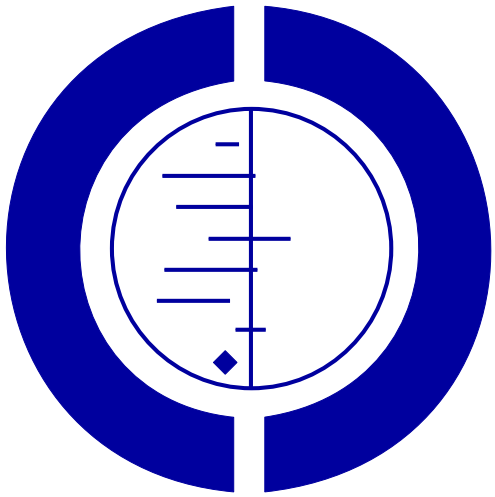
Inhaled magnesium sulfate in the treatment of acute asthma (Review)

Blitz M, Blitz S, Beasely R, Diner BM, Hughes R, Knopp JA, Rowe BH



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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 about inhaled $MgSO_4$.

Objectives
To examine the efficacy of inhaled $MgSO_4$ in the treatment asthma exacerbations.

Search strategy
Randomised controlled trials were identified from the Cochrane Airways Group "Asthma and Wheez*" register. 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 gray literature and conference proceedings.

Selection criteria
Randomised (or pseudo-randomised) controlled trials were eligible for inclusion. Studies were included if patients were treated with nebulised $MgSO_4$ alone or in combination with β_2-agonist and where compared to β_2-agonist alone or inactive control.

Data collection and analysis
Trial selection, data extraction and methodological quality were assessed by two independent reviewers. Efforts were made to collect missing data from authors. Results from fixed effects models are presented as standardized mean differences (SMD) for pulmonary functions and relative risks (RR) for hospital admission; both are displayed with their 95% confidence intervals (95% CI).

Main results
Six trials involving 296 patients were included. Four studies compared nebulised $MgSO_4$ with β_2-agonist to β_2-agonist and two studies compared $MgSO_4$ to β_2-agonist alone. Three studies enrolled only adults and 2 enrolled exclusively pediatric patients; three of the studies enrolled severe asthmatics. Overall, there was a non significant improvement in pulmonary function between patients whose treatments included nebulised $MgSO_4$ in addition to β_2-agonist (SMD: 0.23; 95% CI: -0.03 to 0.50; 4 studies). Hospitalizations were similar between the groups (RR: 0.69; 95% CI: 0.42 to 1.12; 3 studies). Subgroup analyses did not demonstrate significant differences in lung function improvement between adults and children, but in severe asthmatics the lung function difference was significant (SMD: 0.55; 95% CI: 0.12 to 0.98). Conclusions regarding treatment with nebulised $MgSO_4$ alone are difficult to draw due to lack of studies in this area.

Authors' conclusions
Nebulised inhaled magnesium sulfate in addition to β_2-agonist in the treatment of an acute asthma exacerbation, appears to have benefits with respect to improved pulmonary function in patients with severe asthma and there is a trend towards benefit in hospital admission. Heterogeneity between trials included in this review precludes a more definitive conclusion.

PLAIN LANGUAGE SUMMARY

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, oxygen, etc). Intravenous magnesium sulfate has demonstrated efficacy in acute severe asthma and this review identified evidence to demonstrate that using inhaled magnesium sulfate combined with a beta-2-agonist (β_2-agonist) for an acute asthma exacerbation provides beneficial effects with respect to improved pulmonary function. The evidence, however, that nebulised magnesium sulfate positively impacts the clinically more important outcomes, such as hospital admissions, are lacking.

BACKGROUND

Asthma is a chronic respiratory disease that is characterized by periods of relative control and episodes of deterioration referred to as exacerbations. Exacerbations range in severity from mild to status asthmaticus and can result in visits to health care 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 health care system, and the mortality, asthma is responsible for significant personal and social burden.

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. Unfortunately, in acute asthmatic episodes, this is often not enough to relieve the bronchospasm and reduce dyspnoea. The shortcomings of β_2-agonist therapy have resulted in the use of a variety of other treatments in the management of acute asthma. For example, evidence suggests systemic corticosteroids (Rowe 1992), anticholinergics (McDonald 2004; Spooner 2004), delivery of β_2-agonist via metered-dose inhalers with holding chambers or nebulisers (Cates 2004), and inhaled corticosteroids (Edmonds 2004) are effective in the acute treatment of the disease. Other treatments such as intravenous aminophylline (Parameswaran 2004; Littenberg 1988), antibiotics (Graham 2004), and intravenous beta-agonists (Travers 2004) have been found to be ineffective and possibly harmful, so are no longer recommended.

Magnesium sulfate ($MgSO_4$) is an agent that has been proposed as a possible additive treatment in acute asthma, and recently 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, 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 adult asthmatics (Cairns 1996).

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. Until now, there has been no attempt made to examine this effect in a systematic fashion. This systematic review is designed to examine this question and provide a summary estimate of the effect (or lack thereof) of aerosolized $MgSO_4$ in the treatment of acute asthma.

OBJECTIVES

The objective of this review is to determine the efficacy of inhaled $MgSO_4$ administered in acute asthma on pulmonary functions and admissions.

Specific aims
To quantify the effects of inhaled $MgSO_4$ alone or in combination with inhaled β_2-agonist compared to inhaled β_2-agonist alone or placebo. Specific outcomes include:
(1) pulmonary function (forced expiratory volume in one second {FEV-1}, peak expiratory flow rate {PEFR} and their respect % predicted {% FEV-1, % PEFR});
(2) admission to hospital;
(3) vital signs (pulse and respiratory rates; systolic and diastolic blood pressure);
(4) side effects (tremor, nausea, etc).

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Randomised (or quasi-randomised) controlled trials were considered for inclusion.

Types of participants

Only studies restricting enrolment to patients with acute asthma were considered; patients with chronic or "stable" asthma were excluded from the review. Studies involving all ages were considered for inclusion; where possible, the data were categorized into 2-16 years old (pediatric) and > 16 years old (adult). Asthma was defined using several accepted clinical and guideline-based criteria.

Types of intervention

Studies were considered for inclusion if participants were randomised to receive inhaled $MgSO_4$ and compared to a control treatment. That is, studies comparing the efficacy of aerosolized $MgSO_4$ and β_2-agonist versus β_2-agonist alone or inhaled $MgSO_4$ versus β_2-agonist were included. Co-interventions were permitted, and information pertaining to co-interventions received was recorded. Whenever these data were not available, a request was sent to the study authors.

Types of outcome measures

Primary outcome was defined as the change in pulmonary function testing from baseline. Secondary outcomes considered were clinical severity scores, proportion of patients requiring admission, duration of symptoms, vital signs and side effects.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Airways Group methods used in reviews.

See: Collaborative Airways Group search strategy. 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-present), EMBASE (1988 to present), LILACS, Cochrane Clinical Trials Registry, Web of Science and Dissertation Abstracts. The reference lists of all selected articles, primary studies and review articles were examined for relevant studies. Primary authors were contacted for information on additional trials (published and unpublished). Clinicians, colleagues, collaborators and trialists were contacted to identify potentially relevant studies. Since this agent is not currently commercially delivered, no industry sponsor was contacted.

METHODS OF THE REVIEW

STUDY SELECTION
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 (MB, BD) to identify all citations that are RCT's or possible RCT's with potential relevance. The full text of those selected articles was obtained for formal inclusion review. Second, another reviewer (BHR) independently decided on trial inclusion using pre-determined eligibility criteria.

ASSESSMENT OF QUALITY
Assessments of quality were completed independently by two reviewers. First, using the Cochrane approach to assessment of allocation concealment (Schulz 1995), all trials were scored using the following scale:
Grade A: Adequate concealment
Grade B: Uncertain
Grade C: Clearly inadequate concealment

Each study was also evaluated using the previously validated Jadad 5-point scale to assess randomisation, double blinding, and withdrawals and dropouts (Jadad 1996) according to the following criteria:
1) Was the study described as randomised (1=yes; 0=no)?;
2) Was the study described as double-blind (1=yes; 0=no)?;
3) Was there a description of withdrawals and dropouts (1=yes; 0=no)?;
4) Was the method of randomizations well described and appropriate (1=yes; 0=no)?;
5) Was the method of double blinding well described and appropriate (1=yes; 0=no)?;
6) Deduct 1 point if methods for randomizations OR blinding were inappropriate.

In addition, whether the study used intention-to-treat analysis was recorded along with source(s) of funding.

DATA EXTRACTION
Data were extracted independently by two reviewers (MB, BD) using a standardized 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, timing of outcomes, adverse events); and results. Unpublished data were requested from the primary authors when necessary.

DATA ANALYSIS

All data was entered into RevMan (Cochrane Collaboration, Version 4.2.7) by a single reviewer (SB). MetaView was used to combine trial data.

For dichotomous variables, both individual and pooled statistics are expressed as relative risk (RR) with 95% confidence intervals (CI). For continuous data, individual data was reported as standardized mean differences (SMD) with 95% CIs. Results were calculated using both fixed and random effects models.

We tested for heterogeneity with significance set at <0.10 using the Breslow-Day test. Possible sources of heterogeneity were assessed by subgroup and sensitivity analyses.
A priori subgroup analyses were planned to examine the effect of:
(1) age (pediatric, adult);
(2) severity of asthma as measured by pre-administration spirometric deviation from predicted (baseline FEV1 or PEF <50% predicted).

Sensitivity analyses were planned to assess the effect of:
(1) methodological quality of included trials; and
(2) intention-to-treat status.

We also planned to test for publication bias using the funnel plot visually and quantitatively (i.e. the rank correlation test and / or the graphical test with or without heterogeneity) depending on the number of trials included in the review.

DESCRIPTION OF STUDIES

General
Six trials, which included 296 patients, 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, and Argentina all being represented. There was no previous review that focused on this issue. The few times that inhaled magnesium has been mentioned, it has been as (a minor) part of larger reviews (Harari 1998).

Populations
Three of the six included studies involved adults exclusively (Bessmertny 2002; Hughes 2003; Nannini Jr 2000) and one included adults and pediatric patients (Mangat 1998). The remaining 2 studies enrolled pediatric patients (Mahajan 2004; Meral 1996). Subgroup analyses on the pediatric and adult populations were completed.

The severity of disease varied between studies. Two studies (Hughes 2003, Mangat 1998) had specific lung function criteria, while the other 4 studies enrolled patients previously diagnosed with asthma using accepted clinical standards. Based on the baseline demographic data, three studies (Hughes 2003; Mangat 1998; Nannini Jr 2000) were considered to enrol severe asthmatics (FEV-1 or PEF < 50% predicted at baseline). Subgroup analyses on the severe and moderate asthmatic populations were completed.

Five studies enrolled patients presenting to the emergency department. Only one study (Meral 1996) stated that patients were randomised during "asthma attacks". Two studies (Mangat 1998; Meral 1996) excluded patients who had taken asthma medication within the last 12 hours. A third (Nannini Jr 2000) excluded patients who had received oral or parenteral corticosteroids in the last seven days. The most recent study (Mahajan 2004) excluded patients who had received steroids, theophylline or ipratropium bromide within 3 days of presenting to the ED.

Interventions
All studies used nebulised β_2-agonist (with or without normal saline) as the control treatment; however, the total dose varied depending on the number of nebulizations. When the information was available, most included studies used $MgSO_4$ of similar concentration but dose per nebulization and the number of nebulizations varied. All but two studies (Mangat 1998; Meral 1996) described the $MgSO_4$ solution as either isotonic or isosmolar with pleural fluid. The magnesium was uniformly delivered via a nebuliser rather than metered dose inhaler. All studies used a control that was similar in appearance to the treatment drug and is most often described as 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).

Four studies (Bessmertny 2002; Hughes 2003; Mahajan 2004; Nannini Jr 2000) compared β_2-agonist with $MgSO_4$ to β_2-agonist with placebo (normal saline), while two studies (Mangat 1998; Meral 1996) compared $MgSO_4$ to β_2-agonist. The results of this review are reported for pulmonary functions, hospital admissions and side effects based on the two intervention types (β_2-agonist with $MgSO_4$ or $MgSO_4$ alone vs β_2-agonist alone).

Co-interventions
Co-interventions used added complexity and heterogeneity to the studies. In three studies (Hughes 2003; Mangat 1998; 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 3 doses of study treatment (Bessmertny 2002).

Outcomes
All studies report results from pulmonary function tests as an outcome; however, one study (Meral 1996) reported lung function outcome data as a relative change from baseline. As it was not appropriate to combine these data with the other studies (which are not reporting lung function results as a change from baseline), data

from this study are not currently included in the pooled analysis. Attempts to secure the end-of study data have failed so far.

Four studies (Hughes 2003; Mangat 1998; Mahajan 2004; Nannini Jr 2000) also report admission to hospital as an outcome. All studies mentioned serious adverse events; however, the details regarding mild to moderate adverse events were sparse.

None of the studies reported a specific clinical severity score or duration of symptoms. Most studies reported vital signs at baseline but not at follow-up. These outcomes were not investigated in the systematic review.

Pending Assessments

The status of one study (Wijetunge 2002) referenced in a clinical trials register reportedly compared nebulized $MgSO_4$ with placebo in addition to conventional bronchodilator treatment is unknown. The primary authors for this study and the included study (Meral 1996) for which the lung function data is not included in the pooled analysis have been contacted to determine if pertinent data from their studies are available and suitable for inclusion in this review. These studies will be included in updates of this review should information become available.

METHODOLOGICAL QUALITY

Overall, the methodological quality of the included studies was uniformly high. All studies were randomised and placebo controlled. Only one investigator did not explicitly state that the study was double blinded. All included studies used intention-to-treat analyses, therefore the planned sensitivity analysis to determine the effect of intention-to-treat status was not required. All but one study (Meral 1996) scored 3 on the Jadad scale as none of the investigators explicitly mentioned their methods for randomisation or double-blinding. Due to lack of information provided, all studies rated a B in concealment of allocation.

Due to the small number of studies included and the relative size of each the planned tests for publication bias were not carried out.

RESULTS

Computerized Search

The initial search yielded 145 references that were at least potentially relevant controlled trials. 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 reviewers for data extraction.

This review is considered to be up to date as of January 2004.

Pulmonary Function Tests

Most studies did not report change in pulmonary function and pooled results from all studies failed to identify a difference in baseline pulmonary function between the treatment and control groups. There was variation in the specific pulmonary function measure reported (% predicted PEF or FEV-1 and raw PEF or FEV-1) as well as the time after treatment when pulmonary functions were recorded; two studies reported pulmonary function measures only up to 20 minutes after treatment. For these reasons the results are reported using fixed effects, standardized mean difference in pulmonary function measured at or before 60 minutes after treatment. Based on the studies that measured pulmonary functions for 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.

$MgSO_4$ with β_2-agonist compared to β_2-agonist alone:

Pulmonary functions were improved when $MgSO_4$ with β_2-agonist was compared to β_2-agonist alone (SMD: 0.23; 95% CI:-0.03 to 0.50), but there was considerable between study heterogeneity identified (I^2 = 53%; Figure 01.01). When a random effects model was used to pool these studies the confidence interval is considerably wider (SMD 0.27, 95% CI -0.12 to 0.66). In subgroup analyses, there was no significant difference between the results from adults and those in children. In subgroup analysis, there was a significant difference in the results from the severe asthma trials (SMD 0.55, 95% 0.12 to 0.98). When compared to the the mild-moderate group this difference was not significant (SMD between groups -0.51, 95% CI -1.06 to 0.04).

$MgSO_4$ compared to β_2-agonist alone:

There was no evidence of an significant advantage for $MgSO_4$ alone compared to β_2-agonist alone with respect to pulmonary functions (SMD: 0.17; 95% CI: -0.51 to 0.86); Meral (Meral 1996) demonstrated a significant advantage for β_2-agonist alone compared to $MgSO_4$ alone. With a single trial contributing data, not additional analyses were possible.

Admission to Hospital

$MgSO_4$ with β_2-agonist compared to β_2-agonist alone:

One study (Bessmertny 2002) did not report admissions to hospital and correspondence attempts with this author did not yield additional data. In the remaining studies, nebulised $MgSO_4$in combination with an β_2-agonist failed to demonstrate a clear reduction in the probability of admission compared to β_2-agonist alone (RR: 0.69; 95% CI: 0.42 to 1.12) using a fixed-effects model (Figure 01.04), despite a promising trend. The non-significant advantage holds for $MgSO_4$ compared to β_2-agonist for adults and severe asthma (RR: 0.62; 95% CI: 0.38 to 1.02); however, not for children or those with less severe asthma (RR: 2.00; 95% CI: 0.19 to 20.93). There was, however, no significant difference when formal sub-group testing was carried out between adults and children, or between severe and less severe asthma, and the confidence inter-

vals were wide. Results were similar when random effects methods were employed.

$MgSO_4$ compared to β_2-agonist alone:
There was no significant difference between $MgSO_4$ compared to β_2-agonists alone with respect to hospitalisations (RR: 0.50; 95% CI: 0.04 to 6.12); however, the wide confidence intervals suggest that equivalence cannot be claimed. With a single trial contributing data, not additional analyses were possible.

Adverse Events
All studies report that there were no serious adverse events in either arm. The risk of serious adverse events was low in both the studies comparing $MgSO_4$ to β_2-agonists (RD: 0.00; 95% CI: -0.11 to 0.11) or those comparing $MgSO_4$ with β_2-agonist to β_2-agonist alone (RD: 0.00; 95% CI: -0.03 to 0.03). The risk of less severe adverse events was low; however, it appears to be less likely in patients treated with $MgSO_4$, alone (RD: -0.17; 95% CI: -0.41 to 0.06) or in combination with β_2 agonists (RD: -0.09; 95% CI: -0.24 to 0.06), although the differences did not reach statistical significance.

DISCUSSION

This systematic review attempted to synthesize the best available evidence for the use of inhaled $MgSO_4$ in the treatment of acute asthma. From 6 randomised controlled trials involving nearly 300 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-severe 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 to more familiar, inexpensive β_2-agonists in improving pulmonary function and reducing admissions. The evidence for $MgSO_4$ administered *in combination* with β_2-agonists is more convincing. For example, there appears to be a clear additive benefit with respect to pulmonary functions, particularly in patients presenting to the ED with severe asthma, when $MgSO_4$ is administered in combination with β_2-agonists. In addition, while there is no clear evidence that $MgSO_4$ administered in combination with β_2-agonists reduces hospitalisations, the trend demonstrated (Figure 01.04) suggests further research is urgently needed to answer this question.

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 standardized approaches to acute asthma, such as systemic corticosteroids (Rowe 1992), anticholinergics (McDonald 2004; Spooner 2004), intravenous $MgSO_4$ (Rowe 2004), and repeated β_2-agonists (Cates 2004), the control groups in the included studies were surprisingly heterogeneous. A trial 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 is needed. 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 ED treatment period.

There are several possible limitations to the study. First, there is a possibility of study selection bias. However, we employed two independent reviewers, and feel confident that the studies excluded were done so for consistent and appropriate reasons. Our search was comprehensive and has been updated, so it is unlikely that there are any published trials, which were missed.

In addition, 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 magnesium treatment. However, in order to reduce bias, a comprehensive and systematic search of the published and unpublished literature for potentially relevant studies was conducted. This was followed by attempts to contact corresponding and first authors. One unpublished trial was identified and several negative trials were uncovered; however, we recognize 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.

AUTHORS' CONCLUSIONS

Implications for practice

(1) Nebulised $MgSO_4$ appears to be effective and safe to administer to patients experiencing asthma exacerbations.
(2) Treatment with nebulised $MgSO_4$ should be considered *in addition to* inhaled β_2-agonists in asthma exacerbations, particularly in those patients with more severe exacerbations.

Implications for research

(1) The role of nebulised $MgSO_4$ in asthma exacerbations has not been conclusively resolved by this review particularly with respect to $MgSO_4$ alone versus $MgSO_4$ with β_2-agonists. Further research should be encouraged.
(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.
(3) There is a strong argument for asthma researchers to develop a consensus regarding the reporting of pulmonary function results.

POTENTIAL CONFLICT OF INTEREST

Drs. Hughes and Beasley were involved as Primary and Co-investigator on one of the trials included in this review (Hughes 2003). None of the other reviewers has any known conflict of interest.

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* *Indicates the major publication for the study*

TABLES

Characteristics of included studies

Study	Bessmertny 2002
Methods	Design: 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, PEFR between 40 and 80% predicted Exclusions: smoking history >10 pack years, known hypersensitivity to albuterol or MgSO4, known chronic obstructive pulmonary disease, known history of renal impairment, known history of cardiac dysrhythmias, congestive heart failure or angina, fever more than 38C, 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 MgSO4 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	Jadad: 3/5
Allocation concealment	B

Study	Hughes 2003
Methods	Design: 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<100mmHg), required intubation
Interventions	Standard of care: salbutamol 2.5 mg nebulized x 1 or more, hydrocortisone 100 mg IV at presentation Treatment: salbutamol 2.5 mg nebule with 2.5 ml isotonic MgSO4 (250 mmol/L) q 30 min x 3. Control: salbutamol 2.5 mg nebule with 2.5 ml normal saline. q 30 min x3 Subjects 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	Jadad: 3/5
Allocation concealment	B

Characteristics of included studies (*Continued*)

Study	**Mahajan 2004**
Methods	Design: 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 pediatric emergency department in Detroit, Michigan Participants: 62 patients age 5-17, presenting to the emergency department with acute asthma exacerbation, FEV1 between 45 and 75% predicted Exclusions: Fever (>39C), 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 MgSO4 (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	Jadad: 3/5
Allocation concealment	B

Study	**Mangat 1998**
Methods	Design: 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, 12-60 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: MgSO4 3 ml (3.2% solution = 95 mg) nebulized q 20 min x 4. Control: salbutamol 3 ml (2.5 mg) nebulized 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 palpitations, 2 cases fine tremors in hand
Notes	Jadad: 3/5
Allocation concealment	B

Study	**Meral 1996**
Methods	Design: Randomised controlled trial

Characteristics of included studies (*Continued*)

	Method of Randomisation: unknown Concealment of allocation: unknown Blinding: unknown Withdrawals / dropouts: 0
Participants	Location: Department of pediatric 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; PEFR decreased by >/= 25%. Exclusions: Medication within 12 hours of study, cardiac / renal dysfunction.
Interventions	Treatment: MgSO4 2 ml (280 mmol/L, 258 mOsm, pH 6.7) Control: Salbutamol 2.5 mg in 2.5 ml Administration: nebulized, inhaled over 10-15 minutes.
Outcomes	Evaluations at: 5, 15, 30, 60, 180,240 and 360 minutes. Clinical score: Davis-Leffert-Dabbous respiratory distress score pulmonary function: PEFR Adverse reactions / side effects: none observed
Notes	Jadad: 1/5
Allocation concealment	B

Study	**Nannini Jr 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 / drop-outs: 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 nebulized at discretion of physician. Treatment: 0.5 ml salbutamol (2.5 mg) diluted in 3 ml isotonic MgSO4 (286 mOsm, 7.5% = 225 mg). Control: 0.5 ml salbutamol (2.5 mg) diluted in 3 mL normal saline. Administration: jet nebulized 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, blood pressure Duration of emergency room care No adverse events reported in either the experimental or control group
Notes	Jadad: 3/5
Allocation concealment	B

Characteristics of included studies (*Continued*)

Characteristics of excluded studies

Balter 1989	Review
Bernstein 1995	Study does not assess patients with acute asthma
Cairns 1996	Study does not assess patients with acute asthma
Castillo Rueda 1991	Letter to the Editor
Chande 1992	Did not assess outcomes of interest
Corbridge 1995	Review
Emelyanov 1997	Did not assess outcomes of interest
Emelyanov 1990	Did not assess outcomes of interest
Emelyanov 1996	Did not assess outcomes of interest
Fedoseev 1991	Did not assess outcomes of interest
Harari 1998	Review
Hardin 2001	Review
Hill 1995	Study does not assess patients with acute asthma
Hill 1997	Study does not assess patients with acute asthma
Kenyon 2001	Review
Kreutzer 2001	Review
Manzke 1990	Did not assess outcomes of interest
McFadden 1995	Review
Nannini Jr 1997	Study does not assess patients with acute asthma
Pelton 1998	Study does not assess patients with acute asthma
Pelton 1999	Review
Puente-Maestu 1999	Review
Qureshi 1999	Review
Rodrigo 2000	Systematic Review, includes IV MgSO4
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
Scarfone 2000	IV MgSO4
Sinitsina 1991	Did not assess outcomes of interest
Skobeloff 1982	Editorial
Teeter 1999	Review
Tetikkurt 1992	Study does not assess patients with acute asthma
Tetikkurt 1993	Study does not assess patients with acute asthma

Characteristics of ongoing studies

Study	**Wijetunge 2002**
Trial name or title	A trial of nebulised magnesium sulphate versus placebo in addition to conventional bronchodilator treatment in acute asthma of moderate severity

Characteristics of ongoing studies (*Continued*)

Participants	Unknown
Interventions	Unknown
Outcomes	Unknown
Starting date	2002
Contact information	DB Wijetunge St George's Hospital London, UK
Notes	Letter mailed 29JAN2004. Email and faxed attempts were unsuccessful. Reference Source: National Research Register (UK)

ANALYSES

Comparison 01. MgSO4 + B2-agonists vs B2-agonists alone

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Pulmonary Function testing	4	223	Standardised Mean Difference (Fixed) 95% CI	0.23 [-0.03, 0.50]
02 Sub-group: Adult/Pediatric (PFTs)	4	223	Standardised Mean Difference (Fixed) 95% CI	0.23 [-0.03, 0.50]
03 Sub-group: Severity (PFTs)	4	223	Standardised Mean Difference (Fixed) 95% CI	0.23 [-0.03, 0.50]
04 Admission to Hospital	3	149	Relative Risk (Fixed) 95% CI	0.69 [0.42, 1.12]
05 Sub-Group: Adult/Peds (admission)	3	149	Relative Risk (Fixed) 95% CI	0.69 [0.42, 1.12]
06 Sub-group: Severity (Admission)	3	149	Relative Risk (Fixed) 95% CI	0.69 [0.42, 1.12]
07 Serious Adverse Events	4	223	Risk Difference (Fixed) 95% CI	0.00 [-0.03, 0.03]
08 Mild-Moderate Adverse Events	2	109	Risk Difference (Fixed) 95% CI	-0.09 [-0.24, 0.06]

Comparison 02. MgSO4 vs B2-agonist

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Pulmonary Function tests			Standardised Mean Difference (Fixed) 95% CI	Totals not selected
02 Admision to hospital			Odds Ratio (Fixed) 95% CI	Totals not selected
03 Serious Side Effects			Risk Difference (Fixed) 95% CI	Totals not selected
04 Mild-Moderate Side Effects			Risk Difference (Fixed) 95% CI	Totals not selected

INDEX TERMS

Medical Subject Headings (MeSH)

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

MeSH check words

Humans

COVER SHEET

Title Inhaled magnesium sulfate in the treatment of acute asthma

Authors	Blitz M, Blitz S, Beasely R, Diner BM, Hughes R, Knopp JA, Rowe BH
Contribution of author(s)	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.
Issue protocol first published	2004/1
Review first published	2005/2
Date of most recent amendment	25 August 2005
Date of most recent SUBSTANTIVE amendment	22 August 2005
What's New	22 May 2005: Two errors in the first version of this review have been identified following a helpful comment from Dr G Rodrigo. These have now been corrected and as a result there is now a significant difference between subgroups of trials with severe, as opposed to mild, asthma exacerbations. Also the confidence interval of the pooled pulmonary function outcome is wider when a random effects model is employed. 15 Aug 2005: Further comments for Dr G Rodrigo prompted the reviewers to contact the authors to obtain the original data from the Huges 2003 study to obtain verified values for the mean and SD of FEV-1 at 60 min. This version of the review incorporates values provided by Dr R Beasley. The severe subgroup still shows a significant difference in pooled lung function when inhaled magnesium is added to beta2-agonists.
Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	Information not supplied by author
Date authors' conclusions section amended	Information not supplied by author
Contact address	Dr Maurice Blitz Resident, Alberta Cancer Board Cinical Research Fellow Division of General Surgery University of Alberta W.C. Mackenzie Centre 8440-112 Street Edmonton Alberta T6G 2B7 CANADA E-mail: moblitz@shaw.ca Tel: 001 780 407 8822
DOI	10.1002/14651858.CD003898.pub4
Cochrane Library number	CD003898
Editorial group	Cochrane Airways Group

Editorial group code HM-AIRWAYS

GRAPHS AND OTHER TABLES

Analysis 01.01. Comparison 01 MgSO4 + B2-agonists vs B2-agonists alone, Outcome 01 Pulmonary Function testing

Review: Inhaled magnesium sulfate in the treatment of acute asthma

Comparison: 01 MgSO4 + B2-agonists vs B2-agonists alone

Outcome: 01 Pulmonary Function testing

Study	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Standardised Mean Difference (Fixed) 95% CI	Weight (%)	Standardised Mean Difference (Fixed) 95% CI
Bessmertny 2002	37	63.00 (21.90)	37	68.00 (21.90)		33.8	-0.23 [-0.68, 0.23]
Hughes 2003	28	1.86 (0.67)	24	1.44 (0.65)		22.6	0.63 [0.07, 1.19]
Mahajan 2004	31	75.40 (26.00)	31	67.30 (18.00)		28.0	0.36 [-0.14, 0.86]
Nannini Jr 2000	19	332.00 (119.00)	16	282.00 (107.00)		15.6	0.43 [-0.24, 1.10]
Total (95% CI)	115		108			100.0	0.23 [-0.03, 0.50]

Test for heterogeneity chi-square=6.33 df=3 p=0.10 I?? =52.6%

Test for overall effect z=1.71 p=0.09

Analysis 01.02. Comparison 01 MgSO4 + B2-agonists vs B2-agonists alone, Outcome 02 Sub-group: Adult/ Pediatric (PFTs)

Review: Inhaled magnesium sulfate in the treatment of acute asthma

Comparison: 01 MgSO4 + B2-agonists vs B2-agonists alone

Outcome: 02 Sub-group: Adult/Pediatric (PFTs)

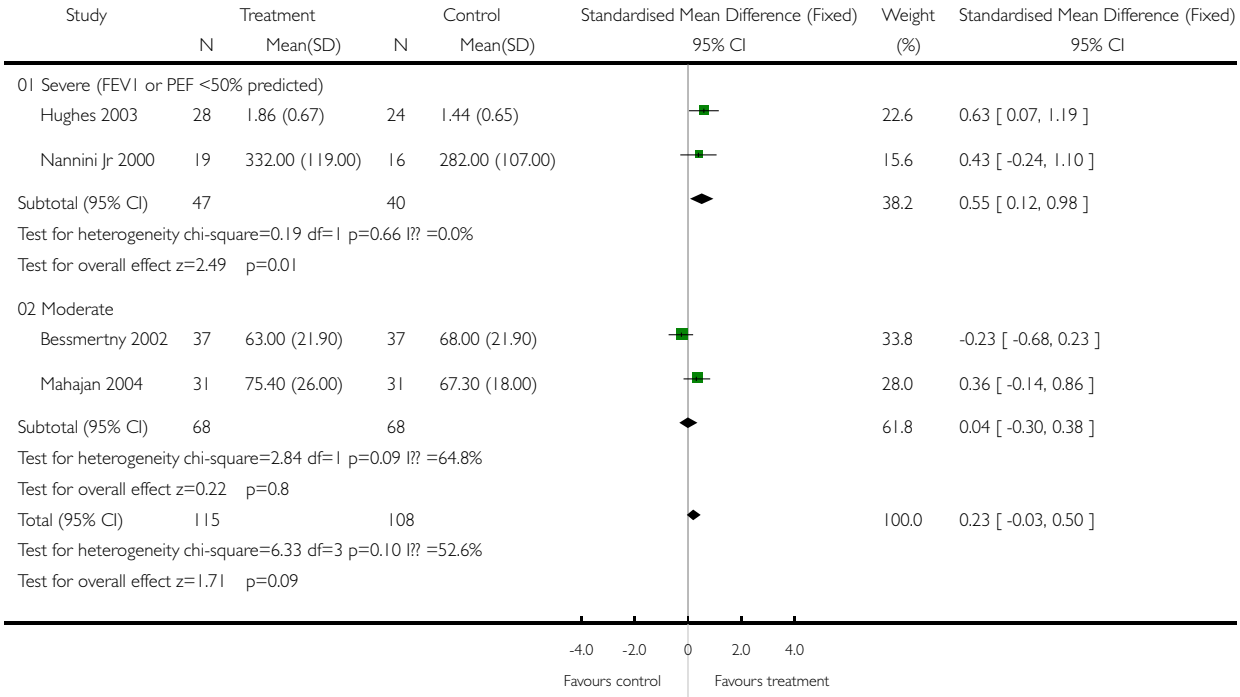
Study	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Standardised Mean Difference (Fixed) 95% CI	Weight (%)	Standardised Mean Difference (Fixed) 95% CI
01 Adult							
Bessmertny 2002	37	63.00 (21.90)	37	68.00 (21.90)		33.8	-0.23 [-0.68, 0.23]
Hughes 2003	28	1.86 (0.67)	24	1.44 (0.65)		22.6	0.63 [0.07, 1.19]
Nannini Jr 2000	19	332.00 (119.00)	16	282.00 (107.00)		15.6	0.43 [-0.24, 1.10]
Subtotal (95% CI)	84		77			72.0	0.18 [-0.13, 0.50]
Test for heterogeneity chi-square=6.00 df=2 p=0.05 I?? =66.6%							
Test for overall effect z=1.15 p=0.3							
02 Pediatric							
Mahajan 2004	31	75.40 (26.00)	31	67.30 (18.00)		28.0	0.36 [-0.14, 0.86]
Subtotal (95% CI)	31		31			28.0	0.36 [-0.14, 0.86]
Test for heterogeneity: not applicable							
Test for overall effect z=1.40 p=0.2							
Total (95% CI)	115		108			100.0	0.23 [-0.03, 0.50]
Test for heterogeneity chi-square=6.33 df=3 p=0.10 I?? =52.6%							
Test for overall effect z=1.71 p=0.09							

Analysis 01.03. Comparison 01 MgSO4 + B2-agonists vs B2-agonists alone, Outcome 03 Sub-group: Severity (PFTs)

Review: Inhaled magnesium sulfate in the treatment of acute asthma

Comparison: 01 MgSO4 + B2-agonists vs B2-agonists alone

Outcome: 03 Sub-group: Severity (PFTs)

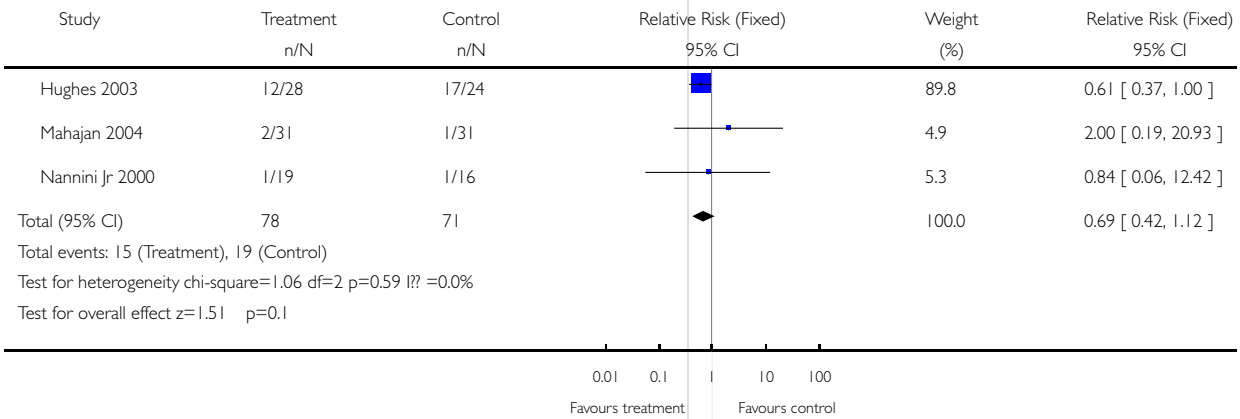


Analysis 01.04. Comparison 01 MgSO4 + B2-agonists vs B2-agonists alone, Outcome 04 Admission to Hospital

Review: Inhaled magnesium sulfate in the treatment of acute asthma

Comparison: 01 MgSO4 + B2-agonists vs B2-agonists alone

Outcome: 04 Admission to Hospital

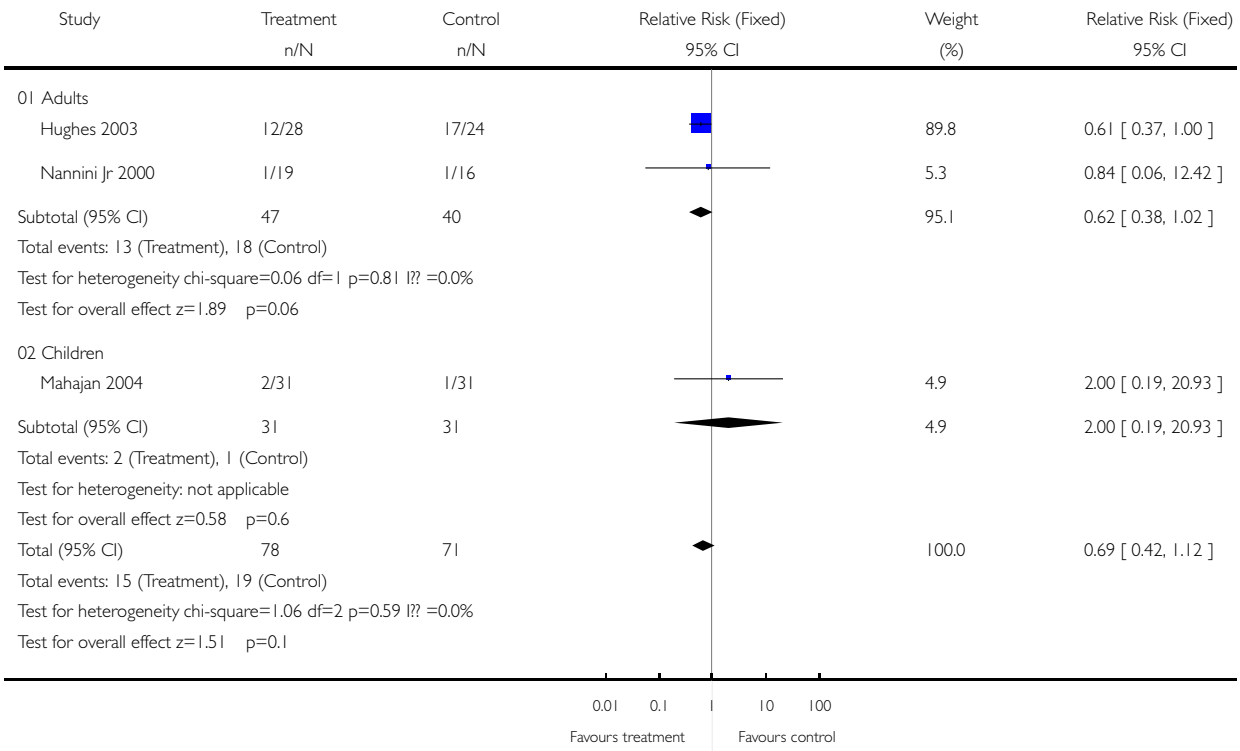


Analysis 01.05. Comparison 01 MgSO4 + B2-agonists vs B2-agonists alone, Outcome 05 Sub-Group: Adult/Peds (admission)

Review: Inhaled magnesium sulfate in the treatment of acute asthma

Comparison: 01 MgSO4 + B2-agonists vs B2-agonists alone

Outcome: 05 Sub-Group: Adult/Peds (admission)

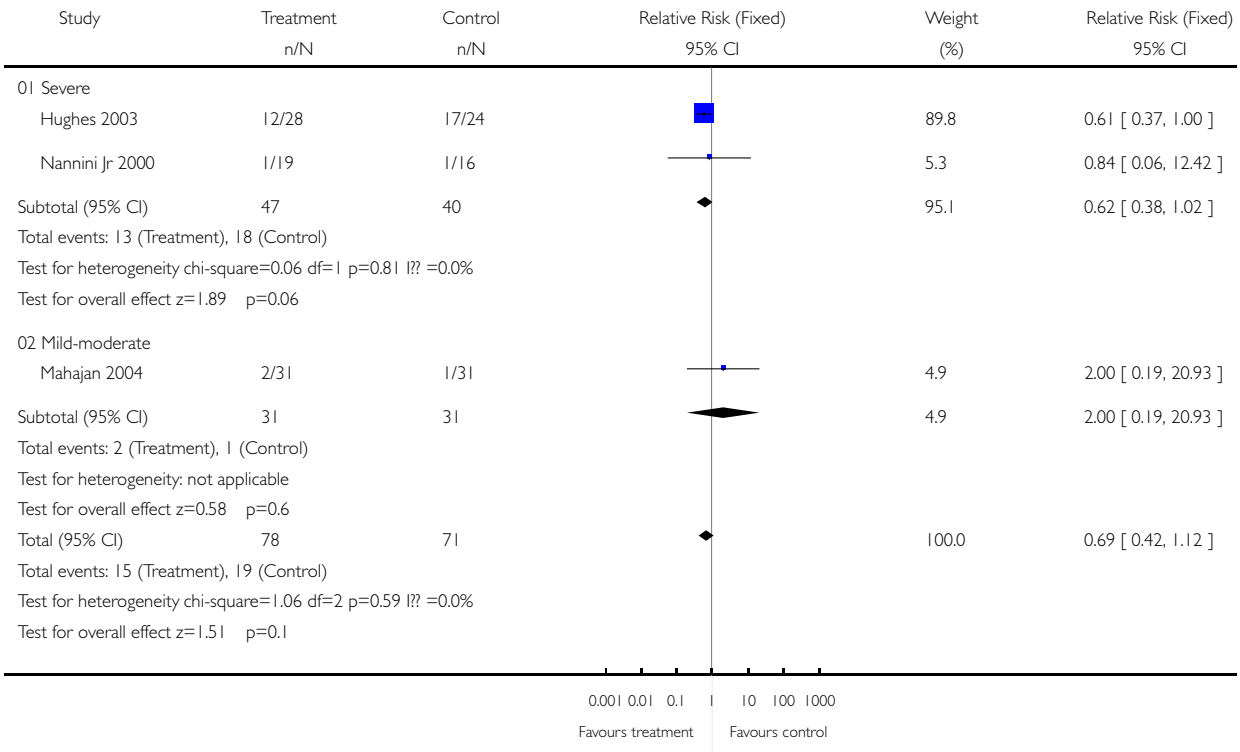


Analysis 01.06. Comparison 01 MgSO4 + B2-agonists vs B2-agonists alone, Outcome 06 Sub-group: Severity (Admission)

Review: Inhaled magnesium sulfate in the treatment of acute asthma

Comparison: 01 MgSO4 + B2-agonists vs B2-agonists alone

Outcome: 06 Sub-group: Severity (Admission)



Analysis 01.07. Comparison 01 MgSO4 + B2-agonists vs B2-agonists alone, Outcome 07 Serious Adverse Events

Review: Inhaled magnesium sulfate in the treatment of acute asthma

Comparison: 01 MgSO4 + B2-agonists vs B2-agonists alone

Outcome: 07 Serious Adverse Events

Study	Treatment n/N	Control n/N	Risk Difference (Fixed) 95% CI	Weight (%)	Risk Difference (Fixed) 95% CI
Bessmertny 2002	0/37	0/37		33.3	0.00 [-0.05, 0.05]
Hughes 2003	0/28	0/24		23.2	0.00 [-0.07, 0.07]
Mahajan 2004	0/31	0/31		27.9	0.00 [-0.06, 0.06]
Nannini Jr 2000	0/19	0/16		15.6	0.00 [-0.11, 0.11]
Total (95% CI)	115	108		100.0	0.00 [-0.03, 0.03]
Total events: 0 (Treatment), 0 (Control)					
Test for heterogeneity chi-square=0.00 df=3 p=1.00 I?? =0.0%					
Test for overall effect z=0.00 p=1					

Analysis 01.08. Comparison 01 MgSO4 + B2-agonists vs B2-agonists alone, Outcome 08 Mild-Moderate Adverse Events

Review: Inhaled magnesium sulfate in the treatment of acute asthma

Comparison: 01 MgSO4 + B2-agonists vs B2-agonists alone

Outcome: 08 Mild-Moderate Adverse Events

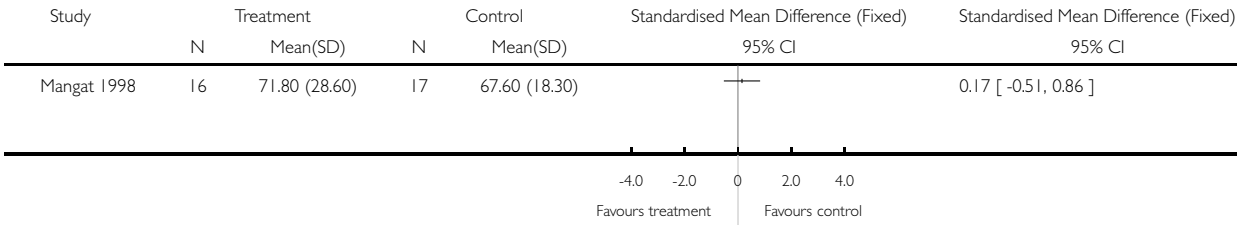
Study	Treatment n/N	Control n/N	Risk Difference (Fixed) 95% CI	Weight (%)	Risk Difference (Fixed) 95% CI
Bessmertny 2002	11/37	16/37		68.1	-0.14 [-0.35, 0.08]
Nannini Jr 2000	0/19	0/16		31.9	0.00 [-0.11, 0.11]
Total (95% CI)	56	53		100.0	-0.09 [-0.24, 0.06]
Total events: 11 (Treatment), 16 (Control)					
Test for heterogeneity chi-square=3.07 df=1 p=0.08 I?? =67.4%					
Test for overall effect z=1.19 p=0.2					

Analysis 02.01. Comparison 02 MgSO4 vs B2-agonist, Outcome 01 Pulmonary Function tests

Review: Inhaled magnesium sulfate in the treatment of acute asthma

Comparison: 02 MgSO4 vs B2-agonist

Outcome: 01 Pulmonary Function tests

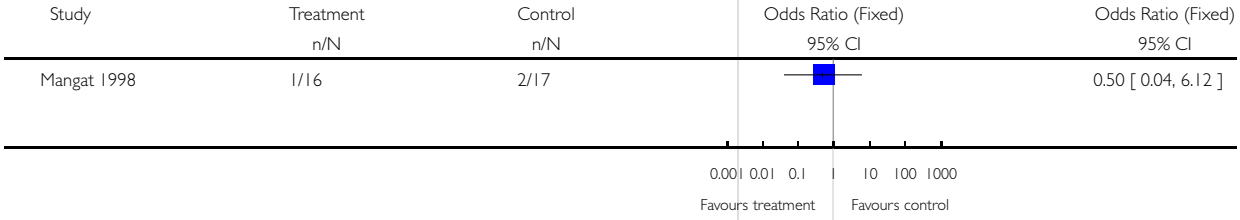


Analysis 02.02. Comparison 02 MgSO4 vs B2-agonist, Outcome 02 Admision to hospital

Review: Inhaled magnesium sulfate in the treatment of acute asthma

Comparison: 02 MgSO4 vs B2-agonist

Outcome: 02 Admision to hospital

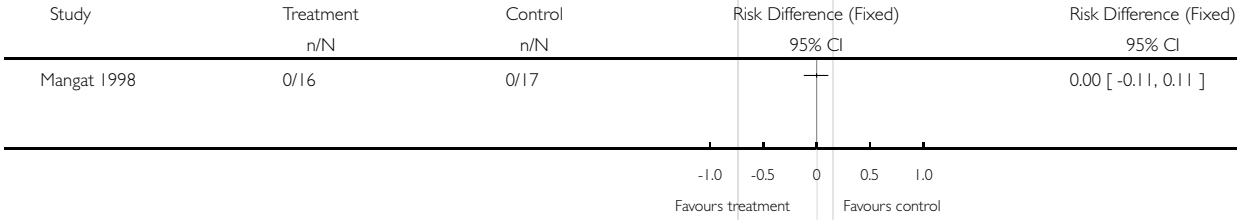


Analysis 02.03. Comparison 02 MgSO4 vs B2-agonist, Outcome 03 Serious Side Effects

Review: Inhaled magnesium sulfate in the treatment of acute asthma

Comparison: 02 MgSO4 vs B2-agonist

Outcome: 03 Serious Side Effects



Analysis 02.04. Comparison 02 MgSO4 vs B2-agonist, Outcome 04 Mild-Moderate Side Effects

Review: Inhaled magnesium sulfate in the treatment of acute asthma

Comparison: 02 MgSO4 vs B2-agonist

Outcome: 04 Mild-Moderate Side Effects

Study	Treatment n/N	Control n/N	Risk Difference (Fixed) 95% CI	Risk Difference (Fixed) 95% CI
Mangat 1998	1/16	4/17		-0.17 [-0.41, 0.06]