Use of intravenous magnesium sulfate in addition to standard first-line treatment with inhaled/nebulised short-acting beta 2 agonist and systemic steroids in the management of acute asthma exacerbations in children: a systematic review and meta-analyses of randomised controlled trials

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ABSTRACT

Background The role of intravenous magnesium sulfate in asthma exacerbation is unclear.

Aims To determine the efficacy and safety of intravenous magnesium sulfate in managing asthma exacerbation in children.

Methods We searched MEDLINE, EMBASE, CINAHL, the Cochrane Central Register of Controlled Trials and the Web of Science up to May 2024. We included randomised controlled trials and followed the international guidelines for conducting systematic reviews. Outcomes included morbidity, escalation of care, length of hospital stay, lung functions, adverse events, and mortality.

Results Nine studies (total participants=473) were included. Hospitalisation rate and the need for non-invasive ventilation were less among the intravenous magnesium sulfate group (mean difference (MD)=0.70, 95% CI 0.54 to 0.90, I^2 7%, n=115) and (risk ratio (RR)=0.17, 95% CI 0.15 to 0.54, p=0.003, n=143), respectively. Asthma severity scores (MD=−0.18, 95% CI −1.35 to 0.98, I^2 2%, n=115), length of hospital stay (MD=−78.86, 95% CI −200.37 to 42.66, I^2 99%, n=284) and the need for invasive ventilation (RR=0.35, 95% CI 0.11 to 1.17, I^2 0%, n=237) were similar. There was no difference in the Paediatric Intensive Care Unit (PICU) admission rate (p=0.43 n=61). Peak expiratory flow improved in the intravenous magnesium group (p<0.001, n=20). No serious adverse events were reported.

Conclusion We found low-certainty evidence that intravenous magnesium sulfate results in a lower hospitalisation rate and less need for non-invasive ventilation. Asthma scores, PICU admission, invasive ventilation and length of hospital stay were similar. While the evidence base is weak, the favourable safety profile suggests that intravenous magnesium sulfate can be considered a treatment for asthma exacerbations.

PROSPERO registration number CRD42023405261.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Simultaneous administration of intravenous magnesium sulfate and a beta 2-agonist might have an additive bronchodilator effect, with varying supportive evidence.

WHAT THIS STUDY ADDS

⇒ Low-certainty evidence that hospitalisation and the need for non-invasive ventilation are less in children with acute asthma exacerbation who receive intravenous magnesium sulfate.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The favourable safety profile suggests that intravenous magnesium sulfate can be considered a second-line treatment for acute asthma exacerbation despite current low-level evidence of efficacy.

INTRODUCTION

This is one of a series of systematic reviews commissioned by the WHO to inform consolidated recommendations for managing common childhood illnesses. The recommendations will update the existing guidance in the Pocket Book of Hospital Care for Children and Integrated Management of Childhood Illness charts.[1 2]

Asthma is one of the most common chronic diseases, with an estimated 262 million people affected in 2019.[3] It is a common cause of morbidity in children and adolescents[4]; hence, the acute and long-term management of asthma was identified by WHO as a priority for evidence appraisal and guideline development.[4 5]

The standard first-line treatment of acute asthma exacerbations includes systemic corticosteroids and inhaled beta 2-agonist medications.[6 7] Additional medications are added to this first-line treatment in the management of more severe asthma exacerbations with varying levels of supportive evidence.[8]

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One of the adjunct treatments for severe asthma exacerbation is intravenous magnesium sulfate, which has a bronchodilator effect.[9] The mode of action of magnesium sulfate is thought to be related to direct smooth muscle relaxation; however, additional mechanisms may be linked to blocking calcium ion influx into smooth muscle cells, thus modulating mast cell histamine release, anti-inflammatory properties and cholinergic neural transmission.[9] Furthermore, evidence suggests that the simultaneous administration of magnesium sulfate and a beta 2-agonist has an additive bronchodilator effect, perhaps owing to magnesium sulfate augmenting the beta-receptor agonist response.[10] A previous systematic review concluded that intravenous magnesium sulfate significantly improved pulmonary functions with less hospitalisation and less escalation of treatment.[11]

This review aimed to assess the safety and efficacy of intravenous magnesium sulfate in addition to the standard first-line treatment with inhaled/nebulised short-acting beta 2 agonist (SABA) and systemic steroids compared with the standard first-line treatment of acute asthma attacks in children and adolescents aged 18 years and under.

MATERIALS AND METHODS

This study followed the international recommendations for conducting systematic reviews and meta-analyses[12] and registered with the International Prospective Register of Systematic Reviews, with the registration number CRD42023405261.

Study selection and search strategy

The following databases were searched from inception to April 2023 and updated on 20 May 2024: MEDLINE, EMBASE, CINAHL, Cochrane Central Register of Controlled Trials and Web of Science. We inspected reference lists from retrieved articles to identify any additional citations the electronic searches missed. We also searched unpublished ongoing clinical trials on the websites www.clinicaltrials.gov and www.controlled-trials.com.

Terms for population, interventions and outcomes were included in our search strategy. Search terms used are (acute or severe or asthma) AND (magnesium sulfate). See online supplemental appendix 1 for the complete search strategy.

Eligibility criteria and outcomes

We included randomised controlled trials (RCTs) that assessed the safety and efficacy of intravenous magnesium sulfate in addition to the standard first-line treatment (nebulised/inhaled SABA and systemic steroid) compared with standard first-line treatment in children and adolescents aged 18 years and under with acute asthma exacerbations.

Outcome measures

Primary outcome

- Morbidity (symptoms, hospitalisation rate and school absence in days).

Secondary outcomes

- Escalation of care (ventilation/Paediatric Intensive Care -PICU- admission).
- Length of hospital stay in hours.
- Adverse events.
- Mortality due to exacerbation.
- Lung functions (change in forced expiratory volume (FEV_1) in litres or per cent of predicted, and peak expiratory flow rate (PEFR) in L/min)

We applied no language restriction and planned to translate relevant studies into English if needed.

Data collection and analysis

Selection of studies

Authors in pairs (SA, RS and AT, AZZ) assessed relevant manuscripts. They independently evaluated the eligibility of all identified trials. Any disagreement among authors was resolved by discussions and consultation with a third author (ISA, CP).

Data extraction and management

The full texts of included studies were reviewed for inclusion in this review. Two authors (NA, AAH) independently extracted data that included demographic information, methodology, intervention details and reported outcomes. They compared the extracted data, and any differences were resolved by consensus and discussion with a third author (AAH) if needed. We analysed the extracted data using the Cochrane Collaboration's Review Manager.[13]

Assessment of risk of bias in included studies

Two review authors (KM, AAH) used the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* to assess the risk of bias.[14] They independently evaluated the risk of bias for each study, and any disagreement was resolved by a mutual discussion or involving a third author (ISA, CP). We assessed the risk of bias according to the following domains:

- Random sequence generation.
- Allocation concealment.
- Blinding of participants and personnel.
- Blinding of outcome assessment.
- Incomplete outcome data.
- Selective outcome reporting.

Each risk of bias will be rated as either low, high or unclear.

Data management

The mean difference (MD) was calculated for continuous data when appropriate. For dichotomous data, we reported the risk ratio (RR). All missing data were highlighted within the results section. We used an intention-to-treat basis of analysis. The review highlighted and discussed any dropout of included children in the primary studies. We planned to contact authors of published primary studies for further clarification and to provide additional information when needed. The I^2 statistic was used[15] to measure heterogeneity among the included trials. We considered an I^2 value of:

- 0–40% might not be as important.
- 30–60% represent moderate heterogeneity.
- 50–90% represent substantial heterogeneity.
- 75–100% represent considerable heterogeneity.

The heterogeneity was explored further using sensitivity analyses when appropriate. We planned to investigate potential publication bias using funnel plots for each outcome if there were 10 or more studies.[16]

Data synthesis

Studies were pooled for meta-analysis when sufficiently similar data was available. Narrative descriptions were used when data could not be combined, or significant heterogeneity was found. The statistical package Review Manager V.5.4, provided by the Cochrane Collaboration, was used for data synthesis and analysis.[13] All measures were reported with 95% CIs. A random-effects model was used for data synthesis.

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Subgroup analysis

If data were available, the following subgroups were planned to be assessed: severity of asthma using the British Thoracic Society 2019 criteria and timing of administration of intravenous magnesium sulfate.

Sensitivity analysis

We planned to perform a sensitivity analysis to explore the potential impact of missing data and any methodological heterogeneity. To assess this impact on the overall results, we omitted the studies at high risk of bias from the meta-analysis and used both random and fixed-effect models of data synthesis.

Summary of findings

The principles of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system[17] were used to assess the quality of the body of evidence associated with the following outcomes: morbidity, escalation of care, length of hospital stay, adverse events and mortality. The quality level of a body of evidence was downgraded based on the following factors:

- Methodological quality.
- The directness of the evidence.
- The heterogeneity of the data.
- The precision of effect estimates.
- The risk of publication bias.

RESULTS

Study selection

We identified 842 citations. After duplicates were removed and titles and abstracts were evaluated, the full texts of 24 citations potentially meeting the inclusion criteria were assessed. 15 studies were excluded: 7 were non-RCTs, 3 assessed different interventions and 5 included only adult participants. We included nine RCTs involving 473 children. Figure 1 shows a flowchart detailing the study's selection process.

Study characteristics

We included only nine RCTs (n=473). The characteristics of the included studies are provided in online supplemental table 1. The definition of the severity of bronchial asthma was based on the primary studies included.

Risk of bias

The risk of bias assessment in the nine trials is shown in figure 2, online supplemental figure 1. Four of the included studies were assessed as low risk of bias regarding randomisation,[18–21] and five studies were classified as unclear risk as no information was provided by the authors.[22–26] Four studies were assessed as low risk for allocation concealment,[18 20 21 26] and the remaining studies were classified as unclear risk, with no information shared by the authors.[19 22–25] Five studies were classified as a low risk of bias with regards to blinding of participants and personnel and outcome assessment,[18–20 25 26] two unblinded studies were classified as high risk,[21 24] and two studies had no information regarding blinding. Two studies were classified as unclear bias.[22 23] All included studies were classified as low risk for incomplete outcome data, selective reporting and other biases.

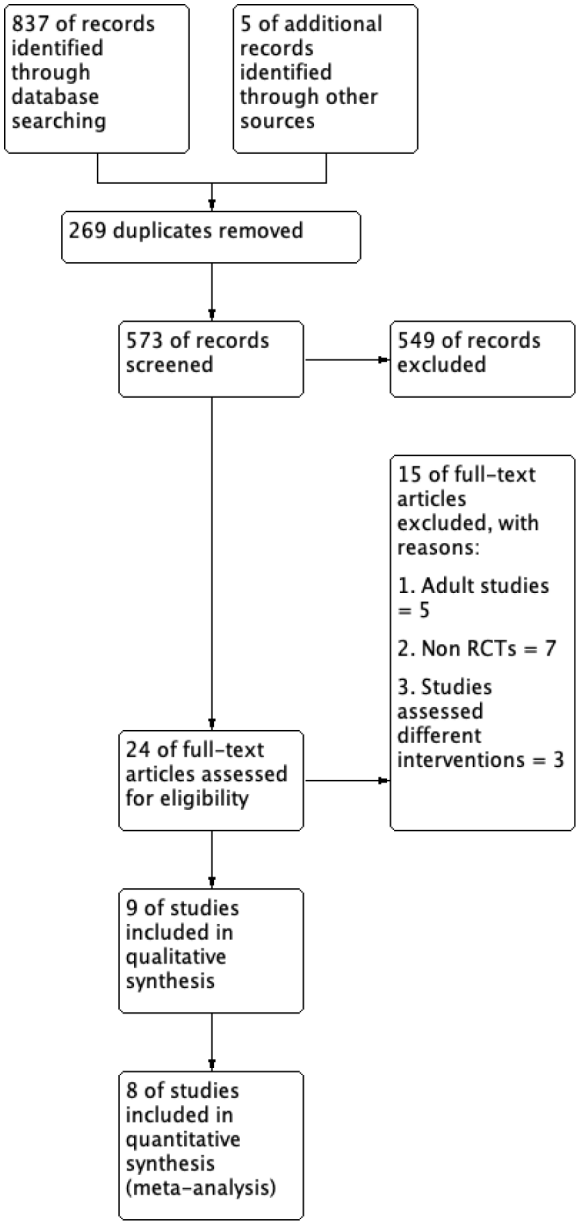

Figure 1 Study flow diagram. RCTs, randomised controlled trials.

Effect of the intervention

Primary outcomes

Change in asthma severity score

The primary studies used asthma severity scores to report morbidity symptoms. Two studies were included in this outcome.[20 26] The asthma severity scores were assessed using Pulmonary Index (PI)[27] and the Respiratory Distress Assessment (RDA) scores (table 1, online supplemental material 1). The overall improvement of asthma scores showed no difference when intravenous magnesium sulfate was compared with other treatments (low certainty evidence) (MD=−0.18, 95% CI −1.35 to 0.98, I^2 2%, n=115) (figure 3).

Hospitalisation rate

Three studies reported this outcome.[18 19 26] The hospitalisation rate was significantly lower in children receiving intravenous magnesium sulfate (low certainty evidence) (RR=0.70, 95% CI 0.54 to 0.90, I^2 7%, n=115) (online supplemental figure 2).

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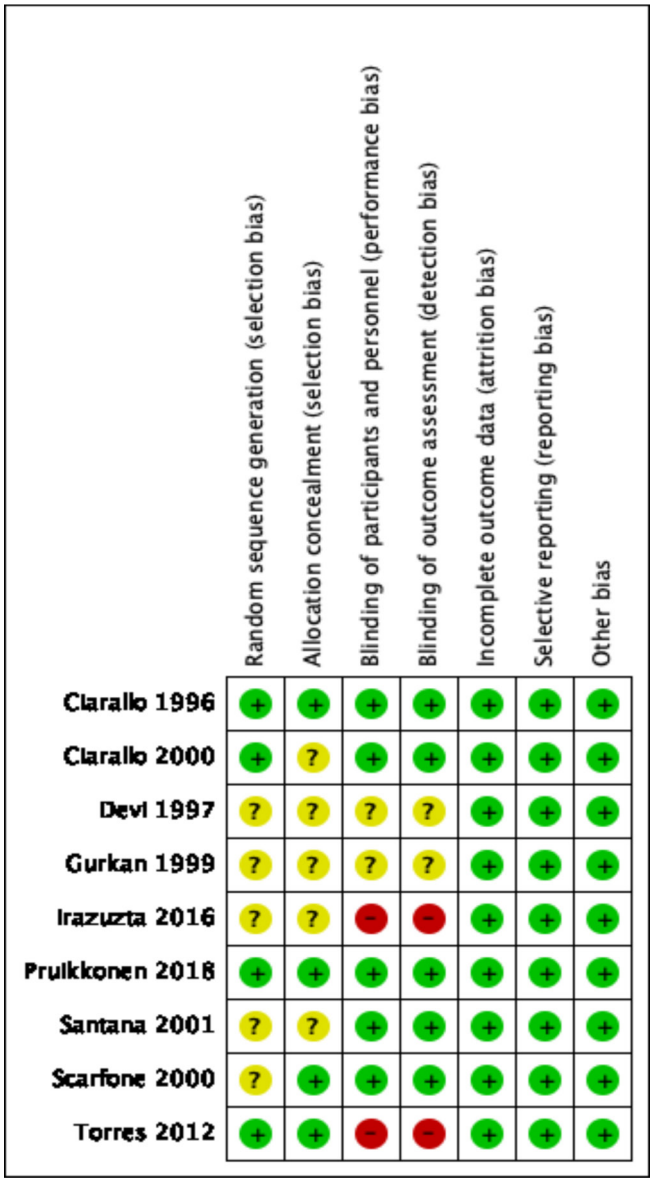

Figure 2 Risk of bias summary: review the authors' judgments regarding each risk of bias item for each included study.

Secondary outcomes

The need for invasive and non-invasive ventilation

Three studies assessed this outcome.[20 21 25] Three studies evaluated the need for invasive ventilation[20 21 25] and reported no statistical difference between the two groups (very low certainty evidence) (RR=0.35, 95% CI 0.11 to 1.17, I^2 0%, n=237) (online supplemental figure 3). One study reported less need for non-invasive ventilation in the intravenous magnesium group[21] (low certainty evidence) (RR=0.17, 95% CI 0.05 to 0.54 n=143) (online supplemental figure 3).

PICU admission rate

One study reported this outcome.[20] The PICU admission rate was not significantly different among both groups (moderate certainty evidence) (RR=0.58, 95% CI 0.15 to 2.22, p=0.43 n=61) (online supplemental figure 4).

Length of hospital stay in hours

Four studies were included.[20–22 25] There was no difference regarding the length of hospital stay in hours (very low certainty evidence) (MD=−78.86, 95% CI −200.37 to 42.66, I^2 99%, n=284) (online supplemental figure 5). Reanalysing the data using the fixed effects model showed a significantly shorter duration of hospital stay among the intravenous magnesium group (MD=−14.03, 95% CI −18.01 to −10.4, I^2 99%, n=284). Further sensitivity analysis was done by omitting the study done by Torres *et al* due to the high risk of blinding, which showed a shorter duration of hospital stay in the intravenous magnesium sulfate group with low heterogeneity (MD=−5.55, 95% CI −9.69 to −1.50, I^2 0% n=141).

Improvement in the PEF

One study reported this outcome.[23] The intravenous magnesium sulfate group improved the PEF at 90 min from the baseline (MD=36.60, 95% CI 33.28 to 39.92, p<0.00001, n=20) (online supplemental figure 6).

Adverse events

One patient (3%) in the intravenous magnesium sulfate group had facial redness and redness around the site of the intravenous cannula during the first 15 min of the intravenous infusion.[20] One study[18] reported minor side effects like epigastric warmth (12.5%), pain (16.6%) and tingling and numbness (12.5%) at the site of infusion in the intravenous magnesium group. The other studies did not report any other significant adverse events.[18 19 21 23]

Other outcomes

The supplementary file shares the results of the following outcomes: the need for supplemental oxygen and the duration of the oxygen supplementation in hours including online supplemental figures 7 and 8.

The primary studies reported no data for the following outcomes: symptoms, school absence and mortality due to exacerbation. There was no data to assess the following subgroups: severity of asthma and timing of administration of intravenous magnesium sulfate.

We have included one study that assessed a high-dose infusion versus a bolus dose of intravenous magnesium sulfate. The result is shared in the online supplemental figures 9–11.

Quality of evidence

The GRADE certainty of evidence for the outcome: change in asthma severity scores, hospitalisation rate and non-invasive ventilation was graded as low certainty of evidence. The length of hospital stay and the need for invasive ventilation were downgraded to very low certainty of evidence. The PICU admission rate was graded as moderate certainty of evidence (table 1).

DISCUSSION

In this review, we assessed the safety and efficacy of intravenous magnesium sulfate as an adjunct to the first-line treatment of acute asthma exacerbation. Nine studies were included (n=473). Overall improvement in asthma severity scores, PICU admission rate and the length of hospital stay were similar among both groups. The hospitalisation rate and the need for non-invasive ventilation were less in children who received intravenous magnesium sulfate. The requirement for oxygen supplements was similar in both groups. A study reported that the intravenous magnesium sulfate group improved the PEF from the baseline at 90 min.[22]

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Table 1 Summary of findings

Intravenous magnesium sulfate in addition to the standard first-line treatment compared with placebo or any other treatment for children 18 years and under with acute asthma

Patient or population: children 18 years and under with acute asthma
Setting: high and middle income-economy countries
Intervention: intravenous magnesium sulfate in addition to the standard first-line treatment
Comparison: placebo or any other treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo or any other treatment	Risk with intravenous magnesium sulfate in addition to the standard first line treatment				
Change in asthma severity score		MD 0.18 lower (1.35 lower to 0.98 higher)	–	115 (2 RCTs)	⊕⊕◯◯ Low†‡	
Hospitalisation	767 per 1000	537 per 1000 (414 to 690)	RR 0.70 (0.54 to 0.90)	115 (3 RCTs)	⊕⊕◯◯ Low‡§	
The need for invasive ventilation	88 per 1000	31 per 1000 (10 to 104)	RR 0.35 (0.11 to 1.17)	237 (3 RCTs)	⊕◯◯◯ Very low‡§¶	
Non-invasive ventilation	239 per 1000	41 per 1000 (12 to 129)	RR 0.17 (0.05 to 0.54)	143 (1 RCT)	⊕⊕◯◯ Low‡¶	
PICU admission rate	167 per 1000	97 per 1000 (25 to 370)	RR 0.58 (0.15 to 2.22)	61 (1 RCT)	⊕⊕⊕◯ Moderate‡	
Length of hospital stay		MD 78.86 lower (200.37 lower to 42.66 higher)	–	284 (4 RCTs)	⊕◯◯◯ Very low‡§¶	

GRADE Working Group grades of evidence.
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.
All included studies were assessed as low risk of selective reporting. The individual studies reported all prespecified outcomes. A comprehensive search, including grey literature, was conducted, and none of the studies were commercially funded.
Paediatric Intensive Care Unit (PICU)
*The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
†Different asthma severity scores measurement tools used.
‡Small sample size.
§Variability of the included studies' designs, including outcomes assessment measures.
¶Non-blinded studies included, and unclear risk of randomisation process and/or blinding on other studies.
GRADE, Grading of Recommendations Assessment, Development and Evaluation; MD, mean difference; PICU, Paediatric Intensive Care Unit; RCT, randomised controlled trial; RR, risk ratio.

Overall, there is limited evidence that hospitalisation rate, respiratory support and lung functions were better in the intravenous magnesium sulfate group.

Griffiths and Kew's comparable results revealed a reduction in hospital length of stay in children who received intravenous magnesium sulfate, with an unclear effect on ED treatment time.[28] However, a meta-analysis by Cheuk *et al* showed that intravenous magnesium sulfate probably provides an additional benefit in moderate to severe acute asthma in preventing hospital admission and significantly improving short-term pulmonary function tests and clinical symptom scores.[29]

One study reported that the hospitalisation rate, length of hospital stay and hospital costs were lower in the group receiving a high intravenous magnesium infusion dose.

A previous systematic review, including adults and children, concluded that intravenous magnesium sulfate might be safe

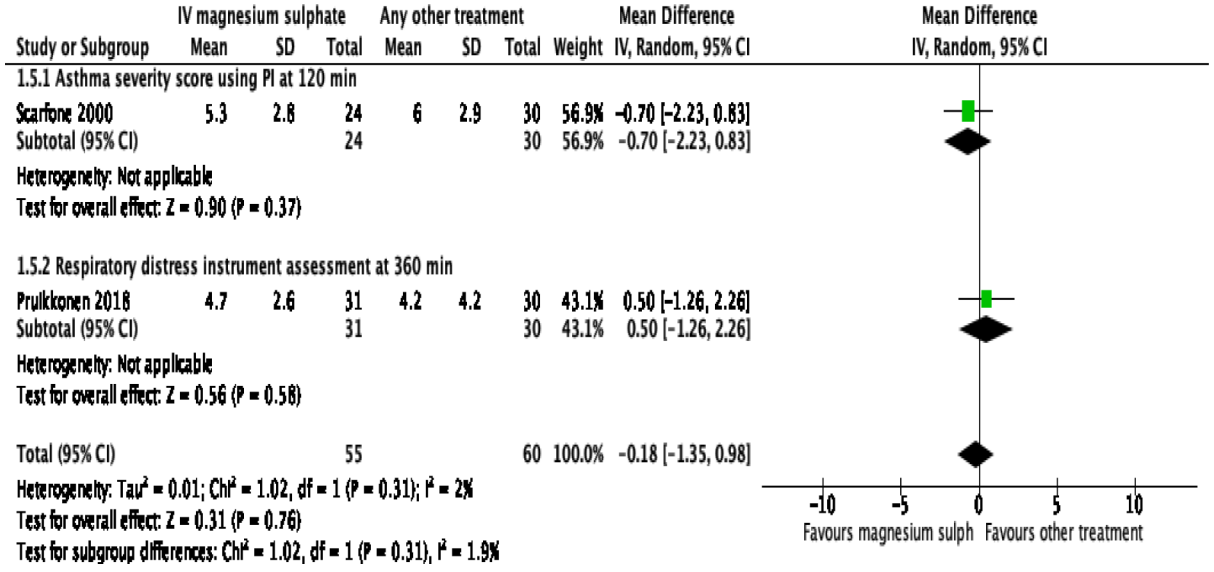

Figure 3 Forest plot of comparison: intravenous magnesium sulfate versus any other treatment, outcome: asthma severity scores.

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and beneficial in patients with severe acute asthma.[30] A recent systematic review of the adult population revealed that intravenous magnesium sulfate benefits FEV_1/PEF and hospital admission rate in treating asthma exacerbations.[31]

To our knowledge, we identified all relevant studies in our search up to May 2024. This result applies to the participants who presented with acute asthma exacerbation and were treated with intravenous magnesium sulfate in addition to the standard treatment. When available, we performed meta-analyses of the data studied. We graded the certainty of evidence for each outcome using the GRADE classification, a four-level rating scale (ie, high, moderate, low and very low).

Limitations

The limitation of this review is due to the number of studies included and the low-to-modest sample size of the studies.

CONCLUSION

This review showed low certainty of evidence that children who received intravenous magnesium sulfate had a lower hospital admission rate and less need for non-invasive ventilation. Moreover, there was limited evidence that PEF was better in the intravenous magnesium sulfate group. Other outcomes, including improvement in asthma severity scores, the need for invasive ventilation, length of hospital stay and PICU admission rate, were similar among both groups with very low-to-moderate certainty of evidence. No serious adverse events were reported.

Future RCTs are needed particularly to address the suggestion that higher doses of intravenous Mg may be more effective than lower doses.

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Contributors CP developed the concept for this review. ISA, KM, AAH, AT, AZZ, NA, RS, SA, AA and AKP selected studies for inclusion and abstracted data. AAH wrote the first draft. AAH, ISA, KM, CP did the data analysis and interpret the data and critically revised the paper for important intellectual content. All authors approved the final version of this article. CP is the guarantor of this work.

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