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Intravenous magnesium sulfate in pulmonary hypertension of the newborn: a systematic review

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ABSTRACT. – OBJECTIVE: Pulmonary hypertension in the newborn (PPHN) is a significant clinical condition characterized by elevated pulmonary artery pressures, leading to serious health consequences. Magnesium sulfate, known for its vasodilatory properties, has been studied for its potential benefits in managing PPHN. This systematic review evaluates the efficacy and safety of magnesium sulfate in neonates with PPHN.

MATERIALS AND METHODS: A systematic literature search was conducted on PubMed and Scopus up to March 10, 2024. Studies were included based on predefined Population, Intervention, Comparison, Outcome, Study (PICOS) criteria focusing on pediatric patients with PPHN treated with magnesium sulfate, compared against placebo or other pharmacological interventions. Outcomes of interest included resolution of PPHN, improved oxygenation, and decreased oxygenation index.

RESULTS: From a total of 1,233 articles screened, four studies met the inclusion criteria, including three randomized controlled trials and one multicentric retrospective study. The comparisons included nebulized magnesium sulfate, oral sildenafil, and inhaled nitric oxide. The outcomes varied, with none reported consistently across more than two studies, making a meta-analysis unfeasible. Results indicated a potential benefit of magnesium sulfate in improving pulmonary pressures and oxygenation, but the evidence was insufficient to establish definitive conclusions due to the heterogeneity and a limited number of studies.

CONCLUSIONS: The limited data suggest that, while magnesium sulfate may have a role in the management of PPHN, it should not replace established therapies. Further research is needed to better define its efficacy and safety profile.

Key Words:
Magnesium sulfate, Pulmonary hypertension, Pediatric, Systematic review, Vasodilatory function, Neonate.

Introduction

Persistent pulmonary hypertension of the newborn (PPHN) is a serious and life-threatening condition characterized by elevated pulmonary vascular resistance and pressure, leading to right ventricular dysfunction and potential failure[1]. PPHN affects approximately 1.9 per 1,000 live births and is associated with significant morbidity and mortality[2]. PPHN generally falls into one of three categories[1,2]: 1) the lung with normal parenchyma and remodeled pulmonary vasculature, also known as idiopathic PPHN; 2) the lung with hypoplastic vasculature as seen in congenital diaphragmatic hernia; or 3) the abnormally constricted pulmonary vasculature due to lung parenchymal diseases like meconium aspiration syndrome, respiratory distress syndrome, or pneumonia. Even though approximately 10-20% of newborns with PPHN have idiopathic pulmonary hypertension, severe patients mostly have both vascular and parenchymal illness[3]. Despite advances in neonatal care, managing PPHN remains challenging, and there is a need for effective and safe therapeutic interventions. Current treatment strategies for PPHN include inhaled nitric oxide, phosphodiesterase inhibitors, and extracorporeal membrane oxy-

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genation (ECMO)[2,4]. However, these therapies have limitations and potential adverse effects. Inhaled nitric oxide, while effective in some cases, is expensive and requires specialized equipment and careful hemodynamic evaluation[5,6]. Phosphodiesterase inhibitors, such as sildenafil, have shown promise but may be associated with systemic hypotension and other side effects[7]. ECMO is a highly invasive procedure reserved for severe cases that do not respond to conventional therapies[8]. Given these limitations, there is a growing interest in exploring alternative treatment options for PPHN in newborns. Magnesium sulfate ($MgSO_4$) has emerged as a potential treatment option for PPHN in newborns due to its vasodilatory properties and its ability to modulate pulmonary vascular resistance[9]. Magnesium is an essential mineral that plays a crucial role in various physiological processes, including vascular smooth muscle relaxation[10]. By acting as a calcium channel blocker and reducing calcium influx into smooth muscle cells, magnesium promotes vasodilation and reduces pulmonary vascular resistance[11]. Additionally, magnesium has anti-inflammatory and antioxidant properties, which may further contribute to its potential therapeutic effects in PPHN[12]. Several studies have investigated the use of magnesium sulfate for treating PPHN, with various results[13-16]. Some studies have reported improvements in oxygenation, reduction in pulmonary arterial pressure, and decreased need for supportive interventions such as mechanical ventilation and inhaled nitric oxide[13,14]. These findings suggest that magnesium sulfate may have a role in the management of PPHN, either as a standalone therapy or as an adjunct to other treatments. However, other studies have found limited or no significant benefits associated with magnesium sulfate therapy in this population[15,16]. These conflicting results highlight the need for a comprehensive and systematic evaluation of the available evidence. The systematic review will focus on key outcomes such as changes in pulmonary arterial pressure, oxygenation indices, duration of mechanical ventilation, length of hospital stay, and adverse events associated with magnesium sulfate therapy for newborn with PPHN.

Materials and Methods

Study Protocol

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline[17], and a PRISMA checklist is provided separately (**Supplementary Table I**). The protocol for the systematic review was previously registered in the International Prospective Register of Systematic Reviews (PROSPERO) (Code: CRD42024519959).

Search Strategy and Criteria

We undertook a systematic web-based advanced literature search through PubMed and Scopus up to March 10, 2024. Our core search was structured by combining three groups of terms: the first group included "pulmonary" OR "hypertension" OR "PAPS" OR "pulmonary hypertension" OR "pulmonary arterial" OR "right arterial". The second group of terms included "pediatric" OR "newborn" OR "infant" OR "neonate" OR "newly born". Finally, the last group included "magnesium" OR "magnesium sulfate". Inclusion criteria were pre-specified according to the PICOS approach (Table I). We decided to include only prospective and retrospective studies with a comparison. Therefore, case series, case reports, uncontrolled studies, reviews, editorials, and letters to the editor were excluded. We read the full manuscript only for articles published in English. We read the abstract for studies published in other languages and, if necessary, contacted the authors for further information.

Extraction of Data

Study selection for determining the eligibility for inclusion in the systematic review and data extraction were performed independently by two reviewers (GC, CM). Discordances were resolved involving a third author (LLV). Data were inserted in a password-protected database in Excel. We extracted data on the characteristics of the included studies, including the first author's name, the year of publication, the study population, as well as gender, age and the therapies administered in the intervention and control groups. We also retrieved data on the investigated outcomes.

Outcomes Analysis

In this systematic review, we compared the effects of magnesium sulfate as an adjunctive therapy for PPHN. We primarily focused on the resolution of pulmonary hypertension with the administration of magnesium sulfate. Our secondary outcomes were the improvement of oxygenation, the decrease of the OI, and survival. We considered the possibility to perform a quantitative assessment (meta-analysis) if at least three studies consistently reported the same outcome.

GRADE of Evidence

The grade of evidence performed according to the recommendations of the Grading of Recommendations Assessment, Development, and Evaluation working group was preliminarily considered only if meta-analysis was feasible.

Results

According to our systematic search, 673 items were found on PubMed and 560 on Scopus, as shown in our PRISMA flowchart of study selection (Figure 1). We assessed all the 1,233 abstracts to identify the potentially relevant articles. We subsequently revised the full text of the selected articles against our PICOS criteria. We initially included nine studies, but five were later excluded. In particular, in all of them, no drug was used as a comparison to magnesium sulfate in the control group[14,15,18-20]. Therefore, we finally selected a total of four studies, including three randomized controlled trials of 65, 28, and 25 patients[16,21,22], respectively, and one multicentric retrospective study of 58 patients[13]. Table II describes the characteristics of the included and excluded studies and the main results reported by the authors.

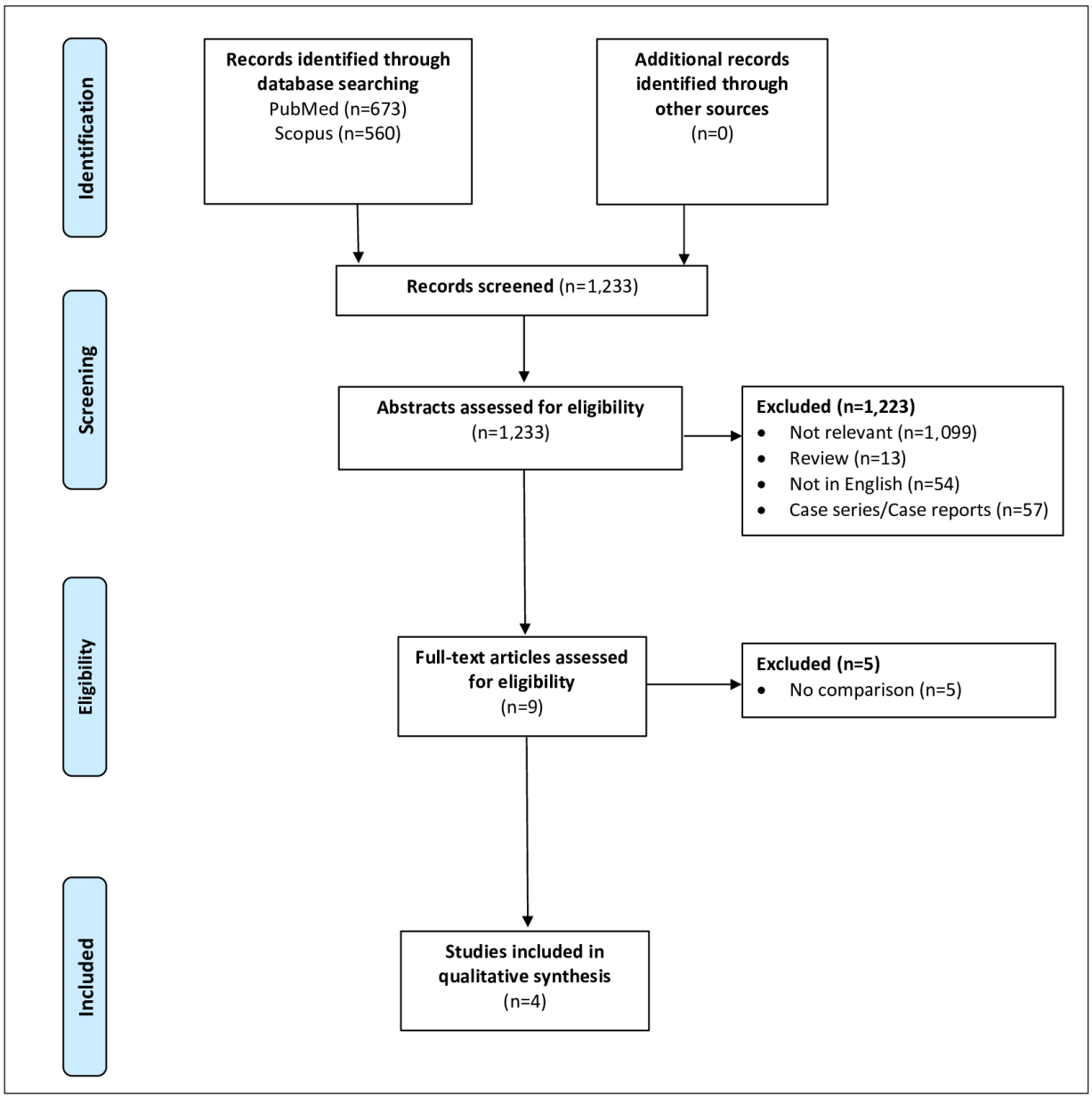

Figure 1. PRISMA flow diagram.

Table I. PICOS approach.

PICOS	
Participants	Neonates with pulmonary hypertension
Intervention	Intravenous Magnesium sulphate
Comparison	Placebo or other pharmacological strategies
Outcomes	Resolution of pulmonary hypertension, improved oxygenation, decreased oxygenation index, survival
Studies included	Randomized controlled trials, prospective non-randomized studies, retrospective studies

This systematic review compared the effects of intravenous magnesium sulfate to orally administered sildenafil[16], nebulized magnesium sulfate[21], or inhaled nitric oxide[13,22]. In particular, one study used sildenafil as a comparison[16]; another one used nebulized magnesium sulphate[21], and two studies compared intravenous magnesium sulfate with inhaled nitric oxide[13,22].

With regard to the study population, there was a large heterogeneity regarding the number of patients included and their gender distribution. However, the median age was similar among the studies (ranging from 38 to 39 weeks), and all four studies excluded patients with PPHN secondary to congenital cardiomyopathy. All papers considered the same dosage of magnesium sulfate for the initial bolus (200 mg/kg), followed by a continuous infusion ranging between 20 and 150 mg/Kg/h. The outcomes reported also varied among the studies. In particular, the authors investigated the resolution of PPHN (defined as OI <15/20 or PAP <20 mmHg), the median time for resolution, the overall survival, the median duration of mechanical ventilation or hospitalization, and the use of inotropic agents. None of the outcomes investigated were reported in more than two studies. Therefore, a meta-analysis was not feasible.

Discussion

To the best of our knowledge, this is the first systematic review on the use of magnesium sulfate in newborns with PPHN that was actually able to include published studies. In fact, the most recent Cochrane Review on the topic, published in 2007[9], did not find any eligible study and was never updated. On the contrary, the review by Ho et al[9] identified five clinical trials on the use of magnesium sulfate for PPHN. However, all of them were uncontrolled trials. The results of this systematic review provide a nuanced picture of the efficacy of magnesium sulfate in the treatment of PPHN. The primary focus of the investigation was to assess whether magnesium sulfate could effectively reduce pulmonary vascular pressures and improve clinical outcomes, such as oxygenation and overall survival in pediatric patients. Our review ultimately included three studies, with two being RCTs[16,22] and one multicentric retrospective study[13]. This selection underscores the stringent inclusion criteria aimed at ensuring a high level of evidence. The studies varied in their comparison groups, with one comparing intravenous magnesium sulfate against oral sildenafil and the other against inhaled nitric oxide. These comparisons are crucial as they position magnesium sulfate against established therapies in PPHN, thereby providing a benchmark for its effectiveness. The findings, however, were mixed and somewhat limited by the heterogeneity in study designs, patient populations, and outcome measures. None of the studies provided sufficient data to conclusively support a meta-analysis. The varied outcomes measured across the studies (resolution of PPHN, median time for resolution, overall survival, duration of mechanical ventilation, and hospitalization) further complicate the synthesis of data. This review highlights several gaps in the current research landscape. The small number of studies and their variable methodology suggest a need for more uniform and larger-scale RCTs to better assess the efficacy and safety of magnesium sulfate in newborns with PPHN. Additionally, future research should aim to standardize outcome measures to allow for more effective comparisons and meta-analyses. From a clinical perspective, the limited evidence on magnesium sulfate's efficacy in treating PPHN suggests that while it may have potential benefits, it should not yet be considered a frontline therapy. The comparison with established treatments like sildenafil and inhaled nitric oxide, which have more robust data supporting their use, indi-

Table II. Characteristics of the included studies.

First author, Year, Journal, Design	Number of patients, Sex, Median age weeks	Magnesium sulfate dose(s) Comparison dose	Outcomes studied by the authors
Included studies			
Boo et al[22], 2010 Singapore Med J Randomized controlled trial	25 (13Mag+HFOV; 12iNO+HFOV) 61% M (Mag) 58% M (iNO) 39 (Mag) 40 (iNO)	IV: 200 mg/kg over 30 min and 150-50 mg/kg/h drip iNO 20 ppm	Resolved PPHN based on echocardiography and OI: 92% (Mag) and 42% (iNO); Alive to discharge: 61% (Mag) and 17% (iNO)
Raimondi et al[13], 2007 Journal of Tropical Pediatrics Multicenter retrospective study	58 (28Mag; 30iNO) 43% M (Mag) 50% M (iNO) 39 (Mag) 39 (iNO)	IV: 200 mg/kg over 20 minutes and 50-20 mg/kg/h drip iNO 40-5 ppm	Improved PaO_2 and decreased OI (<20): 97% (Mag) after 36 h; 100% (iNO) after 6 h
Uslu et al[16], 2011 Journal of Tropical Pediatrics Randomized controlled trial	65 (34Mag; 31Sil) 59% M (Mag) 51% M (Sil) 38 (Mag) 38 (Sil)	IV: 200 mg/kg over 30 min and 100-20/kg/h drip in 1h Sildenafil 2-0,5 mg/kg	Improved OI (<15): 60 h (Mag) and 36 h (Sil); Improve PAP (< 20 mmHg): 3 days (Mag); 2 days (Sil); Duration of ventilation: 6 days (Mag) and 4 days (Sil); Mortality: 2 (Mag) and 1 (Sil)
Abdelkreem et al[21], 2021 Indian Journal of Pediatrics Double-blind randomized controlled, parallel two-arm clinical trial	28 (14NebMag; 14IVMag) 71% M (NebMag) 57%M (IVMag) 39 (NebMag) 39 (IVMag)	IVMag: 200 mg/kg over 30 min (2 ml/kg) and 50 mg/kg/h (0.5 ml/kg/h) for 24 h; NebMag: 1,024 mg/h magnesium for 24 h (277-330 mg/kg/h)	Improved OI: 44% (NebMag) and 35% (IVMag); Higher MAP and lower doses of inotropes and less increase in serum magnesium in NebMag
Excluded studies			
Tolsa et al[14], 1995 Archives of Disease in Childhood Prospective clinical trial	11 64% M 38	IV: 200 mg/kg over 20 minutes and 150-20 mg/kg/h drip	PaO_2 increased from 43 mmHg to 70 mm Hg after 24 h; Improved OI from 47 to 28 after 24 h; Paw reduced from 19 to 14 cmH_20 after 72 h; All infants survived and the neurodevelopmental assessment was normal at 6 and 12 months of age
Chandran et al[15], 2004 Journal of Tropical Pediatrics Prospective clinical trial	12 75% M 39	IV: 200 mg/kg over 20 minutes and 150-20 mg/kg/h drip (54 mg/kg/h mean)	Improved OI from 54 from 25 at 96 h after; PaO_2 increased from 34 mmHg to 72 mmHg at 24 h and to 76 mmHg at 96 h; Paw decreased from 17 to 15 after 96 h
Abu-Osba et al[18], 1992 Archives of Disease in Childhood Prospective clinical trial	9 - 37	IV: 200 mg/kg over 20 minutes and 50-20 mg/kg/h drip (1 infants received $MgSO_4$ IM)	PaO_2 increased from 37 mmHg to 120 mmHg at 8 h; Saturation of O_2 increased from 84% to 95% at 8 h
Daffa e Milaat[19], 2002 Saudi Medical Journal Non-randomized prospective clinical trial	8 87% M 39.5	IV: 200 mg/kg over 30 minutes and 100-20 mg/kg/h drip	PaO_2 increased from 37 mmHg to 94 mmHg at 24 h; PIP reduced from 30 cmH_2O to 18 cmH_2O at 24 h
Wu et al[20], 1995 Pediatrics Non-randomized prospective clinical trial	7 71% M 31	IV: 200 mg/kg over 30 minutes and 50-20 mg/kg/h drip	Improved OI from 40 to 20 at 36 h

Mag: Magnesium Sulphate; iNO: Inhaled Nitric Oxide; PPHN: Persistent Pulmonary Hypertension of the Newborn; OI: Oxygenation Index; IV: Intravenous; PAP: Pulmonary Artery Pressure; PaO_2: Arterial Partial Pressure of Oxygen; Paw: Mean Airway Pressure; PIP: Peak Inspiratory Pressure; MAP: Mean Arterial Pressure.

cates that magnesium sulfate might better serve as an adjunct therapy or be reserved for specific clinical scenarios where traditional treatments are not feasible or have failed. It is also important to underline that magnesium sulfate can be administered both intravenously and nebulized. In a recent RCT published by Abdelkreem et al[21] mechanically ventilated term neonates with severe PPHN were randomized into receiving nebulized isotonic magnesium sulfate (1024 mg/h), or intravenous magnesium. In the 24 hours following the administration, the study showed a decrease in OI by 44.3% in the nebulized group as compared with 35.3% in the intravenous group ($p = 0.003$). Also, patients treated with nebulized magnesium had higher mean arterial blood pressure and lower vasoactive inotropic scores, thus suggesting the nebulized route of administration as a possible effective therapeutic modality for neonates with severe PPHN. Nowadays, magnesium sulfate holds many FDA approvals but also has numerous off-label uses for a variety of clinical situations[23]. FDA-approved indications include constipation[24], hypomagnesemia, prevention of seizures in eclampsia/preeclampsia[25], acute nephritis in pediatric patients[26], cardiac arrhythmias[27], and soaking minor cuts or bruises. However, magnesium is also used for acute asthma exacerbations[28], torsades de pointes during advanced life support[27], and as a tocolytic to prevent preterm labor[29]. In particular, a systematic review of magnesium sulfate as a tocolytic agent found an association between the use of magnesium sulfate and increased mortality in the infant, raising concern for its use[29]. However, other research has suggested that magnesium sulfate is neuroprotective[30]. Moreover, a Cochrane review has shown that magnesium sulfate is neuroprotective for the fetus[31]. Also, the use of magnesium sulfate for vasodilation in PPHN is predicated on its well-documented effects on smooth muscle relaxation. The rationale for its application in PPHN is to exploit these properties to reduce the elevated pulmonary artery pressures that characterize this condition. Despite the theoretical benefits, the practical application and effectiveness of magnesium sulfate in PPHN require further evaluation. Moreover, given the chronic nature of PPHN and its significant morbidity, exploring the long-term outcomes of magnesium sulfate therapy will also be crucial. This encompasses both the immediate influence on pulmonary pressures and the enduring effects on right ventricular function, quality of life, and survival.

Limitations

Our study presents some limitations. First, the number of included studies was low, with a paucity of patients enrolled. Second, the design of the papers was not homogeneous, as we considered both randomized and non-randomized retrospective studies. Third, the results presented by the included studies were clinically heterogeneous, and therefore, a meta-analysis was not feasible.

Conclusions

In conclusion, while magnesium sulfate presents a potentially valuable tool in the management of pediatric PPHN, the current evidence is insufficient to support its routine use over more established therapies. Further high-quality, comparative research is needed to define its role in the therapeutic arsenal against PPHN. Clinicians should remain guided by the current evidence base, using magnesium sulfate judiciously and in the context of controlled clinical trials or carefully considered clinical scenarios.

Conflict of Interest

The authors declare that they have no conflict of interest.

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Ethics Approval and Informed Consent

Not applicable due to the design of the study.

Authors' Contributions

Conceptualization, G.C. and L.L.V.; investigation, G.C., G.B. and C.M. methodology, C.M. and C.Z.; writing–original draft preparation, G.C., Y.L. and L.L.V.; writing–review and editing, C.M., G.B., C.Z.; supervision, L.L.V. All authors have read and agreed to the published version of the manuscript.

Data Availability

Data sharing does not apply to this article as no datasets were generated or analyzed during the current study.

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AI Disclosure

No assisted technologies or artificial intelligence was used in the production of the study (figures included).

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