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# Magnesium sulphate in acute severe asthma in children (MAGNETIC): a randomised, placebo-controlled trial

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## Summary

**Background** **Little evidence is available for the effect of nebulised magnesium sulphate ($MgSO_4$) in acute asthma in children. We assessed the effect of $MgSO_4$ treatment in children with severe acute asthma.**

**Methods** **In this randomised placebo-controlled, multi-centre, parallel trial, we enrolled children (aged 2–16 years) with severe acute asthma who did not respond to standard inhaled treatment from 30 hospitals in the UK. Children were randomly allocated (1:1) to receive nebulised salbutamol and ipratropium bromide with either 2·5 mL of isotonic $MgSO_4$ (250 mmol/L; 151 mg per dose; $MgSO_4$ group) or 2·5 mL of isotonic saline (placebo group) on three occasions at 20-min intervals. Randomisation was done with a computer-generated randomisation sequence, with random block sizes of two to four. Both patients and researchers were masked to treatment allocation. The primary outcome measure was the Yung Asthma Severity Score (ASS) at 60 min post-randomisation. We used a statistical significance level of p<0·05 for a between-group difference, but regarded a between-group difference in ASS of 0·5 as the minimal clinically significant treatment effect. Analysis was done by intention to treat. This trial is registered with controlled-trials.com, number ISRCTN81456894.**

**Findings** **Between Jan 3, 2009, and March 20, 2011, we recruited and randomly assigned 508 children to treatment: 252 to $MgSO_4$ and 256 to placebo. Mean ASS at 60 min was lower in the $MgSO_4$ group (4·72 [SD 1·37]) than it was in the placebo group (4·95 [SD 1·40]; adjusted difference –0·25, 95% CI –0·48 to –0·02; p=0·03). This difference, however, was not clinically significant. The clinical effect was larger in children with more severe asthma exacerbation (p=0·03) and those with symptoms present for less than 6 h (p=0·049). We detected no difference in the occurrence of adverse events between groups.**

**Interpretation** **Overall, nebulised isotonic $MgSO_4$, given as an adjuvant to standard treatment, did not show a clinically significant improvement in mean ASS in children with acute severe asthma. However, the greatest clinical response was seen in children with more severe attacks ($SaO_2$<92%) at presentation and those with preceding symptoms lasting less than 6 h.**

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## Introduction

Acute asthma is a major cause of acute hospital admission in children and accounts for much morbidity for children and their families.[1] The British Thoracic Society and Scottish Intercollegiate Guideline Network (BTS/SIGN) have developed evidence-based guidelines.[2] These guidelines set out criteria for the diagnosis of severe asthma and recommend that initial management be inhaled $\beta_2$ agonists and ipratropium bromide with systemic corticosteroids. For children who do not respond to initial inhaled treatment, intravenous bronchodilators are recommended. In adults with acute severe asthma, magnesium sulphate ($MgSO_4$) has bronchodilatory effects when given intravenously, and when it is mixed with $\beta_2$ agonists and ipratropium bromide and nebulised, it improves lung function compared with standard treatment in those with a more severe exacerbation of asthma.[3,4]

To our knowledge, only four studies have assessed nebulised $MgSO_4$ in children.[4] These studies were insufficiently powered and used differing definitions of asthma, primary outcomes, treatment regimens, and comparative groups. Thus no firm recommendations can be made from the conclusions of these studies. The aim of the MAGNETIC study was to examine the role of nebulised $MgSO_4$ treatment in children presenting with acute severe asthma.

## Methods

### Study design and participants

The MAGNETIC trial was a randomised, placebo-controlled, multicentre trial in severe acute asthma in children unresponsive to standard inhaled treatment, comparing nebulised $MgSO_4$ plus standard treatment versus placebo plus standard treatment. We recruited patients between Jan 3, 2009, and March 20, 2011. Eligible patients were aged 2–16 years presenting to an emergency department or a children's assessment unit in one of 30 hospitals in the UK. Acute severe asthma was defined by the BTS/SIGN guidelines.[2] Potential participants received local hospital-defined conventional treatment on presentation. After 20 min of conventional treatment,

patients were reassessed, and those who still fulfilled the criteria for severe asthma[2] were enrolled into the study and randomly allocated to receive nebulised salbutamol 2·5 mg (for children aged 2–5 years) or 5 mg (for those aged 6 years or older) and ipratropium bromide 0·25 mg mixed with either 2·5 mL of isotonic $MgSO_4$ (250 mmol/L, tonicity 289 milliosmole; 151 mg per dose) or 2·5 mL of isotonic saline on three occasions at roughly 20 min intervals. There is no specific agreed dose of $MgSO_4$ for use in children.[3,4] We chose the $MgSO_4$ dose for this study on the basis of doses shown to be effective and safe in adults with acute asthma.[5] All three drugs were mixed into one nebuliser and nebulised over 15–20 min. The frequency of the dosing was based on the three doses of bronchodilators given in the first hour of treatment.[2] The Yung Asthma Severity Score (ASS) was recorded at presentation,[6] at randomisation, and then at about 20 min (after first nebuliser treatment), 40 min (after second nebuliser treatment), 60 min (after third nebuliser treatment), 120 min, 180 min, and 240 min post-randomisation. Adverse events, concomitant medication, oxygen saturation, respiratory rate, and blood pressure were recorded at these assessment points. Adverse events were monitored and data collection continued until discharge from hospital to assess secondary outcome measures. Data for recruitment, treatment administration, clinical observations, and primary and secondary outcome measurements were collated by trained clinicians and research nurses on the delegation log at each centre, managed by the principal investigator at each site.

The study was approved by the UK National Health Service Multicentre Research Ethics Committee (MREC 07/H1010/101) and by the UK National Health Services Medicines for Children Research Network. Written informed consent was obtained from a parent or guardian of each child who was enrolled in the study. There was a 20 min period in this study from when the patient was being given initial treatment to the obtaining of informed consent.

***Panel 1:* Components of the Yung Asthma Severity Score**

**Wheeze**

- None (0 points)
- Expiratory (1 point)
- Expiratory and inspiratory (2 points)
- Heard without stethoscope (3 points)

**Accessory muscle use**

- No retraction or accessory muscle use (0 points)
- Soft tissue retraction only (1 point)
- Mild retraction of the lower ribs (2 points)
- Pronounced retraction of the lower ribs (3 points)

**Heart rate**

- <80 beats per min (0 points)
- 81–110 beats per min (1 point)
- 111–140 beats per min (2 points)
- >140 beats per min (3 points)

Minimum score is 0. Maximum score is 9. A higher score means more severe disease.

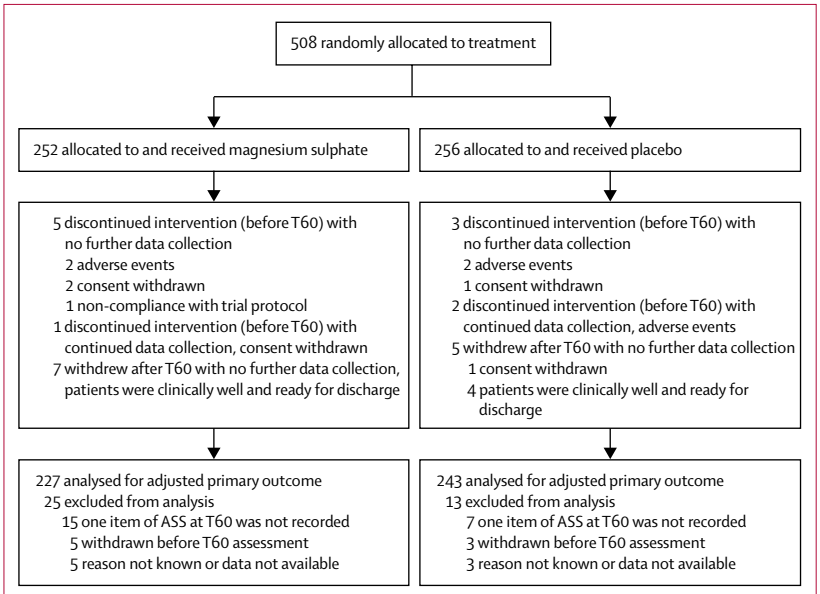


***Figure 1:* Trial profile**
We could not screen all patients presenting to all emergency departments with acute asthma, so we do not have a screening number denominator. ASS=Yung asthma severity score. 60 min post-randomisation.

## Randomisation and masking

Randomisation was stratified by centre. We used a computer-generated randomisation sequence, with random blocks of two to four and a one-to-one ratio of treatment allocation. The randomisation sequence was generated by an independent statistician at the Medicines for Children Research Network Clinical Trials Unit (Liverpool, UK), who had no further involvement in the study. Treatment packs were identical in appearance and numbered sequentially for each centre. Placebo and active treatment were manufactured by St Mary's Pharmaceutical Unit (Cardiff, UK). Both treatments were clear, colourless solutions. All participants (patients, clinicians, research team, and statisticians) were masked to the treatment allocation. The statistical analyses were completed with masked data, with treatment groups revealed only after final analyses had been completed.

## Outcomes

Our primary outcome was ASS score at 60 min post-randomisation (ASS at 1 h). This asthma severity score was chosen as a practical, easy to use, feasible measure (panel 1).[6] This severity score has been shown to have good inter-observer reliability with an overall weighted kappa score of 0·82 (95% CI 0·63–1·00) for the three components together and the score correlates with oxygen saturation, forced expiratory volume in 1 s, and heart rate.[6] A severe attack would be defined as a score greater than 6 (range 0–9).[7,8]

Secondary outcomes during hospitalisation were so-called stepping down of treatment at 1 h (defined as the change to metered dose inhaler and spacer combination only or no further treatment until discharge),[9] additional salbutamol administrations, length of stay in hospital, intravenous bronchodilator treatment, admission to a paediatric intensive care unit or high-dependency unit, and intubation. Health economic data were collected but these data will be published elsewhere.

### Statistical analysis

To detect a difference between the two treatment groups at 1 h of 0·5 points on the ASS at a 5% significance level with 80% power, 500 children were required to participate in the trial. These calculations assumed an SD equal to 1·95, which was based on a similar population in Australia.[6] There is no prior validated value for what is considered to be a clinically important change in an asthma severity score. On the basis of our pilot study of nebulised magnesium in children (MAGNET),[10] the trial steering group regarded a change in ASS of 0·5 to be the minimum worthwhile clinically important difference to be detected.

Baseline characteristics are presented by treatment group, with continuous variables summarised in terms of means (SD) or medians (IQR), depending on the degree of skew, and categorical variables are presented in terms of numbers (%) per category. We used the intention-to-treat principle with a two-sided p value of 0·05 for statistical significance and 95% CIs for the relative treatment effect reported throughout. The primary outcome is presented with means and SDs at 1 h for each treatment group. We used analysis of covariance to present results adjusted for baseline ASS value. We summarised all continuous secondary outcomes, which were non-normally distributed, in terms of medians and IQR for each treatment group and compared them using the Mann-Whitney *U* test. When a secondary outcome was categorical, we compared the two treatment groups using a $\chi^2$ test.

We addressed non-ignorable missing ASS data through joint modelling of the longitudinal data and the time to study dropout. In this analysis, children who withdrew from the study were considered as dropouts and the time they withdrew was the time of event (dropout). Those who did not dropout from the study before 1 h were censored at 1 h. In the joint analysis, dropout due to reasons related to trial treatment was modelled as potentially informative given ASS data over follow-up. Therefore, the joint model combines the information from the dropout pattern (time to event analysis) and ASS over time (longitudinal data analysis).

Evidence exists from studies in adults that the more severe the exacerbation of asthma, the more likely a better response to $MgSO_4$ is.[3,4] The more severe exacerbations in these analyses are based on definitions of forced expiratory volume in 1 s or peak expiratory flow rate of less than 50% to less than 30% predicted. In children, lung function is harder to measure during severe exacerbations.[11] We thus took the transcutaneous oxygen saturation ($SaO_2$) at presentation to be the best marker of severity for examination as a treatment covariate.[2] Therefore, we hypothesised that the effect of the addition of $MgSO_4$ would be greater in children with more severe disease, based on the $SaO_2$ at presentation, after their initial first nebulised bronchodilator before randomisation. Also, evidence from studies done in guinea pig asthma models suggests that as $MgSO_4$ acts as a smooth muscle bronchodilator and that the early response is affected by nebulised $MgSO_4$ to a greater extent than is the later, more inflammatory response,[12] a

| | $MgSO_4$ | Placebo |
|---|---|---|
| Age (in years) | 4·0 (3·0–7·0; 2–15) | 4·0 (3·0–7·0; 2–15) |
| Boys | 143 (57%) | 150 (59%) |
| Age of asthma onset in years | | |
| Number of patients | 165 | 168 |
| Age of asthma onset in years | 2·0 (1·0–3·0; 0–11) | 2·0 (1·0–3·0; 0–10) |
| Undiagnosed | 79 (31%) | 76 (30%) |
| Missing | 8 (3%) | 12 (5%) |
| Time of day that randomisation occurred | | |
| 0900–1700 | 181 (72%) | 168 (66%) |
| 1701–2200 | 49 (19%) | 59 (23%) |
| 2201–0859 | 22 (9%) | 29 (11%) |
| ASS | | |
| Number of patients | 248 | 254 |
| Mean score | 5·7 (1·3; 2–9) | 5·8 (1·4; 2–9) |
| Previous admissions for asthma | | |
| Number of patients | 250 | 255 |
| 0 | 101 (40%) | 99 (39%) |
| 1–4 | 101 (40%) | 95 (38%) |
| >4 | 48 (20%) | 61 (24%) |
| Duration of the most recent asthma attack | | |
| Number of patients | 251 | 254 |
| >24 h | 54 (22%) | 54 (21%) |
| For the past 6–24 h | 162 (64%) | 162 (64%) |
| For less than 6 h | 35 (14%) | 38 (15%) |
| Current asthma medication* | | |
| None | 7 (2%) | 1 (<0·5%) |
| Short-acting β2 agonists | 196 (51%) | 207 (53%) |
| Inhaled corticosteroids | 106 (28%) | 109 (28%) |
| Long-acting β2 agonists | 11 (3%) | 19 (5%) |
| Long-acting β2 agonists/steroid combination | 15 (4%) | 14 (4%) |
| Leucotriene receptor antagonists | 28 (7%) | 28 (7%) |
| Oral steroids | 6 (2%) | 2 (<0·5%) |
| Other | 8 (2%) | 7 (2%) |
| Not completed | 5 (1%) | 6 (1%) |
| Allergy history† | | |
| None/data missing | 118 (40%) | 123 (39%) |
| Hay fever | 38 (13%) | 61 (19%) |
| Eczema | 97 (33%) | 91 (29%) |
| Food allergy | 41 (14%) | 42 (13%) |

(Continues on next page)

| | $MgSO_4$ | Placebo |
|---|---|---|
| (Continued from previous page) | | |
| Treatment received pre-admission | | |
| Steroids only | 21 (8%) | 25 (10%) |
| Nebulisers only | 68 (27%) | 72 (28%) |
| Steroids and nebulisers | 47 (19%) | 55 (21%) |
| Yes, but neither steroids or nebulisers | 20 (8%) | 17 (7%) |
| Not known | 3 (1%) | 10 (4%) |
| None | 79 (31%) | 73 (29%) |
| Nothing ticked | 10 (4%) | 3 (1%) |
| Other treatment missing | 4 (2%) | 1 (<0·5%) |
| Nebuliser received before randomisation | | |
| Number of patients | 250 | 254 |
| Salbutamol | 106 (42%) | 101 (40%) |
| Salbutamol and ipratropium | 144 (58%) | 150 (59%) |
| Not given | 0 | 3 (1%) |
| Transcutaneous oxygen saturation ($SaO_2$) | | |
| Number of patients | 250 | 253 |
| Mean saturation at presentation | 93·8 (3·5; 84–100) | 93·4 (3·4; 81–100) |
| Blood pressure | | |
| Number of patients | 210 | 211 |
| Systolic | 109·5 (14·1; 62–163) | 112·7 (12·5; 70–172) |
| Diastolic | 65·5 (11·6; 30–105) | 66·3 (12·7; 34–123) |
| Respiratory rate | | |
| Number of patients | 247 | 250 |
| Mean rate (breaths per min) | 43·2 (10·5; 20–72) | 42·5 (10·9; 20–70) |
| Oxygen therapy | | |
| Number of patients | 241 | 247 |
| Yes | 94 (39%) | 98 (40%) |
| No | 147 (61%) | 149 (60%) |

Data are median (IQR; range), mean (SD; range), or n (%). Unless otherwise stated, data are for 252 patients in the magnesium group and 256 patients in the placebo group. *Patients could have been on more than one type of drug (173 patients in the magnesium group and 180 patients in the placebo group were diagnosed as having asthma previously). †Patients can be in more than one group.

***Table 1:*** **Baseline characteristics**

further hypothesis would be that patients with a shorter duration of attack might have a better response to treatment. We defined duration of attack in the three groups using parental report of symptoms of less than 6 h, between 6 h and 24 h, and greater than 24 h.[13,14] Our hypothesis concerned those children with a short duration of less than 6 h. These were pre-specified variables. Pre-specified treatment-covariate interactions were tested by including the interaction term in a linear regression model for ASS at 60 min adjusted for the main effects of treatment, ASS at baseline, and the covariate. We used SAS (version 9.1.3) for all statistical analyses and joineR library in R language for modelling.

This trial is registered with controlled-trials.com, number ISRCTN81456894.

### Role of the funding source

The study sponsors had no role in study design, data collection or analysis, interpretation of the data, or writing of the report. PW and RK-D had access to the raw data. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

## Results

We randomly allocated 508 children to treatment: 252 to the $MgSO_4$ group and 256 to the placebo group (figure 1). Of these patients, 227 in the $MgSO_4$ group and 243 to the placebo group were included in the primary analysis. At the end of the 4 h follow-up phase, 30 (6%) children (20 [8%] in $MgSO_4$ group and ten [4%] in placebo) met discharge criteria; 477 (one patient withdrew before admission to the placebo group) did not meet discharge criteria. Of 477 patients, 453 (215 [93%] of 231 in $MgSO_4$ and 238 [97%] of 245 in placebo; transfer details were missing for one patient in $MgSO_4$ group) were admitted to a general paediatric ward and 23 (16 [7%] of 231 given $MgSO_4$ and seven [3%] of 245 given placebo) were admitted to a paediatric intensive care unit. Of 453 patients, 14 (six $MgSO_4$) were later admitted to a paediatric intensive care unit or high-dependency care.

Baseline characteristics were much the same between the two groups (table 1). Most children were randomly allocated between 0900 and 1700, and the most common duration of most recent asthma attack was between 6 h and 24 h (table 1).

ASS at 1 h was lower in the $MgSO_4$ group than it was in the placebo group, but the difference between the two mean scores did not meet the predefined clinically relevant difference of 0·5 (table 2). Diagnostic plots showed no evidence of violation of model assumptions. There were no statistically significant differences between the two treatment groups for any of the five secondary clinical outcomes (table 2). We detected no evidence that treatment effect varied by centre (data not shown). We did sensitivity analyses to investigate the robustness of the conclusions concerning the analysis of the primary outcome to assumptions about the missing data. In these analyses, we assumed that data were missing at random; the statistical significance of the adjusted analysis remained unchanged (data not shown).

We investigated treatment-covariate interactions for the two clinically important baseline covariates: duration of the most recent asthma attack and $SaO_2$. We adjusted the models for treatment group, baseline ASS, and the baseline covariate of interest. Both treatment-covariate interactions were statistically significant (table 3). The model including the duration of the presenting asthma attack, suggested that the effect of magnesium sulphate was greater, and clinically significant, if given when symptoms of the attack lasted for less than 6 h. Because both ASS and $SaO_2$ are measures of severity, we also investigated a second model for $SaO_2$ excluding baseline ASS. Both models suggested that $MgSO_4$ was beneficial for patients with lower $SaO_2$ (more severe attacks; <92% saturation as per BTS definition of acute severe attack[2])

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| | $MgSO_4$ (n=228) | Placebo (n=244) | Difference in mean (95% CI); p value | Adjusted difference in mean (95% CI); p value* |
|---|---|---|---|---|
| **Primary outcome** | | | | |
| ASS at 1 h | .. | .. | −0·24 (−0·49 to −0·02); p=0·006* | −0·25 (−0·48 to −0·02; p=0·034) |
| Number of patients | 228 | 244 | .. | .. |
| Mean (SD), range | 4·72 (1·37), 2 to 9 | 4·95 (1·40), 2 to 9 | .. | .. |
| **Secondary outcomes** | | | | |
| Step-down of treatment at 1 h | .. | .. | 0·03 (−0·05 to 0·11); p=0·527 | .. |
| Number of patients | | | | |
| n/N (%) | 82/248 (33%) | 76/253 (30%) | .. | .. |
| Number of additional salbutamol doses | 247 | 253 | −1·0 (−2·00 to 0·00); p=0·236 | .. |
| Number of patients median (IQR) | 8 (4 to 14) | 9 (4 to 17) | .. | .. |
| Length of stay in hospital | .. | .. | −1·8 (−4·8 to 0·7); p=0·166 | .. |
| Number of patients | 251 | 254 | .. | .. |
| Median hours (IQR) | 26·3 (17·4 to 44·8) | 27·1 (19·2 to 47·6) | .. | .. |
| Proportion requiring intravenous bronchodilator treatment | .. | .. | −0·02 (−0·07 to 0·03); p=0·527 | .. |
| n/N (%) | 24/249 (10%) | 30/255 (12%) | .. | .. |
| Proportion requiring intubation or admission to a paediatric intensive care unit or high-dependency care† | .. | .. | 0·03 (−0·02 to 0·07); p=0·283 | .. |
| n/N (%) | 22/251 (9%) | 15/254 (6%) | .. | .. |

ASS=Yung asthma severity score. *When adjusted for baseline severity score. †35 children were admitted to paediatric intensive care for escalation of treatment and further observation due to the severity of their asthma and lack of response to initial treatment; there was only one child (in the placebo group) who required intubation.

***Table 2:*** **Outcomes**

but no difference for those with higher $SaO_2$ (less severe attacks; figure 2).

We recorded 21 different types of adverse events (table 4). We detected no substantial between-group difference in the occurrence of adverse events. There were 15 serious adverse events but no suspected unexpected serious adverse reactions. The 15 serious adverse events (three on $MgSO_4$, 12 on placebo) were recorded as such because they necessitated extended stays in hospital due to worsening bronchospasm and so all were felt to be related to the disease under study. One child (placebo group) reported increased bronchospasm on two occasions during follow-up. One child (placebo group) who was admitted to a paediatric intensive care unit was subsequently admitted to hospital twice due to worsening symptoms. Seven serious adverse events (worsening of exacerbations) were deemed to be unrelated to study treatment, seven unlikely to be related, and one possibly related (which was in a child in the placebo group).

| | Estimate (95% CI); p value |
|---|---|
| **Duration of the most recent asthma attack** | |
| $MgSO_4$ | 0·01 (−0·48 to 0·51); p=0·955 |
| ASS at baseline | 0·40 (0·31 to 0·48); p<0·0001 |
| For less than 6 h *vs* for the past few days | 0·03 (−0·51 to 0·57); p=0·920 |
| For the past 24 h *vs* for the past few days | 0·24 (−0·16 to 0·64); p=0·250 |
| Addition effect of $MgSO_4$ in patients with an attack in the past 6 h or less *vs* the past few days* | −0·79 (−1·58 to −0·00); p=0·049 |
| Addition effect of $MgSO_4$ in patients with an attack in the past 24 h or less *vs* the past few days* | −0·28 (−0·85 to 0·30); p=0·346 |
| **Transcutaneous oxygen saturation ($SaO_2$)** | |
| $MgSO_4$ | −7·11 (−13·49 to −0·74); p=0·029 |
| ASS at baseline | 0·37 (0·28 to 0·46); p<0·0001 |
| $SaO_2$ | −0·06 (−0·11 to −0·02); p=0·010 |
| $SaO_2$ and $MgSO_4$ interaction effect | 0·07 (0·01 to 0·14); p=0·034 |
| $SaO_2$ and $MgSO_4$ interaction effect (from the model without ASS at baseline) | 0·08 (0·01 to 0·16); p=0·022 |

$MgSO_4$=Magnesium sulphate. ASS=Yung asthma severity score. *p=0·143 for interaction between attack and $MgSO_4$.

***Table 3:*** **Treatment-covariate interaction effects**

## Discussion

Our findings showed that nebulised $MgSO_4$ gave a statistically significant benefit compared with placebo when given with standard treatment to children with acute severe asthma, but this benefit was not clinically significant. However, there are no patient-focused, large datasets defining what is a clinically relevant change in an ASS: we had defined a clinically significant change in the ASS as greater than 0·5 on the basis of data from our pilot study.[10] The $MgSO_4$ regimen in this study did not show any statistically significant differences in secondary outcomes. We examined subgroup effects as per recent recommendations.[15] We planned analyses of two treatment-covariate interactions before beginning the study. The tests of interaction in both cases were statistically significant.

The first of these subgroup analysis findings was that the nebulised $MgSO_4$ effect was more pronounced in children

who had had a more severe exacerbation (p=0·03). Our findings suggest that the greatest clinical response was seen in children with an $SaO_2$ of less than 92% (figure 2).

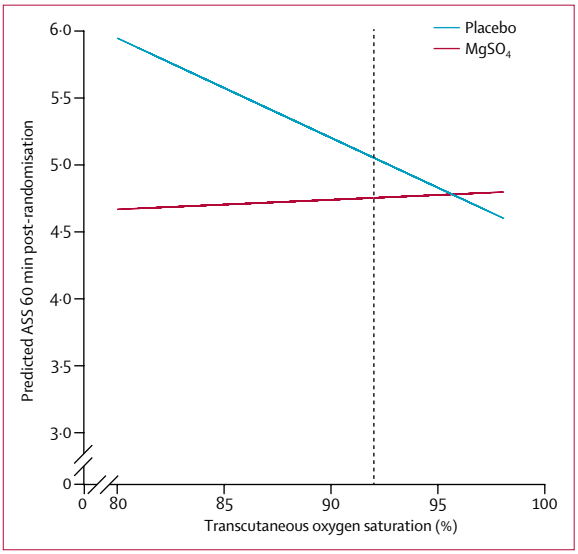


***Figure 2:*** **Relation between asthma severity and transcutaneous oxygen saturation**
Dashed line shows <92% saturation threshold as per BTS definition of acute severe attack.[2]

| | $MgSO_4$ | | Placebo | | Total | |
|---|---|---|---|---|---|---|
| | Children (n=252) | Events (n=47) | Children (n=256)* | Events (n=59) | Children (n=508) | Events (n=106) |
| Abdominal pain | 2 (<0·5%) | 2 | 2 (1%) | 2 | 4 (1%) | 4 |
| Asymptomatic hypotension | 1 (<0·5%) | 1 | 2 (1%) | 2 | 3 (1%) | 3 |
| Back pain | 0 | 0 | 1 (<0·5%) | 1 | 1 (<0·5%) | 1 |
| Blood in stool | 0 | 0 | 1 (<0·5%) | 1 | 1 (<0·5%) | 1 |
| Chest pain | 1 (<0·5%) | 1 | 2 (1%) | 3 | 3 (1%) | 4 |
| Diarrhoea | 0 | 0 | 1 (<0·5%) | 1 | 1 (<0·5%) | 1 |
| Dizziness | 1 (<0·5%) | 1 | 0 | 0 | 1 (<0·5%) | 1 |
| Drowsiness | 1 (<0·5%) | 1 | 0 | 0 | 1 (<0·5%) | 1 |
| Facial flushing | 2 (1%) | 2 | 3 (1%) | 3 | 5 (1%) | 5 |
| Feet cramp | 0 | 0 | 1 (<0·5%) | 1 | 1 (<0·5%) | 1 |
| Fever | 8 (3%) | 8 | 5 (2%) | 5 | 13 (3%) | 13 |
| Headache | 5 (2%) | 5 | 1 (<0·5%) | 1 | 6 (1%) | 6 |
| Hypokalaemia | 0 | 0 | 1 (<0·5%) | 1 | 1 (<0·5%) | 1 |
| Itchy face | 0 | 0 | 1 (<0·5%) | 1 | 1 (<0·5%) | 1 |
| Jitteriness | 1 (<0·5%) | 1 | 0 | 0 | 1 (<0·5%) | 1 |
| Nausea | 4 (2%) | 4 | 2 (1%) | 2 | 6 (1%) | 6 |
| Sleep† | 0 | 0 | 1 (<0·5%) | 1 | 1 (<0·5%) | 1 |
| Teeth whitening | 0 | 0 | 1 (<0·5%) | 1 | 1 (<0·5%) | 1 |
| Urticarial rash | 0 | 0 | 1 (<0·5%) | 2 | 1 (<0·5%) | 2 |
| Vacant episode | 0 | 0 | 2 (1%) | 2 | 2 (<0·5%) | 2 |
| Vomiting | 21 (8%) | 21 | 24 (9%) | 29 | 45 (9%) | 50 |

Data are n (%). *Seven children had more than one event. †Sleep is different from drowsiness: drowsiness suggests an impaired consciousness, which might be more of a concern and is a symptom of severe asthma attack due to hypoxia.

***Table 4:*** **Adverse events**

Findings from a Cochrane review[4] suggest that in adults with acute asthma, the greatest effect is most likely to be seen in patients with more severe asthma, and our data in children would lend support to these findings. Our definition of severe asthma was pragmatically based on the widely utilised BTS/SIGN guidelines.[2]

The second of our subgroup analysis findings was that children who had a shorter duration of exacerbation symptoms (<6 h) seemed to have a better response to nebulised $MgSO_4$ (p=0·049). At least two phenotypes of acute asthma might exist, a sudden onset neutrophil-driven exacerbation and a slower onset eosinophillic inflammatory exacerbation.[13,14] Magnesium sulphate reduces the neutrophil burst in adults with asthma,[16] and data from studies in guinea pig asthma models suggest that because $MgSO_4$ reduces neutrophil concentrations it acts as a smooth muscle bronchodilator by effecting the early response to a greater extent compared with the later, more inflammatory response.[12] These experimental data would lend support to the suggestion that nebulised $MgSO_4$ will have a better effect on patients with a shorter history of symptoms. However, a 2012 Cochrane review found insufficient data to draw firm conclusions about the effectiveness of nebulised $MgSO_4$ in this subgroup of patients (panel 2).[4] Further assessment is therefore needed.

Our trial had several strengths. Although we did not collect reliable data for all the patients attending secondary care on our screening log, data from a national audit of UK asthma admissions of 9428 children, collected between 1998–2005,[17] suggest that we have identified a more severe group of patients than those children admitted to hospitals with acute asthma. Although the presenting arterial oxygen saturation in air in the children in our trial was much the same as the national average,[17] the use of intravenous bronchodilators (a marker of disease severity) in our trial was much higher than the national average (11% *vs* 4–5%).[17] Because the patients recruited represent a more severe end of the spectrum of those admitted to hospital with acute asthma in the UK, our study has external validity. Furthermore, baseline characteristics were much the same between the two study groups in our trial, which suggests internal validity of our results. Use of the Local Research Networks of the Medicines for Children Research Network allowed us to recruit patients from both small and large general hospitals, as well as from tertiary paediatric centres. We recruited patients from both emergency departments and paediatric assessment units, which further strengthens the generalisability of our findings to the general acute paediatric asthma population in the UK.

Our trial had several limitations. Some patients had less severe acute asthma than we aimed to recruit for. The Yung ASS defines severe asthma as a score of greater than 6,[7,8] but some children in our trial had a baseline ASS of less than 6. We pragmatically used the BTS definitions to define asthma severity using any one of the defined criteria

for classification. We feel that the BTS definition needs to be refined further. It is likely that we enrolled several younger children who fulfilled the BTS criteria simply on the basis of their tachycardia. Our study population included phenotypic variability between the youngest pre-school children with likely viral episodic wheeze (155 [31%] of 508 patients) and older children with probable multi-trigger wheeze (353 [70%] of 508 patients). The median age of our study population was 4 years, which would support these children having episodic wheeze where therapeutic interventions may be less successful.[18,19] Indeed, 436 (86%) of 508 children were given steroids, which would suggest that clinicians had held back steroid treatment in younger children. We had set out to do a pragmatic study in which children who came in wheezing would fulfil the criteria as per BTS definitions. It is possible that the effect we have seen has been diluted by these younger children with episodic wheeze and by those who had a less severe asthma exacerbation.

We chose the Yung ASS to measure the primary outcome because it is the most validated, reliable, and easily used score in acute asthma.[6,19] This score was validated on a population of children aged between 0–19 years of age and lung function was used as an outcome; in those younger children measuring lung function is not possible.[20] Other scores such as the Paediatric Respiratory Assessment Measure (PRAM) score might be more appropriate for the younger children, but the PRAM score was further validated only after we had begun recruiting for this trial.[21] More than 20 asthma severity scoring systems are available for use in young children,[22] but we felt that the Yung score was the most easily used score for the overall study age range and had been used in previous studies of severe asthma in which a difference had been shown in response to intravenous bronchodilators.[7,8] It is not known, however, what level of change in this ASS is clinically significant and relevant to patients. The trial management group felt that an improvement of 0·5 would be an important difference. Ultimately, we had sufficient power to show a statistical difference at a change of 0·25. The clinical relevance of this warrants further exploration. Core outcomes for acute asthma studies in children still need to be defined.[4]

The main side-effects reported during the study were flushing, vomiting, headache, and asymptomatic self-correcting and transient hypotension. We recorded no important difference in side-effects between the treatment groups. There were no severe unexpected adverse events associated with the use of $MgSO_4$, and the study suggests that the doses and frequency given in this regimen can be considered safe.

Further analyses are planned to explore in more depth the potential effect of inhaled magnesium sulphate in subgroups of children. Several potential subgroups can be defined by pre-hospital oral steroid use: children who have wheezed for the first time compared with those with recurrent wheezing, children on inhaled steroids (as a marker of chronic asthma versus those who are not on steroids), and children younger than 5 years compared with older children. Using the data from this trial, we are planning to do further post-hoc analyses of these subgroups.

Thus, the addition of nebulised $MgSO_4$ to conventional treatment was safe and without substantial side-effects. There might be a role for nebulised $MgSO_4$ in the treatment of severe acute asthma in children with a severe exacerbation whose $SaO_2$ in air after the first nebulised treatment remains below 92%, and in those with a shorter duration of symptoms.

***Panel 2:* Research in context**

**Systematic review**

CP had updated the Cochrane systematic review on inhaled magnesium sulphate in the treatment of acute asthma (published in 2012).[4] We also identified trials using the Cochrane Airways Group Specialised Register of trials (CAGR), which is derived from systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), Medline, Embase, CINAHL, AMED, and PsycINFO, and manual searching of respiratory journals and meeting abstracts. We searched all records in the CAGR coded as asthma using the following terms: "$MgSO_4$" or "magnesium*". We also searched ClinicalTrials.gov using the same search terms for ongoing studies. Both databases were searched from their inception to November, 2012, with no restriction on the language of publication. Data were extracted independently with a standardised data collection form. The following information was extracted if available: characteristics of the study (design, methods of randomisation, withdrawals or dropouts); participants (age, sex); intervention (type, dose, route of administration, timing and duration of treatment, co-interventions); control (agent and dose); outcomes (types of outcome measures recorded and reported, timing of outcomes, adverse events); and results. Unpublished data were requested from the primary authors when necessary. The authors independently assessed the risk of bias for all included studies for the following six items; random sequence generation; allocation concealment; blinding; incomplete outcome data; selective outcome reporting; and other types of bias. We recorded judgments as high, low, or unclear risk of bias along with a description from the trial reports. Any disagreements were discussed and resolved by consensus. We identified 16 randomised controlled studies examining the role of inhaled magnesium sulphate in acute asthma. Only four of these studies have included children and they are underpowered with differing methodology. Their results are insufficient to make a conclusion about the role of magnesium sulphate in acute asthma in the paediatric population.

**Interpretation**

The MAGNETIC study has shown that magnesium sulphate added to standard treatment has a statistically significant effect but not a clinically significant effect on acute asthma. The effects seemed most beneficial in children with a more severe attack and shorter duration of symptoms. Further post-hoc sub-group analyses are planned. Further assessment of the implementation of the addition of nebulised magnesium sulphate to standard treatment is needed, and should focus on children with more severe asthma, older children with more severe chronic symptoms and recurrent asthma episodes, and children with a shorter duration of symptoms.

**Contributors**

SP, RK-D, AB, CP, JL, ID, KH, and PW were members of the trial management group. CP was responsible for the overall design and conduct of the study, and preparing the paper for publication. RK-D did the statistical analyses and reviewed a draft of the paper. AB did the health economic analyses and reviewed a draft of the paper. SP led the health economics team, contributed to the design of the study, and

reviewed a draft of the paper. JL prepared the paper for publication. ID and KH contributed to the design and conduct of the study, and reviewed a draft of the paper. PW led the statistics team, contributed to the design and conduct of the study, and reviewed a draft of the paper.

**Conflicts of interest**

We declare that we have no conflicts of interest.

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See Online for appendix

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