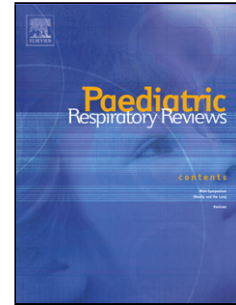


Accepted Manuscript

Title: Intravenous magnesium sulfate for treating children with acute asthma in the emergency department

Author: Benedict Griffiths Kayleigh M Kew Rebecca Normansell



PII: S1526-0542(16)30061-6
DOI: <http://dx.doi.org/doi:10.1016/j.prrv.2016.07.001>
Reference: YPRRV 1150

To appear in: *YPRRV*

Received date: 4-7-2016
Accepted date: 4-7-2016

Please cite this article as: Griffiths B, Kew KM, Normansell R, Intravenous magnesium sulfate for treating children with acute asthma in the emergency department, *Paediatric Respiratory Reviews* (2016), <http://dx.doi.org/10.1016/j.prrv.2016.07.001>

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Intravenous magnesium sulfate for treating children with acute asthma in the emergency department

Benedict Griffiths¹, Kayleigh M Kew², Rebecca Normansell²

¹Evelina London Children's Hospital, St Thomas' Hospital, London, UK

²Population Health Research Institute, St George's, University of London, London, UK

Why was it important to do this Cochrane review?

One in 11 children in the UK, and elsewhere in the western world, suffer from asthma. Morbidity and mortality associated with childhood asthma continues to increase and yet evidence specifically relating to asthma treatments in paediatric populations remains scarce. Prompt treatment of acute asthma in the emergency setting is important to avoid rising asthma-related hospital stays, intensive care admissions (Nyman 2011), and deaths (NRAD 2014).

An earlier version of this Cochrane review published in 2000 included seven studies (5 adult 2 paediatric studies) and found little evidence to support the use of intravenous magnesium sulfate (IV MgSO₄) in children. Despite this, national and international treatment guidelines continued to advocate the use of IV MgSO₄ in the treatment of acute asthma in children who have not responded to first-line treatment (bronchodilators and steroids) (BTS/SIGN 2014; GINA 2015).

It was possible that subsequent research published over the subsequent sixteen years had the potential to impact the conclusions for both adults and children. We split the review update into child and adult populations, allowing us to explore more easily effect modifiers within each age group. The adult review included 14 studies (N=2313) and found IV MgSO₄ reduced the need for hospital admission compared with placebo (Kew 2014), posing an important question of whether the same was true for children.

What were the objectives of the review?

The main aim of the review was to assess whether giving IV MgSO₄ for acute asthma in the ED reduces the need for admission to hospital. Secondary aims were to evaluate adverse events and whether the treatment has additional benefits including reducing the time spent in the ED or the need for intensive care.

What was the evidence base of the review?

Only five studies met all the inclusion criteria (Ciarallo 1996; Ciarallo 2000; Devi 1997; Gürkan 1999; Scarfone 2000), randomising a total of 182 children presenting to the ED: 89 to receive MgSO₄ and 93 to receive a matching placebo infusion of saline. Sample sizes were small, ranging from 20 to 54, meaning that although the studies were mostly at low risk of bias, our confidence in the evidence was generally low because the results were based on so few children.

As per the pre-defined inclusion criteria, all studies were randomised, double-blind, placebo-controlled trials. Populations, interventions and procedures varied across the five studies with respect to age, severity of exacerbation, allowed and disallowed co-medications, and characteristics of the intervention (Table 1). The main measurements were taken between 90 and 120 minutes after the start of the magnesium infusion. Children included in the studies had predominantly moderate to severe acute asthma and had mostly received nebulised bronchodilators, IV corticosteroids and oxygen before randomisation.

Intravenous magnesium sulfate for treating children with acute asthma in the emergency department

Benedict Griffiths¹, Kayleigh M Kew², Rebecca Normansell²

¹Evelina London Children's Hospital, St Thomas' Hospital, London, UK

²Population Health Research Institute, St George's, University of London, London, UK

Classification of asthma severity is widely reported in research but in paediatric practice is more problematic due to the difficulty in obtaining spirometry in the emergency setting. In the review, studies were classified according to their inclusion criteria and the available baseline characteristics of the children recruited (such as respiratory and heart rate, peak flow etc.), in the hope of identifying subgroups of children who are most likely to benefit. However due to the small number of studies and included children teasing out severity response was not possible.

What were the findings of the review? Overall, there was a striking paucity of data, especially with regard to the secondary outcomes (ED treatment duration, intensive care admissions, hospital length of stay, vital signs, spirometry, symptom scores and adverse events).

Admission to hospital was the primary outcome, and analysis of three studies showed the odds were 68% lower in the children given IV MgSO₄ than those given a placebo infusion (OR 0.32, 95% CI 0.14 to 0.74; fixed-effects). While this is a large reduction, it should be interpreted with caution due to the small number of children in the analysis (n = 115) and variation between the individual study results (see Figure 1). It is difficult to explore what caused this variation with so few studies, but their designs and populations were broadly comparable (Table 1). Performing a sensitivity analysis of the same admission data using a random-effects model gave a rather different result (OR 0.18, 95% CI 0.02 to 1.59; random effects) that did not reach statistical significance.

Nothing can be said of the effect of IV MgSO₄ on intensive care admissions, vital signs, spirometry, or scores on symptom scales, and there was very limited data about the likelihood of returning to the ED within 48 hours. Some of the studies narratively reported benefits on lung function and symptom scales, but we found little numerical data. Reported side-effects were generally mild and infrequent, but it is difficult to know whether this is evidence of safety or a consequence of incomplete or inconsistent recording and small sample sizes.

What are the implications of this review for practice and for research?

This review provides very weak evidence to support the use of IV MgSO₄ in the treatment of asthma in children who have not responded to first line treatment. The result favouring the use of IV MgSO₄ to reduce hospital admissions is in keeping with the adult review and other non randomised studies including children. However, due to the small study sizes and degree of heterogeneity we have put less confidence in our findings than the adult review.

The weak evidence favouring reduced hospital admissions combined with the likelihood of minimal harm suggests it is still a reasonable treatment option. However, as data are scarce and there have been few RCTs published in recent years, equipoise still exists. Further studies would help answer the question with more certainty and identify subgroups of children who may benefit most from this treatment. Trialists should clearly document severity, focusing on important clinical outcomes that can further inform clinicians and future guidance on IV magnesium infusions in children with acute asthma in the emergency department.

Intravenous magnesium sulfate for treating children with acute asthma in the emergency department

Benedict Griffiths¹, Kayleigh M Kew², Rebecca Normansell²

¹Evelina London Children's Hospital, St Thomas' Hospital, London, UK

²Population Health Research Institute, St George's, University of London, London, UK

References

- British Thoracic Society/Scottish Intercollegiate Guidelines Network (BTS/SIGN). SIGN 141. British guideline on the management of asthma. <https://www.brit-thoracic.org.uk/document-library/clinical-information/asthma/btssign-asthma-guideline-2014/>
- Ciarallo L, Sauer AH, Shannon MW. Intravenous magnesium therapy for moderate to severe pediatric asthma: results of a randomized, placebo-controlled trial. *Journal of Pediatrics* 1996;129(6):809-14
- Ciarallo L, Brousseau D, Reinert S. Higher-dose intravenous magnesium therapy for children with moderate to severe acute asthma. *Archives of Pediatrics and Adolescent Medicine* 2000;154(10):979-83
- Devi PR, Kumar L, Singhi SC, Prasad R, Singh M. Intravenous magnesium sulfate in acute severe asthma not responding to conventional therapy. *Indian Pediatrics* 1997;34(5):389-97
- Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention. http://www.ginasthma.org/local/uploads/files/GINA_Report_2015_Aug11.pdf
- Griffiths B, Kew KM. Intravenous magnesium sulfate for treating children with acute asthma in the emergency department. *Cochrane Database of Systematic Reviews* 2016, Issue 4. Art. No.: CD011050. DOI: 10.1002/14651858.CD011050.pub2
- Gürkan F, Haspolat K, Boşnak M, Dikici B, Derman O, Ece A. Intravenous magnesium sulphate in the management of moderate to severe acute asthmatic children nonresponding to conventional therapy. *European Journal of Emergency Medicine* 1999;6(3):201-5
- Kew KM, Kirtchuk L, Michell CI. Intravenous magnesium sulfate for treating adults with acute asthma in the emergency department. *Cochrane Database of Systematic Reviews* 2014, Issue 5. Art. No.: CD010909. DOI: 10.1002/14651858.CD010909.pub2
- Nyman A, Durward A. Asthma in PICU. Paediatric Intensive Care Audit Network National Report 2008 - 2010 (published September 2011): Universities of Leeds and Leicester 2011
- Rowe BH, Bretzlaff JA, Bourdon C, Bota GW, Camargo CA Jr. Magnesium sulfate for treating exacerbations of acute asthma in the emergency department. *Cochrane Database of Systematic Reviews* 2000, Issue 2. Art. No.: CD001490. DOI: 10.1002/14651858.CD001490.pub2
- Royal College of Physicians. Why asthma still kills: the National Review of Asthma Deaths (NRAD) Confidential Enquiry report. London: RCP, 2014
- Scarfone RJ, Loiselle JM, Joffe MD, Mull CC, Stiller S, Thompson K, et al. A randomized trial of magnesium in the emergency department treatment of children with asthma. *Annals of Emergency Medicine* 2000;36(6):572-8

Intravenous magnesium sulfate for treating children with acute asthma in the emergency department

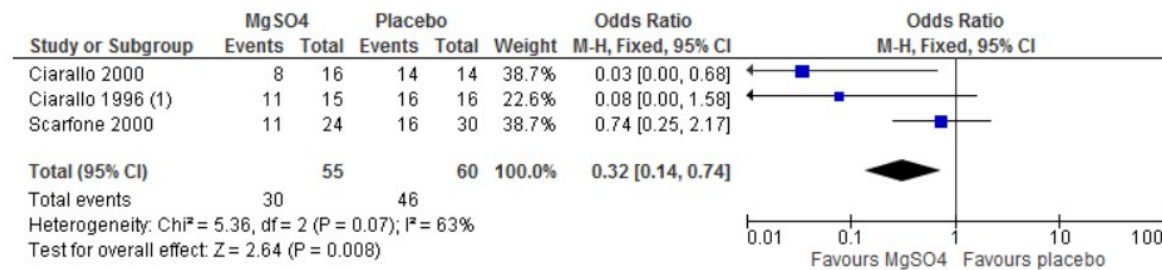
Benedict Griffiths¹, Kayleigh M Kew², Rebecca Normansell²¹Evelina London Children's Hospital, St Thomas' Hospital, London, UK²Population Health Research Institute, St George's, University of London, London, UK

Table 1. Summary of studies included in the review

ID	Country (centres)	N	Age range (mean y)	Inclusion	% PEF	MgSO ₄ infusion	Co-treatments
Ciarallo 1996	USA (2)	30	6 to 18 (11.4)	PEF < 60% predicted after 3 beta ₂ -adrenergic nebuliser treatments	43.4	25 mg/kg 20 mins	3 nebulised bronchodilators (albuterol, ipratropium bromide, or both) IV methylprednisolone (2 mg/kg) if not yet given corticosteroids
Ciarallo 2000	USA (1)	31	6 to 18 (11.4)	PEF < 70% predicted (after 3 nebulised bronchodilator treatments)	31.4	40 mg/kg 20 mins	3 nebulised beta-2 adrenergic treatments IV methylprednisolone (2 mg/kg) if not yet given corticosteroids
Devi 1997	India (1)	47	1 to 12 (6.7)	"Inadequate or poor response to 3 doses of nebulized salbutamol"	28.6	0.2 ml of 50% 35 mins	Nebulised salbutamol Oxygen, IV aminophylline, corticosteroids
Gürkan 1999	Turkey (1)	20	6 to 16 (10.8)	PEF < 60% predicted (after 3 beta-2 adrenergic nebuliser treatments)	46.5	40 mg/kg 20 mins	3 beta-2 adrenergic nebuliser treatments
Scarfone 2000	USA (3)	54	1 to 18 (5.7)	"moderate to severe asthma exacerbation"	NR	75 mg/kg 20 mins	Nebulised albuterol Oxygen, methylprednisolone

Figure 1. Forest plot showing the effect of intravenous magnesium on hospital admissions compared with a placebo infusion.

1.1 Hospital admissions



Footnotes

(1) discharge rate from the emergency department was the rate at which decisions to admit were reversed