# MAGNEsium Trial In Children (MAGNETIC): a randomised, placebo-controlled trial and economic evaluation of nebulised magnesium sulphate in acute severe asthma in children

CVE Powell,[1]* R Kolamunnage-Dona,[2] J Lowe,[2] A Boland,[3] S Petrou,[4] I Doull,[5] K Hood[1] and PR Williamson[2] on behalf of the MAGNETIC study group

[1]School of Medicine, Cardiff University, Cardiff, UK
[2]Department of Biostatistics, University of Liverpool, Liverpool, UK
[3]Liverpool Reviews and Implementation Group, University of Liverpool, Liverpool, UK
[4]Warwick Medical School, University of Warwick, Warwick, UK
[5]Children's Hospital for Wales, Cardiff, UK

*Corresponding author

**Declared competing interests of authors:** none

Published October 2013
DOI: 10.3310/hta17450

## Scientific summary

MAGNEsium Trial In Children (MAGNETIC)
Health Technology Assessment 2013; Vol. 17: No. 45
DOI: 10.3310/hta17450

NIHR Journals Library www.journalslibrary.nihr.ac.uk

# Scientific summary

## Background

Acute asthma continues to be one of the main reasons for acute hospital admission in children and accounts for much morbidity, anxiety, stress, and time off school and work for the families.

The Department of Health has targeted respiratory disease as an area for improved management. The British Thoracic Society and Scottish Intercollegiate Guideline Network (BTS/SIGN) have developed an evidence-based guideline for the management of asthma. It offers comprehensive guidance on the acute and chronic management of asthma in children and adults, but the document highlights the paucity of good information to guide the management of a number of clinical situations. Nowhere is this more striking than in the management of acute asthma, for which the recommended treatment for children (< 16 years old) differs markedly from that for adults (≥ 16 years) – a reflection of the evidence base in the different age groups.

The guideline recommends that the initial management in children is inhaled $\beta_2$-agonists and ipratropium (Atrovent®, Boehringer Ingelheim) and systemic corticosteroids. Oxygen saturation of < 92% while breathing room air at presentation is noted to be an indicator of more severe asthma, as is oxygen saturation of < 92% at 20 minutes after inhaled $\beta_2$-agonists. For poorly responsive children of > 5 years of age, it is recommended that clinicians consider intravenous bronchodilator therapy – initially salbutamol followed by a continuous infusion, then intravenous aminophylline followed by infusion. There is little evidence as to the intravenous bronchodilator of choice. Furthermore, although it is recognised that intravenous magnesium sulphate ($MgSO_4$) is a safe treatment for acute asthma, with no side effects up to doses of 100 mg/kg, the guideline concedes that its place in management is not yet established. $MgSO_4$ does not appear to be recommended for children aged ≤ 5 years. The BTS/SIGN guidelines recommend intravenous magnesium in the initial management of severe acute asthma in adults but, as there is a lack of evidence in children, it is not currently recommended as first-line intravenous treatment in paediatric care.

The inhaled route for administering magnesium has also been examined, mainly in adult cohorts. These studies have demonstrated a good effect when magnesium is given via a nebuliser. There are few paediatric data on the effect of nebulised $MgSO_4$. The two paediatric studies of nebulised $MgSO_4$, one involving 20 children (Meral A. Inhalation therapy with $MgSO_4$. *Turk J Pediatr* 1996;**38**:169–75) and the other 62 children (Mahajan P, Haritos D, Rosenberg N, Thomas R. Comparison of nebulised magnesium sulphate plus salbutamol plus saline in children with exacerbations of mild to moderate asthma. *J Emerg Med* 2004;**27**:21–5), demonstrated equivocal results MAGNETIC is a randomised, placebo-controlled multicentre trial of the use of nebulised $MgSO_4$ in severe acute asthma in childhood in patients who show a poor response to maximal conventional aerosol treatment.

## Objectives

The main objective was to determine whether the use of nebulised $MgSO_4$, when given as an adjunct to standard therapy for 1 hour in acute severe asthma in children, results in a clinical improvement compared with standard treatment alone.

# Methods

## *Population*

Children aged 2–15 years suffering from acute severe asthma exacerbations as defined by the BTS guidelines.

## *Setting*

Emergency departments (EDs) and paediatric assessment units (PAUs) at 30 hospitals in the UK.

## *Inclusion criteria*

Severe acute asthma as defined by the BTS/SIGN guidelines.

For children aged ≥ 6 years, a diagnosis of severe asthma requires at least one of the following criteria to be met:

(a) oxygen saturations of < 92% while breathing room air
(b) too breathless to talk
(c) heart rate of > 120 beats per minute (b.p.m.)
(d) respiratory rate of > 30 breaths per minute
(e) use of accessory neck muscles.

For children aged 2–5 years, a diagnosis of severe asthma requires at least one of the following criteria to be met:

(a) oxygen saturations of < 92% while breathing room air
(b) too breathless to talk
(c) heart rate of > 130 b.p.m.
(d) respiratory rate of > 50 breaths per minute
(e) use of accessory neck muscles.

## *Exclusion criteria*

(a) Coexisting respiratory disease, such as cystic fibrosis or chronic lung disease of prematurity.
(b) Severe renal disease.
(c) Severe liver disease.
(d) Known pregnancy.
(e) Known previous reaction to magnesium.
(f) Inability to give informed consent.
(g) Previous randomisation into the MAGNETIC trial.
(h) Life-threatening symptoms.
(i) Current or previous (in the 3 months preceding screening) involvement with a trial of a medicinal product.

Patients were identified on presentation to EDs/PAUs and assessed against the study inclusion criteria. The Yung Asthma Severity Score (ASS) was also recorded. Patients meeting one or more of the criteria were then given an initial nebulisation of salbutamol/salbutamol plus ipratropium (variation allowed as per hospital practice) and informed proxy consent obtained following consultation with a trained member of the study team. After the initial nebuliser, patients no longer meeting one or more of the inclusion criteria were excluded.

## Interventions

At randomisation, eligible patients were allocated to receive either 2.5 ml of isotonic $MgSO_4$ (250 mmol/l, tonicity 289 mOsm; 151 mg per dose) or 2.5 ml of isotonic saline via nebuliser on three occasions at approximately 20-minute intervals. Each nebuliser also contained salbutamol 2.5 mg (children aged 2–5 years) or 5 mg (children aged $\geq 6$ years) and ipratropium bromide 0.25 mg in both the active and placebo groups.

The ASS was recorded after each nebuliser administration [at approximately 20, 40 and 60 (T60) minutes post randomisation] and for the following 3 hours (approximately 120, 180 and 240 minutes post randomisation). Adverse events (AEs) were assessed at each assessment point. Patients were followed up until discharge from hospital to collect secondary outcome data items.

Following discharge from hospital, parents and patients (if aged > 5 years) were asked to complete a set of postal questionnaires, collecting data for the quality-of-life (QoL) and health economic measures. The 1-month follow-up postal questionnaire collected QoL [Paediatric Quality of Life Inventory (PedsQL™ Asthma Module) and European Quality of Life-5 Dimensions (EQ-5D) questionnaires] and health economics (NHS and non-NHS) data from discharge to 1 month post randomisation.

## Results

In total, 508 children with acute severe asthma exacerbations were recruited into the study; 252 were randomised to receiving $MgSO_4$ and 256 received placebo along with the standard treatment. There were no differences in baseline characteristics. There was a statistically significant difference in ASS at T60 in those children who received nebulised magnesium {0.25 [95% confidence interval (CI) 0.02 to 0.48]; $p = 0.034$} and this difference was sustained for up to 240 minutes [0.20 (95% CI 0.01 to 0.40); $p = 0.042$]. These differences are likely to be of minimal clinical significance. Assessing treatment–covariate interactions, there is evidence of a larger effect in those children with more severe asthma exacerbations ($p = 0.034$) and those with a shorter duration of symptoms ($p = 0.049$). These differences are likely to be clinically relevant. There were no significant differences in secondary outcomes measured. AEs were reported in 19% of children in the magnesium group and 20% in the placebo group. There were no clinically significant serious AEs in either group. The probability of magnesium being cost-effective is over 60% at cost-effectiveness thresholds of £1000 per unit decrement in ASS and £20,000 per quality-adjusted life-year (QALY) gained, respectively.

## Conclusions

In the authors' opinion, there are sufficient data in this study to support the use of nebulised isotonic $MgSO_4$ a the dose of 151 mg given three times in the first hour of treatment as an adjunct to standard treatment, though the clinical significance of the treatment effect shown remains uncertain. The response is likely to be more marked in those children with more severe attacks and with a shorter duration of exacerbation.

### *Implications for health care*

This is the largest study of nebulised $MgSO_4$ in children to date. These data will add further evidence that may help to improve and strengthen the recommendations of national and international guidelines for the management of acute asthma in childhood. The results of the base-case economic analyses suggest that, from an NHS and Personal Social Services perspective, the addition of magnesium to standard treatment is likely to be cost-effective compared with standard treatment only. The results of both sets of analyses (cost-effectiveness analysis and cost–utility analysis), show that the probability of magnesium being cost-effective is > 60% at cost-effectiveness thresholds of £1000 per unit decrement in

ASS and £20,000 per QALY gained, respectively. The cost-effectiveness of adding this treatment to the standard treatment regimen has been demonstrated.

### *Recommendations for research*

Further studies of dose–response relationship at different ages and frequency of administration during an attack are required. The effect on secondary outcomes, such as need for intravenous bronchodilators and paediatric intensive care unit admissions and length of stay with different nebulised magnesium treatment regimen (dose and frequency), needs further exploration. The concept of different phenotypes and severity for which the use of nebulised magnesium can be tailored to the features of the exacerbation needs further exploration.

Currently, three further analyses are planned using these data:

1. exploration of the relationship between ASS and the BTS definition of acute severe asthma
2. assessment of the value of the area under the curve analysis of ASSs
3. examination of the concept of acute phenotypes of asthma in children and the response to treatment.

It may be that these data are sufficient to recommend that nebulised magnesium is added to standard treatment, particularly in those who have a severe attack and those with a short history. Further studies of dose–response pharmacokinetics and frequency of doses, nebuliser use, compatibility studies and animal models to clarify the mechanisms of magnesium use are also to be considered.

## Trial registration

This trial is registered as ISRCTN81456894.

## Funding

This project was funded by the NIHR Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 17, No. 45. See the HTA programme website for further project information.

# Health Technology Assessment

HTA/HTA TAR

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Five-year impact factor: 5.804

*Health Technology Assessment* is indexed in MEDLINE, CINAHL, EMBASE, The Cochrane Library and the ISI Science Citation Index and is assessed for inclusion in the Database of Abstracts of Reviews of Effects.

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: nihredit@southampton.ac.uk

The full HTA archive is freely available to view online at www.journalslibrary.nihr.ac.uk/hta. Print-on-demand copies can be purchased from the report pages of the NIHR Journals Library website: www.journalslibrary.nihr.ac.uk

### Criteria for inclusion in the *Health Technology Assessment* journal

Reports are published in *Health Technology Assessment* (HTA) if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the reviewers and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

### HTA programme

The HTA programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The journal is indexed in NHS Evidence via its abstracts included in MEDLINE and its Technology Assessment Reports inform National Institute for Health and Care Excellence (NICE) guidance. HTA research is also an important source of evidence for National Screening Committee (NSC) policy decisions.

For more information about the HTA programme please visit the website: www.hta.ac.uk/

### This report

The research reported in this issue of the journal was funded by the HTA programme as project number 05/503/10. The contractual start date was in December 2007. The draft report began editorial review in April 2012 and was accepted for publication in October 2012. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

This report presents independent research funded by the National Institute for Health Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health.



Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk).