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[Intervention Review]

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

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ABSTRACT

Background

Acute asthma in children can be life-threatening and must be treated promptly in the emergency setting. Intravenous magnesium sulfate is recommended by various guidelines for cases of acute asthma that have not responded to first-line treatment with bronchodilators and steroids. The treatment has recently been shown to reduce the need for hospital admission for adults compared with placebo, but it is unclear whether it is equally effective for children.

Objectives

To assess the safety and efficacy of intravenous magnesium sulfate (IV MgSO₄) in children treated for acute asthma in the emergency department (ED).

Search methods

We identified studies by searching the Cochrane Airways Review Group Specialised Register up to 23 February 2016. We also searched ClinicalTrials.gov and reference lists of other reviews, and we contacted study authors to ask for additional information.

Selection criteria

We included randomised controlled trials of children treated in the ED for exacerbations of asthma if they compared any dose of IV MgSO₄ with placebo.

Data collection and analysis

Two review authors screened the results of the search and independently extracted data from studies meeting the inclusion criteria. We resolved disagreements through discussion and contacted study authors in cases of missing data and other uncertainties relating to the studies.

We analysed dichotomous data as odds ratios and continuous data as mean differences, both using fixed-effect models. We assessed each study for risk of bias and rated the quality of evidence for each outcome with GRADE and presented the results in a 'Summary of findings' table. There was insufficient evidence to conduct the planned subgroup analyses.

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

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Main results

Five studies (182 children) met the inclusion criteria, and four contributed data to at least one meta-analysis. The included studies were overall at low risk of bias, but our confidence in the evidence was generally low, mainly due to the small sample sizes. Treatment with IV MgSO₄ reduced the odds of admission to hospital by 68% (odds ratio (OR) 0.32, 95% confidence interval (CI) 0.14 to 0.74; children = 115; studies = 3; I² = 63%). This result was based on data from just three studies including 115 children. Meta-analysis for the secondary outcomes was extremely limited by paucity of data. We performed meta-analysis for the outcome 'return to the emergency department within 48 hours', which showed a very imprecise effect estimate that was not statistically significant (OR 0.40, 95% CI 0.02 to 10.30; children = 85; studies = 2; I² = 0%). Side effects and adverse events were not consistently reported and meta-analysis was not possible, however few side effects or adverse events were reported.

Authors' conclusions

IV MgSO₄ may reduce the need for hospital admission in children presenting to the ED with moderate to severe exacerbations of asthma, but the evidence is extremely limited by the number and size of studies. Few side effects of the treatment were reported, but the data were extremely limited.

PLAIN LANGUAGE SUMMARY

Do magnesium sulfate infusions reduce the need for hospital admission in children with acute asthma?

Background

Many children experience life-threatening asthma attacks and require treatment in the hospital emergency department. Some national and international asthma treatment guidelines recommend giving an infusion of a drug called magnesium sulfate (IV MgSO₄) to children having asthma attacks that have not responded well to other treatments. This has been shown to reduce the need for hospital admission for adults, but it is unclear whether it is safe and similarly effective for children.

Study characteristics

We found five studies in children that compared an infusion of MgSO₄ to a placebo infusion when other treatments had not relieved the attack (usually inhaled bronchodilators, steroids, and sometimes oxygen). These five studies included a total of 182 children. Only three of the studies reported the outcome we were most interested in, which was the need to be admitted to hospital. The studies were published between 1996 and 2000; these were the most current studies we could find when we searched in February 2016.

Key results and quality of the evidence

Fewer children who had an infusion of MgSO₄ needed to be admitted to hospital compared with placebo. In fact, for every five children treated with the MgSO₄, one admission to hospital was prevented. However, the included studies were small, with only 115 children in the main analysis, and the results did vary, so we cannot be absolutely sure of the benefits and harms. As there were so few studies, we also could not tell whether the reduction in hospital admissions was associated with age, severity of the asthma exacerbation, or whether it made a difference what other treatments were given. There were no reports of harm when the children received MgSO₄. The review therefore supports the use of MgSO₄ in children, however it must be noted that the evidence for its use is very weak.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

MgSO ₄ compared to placebo for treating children with acute asthma in the emergency department						
Patient or population: children with acute asthma in the emergency department Settings: emergency departments Intervention: MgSO ₄ Comparison: placebo						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	MgSO ₄				
Hospital admissions	767 per 1000	513 per 1000 (315 to 709)	OR 0.32 (0.14 to 0.74)	115 (3 studies)	⊕⊕○○ low ^{1,2}	MgSO ₄ reduced hospital admissions, but low confidence due to inconsistency and small numbers Random-effects sensitivity analysis: OR 0.18, 95% CI 0.02 to 1.59
ED treatment time (minutes)	The mean ED treatment time in the placebo group was 96 minutes	The mean ED treatment time in the intervention group was 5 minutes more (24 less to 34 more)	-	27 (1 study)	⊕⊕○○ low ³	No clear benefit of MgSO ₄ . Based on the subset of children who were discharged home, not those who were admitted
Return to ED within 48 hours	22 per 1000	9 per 1000 (0 to 186)	OR 0.4 (0.02 to 10.3)	85 (2 studies)	⊕⊕○○ low ³	No clear benefit of MgSO ₄

Hospital length of stay (hours)	The mean hospital length of stay (hours) in the placebo group was 18.9 hours	The mean hospital length of stay (hours) in the intervention group was 5.3 hours lower (9.46 to 1.14 lower)	-	47 (1 study)	⊕⊕○○ low ^{4,5}	Possible benefit of MgSO ₄ but based on 1 small study
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4 of the planned outcomes were not reported in a way that could be meta-analysed in any of the included studies (intensive care admissions, vital signs, spirometry, validated paediatric symptom scores, and adverse events)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **ED:** emergency department; **OR:** odds ratio

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹Test for heterogeneity $P = 0.07$, $I^2 = 63\%$ (-1 inconsistency).

²Total number of children included in analysis low with concurrent low event rate, and a sensitivity analysis using random effects seriously reduced the precision of the estimate (-1 imprecision).

³Very imprecise estimate based on data from a single small study. 'Return to ED within 48 hours' analysis included two studies, but [Ciarallo 1996](#) did not observe any events (-2 imprecision).

⁴Only study included limiting the precision of the result (-1 imprecision).

⁵Two other studies reported hospital admission but not length of hospital stay (-1 publication bias).

BACKGROUND

Description of the condition

Asthma is a chronic respiratory condition characterised by inflammation of the airways and partially reversible airflow obstruction. Common symptoms include cough, wheezing, difficulty breathing, reduced exercise tolerance, and chest tightness. In asthma airway inflammation and bronchospasm (contraction of the smooth muscle lining the airways) leads to airflow obstruction. The condition follows a varying course in individuals that is driven by genetic and environmental triggers.

Asthma symptoms vary in severity and frequency. It can cause daily chronic symptoms and exacerbations. An exacerbation is defined as an acute worsening of asthma symptoms. Principles of treatment consist of controlling daily symptoms and preventing exacerbations by providing good education and appropriate inhaler usage. National and international guidelines have been published for the treatment of asthma exacerbations (BTS/SIGN 2014; GINA 2015).

Short-acting bronchodilators are given to relieve bronchospasm, and symptoms of inflammation are treated with corticosteroids; both are usually delivered via inhalers. Depending on the persistence of symptoms, inhalers can be taken regularly (maintenance therapy) or on an as-needed basis (reliever therapy) (BTS/SIGN 2014; GINA 2015). Beta2-agonists are recognised as most effective in relieving bronchospasm (Teoh 2012), however anticholinergic inhalers have also proved effective in the treatment of acute asthma (Griffiths 2013).

Children with asthma are most often managed in primary care, however, in severe cases, secondary-level care by a paediatrician may be necessary. The goal of treatment is to allow a good quality of life while avoiding asthma exacerbations that require a visit to the emergency department (ED) and hospital admission.

In severe exacerbations, which can be life-threatening, further medications may be required, such as oral or intravenous corticosteroids (BTS/SIGN 2014; GINA 2015; Rowe 2001). Intravenous bronchodilators and magnesium sulfate have also been used to treat children with severe asthma exacerbations.

Description of the intervention

Recent clinical guidelines advise that a single dose of intravenous magnesium sulfate (IV MgSO₄) can be considered for children 5 years of age and older with acute severe asthma who have not responded to inhaled bronchodilator therapy and for those with life-threatening or near-fatal asthma (BTS/SIGN 2014).

Magnesium sulfate (MgSO₄) has been used in a nebulised form in the treatment of acute severe asthma; this is the subject of a separate review, which found no significant reduction in hospital admission (Powell 2012). For the purposes of this review, we have considered

only the use of IV MgSO₄. Dosage in children is usually based on weight. The British National Formulary for Children advises 40 mg/kg and up to a maximum total dose of 2 g, delivered by intravenous infusion over 20 minutes. However, larger doses of up to 75 mg/kg have been used (Scarfone 2000).

How the intervention might work

The mechanism of action of IV MgSO₄ in the context of an exacerbation of asthma is not fully understood. It is believed to play a role in bronchial smooth muscle relaxation via its ability to stop calcium ion movement into smooth muscle cells by blocking the voltage-dependent calcium channels (Spivey 1990). Some evidence has also been found of its role in reducing the inflammatory response (Cairns 1996). The combination of smooth muscle relaxation and anti-inflammatory properties provides a theoretical basis for the use of MgSO₄ in cases of acute asthma.

Why it is important to do this review

One in 11 children in the UK suffer from asthma. Asthma presentations in EDs are common, peaking at 26,969 admissions in 2006/2007 (Millet 2013). A total of 216 deaths from asthma were reported in the UK in 2014; 16 of these individuals were children 14 years of age or younger (Asthma UK). In fact, between 2005 and 2010, 1% to 4.2% of all admissions to paediatric intensive care units (PICUs) in the UK were due to asthma; this translates to 1640 admissions (in 1410 patients). Furthermore, the number of admissions to PICUs in the UK due to asthma is rising. Asthma-related admissions increased by 67% (195 to 327 admissions) between 2005 and 2010 (Nyman 2011).

Historically, MgSO₄ is a treatment used in the ED. The National Review of Asthma Deaths reviewed 195 deaths from asthma between February 2012 to January 2013 and found that 45% had attended an ED prior to death (NRAD 2014). When these patients present with life-threatening episodes of asthma, we need effective and safe treatments.

Although current guidelines advocate the use of IV MgSO₄ in the treatment of acute asthma (BTS/SIGN 2014; GINA 2015), it is acknowledged that evidence in the literature has provided conflicting results. An earlier version of this review, Rowe 2000, found little evidence to support the use of IV MgSO₄ in children based on results from seven studies, five of which studied adult participants.

The burden of asthma in children continues to increase and as such it is important to be able to guide treatment based on paediatric evidence. As such, the previous review, Rowe 2000, has been split into adult, Kew 2014, and paediatric reviews, focusing the discussion and conclusions to the respective patient groups. This review has provided the opportunity to review any new evidence

that has emerged over the past 16 years and draw conclusions relevant to current paediatric practice.

OBJECTIVES

To assess the safety and efficacy of intravenous magnesium sulfate (IV MgSO₄) in children treated for acute asthma in the ED.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials of any follow-up duration. We included studies reported as full text, those published as abstract only, and unpublished data.

Types of participants

We included studies of children (18 months to 18 years of age) treated in the ED for acute asthma (all severities). When studies recruited both adults and children, we only used data if provided for children separately. As wheezy symptoms in children younger than 18 months may represent a different disease process (that is bronchiolitis), we examined participant demographics in trials that included children younger than 18 months to determine percentage of the study population. If they made up more than 10% of the population, we excluded the studies.

Types of interventions

We included studies comparing any dose of IV MgSO₄ versus placebo. Because children with acute asthma often require additional treatments, we included studies that allowed other medications provided they were not part of the randomly assigned treatment. We did not include studies of MgSO₄ combined with other intravenous bronchodilator agents unless the study set out to test the effect of MgSO₄, and all other treatments were the same in both groups. We did not intend to assess IV MgSO₄ against nebulised MgSO₄ or other active treatments. We have presented the results in a summary characteristics table that includes a list of medications given in each of the included studies (Table 1).

Types of outcome measures

Primary outcomes

1. Hospital admissions.

Secondary outcomes

1. ED treatment duration.
2. Intensive care admissions.
3. Hospital length of stay.
4. Vital signs (respiratory rate, oxygen saturations).
5. Spirometry (peak expiratory flow rate (PEFR), forced expiratory volume in one second (FEV1)).
6. Validated paediatric symptom scores.
7. Adverse events.

Reporting in the study one or more of the outcomes listed here was not an inclusion criterion for the review.

Search methods for identification of studies

Electronic searches

We identified trials from the Cochrane Airways Group Specialised Register (CAGR), which is maintained by the Information Specialist for the Group. The Register contains trial reports identified through systematic searches of multiple bibliographic databases and by handsearching of respiratory journals and meeting abstracts (see Appendix 1 for further details). We searched all records in the CAGR using the search strategy provided in Appendix 2. The most recent search was conducted on 23 February 2016.

We also conducted a search of ClinicalTrials.gov (www.ClinicalTrials.gov) and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (www.who.int/ictip/en/). We searched all databases from their inception to the present, and imposed no restriction on language of publication.

Searching other resources

We checked reference lists of all primary studies and review articles for additional references. We searched relevant manufacturers' websites for trial information. We also searched for errata or retractions from included studies published in full text on PubMed (www.ncbi.nlm.nih.gov/pubmed) on 8 April 2016.

Data collection and analysis

Selection of studies

Two review authors (BG and KMK) independently screened titles and abstracts of all citations identified by the search for inclusion and coded them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We retrieved the full-text study reports/publications, and both review authors independently screened the full text and identified studies for inclusion. We identified and recorded reasons for exclusion of ineligible studies. We resolved

disagreements through discussion, or, if required, by consulting a third person. We identified and excluded duplicates and collated multiple reports of the same study, so that each study rather than each report was the unit of interest in the review. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram and a [Characteristics of excluded studies](#) table.

Data extraction and management

To record study characteristics and outcome data, we used a data collection form that had been piloted on at least one study in the review. One review author (KMK) extracted study characteristics from the included studies, and both review authors independently extracted outcome data. We extracted the following study characteristics.

1. Methods: study design, duration of observation and follow-up, details of any 'run-in' period, number of study centres and locations, withdrawals, and date of study.
2. Participants: N, mean age, age range, gender, asthma severity, diagnostic criteria, baseline lung function, inclusion criteria, and exclusion criteria.
3. Interventions: intervention, dose, comparison, concomitant and failed treatments, and excluded medications.
4. Outcomes: primary and secondary outcomes specified and collected, and time points reported.
5. Notes: funding for trial and notable conflicts of interest of trial authors.

We noted in the [Characteristics of included studies](#) table if outcome data were not reported in a usable way. We resolved disagreements by consensus or by involving a third person. The two review authors transferred data into the Review Manager (version 5.3) file together ([RevMan 2014](#)). We double-checked that data had been entered correctly by comparing data presented in the systematic review with information in the study reports. A second review author (BG) spot-checked study characteristics for accuracy against the trial report.

Assessment of risk of bias in included studies

Both review authors independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)), resolving disagreements by discussion. We assessed the risk of bias according to the following domains.

1. Random sequence generation.
2. Allocation concealment.
3. Blinding of participants and personnel.
4. Blinding of outcome assessment.
5. Incomplete outcome data.
6. Selective outcome reporting.
7. Other bias.

We graded each potential source of bias as high, low, or unclear and provided a quote from the study report together with a jus-

tification for our judgement in the 'Risk of bias' table. We summarised the 'Risk of bias' judgements across different studies for each of the domains listed. We considered blinding separately for different key outcomes when necessary (for example for unblinded outcome assessment, risk of bias for hospital admissions may be very different than for a participant-reported scale). When information on risk of bias related to unpublished data or correspondence with a study author, we noted this in the 'Risk of bias' table. When considering treatment effects, we took into account the risk of bias for studies that contributed to that outcome.

Assessment of bias in conducting the systematic review

We conducted the review according to this published protocol and have reported any deviations from it in the [Differences between protocol and review](#) section of the systematic review.

Measures of treatment effect

We analysed dichotomous data as odds ratios and continuous data as mean differences or standardised mean differences. If studies reported several validated symptom measures, or if different scales were reported across studies, we analysed the data as standardised mean differences in one analysis to reduce measurement error and enhance precision. We entered the presented data as a scale with a consistent direction of effect. We narratively described skewed data reported as medians and interquartile ranges.

We undertook meta-analyses only when this was meaningful (that is when treatments, participants, and the underlying clinical question were similar enough for pooling to make sense).

When multiple trial arms were reported in a single trial, we included only the relevant arms. If two relevant comparisons from a single study were combined in the same meta-analysis, we halved the control group to avoid double-counting.

Unit of analysis issues

For dichotomous outcomes, we used participants rather than events as the unit of analysis (that is number of children with any adverse events rather than the total number of events).

Dealing with missing data

We contacted investigators or study sponsors to verify key study characteristics and to obtain missing numerical outcome data when possible (for example when we identified a study as an abstract only). When this was not possible and the missing data were thought to introduce serious bias, we explored the impact of including such studies in the overall assessment of results by performing a sensitivity analysis.

Assessment of heterogeneity

We used the I^2 statistic to measure heterogeneity among the trials in each analysis. When we identified substantial heterogeneity, we reported this and explored possible causes by prespecified subgroup analysis.

Assessment of reporting biases

We were not able to pool more than 10 studies, and so could not create and examine a funnel plot to explore possible small-study and publication biases. We considered the impact of unpublished studies in the GRADE ratings for each outcome.

Data synthesis

We used a fixed-effect model and performed a sensitivity analysis with random-effects when we observed significant heterogeneity (I^2 greater than 30%).

Summary of findings table

We created a 'Summary of findings' table for all five outcomes. We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of a body of evidence as it relates to the studies that contribute data to the meta-analyses for the prespecified outcomes. We used methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), using GRADEpro GDT. We justified all decisions to downgrade or upgrade the quality of studies using footnotes, and made comments to aid readers' understanding of the review when necessary.

Subgroup analysis and investigation of heterogeneity

Based on observations in previous versions of this review and to focus recommendations about the appropriateness of the intervention within specific patient groups, we planned the following subgroup analyses.

1. Baseline severity of exacerbation (moderate, severe, life-threatening*).
2. Age (\leq and $>$ 5 years).

We used the formal test for subgroup differences in RevMan 2014 *As no single metric has been accepted for assessing asthma severity in children, we planned to extract baseline data relevant to the following severity criteria as stated in the recent asthma guidelines (BTS/SIGN 2014).

1. Ability to speak and eat.

2. Breaths per minute.
3. Pulse.
4. Pulse oximetry.
5. Peak flow.
6. Arterial (oxygen saturation).

BG labelled study populations as moderate, severe, and life-threatening based on available data. The judgements were not made by an independent assessor as planned because we were not able to perform the subgroup analysis, so classification was made for descriptive purposes only. If additional studies allow the subgroup analysis to be undertaken in a future update of this review, this will be done by an assessor blinded to the study results.

Sensitivity analysis

We planned the following sensitivity analyses.

1. Studies at high risk of bias for blinding.
2. Studies including children $<$ 18 months of age.
3. Unpublished data.

RESULTS

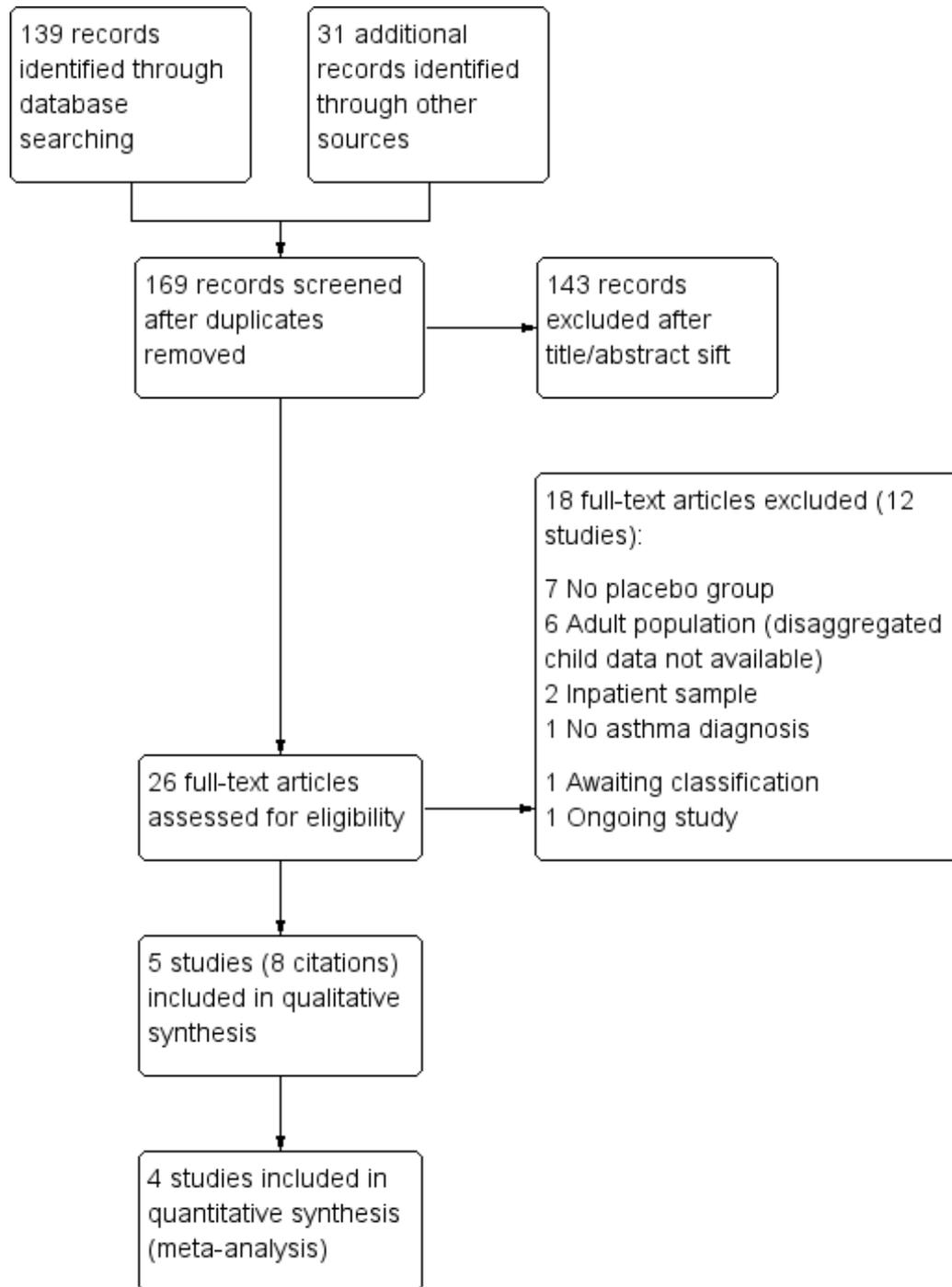
Description of studies

We have provided full details of the conduct and participant characteristics of each included study in the [Characteristics of included studies](#) table, and reasons for excluding full texts in the [Characteristics of excluded studies](#) table.

Results of the search

We identified 139 records in the electronic database searches and 31 additional records by searching ClinicalTrials.gov. We removed one duplicate record, screened 169 records, and excluded 143 by looking at the titles and abstracts alone. We retrieved full texts for the remaining 26, of which 18 were excluded for the following reasons: 'no placebo group' ($n = 7$), 'adult population' ($n = 6$), 'in-patient sample' ($n = 2$), no asthma diagnosis ($n = 1$), awaiting classification because we were unable to locate the publication (Abd El Kader 1997), and ongoing (NCT01522040). The remaining eight citations related to five studies, which we included in the systematic review (Ciarallo 1996; Ciarallo 2000; Devi 1997; Gürkan 1999; Scarfone 2000). We have presented the study flow in Figure 1.

Figure 1. Study flow diagram.



Included studies

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. Sample sizes were small, ranging from 20 to 54 (median 31). We have provided a summary of study characteristics in Table 1.

All of the included studies were randomised, double-blind, placebo-controlled trials, which were conducted at between one and three centres. Three studies were conducted in the USA (Ciarallo 1996; Ciarallo 2000; Scarfone 2000), one in India (Devi 1997), and one in Turkey (Gürkan 1999). The main time of follow-up measurement was not reported in Devi 1997, but in the remaining four studies it ranged from 90 to 120 minutes after the start of the infusion.

Inclusion and exclusion criteria varied across the five studies with respect to age, severity metrics such as lung function and vital statistics, and allowed and disallowed comedications. The minimum age was 6 years in three studies, and 1 year in two studies (Devi 1997; Scarfone 2000). The upper age for inclusion was 16 or 18 in all studies except Devi 1997, which used a maximum age of 12 years.

We have provided a summary of the characteristics of children included in the studies in Table 2, including mean age, percentage male, and key measures of lung function and vital signs when they entered the ED.

Across the five studies, 89 children were randomised to receive MgSO₄ and 93 to placebo. In four studies, between 25 and 75 mg/kg MgSO₄ was administered over 20 minutes, and Devi 1997 gave 0.2 ml of 50% over 35 minutes (100 mg). The placebo was always delivered in a matching saline infusion. The administration of nebulised bronchodilators, usually multiple times, was common across studies. All studies except Gürkan 1999 described the use of corticosteroids, usually methylprednisolone, and two also stated

that oxygen had been used (Devi 1997; Scarfone 2000).

Three of the five studies reported the primary outcome (Ciarallo 1996; Ciarallo 2000; Scarfone 2000); the secondary outcomes were generally poorly reported. No data could be analysed for intensive care admissions, vital signs, spirometry, symptom scales, or adverse events.

Excluded studies

We excluded 17 articles relating to 12 studies after viewing the full texts. Bijani 2001, Bilaceroglu 2001, Boonyavorakul 2000, del Castillo Rueda 1991, and Skobeloff 1989 were all included in the adult review (Kew 2014); although these studies included some participants under 18, they were classified as adult populations and disaggregated data could not be obtained. Singhi 2011 and Torres 2012 used the correct population and intervention and were relatively large compared to the included studies (100 and 143 respectively), but these were open-label studies that did not use a placebo comparison. Irazuzta 2016 studied children with status asthmaticus and did not use a placebo comparison, and Watanatham 2015 compared nebulised MgSO₄ with IV MgSO₄ without a placebo group. We excluded Santana 2001 because the study recruited children who had already been admitted to a special paediatric care unit before they were given IV MgSO₄. Similarly, Okayama 1987 recruited children from mixed settings, including those already admitted to hospital, which could not be separated from the children who met the inclusion criteria for this review. The remaining study, Liang 1998, did not require that children had a diagnosis of asthma to be included in the study.

Risk of bias in included studies

Overall, the risk of bias across the studies was low, with some uncertainties relating to attrition and methods of allocation, and some issues with selective reporting (Figure 2).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Ciarallo 1996	+	?	+	+	?	-	-
Ciarallo 2000	+	+	+	+	?	-	+
Devi 1997	?	?	+	+	+	+	+
Gürkan 1999	?	?	+	?	?	+	+
Scarfone 2000	?	+	+	+	+	+	+

Allocation

We rated no studies as having a high risk of bias for sequence generation or allocation concealment. We rated only one study as low risk for both selection bias domains (Ciarallo 2000), and rated the other four as unclear in one domain, in Ciarallo 1996 and Scarfone 2000, or both domains, in Devi 1997 and Gürkan 1999.

Blinding

It is unlikely that biases related to insufficient blinding affected the results. All studies used matched placebos and double-blind procedures, although outcome assessor blinding was unclear in one study that was only reported as a conference abstract (Gürkan 1999).

Incomplete outcome data

There were some uncertainties in this domain, but no study reported drop-out rates that were high or unbalanced enough that we considered it to be at high risk of bias. Two studies did not report how many children were not accounted for in the analyses (Ciarallo 2000; Gürkan 1999), and we rated the other three as at low risk of bias (Ciarallo 1996; Devi 1997; Scarfone 2000).

Selective reporting

There was evidence of selective reporting in two studies conducted by the same author (Ciarallo 1996; Ciarallo 2000). Both reported some outcomes without variance, with inexact P values, or only in graphs, meaning the data could not contribute to the meta-analyses. We rated the other three studies as at low risk (Devi 1997; Gürkan 1999; Scarfone 2000).

Other potential sources of bias

Ciarallo 1996 was terminated before the specified sample was reached due to a change in ED practice (intravenous access was used less frequently in the care of status asthmaticus), which slowed the rate at which eligible patients were enrolled. There were also baseline imbalances in lung function between the two groups, which the study authors recognised may have magnified the difference between magnesium and placebo. We noted no additional sources of bias in the other studies (Ciarallo 2000; Devi 1997; Gürkan 1999; Scarfone 2000).

Effects of interventions

See: [Summary of findings for the main comparison MgSO₄ compared to placebo for treating children with acute asthma in the emergency department](#)

A summary of the main results, including absolute effects and an assessment of the quality of the evidence, can be found in [Summary of findings for the main comparison](#).

Primary outcomes

Hospital admissions

Treatment with IV MgSO₄ reduced the odds of admission to hospital by 68% (odds ratio (OR) 0.32, 95% confidence interval (CI) 0.14 to 0.74; children = 115; studies = 3; I² = 63%; [Analysis 1.1](#)). This result was based on data from three studies including 115 children (Ciarallo 1996; Ciarallo 2000; Scarfone 2000). The result was statistically significant (P = 0.008) but had a wide confidence interval that estimated a true population reduction in admission between 86% and 26%. In absolute terms, 767 out of 1000 people given placebo needed a hospital admission, compared with 513 (95% CI 315 to 709) out of 1000 given IV MgSO₄. This translates to a number needed to treat for an additional beneficial outcome of 4. There was statistically significant heterogeneity in the analysis (I² = 63%, P = 0.07) and a sensitivity analysis using a random-effects model provided a much less precise result that was not statistically significant (OR 0.18, 95% CI 0.02 to 1.59), but the direction and size of the effect was still in favour of IV MgSO₄. The studies were of good methodological quality, however the small number of study participants and heterogeneity reduced our confidence in the result to low.

Secondary outcomes

Emergency department treatment duration

In the one study that reported data for duration of treatment in the ED (Scarfone 2000), use of IV MgSO₄ caused children to spend an extra five minutes in the ED. However, the effect estimate was very imprecise, and the result was neither statistically nor clinically significant (mean difference (MD) 5.00, 95% CI -24.40 to 34.40; children = 27; studies = 1; [Analysis 1.2](#)). We downgraded the quality of this evidence twice for imprecision and rated as low because just one small study contributed to the analysis.

Intensive care admissions

No studies reported admission to intensive care in a way that we could include in our analyses.

Return to emergency department within 48 hours

We did not specify this outcome in the protocol for this systematic review, but chose to present the results because it is related to other named outcomes which were not well reported across the studies. Two studies with 85 children reported data for this outcome (Ciarallo 1996; Scarfone 2000), but one did not observe any events and so did not contribute to a pooled effect. In both groups the event rate was low, and the confidence intervals suggest a very imprecise effect estimate that was not statistically significant (OR 0.40, 95% CI 0.02 to 10.30; children = 85; studies = 2; $I^2 = 0\%$; Analysis 1.3). The small number of studies and events in this analysis resulted in a very imprecise estimate that warranted downgrading the quality of evidence twice for imprecision and rating as low.

Hospital length of stay

One study with 47 children reported data for this outcome (Devi 1997). Treatment with IV MgSO₄ reduced the length of hospital admission by 5.3 hours (MD -5.30, 95% CI -9.46 to -1.14; children = 47; studies = 1; Analysis 1.4). The effect estimate was imprecise but favours the treatment group at each extreme, and the result was statistically significant. Again this analysis was based on one study with very few children; we also downgraded for publication bias because two other studies reported hospital admission but not length of hospital stay, rating the evidence as low quality.

Vital signs (respiratory rate, oxygen saturations)

No studies reported vital signs in a way that we could include in our analyses. Devi 1997 reported oxygen saturations in graphical form, therefore data could not be accurately collected, however they did report a statistically significant difference favouring the treatment group. Examining the graph the effect was seen from 0 to 15 hours postinfusion.

Spirometry

No studies reported peak expiratory flow rate (PEFR) or forced expiratory volume in one second (FEV1) in a way that we could include in our analyses. Ciarallo 1996 reported the outcome for FEV1, forced vital capacity (FVC), and PEFR as a statistical difference between groups after treatment favouring the magnesium group. Devi 1997 reported PEFR in graphical form, therefore data could not be accurately collected, however they again reported a statistically significant difference favouring the treatment group. Examining the graph the effect was seen from 0 to 15 hours postinfusion. Gürkan 1999 reported a significant increase in the mean

of percentage of improvement from baseline in PEFR at 30 minutes after initiation of magnesium infusion ($P = 0.0002$), and they found an even greater improvement at the end of the observation period ($P = 0.0001$). Ciarallo 2000 found the PEFR and FEV1 improvement from baseline was statistically greater in the group that had received IV MgSO₄. They reported that this effect was apparent at all study time points.

Validated paediatric symptom scores

No studies reported validated asthma symptom scores. Gürkan 1999 reported a significant change in mean clinical asthma score of the children in the magnesium group at 90 minutes ($P = 0.005$). Ciarallo 2000 reported that there were statistically significant differences in the clinical asthma scores between the two groups, which occurred later in the study period at 95 minutes (1.4 IV MgSO₄ group versus 2.5 placebo group) and 110 minutes (1.1 IV MgSO₄ group versus 2.4 placebo group). Scarfone 2000 reported a pulmonary index score at 7 points and found no statistical difference between groups ($P = 0.37$).

Adverse events

The included studies did not report enough data to enable meta-analysis, however reviewing the narrative results revealed a low incidence of adverse events in both groups. Gürkan 1999 reported no significant difference in side effects (but did not report which symptoms this included) and no significant difference in heart rate or blood pressure. Scarfone 2000 reported no episodes of hypotension in either group and no difference between groups in degree of tachycardia. Only one child in the placebo group experienced emesis. Ciarallo 2000 reported no intergroup difference in systolic blood pressure. Ciarallo 1996 also reported no difference in blood pressure. They did state that two children in the treatment group reported a relaxed sensation compared to none in the placebo group. There were no reports of dizziness, fatigue, or any other adverse symptoms.

Devi 1997 reported the following adverse effects in the treatment group: epigastric warmth (12.5%), pain (16.6%), and tingling and numbness (12.5%) at the site of infusion. There were no reported incidents of these symptoms in the control group.

Subgroup and sensitivity analyses

Since there were only three studies in the primary analysis (and fewer in the secondary), we did not consider the planned subgroup analyses on the basis of baseline severity of exacerbation and age to be justified. Similarly, we were unable to conduct the planned sensitivity analyses to test the robustness of the results in relation to detection bias, the inclusion of very young children, and unpublished data.

DISCUSSION

Summary of main results

Children with predominantly moderate to severe asthma presenting to the ED who were treated with IV MgSO₄ in addition to standard therapy showed a 68% reduction in the odds of hospital admission (OR 0.32, 95% CI 0.14 to 0.74). This result represents a dramatic reduction in admission rates, however confidence in the result was low due to the small number of children included in the analysis (n = 115) and variability between study results.

The variability in study results was reflected in the estimate of heterogeneity for the primary outcome. Examining the primary analysis, the data from Scarfone 2000 appears to lie outside those reported in the other two studies. It is difficult to explain the heterogeneity, as the studies were very similar in design and study population included. All of the studies were relatively small in size, increasing the imprecision in the reporting of effects. Repeating the analysis using a random-effects model gave a result that was not statistically significant (OR 0.18, 95% CI 0.02 to 1.59). This again highlights that although the results favour the use of MgSO₄, the strength of that conclusion is very limited.

Data for the secondary outcomes was also limited. Two studies provided data for the outcome 'return to the emergency department within 48 hours' (Ciarallo 1996; Scarfone 2000), which favoured IV MgSO₄, but the confidence intervals did not exclude no difference (OR 0.40, 95% CI 0.02 to 10.30). Several studies reported improvements in spirometric data with treatment, but did not include the raw data for meta-analysis. The message from the narrative description of results for symptoms score and spirometry in all but one case favoured treatment with IV MgSO₄. However, interpreting these results requires even greater caution.

Traditionally asthma has been referred to in the literature in terms of severity, and as such national guidelines are often framed in this manner. We intended to perform a subgroup analysis by severity subgroup. We had proposed to get a blinded review author to rate the severity of each study based on the inclusion criteria, but the limited amount of available data prevented this subgroup analysis. However, examining the inclusion criteria for the three studies that presented data for the primary outcome (Ciarallo 1996; Ciarallo 2000; Scarfone 2000), we can see that all children had a peak expiratory flow (PEF) less than 70%, which would have traditionally been referred to as moderate to severe exacerbations. While the evidence is based on a moderate-to-severe cohort, it is acknowledged that severity in paediatric practice is often a clinical judgement as spirometry in young children is frequently limited in its accuracy.

Again, data on side effects was inconsistently reported, which limited the meta-analysis, but on the whole the number of side effects was small. In fact, the only reported side effect was a relaxed sensation in two children (Ciarallo 1996). There was no reported evidence of the haemodynamic instability that is often historically

reported with the use of MgSO₄. The lack of any reported harm is encouraging, but the ability to extrapolate this result is again limited by the small number of studies included in the review.

If we accept that there is weak evidence of the effectiveness of MgSO₄, the question of timing of administration needs to be addressed. The included study protocols administered IV MgSO₄ after failure to improve with first-line nebulised bronchodilator therapy. We would agree that MgSO₄ remains a second-line therapy after patients have failed to respond to more evidence-based nebulised bronchodilator therapies. In clinical practice IV MgSO₄ is often used in conjunction with other IV bronchodilators (salbutamol and aminophylline). As the studies included in this review only examined MgSO₄ as a single IV agent, evaluating any possible synergistic interaction was beyond the scope of this review.

Overall completeness and applicability of evidence

Three studies contributed data to the primary outcome assessing the potential effect of IV MgSO₄ on preventing hospital admission (Ciarallo 1996; Ciarallo 2000; Scarfone 2000). The studies used between 25 and 75 mg/kg of MgSO₄, but all were given in a 20-minute infusion. We cannot comment on optimal dosing given the limited data in the review; at this time it would be prudent to comply with national guidance which is in line with the range in this review. All three studies were conducted in the USA, which has implications on the applicability of the evidence to other healthcare systems, especially with regard to the comedications administered previous to MgSO₄. The US studies gave children nebulised bronchodilators (albuterol, ipratropium bromide, or both) and IV methylprednisolone, which may not be the practice in other countries.

A common criticism of hospital admission as an outcome is that the criteria to make this decision is often not standardised, and it is widely acknowledged that admission rates vary by country and even region. However, where randomisation is appropriate it should provide a reliable between-group difference in moderate-to-severe patients. It may be argued that severe asthma by its nature requires admission to hospital, in which case admission to paediatric intensive care unit (PICU) may be a possible outcome. However, it must also be acknowledged that in some institutions some therapies mandate admission to a PICU (certain IV therapies), in which case the need for intubation and mechanical ventilatory support may represent an alternative. Rightly or wrongly, burden of disease is widely reported as a rising admission rate, therefore it stands to reason we should attempt to use this as an outcome of treatment efficacy.

The children in the studies had a mean age of around 11 in Ciarallo 1996 and Ciarallo 2000 and were younger on average in Scarfone 2000, at around 7 in the active group and 5 in the placebo group. This mean age would support the recommendation

in British Thoracic Society guidance, however younger children were also included and treated safely in the studies.

The age imbalance within [Scarfone 2000](#) may have affected the results and suggests that the sample sizes of the included studies, of which [Scarfone 2000](#) is the largest at 54, are unlikely to have been sufficiently large enough to assume that important baseline variables were evenly distributed by randomisation. These differences and limitations in the design and conduct of the studies contributing data means that the implications for practice must be carefully considered.

No more than two studies contributed to any of the secondary outcomes, and we were unable to conduct a meta-analysis for five of the eight secondary outcomes. As such, even the three secondary outcomes for which we could include data (duration in ED, return to ED within 48 hours, and duration of hospital stay) included data for no more than 88 children, which severely limits the applicability of any conclusions that can be drawn. Outcomes that could not be supported by analyses included admission to intensive care unit, spirometry, and adverse events, which we fully expected to be better reported in studies conducted in an emergency setting. For these outcomes, we tried to describe narratively information in the studies that was not fully reported in order to give the fullest picture possible, but they represent an important gap in the evidence base.

Previous reviews have examined subgroups based on exacerbation severity and concluded that IV MgSO₄ has a role primarily in the treatment of severe exacerbations. We have already alluded to the difficulties of assessing asthma severity in children, but our results are most applicable to children with moderate or severe asthma attacks. This group of patients is more likely to present to the ED, therefore we would agree that currently the role of IV MgSO₄ would be in moderate to severe patients who have failed to respond to inhaled therapies, and not to children presenting in primary care. Clinically MgSO₄ is also used prior to or concurrently with nebuliser therapy in severe life-threatening episodes where severe obstruction to air flow limits the effectiveness of inhaled therapies. Studies in this review did not test IV MgSO₄ in these situations, but we excluded a study recruiting children in status asthmaticus that did not include a placebo group ([Irazuzta 2016](#)). Prioritisation of therapies in extremis needs to be based on sound clinical judgement and experience. It is important to recognise that asthma attacks run a continuum, often lapsing and relapsing over several days, and what role magnesium has in altering the course of an exacerbation is unknown.

Quality of the evidence

While there were some uncertainties in the study procedures, particularly with selection and attrition bias, we considered the included studies to be of good methodological quality overall, and so none of the outcomes were downgraded for risk of bias. Additionally, the five studies closely matched the inclusion criteria set

out in the protocol, therefore we did not consider the evidence to be compromised by indirectness.

However, our confidence in the findings was reduced by serious imprecision in the estimates, largely due to very small numbers of studies and participants. In the case of the primary outcome, serious differences in what the three studies found resulted in the effect becoming imprecise when we performed a random-effects sensitivity analysis, and this reduced our confidence in the main finding.

Incomplete outcome reporting in two studies affected some of the secondary outcomes that we were not able to meta-analyse (spirometry, intensive care admissions, vital signs). As mentioned above, the small number of included studies overall and the very small amount of data suitable for meta-analysis may suggest publication bias, and limits the conclusions that can be drawn.

Potential biases in the review process

This review examined included studies for bias against predetermined criteria as specified by current Cochrane methodology. We identified internal reporting biases in two of the included studies ([Ciarallo 1996](#); [Ciarallo 2000](#)), which may have impacted on the completeness of our results, but this was considered in the relevant GRADE ratings. [Ciarallo 1996](#) reported in their methodology a wide range of parameters that were collected on participants but only reported some of these outcomes, which all had significant results. The authors stated that the trial recruitment period was cut short because of a change in ED practice. Their original power calculation stipulated 40 participants to detect a 25% difference in PEFR; only 31 participants were enrolled, and as such the estimate of effect can be exaggerated. However, we did not include PEFR in our meta-analysis, and so our results were not affected. The authors also note there was a difference in the baseline characteristic (FEV1) between the groups, which could again have led to an overestimate of the effect in the treatment group.

We implemented the planned methods as far as possible, but in some cases the small number of studies meant this was not possible or valid. We have listed these instances in [Differences between protocol and review](#).

Agreements and disagreements with other studies or reviews

Having urged caution in the interpretation of the primary analysis, it can be seen that the result favouring admission reduction in the IV MgSO₄ group is in keeping with the recently published adult review. A recent review of IV MgSO₄ for acute asthma in the ED in adult patients reported a reduction in the odds of hospital admission of 25% (OR 0.75, 95% CI 0.60 to 0.92) based on 11 studies including 1769 participants ([Kew 2014](#)). This systematic review of the adult evidence contains new data from the largest

adult study to date (Goodacre 2013, n = 752). They also found an improvement in spirometric parameters in participants treated with IV MgSO₄. An older Cochrane review that assessed adults and children together only found a treatment effect in a severe patient subgroup (Rowe 2000).

Caution is required in extrapolating results from adult asthma studies, as childhood asthma is reported to respond differently to some established therapies.

Cheuk 2005 published a meta-analysis of paediatric patients, which reported hospital admission as its primary outcome. It included four studies in this analysis, three of the studies presented here and also admission data for Devi 1997 (admission data not included in published article and was not made available despite attempts to contact the study author). The meta-analysis concluded that magnesium was likely to reduce hospital admission and improve bronchospasm.

Most recently in the paediatric literature Ohn 2014 published a review stating magnesium should be given to all children presenting to hospital with acute severe asthma. This conclusion was based on two meta-analyses that included adult and paediatric patients, Rowe 2001 and Shan 2013, and one recent randomised controlled trial, Torres 2012, which was excluded from this review as it compared IV MgSO₄ versus standard care and not placebo. Torres 2012 reported a statistically significant reduction in the need for mechanical ventilation in the IV MgSO₄ group.

MgSO₄ can also be administered as an aerosol by nebuliser devices. There has been increasing interest in its use in adults and children with acute asthma, and a Cochrane review in 2012 found no improvement in lung function and no decrease in hospital admission with its use (Powell 2012). A large paediatric randomised controlled trial examining its use in children in the ED (N = 508) was recently published (Powell 2013), and while the new study is yet to be incorporated in to their Cochrane review (Powell 2012), the study did not find a clinical difference in asthma severity score and did not report hospital admission data. Admission to PICU/high dependency unit was reported and was required by 35 out of 508 children (9% in the treatment group versus 6% in the placebo group).

IV MgSO₄ is commonly used in paediatric practice. In a survey of 183 ED consultants in the UK and Ireland, 94.5% report using it in their management of acute wheeze, and nearly one-third (28.4%) use it as their first-line intravenous agent (Lyttle 2015). The overwhelming narrative from the paediatric and adult literature supports the use of IV MgSO₄. This conclusion, while in keeping with this review, has at times been based on a very limited evidence base. Despite the largest adult trial to date showing no statistical difference, its inclusion in the most recent Cochrane analysis has provided a more robust base for the use of IV MgSO₄ in adults. In paediatric practice the literature has often drawn from adult data and paediatric data not obtained from randomised controlled trials. This review does draw a similar conclusion to the previous paediatric meta-analysis, but highlights the very severe

limitations of the evidence.

AUTHORS' CONCLUSIONS

Implications for practice

IV MgSO₄ may reduce the need for hospital admission in children presenting to the ED with moderate to severe exacerbations of asthma, but the evidence is extremely limited by the number and size of studies. There was a notable lack of data for many of the secondary outcomes, on which limited conclusions can be drawn (intensive care admissions, length of hospital stay, vital signs, spirometry, and symptom scales).

While the evidence of the efficacy of IV MgSO₄ is low quality, the meta-analyses and a narrative synthesis of adverse events suggest it is unlikely to cause harm, however data were extremely limited. Further analysis according to severity of exacerbation was not possible, but the evidence does not apply to mild exacerbations outside of the emergency setting.

Implications for research

The choice of outcome in paediatric clinical asthma trials is varied and has often hampered our ability to combine and meta-analyse data. Spirometry in young children is challenging, especially in the acute situation, and linking data to morbidity is difficult. Multiple asthma severity scores have been published, but few are validated, and no one score is reported consistently in the literature. Despite the number of asthma deaths remaining unacceptably high, the numbers are too low for mortality to be a useful outcome in paediatric trials. We therefore reported hospital admission data as the primary outcome. Widespread use of internationally agreed core outcome sets would facilitate future meta-analyses.

Studies in asthma have often framed treatment by severity. Measuring severity in the ED is problematic and may be best assessed clinically. Where the outcome is hospital admission, the event rate is obviously higher in the severe group, and it is therefore easier to detect a between-group difference in this subset of patients. These analyses are often secondary analyses, and the studies are not designed to power these analyses adequately. In the future it is important to classify treatment by severity to power studies adequately to detect these subgroup differences. Withholding therapy from less severe attacks may mean missed opportunities to stop the progression of an attack to severe or life-threatening.

The results of this review are in keeping with those from the recent adult review, but there are inherent dangers in extrapolating adult data to paediatric populations. At present, the use of IV MgSO₄ is under-reported in paediatric practice, and this review's conclusions

are based on results from three small studies. Only with more data can we truly answer the question as to the efficacy of IV MgSO₄, and despite no new data in the last 16 years, we would argue that clinical equipoise still exists. A subsequent trial should examine the use of IV MgSO₄ in paediatric populations using pragmatic markers of severity and practical outcome measures not dependent on spirometry.

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The Background and Methods sections of this review are based on a standard template used by Cochrane Airways.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Ciarallo 1996

Methods	Design: Randomised, double-blind, parallel-group, placebo-controlled trial Urban paediatric emergency department in Boston, USA Conducted from 20 September 1993 to 20 December 1994	
Participants	Participants: 31 participants were randomised to IV MgSO ₄ (15) and placebo (16) Inclusion criteria: Children aged 6 to 18 years who were being treated for an acute asthma exacerbation with PEFr less than 60% of the predicted value after receiving 3 beta-2 adrenergic nebuliser treatments Exclusion criteria: Body temperature greater than 38.5 °C; systolic blood pressure at less than the 25th percentile for age; recent use of theophylline; history of cardiac, renal, or pulmonary disease; and pregnancy	
Interventions	Treatments: 1. IV MgSO ₄ 25 mg/kg over 20 minutes 2. Saline infusion over 20 minutes Comedications: 3 beta-2 adrenergic nebuliser treatments; intravenous methylprednisolone infusion (2 mg/kg) was given to children who had not received corticosteroids Timing of intervention: If PEFr was less than 60% of the predicted value after 3 nebulised beta-2 adrenergic agents, and if the medical team caring for the child concluded that intravenous access was necessary for further medical management, placebo or MgSO ₄ was then administered	
Outcomes	Vital signs, O ₂ saturations, PEFr, FVC, FEV1 Main follow-up 110 minutes after start of infusion	
Notes		
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed in blocks of 10 by the pharmacy department, using a random-number table
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"assigned to receive magnesium sulfate (25 mg/kg; maximum, 2 gm in 100 ml of normal saline solution) or an equivalent volume of normal saline solution (placebo) in a double-blind fashion". The magnesium and placebo solutions were prepackaged by the hospital pharmacy in identi-

		cal containers that were coded according to a randomised sequence. The magnesium solution was given in 100 ml of normal saline solution to prevent the warm sensation at the intravenous line site described when magnesium sulfate is infused undiluted, thus maintaining the masked protocol
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unclear if those taking measurements were blind. All children had arrangements for admission instituted at the time of enrolment into the study, as decided by their physicians, independent of the study. "In this setting the discharge rate from the emergency department was the rate at which decisions to admit were reversed." "Criteria for discharge from the emergency department included (1) SaO ₂ greater than 94%, (2) no evidence of respiratory distress such as tachypnoea, flaring, or retractions, (3) minimal to no wheezes on auscultation, (4) PEFr greater than 70% of the predicted value, and (5) normal cerebral function - all maintained for 3 h after a nebulization"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No mention of non-completers
Selective reporting (reporting bias)	High risk	Only significant results were reported for FEV ₁ , PEFr, FVC. No data reported for oxygen saturations, respiratory rates, length of hospital stay, or blood pressure. Full results only graphical. PICU admission data not reported
Other bias	High risk	The study was terminated before the specified sample was reached because of a change in ED practice (intravenous access was used less frequently in the care of status asthmaticus), which impaired the rate at which eligible patients were enrolled "magnesium group started with a lower FEV ₁ gave this group more room for improvement, potentially magnifying differences in the rates of improvement in FEV ₁ between the two groups and overestimating the effect of magnesium in our study population."

Ciarallo 2000

Methods	Design: Randomised, double-blind, parallel-group, placebo-controlled trial 2 urban tertiary care paediatric emergency departments in the USA Recruited from September 1996 to August 1997	
Participants	Participants: 30 participants were randomised to IV MgSO ₄ (16) and placebo (14) Inclusion criteria: Children aged 6 to 17.9 who required 3 nebulised bronchodilating treatments (albuterol or ipratropium bromide or a combination of the 2); PEFr less than 70% Exclusion criteria: Body temperature greater than 38.5 °C, use of theophylline within the previous week, and a history of cardiac, renal, or pulmonary disease other than asthma	
Interventions	Treatments: 1. IV MgSO ₄ 40 mg/kg (maximum 2 g) over 20 minutes 2. Saline infusion over 20 minutes Comedications: 3 nebulised bronchodilating treatments (albuterol or ipratropium bromide or a combination of the 2). IV methylprednisolone (2 mg/kg) was administered to children who had not yet received corticosteroids Timing of treatment: If PEFr was less than 70% of the predicted value after 3 nebulised bronchodilators, and if the medical team caring for the child perceived them to be resistant to nebuliser, they received the placebo or MgSO ₄	
Outcomes	Change in PEFr, FEV ₁ , and FVC; ED disposition; serial clinical asthma scores; BP; deep tendon reflexes Main follow-up 105 minutes after start of infusion	
Notes		
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was blocked in groups of 10
Allocation concealment (selection bias)	Low risk	Randomly assigned by the investigational drug pharmacist
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The magnesium and placebo solutions were prepared by the hospital pharmacy
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The physicians on the medical team acted independently from the study physicians and were blinded to the child's magnesium treatment status
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No mention of non-completers. 8 were excluded because of unacceptable spirometry efforts (unclear which group, assumed pre-

Ciarallo 2000 (Continued)

		randomisation)
Selective reporting (reporting bias)	High risk	Lung function parameters were only reported graphically or with no variance or inexact P values in the text
Other bias	Low risk	None detected

Devi 1997

Methods	Design: Randomised, double-blind, parallel-group, placebo-controlled trial Pediatric Emergency Department of teaching hospital in India Recruited from January 1994 to January 1995	
Participants	Participants: 47 participants were randomised to IV MgSO ₄ (24) and placebo (23) Inclusion criteria: Children aged 1 to 12 with inadequate or poor response to initial 3 doses of nebulised salbutamol given at an interval of 20 minutes over a period of 1 hour, and (ii) where a written consent could be obtained from the parents accompanying the child Exclusion criteria: Children with axillary temperature greater than 38 °C, and (ii) blood pressure less than 50th percentile for age	
Interventions	Treatments: 1. IV MgSO ₄ 0.2 ml of 50% over 35 minutes 2. Saline infusion over 35 minutes Comedications: All the children received oxygen, nebulised salbutamol, IV aminophylline, and corticosteroids Timing of treatment: Placebo or MgSO ₄ was given after 60 minutes from entry to the ED and 3 nebulised bronchodilator treatments	
Outcomes	Respiratory and heart rates, pulsus paradoxus (measured using a stethoscope as the difference in systolic blood pressure between the pressure at which the first sporadic, faint pulse sounds were heard and the pressure at which all sounds were heard), accessory muscle usage, dyspnoea, colour, wheeze, PEFr in children 5 years of age or older, and SaO ₂ Main follow-up time unclear	
Notes		

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised. No details
Allocation concealment (selection bias)	Unclear risk	No details

Devi 1997 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind. "Decoding was done at the completion of the study. Magnesium sulfate and placebo solutions (normal saline) were prepared in the hospital pharmacy, coded and dispensed in identical vials."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unclear if those taking measurements were blind. Predetermined discharge criteria used for sending children home from the ED (primary outcome)
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 children were excluded during the study period as they became febrile (unclear which group). 2/49 only 4%
Selective reporting (reporting bias)	Low risk	SaO ₂ and %PEFR in graph format only
Other bias	Low risk	None detected

Gürkan 1999

Methods	Design: Randomised, double-blind, parallel-group, placebo-controlled trial Emergency department in Dicle University Hospital, Turkey	
Participants	Participants: 20 participants were randomised to IV MgSO ₄ (10) and placebo (10) Inclusion criteria: Children aged 6 to 16 with moderate to severe acute asthma exacerbation admitted to the ED; PEFr less than 60% of the predicted value after receiving 3 beta-2 adrenergic nebuliser treatments Exclusion criteria: fever, systolic BP at less than 25th percentile for age, recent use of theophylline, and history of cardiac, renal, or pulmonary disease	
Interventions	Treatments: 1. IV MgSO ₄ 40 mg/kg (maximum 2 g), 20 minutes 2. Saline infusion, 20 minutes Comedications: 3 beta-2 adrenergic nebuliser treatments Timing of treatment: 3 beta-2 adrenergic agents at 20-minute intervals, then if PEFr was less than 60% of the predicted value placebo or MgSO ₄ was administered	
Outcomes	Clinical asthma scores, PEFr, side effects Main follow-up 90 minutes after start of infusion	
Notes		
Risk of bias		
Bias	Authors' judgement	Support for judgement

Gürkan 1999 (Continued)

Random sequence generation (selection bias)	Unclear risk	Randomised. No details
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	“The investigators performing the study were completely blinded to the treatment offered”
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear if those taking measurements were blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No mention of non-completers
Selective reporting (reporting bias)	Low risk	30- and 90-minute data provided for named outcomes
Other bias	Low risk	None detected

Scarfone 2000

Methods	Design: Randomised, double-blind, parallel-group, placebo-controlled trial 3 emergency departments in Philadelphia, USA
Participants	Participants: 54 participants were randomised to IV MgSO ₄ (24) and placebo (30) Inclusion criteria: Children aged 1 to 18 years with a past history of at least 1 episode of wheezing who presented to the ED with a moderate to severe asthma exacerbation (defined as a pulmonary index score of 8 to 13). To avoid enrolling young children with bronchiolitis, the lower age limit for study inclusion was raised to 2 years from 15 November through 30 March Exclusion criteria: More mild (pulmonary index score less than or equal to 7) or severe (pulmonary index score greater than or equal to 14) asthma exacerbation, children who had used corticosteroids within the preceding 72 hours, had concurrent bronchiolitis, lobar pneumonia, croup, or suspected foreign body aspiration, a history of cystic fibrosis, bronchopulmonary dysplasia, congenital heart disease, liver or renal disease, sickle cell anaemia, or who were pregnant
Interventions	Treatments: 1. IV MgSO ₄ 75 mg/kg over 20 minutes 2. Saline infusion over 20 minutes Comedications: nebulised albuterol and methylprednisolone, oxygen Timing of treatment: After completion of a second nebulised dose of albuterol (run immediately after first), study drug or placebo was given
Outcomes	Improvement on the pulmonary index, hospitalisation rate, time required to discharge Main follow-up 120 minutes after start of infusion

Scarfone 2000 (Continued)

Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised, no details given
Allocation concealment (selection bias)	Low risk	Quote from study: "hospital pharmacists ... created and concealed the allocation schedule, broken only at study's end"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The magnesium and placebo were identical in appearance and prepared by hospital pharmacists who also created and concealed the allocation schedule, broken only at study's end
Blinding of outcome assessment (detection bias) All outcomes	Low risk	In the absence of the study investigator, either study drug was administered by a nurse not involved with study measurements. Children remained in the study for 150 minutes, at which time the blinded investigator decided patient disposition, independent of the emergency physician's disposition. Guidelines for admission (saturation < 92%). Discharge criteria included sustained good aeration, absent or minimal wheezing, minimal work of breathing, and oxygen saturation greater than 95% in room air
Incomplete outcome data (attrition bias) All outcomes	Low risk	"One child in the placebo group required more aggressive asthma therapy than allowed for by the protocol after 95 minutes. Another child in the magnesium group was mistakenly given an inadequate dose of magnesium. Importantly, there were no changes in outcome measures when a secondary analysis was performed excluding these 2 children
Selective reporting (reporting bias)	Low risk	Named outcomes well reported
Other bias	Low risk	None detected

BP = blood pressure

ED = emergency department
 FEV1 = forced expiratory volume in one second
 FVC = forced vital capacity
 IV = intravenous
 MgSO₄ = magnesium sulfate
 O₂ = oxygen
 PEFr = peak expiratory flow rate
 PICU = paediatric intensive care unit
 SaO₂ = oxygen saturation
 h = hours

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Bijani 2001	Participants were 15 years and above. Included in adult review. Authors cannot provide disaggregated data
Bilaceroglu 2001	Participants were 6 years and above, but only 10/81 participants were under 18 and the mean age was 36 (+/- 13.4). Included in adult review
Boonyavorakul 2000	Participants were 15 years and above. Included in adult review. Authors cannot provide disaggregated data
del Castillo Rueda 1991	Included in adult review, no data
Irazuzta 2016	Children with status asthmaticus and not a placebo comparison
Liang 1998	Population did not have asthma
Okayama 1987	Half of the participants included in the study were inpatients and could not be separated out from the patient sample
Santana 2001	Children were all admitted to the Special Pediatric Care Unit prior to commencement of therapy (i.e. not managed in the emergency department)
Singhi 2011	No placebo group
Skobeloff 1989	Adults
Torres 2012	Compared with usual care, not placebo
Watanatham 2015	Nebulised vs intravenous with no placebo group

Characteristics of studies awaiting assessment *[ordered by study ID]*

Abd El Kader 1997

Methods	“Comparative study”
Participants	People with bronchial asthma
Interventions	Salbutamol, ipratropium bromide, and magnesium sulfate
Outcomes	Ventilatory, cardiovascular, and metabolic responses
Notes	Numerous attempts made to locate paper, but no library holdings found

Characteristics of ongoing studies *[ordered by study ID]*

NCT01522040

Trial name or title	A pilot study of magnesium infusions (drips) for moderate-to-severe pediatric asthma exacerbations
Methods	Prospective randomised pilot study that seeks to address the research question: In children with moderate to severe asthma, do intravenous magnesium infusions added to standard PICU-level asthma care significantly decrease time from patient presentation until PICU discharge?
Participants	Male and female children and adolescents aged 2 to 20 years
Interventions	Drug: magnesium sulfate continuous magnesium drip, titrated to effect until patient’s symptoms improve Placebo: Simple saline drip, without active drug
Outcomes	Time to discharge, beta receptor haplotype
Starting date	January 2012
Contact information	Keith Cross, MD, 502-689-2457, keith.cross@louisville.edu Kendra Sikes, 502-629-7212
Notes	Updated as “Still recruiting” in February 2016 at http://www.trialdetails.com/detail/NCT01522040/Pilot-Study-of-Magnesium-Infusions-in-Pediatric-Asthma

PICU = paediatric intensive care unit

DATA AND ANALYSES

Comparison 1. IV MgSO₄ versus placebo

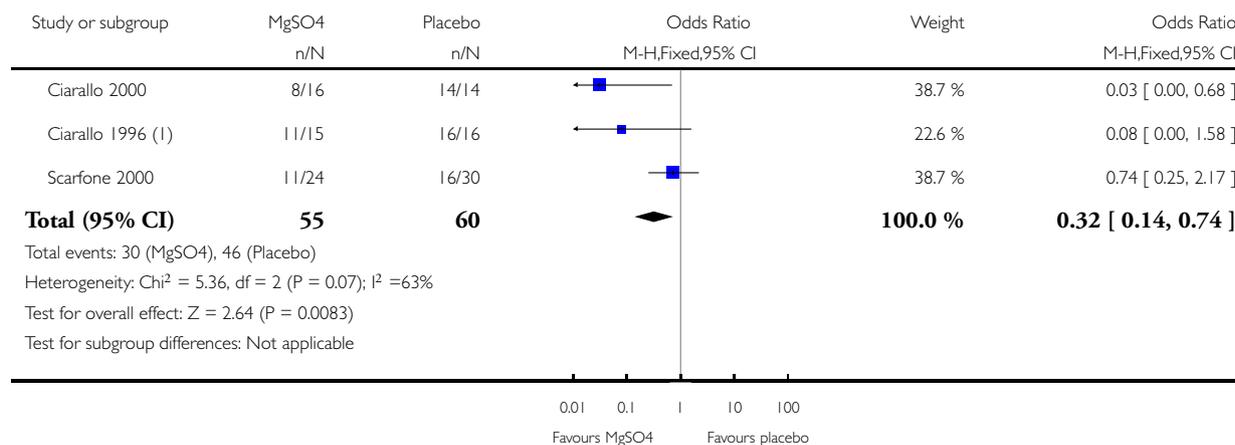
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Hospital admissions	3	115	Odds Ratio (M-H, Fixed, 95% CI)	0.32 [0.14, 0.74]
2 ED treatment time (minutes)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3 Return to ED within 48 hours	2	85	Odds Ratio (M-H, Fixed, 95% CI)	0.40 [0.02, 10.30]
4 Hospital length of stay (hours)	1	47	Mean Difference (IV, Fixed, 95% CI)	-5.30 [-9.46, -1.14]

Analysis 1.1. Comparison 1 IV MgSO₄ versus placebo, Outcome 1 Hospital admissions.

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

Comparison: 1 IV MgSO₄ versus placebo

Outcome: 1 Hospital admissions



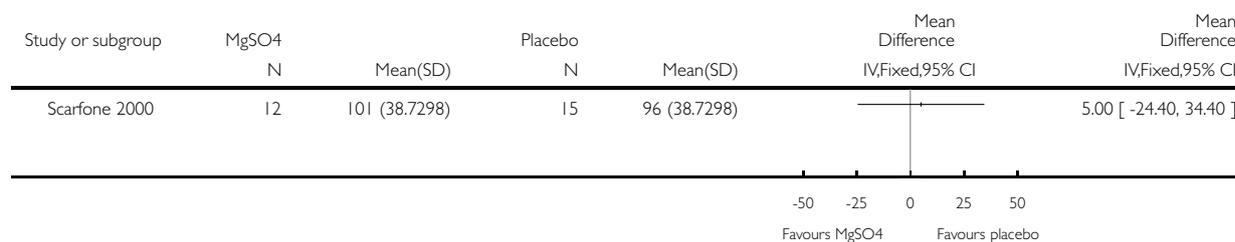
(1) discharge rate from the emergency department was the rate at which decisions to admit were reversed

Analysis 1.2. Comparison 1 IV MgSO₄ versus placebo, Outcome 2 ED treatment time (minutes).

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

Comparison: 1 IV MgSO₄ versus placebo

Outcome: 2 ED treatment time (minutes)

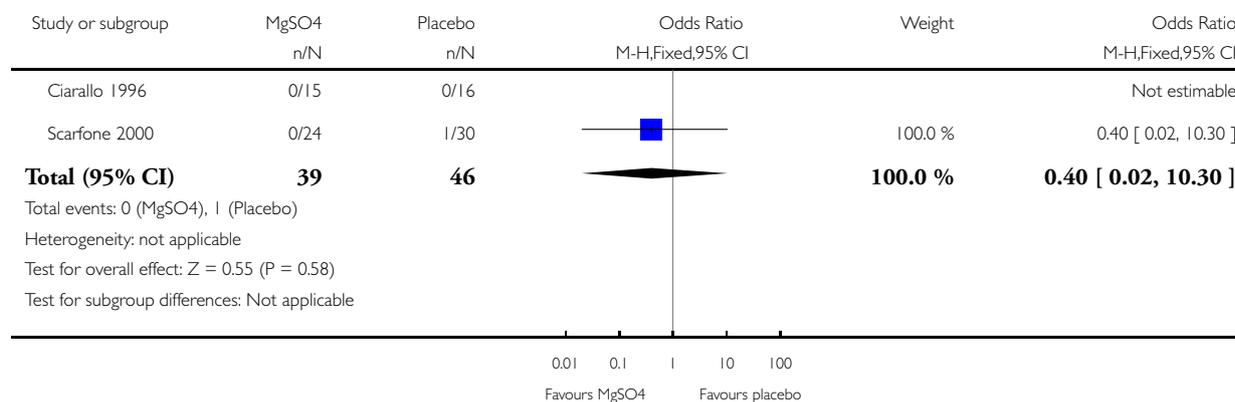


Analysis 1.3. Comparison 1 IV MgSO₄ versus placebo, Outcome 3 Return to ED within 48 hours.

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

Comparison: 1 IV MgSO₄ versus placebo

Outcome: 3 Return to ED within 48 hours

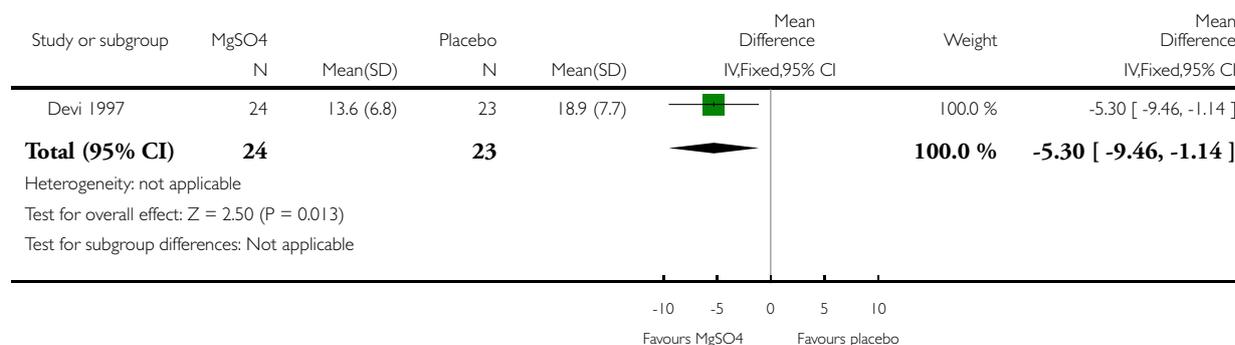


Analysis 1.4. Comparison 1 IV MgSO₄ versus placebo, Outcome 4 Hospital length of stay (hours).

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

Comparison: 1 IV MgSO₄ versus placebo

Outcome: 4 Hospital length of stay (hours)



ADDITIONAL TABLES

Table 1. Summary characteristics of included studies

Study ID	Country (centres)	Total N	Study design	Age range (yrs)	Dose (infusion)	Comedications
Ciarallo 1996	USA (2)	30	R, DB, PC	6 to 18	25 mg/kg 20 minutes	3 nebulised bronchodilators (albuterol, ipratropium bromide, or both) IV methylprednisolone (2 mg/kg) if not yet given corticosteroids
Ciarallo 2000	USA (1)	31	R, DB, PC	6 to 18	40 mg/kg 20 minutes	3 nebulised beta-2 adrenergic treatments IV methylprednisolone (2 mg/kg) if not yet given corticosteroids
Devi 1997	India (1)	47	R, DB, PC	1 to 12	0.2 ml of 50% 35 minutes	Nebulised salbutamol Oxygen, IV aminophylline, corticosteroids

Table 1. Summary characteristics of included studies (Continued)

Gürkan 1999	Turkey (1)	20	R, DB, PC	6 to 16	40 mg/kg 20 minutes	3 beta-2 adrenergic nebuliser treatments
Scarfone 2000	USA (3)	54	R, DB, PC	1 to 18	75 mg/kg 20 minutes	Nebulised albuterol Oxygen, methylprednisolone

R = randomised; DB = double-blind; PC = placebo-controlled

Table 2. Baseline characteristics

Study ID	Inclusion	Group	Age (SD)	% Male	% PEF	FEV ₁	Other	Classification
Ciarallo 1996	PEF < 60% predicted (after 3 beta-2 adrenergic nebuliser treatments)	MgSO ₄	10.8	46.7	43.8	33.1	RR = 35 BP = 120 SaO ₂ = 92	Moderate
		Placebo	11.9	43.8	43.0	45.1	RR = 30 BP = 123 SaO ₂ = 94	
Ciarallo 2000	PEF < 70% predicted (after 3 nebulised bronchodilating treatments)	MgSO ₄	10.9	68.8	29.9	28.9	BP = 120, SaO ₂ = 92	Severe
		Placebo	12.0	50.0	33.1	31.3	BP = 114, SaO ₂ = 92	
Devi 1997	“Inadequate or poor response to 3 doses of nebulized salbutamol”	MgSO ₄	6.7	79.2	30.1	NR	HR = 142	Severe
		Placebo	6.8	73.9	27.1	NR	HR = 138	
Gürkan 1999	PEF < 60% predicted (after 3 beta-2 adrenergic nebuliser treatments) “moderate to severe acute asthma exacerbation”	MgSO ₄	10.4	60	46.8	NR	HR = 118 BP = 118 SaO ₂ = 91.8	Moderate
		Placebo	11.2	50	46.2	NR	HR = 120 BP = 116 SaO ₂ = 91.4	
Scarfone 2000	“moderate to severe	MgSO ₄	6.8	58	NR	NR	SaO ₂ = 93.9	Moderate

Table 2. Baseline characteristics (Continued)

	asthma exacerbation ^a						
		Placebo	4.8	47	NR	NR	SaO ₂ = 94.1

SD = standard deviation; % PEF = percentage predicted peak expiratory flow; FEV₁ = forced expiratory volume in one second; HR = heart rate; RR = respiration rate; BP = systolic blood pressure; SaO₂ = oxygen saturation; NR: not reported

APPENDICES

Appendix I. Sources and search methods for the Cochrane Airways Group Specialised Register (CAGR)

Electronic searches: core databases

Database	Frequency of search
CENTRAL	Monthly
MEDLINE (Ovid)	Weekly
EMBASE (Ovid)	Weekly
PsycINFO (Ovid)	Monthly
CINAHL (EBSCO)	Monthly
AMED (EBSCO)	Monthly

Handsearches: core respiratory conference abstracts

Conference	Years searched
American Academy of Allergy, Asthma and Immunology (AAAAI)	2001 onwards
American Thoracic Society (ATS)	2001 onwards
Asia Pacific Society of Respiriology (APSR)	2004 onwards
British Thoracic Society Winter Meeting (BTS)	2000 onwards
Chest Meeting	2003 onwards
European Respiratory Society (ERS)	1992, 1994, 2000 onwards
International Primary Care Respiratory Group Congress (IPCRG)	2002 onwards
Thoracic Society of Australia and New Zealand (TSANZ)	1999 onwards

MEDLINE search strategy used to identify trials for the CAGR

Asthma search

1. exp Asthma/
2. asthma\$.mp.
3. (antiasthma\$ or anti-asthma\$).mp.
4. Respiratory Sounds/
5. wheez\$.mp.
6. Bronchial Spasm/
7. bronchospas\$.mp.
8. (bronch\$ adj3 spasm\$).mp.
9. bronchoconstrict\$.mp.
10. exp Bronchoconstriction/
11. (bronch\$ adj3 constrict\$).mp.
12. Bronchial Hyperreactivity/
13. Respiratory Hypersensitivity/
14. ((bronchial\$ or respiratory or airway\$ or lung\$) adj3 (hypersensitiv\$ or hyperreactiv\$ or allerg\$ or insufficiency)).mp.
15. ((dust or mite\$) adj3 (allerg\$ or hypersensitiv\$)).mp.
16. or/1-15

Filter to identify RCTs

1. exp "clinical trial [publication type]"/
2. (randomised or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.

7. groups.ab,ti.
8. or/1-7
9. Animals/
10. Humans/
11. 9 not (9 and 10)
12. 8 not 11

The MEDLINE strategy and RCT filter are adapted to identify trials in other electronic databases.

Appendix 2. Search strategy to identify relevant trials from the CAGR

- #1 AST:MISC1
- #2 MeSH DESCRIPTOR Asthma Explode All
- #3 asthma*:ti,ab
- #4 #1 or #2 or #3
- #5 magnesium*
- #6 MgSO₄
- #7 #5 or #6
- #8 #4 and #7
- #9 (#8) AND (INREGISTER)

[Note: in search line #1, MISC1 refers to the field in which the reference record has been coded for condition, in this case, asthma]

CONTRIBUTIONS OF AUTHORS

Ben Griffiths wrote the background and managed the clinical implications of the methods. Kayleigh Kew wrote the methods. Review authors extracted the data independently, and constructed the analyses and assessed the evidence together. Both review authors contributed to and approved the final draft.

DECLARATIONS OF INTEREST

Benedict Griffiths: None known

Kayleigh Kew: None known

SOURCES OF SUPPORT

Internal sources

- Kayleigh Kew, UK.
St George's, University of London

External sources

- NIHR, UK.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We were not able to pool more than 10 studies, and so could not create and examine a funnel plot to explore possible small-study and publication biases. Since there were only three studies in the primary analysis (and fewer in the secondary), we did not consider the planned subgroup and sensitivity analyses to be justified.

We did not use an independent assessor as planned to classify the study populations as having moderate, severe, and life-threatening exacerbations because we were not able to perform the associated subgroup analysis. Instead, the classification was made for descriptive purposes only by one of the review authors (BG). If additional studies allow the subgroup analysis to be undertaken in a future update of this review, this will be done by an assessor blinded to the study results.

We did not specify 'Return to the emergency department within 48 hours' as an outcome in the protocol for this systematic review, but chose to present the results because it is related to other named outcomes which were not well reported across studies.