Inhaled magnesium sulfate in the treatment of acute asthma (Review)

Powell C, Dwan K, Milan SJ, Beasley R, Hughes R, Knopp-Sihota JA, Rowe BH

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TABLE OF CONTENTS

[Intervention Review]

Inhaled magnesium sulfate in the treatment of acute asthma

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ABSTRACT

Background

Asthma exacerbations can be frequent and range in severity from relatively mild to *status asthmaticus*. The use of magnesium sulfate ($MgSO_4$) is one of numerous treatment options available during acute exacerbations. While the efficacy of intravenous $MgSO_4$ has been demonstrated, little is known of the role of inhaled $MgSO_4$.

Objectives

To determine the efficacy of inhaled $MgSO_4$ administered in acute asthma on pulmonary functions and admission rates.

Specific aims: To quantify the effects of inhaled $MgSO_4$ i) in addition to inhaled β_2-agonist, ii) in comparison to inhaled β_2-agonist alone or iii) in addition to combination treatment with inhaled β_2 -agonist and ipratropium bromide.

Search methods

Randomised controlled trials were identified from the Cochrane Airways Group register of trials in September 2012. These trials were supplemented with trials found in the reference list of published studies, studies found using extensive electronic search techniques, as well as a review of the grey literature and conference proceedings.

Selection criteria

Randomised (or pseudo-randomised) controlled trials including adults or children with acute asthma were eligible for inclusion in the review. Studies were included if patients were treated with nebulised $MgSO_4$ alone or in combination with β_2-agonist and/or ipratropium bromide and were compared with β_2-agonist alone or inactive control.

Data collection and analysis

Trial selection, data extraction and risk of bias were assessed independently by two review authors. Efforts were made to collect missing data from authors. Results are presented as standardised mean differences (SMD) for pulmonary function and risk ratios (RR) for hospital admission; both are displayed with their 95% confidence intervals (CI).

Main results

Sixteen trials (21 references) of unclear and high risk of bias were eligible and included 896 patients who were randomised (838 patients completed). Seven of the 16 included studies involved adults exclusively, three included adults and paediatric patients, four studies enrolled paediatric patients and in the remaining two studies the age of participants was not stated.

The design, definitions, intervention and outcomes were different in all 16 studies; this heterogeneity made direct comparisons difficult (see additional tables 1-3).

The overall risk of bias among the included studies was variable and this is reflected in the 'Summary of findings' table with most outcomes being judged as only moderate or less.

Inhaled magnesium sulfate in addition to inhaled β_2-agonist

There was no statistically significant improvement in pulmonary function when inhaled $MgSO_4$ and β_2-agonist was compared with β_2-agonist alone (SMD 0.23; 95% CI -0.27 to 0.74; three studies, n = 188); however, there was considerable between study heterogeneity. There was no clear advantage in terms of hospital admissions (RR 0.76 95% CI 0.49, 1.16; four studies, n = 249), and there were no serious adverse events reported.

Inhaled magnesium sulfate versus inhaled β_2-agonist

The results of pulmonary function in three studies that compared inhaled $MgSO_4$ versus β_2-agonist were too heterogeneous to combine; however, two of the studies found poorer lung function on $MgSO_4$. There was no significant difference in terms of hospital admissions in a single small study when $MgSO_4$ was compared to β_2-agonist (RR 0.53 95% CI 0.05, 5.31; one study, n = 33), and there were no serious adverse events reported.

Inhaled magnesium sulfate in addition to inhaled β_2-agonist and ipratropium

A further comparison has been included in the 2012 update of this review of $MgSO_4$ given in addition to inhaled ipratropium and β_2-agonist therapy (as recommended by the GINA guidelines). However, there is not yet enough data for this outcome to come to any definite conclusions, but both small studies in adults with severe asthma exacerbation found improvements in pulmonary function with additional inhaled $MgSO_4$.

Authors' conclusions

There is currently no good evidence that inhaled $MgSO_4$ can be used as a substitute for inhaled β_2-agonists. When used in addition to inhaled β_2-agonists (with or without inhaled ipratropium), there is currently no overall clear evidence of improved pulmonary function or reduced hospital admissions. However, individual study results from three trials suggest possible improved pulmonary function in those with severe asthma exacerbations (FEV1 less than 50% predicted). Heterogeneity among trials included in this review precludes a more definitive conclusion. Further studies should focus on inhaled $MgSO_4$ in addition to the current guideline treatment for acute asthma (inhaled β_2 -agonist and ipratropium bromide). As the evidence suggests that the most effective role of nebulised $MgSO_4$ may be in those with severe acute features and this is where future research should be focused. A set of core outcomes needs to be agreed upon both in adult and paediatric studies to allow improved study comparison in future.

PLAIN LANGUAGE SUMMARY

Inhaled magnesium sulfate in the treatment of acute asthma

Acute asthma is a common emergency department problem usually treated with systemic corticosteroids, inhaled beta-agonists and a variety of other agents (including inhaled corticosteroids, inhaled anticholinergics, intravenous magnesium sulfate and oxygen). A Cochrane review showed that intravenous treatment with magnesium sulfate was helpful in improving peak expiratory flow measures (patients capacity to breathe more freely) in acute severe exacerbations of asthma. Therefore, we were interested in finding out if inhaled magnesium sulfate is helpful to people suffering an asthma attack and we undertook this review to explore this question.

Inhaled magnesium sulfate is recommended only after someone experiencing an asthma attack has been given bronchodilators, steroids and has failed to respond adequately to them. This review found that using inhaled magnesium sulfate combined with a beta-2-agonist (with or without ipratropium) for an acute asthma attack does not significantly improve pulmonary function (and therefore does not help people to breathe more freely) overall, but there may be improvement in adults with particularly severe asthma attacks, which merits

further study The evidence, however, that the addition of nebulised magnesium sulfate is helpful with regard to clinically important outcomes, such as reducing hospital admissions, is not proven by the clinical trials included in this review.

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

$MgSO_4$ + B2-agonists versus B2-agonists alone for acute asthma

Patient or population: people with acute asthma
Settings: hospital and ED
Intervention: $MgSO_4$ + B_2-agonists
Comparison: B_2-agonists alone

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	B2-agonists alone	$MgSO_4$ + B2-agonists				
Pulmonary Function testing FEV1		The mean pulmonary function testing FEV1 in the intervention groups was **0.23 standard deviations higher** (0.27 lower to 0.74 higher)	SMD 0.23 (-0.27 to 0.74)	188 (3 studies)	⊕⊕⊕◯ **moderate**[1]	
Pulmonary function testing PEF - up to 60 minutes		The mean pulmonary function testing PEF- up to 60 minutes in the intervention groups was **7.07 L/min higher** (11.69 lower to 25.84 higher)	MD 7.07 [-11.69, 25.84]	135 (2 studies)	⊕⊕⊕◯ **moderate**[2]	

Pulmonary function testing PEF - Discharge		The mean pulmonary function testing PEF - discharge in the intervention groups was **0.68 L/min higher** (8.56 lower to 9.92 higher)	MD 0.68 [-8.56, 9.92]	26 (1 study)	⊕⊕◯◯ **low** [3]	
Admission to Hospital	**240 per 1000**	**182 per 1000** (117 to 278)	**RR 0.76** (0.49 to 1.16)	249 (4 studies)	⊕⊕⊕◯ **moderate**[4]	Please see footnote 4
Serious Adverse Events	See comment	See comment	RD 0.00 [-0.03, 0.03]	223 (4 studies)	⊕⊕⊕◯ **moderate**[5]	Risks were calculated from pooled risk differences
Mild-Moderate Adverse Events	**262 per 1000**	**233 per 1000** (123 to 343)	RD -0.03 [-0.14, 0.08]	209 (3 studies)	⊕⊕⊕◯ **moderate**[6]	Risks were calculated from pooled risk differences

*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% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk 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.

1 The I2 on the pulmonary function FEV1 analysis is 66%. We feel that this high level of heterogeneity should be reflected in a deduction of 1 point. A degree of variability across the studies with respect to risk of bias led us to consider that issue closely but on balance it was decided that an additional point should not be deducted

2 The overall risk of bias for pulmonary function testing PEF (up to 60 minutes post-dose) clearly differed between the two studies in this analysis with one scoring low throughout and the other indication considerable variability among the items. On balance we deducted a point to reflect the variability in the risk of bias

3 With regard to pulmonary function testing PEF - discharge only one study contributed to the analysis and the risk of bias on all items was unclear. One point is deducted to reflect the overall lack of clarity in the risk of bias and a further point is deducted to reflect that only one trial on 26 participants contributes to the outcome

4 The risk of bias for hospital admission was variable across the 4 studies. On balance to reflect this variation one point was deducted
5 The risk of bias for serious adverse events was variable across the 4 studies. On balance to reflect this variation one point was deducted
6 There was clear variability in the risk of bias for mild-moderate adverse events across the 3 studies. To reflect this variation one point was deducted

BACKGROUND

Description of the condition

Asthma is a chronic respiratory disease that is characterised by periods of relative control and episodes of deterioration referred to as exacerbations. Exacerbations range in severity from mild to *status asthmaticus* (acute asthma attacks that do not respond to standard bronchodilator and steroids therapy) and can result in visits to healthcare providers, emergency departments, and may at times require hospitalisations. While rare, intubations, admissions to the intensive care setting and deaths from severe acute asthma do still occur. In most people, even though the serious consequences are avoided, the prevention and treatment of asthma exacerbations are an important consideration of their disease. Due to this impact on lifestyle, the costs to the patient and the healthcare system, and the mortality, asthma is responsible for a significant personal and social burden.

Description of the intervention

The evidence-based guideline for the management of asthma developed by the British Thoracic Society (BTS) and the Scottish Intercollegiate Guideline Network (SIGN) (BTS 2008; BTS/SIGN 2011) offers comprehensive guidance on the acute and chronic management of asthma in children and adults. Although the management of children and adults is broadly similar, there is a striking difference between the management of acute severe exacerbations of asthma between children (less than 16 years old) and adults (16 years and older) (BTS 2008, BTS/SIGN 2011).

Acute episodes of bronchoconstriction caused by airway inflammation are a hallmark of the exacerbation. These episodes generally result in increased requirements for inhaled beta-2-agonist (β_2-agonist) therapy (Cates 2004). Unfortunately, in acute asthmatic episodes, this is often not enough to relieve the bronchospasm and reduce dyspnoea. For both children and adults the guideline initially recommends inhaled (or nebulised) β_2-agonists, nebulised ipratropium and systemic corticosteroids. However, for poorly responsive children, the next steps are intravenous bronchodilator therapy - either salbutamol or aminophylline, while the role of intravenous magnesium sulfate ($MgSO_4$) is not yet established. In contrast, for poorly responsive adults the guideline recommends continuous nebulised β2 agonists and an infusion of intravenous $MgSO_4$ (Rowe 2004), while the use of intravenous salbutamol (Travers 2004) or aminophylline (Littenberg 1988; Nair 2012) is not promoted.

How the intervention might work

Magnesium sulfate is an agent that has been proposed as a possible additive treatment in acute asthma, and has been shown to be effective in severe acute asthma when delivered parenterally (Rowe 2004). Magnesium may be effective in acute asthma through one or more of a variety of mechanisms. Magnesium has been shown to relax smooth muscle (Gourgoulianis 2001), and may be involved with inhibition of smooth muscle contraction. This theory has been proposed as an explanation for the effects of $MgSO_4$ in acute asthma; however, this explanation may be too simplistic. Magnesium is also involved with cellular homeostasis through its role as an enzymatic cofactor, as well as being involved in acetylcholine and histamine release, from cholinergic nerve terminals and mast cells, respectively. Recently, investigators have proposed that the effect of $MgSO_4$ is related to its ability to block the calcium ion influx to the smooth muscles of the respiratory system (Gourgoulianis 2001). Finally, the role of $MgSO_4$ as an anti-inflammatory has been identified in adults with asthma (Cairns 1996).

Why it is important to do this review

The potential clinical benefits of inhaled $MgSO_4$ have been studied and research publications have produced conflicting results. Consequently, this agent is not currently recommended as part of the current guidelines and has not been used widely in most acute care settings. In the previous version of this Cochrane review (Blitz 2005b) six trials involving 296 patients were included. Four studies compared nebulised $MgSO_4$ with β2-agonist to β2-agonist and two studies compared $MgSO_4$ to β2-agonist alone. Three of the six included studies involved adults exclusively (Nannini 2000; Bessmertny 2002; Hughes 2003) and one included adults and paediatric patients (Mangat 1998). The remaining two studies enrolled paediatric patients (Meral 1996;Mahajan 2004). Subgroup analyses on the paediatric and adult populations were completed.

Overall, there was a non significant improvement in pulmonary function between patients whose treatments included nebulised $MgSO_4$ in addition to β2-agonist (standardised mean difference (SMD): 0.23; 95% confidence interval (CI): -0.03 to 0.50; four studies). Hospitalisations were similar between the groups (risk ratio (RR): 0.69; 95% CI: 0.42 to 1.12; three studies). Subgroup analyses did not demonstrate significant differences in lung function improvement between adults and children, but in severe acute exacerbations of asthma, the lung function difference was significant (SMD: 0.55; 95% CI: 0.12 to 0.98). Conclusions regarding treatment with nebulised $MgSO_4$ alone were difficult to draw due to lack of studies in this area.

Thus, nebulised inhaled $MgSO_4$ in addition to β2-agonist in the treatment of an acute asthma exacerbation, appears to have benefits with respect to improved pulmonary function in patients with acute severe exacerbations of asthma and there is a trend towards benefit in hospital admission. Heterogeneity among trials included in this review precluded a more definitive conclusion. The data were too sparse to make recommendations in paediatric populations.

In a more recent systematic review of both intravenous and nebulised $MgSO_4$, three further studies of nebulised $MgSO_4$ were identified (Mohammed 2007). There were no exclusively paediatric studies but two studies included teenage children and adults (Aggarwal 2006; Drobina 2006) and one further adult study (Kokturk 2005) was identified. Their conclusions were similar. Further trials of nebulised $MgSO_4$ in adults and children are needed.

The rationale for completing this updated systematic review was to examine the influence any further studies would make on these conclusions.

OBJECTIVES

To determine the efficacy of inhaled $MgSO_4$ administered in acute asthma on pulmonary functions and admission rates.

Specific aims

To quantify the effects of inhaled $MgSO_4$, alone or in combination with inhaled β_2-agonist, compared with inhaled β_2-agonist alone or placebo or in combination with inhaled β_2-agonist and ipratropium bromide or placebo.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised (or quasi-randomised) controlled trials. We included only parallel study designs; cross-over trials were excluded.

Types of participants

We included studies restricting enrolment to patients with acute asthma; patients with chronic or "stable" asthma were excluded from the review. We included studies involving all ages; however, we sub-grouped data into adults and children where possible. We accepted any reasonable diagnosis of asthma, namely clinical and guideline-based criteria.

Types of interventions

We included studies where participants were randomised to receive inhaled $MgSO_4$ compared with a control treatment. That is, studies comparing the efficacy of aerosolised $MgSO_4$ and β_2-agonist versus β_2-agonist alone or inhaled $MgSO_4$ versus β_2-agonist. Co-interventions were permitted, and information pertaining to co-interventions received was recorded.

Types of outcome measures

Primary outcomes

Change in pulmonary function from baseline using the following indices:

1. forced expiratory volume in one second (FEV1) and percentage predicted FEV1;
2. peak expiratory flow (PEF) and percentage predicted PEF.

Secondary outcomes

1. clinical severity scores;
2. proportion of patients requiring admission to hospital;
3. duration of symptoms;
4. vital signs (pulse and respiratory rates; systolic and diastolic blood pressure);
5. adverse events (tremor, nausea, etc).

Search methods for identification of studies

Electronic searches

We identified trials using the Cochrane Airways Group Specialised Register of trials (CAGR), which is derived from systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, AMED, and PsycINFO, and handsearching of respiratory journals and meeting abstracts (please see Appendix 1 for further details). All records in the CAGR coded as 'asthma' were searched using the following terms: MgSO4 or magnesium*. A search of ClinicalTrials.gov was also conducted (Appendix 2). Both databases were searched from their inception to the present and there was no restriction on the language of publication. The search was conducted in November 2011 and updated in September 2012. Search methods for the previous version of this review are in Appendix 3.

Searching other resources

The reference lists of all selected articles, primary studies and review articles were examined for relevant studies. We contacted primary authors of studies to request information on additional trials (published and unpublished). Clinicians, colleagues, collaborators and trialists were contacted to identify potentially relevant studies. Since $MgSO_4$ is not currently commercially delivered, no industry sponsor was contacted.

Data collection and analysis

Selection of studies

The selection of studies involved two steps. First, to retrieve studies, the initial search of all databases and reference lists was screened by title, abstract, MeSH Headings and keywords by two independent investigators to identify all citations of randomised controlled trials (RCT's) or possible RCT's with potential relevance. The full texts of those selected articles were obtained for formal inclusion review. Second, another review author independently decided on trial inclusion using pre-determined eligibility criteria.

Data extraction and management

Data were extracted independently using a standardised data collection form. The following information was extracted if available: characteristics of the study (design, methods of randomisation, withdrawals/dropouts); participants (age, gender); intervention (type, dose, route of administration, timing and duration of therapy, co-interventions); control (agent and dose); outcomes (types of outcome measures measured and reported, timing of outcomes, adverse events); and results. Unpublished data were requested from the primary authors when necessary. One review author (KD) entered data into RevMan 2011.

Assessment of risk of bias in included studies

We retrospectively applied the Cochrane 'Risk of bias' tool in this 2012 update (Higgins 2011). Three review authors independently assessed the risk of bias for all included studies for the following six items; random sequence generation; allocation concealment; blinding; incomplete outcome data; selective outcome reporting; and other types of bias. The judgement was recorded as high, low or unclear risk of bias along with a description from the trial reports. Any disagreements were discussed and resolved by consensus.

Measures of treatment effect

For dichotomous variables, we expressed data as risk ratio (RR) with 95% confidence intervals (CI) and reported adverse events as risk difference (RD) together with 95% CIs. For the continuous variables pulmonary function and clinical severity score, we reported data as standardised mean differences (SMD) with 95% CIs. Other continuous variables were reported as mean difference (MD) with 95% CIs.

Unit of analysis issues

The unit of analysis was the patient.

Dealing with missing data

If outcome data or information on trial design were missing, we contacted trial authors. We requested information on co-interventions from any trial report that did not state what co-interventions were, or were not, permitted.

Assessment of heterogeneity

We assessed heterogeneity by visual inspection of the forest plots. We also used the chi-squared ($Chi^{2)}$ test (where a P value < 0.10 indicated substantial heterogeneity), however, we exercised caution in interpretation due to the low power associated with this test. I^2 was calculated and a guide to interpretation is:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity (Higgins 2011).

Assessment of reporting biases

We also planned to test for publication bias using a funnel plot if there was a sufficient number of trials included in a single forest plot (more than 10). It should be noted that an asymmetrical funnel plot can be caused by heterogeneity, outcome reporting bias and small study effects as well as publication bias.

Data synthesis

We combined data using a fixed-effect model except in cases where we identified substantial heterogeneity, as defined above, where we employed a random-effects model.

Subgroup analysis and investigation of heterogeneity

A priori subgroup analyses were planned to examine the effect of:

1. age (two to 16 years old (paediatric) and > 16 years old (adult));
2. severity of asthma as measured by pre-administration spirometric deviation from predicted (baseline FEV1 or PEF < 50% predicted).

Sensitivity analysis

We planned to conduct sensitivity analyses to assess the effect of the overall risk of bias of included trials.

RESULTS

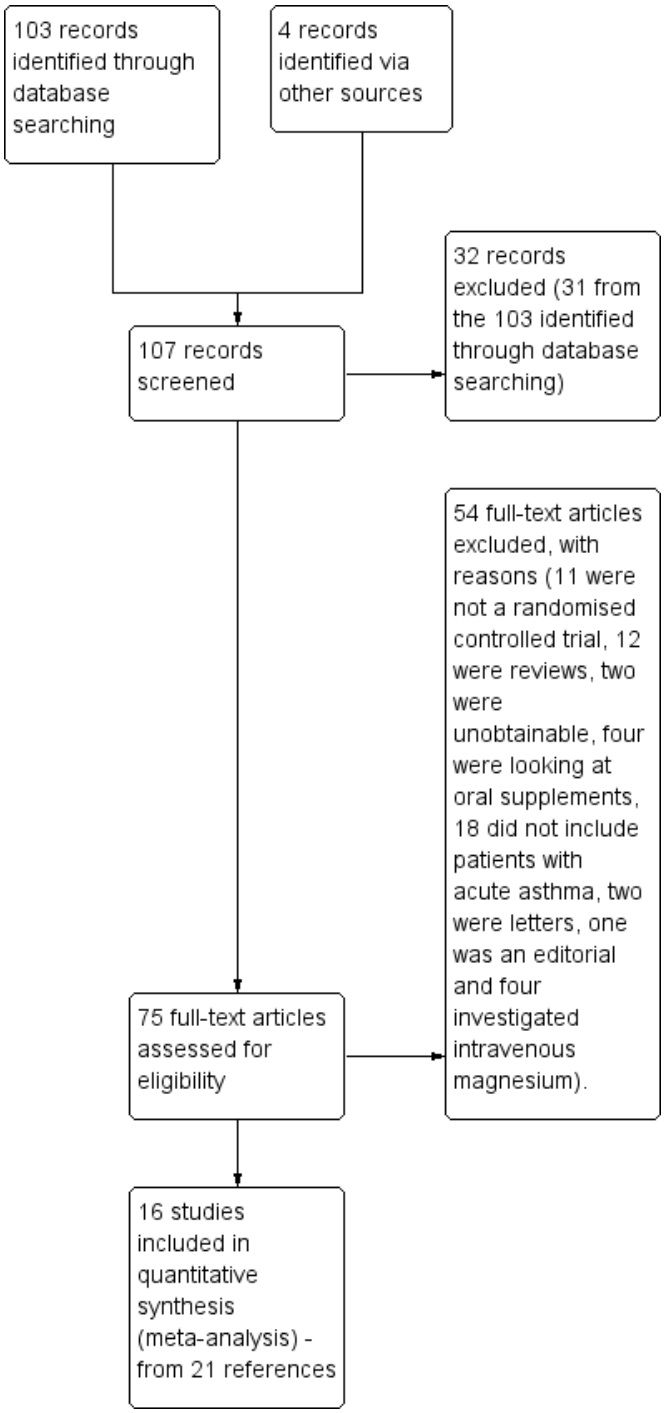
Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

Results of the search

The initial search yielded 103 references that were at least potentially relevant controlled trials, 31 of which were excluded based on the title and abstract. Published reports were obtained for the remaining references (Figure 1). Two additional references were identified from bibliographic searching of relevant studies. The author for one study that was originally identified as an abstract was contacted and the conditionally accepted paper was provided to the review authors for data extraction. Two further references were identified through a published review (Mohammed 2007).

Figure 1. Study flow diagram.



Included studies

Sixteen trials (21 references), that included 896 patients who were randomised (838 patients who completed), were incorporated into the review (see Characteristics of included studies). All of the studies included in this manuscript were published since 1995. There is no particular geographic preference with the U.S., India, New Zealand, Turkey, Argentina, Mexico, Tenerife and Wales all being represented.

We requested lung function data from the primary authors for one included study (Meral 1996) and further information on trials design from another trialist (Neki 2006). We did not receive a reply before this review went to press, therefore, should information become available, we will include it in a future update.

Populations

Seven of the 16 included studies involved adults exclusively (Nannini 2000; Abreu-Gonzalez 2002; Bessmertny 2002; Hughes 2003; Kokturk 2005; Gaur 2008; Gallegos-Solórzano 2010) and three included adults and paediatric patients (Mangat 1998; Aggarwal 2006; Neki 2006). Four studies enrolled paediatric patients (Meral 1996; Mahajan 2004; Khashabi 2008; Ashtekar 2008) and in the remaining two studies the age of participants was not stated (Dadhich 2005; Drobina 2006). We were therefore able to perform subgroup analyses on the paediatric and adult populations.

The severity of disease varied between studies (Table 1). Ten studies had specific lung function criteria (Meral 1996; Mangat 1998; Nannini 2000; Bessmertny 2002; Hughes 2003; Mahajan 2004; Dadhich 2005; Neki 2006; Gaur 2008; Gallegos-Solórzano 2010), while the other six studies enrolled patients previously diagnosed with asthma using accepted clinical standards. Based on the baseline demographic data, 13 studies were considered to enrol severe acute exacerbations of asthma (FEV1 or PEF < 50% predicted at baseline or symptom criteria defined by BTS/SIGN 2011) (Meral 1996; Mangat 1998; Nannini 2000; Bessmertny 2002; Hughes 2003; Mahajan 2004; Dadhich 2005; Kokturk 2005; Aggarwal 2006; ; Neki 2006; Ashtekar 2008; Gaur 2008; Gallegos-Solórzano 2010).

Eleven studies recruited their patients in emergency departments and one in a children's assessment unit after general practitioner referral (Ashtekar 2008). Department of presentation was unclear in the remaining four studies (see Table 2).

Participants were excluded for a number of reasons but there was great variation in pharmaceutical exclusion due to drugs taken before recruitment (see Table 2).

Duration of symptoms

Aggarwal 2006, Mahajan 2004 and Gallegos-Solórzano 2010 reported the duration of present attack in days. The mean duration was 4.16 (standard deviation (SD) 1.69) days in the $MgSO_4$ group and 4.28 (SD 1.99) days in the control group (Aggarwal 2006), 42 (SD 27) hours in the $MgSO_4$ group and 41 (SD 32) hours in the control group (Mahajan 2004), 23.5 (SD 37.8) days in the control group and 15.5 (SD 17.7) days in the $MgSO_4$ group (Gallegos-Solórzano 2010).

Interventions

Magnesium sulfate was uniformly delivered via a jet nebuliser and not a metered dose inhaler (MDI) (two were noted to be an ultrasonic nebuliser (Meral 1996; Aggarwal 2006)). All studies use nebulised $MgSO_4$ in the intervention group but the comparison and placebo nebulised solutions varied (Table 3): three studies compared $MgSO_4$ with β_2-agonist directly but no placebo (Meral 1996; Mangat 1998; Neki 2006) and the $MgSO_4$ given alone. Aggarwal 2006 used distilled water (as well as normal saline) for placebo and β_2-agonist and Abreu-Gonzalez 2002 used 'physiological serum' as placebo and beta agonist (salbutamol 400 mcg presumably via MDI in each group). Six studies (Nannini 2000; Bessmertny 2002; Hughes 2003; Mahajan 2004; Kokturk 2005; Khashabi 2008) compared β_2-agonist with $MgSO_4$ versus β_2-agonist with placebo (normal saline). Four studies (Drobina 2006; Ashtekar 2008; Gaur 2008; Gallegos-Solórzano 2010) used saline as placebo and ipratropium and β_2-agonist in the control group using β_2-agonist and ipratropium mixed with the $MgSO_4$ for the intervention group.

Dadhich 2005 had three groups and compared all three directly; one with β_2-agonist, one with β_2-agonist and $MgSO_4$ and one with $MgSO_4$ only. Drobina 2006 used $MgSO_4$ and β_2-agonist and compared them with β_2-agonist but no placebo solution.

We identified the following comparisons which have been used throughout the review to lend structure:

- $MgSO_4$ with β2-agonist versus placebo (normal saline) and β2-agonist (seven studies; Nannini 2000; Bessmertny 2002; Hughes 2003; Mahajan 2004; Kokturk 2005; Aggarwal 2006; Khashabi 2008).
- $MgSO_4$ versus β2-agonist alone (three studies Meral 1996; Mangat 1998; Neki 2006).
- $MgSO_4$ and β2-agonist and ipratropium versus placebo (saline) and β2-agonist and ipratropium (four studies Drobina 2006; Ashtekar 2008; Gaur 2008; Gallegos-Solórzano 2010).
- $MgSO_4$ and salbutamol (400 mcg via MDI) versus placebo (nebulised physiological serum) and salbutamol (one study; Abreu-Gonzalez 2002).

- $MgSO_4$ and salbutamol versus $MgSO_4$ alone versus salbutamol alone (one study; Dadhich 2005).

Doses and formulation of $MgSO_4$ differed and as dose frequency differed substantially the and total dose of $MgSO_4$ in each study differed (Table 3). When the information was available, most included studies used $MgSO_4$ of similar concentration and osmolality but dose per nebulisation and the number of nebulisations varied.

Kokturk 2005 nebulised hourly up to four hours after treatment after the initial treatment of three doses in one hour. Four studies (Meral 1996; Nannini 2000; Abreu-Gonzalez 2002; Mahajan 2004) nebulised only one treatment. Five studies (Bessmertny 2002; Hughes 2003; Aggarwal 2006; Ashtekar 2008; Gallegos-Solórzano 2010) nebulised every 20 minutes for an hour. Khashabi 2008 gave two doses of treatment but the timing was unclear. Three studies (Dadhich 2005; Drobina 2006; Gaur 2008) were unclear how frequent the doses were given but probably only one dose was given and two studies (Mangat 1998; Neki 2006) gave four doses every 20 minutes.

All control, or placebo, interventions were similar in appearance to the treatment drug. The most frequent placebo was saline. One study (Hughes 2003) collected data on patients' ability to distinguish between the treatment and control, and noted no ability to discern. Even when not expressly stated, it can reasonably be assumed that the control (placebo) would be similar in appearance to the treatment drug (especially if given in a β_2-agonist vehicle).

Co-interventions

Co-interventions used added complexity and heterogeneity to the review (Table 2). In three studies (Mangat 1998; Hughes 2003; Mahajan 2004), systemic corticosteroids were administered to all patients, although the timing (before/after nebulised treatment) varied. In one study, systemic corticosteroids were administered if there was no improvement after the three doses of study treatment (Bessmertny 2002). Overall, 10 studies routinely administered corticosteroids, but in different doses, routes and frequency. Four studies made no comments (Nannini 2000; Abreu-Gonzalez 2002; Dadhich 2005; Khashabi 2008). In one study the clinicians were free to administer whatever they felt necessary (Aggarwal 2006). Meral 1996 gave no further medication as a co-intervention.

Ongoing trials and unpublished data

The status of one study (Wijetunge 2002) referenced in a clinical trials register reportedly, compared nebulised $MgSO_4$ with placebo in addition to conventional bronchodilator treatment is unknown; repeated attempts have failed to find out any further information regarding this trial. There is one ongoing study (Goodacre 2007). Following discussion with the chief investigator this was close to finishing recruitment with over 1000 participants recruited (personal communication Professor Steve Goodacre March 2012). MAGNETIC (Powell 2012) is a multicentre RCT which has just been completed in the UK and has recruited 508 paediatric patients with acute asthma and is due to be reported after the publication of this review. (http://www.controlled-trials.com/ISRCTN81456894)

Excluded studies

Fifty-four studies were excluded for the following reasons; 11 were not randomised controlled trials, 12 were reviews, two were unobtainable, four examined oral supplements, 18 did not include patients with acute asthma, two were letters, one was an editorial and four investigated intravenous $MgSO_4$ (see Characteristics of excluded studies).

Risk of bias in included studies

Allocation

Ten studies (Meral 1996; Mangat 1998; Nannini 2000; Abreu-Gonzalez 2002; Kokturk 2005; Dadhich 2005; Drobina 2006; Gaur 2008; Khashabi 2008; Gallegos-Solórzano 2010) were described as 'randomised' and the method of sequence generation was not described, these studies are therefore at an unclear risk of bias. One further study was at an unclear risk of bias as it is not clear if the study is randomised, the author has been contacted for clarification (Neki 2006). The remaining five studies were at a low risk of bias, the randomisation lists were produced by the pharmacy for two studies (Hughes 2003; Ashtekar 2008), random number tables were used in two studies (Mahajan 2004; Aggarwal 2006) and the randomisation numbers were computer-generated in one study (Bessmertny 2002).

No details were provided on allocation concealment in 11 studies and they were therefore assessed as an unclear risk of bias (Meral 1996; Mangat 1998; Nannini 2000; Abreu-Gonzalez 2002; Hughes 2003; Dadhich 2005; Kokturk 2005; Drobina 2006; Neki 2006; Gaur 2008; Khashabi 2008). A description of allocation concealment was provided in five studies and they were assessed as a low risk of bias (Bessmertny 2002; Mahajan 2004; Aggarwal 2006; Ashtekar 2008; Gallegos-Solórzano 2010).

Blinding

Eleven studies were described as double blind and therefore at low risk of bias (Mangat 1998; Nannini 2000; Abreu-Gonzalez 2002; Bessmertny 2002; Hughes 2003; Mahajan 2004; Drobina 2006; Aggarwal 2006; Khashabi 2008; Ashtekar 2008; Gallegos-Solórzano 2010). Two studies were single blind (Kokturk 2005; Gaur 2008) and therefore at unclear risk of performance and assessment bias. No details were provided for three studies so they were

deemed as having an unclear risk of bias (Meral 1996; Dadhich 2005; Neki 2006).

Incomplete outcome data

Five studies were reported as conference abstracts only and no details were provided regarding dropouts (Abreu-Gonzalez 2002; Dadhich 2005; Drobina 2006; Khashabi 2008; Gaur 2008) and no dropouts were described in four studies (Meral 1996; Mangat 1998; Mahajan 2004; Neki 2006). In Kokturk 2005 it appears as though there were no dropouts but the published report states that a patient was later excluded because the final diagnosis was COPD and the treatment group is not stated. These studies were therefore assessed as having an unclear risk of bias

There was a low risk of bias in five studies, with all patients randomised completing the study in two studies (Aggarwal 2006; Ashtekar 2008) and reasons fully described for dropouts in three studies (Bessmertny 2002; Hughes 2003; Gallegos-Solórzano 2010).

There was a high risk of bias in one study as three patients were enrolled more than once, only the initial visit was used in the analysis but the treatment group was not stated. (Nannini 2000).

Selective reporting

Six studies were only reported in conference abstracts and therefore the risk of selective reporting bias is unclear (Abreu-Gonzalez 2002; Dadhich 2005; Drobina 2006; Neki 2006; Ashtekar 2008; Khashabi 2008). One further study was presented as a conference abstract but was considered at high risk of bias as outcomes were partially reported and not statistically significant (Gaur 2008). Another study (Bessmertny 2002) was considered at high risk of bias as outcomes were reported as not statistically significant and no data were presented and only means were presented for FEV1. Hughes 2003, Meral 1996 and Nannini 2000 were also at high risk of bias as the trial report stated there was no difference in blood pressure and heart rate between the groups and no data were reported.

Four studies were at low risk of bias as all outcomes stated in the methods were reported in the results section, although no protocols were available (Mahajan 2004; Kokturk 2005; Aggarwal 2006; Gallegos-Solórzano 2010).

Mangat 1998 was at an unclear risk of bias as two outcomes were mentioned but not reported.

Other potential sources of bias

No other risks of bias were identified.

Effects of interventions

See: **Summary of findings for the main comparison** $MgSO_4$ + B2-agonists compared to B2-agonists alone for acute asthma; **Summary of findings 2** $MgSO_4$ compared to B2-agonist for people with acute asthma

Figure 1 indicates the outcomes reported by each study (Kirkham 2010).

Pulmonary function

Most studies did not report change in pulmonary function and there was variation in the specific pulmonary function measure reported (percentage predicted PEF or FEV1 and raw PEF or FEV1) as well as the time after treatment when pulmonary functions were recorded. For these reasons, the results are reported using fixed-effect method and standardised mean difference (SMD). We reported lung function measurements at or before 60 minutes after treatment and pooled absolute differences with change in percentage predicted using SMD. Based on the studies that measured pulmonary function over longer durations, we noted that the largest change in pulmonary function appeared to be early after treatment. Consequently, we were satisfied grouping the 20-minute and 60-minute pulmonary function test results as the outcome of interest. For overall reporting of outcomes, see Table 4.

$MgSO_4$ and β_2-agonist versus β_2-agonist alone

Six studies involving 349 participants reported at least one measure of lung function (Nannini 2000; Bessmertny 2002; Hughes 2003; Mahajan 2004; Kokturk 2005; Aggarwal 2006).

Three studies reported FEV1 in litres or per cent predicted, two at 60 minutes (Bessmertny 2002; Hughes 2003) and one at 20 minutes (Mahajan 2004). Pulmonary function was not significantly improved in patients who received $MgSO_4$ and a β_2-agonist and compared to those on β_2-agonist alone (SMD 0.20; 95% confidence interval (CI) -0.09 to 0.49; fixed-effect ; three studies, n = 188); however, there was considerable between study heterogeneity identified (I^2 = 66%). When a random-effects model was used to pool these studies, the confidence interval is considerably wider (SMD 0.23, 95% CI -0.27 to 0.74; three studies, n = 188 Analysis 1.1).

Three studies reported PEF in litres or per cent predicted, one at 20 minutes (Nannini 2000), one at 60 minutes (Aggarwal 2006) and one at discharge (Kokturk 2005). Pulmonary function was not significantly improved in people given $MgSO_4$ and a β_2-agonist compared with those given β_2-agonist alone at up to 60 minutes (mean difference (MD) 7.07; 95% CI -11.69 to 25.84; I^2 = 26%; two studies, n = 135) and at discharge (MD 0.68; 95% CI -8.56 to 9.92; one study, n = 26 Analysis 1.2).

In subgroup analyses for FEV1, there was no significant difference between the results from adults and those in children (Analysis 1.3). In subgroup analysis (Analysis 1.4), there was a significant difference in the results from the severe acute asthma trial (SMD

0.63, 95% 0.07 to 1.19; one study, n = 52), but the test for interaction between severe and moderate exacerbations failed to reach statistical significance (test for subgroup differences: $Chi^2 = 1.95$, df = 1 (P = 0.16), $I^2 = 48.7\%$).

$MgSO_4$ versus β_2-agonist alone

Three studies involving113 participants reported PEF and we present the results as subgroups by time point reported (Meral 1996; Mangat 1998; Neki 2006). Mangat 1998 found no significant difference in PEF for $MgSO_4$ alone compared with β_2-agonist alone (MD 4.20; 95% CI -12.29 to 20.69; one study, n = 33 Analysis 2.1). Neki 2006 shows a significant advantage for β_2-agonist alone but the time point reported is unclear (MD -50; 95% CI-67.83 to -32.17; one study, n = 40).

$MgSO_4$ and β_2-agonist and ipratropium versus placebo (saline) and β_2-agonist and ipratropium

Ashtekar 2008 did not report this outcome. Drobina 2006 reported that "peak flow measurements improved over time in both groups (p < 0.001). The addition of aerosolized magnesium sulfate did not result in a statistically significant increase in either the maximum or the average peak flow over time (p = 0.279 and p = 0.399, respectively). While there does appear to be a trend toward greater improvement in peak flow measurements in the magnesium sulfate group, this lacks significance clinically as well as statistically." As this research is only available in abstract form, it is unclear how many participants were in each group and no data were reported to include in the meta-analysis.

Gallegos-Solórzano 2010 and Gaur 2008 show an improvement in the $MgSO_4$ group at 90 minutes (MD: 8.57; 95% CI 1.99 to 15.15; one study, n = 60) and 120 minutes (MD: 2.60; 95% CI 0.25 to 4.95; one study, n = 60), respectively (Analysis 3.1).

$MgSO_4$ and salbutamol versus placebo (physiological serum) and salbutamol

Abreu-Gonzalez 2002 shows a significant improvement in the percentage increase in PEF at 30 minutes (SMD: 1.18; 95% CI 0.30 to 2.06; one study, n = 24) in people on β_2-agonist and $MgSO_4$ compared with those on salbutamol and placebo but a later significant improvement was reported in the percentage increase in FEV1 at 45 minutes on β_2 -agonist alone with placebo (SMD: -1.05; 95% CI -1.91 to -0.18; one study, n = 24).

$MgSO_4$ and salbutamol versus $MgSO_4$ alone versus salbutamol alone

Dadhich 2005 reported an increase in PEF and FEV1; however, it was not significant (P > 0.05). They also state that the mean increase % over baseline at 10 minutes and 20 minutes was significantly improved (P < 0.01) in group B and group C but no further results are reported in the abstract and it is not clear to which measure this is referring.

Clinical Severity Score

Studies reported a variety of clinical severity scores, including the Yung Asthma Severity Score (ASS), the Davies, Leffert and Drabous score and FISCHL index (see Table 2).

$MgSO_4$ with β_2-agonist compared to placebo (normal saline) and β_2-agonist

Kokturk reported clinical severity score in a graph and stated that both groups displayed comparable improvement in clinical scores over 120 minutes (Kokturk 2005). Khashabi 2008 report a non significant difference in respiratory distress scores, but it is not clear which score was used and the number of participants in each group is not clear. The author has been contacted for further information.

While five studies collected clinical severity scores, they were not reported in sufficient detail,to use in this review (Aggarwal 2006; Bessmertny 2002; Hughes 2003; Mahajan 2004; Nannini 2000).

$MgSO_4$ compared to β_2-agonist alone

The FISCHL index was reported in two studies (Mangat 1998; Neki 2006) and the Davies, Leffert, Drabous score in one study (Meral 1996). The MD at one hour (-0.33; 95% CI -1.07 to 0.41; one study, n = 33) favoured $MgSO_4$ (Mangat 1998). The time point at which clinical severity score was reported was unclear in Neki 2006 (MD -0.20; 95% CI -1.11 to 0.71; one study, n = 40). Meral 1996 reported the maximum clinical severity score in the first hour (MD -3.20; 95% CI -17.62 to 11.22 one study, n = 40) (Analysis 2.2).

$MgSO_4$ and β_2-agonist and ipratropium versus placebo (saline) and β_2-agonist and ipratropium

Ashtekar 2008 reported that there was no significant difference between the median area under the curve of ASS of the $MgSO_4$ compared with the placebo-treated group (1530 versus 1355).

$MgSO_4$ and salbutamol versus placebo (physiological serum) and salbutamol

One study did not appear to measure or report this outcome (Abreu-Gonzalez 2002).

$MgSO_4$ and salbutamol versus $MgSO_4$ alone versus salbutamol alone

One study did not appear to measure or report this outcome (Dadhich 2005).

Admission to hospital

$MgSO_4$ with β_2-agonist compared versus placebo (normal saline) and β_2-agonist

Four studies involving 249 participants reported admissions for the comparison nebulised $MgSO_4$ in combination with an β_2-agonist compared with β_2-agonist alone (Nannini 2000; Hughes 2003; Mahajan 2004; Aggarwal 2006). These studies failed to demonstrate a clear reduction in the probability of admission (risk ratio (RR) 0.76; 95% CI 0.49 to 1.16; four studies, n = 249 Analysis 1.5) using a fixed-effect model. The non-significant advantage holds for $MgSO_4$ compared with β_2-agonist for adults and severe exacerbations of asthma (RR 0.71; 95% CI 0.46 to 1.10; three studies, n = 187); however, not for children or those with less acute severe exacerbations of asthma (RR 2.00; 95% CI 0.19 to 20.93; one study n = 62). There was, however, no significant difference when formal subgroup testing was carried out between adults and children (Analysis 1.6), or between severe and less acute severe exacerbations of asthma (Analysis 1.7), and the confidence intervals were wide. Results were similar when random-effects methods were employed.

One study (Bessmertny 2002) did not report admissions to hospital and correspondence attempts with this author did not yield additional data. Kokturk 2005 measured admission to hospital but no data were reported; we have contacted the authors to obtain the data. Khashabi 2008 reported mean days of hospitalisation and again, we have contacted the authors to request whether hospital admission was also recorded.

$MgSO_4$ compared to β_2-agonist alone

There was no significant difference between people on $MgSO_4$ compared with those on β_2-agonists alone with respect to hospitalisations (RR 0.53; 95% CI 0.05 to 5.31; one study, n = 33 Analysis 2.3); however, the wide confidence interval indicates that equivalence cannot be claimed. With a single trial contributing data (Mangat 1998), no additional analyses were possible. Two studies did not appear to measure or report this outcome (Meral 1996; Neki 2006).

$MgSO_4$ and β_2-agonist and ipratropium versus placebo (saline) and β_2-agonist and ipratropium

Gallegos-Solórzano 2010 reported admissions to the emergency department (RR 0.38; 95% CI 0.16 to 0.94; one study, n = 60), the general ward (RR 0.29; 95% CI 0.06 to 1.26; one study, n = 60) and readmissions (RR 0.67; 95% CI 0.12 to 3.71; one study, n = 60 Analysis 3.2).

Three studies did not appear to measure or report this outcome (Drobina 2006; Ashtekar 2008; Gaur 2008)

$MgSO_4$ and salbutamol versus placebo (physiological serum) and salbutamol

One study did not appear to measure or report this outcome (Abreu-Gonzalez 2002).

$MgSO_4$ and salbutamol versus $MgSO_4$ alone versus salbutamol alone

One study did not appear to measure or report this outcome (Dadhich 2005).

Duration of symptoms

No studies reported information on duration of symptoms.

Vital Signs

$MgSO_4$ with β_2-agonist versus placebo (normal saline) and β_2-agonist

Aggarwal 2006 reported that the pulse rate declined significantly with treatment ($P < 0.05$) in each group at 120 minutes but there was no significant change in the systolic or diastolic blood pressures (Analysis 1.8). Data were also reported at 0, 15, 60 and 75 minutes in the trial report. Six studies did not appear to measure or report vital signs (Nannini 2000; Bessmertny 2002; Hughes 2003; Mahajan 2004; Kokturk 2005; Khashabi 2008).

$MgSO_4$ versus β_2-agonist alone

Neki 2006 reported respiratory rate (MD -2.50; 95% CI -4.18 to -0.82; one study , n = 40 Analysis 2.4). Two studies did not appear to measure or report this outcome (Meral 1996; Mangat 1998).

$MgSO_4$ and β_2-agonist and ipratropium versus placebo (saline) and β_2-agonist and ipratropium

Three studies comparing $MgSO_4$ and β_2-agonist and ipratropium versus placebo (saline) and β_2-agonist and ipratropium did not report vital signs (Drobina 2006; Ashtekar 2008; Gaur 2008). Drobina 2006 stated that vital signs were measured in the conference abstract but data were not reported. Gallegos-Solórzano 2010 reported blood pressure, temperature, respiratory rate, O2 saturation, and pulse rate; none of these vital signs were statistically significant.

$MgSO_4$ and salbutamol versus placebo (physiological serum) and salbutamol

One study did not appear to measure or report this outcome (Abreu-Gonzalez 2002).

$MgSO_4$ and salbutamol versus $MgSO_4$ alone versus salbutamol alone

One study did not appear to measure or report this outcome (Dadhich 2005).

Adverse events

Please refer to Table 2.

$MgSO_4$ with β_2-agonist versus placebo (normal saline) and β_2-agonist

Four studies involving 223 participants reported that there were no serious adverse events in either arm (risk difference (RD) 0.00; 95% CI -0.11 to 0.11; four studies, n = 223 Analysis 1.9). The risk of less severe adverse events was low (RD -0.03; 95% CI -0.14 to 0.08; three studies, n = 209) as reported by three studies on 209 participants (Nannini 2000; Bessmertny 2002; Aggarwal 2006), although the differences did not reach statistical significance (Analysis 1.10). Aggarwal 2006 reported that tremor was the same in both groups. Khashabi 2008 reported no side effects but it is not clear how many participants were in each group, so can not be included in the meta-analysis.

Kokturk 2005 reported that two patients in the $MgSO_4$ group and four patients in the placebo group required additional therapy. Two patients developed transient hypotension after receiving nebulised salbutamol plus $MgSO_4$. None of them needed to withhold nebulisation. Deep tendon reflexes were present in every patient. One patient in the saline group suffered palpitations after the second salbutamol nebulisation. No other side effects were reported.

$MgSO_4$ versus β_2-agonist alone

One study (Mangat 1998) reported that there were no serious adverse events in either arm (RD 0.00; 95% CI -0.11 to 0.11; Analysis 2.5). The risk of less severe adverse events was low (RD -0.17; 95% CI -0.41 to 0.06; one study, n = 33 Analysis 2.6). Meral 1996 also reported that there were no adverse effects in either group. One study did not report adverse effects (Neki 2006).

$MgSO_4$ and β_2-agonist and ipratropium versus placebo (saline) and β_2-agonist and ipratropium

Ashtekar 2008 reported that one child had a transiently low blood pressure, whereas, another had tingling of the fingers and both received nebulised $MgSO_4$. Drobina 2006 reported that there were no significant side effects noted in either treatment group, but did not report data. Gaur 2008 did not report adverse effects.

Gallegos-Solórzano 2010 reported that the most common adverse reaction associated with $MgSO_4$ was a dry and bitter mouth, but no other side effect was associated with treatment. ECG was abnormal in some patients (43% versus 36%): most commonly, sinus tachycardia (40% versus 36%) but similar in both groups. One patient in the $MgSO_4$ group developed supraventricular extrasystole that did not require additional management. One patient from each group presented with dizziness.

$MgSO_4$ and salbutamol versus placebo (physiological serum) and salbutamol

One study did not report adverse effects (Abreu-Gonzalez 2002).

$MgSO_4$ and salbutamol versus $MgSO_4$ alone versus salbutamol alone

Dadhich 2005 reported that no additional side effects were noted either alone or with salbutamol.

Reporting biases

Too few studies were included to produce a funnel plot. However, the impact of publication bias was limited through a thorough search strategy which identified many conference abstracts that were included.

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

$MgSO_4$ compared to B2-agonist for people with acute asthma

Patient or population: patients with people with acute asthma
Settings:
Intervention: $MgSO_4$
Comparison: B2-agonist

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	B2-agonist	$MgSO_4$				
Pulmonary Function testing PEF	See comment	See comment	Studies not totaled. Not estimable	113 (3 studies)	⊕⊕⊕◯ **moderate**[1]	
Admision to hospital	See comment	See comment	RR 0.53 [0.05, 5.31]	33 (1 study)	⊕⊕◯◯ **low** [2]	
Serious Side Effects	See comment	See comment	RD 0.00 [-0.11, 0.11]	33 (1 study)	⊕⊕◯◯ **low** [2]	Risks were calculated from pooled risk differences
Mild-Moderate Side Effects	See comment	See comment	RD -0.17 [-0.41, 0.06]	33 (1 study)	⊕⊕◯◯ **low** [2]	Risks were calculated from pooled risk differences

*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% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval;

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.

1 With regard to pulmonary function (PEF) the majority of assessments for risk of bias were unclear and a point is deducted here to reflect this. There are clear issues around heterogeneity and precision when considering all three subgroups together; however, as they are not totaled we judged on balance not to deduct additional points

2 The lack of clarity around randomisation procedures for the one included trial is reflected by a deducted point and a further point is deducted to reflect that only one trial on 33 participants contributes to the outcome

DISCUSSION

Summary of main results

This systematic review attempted to synthesise the best available evidence for the use of inhaled $MgSO_4$ in the treatment of acute asthma. From 16 randomised controlled trials involving nearly 900 patients, the results of this systematic review provide somewhat weak and conflicting conclusions. First, based on the available data it appears that nebulised $MgSO_4$ with or without β_2-agonist can be safely administered to patients with acute moderate-acute severe exacerbations of asthma. Since it is readily available and inexpensive, its role in acute asthma deserves more scrutiny. Used alone, it appears to be of little advantage compared with β_2-agonists in improving pulmonary function and reducing admissions. The evidence for $MgSO_4$ administered *in combination* with β_2-agonists alone or in combination with β_2-agonist and ipratropium bromide is more convincing. For example, there may be some benefit with respect to pulmonary functions in patients presenting to the emergency department with severe acute exacerbations of asthma, when $MgSO_4$ is administered in combination with β_2-agonists (with or without ipratropium), and further research in this area, in relation to patients with that degree of severity, may provide further clarity on this point. As things stand, this remains an area of some uncertainty. In addition, while there is no clear evidence that $MgSO_4$ administered in combination with β_2-agonists reduces hospitalisations, the trend demonstrated (Analysis 1.5) suggests further research is urgently needed to answer this question.

Overall completeness and applicability of evidence

Several interesting methodological issues were encountered during the completion of this review that deserve brief mention. The investigations in this field are limited by the heterogeneity of both treatments and outcome measures. Unfortunately, despite adequate evidence for the use of standardised approaches to acute asthma, such as systemic corticosteroids (Rowe 1992), anticholinergics (McDonald 2004), intravenous $MgSO_4$ (Rowe 2004), and repeated β_2-agonists (Cates 2004), the control groups in the included studies were surprisingly heterogeneous. More trials where systemic corticosteroids, β_2-agonists and anticholinergics are administered to both groups and inhaled $MgSO_4$ or placebo is added to the treatment regimen in a double-blind manner are needed. This would be in line with the current BTS guidelines and international guidelines for the treatment of acute severe exacerbations of asthma (BTS/SIGN 2011; GINA 2011). Furthermore, there is a lack of consensus among researchers regarding the most appropriate pulmonary function outcome measure to report. The aforementioned trial should insist on both pulmonary function data as well as admission status at the conclusion of the emergency department treatment period. This is of course aimed at adult studies. In the paediatric studies, lung function may not be practical or applicable in the younger children and so there needs to be agreement on what is the most important core outcome to measure in children with acute asthma.

Quality of the evidence

Several included studies were only published as conference abstracts and all studies were at a high or unclear risk of bias (Figure 2; Figure 3), therefore, results should be interpreted with caution.

Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

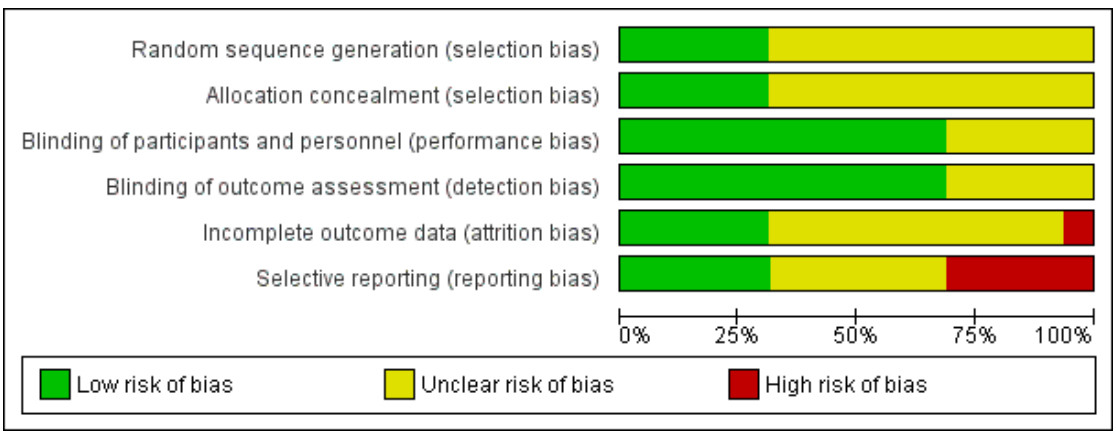
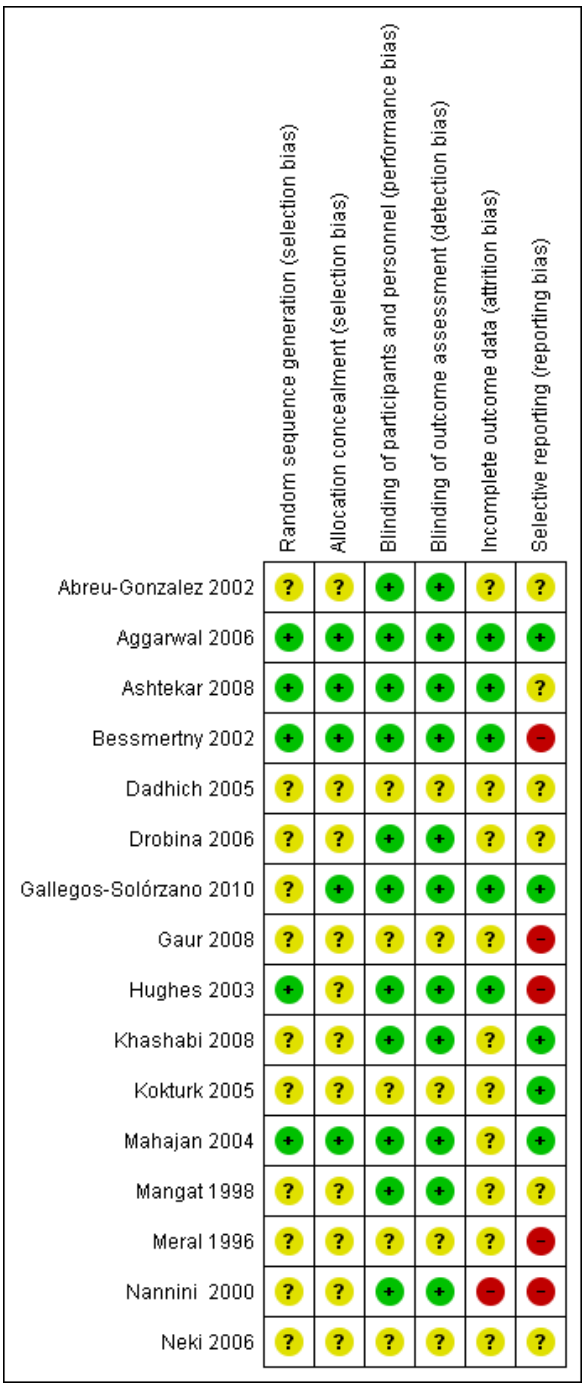


Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Potential biases in the review process

Publication bias may have influenced the result of this meta-analysis. For example, by missing unpublished negative trials we may be over-estimating the effect of $MgSO_4$ treatment. However, in order to reduce bias, a comprehensive and systematic search of the published and unpublished literature for potentially relevant studies was conducted and has recently been updated. This was followed by attempts to contact corresponding and first authors. One unpublished trial was identified and several negative trials were uncovered; however, we recognise that more of these types of trials may exist. Finally, due to the recent emergence of inhaled $MgSO_4$ treatment, there are possibly more small trials that have been conducted which for one reason or another remain unknown to us and unpublished. Without a central trial registry we may never find these results and in a review of this nature, made up of smaller studies, these small studies may make an important difference in our conclusions.

Agreements and disagreements with other studies or reviews

The conclusions in this updated Cochrane review are broadly consistent with the previous version Blitz 2005b, and although there are now a further 10 studies published on nebulised$MgSO_4$, the conclusions remain the same - that there is a role for nebulised $MgSO_4$ in acute severe exacerbations of asthma in adults but there is limited data to make firm conclusions about its role in children. They are also consistent with the systematic review by Mohammed 2007

AUTHORS' CONCLUSIONS

Implications for practice

1. Treatment with nebulised $MgSO_4$ could be considered *in addition to* inhaled β_2-agonists and ipratropium bromide in combination as per most national guidelines in asthma exacerbations, particularly in those patients with more severe exacerbations. However this point, regarding severity, requires further investigation in clinical trials. More data are required especially in paediatric studies.

2. There is no evidence that nebulised $MgSO_4$ can be used as a substitute for inhaled β_2-agonists.

3. Nebulised $MgSO_4$ appears to be effective and safe to administer to patients experiencing asthma exacerbations.

Implications for research

An agreement on the core outcomes for studies in acute asthma is needed so that any acute asthma study has the same outcomes measured - physiological, cost and those relevant to patients. This is particularly important in paediatric studies where lung function data may not be possible. There needs to be an agreement on which asthma severity score is the most valid score for use in paediatric acute asthma studies.

Although standard treatment has been agreed upon in the national guidelines, there are still studies that do not follow those guidelines and this makes the comparison of studies due to heterogeneity more difficult.

1. The role of nebulised $MgSO_4$ in asthma exacerbations has not been conclusively resolved by this review. Further research should be encouraged focusing on placebo-controlled studies using standard treatment for acute severe exacerbations of asthma, i.e. the combination of β_2 -agonists and ipratropium bromide in the comparison arm.

2. In addition, studies of acute asthma should stratify patients by presenting severity of the exacerbation and specify outcomes which are clinically valid such as relapse or hospital admission and a more short-term outcome such as change in pulmonary function, clinical asthma severity score and side effects of treatment.

3. There is a strong argument for asthma researchers to develop a consensus regarding the reporting of pulmonary function results.

4. The appropriate dose of nebulised $MgSO_4$ needs further clarification both in adult and paediatric studies.

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REFERENCES

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Abreu-Gonzalez 2002

Methods	Randomised, controlled, double blind study two groups. One centre in Tenerife.
Participants	24 patients (Intervention 13, Control 11), adults, acute asthma, moderate obstruction
Interventions	Intervention: 2 mL of magnesium sulfate (isotonic) dose and 400 mcg of salbutamol (delivery probably by MDI) Control: 2 mL of a physiological serum of an inhaled form, 400 mcg of salbutamol (delivery probably by MDI) Nebuliser: no details.
Outcomes	FEV1 and PEF at 0, 15, 30 45 minutes.
Notes	Funding: Gobierno Autonomo Canarias. Abstract only.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details but stated as 'randomised'.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double blind.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No details.
Selective reporting (reporting bias)	Unclear risk	Abstract only and not all time points reported.

Aggarwal 2006

Methods	Double blind, randomised controlled trial, parallel. One emergency department in India.
Participants	Inclusion criteria: Participants ages 13 to 60, BTS definition acute asthma (PEF and clinical features) Exclusion criteria: First episode of wheeze, chronic bronchitis or emphysema, heart failure, angina, renal failure, temperature > 38 ºC, ET tube required, no consent, pregnancy, failure to do peak flow Intervention: 50 randomised. Mean age (years): 46.26 (13.96). Men: Women: 27:23. Acute severe: 29. Acute life threatening: 21. Smokers: 9. Baseline PEF: 118.6 (41.3). Duration of attack; days (SD) 4.16 (1.69). Control: 50 randomised. Mean age (years): 41.00 (16.66). Men: Women: 33:17. Acute severe: 30. Severe life threatening: 20. Smokers: 5. Baseline PEF: 111.6 (43.3). Duration of attack; days (SD) 4.28 (1.99).
Interventions	Intervention: Magnesium sulfate (1 mL of 500 mg/mL magnesium sulfate) and salbutamol (1 mL of salbutamol) 8 mL distilled water - 295 mosmol/kg times 3 in an hour Control: salbutamol 1 mL, 1.5 mL distilled water, 7.5 mL normal saline - 287 mosmol/kg times 3 in an hour Treatment over 1 hour; three nebulisers twenty minutes apart. Follow-up for 20 minutes. Ultrasonic nebuliser.
Outcomes	PEF, heart rate, systolic pressure, diastolic pressure, time in ED, blood gases (0_2 and CO_2);(0 and 120 minutes), magnesium levels (0 and 120 minutes). Time points 0, 15, 60, 75, 120.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number tables.
Allocation concealment (selection bias)	Low risk	Separate envelopes to ensure concealment until inclusion (where they were kept - tamper proof not mentioned)

Aggarwal 2006 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The two researchers were blinded to the treatments so measurements (normal clinical outcomes) remained blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	50 participants both sides at beginning and 50 participants both sides completed the study with full outcome data
Selective reporting (reporting bias)	Low risk	Follow-up data and longer-term outcome data not collected. No apparent indication of selective reporting

Ashtekar 2008

Methods	Parallel One Children's assessment Unit one hospital (UHW).
Participants	Inclusion criteria: Age range 2 to 16 years, acute severe asthma Exclusion criteria: chronic lung disease, congenital heart disease, unable to understand English 17 randomised (8 boys). Intervention: 7 completed. Control 10 completed.
Interventions	Intervention: 2.5 mL isotonic magnesium sulfate (three occasions at 20-minute intervals) , salbutamol and ipratropium bromide Control: 2.5 mL isotonic saline (three occasions at 20-minute intervals), salbutamol and ipratropium bromide Three dosages over one hour : follow-up for 240 minutes.
Outcomes	Asthma severity scores (ASS), the sum of wheeze, accessory muscle use and heart rate, were computed on six occasions over 4 h. The primary endpoint was the area under the curve of the ASS at the six time points for each child
Notes	Funding: Local R and D pilot funding.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Block randomisation by pharmacy at source -in ED as sequential vials (code in pharmacy)

Ashtekar 2008 (*Continued*)

Allocation concealment (selection bias)	Low risk	As above - absolute concealment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial described as double blind: as above.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Trial described as double blind: as above.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All data collected for the 17 patients.
Selective reporting (reporting bias)	Unclear risk	Abstract only. Outcomes partially reported.

Bessmertny 2002

Methods	Design: parallel randomised controlled trial. Method of randomisation: computer-generated random numbers. Concealment of allocation: yes. Blinding: double-blinded, placebo-controlled. Withdrawals/dropouts: 6 (4 unable to complete spirometry, 2 inappropriate randomisation)
Participants	Location: One university hospital in Brooklyn, NY. Participants: 74 patients, presenting to the emergency department with acute asthma exacerbation, PEF between 40% and 80% predicted. Exclusions: smoking history > 10 pack years, known hypersensitivity to albuterol or $MgSO_4$, known chronic obstructive pulmonary disease, known history of renal impairment, known history of cardiac dysrhythmias, congestive heart failure or angina, fever more than 38 ^oC, receipt of theophylline or anti-cholinergic within 2 hours of arrival to ED
Interventions	Treatment: albuterol 2.5 mg/3 mL nebule followed by 384 mg isotonic $MgSO_4$ q 20 min x 3. Control: albuterol 2.5 mg/3 mL nebule followed by normal saline q 20 min x 3
Outcomes	Measured FEV1 every 20 minutes for 2 hours. Adverse events: No serious adverse events noted.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	An assigned third party randomised patients by means of a computer-generated

Bessmertny 2002 (*Continued*)

		random table (1:1 randomisation) to either the treatment or control group
Allocation concealment (selection bias)	Low risk	An assigned third party randomised patients by means of a computer-generated random table (1:1 randomisation) to either the treatment or control group
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded, placebo-controlled. A log of the identification number and specific treatment of each patient was kept and remained closed to the investigators until the completion of the study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blinded, placebo-controlled. A log of the identification number and specific treatment of each patient was kept and remained closed to the investigators until the completion of the study. Outcomes were assessed every 20 minutes for 2 hours
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts: 3 in each group. Albuterol plus normal saline solution (3 unable to complete spirometry) and, Albuterol plus magnesium (2 inappropriate randomisation, 1 unable to perform spirometry)
Selective reporting (reporting bias)	High risk	Mean values only given for FEV1, no SDs and the text reports that there were no statistically significant differences in FEV1 between the groups. The text also states "The analysis of continuous safety variables (BP, pulse rate, respiratory rate, oxygen saturation, and serum magnesium concentrations) did not demonstrate any clinically or statistically significant differences between the 2 groups at any point during the study. "

Dadhich 2005

Methods	Random allocation into three groups parallel study.
Participants	Location: One emergency department teaching hospital in India Acute severe asthma , PEF < 50%. Group A = 24 Group B = 26

Dadhich 2005 (*Continued*)

	Group C = 21
Interventions	Group A: salbutamol, Group B; salbutamol and magnesium sulfate, Group C magnesium sulfate alone; no details on dose or frequency
Outcomes	FEV1, FVC, FEV1/FVC, PEF, 'Vital parameters'
Notes	Two abstracts only (the same).

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomly allocated.
Allocation concealment (selection bias)	Unclear risk	No details.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No details.
Selective reporting (reporting bias)	Unclear risk	Abstract only and no data reported except there was a significant improvement in groups B and C compared to group A

Drobina 2006

Methods	Parallel.
Participants	A total of 110 participants.
Interventions	Intervention: received the control treatment with the addition of 150 mg of magnesium sulfate (0.3 mL of 50% magnesium sulfate heptahydrate) to each nebulised dose of medication Control: received nebulised treatments of albuterol sulfate 0.5% (5 mg/mL) combined with 0.5 mg of ipratropium bromide 0.02% inhalation solution (Atrovent)
Outcomes	Vital signs and peak flow measurements were also assessed at the end of each treatment (a maximum of three treatments) and just prior to discharge

Drobina 2006 (*Continued*)

	A 24-hour follow-up call was made to each participant, during which peak flow measurements were again obtained
Notes	Abstract only

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised but no detail.
Allocation concealment (selection bias)	Unclear risk	Described as randomised but no detail.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as double blind but no detail.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Described as double blind but no detail.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Very limited information - impossible to judge.
Selective reporting (reporting bias)	Unclear risk	Abstract only. No apparent indication of reporting bias.

Gallegos-Solórzano 2010

Methods	RCT, parallel
Participants	Inclusion criteria: Adults, >18 years in the emergency dept with asthmatic crisis, FEV1 < 60% predicted Exclusion criteria: smokers, those with ambulatory use of systemic steroids, with associated co-morbidities (neuropathy, nephropathy, heart disease, liver disease), fever at admission, use of dietary supplements with $MgSO_4$, irreversible airway obstruction (persistent abnormal spirometry), near-fatal asthma, requirement of endotracheal intubation at admission, anatomic abnormalities of the bronchial tree (bronchiectasis, tuberculosis) , history of pulmonary or thoracic surgery, hypersensitivity to $MgSO_4$, and pregnancy or breastfeeding. Location: National Institute of tertiary diseases, a tertiary care teaching hospital and national referral centre in Mexico City Date of study: June 2008 to March 2009. Intervention: 60 randomised, 30 completed. Mean age (years) 34.3 (12.4). Men: Women: 9:21. Control: 52 randomised, 30 completed. Mean age (years) 40.3 (11.6).

	Men: Women: 9:21.
Interventions	Each nebulisation lasted 20 mins. Intervention: standard nebulisation but diluted with 3 mL (333 mg) of 10% isotonic $MgSO_4$ (Magnefusin PISA, Guadalajara, Mexico; 1 g/10 mL). Also received 125 mg of IV methylprednisolone Control: one IV dose of 125 mg methylprednisolone and nebulisation with 7.5 mg of albuterol and 1.5 mg of ipratropium bromide in three divided doses. Standard nebulisation diluted in 3 mL of isotonic saline solution (SS) as placebo
Outcomes	FEV1 post-BD (absolute in litres and as percentage of predicted), clinical improvement, oxygen saturation, admission to the ED, admission to the asthma ward, hospital readmissions At 30-min post-nebulisation, patients were clinically and functionally re-evaluated. Also evaluated at 30 days
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomised.
Allocation concealment (selection bias)	Low risk	After randomisation, diluents were prepared by a physician outside the study who was not responsible for the patients' care and only had control of the pre-filled syringes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind. Both diluents are odourless, tasteless and colourless to the eye and did not differ when transparency was measured
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The physician responsible for the patients' care along with the nurse and inhalotherapists were blinded to the type of treatment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons given for dropouts in both groups in the CONSORT diagram. It seems as though there are a high percentage of dropouts but the majority are post randomisation exclusions based on exclusion criteria
Selective reporting (reporting bias)	Low risk	All outcomes stated in the methods section are reported. Best judgement with no access to trial protocol

Gaur 2008

Methods	Parallel RCT.
Participants	Age: 18 to 60 years. Location: Emergency department of a tertiary referral centre in India Acute asthma and FEV1 < 30% predicted. Intervention: 30. Control: 30.
Interventions	Intervention: Nebulised similarly using isotonic $MgSO_4$ (3 mL of 3.2 g%) as a vehicle - unsure if this is "Nebulized salbutamol and ipratropium" Control: Nebulised salbutamol and ipratropium using isotonic saline as a vehicle thrice at 20-minintervals
Outcomes	FEV% pred at 120 minutes, Pooled discharge rate proportion of groups attaining PEF > 60% pred and relief in dyspnoea at 30, 60, 90, 120 min)
Notes	Abstract only.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomised.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Single blind - no further details
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Single blind - no further details
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated.
Selective reporting (reporting bias)	High risk	One outcome partially reported and not significant. Abstract only

Hughes 2003

Methods	Design: parallel randomised controlled trial. Method of Randomisation: unknown. Concealment of allocation: yes. Blinding: Double-blinded, placebo-controlled. Withdrawals / Dropouts: 6 (4 CAL, 2 pneumonia).
Participants	Location: Two university hospitals in New Zealand. Participants: 52 patients, presenting to the emergency department with acute asthma exacerbation, FEV1 < 50% predicted. Exclusions: Known irreversible lung disease, pneumonia, pregnancy, significant renal / cardiac impairment, hypotension (sBP < 100 mmHg), required intubation
Interventions	Standard of care: salbutamol 2.5 mg nebulised x 1 or more, hydrocortisone 100 mg IV at presentation. Treatment: salbutamol 2.5 mg nebule with 2.5 mL isotonic $MgSO_4$ (250 mmol/L) q 30 min x 3. Control: salbutamol 2.5 mg nebule with 2.5 mL normal saline. q 30 min x3. Participants were unable to distinguish solutions.
Outcomes	Measured at baseline and after each treatment (q 30 min x 3): FEV1, %predicted FEV1, BP, heart rate, O2 saturation. Requirement for admission at 90 minutes. Adverse events: No serious adverse events noted.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomly assigned to their treatment groups in accordance with the allocation sequence determined by the hospital pharmacy
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded, placebo-controlled. Patients and investigators were unaware of treatment allocation through provision by the hospital pharmacy of pre prepared identical unmarked syringes containing the study drug
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blinded, placebo-controlled. Patients and investigators were unaware of treatment allocation through provision by the hospital pharmacy of pre prepared identical unmarked syringes containing the

Hughes 2003 (*Continued*)

		study drug. Outcomes assessed every 30 minutes
Incomplete outcome data (attrition bias) All outcomes	Low risk	6 in total. Magnesium sulfate (1 COPD, 1 pneumonia). Saline (3 COPD, 1 pneumonia).
Selective reporting (reporting bias)	High risk	The primary outcome, FEV1 was fully reported but other outcomes were not. "The change in blood pressure and heart rate did not differ between the two groups. No clinically significant adverse events were reported."

Khashabi 2008

Methods	Parallel RCT.
Participants	Location: authors based in Iran. Participants: 40 Asthmatic children in total between 2 groups Mean age 3.55 years.
Interventions	Intervention: Nebulised salbutamol, as a vehicle isotonic magnesium sulfate mixed with salbutamol Control: Nebulised salbutamol, as a vehicle 2.5 mL of normal saline
Outcomes	Days of hospital stay, Hours of need for oxygen, Respiratory distress Measured one hour before and one hour after the second course of treatment
Notes	Abstract only

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomly enrolled.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double blind.

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated.
Selective reporting (reporting bias)	Low risk	Outcomes stated as measured, reported. Abstract only.

Kokturk 2005

Methods	Parallel RCT
Participants	Inclusion criteria: moderate to severe asthma attacks, 18 to 60 years Exclusion criteria: patients with febrile disease, diabetes, congestive heart failure, atherosclerotic heart disease, intractable hypertension, chronic obstructive lung disease, renal and hepatic failure and, arrhythmia were excluded from the study. Pregnant and breast feeding women, patients who had already taken theophylline, antihistaminics, and systemic steroids in the previous 24 h, who had acute or chronic respiratory failure, who had been on long-term oxygen therapy, and a history of allergy to salbutamol and MgSO4 have been excluded as well Location: Emergency department, Turkey. Intervention: 14. Mean age: 46.43 (years) (3.31) range 18 to 3. Men: Women: 4:10. Control: 12. Mean age: 37.83 (years) (9.26) range 20 to 52. Men: Women: 3:9.
Interventions	Every 20 mins for first hour and every hour for the rest of 4 hours Intervention: Isotonic $MgSO_4$ (2.5mL) +salbutamol (2.5 mL). Control:salbutamol (2.5 mL) + saline (2.5 mL).
Outcomes	PEF, Clinical scores, Discharge rates, Admission rates. 20^{th}, 60^{th}, 120^{th}, 180^{th}, 240^{th} minute (180 and 240 not compared as most patients completed study in 2 hours)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomised - details of sequence generation not included in trial report
Allocation concealment (selection bias)	Unclear risk	Information not available in trial report.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Single blind - no further details

Kokturk 2005 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Single blind - no further details
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information provided in trial report on discharges from both groups up to 240 minutes
Selective reporting (reporting bias)	Low risk	No apparent indication of selective reporting.

Mahajan 2004

Methods	Design: parallel randomised controlled trial. Method of randomisation: table of random numbers. Concealment of allocation: not stated. Blinding: double-blinded, placebo-controlled. Withdrawals/dropouts: none described.
Participants	Location: One paediatric emergency department in Detroit, Michigan. Participants: 62 patients age 5- to 17, presenting to the emergency department with acute asthma exacerbation, FEV1 between 45% and 75% predicted. Exclusions: Fever (> 39 °C), chronic disease (bronchopulmonary dysplasia, cystic fibrosis) , known allergy to albuterol or magnesium, received any of steroids, theophylline or ipratropium bromide in the prior 3 days
Interventions	Treatment: albuterol 2.5 mg nebule with 2.5 cc isotonic $MgSO_4$ (6.3% solution); 1 dose. Control: albuterol 2.5 mg nebule with 2.5 cc normal saline; 1 dose. Both groups received corticosteroids (2 mg/kg) after inhaled treatment
Outcomes	Lung function (FEV1 and %predicted FEV1) at baseline, then at 10 and 20 minutes after treatment. Also report vital signs and hospital admission rates. State that none of the patients showed any side effects.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	A table of random numbers was used to provide randomisation and this was performed by a senior research pharmacist at the institution
Allocation concealment (selection bias)	Low risk	A table of random numbers was used to provide randomisation and this was performed by a senior research pharmacist at

Mahajan 2004 (*Continued*)

		the institution
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded, placebo controlled. The study medications were provided in identical syringes and both the pharmacy and the investigator were blinded to their contents
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blinded, placebo controlled. The study medications were provided in identical syringes and both the pharmacy and the investigator were blinded to their contents. Outcomes assessed at 10 and 20 minutes after treatment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	None described.
Selective reporting (reporting bias)	Low risk	All outcomes stated in the methods section are reported.

Mangat 1998

Methods	Design: Parallel randomised controlled trial. Method of randomisation: unknown. Concealment of allocation: yes. Blinding: double-blind, placebo-controlled. Withdrawals/dropouts: 0.
Participants	Location: Emergency Department, St John's Medical College Hospital, India. Screened: 63. Participants: 33, 12 to 60 years of age, known or newly diagnosed asthmatics with PEF < 300 L/min. Exclusions: Patient enrolled at prior presentation, febrile, lower respiratory tract infection, history or evidence of cardiac/renal/hepatic dysfunction. pregnancy, requirement for ventilatory care, oral/parenteral bronchodilators within previous 6 hours, steroids within previous 12 hours
Interventions	Standard of care: hydrocortisone 100 mg IV. Treatment: $MgSO_4$ 3 mL (3.2% solution = 95 mg) nebulised q 20 min x 4. Control: salbutamol 3 mL (2.5 mg) nebulised q 20 min x 4.
Outcomes	Clinical score: Fischl Index, clinical examination. Pulmonary function: PEF. Vitals: Respiratory rate, heart rate, BP, pulsus paradoxus. Admission rates, vital signs. Adverse events/side effects: Treatment: 1 case mild transient hypotension with spontaneous resolution. Control group: 1 case mild transient hypotension with spontaneous resolution, 1 case

Mangat 1998 (*Continued*)

	palpitations, 2 cases fine tremors in hand	
Notes		

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomised.
Allocation concealment (selection bias)	Unclear risk	Information not available.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, placebo-controlled.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind, placebo-controlled. Outcomes assessed at 20 minute intervals
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	None described.
Selective reporting (reporting bias)	Unclear risk	Pulsus paradoxus and BP are mentioned but not reported, but pulsus paradoxus is included as part of the Fischl index

Meral 1996

Methods	Design: Randomised controlled trial. Method of randomisation: unknown. Concealment of allocation: unknown. Blinding: unknown. Withdrawals/dropouts: 0.
Participants	Location: Department of paediatric asthma of Ege University Hospital, Turkey. Participants: 40 divided randomised into 2 groups of 20. Mean ages 10.6 and 11 years of age. Previously diagnosed as asthmatic using ATS definitions; PEF decreased by >/= 25%. Exclusions: Medication within 12 hours of study, cardiac/renal dysfunction
Interventions	Treatment: $MgSO_4$ 2 mL (280 mmol/L, 258 mOsm, pH 6.7). Control: Salbutamol 2.5 mg in 2.5 mL. Administration: nebulised, inhaled over 10 to 15 minutes.
Outcomes	Evaluations at: 5, 15, 30, 60, 180,240 and 360 minutes. Clinical score: Davis-Leffert-Dabbous respiratory distress score pulmonary function: PEF.

Meral 1996 (*Continued*)

	Adverse reactions/side effects: none observed.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Patients were randomly selected for the study and divided into 2 groups
Allocation concealment (selection bias)	Unclear risk	Information not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	None described.
Selective reporting (reporting bias)	High risk	No statistical differences were found between the groups for respiratory rate, heart rate and BP. It is also unclear as to the time point reported as although 5 minutes was prespecified there were also several other time points specified and only the maximum values were presented

Nannini 2000

Methods	Design: Randomised controlled trial. Method of randomisation: unknown. Concealment of allocation: yes. Blinding: double-blind, placebo-controlled. Solutions were pre-packaged in identical appearing vials. Withdrawals/dropouts: 3 patients were enrolled more than once, only the initial visit was used in the analysis
Participants	Location: Emergency departments in 4 Argentinian hospitals. Participants: 35 patients at least 18 years of age presenting to the emergency department with an acute asthma exacerbation who were able to have PEF measured were enrolled. (%predicted PEF: 38 +/- 18 in treatment group, 38 +/- 12 in control group). Exclusions: current smokers of >/= 5 pack years. Concurrent medical illness, pregnant, breast feeding, oral or parenteral steroids within the previous 7 days

Interventions	Standard of care: all patients received supplemental oxygen. If patient condition worsened patient may receive salbutamol 2.5 mg nebulised at discretion of physician. Treatment: 0.5 mL salbutamol (2.5 mg) diluted in 3 mL isotonic $MgSO_4$ (286 mOsm, 7.5% = 225 mg). Control: 0.5 mL salbutamol (2.5 mg) diluted in 3 mL normal saline. Administration: jet nebulised using oxygen at 10 L/min via mouthpiece until dry
Outcomes	Measurements made at baseline, 10 minutes after treatment and 20 minutes after treatment. Pulmonary functions: Primary endpoint : % increase in peak flow = [(change/baseline) x100]. Other: Peak flow (best of 3 attempts). Vital signs: respiratory rate, pulse rate, BP. Duration of emergency room care. No adverse events reported in either the experimental or control group
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomised.
Allocation concealment (selection bias)	Unclear risk	Information not available.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, placebo-controlled.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind, placebo-controlled.
Incomplete outcome data (attrition bias) All outcomes	High risk	3 patients were enrolled more than once, only the initial visit was used in the analysis but treatment group not stated
Selective reporting (reporting bias)	High risk	There were no significant differences between the groups in changes in BP, heart rate, or respiratory rate at either 10 minutes or 20 minutes

Neki 2006

Methods	Parallel
Participants	Inclusion criteria: patients in age group of 15-60 years with severe bronchial asthma, as judged by Fischl index having PEF< 300 L/min or FEV in 1st second less than 40% of the predicted value were included in the study Exclusion criteria: all patients, who had received oral, inhaler or parenteral bronchodilators in the past 6 hours or steroid in the previous 12 hours were excluded from the study ADULT and Paediatric with severe asthma (15-60 years) 40 patients 30 women and 10 men but unclear how divided between groups. Intervention: 20 completed. Control: 20 completed.
Interventions	Intervention: given 4 doses of nebulised solution of 3.2G% magnesium sulfate, 20 minutes apart Control: received four doses of nebulised salbutamol (each dose of 3 mL containing 25 mg), 20 minutes apart
Outcomes	PEF (L/min), Respiratory rate was, Fischl index and SaO_2
Notes	Abstract only.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Details of random sequence generation not included in trial report. There is no reference to randomisation in trial report and trial not reported as randomised - seeking clarification from author
Allocation concealment (selection bias)	Unclear risk	Details of allocation concealment not included in trial report. There is no reference to randomisation in trial report and trial not reported as randomised - seeking clarification from author
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details of blinding.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	If the trial was not blinded, there is a strong likelihood that outcome assessment was not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information.
Selective reporting (reporting bias)	Unclear risk	Abstract only. No apparent indication of selective reporting

ASS: Asthma Severity Score (ASS)

ATS: *American Thoracic Society*
BP: blood pressure
BTS: British Thoracic Society
COPD: Chronic obstructive pulmonary disease
ED: emergency department
FEV1: Forced expiratory volume in one second
FVC: Forced vital capacity
h: hours
IV: intravenous
MDI: metered dose inhaler
$MgSO_4$: magnesium sulfate
PEF: Peak Expiratory Flow Rate
R&D: research and development
sBP: systolic blood pressure
SD: standard deviation

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

Study	Reason for exclusion
Abd 1997	Unobtainable but probably intravenous
Balter 1989	Review
Bede 2003	Oral supplementation in chronic asthma
Bede 2004	Oral supplementation in chronic asthma
Bede 2008	Oral supplementation in chronic asthma
Bernstein 1995	Study does not assess patients with acute asthma
Bustamante 2000	Paper not obtainable
Cairns 1996	Study does not assess patients with acute asthma
Castillo Rueda 1991	Letter to the Editor
Chande 1992	Study of stable asthma and methacholine challenge tests
Corbridge 1995	Review
DiGregorio 1999	Not a randomised controlled study
Emelyanov 1997	Study not a randomised trial and in mild to moderate persistent asthma rather than acute asthma
Emelyanov 1990	Not a randomised controlled trial

(*Continued*)

Emelyanov 1996	Exercise induced bronchospasm and challenge test. Not a randomised controlled trial
Fedoseev 1991	Study does not assess patients with acute asthma and is not a randomised controlled trial
Harari 1998	Review
Hardin 2001	Review
Harmanci 1996	Stable asthma histamine-induced bronchospasm adults
Hill 1995	Study does not assess patients with acute asthma. Dose response study in 20 normal individuals and 19 with chronic asthma
Hill 1997	Study does not assess patients with acute asthma. Stable asthma histamine challenge tests
Hill 1997a	Stable adult asthmas with histamine challenges
Kenyon 2001	Review
Kreutzer 2001	Review
Manzke 1990	Paediatric exercise-induced bronchospasm. Not a randomised controlled trial
McFadden 1995	Review
Nannini 1997	Study does not assess patients with acute asthma
Nunez-Torres 1995	Not a randomised controlled trial
Pelton 1998	Study does not assess patients with acute asthma
Pelton 1999	Review
Puente-Maestu 1999	Review
Qureshi 1999	Review
Rodger 2003	Oral supplementation on patients with unstable asthma
Rodrigo 2000	Systematic review, includes intravenous $MgSO_4$
Rolla 1987	Study does not assess patients with acute asthma
Rolla 1987a	Study does not assess patients with acute asthma
Rolla 1988a	Study does not assess patients with acute asthma
Rolla 1988b	Letter to the editor

(*Continued)*

Scarfone 1998	RCT of intravenous magnesium sulfate
Scarfone 2000	Intravenous $MgSO_4$
Singh 2008	Intravenous $MgSO_4$
Singh 2008a	Comparison between inhaled versus intravenous $MgSO_4$
Sinitsina 1991	Not a randomised controlled trial
Skobeloff 1982	Editorial
Talukdar 2005	Not a randomised controlled trial
Teeter 1999	Review
Telia 2005	Study does not assess patients with acute asthma
Tereshchenko 2006	Looking at ipratropium bromide mixed with either magnesium sulfate or saline for bronchiolitis (up to age 11.5 months)
Tetikkurt 1992	Study does not assess patients with acute asthma
Tetikkurt 1993	Study does not assess patients with acute asthma
Xu 2002	Not a randomised controlled trial
Yemelyanov 1997	Study does not assess patients with acute asthma
Zandsteeg 2009	Study does not assess patients with acute asthma (stable chronic asthma) and is not a randomised controlled trial
Zhu 2003	Intravenous $MgSO_4$ and not a randomised controlled trial

$MgSO_4$: magnesium sulfate

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

Goodacre 2007

Trial name or title	3Mg
Methods	Three-armed RCT
Participants	Adult

Goodacre 2007 (*Continued*)

Interventions	Nebulised and intravenous magnesium and standard treatment
Outcomes	Lung function, admissions
Starting date	2007
Contact information	
Notes	Still recruiting (over 1000 patients in study due to stop recruiting soon as of 14/3/12)

Powell 2012

Trial name or title	MAGNETIC
Methods	Randomised placebo-controlled multicentre study
Participants	Paediatric population
Interventions	Nebulised magnesium and standard treatment
Outcomes	
Starting date	
Contact information	
Notes	

Wijetunge 2002

Trial name or title	A trial of nebulised magnesium sulfate versus placebo in addition to conventional bronchodilator treatment in acute asthma of moderate severity
Methods	
Participants	Unknown
Interventions	Unknown
Outcomes	Unknown
Starting date	2002
Contact information	DB Wijetunge St George's Hospital London, UK

Notes	Letter mailed 29 Jan 2004. Email and faxed attempts were unsuccessful when the review was first published and again during the update in 2012. Reference Source: National Research Register (UK)

RCT: randomised controlled trial

DATA AND ANALYSES

Comparison 1. MgSO4 + SABA versus SABA alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pulmonary function FEV1 and %predicted FEV1	3	188	Std. Mean Difference (IV, Fixed, 95% CI)	0.20 [-0.09, 0.49]
2 Pulmonary function PEF	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 up to 60 minutes	2	135	Mean Difference (IV, Fixed, 95% CI)	7.07 [-11.69, 25.84]
2.2 Discharge	1	26	Mean Difference (IV, Fixed, 95% CI)	0.68 [-8.56, 9.92]
3 FEV1: sub-group: adult/children	3	188	Std. Mean Difference (IV, Random, 95% CI)	0.23 [-0.27, 0.74]
3.1 Adult	2	126	Std. Mean Difference (IV, Random, 95% CI)	0.18 [-0.65, 1.02]
3.2 Pediatric	1	62	Std. Mean Difference (IV, Random, 95% CI)	0.36 [-0.14, 0.86]
4 FEV1: subgroup: severity	3	188	Std. Mean Difference (IV, Random, 95% CI)	0.23 [-0.27, 0.74]
4.1 Severe (FEV1 <50% predicted)	1	52	Std. Mean Difference (IV, Random, 95% CI)	0.63 [0.07, 1.19]
4.2 Moderate	2	136	Std. Mean Difference (IV, Random, 95% CI)	0.06 [-0.52, 0.63]
5 Admission to hospital	4	249	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.49, 1.16]
6 Admission to hospital, subgroup: adult/children	4	249	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.49, 1.16]
6.1 Adults	2	87	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.38, 1.02]
6.2 Children	1	62	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.19, 20.93]
6.3 Mixed	1	100	Risk Ratio (M-H, Fixed, 95% CI)	0.9 [0.40, 2.02]
7 Admission to hospital, subgroup: severity	4	249	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.49, 1.16]
7.1 Severe	3	187	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.46, 1.10]
7.2 Mild-moderate	1	62	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.19, 20.93]
8 Vital signs	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
8.1 Pulse	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.2 Systolic Pressure	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.3 Diastolic Pressure	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 Serious adverse events	4	223	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.03, 0.03]
10 Mild-moderate adverse events	3	209	Risk Difference (M-H, Fixed, 95% CI)	-0.03 [-0.14, 0.08]

Comparison 2. $MgSO_4$ versus SABA

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pulmonary function testing PEF	3		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 60 minutes	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Time point unclear	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Max response in first hour	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Clinical severity score	3		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 60 minutes	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

2.2 Time point unclear	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 Max response in first hour	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Admision to hospital	1	Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Respiratory rate	1	Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5 Serious Side Effects	1	Risk Difference (M-H, Fixed, 95% CI)	Totals not selected
6 Mild-Moderate Side Effects	1	Risk Difference (M-H, Fixed, 95% CI)	Totals not selected

Comparison 3. $MgSO_4$ and SABA and ipratropium versus placebo (saline) and SABA and ipratropium

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pulmonary function (FEV1)	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 90 minutes	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 120 minutes	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Admission to hospital	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 Emergency department	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 General ward	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 Readmitted	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 MgSO4 + SABA versus SABA alone, Outcome 1 Pulmonary function FEV1 and %predicted FEV1.

Review: Inhaled magnesium sulfate in the treatment of acute asthma

Comparison: 1 MgSO4 + SABA versus SABA alone

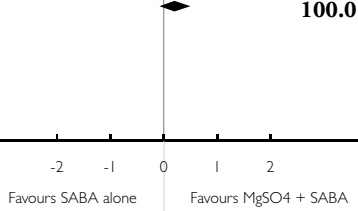
Outcome: 1 Pulmonary function FEV1 and %predicted FEV1

Study or subgroup	$MgSO_4$ + SABA N	Mean(SD)	SABA N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
Bessmertny 2002	37	63 (21.9)	37	68 (21.9)		40.0 %	-0.23 [-0.68, 0.23]
Hughes 2003	28	1.86 (0.67)	24	1.44 (0.65)		26.8 %	0.63 [0.07, 1.19]
Mahajan 2004	31	75.4 (26)	31	67.3 (18)		33.2 %	0.36 [-0.14, 0.86]
Total (95% CI)	**96**		**92**			**100.0 %**	**0.20 [-0.09, 0.49]**

Heterogeneity: Chi^2 = 5.94, df = 2 (P = 0.05); I^2 =66%

Test for overall effect: Z = 1.33 (P = 0.18)

Test for subgroup differences: Not applicable

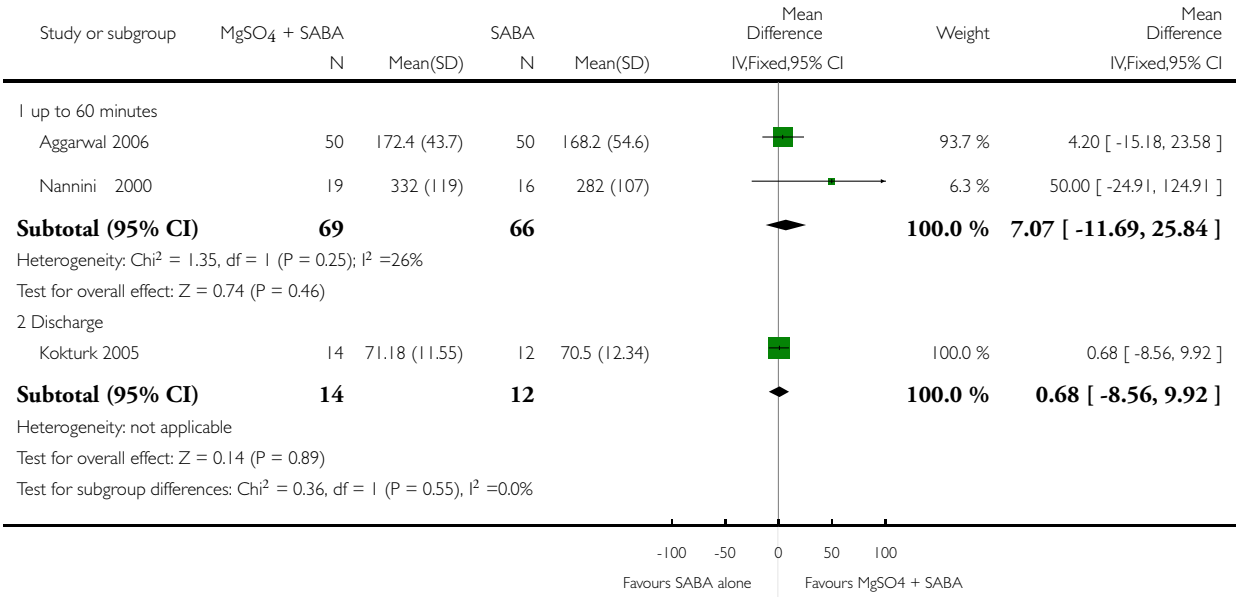


Analysis 1.2. Comparison 1 MgSO4 + SABA versus SABA alone, Outcome 2 Pulmonary function PEF.

Review: Inhaled magnesium sulfate in the treatment of acute asthma

Comparison: 1 MgSO4 + SABA versus SABA alone

Outcome: 2 Pulmonary function PEF

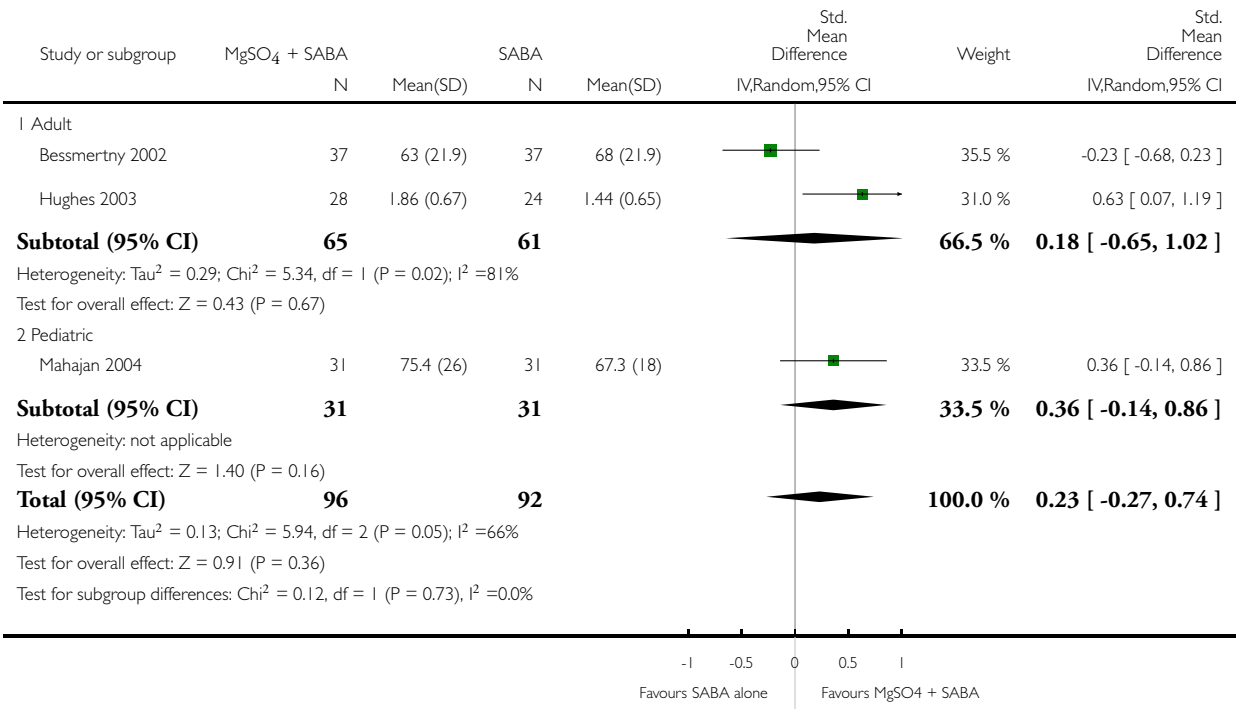


Analysis 1.3. Comparison 1 MgSO4 + SABA versus SABA alone, Outcome 3 FEV1: sub-group: adult/children.

Review: Inhaled magnesium sulfate in the treatment of acute asthma

Comparison: 1 MgSO4 + SABA versus SABA alone

Outcome: 3 FEV1: sub-group: adult/children

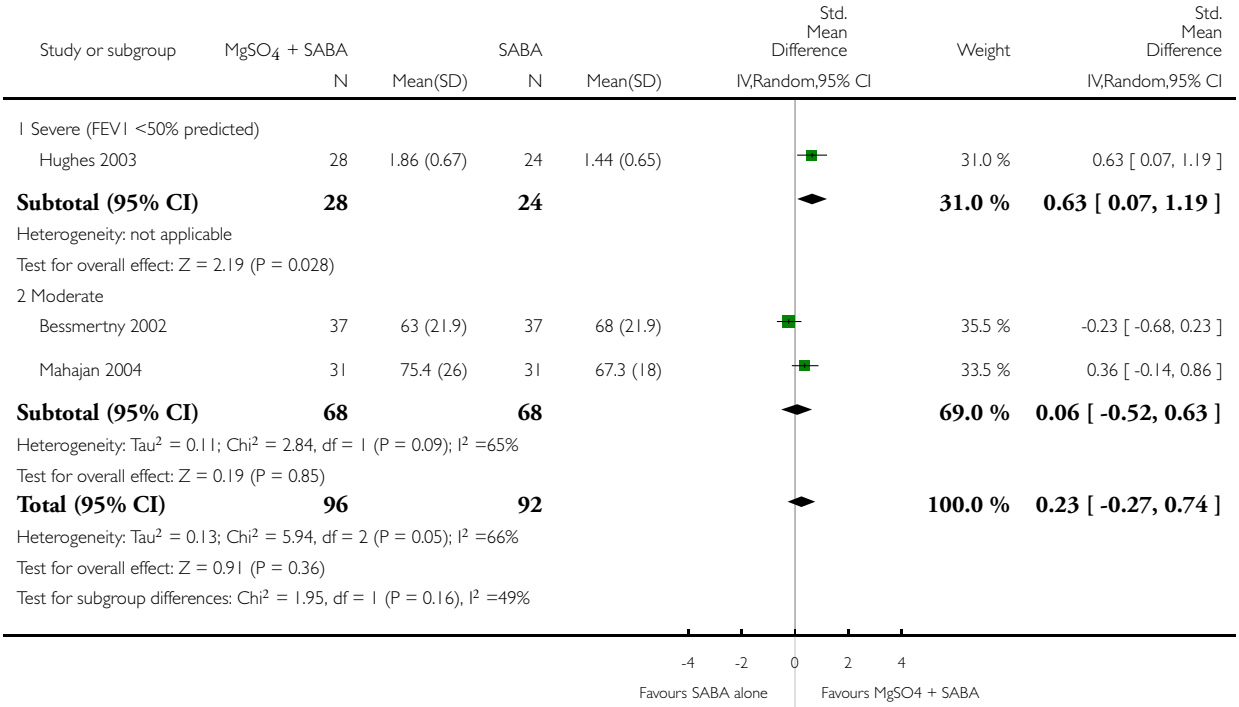


Analysis 1.4. Comparison 1 MgSO4 + SABA versus SABA alone, Outcome 4 FEV1: subgroup: severity.

Review: Inhaled magnesium sulfate in the treatment of acute asthma

Comparison: 1 MgSO4 + SABA versus SABA alone

Outcome: 4 FEV1: subgroup: severity



Analysis 1.5. Comparison 1 MgSO4 + SABA versus SABA alone, Outcome 5 Admission to hospital.

Review: Inhaled magnesium sulfate in the treatment of acute asthma

Comparison: 1 MgSO4 + SABA versus SABA alone

Outcome: 5 Admission to hospital

Study or subgroup	$MgSO_4$ + SABA n/N	SABA n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Hughes 2003	12/28	17/24		60.2 %	0.61 [0.37, 1.00]
Aggarwal 2006	9/50	10/50		32.9 %	0.90 [0.40, 2.02]
Mahajan 2004	2/31	1/31		3.3 %	2.00 [0.19, 20.93]
Nannini 2000	1/19	1/16		3.6 %	0.84 [0.06, 12.42]
Total (95% CI)	**128**	**121**		**100.0 %**	**0.76 [0.49, 1.16]**

Total events: 24 ($MgSO_4$ + SABA), 29 (SABA)

Heterogeneity: Chi^2 = 1.61, df = 3 (P = 0.66); I^2 =0.0%

Test for overall effect: Z = 1.28 (P = 0.20)

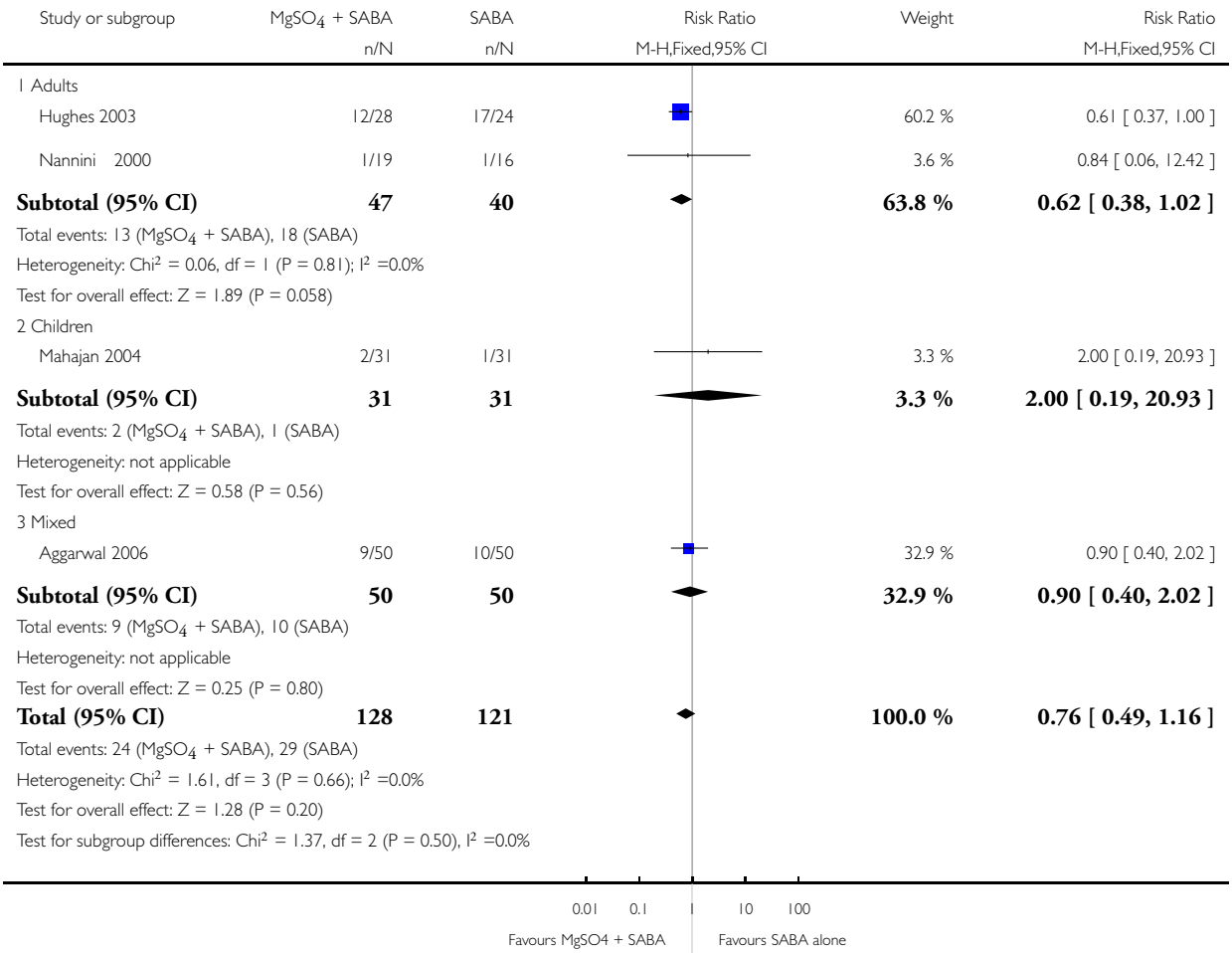
Test for subgroup differences: Not applicable

Analysis 1.6. Comparison 1 MgSO4 + SABA versus SABA alone, Outcome 6 Admission to hospital, subgroup: adult/children.

Review: Inhaled magnesium sulfate in the treatment of acute asthma

Comparison: 1 MgSO4 + SABA versus SABA alone

Outcome: 6 Admission to hospital, subgroup: adult/children



Analysis 1.7. Comparison 1 MgSO4 + SABA versus SABA alone, Outcome 7 Admission to hospital, subgroup: severity.

Review: Inhaled magnesium sulfate in the treatment of acute asthma

Comparison: 1 MgSO4 + SABA versus SABA alone

Outcome: 7 Admission to hospital, subgroup: severity

Study or subgroup	$MgSO_4$ + SABA n/N	SABA n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Severe					
Hughes 2003	12/28	17/24		60.2 %	0.61 [0.37, 1.00]
Aggarwal 2006	9/50	10/50		32.9 %	0.90 [0.40, 2.02]
Nannini 2000	1/19	1/16		3.6 %	0.84 [0.06, 12.42]
Subtotal (95% CI)	**97**	**90**		**96.7 %**	**0.71 [0.46, 1.10]**
Total events: 22 ($MgSO_4$ + SABA), 28 (SABA)					
Heterogeneity: Chi^2 = 0.75, df = 2 (P = 0.69); I^2 =0.0%					
Test for overall effect: Z = 1.52 (P = 0.13)					
2 Mild-moderate					
Mahajan 2004	2/31	1/31		3.3 %	2.00 [0.19, 20.93]
Subtotal (95% CI)	**31**	**31**		**3.3 %**	**2.00 [0.19, 20.93]**
Total events: 2 ($MgSO_4$ + SABA), 1 (SABA)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.58 (P = 0.56)					
Total (95% CI)	**128**	**121**		**100.0 %**	**0.76 [0.49, 1.16]**
Total events: 24 ($MgSO_4$ + SABA), 29 (SABA)					
Heterogeneity: Chi^2 = 1.61, df = 3 (P = 0.66); I^2 =0.0%					
Test for overall effect: Z = 1.28 (P = 0.20)					
Test for subgroup differences: Chi^2 = 0.71, df = 1 (P = 0.40), I^2 =0.0%					

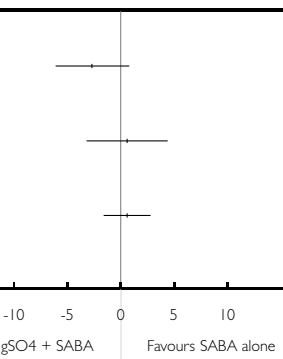
Analysis 1.8. Comparison 1 MgSO4 + SABA versus SABA alone, Outcome 8 Vital signs.

Review: Inhaled magnesium sulfate in the treatment of acute asthma

Comparison: 1 MgSO4 + SABA versus SABA alone

Outcome: 8 Vital signs

Study or subgroup	$MgSO_4$ + SABA N	Mean(SD)	SABA N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Pulse						
Aggarwal 2006	50	94.6 (8.4)	50	97.3 (9.2)		-2.70 [-6.15, 0.75]
2 Systolic Pressure						
Aggarwal 2006	50	138.8 (8.7)	50	138.2 (10.5)		0.60 [-3.18, 4.38]
3 Diastolic Pressure						
Aggarwal 2006	50	89.3 (5.5)	50	88.7 (5.6)		0.60 [-1.58, 2.78]



Analysis 1.9. Comparison 1 MgSO4 + SABA versus SABA alone, Outcome 9 Serious adverse events.

Review: Inhaled magnesium sulfate in the treatment of acute asthma

Comparison: 1 MgSO4 + SABA versus SABA alone

Outcome: 9 Serious adverse events

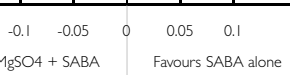
Study or subgroup	$MgSO_4$ + SABA n/N	SABA n/N	Risk Difference M-H,Fixed,95% CI	Weight	Risk Difference M-H,Fixed,95% CI
Bessmertny 2002	0/37	0/37		33.3 %	0.0 [-0.05, 0.05]
Hughes 2003	0/28	0/24		23.2 %	0.0 [-0.07, 0.07]
Mahajan 2004	0/31	0/31		27.9 %	0.0 [-0.06, 0.06]
Nannini 2000	0/19	0/16		15.6 %	0.0 [-0.11, 0.11]
Total (95% CI)	**115**	**108**		**100.0 %**	**0.0 [-0.03, 0.03]**

Total events: 0 ($MgSO_4$ + SABA), 0 (SABA)

Heterogeneity: Chi^2 = 0.0, df = 3 (P = 1.00); I^2 =0.0%

Test for overall effect: Z = 0.0 (P = 1.0)

Test for subgroup differences: Not applicable



Analysis 1.10. Comparison 1 MgSO4 + SABA versus SABA alone, Outcome 10 Mild-moderate adverse events.

Review: Inhaled magnesium sulfate in the treatment of acute asthma

Comparison: 1 MgSO4 + SABA versus SABA alone

Outcome: 10 Mild-moderate adverse events

Study or subgroup	$MgSO_4$ + SABA n/N	SABA n/N	Risk Difference M-H,Fixed,95% CI	Weight	Risk Difference M-H,Fixed,95% CI
Aggarwal 2006	13/50	11/50		47.9 %	0.04 [-0.13, 0.21]
Bessmertny 2002	11/37	16/37		35.5 %	-0.14 [-0.35, 0.08]
Nannini 2000	0/19	0/16		16.6 %	0.0 [-0.11, 0.11]
Total (95% CI)	**106**	**103**		**100.0 %**	**-0.03 [-0.14, 0.08]**

Total events: 24 ($MgSO_4$ + SABA), 27 (SABA)

Heterogeneity: Chi^2 = 1.86, df = 2 (P = 0.40); I^2 =0.0%

Test for overall effect: Z = 0.50 (P = 0.62)

Test for subgroup differences: Not applicable

Analysis 2.1. Comparison 2 $MgSO_4$ versus SABA, Outcome 1 Pulmonary function testing PEF.

Review: Inhaled magnesium sulfate in the treatment of acute asthma

Comparison: 2 $MgSO_4$ versus SABA

Outcome: 1 Pulmonary function testing PEF

Study or subgroup	$MgSO_4$ N	Mean(SD)	SABA N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 60 minutes						
Mangat 1998	16	71.8 (28.6)	17	67.6 (18.3)		4.20 [-12.29, 20.69]
2 Time point unclear						
Neki 2006	20	56 (31.18)	20	106 (26.12)		-50.00 [-67.83, -32.17]
3 Max response in first hour						
Meral 1996	20	42.63 (20.21)	20	79.4 (52.09)		-36.77 [-61.26, -12.28]

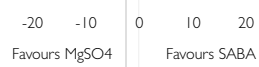
Analysis 2.2. Comparison 2 $MgSO_4$ versus SABA, Outcome 2 Clinical severity score.

Review: Inhaled magnesium sulfate in the treatment of acute asthma

Comparison: 2 $MgSO_4$ versus SABA

Outcome: 2 Clinical severity score

Study or subgroup	$MgSO_4$ N	Mean(SD)	SABA N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 60 minutes						
Mangat 1998	16	0.43 (0.89)	17	0.76 (1.25)		-0.33 [-1.07, 0.41]
2 Time point unclear						
Neki 2006	20	4.61 (1.62)	20	4.81 (1.29)		-0.20 [-1.11, 0.71]
3 Max response in first hour						
Meral 1996	20	79.97 (19.18)	20	83.17 (26.73)		-3.20 [-17.62, 11.22]



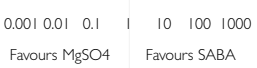
Analysis 2.3. Comparison 2 $MgSO_4$ versus SABA, Outcome 3 Admision to hospital.

Review: Inhaled magnesium sulfate in the treatment of acute asthma

Comparison: 2 $MgSO_4$ versus SABA

Outcome: 3 Admision to hospital

Study or subgroup	$MgSO_4$ n/N	SABA n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Mangat 1998	1/16	2/17		0.53 [0.05, 5.31]



Analysis 2.4. Comparison 2 $MgSO_4$ versus SABA, Outcome 4 Respiratory rate.

Review: Inhaled magnesium sulfate in the treatment of acute asthma

Comparison: 2 $MgSO_4$ versus SABA

Outcome: 4 Respiratory rate

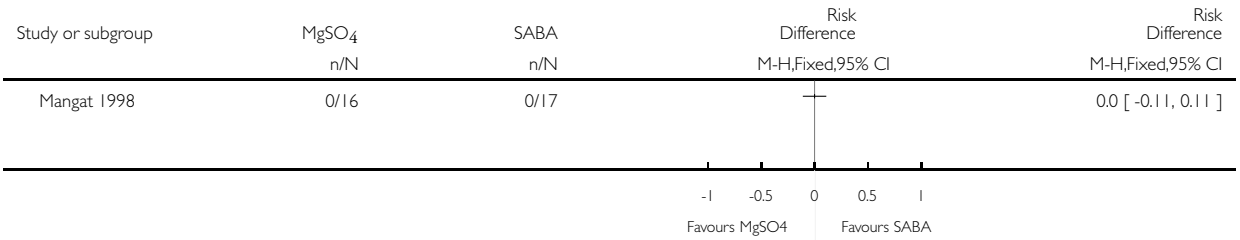
Study or subgroup	$MgSO_4$ N	Mean(SD)	SABA N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Neki 2006	20	10.66 (3.18)	20	13.16 (2.14)		-2.50 [-4.18, -0.82]

Analysis 2.5. Comparison 2 $MgSO_4$ versus SABA, Outcome 5 Serious Side Effects.

Review: Inhaled magnesium sulfate in the treatment of acute asthma

Comparison: 2 $MgSO_4$ versus SABA

Outcome: 5 Serious Side Effects

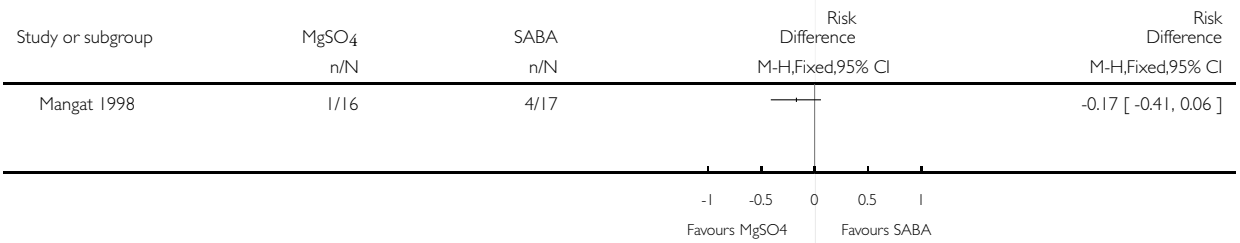


Analysis 2.6. Comparison 2 $MgSO_4$ versus SABA, Outcome 6 Mild-Moderate Side Effects.

Review: Inhaled magnesium sulfate in the treatment of acute asthma

Comparison: 2 $MgSO_4$ versus SABA

Outcome: 6 Mild-Moderate Side Effects



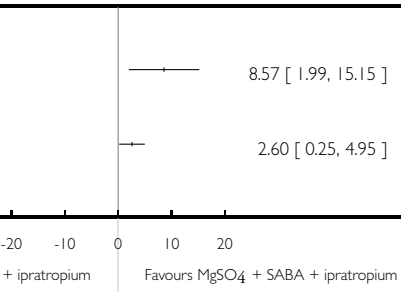
Analysis 3.1. Comparison 3 $MgSO_4$ and SABA and ipratropium versus placebo (saline) and SABA and ipratropium, Outcome 1 Pulmonary function (FEV1).

Review: Inhaled magnesium sulfate in the treatment of acute asthma

Comparison: 3 $MgSO_4$ and SABA and ipratropium versus placebo (saline) and SABA and ipratropium

Outcome: 1 Pulmonary function (FEV1)

Study or subgroup	MgSO4+SABA+ipra N	Mean(SD)	Placebo+SABA+ipra N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 90 minutes						
Gallegos-Sol rzano 2010	30	69.7 (13.3)	30	61.13 (12.7)		8.57 [1.99, 15.15]
2 120 minutes						
Gaur 2008	30	60.3 (4.8)	30	57.7 (4.5)		2.60 [0.25, 4.95]



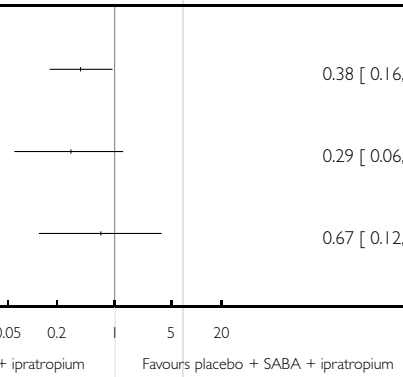
Analysis 3.2. Comparison 3 $MgSO_4$ and SABA and ipratropium versus placebo (saline) and SABA and ipratropium, Outcome 2 Admission to hospital.

Review: Inhaled magnesium sulfate in the treatment of acute asthma

Comparison: 3 $MgSO_4$ and SABA and ipratropium versus placebo (saline) and SABA and ipratropium

Outcome: 2 Admission to hospital

Study or subgroup	MgSO4+SABA+ipra n/N	Placebo+SABA+ipra n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Emergency department				
Gallegos-Sol rzano 2010	5/30	13/30		0.38 [0.16, 0.94]
2 General ward				
Gallegos-Sol rzano 2010	2/30	7/30		0.29 [0.06, 1.26]
3 Readmitted				
Gallegos-Sol rzano 2010	2/30	3/30		0.67 [0.12, 3.71]



ADDITIONAL TABLES

Table 1. Summary of Severity

Study	Severity	Based on	Adult/mixed/paediatric
Abreu-Gonzalez 2002	Moderate	FEV1 and PEF at baseline	Adults
Aggarwal 2006	Severe and life threatening	BTS definition clinical features and PEF	Mixed (13 to 60)
Ashtekar 2008	Severe	BTS definition clinical features	Paediatric (2 to 16)
Bessmertny 2002	Moderate to severe	PEF between 40%-80%	Adults (18 to 65)
Dadhich 2005	Severe	PEF < 50%	Adults
Drobina 2006	Unclear	Used PEF and clinical signs	Adults
Gallegos-Solórzano 2010	Moderate to severe	FEV1 < 60%	Adults >18
Gaur 2008	Severe	FEV1 < 30%	Adults (18 to 60)
Hughes 2003	Severe	FEV1 < 50%	Adults (16 to 65)
Khashabi 2008	Unclear	Clinically defined as respiratory distress	Paediatric (mean age 3.55 years)
Kokturk 2005	Moderate to severe	Clinical scores and PEF	Adults (18 to 60)
Mahajan 2004	Moderate to severe	FEV1 between 45% and 75%	Paediatric (5-17)
Mangat 1998	Moderate to severe	PEF < 300 L/Min	Mixed (12 to 60)
Meral 1996	Moderate to severe	PEF < 75%	Paediatric
Nannini 2000	Severe	PEF < 50%	Adult (> 18)
Neki 2006	Severe	FEV1 < 40% or PEF < 300 L/Min	Adult (15- to 60)

BTS: British Thoracic Society
FEV1: Forced expiratory volume in one second
PEF: Peak Expiratory Flow Rate

Table 2. Summary of Characteristics of the studies - where patients were recruited from, additional treatment, exclusion criteria and side effects.

Study	Presentation to which department?	Origin	Primary outcome (s)	Side effects (patients in study)	Pharmaceutical Exclusions	Other Interventions
Abreu-Gonzalez 2002	Not clear	Tenerife Spain	FEV1 and PEF	None documented (24)	None documented	None documented
Aggarwal 2006	Emergency department	New Delhi India	PEF	Palpitations ($MgSO_4$/salbutamol 13 and salbutamol/placebo 11) and tremors (7 and 7). Nothing else noted (100)	None documented	Clinicians free to administer steroids, more salbutamol if needed -iv hydrocortisone
Ashtekar 2008	Children's Assessment Unit after GP referral	Cardiff, Wales	ASS (Yung)	One tingling in fingers and one transient hypotension (17)	None documented	2 mg/kg prednisolone
Bessmertny 2002	Emergency department	Brooklyn, USA	FEV1 (% pred)	No serious adverse events noted (74)	No theophylline or anticholinergics 2 hours prior to presentation	2 mg/kg hydrocortisone 6 hourly
Dadhich 2005	Emergency department	Ajmer India	PEF	'Side effects were self limiting' (71)	Not stated	Not stated
Drobina 2006	Emergency department	USA	PEF and admissions	No comment (110)	Not stated	50 mg oral prednisolone
Gallegos-Solórzano 2010	Emergency department	Mexico City, Mexico	% change FEV1 O2 post treatment and admission rates	Dry and bitter mouth in Mg group (1) and dizziness one in each (60)	Use of steroids prior to presentation	1 mg/kg/day for 10 days prednisolone,
Gaur 2008	Emergency Department	Delhi, India	FEV1	None documented (60)	None stated	IV hydrocortisone
Hughes 2003	Emergency departments	Wellington New Zealand	FEV1	No side effects reported (52)	None	100 mg hydrocortisone (IV)

Table 2. Summary of Characteristics of the studies - where patients were recruited from, additional treatment, exclusion criteria and side effects. (*Continued*)

Khashabi 2008	Unclear	Urmia, Iran	Reduced mean duration of O2 therapy in Mg group No change in Respiratory Distress Score)	There were no side effects (40)	Not stated	Not stated
Kokturk 2005	Emergency department	Gazi, Turkey	PEF difference	Transient hypotension in Mg group (2) palpitation (1) in salbutamol only group looked for vomiting, tremor, dizziness, light headedness, DTR. No other side effect reported (26)	None mentioned	1 mg/kg prednisolone to all but additional theophylline, anticholinergics and salbutamol given at clinicians discretion (no difference in group)
Mahajan 2004	Emergency department	Detroit, USA	% change in FEV1	No side effects (nausea, vomiting, deep tendon jerks, tremors, hypotension and headache were recorded) (62)	Having received steroids, ipratropium or theophylline in the last three days	2 mg/kg prednisolone
Mangat 1998	Emergency department	St John's College, India	PEF, Fischl index score and admissions	Transient self limiting hypotension,(1) palpitation (1) tremors (2) all in control group and only one transient hypotension in Mg group (33)	Oral parenteral bronchodilators (6 hours) steroids (last 12 hours)	100 mg hydrocortisone IV
Meral 1996	Not clear	Izmir, Turkey	% change in PEF ASS (Davies Leffert, Dabbous score)	No side effects noted (BP and HR monitored) (40)	No medication taken in the previous 12 hours (beta two ago-	No other medication given

Table 2. Summary of Characteristics of the studies - where patients were recruited from, additional treatment, exclusion criteria and side effects. (*Continued*)

					nists and theophylline)	
Nannini 2000	Emergency Department	Four hospitals in Argentina	PEF and admissions	None observed (35)	Oral or parenteral steroids in the last 7 days	Note stated
Neki 2006	Not clear	Amritsar Punjab	PEF, RR and Fischl index	Not commented upon (40)	Oral, inhaled or parenteral bronchodilators in past six hours and steroids in last 12 hours	All given 100 mg hydrocortisone IV.

ASS: Asthma Severity Score
BP: blood pressure
FEV1: Forced expiratory volume in one second
HR: heart rate
IV: intravenous
MGSO4: magnesium sulfate
PEF: Peak Expiratory Flow Rate

Table 3. Summary of Interventions

Study	Magnesium sulfate dose	Co-interventions for intervention group	Control comparison	Co-intervention for control group
Abreu-Gonzalez 2002 24 patients	2 mL $MgSO_4$ (isotonic) 13 patients	400 mcg salbutamol (once*)	2 mL of a physiological serum of an inhaled form 11 patients	400 mcg salbutamol
Aggarwal 2006 100 patients	1 mL of 500 mg/mL $MgSO_4$ AS - 29 ALT - 21	1 mL salbutamol (dose?) 8 mL distilled water (295 mosml/kg) times three in an hour (ultrasonic nebuliser)	7.5 mL normal saline AS - 30 ALT - 20	1 mL salbutamol (dose*) 1.5 mL distilled water (287 mosml/kg) three times on one hour
Ashtekar 2008 17 patients	2.5 mL isotonic $MgSO_4$ (151 mg /dose) 7 patients	500 mcg Ipratropium bromide 2.5 mg salbutamol or 5 mg salbutamol (2-5 and >5 years) three times in one hour	2.5 mL of isotonic saline) 10 patients	500 mcg Ipratropium bromide 2.5 mg salbutamol or 5 mg salbutamol (2-5 and >5 years) three times in one hour

Table 3. Summary of Interventions (*Continued*)

Bessmertny 2002 74 patients	$MgSO_4$ (384 mg) 34 patients (3 withdrawn)	Followed by (i.e. not mixed) albuterol 2.5 mg/mL Three times I one hour	Normal saline (no volume documented) 34 patients (3 withdrawn)	Follwed by (i.e. not mixed) Albuterol 2.5 mg/mL three times in one hour
Dadhich 2005 71 patients	Gp A n = 24 salbutamol Gp B n = 26 salbutamol and magnesium sulfate Gp C n = 21 Magnesium sulfate alone	No doses in any group		
Drobina 2006 110 patients	150mg $MgSO_4$ (0.3 mL of 50% magnesium sulfate heptahydrate) 60 patients (from Goodacre)	Albuterol sulfate (0.5%) 5 mg/mL) and 0.5mg ipratropium bromide (0. 02% inhalation solution) Unclear how frequent	No placebo so volume will be less -i.e. blinding my be an issue) 50 patients (from Goodacre)	Albuterol sulfate (0.5%) 5mg/mL) and 0.5mg ipratropium bromide (0. 02% inhalation solution)
Gallegos-Solórzano 2010 112 patients (60 completed)	3 mL (333mg) of 10% isotonic $MgSO_4$ (1 g/10 mL) 60 randomised 30 completed	2.5 mg albuterol and 500 mcg ipratropium three doses in an hour	3 mL of isotonic saline 52 randomised 30 completed	2.5 mg albuterol and 500 mcg ipratropium three doses in an hour
Gaur 2008 60 patients	3 mL (3.2 g%) 30 patients isotonic $MgSO_4$ 30 patients	Salbutamol and ipratropium (no doses cited) No comment about frequency	Saline as placebo 30 patients	Salbutamol and ipratropium (no doses cited) No comment about frequency
Hughes 2003 52 patients	2.5 mL isotonic $MgSO_4$ (250 mmol/L 151 mg) 28 patients	2.5 mg salbutamol Patients unable to distinguish solutions) Three times every 30 minutes	2.5 mL normal saline 24 patients	2.5 mg salbutamol Three times every 30 minutes
Khashabi 2008 40 patients	Isotonic $MgSO_4$ (dose*) Unclear how many	Salbutamol (dose*) Possible 2 doses	2.5 mL normal saline Unclear how many	Salbutamol (dose?) Possibly 2 doses
Kokturk 2005 *26 patients*	Isotonic $MgSO_4$ (2.5 mL) 14 patients	Salbutamol (dose*) Three doses in an hour then hourly for the rest of the four hours	2.5 mL normal saline 12 patients	Salbutamol (dose?) Three doses in an hour then hourly for the rest of the four hours

Table 3. Summary of Interventions (*Continued*)

Mahajan 2004 62 patients	2.5 mL Isotonic (6.3%) $MgSO_4$ solution 31 patients	Albuterol 2.5mg One dose only	2.5 mL normal saline 31 patients	Albuterol 2.5 mg one dose only
Mangat 1998 33 patients	3.2% solution $MgSO_4$ = 95 mg) 16 patients	Four does every 20 minutes	3 mL (2.5mg) salbutamol 17 patients	Four doses every 20 minutes
Meral 1996 40 patients	2 mL $MgSO_4$ (280 mmol/L 258 mOsm, pH 6.7) 20 patients	one dose (?) given over 10-15 minutes	Salbutamol 2.5 mg in 2.5 mL 20 patients	one dose* given over 10-15 minutes
Nannini 2000 35 patients	3 mL isotonic $MgSO_4$ (286 mOsml, 7.5%, 225 mg) 19 patients	0.5 mL 2.5 mg salbutamol one dose (?) given only	3 mL normal saline 16 patients	0.5 mL 2.5 mg salbutamol one dose* given only
Neki 2006 40 patients	20 patients 3.2G% $MgSO_4$ 20 patients	Four dose twenty minutes apart	3 mL of 25mg * salbutamol 20 patients	Four dose 20 minutes apart
Total 896 randomised but 33 interventions and 25 controls withdrawn after randomisation so TOTAL completed studies 838	**452 + the Drobina presumed 20 = 472 minus the 33 withdrawals = 439 completed intervention studies**		**404 + the Drobina presumed 20 = 424 minus the 25 controls withdrawn = 399 completed the control studies**	

mosmol: osmole (Osm or osmol) is a non-SI unit of measurement that defines the number of moles of a chemical compound that contribute to a solution's osmotic pressure ; mOsml: milliosmole

* denotes uncertainty

Table 4. Outcomes

Study ID (author, date of publication)	Review primary outcomes		Review secondary outcomes				
	FEV1	PEF	Clinical severity scores	Hospital admissions	Duration of symptoms	Vital signs	Adverse effects

Table 4. Outcomes (*Continued*)

Abreu-Gonzalez 2002	Y	Y	N	N	N	N	N
Aggarwal 2006	N	Y	N	Y	N	Y	Y
Ashtekar 2008	N	N	Y	N	N	N	Y
Bessmertny 2002	P	N	N	N	N	N	Y
Dadhich 2005	P	P	N	N	N	N	Y
Drobina 2006	N	P	N	N	N	N	P
Gallegos-Solórzano 2010	Y	N	N	N	N	N	Y
Gaur 2008	Y	N	N	N	N	N	N
Hughes 2003	Y	N	Y	Y	N	N	Y
Khashabi 2008	N	N	N	N	N	N	N
Kokturk 2005	N	Y	P	N	N	N	Y
Mahajan 2004	Y	N	N	Y	N	N	Y
Mangat 1998	N	Y	N	Y	N	N	Y
Meral 1996	N	Y	N	N	N	N	Y
Nannini 2000	N	Y	N	Y	N	N	Y
Neki 2006	N	Y	N	N	N	Y	N

N - the study did not report the outcome but it is not clear whether the outcome was measured or not
Y - full reporting
P - partial reporting

APPENDICES

Appendix 1. Sources and search methods for the Cochrane Airways Group Specialised Register (CAGR)

Electronic searches: core databases

Database	Frequency of search
MEDLINE (Ovid)	Weekly
EMBASE (Ovid)	Weekly
CENTRAL (*The Cochrane Library*)	Monthly
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 Respirology (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. Clinicaltrials.gov search

Search terms: magnesium and asthma
Study type: Interventional Studies

Appendix 3. Search methods for previous version of review (2005)

Electronic searches

The Cochrane Airways Groups "Asthma and Wheez* RCT" register was searched for the following terms: magnesium OR MgSO4 OR Mg OR MS OR magnesium sulfate or magnesium sulphate. The results of this search were screened to omit studies that clearly involved only intravenous or parenteral administration of magnesium.
In addition, searches were also conducted on the following computerized bibliographic databases: MEDLINE (1966-2005), EMBASE (1988 to 2005), LILACS, Cochrane Clinical Trials Registry, Web of Science and Dissertation Abstracts.

WHAT'S NEW

Last assessed as up-to-date: 28 September 2012.

Date	Event	Description
28 September 2012	New search has been performed	New literature search run.
28 September 2012	New citation required and conclusions have changed	Ten new trials with 600 participants added to the 296 in the previous version of the review. We added a new comparison of inhaled magnesium sulfate in addition to inhaled β_2 -agonist and ipratropium bromide. The evidence remains inconclusive, but whilst there is no good evidence that inhaled magnesium sulfate can be used as a substitute for inhaled beta$_2$-agonists, there is a suggestion of benefit in pulmonary function when used in addition to inhaled beta$_2$-agonists (with or without ipratropium) in severe asthma exacerbations

HISTORY

Protocol first published: Issue 1, 2004

Review first published: Issue 2, 2005

Date	Event	Description
28 July 2008	Amended	Converted to new review format.
22 August 2005	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

KD:Study identification, data abstraction; data analysis.

SM:Study identification, data abstraction; manuscript editing.

CP: Study identification, data abstraction; manuscript editing.

MB: Protocol preparation, data abstraction, manuscript editing.

SB: Data analysis, manuscript preparation.

RD: Manuscript editing.

BD: Data abstraction, manuscript editing.

RH: Manuscript editing.

JK: Data abstraction.

BHR: Protocol preparation, study screening, manuscript preparation and editing.

In the 2012 revision of this review KD and SM updated the 'Risk of bias' tables for trials already included in the review and similarly for any new trials identified in the update.

DECLARATIONS OF INTEREST

Drs. Hughes and Beasley were involved as Primary and Co-investigator on one of the trials included in this review (Hughes 2003). Dr Powell was a co-author of the pilot work completed in Ashtekar 2008 and is the chief investigator of the MAGNETIC study in children (http://www.controlled-trials.com/ISRCTN81456894). None of the other review authors has any known conflict of interest.

SOURCES OF SUPPORT

Internal sources

- Department of Emergency Medicine, University of Alberta, Edmonton, AB, Canada.
- National Institute of Health Research (SJM), UK.

External sources

- Alberta Cancer Board, Canada.
- Canadian Institutes of Health Research (CIHR), Ottawa (BHR), Canada.
- Canadian Institutes of Health Research (CIHR), Ottawa, ON (BH Rowe)„ Canada.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The 'Risk of bias' tool has been updated to that advised in Chapter 8 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). Three new review authors have been added and the sensitivity analyses have been amended to investigating risk of bias rather than methodological quality.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Administration, Inhalation; Adrenergic beta-Agonists [*administration & dosage]; Anti-Asthmatic Agents [*administration & dosage]; Asthma [*drug therapy]; Hospitalization; Magnesium Sulfate [*administration & dosage]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Child; Humans