

Intravenous Magnesium as an Adjuvant in Acute Bronchospasm: A Meta-Analysis

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Received for publication October 12, 1999. Revisions received May 1, 2000, and May 3, 2000. Accepted for publication May 17, 2000.

Presented in poster format at the Society for Academic Emergency Medicine, Boston, MA, May 1999.

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0196-0644/2000/\$12.00 + 0

47/1/109170

doi:10.1067/mem.2000.109170

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Study objective: Although several trials have been published evaluating intravenous magnesium sulfate as treatment for acute bronchospasm, its effectiveness for this indication remains unclear, prompting this meta-analysis.

Methods: All randomized controlled trials of adjuvant bolus intravenous magnesium sulfate for acute bronchospasm in the emergency department were eligible. Trials were identified using MEDLINE, EMBASE, bibliographies of selected articles, and review of abstracts of 4 scientific societies. Two reviewers abstracted data, one of whom was blinded to author and journal. Because studies used different spirometric outcome measures, effect size was calculated for each study by Hedges' method. The analysis used a fixed-effects model. One-way sensitivity analyses were performed to assess the influence of study quality and to search for publication bias.

Results: Abstracts from 210 articles were reviewed, yielding 40 trials, of which 9 were specific to bolus intravenous magnesium sulfate in the ED, in doses from 1.2 to 2 g, or an equivalent pediatric dose. Combined results across 9 studies including 859 patients showed a posttreatment effect size of 0.162 for patients treated with intravenous magnesium sulfate (95% confidence interval 0.028, 0.297; $P=.02$). In sensitivity analyses exploring the effects of study quality and publication bias, the summary effect ranged from 0.127 to 0.206. No serious adverse events were reported.

Conclusion: Adjuvant bolus intravenous magnesium sulfate in acute bronchospasm appears statistically beneficial in improving spirometric airway function by 16% of a SD. Although the clinical significance of this is uncertain, given the safety of intravenous magnesium sulfate therapy and its relatively low cost, it should be considered, absent contraindications, in patients with moderate to severe acute bronchospasm.

[Alter HJ, Koepsell TD, Hilty WM. Intravenous magnesium as an adjuvant in acute bronchospasm: a meta-analysis. *Ann Emerg Med.* September 2000;36:191-197.]

INTRODUCTION

As both the incidence and mortality of asthma increase, so does interest in new effective treatments. As maintenance therapy for chronic bronchospasm, the introduction of frequent inhaled β_2 -agonists and anticholinergics, leukotriene inhibitors, inhaled steroids, and inhaled cromolyn sodium have improved the outpatient regimen, supplanting aminophylline therapy. For acute exacerbations, intravenous and oral steroids, continuous nebulized β_2 -agonists, and nebulized anticholinergics are the mainstays of treatment, as epinephrine use wanes. Still, acute decline into status asthmaticus remains a tenacious problem. For this reason, several alternative treatments, such as intravenous magnesium, are in growing use.

Interest in the bronchodilating effects of magnesium dates back half a century to the reports of Rosello and Haury.¹ More recently, researchers attempting to elucidate magnesium's mechanism have focused primarily on its calcium antagonist properties, which inhibit calcium-mediated smooth muscle contraction.² Other proposed mechanisms include interference with parasympathetic stimulation² and potentiation of β_2 -agonist effects.¹ In 1989, Skobeloff et al³ published the first double-blind, placebo-controlled, randomized clinical trial, suggesting the beneficial effect of intravenous magnesium in the setting of an acute asthma exacerbation. Since that study, several other authors have attempted to replicate this finding, with variable results. Recently, meta-analysts affiliated with the Cochrane Group published a systematic review on the subject, concluding in a stratified analysis of 7 trials that intravenous magnesium sulfate therapy was beneficial in severe asthma.⁴

Because the treating physician often cannot differentiate bronchospasm related to asthma from that caused by chronic obstructive pulmonary disease (COPD), both are included here. The purpose of this meta-analysis was to determine whether the addition of intravenous magnesium to standard therapy improves acute bronchospasm.

MATERIALS AND METHODS

One author (HJA) identified the trials using 2 search algorithms on MEDLINE covering 1966 to 1998, with no language restriction: (1) [asthma OR whee*] AND magne-

sium; and (2) [asthma OR COPD OR "chronic obstructive pulmonary disease"] AND magnesium. The search author then replicated the algorithms on the Drugs & Pharmacology EMBASE database covering 1990 to 1998, its dates of electronic access. We then reviewed the bibliographies and attempted to query authors of relevant clinical research and review articles. To capture recent unpublished trials, we reviewed abstracts from 5 years of scientific meetings of 4 specialty societies: the Society for Academic Emergency Medicine, the American Thoracic Society, the American College of Chest Physicians, and the European Respiratory Society. The search author reviewed all abstracts for eligibility.

We determined a priori that trials meeting the following criteria would be eligible for inclusion: ED or equivalent setting with acutely ill patients; acutely bronchospastic trial subjects; and random assignment of patients to receive bolus dosing of either intravenous magnesium sulfate or placebo. We did not specify a priori a dose of magnesium, because of a paucity of evidence on dose-response mechanics, or a method of blinding, or a specific spirometric outcome.

Studies specifically excluded from the review included case reports and case series, studies not specifying the clinical condition (ie, acute versus stable asthma), and those in which magnesium was not delivered intravenously.

The following data were abstracted in an unblinded fashion from each included study: author, country, year and source of publication, number of treatment arms, number of subjects in each arm, their inclusion criteria, whether all were accounted for, method of blinding, number and dosage of all medications used, outcome measures and approach to assessing them, means and SDs of the baseline and outcome data for each arm, time of posttreatment measurement, and incidence of complications.

We chose as the main outcome of interest peak expiratory flow rate (PEFR) where available, because this is a spirometric result easily available to emergency clinicians, and widely used and understood.

All but 3 studies used PEFR as a clinical outcome. Several studies also used FEV₁, and 2 trials used only this measure. Our analysis used PEFR when available to promote comparability. All but 3 studies also reported hospitalization rates as an outcome measure.

Several studies reported their results in graphical form only, without corresponding numerical values. To determine estimates of these effects, graphs were photostatically enlarged, and the height of the data point and length of the error bars were measured in millimeters from the datum. This distance was converted to outcome units by

measuring the units on the y axes, using a method previously published in the asthma literature.⁵ In cases in which the graph or tables depicted SE, these were converted to SD by multiplying the reported value by the square root of the number of patients in that study.

Study quality was judged on a 5-point scale modified from Jadad et al.⁶ This method assigns 1 point for each ordered criterion: randomization; blinding; descriptions of procedures for withdrawals and dropouts; descriptions of procedures for appropriate randomization and finally, 5 points total if all prior criteria are met and there is a description of an appropriate blinding procedure.

Because of the absence of a common outcome, a unitless summary effect size was estimated for each study, according to the technique known as Hedges' *g*,⁷ and later explicated by Pettiti⁸ (Appendix). This analysis yielded an estimate of the summary effect size and its 95% confidence limits (CIs), using modifications of both the fixed-effects method and of the random-effects method described by DerSimonian and Laird,⁹ as appropriate (Appendix). The sample size was the absolute number of studies for each calculation. Combinability was explored with the *Q* statistic for heterogeneity, as described by Fleiss.¹⁰ Studies were deemed to be not comparable under a fixed-effects model if *Q* was significant at values of *P* less than .05 (Appendix).

We explored publication bias using a funnel plot, in which study results are arrayed by sample size, and in

which symmetry about the line of no effect suggests little influence of publication bias.¹¹ We also used a linear regression model proposed by Egger et al¹² for quantifying funnel plot asymmetry, which regresses the effect size divided by its standard error against the inverse of the standard error, a measure of precision. This test uses a value of *P* less than .1 to judge the significance of the intercept's dispersion from the origin as a means of judging asymmetry of the funnel plot. To further assess the potential for publication bias, correlation between effect size and the number of subjects in each study was explored using Spearman rank correlation. Following the precedent of Oler et al,¹³ this analysis assumes that since "small studies with negative results were less likely to be published, then the correlation... would be high" in the setting of frank bias.

A sensitivity analysis examined the effects of calculating the summary result when certain studies were excluded. For example, this approach tests the effect on the summary result of excluding pediatric studies. We used this method also to explore the influence of study quality on the overall effect. For the purposes of the sensitivity analyses, we used the more conservative random-effects model.

RESULTS

The MEDLINE search and review of reference lists yielded 208 articles. Of these, 103 were unrelated to the specific

Table.

Key attributes of 9 selected trials.

Reference	Year	No. of Subjects	Mean Age (y)	Magnesium Regimen	Standard Therapy*	Inclusions	Measure/Min After Bolus	Blinding	Effect Size [†]	Authors' Conclusion	Jadad Score ⁶
Skobeloff et al ³	1989	38	38	1.2 g	BA ×2, MP, APn	PEFR <200 L/min	PEFR/45	Double	0.732	Effective; <i>P</i> <.05	5
Green & Rothrock ⁴⁷	1992	120	40	2 g	BA, MP, APn	Needs IV MP 125	PEFR/end	Patients only	-0.133	No significant difference	1
Tiffany et al ⁴⁵	1993	36	40	2 g	BA ×2, MP, APn	PEFR <200 L/min	PEFR/50	Double	-0.371	No significant difference	2
Matusiewicz et al ^{50†}	1994	131	Adults	1.2 g	BA, IP, MP, APn	PEFR <250 or FEV ₁ <50%	PEFR/45	Double	0.211	No significant difference	2
Skorodin et al ⁴⁶	1995	72	65	1.2 g	BA ×2	PEFR <250 L/min [§]	PEFR/45	Double	0.241	Effective; <i>P</i> =.03	2
Bloch et al ⁴³	1995	135	37	2 g	BA ×2, MPn	FEV ₁ <75%	FEV ₁ /100	Double	-0.036	No significant difference	5
Ciarallo et al ⁴⁴	1996	31	11	25 mg/kg	BA ×3, MP	PEFR<60% after BA ×3, needs IV	PEFR/50	Double	0.920	Effective; <i>P</i> =.05	2
Silverman et al ^{49†}	1996	249	Adults	2 g	BA, MP	PEFR<30%	FEV ₁ /240	Double	0.250	Effective; <i>P</i> <.01	2
Devi et al ⁴⁸	1997	47	7	10 mg/kg	BA ×3, MPn	PEFR<70%, after BA ×3	PEFR/60	Double	0.216	Effective; <i>P</i> <.05	5

BA, β_2 -agonist; MP, methylprednisolone; AP, Aminophylline; n, as needed; IV, intravenous; IP, ipratropium.

*Standard therapy administered in addition to placebo or intravenous magnesium sulfate.

†Calculated as Hedges' *g* (see Methods).

‡Published as abstract only.

§Patients excluded if PEFR doubled in response to an initial dose of inhaled β_2 -agonist.

||Result reported as percent improvement from baseline.

topic of interest, or were related only to properties of endogenous magnesium. Fifty-one articles were general reviews, either of asthma management or uses of magnesium, or letters containing no new trial data. Nineteen articles dealt with the pharmacology of administered magnesium, such as trials of intravenous magnesium sulfate therapy in induced conditions,¹⁴⁻¹⁶ or effects or intravenous magnesium sulfate on cell biology. Eight articles were excluded because of nonacute or inpatient settings,¹⁷⁻²⁴ and 9 because they examined the effect of inhaled magnesium.²⁵⁻³³ Eleven articles described uncontrolled case series or case reports of intravenous magnesium therapy in acute bronchospasm.^{1,16,34-42} The remaining 7 articles described randomized ED-based trials eligible for inclusion.^{3,43-48} The EMBASE search yielded no further articles, but the abstract review and author consultation procedures resulted in the identification of 2 published abstracts containing trial data.^{49,50} The 9 final studies are depicted in the Table. All 9 were placebo-controlled studies and all but 1 were double-blind⁴⁷; in this study, only the patients were blinded. All trials randomly allocated subjects to receive placebo or intravenous magnesium sulfate therapy, except for one, which instituted experimental and control treatments on alternate days.⁴⁷ The total number of studied patients was 859.

In 4 studies,^{43,45,47,49} the dose of magnesium was 2.0 g; in 1 study, an analogous dose of 25 mg/kg was used.⁴⁴ In 3 studies, a smaller 1.2-g dose was used^{3,46,50}; in 1 trial, a similarly smaller weight-based dose of 10 mg/kg was administered.⁴⁸ In studies using both a continuous infusion arm and a bolus arm, only the bolus arm was examined. All published protocols specified a 20-minute infusion period, and defined measurement times from the initiation of the bolus.

Each of the trials attempted to exclude mild exacerbations, either with a fixed maximum threshold for baseline PEF_r or FEV₁,^{3,45,46,50} a maximum threshold for baseline against predicted performance,^{43,44,48-50} or with a determination by the treating physician (before randomization) that a patient required intravenous steroid treatment.⁴⁷ The threshold severity of illness varied among the trials, from FEV₁ of less than 75% of the predicted value,⁴³ to a PEF_r of less than 30% of predicted. Two studies focused exclusively on children,^{44,48} and 1 attempted to include only patients with an exacerbation of COPD. There were no reports of major adverse events requiring treatment.

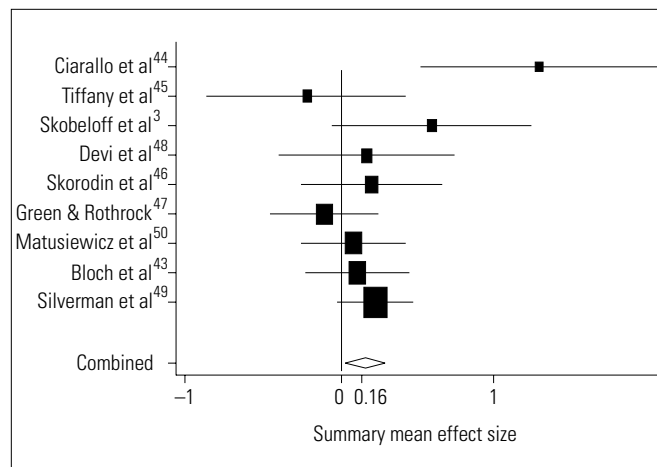
The summary effect size using the fixed-effects model was 0.162 (95% CI 0.028, 0.297; *P*=.02). Figure 1 shows

the contributions of each trial to the calculation of the summary statistic. The effect size signifies the degree to which outcomes may vary relative to their SDs. In this analysis, the summary effect size of 0.162 suggests that the intervention improved the outcome of interest by 16% of its SD in a population. In this setting, for example, the pooled SD of the 6 adult studies reporting peak flow was ± 101 L/min. The more conservative random-effects summary result of these 6 trials was 0.127 (95% CI -0.016, 0.265; *P*=.08). Thus, we can estimate that the addition of intravenous magnesium sulfate to standard therapy will, on average, improve peak flow by approximately $0.127 \times 101 = 12.8$ L/min compared with placebo.

The *Q* statistic, which denotes the degree of heterogeneity among the study populations, was 13.9 (*P*=.084). The fixed-effects model, which may be used when between-studies variation is not significant, assumes that each study represents an estimate of a true effect that is common to all studies. The random-effects model, which assumes that the trials represent a random sample of a universe of trials exploring a given effect, allows for random variability both within and between studies, and generally yields more conservative results. Using the random-effects model, our summary effect was slightly larger, 0.181 (95% CI -0.010,

Figure 1.

Individual and summary effect sizes for 9 trials. The trials are arrayed by sample size with the smallest at the top. Black boxes represent point estimates whose area is proportionate to sample size; bars represent 95% CI. Open diamond represents summary estimate of effect size and its 95% CI using a fixed-effects model. The vertical line at an effect size=0 is the line of no effect. The effect size is calculated by the method described by Rosenthal⁷ in Cooper and Hedges (see Appendix).



0.327; $P=.06$), but barely crossed the line of no effect. Heterogeneity was decreased substantially by the exclusion of the positive and negative outlier studies^{44,45}; in this analysis, the Q is 7.5 ($P=.28$), without substantial effect on the summary result, now 0.155 (95% CI 0.015, 0.295; $P=.03$) in a fixed-effects model.

Figure 2 illustrates one attempt to address the question of publication bias. The studies are arrayed by sample size in a "funnel plot," with the largest at the top. Relative symmetry and clustering around the line of no effect suggests that publication bias plays little role in the result. A regression model relating the standard normal deviate to study precision yielded an intercept of 1.4 ($P=.32$), suggesting statistically insignificant asymmetry. Another means of exploring this question, correlating sample size with effect size, yielded a Spearman's ρ of -0.20 , suggesting a small but not statistically significant inverse relation. This result supports the finding in the funnel plot.

To test the sensitivity of the summary result to study quality and other idiosyncrasies among specific trials, we recalculated summary effect sizes excluding one study per iteration. In Figure 3, the recalculated effects are arrayed in descending order of the Jadad score of the excluded trial. The observed pattern suggests that the exclusion of no single study, for quality or other reason, importantly alters the main finding. We also explored

stratification by adult or pediatric population, and by abstractor, with similar results.

DISCUSSION

The 9 trials constituting this meta-analysis, taken individually, present a paradoxical picture, with 4 authors reporting no statistically significant benefit to intravenous magnesium,^{43,45,47,50} and 5 reporting a statistically significant improvement in outcome among patients given this drug.^{3,44,46,48,49} The finding of the meta-analysis of 9 trials involving 859 patients, with a statistically significant positive point estimate and no major adverse events, provides statistical support to those seeking to optimize patient outcomes in acute bronchospasm. This result is consistent, although not duplicative, of the findings of a recent related meta-analysis. Rowe et al⁴ used the Cochrane analytic framework to examine the effect of intravenous magnesium sulfate on acute asthma. Their study excluded one trial included herein because it focuses on patients with COPD,⁴⁶ and another for reasons not made clear in the abstract, possibly because it fell outside of the search protocol. These authors also analyzed post hoc stratification by severity, thus concluding that the drug was useful only in severe exacerbations. As we sought to use data only from the trials as designed, we did not perform such a selective analysis.

Figure 2.

Funnel plot. Open circles represent effect sizes, arrayed by sample size. In the absence of significant publication bias, increased precision with larger sample size should reduce dispersion from the vertical line of no effect, producing a roughly triangular array of points in the shape of an inverted funnel.

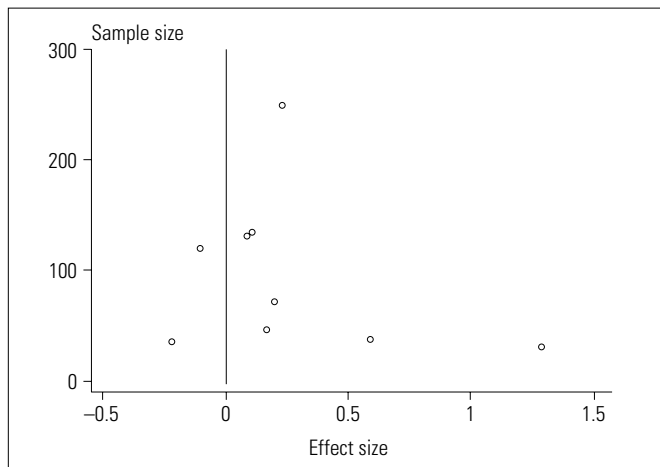
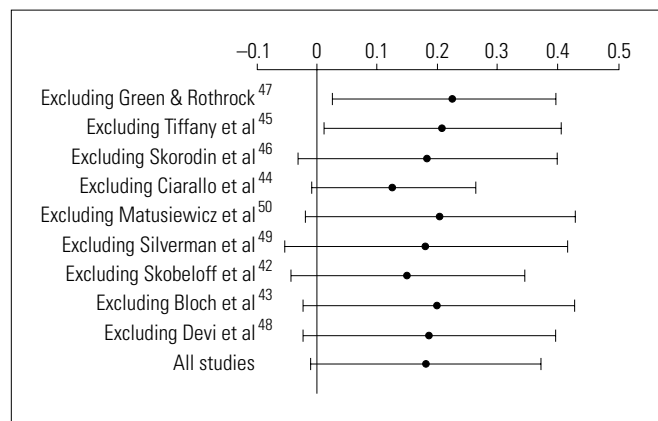


Figure 3.

Sensitivity analysis. Summary effects are recalculated excluding one study per iteration, and arrayed in order of the quality score of the excluded trial, with the lowest at the top. Sensitivity analysis used the more conservative random-effects model. All point estimates fall within the 95% CI of the overall result, suggesting that the quality of any single study does not significantly affect the outcome.



Our effect size, roughly 0.16, parallels the result of a recent meta-analysis of another adjuvant, inhaled ipratropium bromide, in acute asthma.⁵¹ Rodrigo et al⁵¹ summarized 10 trials studying 1,483 adults; their summary effect size was 0.14 (95% CI 0.04, 0.24).

The basic science behind the bronchodilatory effect of magnesium provides substantial biologic plausibility for our finding, and has been well studied both in vitro and in vivo. Its smooth muscle-relaxing effects operate independently of the β_2 -receptor, which suggests an adjunctive role,²⁵ and its parenteral administration allows magnesium to be delivered without interfering with inhaled therapy.

This study has several limitations. Results from our use of data gleaned from graphs may have led to some loss of precision. This shortcoming was unlikely to introduce a systematic bias, as both placebo and magnesium recipients were measured by the same technique. Also, we included data from both pediatric and adult populations, which may respond differently to medications. Our sensitivity analysis suggests that the adult finding is robust to the exclusion of the 2 small pediatric studies.

Finally, the summary estimate is only as good as the data contributing to its formulation. However, these are the same data that comprise the literature. We elected not to use hospital admission, which some may consider a more meaningful endpoint, as the outcome of analysis because of several sources of potential bias. For example, in at least 2 studies, consideration for admission appeared to be related to an inclusion criterion.^{44,48} In another study, the clinicians were not blinded to treatment assignment,⁴⁷ which may have influenced the admission decision. We also believed that, although regional variation in admission practices might not result in bias within a study, it would introduce substantial heterogeneity between the studies.

Two other sources of heterogeneity may influence our result in ways that are difficult to assess. The Table shows the varying degrees of severity among enrolled patients, as well as the fact that steroid use, and the dose administered, also varied widely. However, our summary result demonstrates nonsignificant between-study heterogeneity, suggesting that such effects may be unrelated to the true effect of intravenous magnesium sulfate therapy.

Our clinical example, using the pooled SD of adult trials reporting PEFr, is one way of assessing the small clinical benefit of intravenous magnesium sulfate therapy. Cohen⁵² has proposed another, an operational convention for the significance of effect sizes, in which those less than 0.2 are by definition considered "small," those in the range of 0.5 are defined as "medium," and effect sizes around a value of 0.8 are known as "large."

Given the known safety of the drug and its relatively low cost, the addition of intravenous magnesium sulfate therapy should be considered, absent contraindications, in patients with moderate to severe bronchospasm. This recommendation should be refined in the future by an analysis of the cost-effectiveness of such an approach.

REFERENCES

- Noppen M, Vanmaele L, Impens N, et al. Bronchodilating effect of intravenous magnesium sulfate in acute severe bronchial asthma. *Chest*. 1990;97:373-376.
- Corbridge TC, Hall JB. The assessment and management of adults with status asthmaticus. *Am J Respir Crit Care Med*. 1995;151:1296-1316.
- Skobeloff EM, Spivey WH, McNamara RM, et al. Intravenous magnesium sulfate for the treatment of acute asthma in the emergency department. *JAMA*. 1989;262:1210-1213.
- Rowe BH, Bretzlaff JA, Bourdon C, et al. Magnesium sulfate is effective for severe acute asthma treated in the emergency department. *ACP J Club*. 1999;131:36.
- Littenberg B. Aminophylline treatment in severe, acute asthma. A meta-analysis. *JAMA*. 1988;259:1678-1684.
- Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials*. 1996;17:1-12.
- Rosenthal R. Parametric measures of effect size. In: Cooper H, Hedges LV, eds. *The Handbook of Research Synthesis*. New York, NY: Russell Sage Foundation; 1994:231-244.
- Pettiti DB. *Meta-Analysis, Decision Analysis, and Cost-effectiveness Analysis: Methods for Quantitative Synthesis in Medicine*. New York, NY: Oxford University Press; 1994.
- DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7:177-188.
- Fleiss JL. The statistical basis of meta-analysis. *Stat Methods Med Res*. 1993;2:121-145.
- Ferret RL. Graphical methods for detecting bias in meta-analysis. *Fam Med*. 1998;30:579-583.
- Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test [see comments]. *BMJ*. 1997;315:629-634.
- Oler A, Whooley MA, Oler J, et al. Adding heparin to aspirin reduces the incidence of myocardial infarction and death in patients with unstable angina. A meta-analysis. *JAMA*. 1996;276:811-815.
- Rolla G, Bucca C, Bugiani M, et al. Reduction of histamine-induced bronchoconstriction by magnesium in asthmatic subjects. *Allergy*. 1987;42:186-188.
- Rolla G, Bucca C, Arossa W, et al. Magnesium attenuates methacholine-induced bronchoconstriction in asthmatics. *Magnesium*. 1987;6:201-204.
- Rolla G, Bucca C, Brussino L, et al. Effect of intravenous magnesium infusion on salbutamol-induced bronchodilatation in patients with asthma. *Magnesium Res*. 1994;7:129-133.
- Bernstein WK, Khastgir T, Khastgir A, et al. Lack of effectiveness of magnesium in chronic stable asthma. A prospective, randomized, double-blind, placebo-controlled, crossover trial in normal subjects and in patients with chronic stable asthma. *Arch Intern Med*. 1995;155:271-276.
- Rolla G, Bucca C, Carla E, et al. Acute effect of intravenous magnesium sulfate on airway obstruction of asthmatic patients. *Ann Allergy*. 1988;61:388-391.
- Sharma SK, Bhargava A, Pande JN. Effect of parenteral magnesium sulfate on pulmonary functions in bronchial asthma. *J Asthma*. 1994;31:109-115.
- Chande VT, Skoner DP. A trial of nebulized magnesium sulfate to reverse bronchospasm in asthmatic patients. *Ann Emerg Med*. 1992;21:1111-1115.
- Hill JM, Britton J. Effect of intravenous magnesium sulphate on airway calibre and airway reactivity to histamine in asthmatic subjects. *Br J Clin Pharmacol*. 1996;42:629-631.
- Brunner EH, Delabroise AM, Haddad ZH. Effect of parenteral magnesium on pulmonary function, plasma cAMP, and histamine in bronchial asthma. *J Asthma*. 1985;22:3-11.
- Sydow M, Crozier TA, Zielmann S, et al. High-dose intravenous magnesium sulfate in the management of life-threatening status asthmaticus [see comments]. *Intensive Care Med*. 1993;19:467-471.

24. Lemesle FG. High-dose intravenous magnesium sulfate in the management of life-threatening status asthmaticus [letter; comment]. *Intensive Care Med.* 1995;21:94-95.

25. Hill J, Lewis S, Britton J. Studies of the effects of inhaled magnesium on airway reactivity to histamine and adenosine monophosphate in asthmatic subjects. *Clin Exp Allergy.* 1997;27:546-551.

26. Emel'ianova AV, Goncharova VA, Sinitsina TM. The efficacy of the magnesium sulfate aerosol treatment of bronchial asthma patients [Russian]. *Ter Arkh.* 1997;69:35-39.

27. Manzke H, Thiemeier M, Elster P, et al. Magnesium sulfate as adjuvant in beta-2-sympathomimetic inhalation therapy of bronchial asthma [German]. *Pneumologie.* 1990;44:1190-1192.

28. Emel'ianova AV, Goncharova VA, Sinitsina TM. Magnesium sulfate in management of bronchial asthma [Russian]. *Klin Med (Mosk).* 1996;74:55-58.

29. Mangat HS, D'Souza GA, Jacob MS. Nebulized magnesium sulphate versus nebulized salbutamol in acute bronchial asthma: a clinical trial. *Eur Respir J.* 1998;12:341-344.

30. Meral A, Coker M, Tanac R. Inhalation therapy with magnesium sulfate and salbutamol sulfate in bronchial asthma. *Turk J Pediatr.* 1996;38:169-175.

31. Hill J, Britton J. Dose-response relationship and time-course of the effect of inhaled magnesium sulphate on airflow in normal and asthmatic subjects. *Br J Clin Pharmacol.* 1995;40:539-544.

32. Emel'ianova AV, Fedoseev GB, Emanuel VL. Effects of magnesium sulfate aerosol on indices of external respiration in patients with bronchial asthma [Russian]. *Klin Med (Mosk).* 1990;68:31-34.

33. Fedoseev GB, Emel'ianov AV, Malakauskas KK, et al. The therapeutic potentials of magnesium sulfate in bronchial asthma [Russian]. *Ter Arkh.* 1991;63:27-29.

34. Portel L, Hilbert G, Gruson D, et al. Malignant hyperthermia and neuroleptic malignant syndrome in a patient during treatment for acute asthma. *Acta Anaesthesiol Scand.* 1999;43:107-110.

35. Pabon H, Monem G, Kisson N. Safety and efficacy of magnesium sulfate infusions in children with status asthmaticus. *Pediatr Emerg Care.* 1994;10:200-203.

36. Okayama H, Aikawa T, Okayama M, et al. Bronchodilating effect of intravenous magnesium sulfate in bronchial asthma. *JAMA.* 1987;257:1076-1078.

37. Hauser SP, Braun PH. Intravenous magnesium administration in bronchial asthma [German]. *Schweiz Med Wochenschr.* 1989;119:1633-1635.

38. Leber MJ, Rao S, Birrer RB. Magnesium sulfate used as an adjunct to beta-agonists in acute asthma: a case report [letter]. *J Emerg Med.* 1991;9:377.

39. Kuitert LM, Kletchko SL. Intravenous magnesium sulfate in acute, life-threatening asthma [published erratum appears in *Ann Emerg Med.* 1992;21:1272]. *Ann Emerg Med.* 1991;20:1243-1245.

40. Schiermeyer RP, Finkelstein JA. Rapid infusion of magnesium sulfate obviates need for intubation in status asthmaticus. *Am J Emerg Med.* 1994;12:164-166.

41. Mills R, Leadbeater M, Ravalia A. Intravenous magnesium sulphate in the management of refractory bronchospasm in a ventilated asthmatic. *Anaesthesia.* 1997;52:782-785.

42. Skobeloff EM, Kim D, Spivey WH. Magnesium sulfate for the treatment of bronchospasm complicating acute bronchitis in a four-months'-pregnant woman. *Ann Emerg Med.* 1993;22:1365-1367.

43. Bloch H, Silverman R, Mancherje N, et al. Intravenous magnesium sulfate as an adjunct in the treatment of acute asthma. *Chest.* 1995;107:1576-1581.

44. 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;129:809-814.

45. Tiffany BR, Berk WA, Todd IK, et al. Magnesium bolus or infusion fails to improve expiratory flow in acute asthma exacerbations. *Chest.* 1993;104:831-834.

46. Skorodin MS, Tenholder MF, Yetter B, et al. Magnesium sulfate in exacerbations of chronic obstructive pulmonary disease. *Arch Intern Med.* 1995;155:496-500.

47. Green SM, Rothrock SG. Intravenous magnesium for acute asthma: failure to decrease emergency treatment duration or need for hospitalization. *Ann Emerg Med.* 1992;21:260-265.

48. Devi PR, Kumar L, Singhi SC, et al. Intravenous magnesium sulfate in acute severe asthma not responding to conventional therapy. *Indian Pediatr.* 1997;34:389-397.

49. Silverman R, Osborne H, Runge J, et al. Magnesium sulfate as an adjunct to standard therapy in acute severe asthma [abstract]. *Acad Emerg Med.* 1996;3:467-468.

50. Matusiewicz SP, Cusack S, Greening AP, et al. A double blind placebo controlled parallel group study of intravenous magnesium sulphate in acute severe asthma [abstract]. *Eur Respir J.* 1994;18:14S.

51. Rodrigo G, Rodrigo C, Burschtin O. A meta-analysis of the effects of ipratropium bromide in adults with acute asthma. *Am J Med.* 1999;107:363-370.

52. Cohen J. *Statistical Power Analysis for the Behavioral Sciences.* 2nd ed. Hillsdale, NJ: Lawrence Erlbaum Associates; 1988:567.

53. Sharp S, Steme J. sbe16: Meta-analysis. *Stata Technical Bulletin.* 1997;38:9-14.

APPENDIX

Formulas used to derive results

According to the technique known as Hedges' g ,⁷ and later explicated by Pettiti,⁸ effect size can be quantified as a quotient expressed as:

$$d_j = \frac{(\text{mean}_e - \text{mean}_c)}{SD_{pi}}$$

where d_j measures effect size in the j th study, mean_e is the mean in the experimental group, mean_c is the mean in the control group, and SD_{pi} is the pooled estimate of the SD of the effect measure for each study, or of the control group. The effect size thus relates mean differences between treatment groups to the SD. The sampling variance of d_j was then estimated by the equation:

$$\text{Variance}_j = \frac{(8 + d_j^2)}{2N_j}$$

The standard error was taken as the square root of the variance. The "meta" procedure in the Stata statistical package⁵³ was used to obtain a weighted average of the d_j across studies, weighting each d_j by the inverse of its estimated sampling variance, using the following computational methods.

The fixed-effects model is calculated assuming a true treatment effect across studies:

$$\theta_F = \frac{\sum_{i=1}^k w_i \theta_i}{\sum_{i=1}^k w_i}$$

Where $w_i = 1/v_i$. The variance of θ_F is $1/\sum_{i=1}^k w_i$.

The test for comparability, or heterogeneity across studies, is:

$$Q = \sum_{i=1}^k w_i (\theta_i - \theta)^2$$

Q has a χ^2_{k-1} distribution.

The random-effects model uses an estimator of between-studies variation, τ^2 :

$$\tau^2 = \max \left[0, \frac{Q - (k - 1)}{\sum_{i=1}^k w_i - \left(\frac{\sum_{i=1}^k w_i^2}{\sum_{i=1}^k w_i} \right)} \right]$$

The studies are combined in a fashion similar to the fixed-effects model, only in this case $w_j = 1/(v_j + \tau^2)$ for both θ_R and the variance of θ_R . For this reason, w_j is sometimes denoted w_j^* .