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REVIEW

# Intravenous and nebulized magnesium sulfate for treating acute asthma in adults and children: A systematic review and meta-analysis

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Asthma;
Magnesium sulfate;
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**Summary**
*Objectives:* This systematic review and meta-analysis was conducted to estimate the effects of intravenous and nebulized magnesium sulfate on treating adults and children with acute asthma.
*Methods:* Electronic literature search and the manual search of key respiratory journals were performed up to October 18, 2011. Randomized controlled trials were included if patients had been treated with intravenous or nebulized magnesium sulfate in combination with β2-agonists and were compared with the use of β2-agonists. Standardized mean differences (SMDs) and the relative risks (RRs) were calculated for pulmonary functions and hospital admission respectively.
*Results:* 25 trials (16 intravenous, 9 nebulized) involving 1754 patients were included. In adults intravenous treatment was associated with a significant effect upon respiratory function

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(SMD, 0.30; 95% confidence interval (CI), 0.05 to 0.55; $p = 0.02$) but weak evidence of effect upon hospital admission (RR 0.86,95% CI 0.73 to 1.01; $p = 0.06$) in adults, and in children with significant effects upon both respiratory function (SMD, 1.94; 95% CI, 0.80 to 3.08; $p = 0.0008$) and hospital admission (RR, 0.70; 95% CI, 0.54 to 0.91; $p = 0.008$). Nebulized treatment was associated with significant effects upon respiratory function (SMD, 0.23; 95% CI, 0.06 to 0.41; $p = 0.009$) and hospital admission (RR, 0.63; 95% CI, 0.43 to 0.92; $p = 0.02$) in adults.

*Conclusion:* The use of intravenous magnesium sulfate, in addition to β2-agonists and systemic steroids, in the treatment of acute asthma appears to produce benefits with respect to improve pulmonary function and reduce the number of hospital admissions for children, and only improve pulmonary function for adults. However, the use of nebulized magnesium sulfate just appears to produce benefits for adults.



**Contents**



## Introduction

Multicentre studies conducted in large general populations indicate that asthma is a disease extremely prevalent with up to 1 out of 10 adults and 1 out of 3 children worldwide.[1] During the past ten years, the prevalence of asthma, especially in children, appears an obviously ascendant trend, causing a significant personal and social burden. However, the control of asthma remains poorly conducted in general population.

Standard treatment for asthma crisis includes short-acting bronchodilator (SAB), β2-agonists, inhaled anticholinergic agents and corticosteroids, in addition to general managements.[2] However, there are still patients with moderate to severe acute asthmatic attacks that may have insufficient improvement, leading to hospital admission, severe morbidity and even mortality. Numbers of studies suggest magnesium sulfate as an additional treatment option in patients resistant to standard therapy. In smooth muscle, magnesium decreases intracellular calcium by blocking its entry and its release from the endoplasmic reticulum and activating sodium−calcium pumps. Furthermore, inhibition of the interaction between calcium and myosin results in muscle cell relaxation. Magnesium also stabilizes T cells and inhibits mast cell degranulation, leading to a reduction in inflammatory mediators. In cholinergic motor nerve terminals, magnesium depresses muscle fiber excitability by inhibiting acetylcholine release. Lastly, magnesium stimulates nitric oxide and prostacyclin synthesis, which might reduce asthma severity.[3,4]

In some countries intravenous magnesium sulfate is widely used for acute asthma, usually for patients with severe or life-threatening asthma who have not responded to initial treatments. For example, the most recent revised (2012) BTS/SIGN guidelines state that a single dose of intravenous magnesium sulfate has been shown to be safe and effective in adults, and should be considered in adults with life threatening features or acute severe asthma that has not responded to inhaled bronchodilator treatment. The guidelines for children are more equivocal, suggesting that intravenous magnesium sulfate is safe but its place in management is not yet established.[5] In addition, in the UK intravenous magnesium sulfate is used in the treatment of acute asthma in over 90% of adult emergency departments, usually for patients with severe or life-threatening asthma who have not responded to initial treatments in 2009.[6] However, in the BTS/SIGN guidelines, they do not mention nebulized magnesium sulfate.[5] And in the UK, nebulized magnesium sulfate is hardly used at all, with most emergency practitioners feeling that there was insufficient evidence to justify its use.[6]

We therefore aimed to undertake a systematic review and meta-analysis of both intravenous and nebulized magnesium sulfate to determine their roles in adults and children with acute asthma.

## Methods and materials

### Selection criteria and identification of studies

We planned to identify all randomized or quasi-randomized trials of intravenous or nebulized magnesium sulfate as an adjuvant in combination with β2-agonists in adults or children with acute asthma, which reported a measure of pulmonary function or hospital admission as an outcome. Age restriction was considered for patients included in the studies and the participants were categorized into two groups: 2—16 years old (the children group) and ≥16 years old (the adults group). This study included studies comparing magnesium sulfate & β2-agonists with β2-agonists & placebo, but excluded those comparing magnesium sulfate with β2-agonists.

Two investigators searched electronic databases including PubMed/MEDLINE, EMBASE, CENTRAL, CINAHL databases and manually searched key respiratory journals up to October 18, 2011. The PubMed search strategy was as follows: ((magnesium) AND (asthma)) AND ((randomized controlled trial) OR (quasi-randomized controlled trial)). Similar search terms were used for EMBASE and other databases. In addition, references of relevant original papers and review articles were screened.

### Quality assessment

The quality of each included study was assessed using the five point Jadad score.[4,7—30] This scale is used to assess randomization, double blinding and withdrawals/dropouts. All trials were scored using a scale of 1—5 (score of 5 being the highest).

### Data extraction

Data extraction was carried out independently by two authors using a unanimous extraction form. To resolve discrepancies, group consensus and consulting with a third reviewer were employed. The following data were extracted: title, authors, year of publication, participants (sample size, age, gender, severity of asthma); interventions (route of administration, dose, timing and duration of therapy,

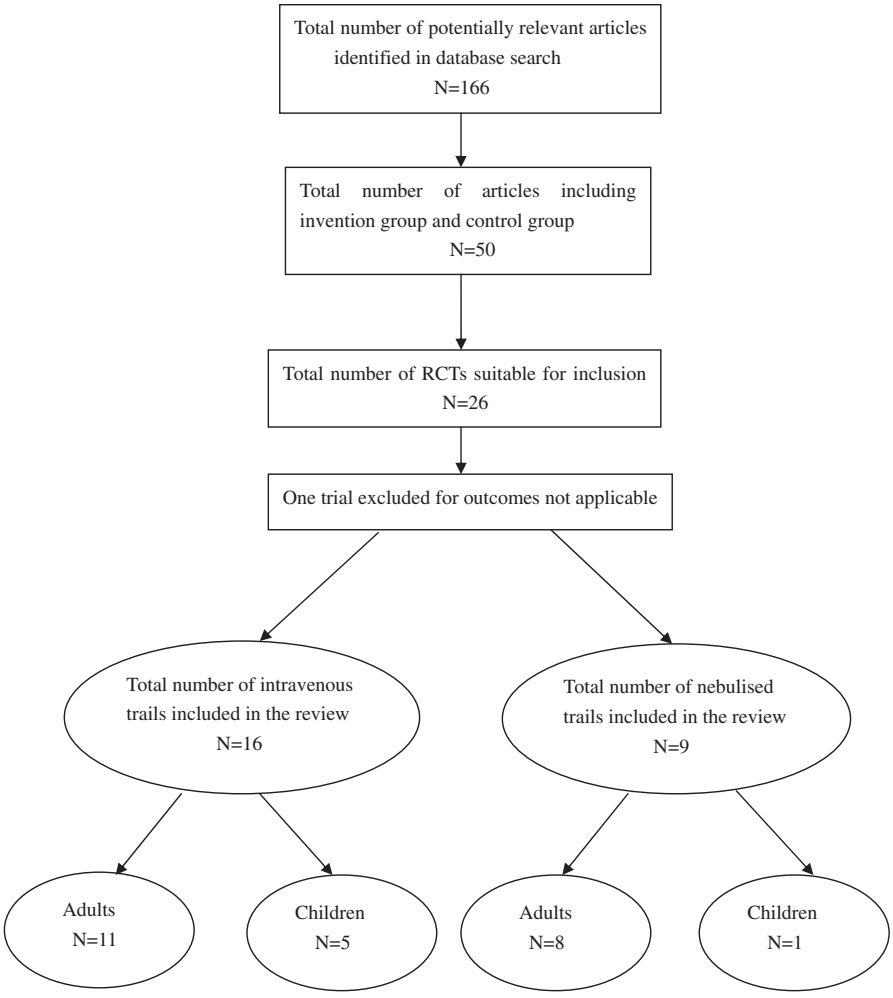


**Figure 1** Flow chart showing the selection of trials in the review. RCTs, randomized controlled trials.

**Table 1** Characteristics of studies of intravenous magnesium sulfate.

| Study | Location | Publication year | Sample size | Age range | Sex %F:M | Asthma severity | Jadad score | Outcome measures used |
|---|---|---|---|---|---|---|---|---|
| Singh | India | 2008 | 60 | 18—60 | 52:48 | Severe | 5 | $FEV_1$ (% predicted) and admissions |
| Bijani | Iran | 2002 | 81 | 12—85 | 47:53 | Severe | 3 | PEFR |
| Silverman | USA | 2002 | 248 | 18—60 | 42:58 | Severe | 5 | PEFR and admissions |
| Porter | USA | 2001 | 42 | 18—55 | 64:36 | Moderate—severe | 5 | PEFR and admissions |
| Bilaceroglu | Turkey | 2001 | 81 | 16—65 | 69:31 | Moderate—severe | 2 | $FEV_1$ (% predicted) and admissions |
| Boonyavorakul | Thailand | 2000 | 33 | 15—65 | 88:12 | Severe | 5 | Admissions |
| Scarfone | USA | 2000 | 54 | 1—18 | 48:52 | Moderate—severe | 5 | Admissions |
| Ciarallo | USA | 2000 | 30 | 6—18 | 40:60 | Moderate—severe | 4 | PEFR (change in % predicted) and admissions |
| Gurkan | Turkey | 1999 | 20 | 6—16 | 55:45 | Moderate—severe | 3 | PEFR (% change from baseline) |
| Devi | India | 1997 | 47 | 1—12 | 23:77 | Severe | 4 | PEFR (% predicted) |
| Ciarallo | USA | 1996 | 31 | 6—18 | 55:45 | Moderate—severe | 4 | PEFR (% change from baseline) and admissions |
| Bloch | USA | 1995 | 135 | 18—65 | 72:28 | Moderate—severe | 5 | $FEV_1$ (% predicted) and admissions |
| Matusiewicz | UK | 1994 | 129 | >16 | 57:42 | Moderate—life threatening | 5 | PEFR and admissions |
| Tiffany | USA | 1993 | 48 | 18—60 | 59:41 | Severe | 4 | PEFR |
| Green | USA | 1992 | 120 | 18—65 | 77:23 | Acute exacerbation | 1 | PEFR and admissions |
| Skobeloff | USA | 1989 | 38 | 18—70 | 74:26 | Moderate—severe | 5 | PEFR and admissions |

$FEV_1$, forced expiratory volume in 1 s; PEFR, peak expiratory flow rate.

co-interventions); control (agents and doses used); outcomes (types of outcome measures and hospital admission rates) and results. In some early publications with missing data, we collected the data from a previous meta-analysis.[31]

## Statistical analysis

We computed standardized mean differences (SMDs) for pulmonary functions and the relative risks (RRs) for hospital admission. The Cochran Q test and the $I^2$ statistic were employed to estimate the heterogeneity between studies.[32] Heterogeneity was confirmed with a significance level of $P < 0.10$. $I^2$ statistic describes the percentage of total variation in point estimates that can be attributed to heterogeneity.[33] Fixed-effect model (Mantel—Haenszel method) was used when heterogeneity was negligible and random-effect model (DerSimonian and Laird method) was used when heterogeneity was significantly present.[34] Forest plot and funnel plot were used to observe the overall effect and assess the publication bias, respectively. Sensitivity analyses were used to evaluate the influence of each study by omitting one study at one time. All tests were 2-sided with a significance level of 0.05.

**Table 2** Characteristics of studies of nebulized magnesium sulfate.

| Study | Location | Publication year | Sample size | Age range | Sex %F:M | Asthma severity | Jadad score | Outcome measures used |
|---|---|---|---|---|---|---|---|---|
| Allegos-Solórzano | Mexico | 2010 | 60 | >18 | 70:30 | Severe | 5 | $FEV_1$ (%predicted)and admissions |
| Aggarwal | India | 2006 | 100 | 13—60 | 40:60 | Severe or life threatening | 5 | PEFR and admissions |
| Drobina | USA | 2006 | 110 | 12—60 | 43:67 | Mild—severe | 5 | PEFR and admissions |
| Kokturk | Turkey | 2005 | 26 | 18—60 | 73:27 | Moderate—severe | 2 | PEFR (%predicted) and admissions |
| Mahajan | USA | 2004 | 62 | 5—17 | 45:55 | Mild—moderate | 4 | $FEV_1$ (%predicted) and admissions |
| Hughes | New Zealand | 2003 | 52 | 16—65 | 52:48 | Severe—life threatening | 5 | $FEV_1$ and admissions |
| Bessmertny | USA | 2002 | 74 | 18—65 | 73:27 | Mild—moderate | 5 | $FEV_1$ (%predicted) |
| Changqiong Xu | China | 2002 | 50 | 20—66 | 46:54 | Acute exacerbation | | $FEV_1$ (%predicted) |
| Nannini | Argentina | 2000 | 35 | >18 | 63:37 | Acute exacerbation | 3 | PEFR and admissions |

$FEV_1$, forced expiratory volume in 1 s; PEFR, peak expiratory flow rate.

**Table 3** Treatment regimens and co-interventions used in studies of intravenous magnesium sulfate.

| Study | Magnesium regimen | Control regimen | β-agonist regimen | Corticosteroid regimen | Co-interventions |
|---|---|---|---|---|---|
| Singh | 2 g loading dose over 20 min | 250 ml saline solution. | Salbutamol 2.5 mg 0, 20, 40 min | 100 mg IV hydrocortisone | Ipratropium |
| Bijani | 25 mg/kg over 30—45 min | 100 ml saline solution | Salbutamol (interval not stated) | Corticosteroids (type not stated) | Aminophylline |
| Silverman | 2 g loading dose over 10—15 min | 50 ml saline solution | Albuterol 0, 30, 60, 120, 180 min | 125 mg IV MP | None stated |
| Porter | 2 g loading dose over 20 min | 50 ml saline solution | Albuterol 20 min intervals | 125 mg IV MP | None stated |
| Bilaceroglu | 2 g loading dose | 100 ml of 5% dextrose | Salbutamol 0, 30, 60, 120,180 min | 125 mg MP if PEFR,40%predicted | Theophylline |
| Boonyavorakul | 2 g loading dose | 2 ml sterile water in 50 ml saline | Salbutamol 0, 20, 40, 60 min | 5 mg IV dexamethasone | None stated |
| Scarfone | 75 mg/kg over 20 min (max 2.5 g) | Saline solution | Albuterol 0.15 mg/kg 0, 40, 80, 120 min | 1.0 mg/kg MP IV (max 125 mg) | None stated |
| Ciarallo | 40 mg/kg over 20 min (max 2 g) | 100 ml saline solution | Albuterol | 2 mg/kg MP IV (max 100 mg) | Ipratropium |
| Gurkan | 40 mg/kg over 20 min (max 2 g) | Saline solution equivalent volume | Salbutamol 0.15 mg/kg | 2 mg/kg MP IV (max 100 mg) | None stated |
| Devi | 100 mg/kg over 35 min | Saline solution equivalent volume | Salbutamol 0.15 mg/kg | Hydrocortisone IV/oral (no dose provided) | Aminophylline |
| Ciarallo | 25 mg/kg over 20 min (max 2 g) | Saline solution equivalent volume | Albuterol 0.15 mg/kg | 2 mg/kg IV MP | None stated |
| Bloch | 2 g loading dose over 20 min | 50 ml saline solution | Albuterol 0, 30, 60, 120, 180 min | 125 mg IV MP if initial $FEV_1 \leq 40\%$ or oral steroids within last 6 months | Theophylline |
| Matusiewicz | 1.2 g loading dose over 15 min | 50 ml saline solution | Salbutamol at discretion of physician | 200 mg IV hydrocortisone | Ipratropium neb, aminophylline IV |
| Tiffany | 2 g loading dose over 20 min followed by infusion of $MgSO_4$ or placebo | Saline solution | Albuterol 30 min intervals | 125 mg IV MP | Aminophylline |
| Green | 2 g loading dose over 20 min | No placebo | Albuterol initially then hourly | 125 mg IV MP | Theophylline bagonist injection ephedrine |
| Skobeloff | 1.2 g loading dose over 20 min | 50 ml saline solution | Metaproterol/Albuterol at physician discretion | 125 mg IV MP | Theophylline IV |

$FEV_1$, forced expiratory volume in 1 s; IV, intravenous; MP, methylprednisolone; PEFR, peak expiratory flow rate.

RevMan software (version 5.1) was used for all statistical analyses.

## Results

### Characteristics of the included studies

After reviewed by two independent reviewers, our searches generated 194 reports prior to October 18, 2011, of which 25 studies (16 intravenous, 9 nebulized)[4,7–30] met the inclusion criteria. The flow of identified studies through the selection process is shown in Fig. 1. Tables 1 and 2 showed the characteristics of the 16 identified studies of intravenous magnesium sulfate and 9 identified studies of nebulized magnesium sulfate, respectively, for treating acute asthma. Tables 3 and 4 showed the interventions and co-interventions used in each study.

### Intravenous magnesium sulfate in acute asthma

For intravenous magnesium sulfate, 16 studies (12 adults, 4 children) were included for the analyses of the effects of intravenous magnesium sulfate upon respiratory function and hospital admission in acute asthma (Table 1). In all studies patients were treated with β2-agonists and systemic steroids together. SMDs for pulmonary functions and RRs for hospital admission were pooled using random-effect model and fixed-effect model, respectively, according to results from heterogeneity tests. In adults, intravenous magnesium sulfate treatment is associated with a significant effect upon respiratory function (SMD, 0.30; 95% CI, 0.05 to 0.55; $p = 0.02$), but weak evidence of effect upon hospital admission (RR, 0.86; 95% CI, 0.73 to 1.01; $p = 0.06$) (Fig. 2). In children, intravenous magnesium sulfate treatment is associated with significant effects upon respiratory function (SMD, 1.94; 95% CI, 0.80 to 3.08; $p = 0.0008$) and hospital admission (RR, 0.70; 95% CI, 0.54 to 0.91; $p = 0.008$) (Fig. 3). Funnel plot analyses were employed and no publication bias was found in the included studies (Supplementary Figs. 1 and 2). In addition, the final conclusion of both adults and children groups never changed in the sensitivity analyses by omitting one study at one time.

### Nebulized magnesium sulfate in acute asthma

For nebulized magnesium sulfate, 9 studies (8 adults, 1 children) were included for the analyses of the effects of nebulized magnesium sulfate upon respiratory function and hospital admission in acute asthma (Table 2). In most studies except two[15,21] patients were treated β2-agonists and systemic steroids together. Fixed-effect model was applied for SMRs for pulmonary functions and RRs for hospital admission because the test for heterogeneity was not significant. In adults, nebulized treatment is associated with significant effects upon respiratory function (SMD, 0.23; 95% CI, 0.06 to 0.41; $p = 0.009$) and hospital admission (RR, 0.63; 95% CI, 0.43 to 0.92; $p = 0.02$) (Fig. 4). However, in children there is only one study included and shows no significant effect upon respiratory function

**Table 4** Treatment regimens and co-interventions used in studies of nebulized magnesium sulfate.

| Study | Magnesium regimens | Control regimen | β-agonist regimen | Corticosteroid regimen | Co-interventions |
|---|---|---|---|---|---|
| Gallegos-Solórzano | 3 ml (333 mg) of 10% isotonic $MgSO_4$ (3 doses, 20 min apart) with β-agonist | 3 ml of isotonic saline solution | 7.5 mg of albuterol | 125 mg MP IV | Ipratropium bromide |
| Aggarwal | 1 ml $MgSO_4$ (500 mg) (3 doses, 20 min apart) with β-agonist | 1.5 ml distilled water 7.5 ml normal saline | Salbutamol 1 ml or more at discretion of physician | IV hydrocortisone at discretion of physician | None stated |
| Drobina | 125 mg $MgSO_4$ 0.25 ml of 50% solution (3 doses, 20 min apart) with b-agonist | 0.25 ml saline solution | 5 mg/ml albuterol | 50 mg oral prednisolone | Ipratropium bromide |
| Kokturk | Iso-osmolar $MgSO_4$ (6.3%, 145 mg/dose) (20 min intervals) with β-agonist | 2.5 ml isotonic saline solution | 2.5 mg salbutamol | 1 mg/kg MP IV | None stated |
| Mahajan | 2.5 ml isotonic $MgSO_4$ (6.3%) solution) single dose with β-agonist | 2.5 ml saline solution | Albuterol 2.5 mg(0.5 ml) | 2 mg/kg prednisolone | None stated |
| Hughes | 2.5 ml isotonic $MgSO_4$ (151 mg/dose)(3 doses at 30 min intervals) with β-agonist | 2.5 ml isotonic saline solution | 2.5 mg salbutamol | 100 mg hydrocortisone IV | None stated |
| Bessmertny | $MgSO_4$ 384 mg (64 mg/ml) in 6 ml sterile water (3 doses at 20 min intervals) after β-agonist | 6 ml saline solution | Albuterol 7.5 mg/3 ml | 2 mg/kg hydrocortisone IV 6 hourly | None stated |
| Changqiong Xu | 3 ml 7.5% isotonic $MgSO_4$ single dose with β-agonist | 3 ml saline solution | 3 ml albuterol | None stated | None stated |
| Nannini | 3 ml isotonic $MgSO_4$ (7.5 g/100 ml) single dose with β-agonist | 3 ml saline solution | Salbutamol | None stated | None stated |

IV, intravenous; MP, methylprednisolone.

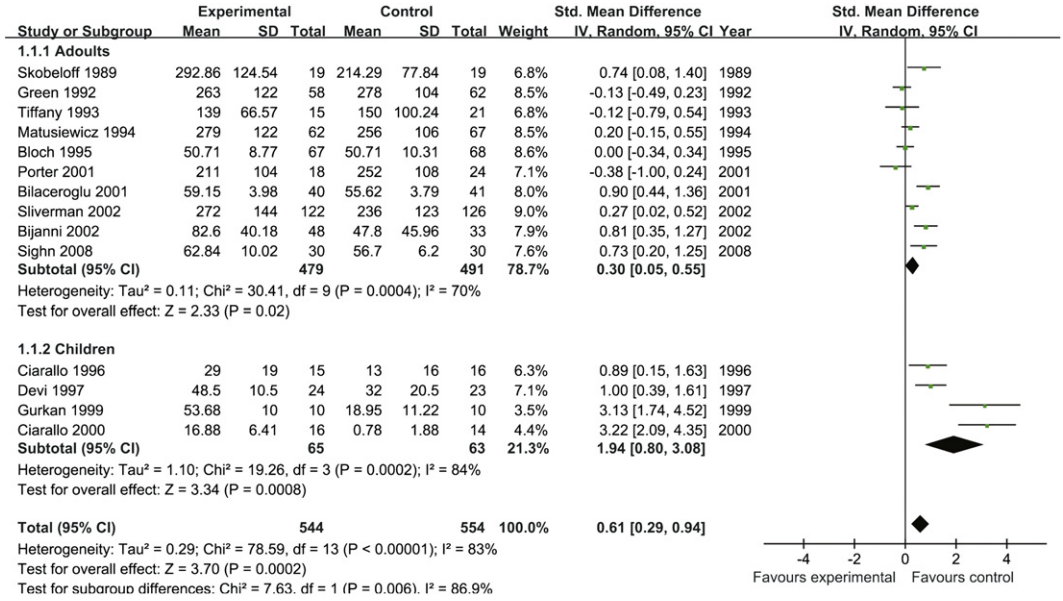


**Figure 2** Effect of intravenous magnesium sulfate upon respiratory function.

(SMD, 0.36; 95% CI, −0.14 to 0.86; $p = 0.16$) or hospital admission (RR, 2.0, 95% CI, 0.19 to 20.93; $p = 0.56$) (Fig. 5). Funnel plot analyses were employed and no publication bias was found in the included studies (Supplementary Figs. 3 and 4). By omitting two studies in which patients were not treated with systemic steroids, the conclusion never changed. In the adults group the final conclusion never changed in the sensitivity analysis by omitting one study at one time, while there was no sensitivity analysis in the children group for there was only one study included.

## Discussion

This systematic review and meta-analysis attempted to synthesize the most comprehensive review to date of the role of magnesium sulfate in acute asthma. It provided a systematic assessment of the effects of intravenous and nebulized magnesium sulfate on treating adults and children with acute asthma after reviewing 25 articles (16 intravenous, 585 treatments and 600 controls; 9 nebulized, 294 treatments and 275 controls).

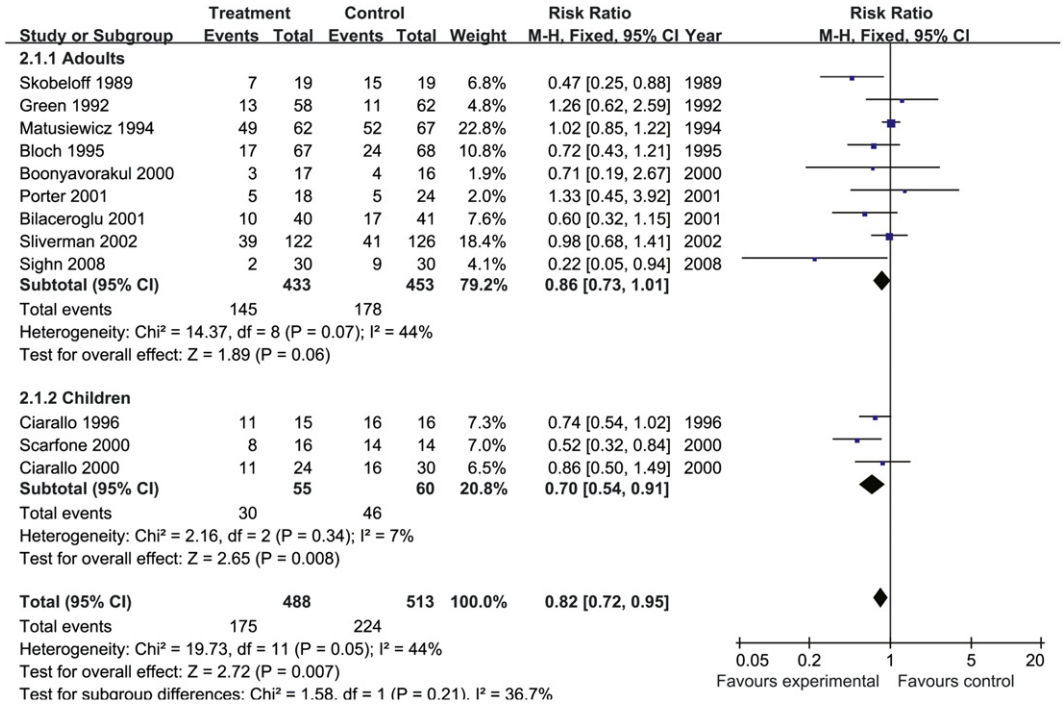


**Figure 3** Effect of intravenous magnesium sulfate upon hospital admission.

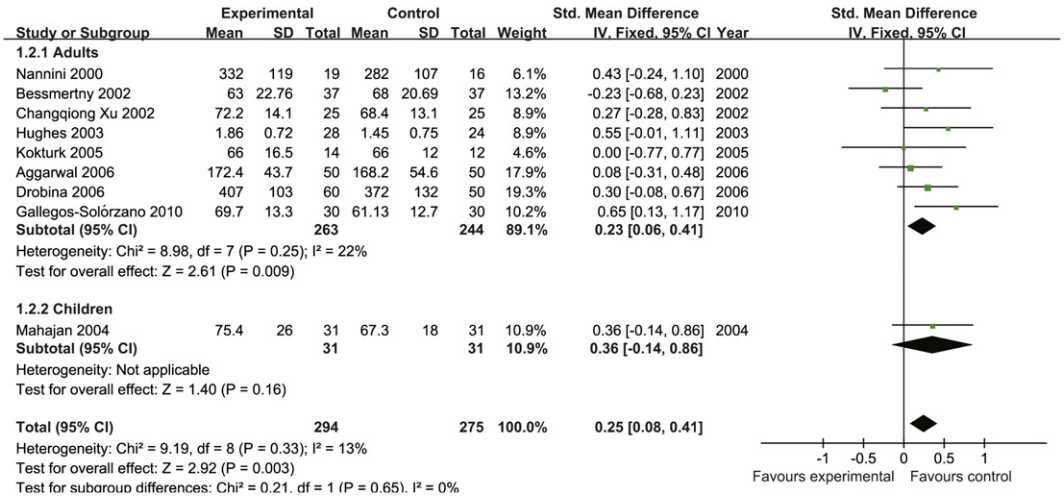


**Figure 4** Effect of nebulized magnesium sulfate upon respiratory function.

There appeared to be a significant difference in effectiveness between adults and children, so our meta-analysis analyzed the articles for adults and children separately. One possible explanation might be the difference of susceptibility of their smooth muscle to magnesium sulfate or the different doses used.

For intravenous magnesium sulfate, our results suggested that treatment in addition to β2-agonists and systemic steroids produced benefits with respect to improved pulmonary function in both adults and children, and reduced the number of hospital admissions by 30% in children. Moreover, it might reduce the number of hospital admissions in adults ($p = 0.06$). For nebulized magnesium sulfate, our results suggested that treatment in addition to β2-agonists and systemic steroids was associated with improved pulmonary function and reduced the number of hospital admissions by 37% in adults. There was only one trial in children included and it suggested that there was no significant effect of nebulized magnesium sulfate upon respiratory function or hospital admission. However, it was not considered to be sufficient to judge the effect of nebulized magnesium sulfate for children patients.

Our results were inconsistent to a previous meta-analysis by Mohammed S,[31] which just showed intravenous magnesium sulfate appeared to be an effective treatment in children. Several factors might contribute to the difference. First, we included three articles[8–10] (2 intravenous intervention with 92 treatments and 97 controls; 1 nebulized intervention with 30 treatments and 30 controls) after 2006. Meanwhile, we included one article[17] (intravenous intervention with 25 treatments and 25 controls) excluded by Mohammed S because it was only in Chinese. Second, two studies[35,36] were excluded in our analysis where magnesium alone was compared directly with a β2-agonist (salbutamol), which was more reasonable.

There are several potential limitations in this meta-analysis. Firstly, the sample sizes in the included studies were rather small, for example, no study included more than 150 treatments and 150 controls, which brought us to undertake this meta-analysis to reach higher statistical

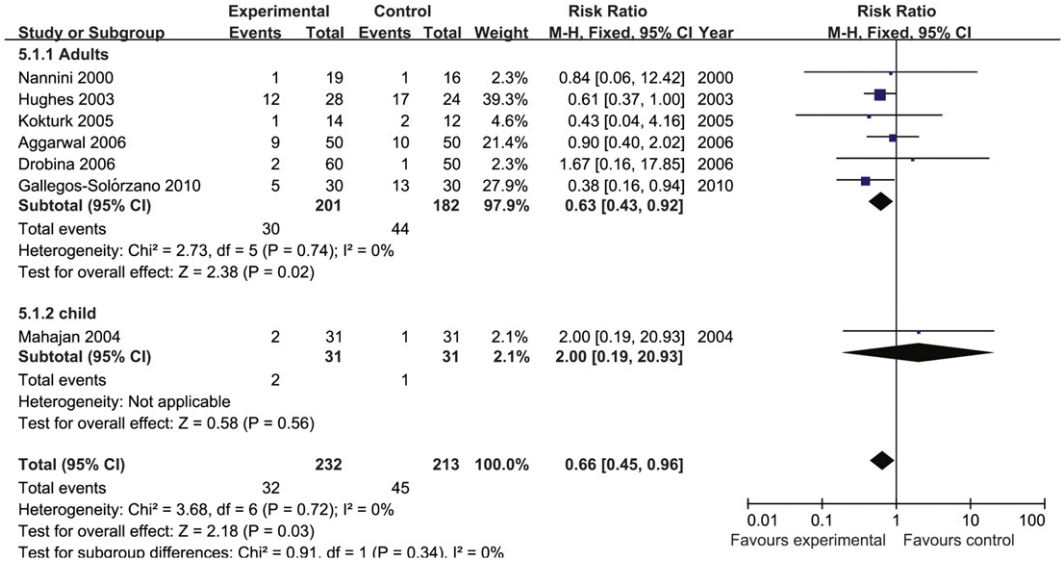


**Figure 5** Effect of nebulized magnesium sulfate upon hospital admission.

power. In addition, we calculated the weights of studies according to their sample sizes. Secondly, there was a possibility of study selection bias. However, two independent reviewers felt confident that the reasons for the inclusion and exclusion of studies were consistent and appropriate. Our search was comprehensive and has been updated, so it is unlikely that there are any published trials that were missed. Thirdly, there was a lack of consensus among researchers regarding the most appropriate pulmonary function outcome measure to report. Consequently, we computed standardized mean differences (SMDs) for pulmonary functions to avoid the influence of different outcome measures. Fourthly, the included studies were not stratified by asthma severity based on the consideration of preserving the study power, for example, if we evaluated the effect of intravenous magnesium sulfate for acute severe asthma, there was only one study included for children reflecting the effect on hospital admission. However, it might still be a limitation. Finally, in most studies, patients were not treated with ipratropium which is currently a standard treatment for acute severe asthma. This means that magnesium has not been widely tested against what is considered as guideline based therapy. The results might change with ipratropium usage, so further studies in this respect should be warranted.

Our analysis implies that intravenous and nebulized magnesium sulfate could be additional standard treatments for children and adults respectively, especially for the patients with acute asthma that has not responded to initial treatments, while the roles of both intravenous magnesium sulfate in adults and nebulized magnesium sulfate in children require further investigation. Considering the low risk of serious side effects from magnesium sulfate and readily availableness it would seem reasonable to use intravenous and nebulized magnesium sulfate to treat patients with life threatening features. Further studies with larger sample sizes, especially involving nebulized magnesium sulfate in children, should be warranted. Meanwhile, large randomized controlled trials are required to compare nebulized and intravenous magnesium sulfate with each other and with placebo, in patients with acute asthma, to establish the optimal dosage and the most effective route of administration.

## Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.rmed.2012.12.001.

## Conflict of interest statement

All the authors declare that they do not have a conflict of interest and that they do not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

## References


1. Annesi-Maesano I. Epidemiology of asthma in the world and in France. *Rev Prat* 2011;**61**(3):329—35.
2. Bateman ED, et al. Global strategy for asthma management and prevention: GINA executive summary. *Eur Respir J* 2008; **31**(1):143—78.
3. Gontijo-Amaral C, et al. Oral magnesium supplementation in asthmatic children: a double-blind randomized placebo-controlled trial. *Eur J Clin Nutr* 2007;**61**(1):54—60.
4. Skobeloff EM, et al. Intravenous magnesium sulfate for the treatment of acute asthma in the emergency department. *J Am Med Assoc* 1989;**262**(9):1210—3.
5. Society BT. *British guideline on the management of asthma* May 2008 [Revised January 2012].
6. Jones LA, Goodacre S. Magnesium sulphate in the treatment of acute asthma: evaluation of current practice in adult emergency departments. *Emerg Med J* 2009;**26**(11): 783—5.
7. Gallegos-Solorzano MC, Perez-Padilla R, Hernandez-Zenteno RJ. Usefulness of inhaled magnesium sulfate in the coadjuvant management of severe asthma crisis in an emergency department. *Pulm Pharmacol Ther* 2010;**23**(5): 432—7.
8. Singh AK, Gaur S, Kumar R. A randomized controlled trial of intravenous magnesium sulphate as an adjunct to standard therapy in acute severe asthma. *Iran J Allergy Asthma Immunol* 2008;**7**(4):221—9.
9. Aggarwal P, et al. Comparison of nebulised magnesium sulphate and salbutamol combined with salbutamol alone in the treatment of acute bronchial asthma: a randomised study. *Emerg Med J* 2006;**23**(5):358—62.
10. Kokturk N, et al. A randomized clinical trial of magnesium sulphate as a vehicle for nebulized salbutamol in the treatment of moderate to severe asthma attacks. *Pulm Pharmacol Ther* 2005;**18**(6):416—21.
11. Blitz M, et al. Inhaled magnesium sulfate in the treatment of acute asthma. *Cochrane Database Syst Rev* 2005;**2**:CD003898.
12. Mahajan P, et al. Comparison of nebulized magnesium sulfate plus albuterol to nebulized albuterol plus saline in children with acute exacerbations of mild to moderate asthma. *J Emerg Med* 2004;**27**(1):21—5.
13. Hughes R, et al. Use of isotonic nebulised magnesium sulphate as an adjuvant to salbutamol in treatment of severe asthma in adults: randomised placebo-controlled trial. *Lancet* 2003; **361**(9375):2114—7.
14. Fogarty A, et al. Oral magnesium and vitamin C supplements in asthma: a parallel group randomized placebo-controlled trial. *Clin Exp Allergy* 2003;**33**(10):1355—9.
15. Xu CQ, Yang J, Meng XK. Clinical study of salbutamol combined with magnesium sulphate by nebulization in the treatment of paroxysmal asthma. *Chin J Clin Pharmacol Ther* 2002;**7**(3): 446—8.
16. Silverman RA, et al. IV magnesium sulfate in the treatment of acute severe asthma: a multicenter randomized controlled trial. *Chest* 2002;**122**(2):489—97.
17. Bessmertny O, et al. A randomized clinical trial of nebulized magnesium sulfate in addition to albuterol in the treatment of acute mild-to-moderate asthma exacerbations in adults. *Ann Emerg Med* 2002;**39**(6):585—91.
18. Porter RS, et al. Intravenous magnesium is ineffective in adult asthma, a randomized trial. *Eur J Emerg Med* 2001; **8**(1):9—15.
19. Bilaceroglu S, et al. Intravenous magnesium sulphate in acute asthma. In: *Annual Thoracic Society 97th international conference*. San Francisco; 18—23 May 2001.
20. Scarfone RJ, et al. A randomized trial of magnesium in the emergency department treatment of children with asthma. *Ann Emerg Med* 2000;**36**(6):572—8.
21. Nannini Jr LJ, et al. Magnesium sulfate as a vehicle for nebulized salbutamol in acute asthma. *Am J Med* 2000;**108**(3): 193—7.

22. Ciarallo L, Brousseau D, Reinert S. Higher-dose intravenous magnesium therapy for children with moderate to severe acute asthma. *Arch Pediatr Adolesc Med* 2000;**154**(10):979—83.
23. Boonyavorakul C, Thakkinstian A, Charoenpan P. Intravenous magnesium sulfate in acute severe asthma. *Respirology* 2000; **5**(3):221—5.
24. Gurkan F, et al. Intravenous magnesium sulphate in the management of moderate to severe acute asthmatic children nonresponding to conventional therapy. *Eur J Emerg Med* 1999; **6**(3):201—5.
25. Devi PR, et al. Intravenous magnesium sulfate in acute severe asthma not responding to conventional therapy. *Indian Pediatr* 1997;**34**(5):389—97.
26. Ciarallo L, Sauer AH, Shannon MW. Intravenous magnesium therapy for moderate to severe pediatric asthma: results of a randomized, placebo-controlled trial. *J Pediatr* 1996;**129**(6): 809—14.
27. Bloch H, et al. Intravenous magnesium sulfate as an adjunct in the treatment of acute asthma. *Chest* 1995;**107**(6):1576—81.
28. Matusiewicz SP, Cusack S, Greening AP. A double blind placebo controlled parallel group study of intravenous magnesium sulphate in acute severe asthma. *Eur Respir J* 1994;**7**(Suppl. 18): 14s [abstract].
29. Tiffany BR, et al. Magnesium bolus or infusion fails to improve expiratory flow in acute asthma exacerbations. *Chest* 1993; **104**(3):831—4.
30. Green SM, Rothrock SG. Intravenous magnesium for acute asthma: failure to decrease emergency treatment duration or need for hospitalization. *Ann Emerg Med* 1992;**21**(3): 260—5.
31. Mohammed S, Goodacre S. Intravenous and nebulised magnesium sulphate for acute asthma: systematic review and meta-analysis. *Emerg Med J* 2007;**24**(12):823—30.
32. Higgins JP, et al. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**(7414):557—60.
33. Higgins JP. Commentary: heterogeneity in meta-analysis should be expected and appropriately quantified. *Int J Epidemiol* 2008;**37**(5):1158—60.
34. Lau J, Ioannidis JP, Schmid CH. Quantitative synthesis in systematic reviews. *Ann Intern Med* 1997;**127**(9):820—6.
35. Mangat HS, D'Souza GA, Jacob MS. Nebulized magnesium sulphate versus nebulized salbutamol in acute bronchial asthma: a clinical trial. *Eur Respir J* 1998;**12**(2):341—4.
36. Meral A, Coker M, Tanac R. Inhalation therapy with magnesium sulfate and salbutamol sulfate in bronchial asthma. *Turk J Pediatr* 1996;**38**(2):169—75.