Systematic Review on Efficacy of Magnesium (Intravenous or Nebulized) for Acute Asthma Episodes in Children

***Source Citation*:** Su Z, Li R, Gai Z. Intravenous and nebulized magnesium sulfate for treating acute asthma in children: A systematic review and meta-analysis. Pediatr Emerg Care. 2016 Oct 4. [Epub ahead of print]

***Section Editor*:** ABHIJEET SAHA

SUMMARY

This systematic review and meta-analysis aimed to evaluate the efficacy of intravenous (IV) and nebulized magnesium sulfate for acute asthma in children. Ten randomized and quasi-randomized trials (6 IV, 4 nebulized) were identified through search of databases (PubMed, Cochrane Library, and EMBASE). Intavenous magnesium sulfate treatment was associated with significant effects on respiratory function (standardized mean difference 1.94; 95% CI 0.80,3.08; *P*=0.0008) and hospital admission (RR 0.55; 95% CI 0.31,0.95; *P*=0.03). But nebulized magnesium sulfate treatment showed no significant effect on respiratory function (standardized mean difference 0.19; 95% CI –0.01, 0.40; *P*=0.07) or hospital admission (RR 1.11; 95% CI 0.86,1.44; *P*=0.42). Authors concluded that IV magnesium sulfate is an effective treatment in children, with significant improvement in pulmonary function and decrease in hospitalization and need for further treatment, but nebulized magnesium sulfate treatment showed no significant effect on respiratory function or hospital admission and further treatment.

COMMENTARIES

Evidence-based Medicine Viewpoint

Relevance: In recent years, magnesium sulphate therapy has gained popularity for managing acute asthma exacerbations in adults and children, on account of its perceived efficacy, mechanism of action distinct from conventional bronchodilator(s), and relative safety. A Pubmed search on 13 January 2017 using the terms 'magnesium (acute asthma)' with filter for 'Child: birth-18 years' yielded 21 citations with the 'Systematic Review' filter, and 26 citations using the 'Randomized Controlled Trial' filter. Among the 21 citations, a recent Cochrane systematic review [1], including five double blind, placebo-controlled randomized trials, reported that IV magnesium decreased hospitalization, but had no impact on hospital revisits. A 2013 systematic review [2] showed that IV magnesium decreased both hospital admissions, and also resulted in better lung function parameters. The same review showed that nebulized magnesium improved both these outcomes in adults, although not in children [2]. A recent analysis of multiple systematic reviews on management of acute asthma in children confirmed the beneficial effect of IV magnesium on hospitalization rates and pulmonary function parameters [3].

However, the 2016 GINA (Global Initiative for Asthma) guidelines explicitly stated that IV magnesium sulfate is not recommended in children, although it could work in children who do not respond to initial therapy [4]. Similarly, the guideline did not recommend nebulized magnesium sulfate, although it improved lung function parameters in children with severe exacerbations [4]. The 2014 British guideline [5] also recommended against using nebulized magnesium sulfate in children with asthma exacerbations, citing the need for more robust evidence on the subject. This position was reiterated in the September 2016 revision of the guideline [6]. For IV magnesium, the 2014 guideline [5] reported the intervention to be safe, but did not explicitly recommend its usage; whereas the 2016 guideline [6] recommended 40 mg/kg IV magnesium for those not responding to initial treatment. However, guarded language was used *viz* to consider IV magnesium as first-line IV treatment for those who do not respond adequately to first-line treatment. The reason for the ambiguous statement is unclear, despite the latest evidence available.

Against this backdrop, yet another systematic review by Su, *et al.* [7] evaluating efficacy of magnesium sulfate (intravenous and nebulized) has been published.

Critical appraisal: At the outset, the need for a new systematic review has to be considered carefully. The Cochrane review [1] on IV magnesium, published in April 2016 included literature search till 23 February 2016. In contrast, Su *et al*, [7] included studies on

intravenous magnesium till June 2015. Thus, for IV magnesium, the Cochrane review [1] is the most up-to-date evidence. The immediate online publication of Cochrane reviews meeting the stringent publication criteria of the Cochrane Collaboration greatly facilitates them to be up-to-date. Since the Cochrane review protocol was published in April 2014 [8], the justification for undertaking a new review on IV magnesium is unclear.

In contrast, the last systematic review on nebulized magnesium was published in 2013 [2], and included only one pediatric trial with 62 children. Hence, the updated review on nebulized magnesium by Su, *et al*. [7] is timely. ***Table*** **I** present a critical appraisal of the systematic review using one of the various tools available for the purpose [9]. Overall, the review met the major criteria for a good quality review.

One of the main limitations with the literature search strategy in the review [7] is the lack of clarity about the Comparator against which magnesium (both IV and nebulized) was evaluated. The Cochrane review on intravenous magnesium [1] included only placebo-controlled trials; whereas Su, *et al*, [7] did not state this. They included a study by Torres [10] which is a non-placebo controlled trial (shown in the meta-analysis as Silvio 2012), which suggests that they did not intend to exclude non-placebo trials. In fact, the authors stated only the exclusion of trials comparing IV magnesium *versus* beta-2 agonist. But, this does not explain the exclusion of the trial by Singhi, *et al*. [11], comparing IV magnesium versus terbutaline and aminophylline. The arm comparing magnesium *versus* aminophylline would be eligible for the review (although the trial outcome was treatment success, hence different from the systematic review outcomes). All such difficulties could have been avoided if authors had framed and reported a clear clinical question in the PICO format.

The issue about the trial eligibility criteria is more than academic, as the lack of clarity enabled Su, *et al*. [7] to include data from the trial by Torres, *et al* [10] in their meta-analysis on hospitalization. Torres, *et al*. [10] reported about children requiring ventilation support, which Su, *et al*. [7] included in the outcome of 'hospitalization' as a subgroup analysis. The inappropriate clubbing of a clearly distinct outcome resulted in an apparently more impressive pooled outcome (RR 0.55) compared to pooled RR of 0.70 for trials reporting hospitalization. Further, inclusion of the Torres trial [10] makes the review by Su, *et al*. [7] 'look different' from the Cochrane review on IV magnesium as there appear to be six trials compared to five in the Cochrane review. Another 'cosmetic difference' is the choice of 'risk ratio' for reporting outcomes in contrast to 'odds ratio' stated a priori in the Cochrane review protocol [8].

Another major limitation is that Su, *et al*. [7] did not specify the timing of administering magnesium as a criterion for including trials. Given that IV magnesium was already shown to be efficacious [5,6] when administered to children who do not respond to standard first-hour therapy, it is of great relevance to know whether the authors intended to study magnesium administered *after* initial therapy, or *with* initial therapy (note emphasis). The Cochrane review on intravenous magnesium [1] included four trials administering IV magnesium to children who did not respond to initial treatment (three doses of nebulized bronchodilator). The fifth trial included children who did not respond to one dose of nebulized salbutamol combined with IV methyl prednisolone. Since Su, *et al*. [7] included the same trials as the Cochrane review; the difficulty about the timing of administration is overcome. The sixth trial [10] included by them enrolled children who did not responded to three doses of inhaled salbutamol and IV methyl prednisolone. This suggests that the various trials included in the systematic review did not have uniform protocols for initial therapy (*i.e*. before using magnesium). The issue has greater importance considering that the more recent trials and current therapy protocols include systemic steroid administration within the first hour itself, whereas the older trials so not.

Therefore, one can argue that since the real role of magnesium (by any route) is after initial therapy has failed; hence it is important to compare it against other options used in the second hour, rather than placebo. This aspect has been studied only by Singhi *et al*, [11] who randomized non-responders to IV magnesium or IV terbutaline or aminophylline. They demonstrated greater therapeutic success and less side effects with magnesium compared to either of the other two medications. This firmly places IV magnesium as the preferred agent for children who do not respond to initial treatment.

In addition to these limitations in the systematic review [7], there are some errors in data extraction. Some of these (such as lack of intention-to-treat analysis, incorrect entry of mean/standard deviation) could affect the results marginally, while others (interchange of data of two trials in the forest plot reporting hospitalization with intravenous magnesium) do not.

The abstract of the review [7] mentions a third outcome *viz* need for further treatment, but there is no mention if this subsequently. One would also expect a

TABLE I: CRITICAL APPRAISAL OF THE TRIAL

Question	*Comments*
Validity	
1. Is there a clearly focused clinical question?	A clinical question in the traditional PICO format is missing, but the following can be presumed: What is the efficacy of intravenous and nebulized magnesium (Interventions) versus no magnesium (Comparator) on hospitalization and lung function parameters (Outcomes) among children with acute asthma exacerbation (Population)?
2. What are the criteria for selection of studies?	The authors selected randomized controlled trials (RCT) and quasi-randomized trials evaluating intravenous or nebulized magnesium in children (<18 y) with acute asthma episodes. They excluded trials comparing magnesium against â2-agonists. No efforts were made to include pediatric data from trials that included both children and adults.
3. Is the literature search method specified?	The authors searched three databases (Medline, Embase and the Cochrane Library) for randomized trials till June 2015. No language restrictions were used. Additional searches were made through bibliography section of selected citations and review articles (although the output is not presented separately).
4. Have the identified studies been evaluated for methodological quality?	The authors used the Cochrane Collaboration Risk of Bias tool for methodological assessment. However, they did not present the evaluation of each trial with the Tool criteria, but presented an overall summary estimate.
5. Is it appropriate to combine the results from different studies?	In general, it appears reasonable to combine data from 5 of the 6 included trials in the iv magnesium meta-analysis; the sixth had a distinct outcome that has been used as a surrogate for hospitalization. The 4 trials in the nebulized magnesium are suitable for combining data.
Results	
1. Were the results consistent from one study to another?	There was significant heterogeneity for both outcomes in the two meta-analyses (*ie* iv and nebulized magnesium). However, other than using the more conservative random effects model for analysis, no further exploration was undertaken.
2. What were the overall results of the review?	*IV Magnesium*Hospitalization: RR 0.70 (95% CI 0.54,0.90), 3 trials, 155 participants, I^2 7% (Note: One trial included by the authors had an entirely different outcome, hence is not included here). Lung function improvement: SMD 1.94 (95% CI 0.80, 3.08), 128 participants, I^2 84%.*Nebulized Magnesium*Hospitalization: RR 1.11 (95% CI 0.86,1.44), 2 trials, 563 participants, I^2 0% .Lung function improvement: SMD 0.19 (95% CI –0.01,0.40), 3 trials, 362 participants, I^2 40%.
3. How precise were the results?	For IV magnesium, the pooled results had fair degree of precision. The confidence intervals for outcomes with nebulized magnesium overlapped the line of no effect, although the intervals were not very wide.
Applicability	
1. Is the local population similar to the people included in the original studies?	The clinical problem and patient profile are not vastly different from the settings involved in the included trials.
2. Is the intervention feasible in my setting?	Magnesium administration is feasible in most pediatric emergency rooms in India. Fortunately it does not require intensive biochemical monitoring for adverse events (unlike aminophylline). However there is variable access to higher-level care such as intensive care units, mechanical ventilation etc.
3. Have all the clinically relevant results been taken into consideration?	This systematic review did not include any safety outcomes. In terms of efficacy, some relevant outcomes such as hospital revisits, duration of Emergency stay, treatment failure, cost *etc* have not been considered.
4. Do the benefits outweigh the potential harm?	There is clear benefit with IV magnesium compared to placebo; but this review is insufficient to address the theoretical risks of adverse events. However, there is insufficient evidence of benefit for nebulized magnesium.

systematic review of interventions to report on safety (in addition to efficacy). Although magnesium is generally well tolerated and hence deemed safe, some outcomes related to safety (such as side effects, tolerance) should have been incorporated.

On the plus side, the authors [7] presented the review in simple, easy-to-understand language, without undue statistical (or other) jargon. They also acknowledged some of the limitations with methodology. However no efforts were made to evaluate publication bias.

Extendibility: The clinical problem, type of patients, therapeutic options and mode of administration (intravenous magnesium) is extendible to hospital-based settings in India. In fact, IV magnesium is already the standard of care in most pediatric emergency rooms. In contrast, the lack of clear benefit with nebulized magnesium precludes its application in routine practice.

Conclusion: IV magnesium is efficacious in children with asthma exacerbations who do not respond to first hour therapy. Limited data suggest that it is preferable to other options such as aminophylline or terbutaline infusions. However, there is insufficient evidence to support the use of nebulized magnesium.

Funding: None; *Competing interest*: None stated.

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Pediatric Pulmonologist's Viewpoint

The authors in this systematic review and meta-analysis of randomized and quasi-randomized controlled trials have synthesized available evidence to evaluate the efficacy of intravenous (IV) and nebulized magnesium sulfate ($MgSO_4$) as an adjunctive therapy in acute asthma in children (1-18 years). For IV magnesium sulfate, six studies (n=325), and for nebulized $MgSO_4$, four studies (n=870) were included in the analysis. Dose of IV $MgSO_4$ ranged from 25-100 mg/kg infusion over 20-35 minutes, and the dose of nebulized $MgSO_4$ used was 2-3 mL. Patients included had moderate-severe acute asthma, and outcomes studied were respiratory function and hospital admission. Most children received nebulized bronchodilators and systemic steroids as standard therapy. Results indicated IV $MgSO_4$ was associated with a significant improvement in respiratory function (SMD 1.94; 95% CI 0.80,3.08; P=0.0008), and reduced the number of hospital admissions by 45% (RR 0.55; 95% CI 0.31,0.95; P=0.03). Nebulized $MgSO_4$ showed no significant effect on respiratory function (SMD 0.19; 95% CI, –0.01,0.40; P=0.07) or hospital admission (RR 1.11; 95% CI 0.86,1.44; P=0.42). Most trials indicate both routes of $MgSO_4$ to be safe in children.

A recent Cochrane review [1] based on only randomized controlled trials in children has also shown that adjunctive treatment with IV $MgSO_4$ reduced the odds of admission to hospital by 68%, though results were based on only three studies. Analysis for the

outcome 'return to the emergency department within 48 hours' was not found to be statistically significant.

The standard first line therapy in the emergency department (ED) for moderate-to-severe acute asthma in children includes oxygen, nebulized short-acting β_2 agonist, systemic steroids and ipratropium. Most pediatric asthma guidelines seem to suggest the use of IV $MgSO_4$ to augment therapy in patients with severe exacerbations, who do not adequately respond to initial therapy, although evidence for its efficacy was based on adult studies. The BTS/SIGN guideline (2014) states: "although IV $MgSO_4$ is safe in children but its place in management is not yet established." GINA 2016 report recommends IV $MgSO_4$ in severe exacerbations that fail to respond to initial therapy. Regarding nebulized $MgSO_4$, GINA 2016 states that nebulized salbutamol can be mixed with $MgSO_4$ instead of isotonic saline. Although overall efficacy of this combination is unclear, pooled data from three trials suggests improved pulmonary functions. This was based on adult studies.

This systematic review shows evidence of efficacy of IV $MgSO_4$ in improving respiratory functions and reducing hospital admission, but no evidence to support the use of nebulized $MgSO_4$ in moderate-severe acute asthma in children. However, these results are based on a small sample size and further trials are warranted to firmly cement the efficacy of $MgSO_4$ in asthma management. While the use of nebulized $MgSO_4$ looks inviting, due to its ease of delivery along with nebulized salbutamol, it will have to await future adequately-powered trials to establish or refute its role in acute asthma care. Whether a higher dose of nebulized $MgSO_4$ will bring any change to the results can also be explored. Most trials have used nebulized $MgSO_4$ as 150 mg or 2-3 mL. Future trials are also warranted to assess the effect of IV $MgSO_4$ on other clinically relevant outcomes, including intensive care admissions, return to ED within 48 hours and respiratory scores. Dose of IV $MgSO_4$ also needs to be standardized, as most trials have used different doses. Role of $MgSO_4$ is not yet established for children 5 years and younger, due to limited data in this age group.

Funding: None; *Competing interest*: None stated.

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