The 3Mg trial: a randomised controlled trial of intravenous or nebulised magnesium sulphate versus placebo in adults with acute severe asthma

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Declared competing interests of authors: none

Scientific summary

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Background

Magnesium sulphate, administered by the intravenous (i.v.) or inhaled (nebulised) route, has been proposed as a treatment for acute severe asthma. Meta-analysis of 11 trials (1018 patients) of i.v. magnesium sulphate in adults with acute asthma showed evidence of an effect on respiratory function [standardised mean difference (SMD) 0.35, 95% confidence interval (CI) 0.06 to 0.64; $p = 0.02$] but not hospital admission [relative risk (RR) 0.85, 95% CI 0.68 to 1.06; $p = 0.14$]. Meta-analysis of seven trials (430 patients) of nebulised magnesium sulphate in adults with acute asthma showed weak evidence of improved respiratory function (SMD 0.17, 95% CI –0.02 to 0.36; $p = 0.09$) but not hospital admission (RR 0.87, 95% CI 0.70 to 1.08; $p = 0.22$). No previous trials have directly compared i.v. with nebulised magnesium sulphate. It is not clear whether changes in measures of respiratory function are associated with important changes in patient management or a clinically meaningful improvement in symptoms.

Objectives

We aimed to measure the effectiveness and cost-effectiveness of i.v. and nebulised magnesium sulphate in acute severe asthma. Our specific objectives were to determine whether (1) i.v. or nebulised magnesium sulphate reduces the proportion of patients who require admission at initial presentation or during the following week and (2) i.v. or nebulised magnesium sulphate improves patients' assessment of their breathlessness over 2 hours after initiation of treatment. We also measured the effect of i.v. 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; and health and social care costs.

Methods

We undertook a multicentre, double-blind, placebo-controlled, three-arm, randomised trial in 34 emergency departments (EDs) in the UK. Adults (age > 16 years) attending the ED with acute severe asthma were eligible for recruitment (i.e. acute asthma with either PEFR < 50% of best or predicted, respiratory rate > 25 breaths per minute, heart rate > 110 beats per minute or inability to complete sentences in one breath). We excluded patients who had life-threatening features, a contraindication to either nebulised or i.v. 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 patients 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) i.v. magnesium sulphate, 8 mmol (2 g) in 100 ml normal saline given over 20 minutes and three 7.5-ml vials of 0.9% saline nebulised at 20-minutes intervals; or (2) i.v. normal saline, 100 ml given over 20 minutes and three 7.5-ml vials of 2 mmol (500 mg) magnesium sulphate nebulised at 20-minute intervals; or (3) i.v. normal saline, 100 ml given over 20 minutes and three 7.5-ml vials of 0.9% saline nebulised at 20-minute intervals.

Standard therapy was provided in accordance with guidelines from the British Thoracic Society and Scottish Intercollegiate Guidelines Network (SIGN) and consisted of oxygen, nebulised salbutamol, nebulised ipratropium bromide and oral prednisolone administered during recruitment, followed by up to 5 mg of 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, and (2) visual analogue scale (VAS) for breathlessness over 2 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 2 hours; quality of life at baseline and at 1 month; number of unscheduled health-care contacts over the subsequent month; and satisfaction with care.

We planned to recruit 1200 participants divided equally between the three trial arms (400 participants 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 $\alpha = 0.05$); and (2) assuming that 80% of participants have their VAS measured, then the study would have 90% power to detect a 0.8-cm difference in a 10-cm VAS at 2 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 (i.v. and nebulised combined) compared with placebo and (2) i.v. compared with nebulised treatment. Secondary comparisons were undertaken between i.v. treatment and placebo, and between nebulised treatment and placebo.

Economic evaluation took an approach consistent with the National Institute for Health and Care 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 European Quality of Life-5 Dimensions (EQ-5D) over a 30-day time horizon and (2) breathlessness on 100-mm VAS at 1 and 2 hours after the initiation of study treatment. Resource use data relating to hospital care, community health and social services, and medications were collected using either the hospital records or a patient questionnaire. Productivity loss as a consequence of the number of days patients took off work during the study was determined 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, focusing 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) and (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 July 2008 and 30 June 2012. Of the 1109 patients recruited, 25 either withdrew or were recruited in error (protocol violations) and, therefore, 1084 were

included in the analysis. The mean age of patients was 36.1 years; 763 (70%) were female, 974 (90%) were white and 363 (33%) were current smokers. Salbutamol was given to 1074 out of 1084 participants (99%) in the ambulance or ED prior to randomisation or up to 4 hours after, with a mean total dose of 8.3 mg [standard deviation (SD) 3.4 mg]. Overall, 1032 out of 1084 (95%) of the trial population received corticosteroid therapy at some point from 24 hours prior to hospital attendance to 4 hours after randomisation. Adherence to the trial protocol was high, with 89% receiving the full 100-ml i.v. infusion and 99% receiving three trial nebulisers.

The proportion of participants admitted to hospital was 285 out of 394 (72%) in the i.v. magnesium sulphate group, 261 out of 332 (79%) in the nebulised group and 281 out of 358 (78%) in the placebo group. The odds ratios (ORs) for admission to hospital were 0.84 (95% CI 0.61 to 1.15; $p = 0.276$) for active treatment compared with placebo, 0.76 (95% CI 0.53 to 1.10; $p = 0.146$) for i.v. compared with nebuliser, 0.73 (95% CI 0.51 to 1.04; $p = 0.083$) for i.v. compared with placebo and 0.96 (95% CI 0.65 to 1.40; $p = 0.819$) for nebuliser compared with placebo.

The change in VAS at 2 hours was recorded in 976 out of 1084 (90%) of the cohort. The mean (SD) change from baseline to 2 hours was 34.3 mm (SD 27.7 mm) in the i.v. group, 28.2 mm (SD 27.4 mm) in the nebulised group and 31.3 mm (SD 29.4 mm) in the placebo group. The mean differences in improvement in VAS were 0.0 mm (95% CI –3.7 to 3.7 mm; $p = 0.999$) for active treatment compared with placebo, 5.1 mm (95% CI 0.8 to 9.4 mm; $p = 0.019$) for i.v. compared with nebuliser, 2.6 mm (95% CI –1.6 to 6.8 mm; $p = 0.231$) for i.v. compared with placebo and –2.6 mm (95% CI –7.0 to 1.8, $p = 0.253$) for nebuliser compared with placebo.

Mean (SD) length of hospital stay was 57.0 hours (SD 75.1 hours) in the i.v. group, 63.2 hours (SD 79.7 hours) in the nebuliser group and 63.3 hours (SD 84.3 hours) in the placebo group (overall log-rank test, $p = 0.48$). The number of participants (%) in each group admitted to ICU was 11 (3%) in the i.v. group, nine (3%) in the nebulised group and five (1%) in the placebo group ($p = 0.161$ active vs. placebo; $p = 0.947$ i.v. vs. nebuliser). The number of participants (%) admitted to HDU was 23 (6%) in the i.v. group, 22 (7%) in the nebuliser group and 20 (6%) in the placebo group ($p = 0.690$ active vs. placebo, $p = 0.661$ i.v. vs. nebuliser). The number of participants (%) requiring ventilator support was six (2%) in the i.v. group, three (1%) in the nebuliser group and four (1%) in the placebo group ($p = 0.936$ active vs. placebo; $p = 0.458$ i.v. vs. nebuliser).

The mean (SD) change from baseline to 2 hours in PEFR was 61.0 l/minute (SD 73.6 l/minute) in the i.v. group, 58.3 l/minute (SD 77.3 l/minute) in the nebulised group and 62.5 l/minute (69.4 l/minute) 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 compared with placebo, 0.3 (95% CI –11.2 to 11.7; $p = 0.964$) for i.v. compared with nebuliser, –2.4 (95% CI –13.6 to 8.8; $p = 0.680$) for i.v. compared with placebo and –2.6 (95% CI –14.5 to 9.2; $p = 0.664$) for nebuliser compared with 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 i.v. group, 52 (15.7%) in the nebuliser group and 36 (10.1%) in the placebo group. The ORs for suffering any side effect were 1.68 (95% CI 1.11 to 2.52; $p = 0.014$) for active treatment compared with placebo, 1.00 (95% CI 0.66 to 1.52; $p = 0.988$) for i.v. compared with nebuliser, 1.68 (95% CI 1.07 to 2.63; $p = 0.025$) for i.v. compared with placebo and 1.67 (95% CI 1.05 to 2.66; $p = 0.031$) for nebuliser compared with 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.

The mean EQ-5D scores at baseline were 0.726 (SD 0.354) in the i.v. group, 0.734 (SD 0.327) in the nebulised group and 0.746 (SD 0.323) in the placebo group. Corresponding scores at 1 month were 0.731 (SD 0.329), 0.721 (SD 0.326) and 0.810 (SD 0.250). There were no significant differences in any of the comparisons between treatment groups.

The primary economic analysis (without productivity costs) showed mean QALYs per patient of 0.060 (SD 0.0033), 0.060 (SD 0.0028) and 0.063 (SD 0.0030), and mean costs per patient of £1870 (SD £110.80), £1974 (SD £115.30) and £1610 (SD £89.70) for the i.v., nebulised and placebo groups respectively. Mean costs per patient increased to £2219 (SD £120.40), £2401 (SD £120.80) and £2007 (SD £107.20), respectively, when productivity costs were included. There was a 93% and 92% chance that the placebo had the highest net benefit at thresholds of £20,000 and £30,000 respectively.

The baseline PEFR ($p = 0.017$), baseline heart rate ($p < 0.001$), change in PEFR after treatment ($p = 0.015$), change in heart rate after treatment ($p < 0.001$) and the presence of another serious illness ($p = 0.019$) predicted the need for critical care. The baseline PEFR ($p = 0.010$), baseline heart rate ($p < 0.001$), baseline respiratory rate ($p = 0.017$), change in PEFR after treatment ($p = 0.003$), change in heart rate after treatment ($p = 0.001$) and the presence of another serious illness ($p = 0.023$) predicted the need for emergency medical treatment within 7 days.

Conclusions

We were unable to demonstrate a clinically worthwhile benefit from magnesium sulphate in acute severe asthma. Intravenous 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 on VAS breathlessness compared with placebo. There was also no evidence of any clinically worthwhile effect from i.v. magnesium sulphate on 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 the placebo.

Adherence to the trial protocol was high and most patients received appropriate cotreatments. 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 bromide and corticosteroids may leave little scope for further improvement with magnesium sulphate.

Trial registration

This trial is registered as ISRCTN04417063.

Funding

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