment for acute severe asthma. We examined the ability of PEFR, physiological variables, age, sex, ethnicity, smoking status, and previous hospital, high dependency and intensive care admissions to predict unsuccessful treatment, defined at two levels: 1) Need for critical care (HDU or ICU admission, ventilator support, respiratory arrest, cardiac arrhythmia or death); 2) Need for emergency medical treatment, either by return to the ED or unscheduled medical review as an inpatient. Univariate analysis was undertaken to identify factors that are associated with either outcome ($p<0.15$), which were then entered into multivariate models for each outcome to identify independent predictors of unsuccessful treatment.

Results

Patients were recruited across 34 hospitals between 30/7/2008 and 30/6/2012.

The CONSORT flow chart (Figure 1) shows the flow of participants through the trial. Of the 1109 participants randomised, 25 were excluded from the analysis. Eleven patients received no medication and no data were collected after randomisation. These patients either withdrew consent prior to any medication being delivered or recruiting doctors had randomised them before taking consent and patients subsequently refused consent. Two patients self-discharged without being treated. There were nine occasions where the numbered medication pack was not available in the ED and no treatment was subsequently given. The remaining three patients received treatment but there were protocol violations and these patients should not have been recruited: two were subsequently found to be previous participants and one was a prisoner. All remaining 1084 patients were included in analyses according to intention-to-treat principles, regardless of whether or not they received any medication.

Figure 1: CONSORT flow chart



Mean age of participants was 36.1 years, 763 (70%) were female, 974 (90%) were white and 363 (33%) were current smokers. Salbutamol was given to 1074/1084 participants (99%) in the ambulance or ED prior to randomisation or up to four hours after, with a mean total dose of 8.3mg (standard deviation (SD) 3.4). Overall, 1032/1084 (95%) of the trial population received corticosteroid therapy at some point from 24 hours prior to hospital attendance to four hours after randomisation. Adherence to the trial protocol was high with 89% receiving the full 100ml IV infusion and 99% receiving three trial nebulisers.

The proportion admitted to hospital was 285/394 (72%) in the IV magnesium sulphate group, 261/332 (79%) in the nebulised group and 281/358 (78%) in the placebo group. The odds ratios for admission to hospital were 0.84 (95% CI 0.61 to 1.15, p=0.276) for active treatment versus placebo, 0.76 (0.53 to 1.10, p=0.146) for IV versus nebuliser, 0.73 (0.51 to 1.04, p=0.083) for IV versus placebo, and 0.96 (0.65 to1.40, p=0.819) for nebuliser versus placebo.

The change in VAS at two hours was recorded in 976/1084 (90%) of the cohort. The mean (SD) change from baseline to two hours was 34.3 (27.7) mm in the IV group, 28.2 (27.4) mm in the nebulised group and 31.3 (29.4) mm in the placebo group. The mean differences in improvement in VAS were 0.0 (95% CI -1.9 to 1.9, p=0.999) for active treatment versus placebo, 5.1 (0.8 to 9.4, p=0.019) for IV versus nebuliser, 2.6 (-1.6 to 6.8, p=0.231) for IV versus placebo, and -2.6 (-7.0 to 1.8, p=0.253) for nebuliser versus placebo.

Mean (SD) length of hospital stay was 57.0 (75.1) hours in the IV group, 63.2 (79.7) in the nebuliser group and 63.3 (84.3) in the placebo group (overall logrank test, p=0.48). The number (%) in each group admitted to ICU was 11 (3%) in the IV group, 9 (3%) in the nebulised group and 5 (1%) in the placebo group (p=0.161 active versus placebo, p=0.947 IV versus nebuliser). The number (%) admitted to HDU was 23 (6%) in the IV group, 22 (7%) in the nebuliser group and 20 (6%) in the placebo group (p=0.690 active versus placebo, p=0.661 IV versus nebuliser). The number (%) requiring ventilator support was 6 (2%) in the IV group, 3 (1%) in the nebuliser group and 4 (1%) in the placebo group (p=0.936 active versus placebo, p=0.458 IV versus nebuliser).

The mean (SD) change from baseline to two hours in PEFR was 61.0L/min (73.6) in the IV group, 58.3L/min (77.3) in the nebulised group and 62.5L/min (69.4) in the placebo group. The

mean differences in improvement in PEFR were -2.5 (95% CI -12.5 to 7.5, p=0.625) for active treatment versus placebo, 0.3 (-11.2 to 11.7, p=0.964) for IV versus nebuliser, -2.4 (-13.6 to 8.8, p=0.680) for IV versus placebo, and -2.6 (-14.5 to 9.2), p=0.664) for nebuliser versus placebo. There were no significant differences in the primary comparisons for other physiological secondary outcomes (heart rate, respiratory rate, blood pressure and oxygen saturation).

Rates of adverse events were low, with most of the events recorded being hospital admission due to underlying asthma or other unrelated conditions. There were two deaths, one cardiac arrest, two cases of arrhythmia, seven intubations and seven cases requiring non-invasive ventilation (17 patients). The number (%) of patients reporting any side effect was 61 (15.5%) in the IV group, 52 (15.7%) in the nebuliser group and 36 (10.1%) in the placebo group. The odds ratios for suffering any side effect were 1.68 (95% CI 1.11 to 2.52, p=0.014) for active treatment versus placebo, 1.00 (0.66 to 1.52, p=0.988) for IV versus nebuliser, 1.68 (1.07 to 2.63, p=0.025) for IV versus placebo, and 1.67 (1.05 to 2.66, p=0.031) for nebuliser versus placebo.

Satisfaction with care was generally high across all three treatment groups and across most dimensions of care. The dimensions of care relating to personal interest in the patient and their medical problems, the amount of time given by hospital staff, and especially advice given about ways to avoid illness and stay healthy were generally rated lower. There were no significant differences in any of the primary comparisons between the treatment groups.

Mean EQ5D (SD) scores at baseline were 0.726 (0.354) in the IV group, 0.734 (0.327) in the nebulised group and 0.746 (0.323) in the placebo group. Corresponding scores at one month were 0.731 (0.329), 0.721 (0.326) and 0.810 (0.250). There were no significant differences in any of the comparisons between treatment groups.

Conclusions

We were unable to demonstrate a clinically worthwhile benefit from magnesium sulphate in acute severe asthma. IV magnesium sulphate was associated with a lower rate of hospital admission than placebo, but the difference was not significant, and there was no evidence of an effect upon VAS breathlessness compared to placebo. There was also no evidence of any clinically worthwhile effect from IV magnesium sulphate upon secondary outcome measures, including PEFR. We found no evidence that nebulised magnesium sulphate was more effective than placebo. In fact, any non-significant trends in the outcomes involving nebulised magnesium sulphate tended to favour placebo.

Adherence to the trial protocol was high and most patients received appropriate co-treatments. Patients generally responded well to treatment with improvements in breathlessness and PEFR, and a low rate of requirement for ventilator support, HDU or ICU care. This suggests that optimal treatment with salbutamol, ipratropium and corticosteroids may leave little scope for further improvement with magnesium sulphate.

Literature

Results of the 3Mg trial have been published in The Lancet Respiratory Medicine Journal and as a HTA Monograph:

Goodacre S, Cohen J, Bradburn M, Gray A, Benger J & Coats T (2013). Intravenous or nebulised magnesium sulphate versus standard therapy for severe acute asthma (3Mg trial): A double-blind, randomised controlled trial. *The Lancet Respiratory Medicine*, 1(4), 293-300.

Goodacre S, Cohen J, Bradburn M, Stevens J, Gray A, Benger J, *et al* (2014). The 3Mg trial: a randomised controlled trial of intravenous or nebulised magnesium sulphate versus placebo in adults with acute severe asthma. *Health Technol Assess,* 18 (22).