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Nebulized Magnesium Sulfate as an Adjunct to Standard Therapy in Infants with Acute Bronchiolitis: A Double Blind Randomized Controlled Trial

Pegah Karimian[1], Fahimeh Dehghani Mohammadabadi[2], Forugh Charmduzi[3], Hamidreza Khoshnezhad Ebrahimi[3], Alireza Javan[3], Negin Mousaeinejad[3], Somayeh Esmaeilian[4], Motahare Aghajani Delavar[3]*

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Abstract

Background: The evidence regarding the efficacy of magnesium sulfate ($MgSO_4$) in bronchiolitis is conflicting, and high-quality trials involving very young infants are limited. To compare the efficacy of nebulized magnesium sulfate, salbutamol, and 3% hypertonic saline against nebulized salbutamol and 3% hypertonic saline in infants aged 1-6 months who are admitted with a first episode of mild-to-moderate bronchiolitis. The primary outcomes were physiological parameters including oxygen saturation (SpO_2), respiratory rate (RR), and pulse rate (PR). Length of hospital stay (LOS), and Respiratory Distress Assessment Instrument (RDAI) score were evaluated as exploratory outcomes, along with escalation of care and adverse events.

Methods: In this parallel, double-blind randomized controlled trial conducted from August 2022 to February 2023, 62 eligible infants were allocated (1:1) to receive three consecutive 20-minute nebulizations of salbutamol, $MgSO_4$, and 3% saline (intervention) or salbutamol and 3% saline (control), followed by identical doses every 6 hours for up to 72 hours. All caregivers, clinicians, and outcome assessors were blinded. Outcome assessments were performed at baseline (pre-intervention), 1 hour after the initial dose, and every 24 hours thereafter (± 2 hours) until discharge or 72 hours, whichever occurred first. LOS was defined as the duration (in hours) from randomization until predefined discharge criteria were met ($SpO_2 \geq 94\%$ in room air for ≥ 12 hours, adequate oral intake, respiratory rate within age norms, RDAI ≤ 3).

Results: Among the 62 infants, 33 (53.2%) received triple-drug therapy, while 29 (46.8%) received standard dual therapy. The baseline characteristics were comparable, with a mean age as 3.6 ± 1.25 months and 56.5% male. The median Length of stay (LOS) was shorter in the $MgSO_4$ group (6.0 days, IQR 5–7) compared to the control group (7.0 days, IQR 6–9; $P = 0.046$, Mann-Whitney U). No significant differences were observed between groups for daily RDAI, RR, PR, or SpO_2 (repeated-measures ANOVA, $P > 0.05$). None of the infants required intensive care, mechanical ventilation, or experienced serious drug-related events.

Conclusion: This double-blind randomized trial did not demonstrate a statistically significant effect on its prospectively registered primary outcomes (oxygen saturation, respiratory rate, heart rate). The observed difference in length of hospital stay (a secondary, unregistered outcome; median 6.0 vs. 7.0 days; unadjusted $P = 0.046$) did not reach statistical significance after Bonferroni correction for multiple comparisons (corrected threshold: $P < 0.01$) and should be regarded as exploratory and hypothesis-generating only. This trial should be interpreted as null and inconclusive. Adequately powered, prospectively registered confirmatory trials are necessary before any clinical recommendations can be made.

Keywords: Magnesium sulfate, Nebulizer, Bronchiolitis, Infants, Randomized controlled trial

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Corresponding author: Dr Motahare Aghajani Delavar, Aghajani_14@yahoo.com

1. Department of Pediatric Endocrinology, School of Medicine, Iran University of Medical Sciences, Ali Asghar Children's Hospital, Tehran, Iran
2. School of Medicine, Iran University of Medical Sciences, Tehran, Iran
3. Emergency Medicine Management Research Center, Health Management Research Institute, Iran University of Medical Sciences, Tehran, Iran
4. Department of Emergency Medicine, School of Nursing, Iran University of Medical Sciences Tehran, Iran

Key Messages:

↑What is "already known" in this topic:

Acute bronchiolitis, primarily caused by RSV, is the leading lower respiratory infection in infants and is managed supportively through hydration and oxygen therapy, as bronchodilators and antivirals demonstrate limited efficacy. Nebulized MgSO4, which exhibits bronchodilatory and anti-inflammatory properties in asthma, has yielded mixed results in the treatment of bronchiolitis; some studies report improvements in severity and oxygenation, while others find no benefits in LOS. Additionally, data concerning infants remains scarce.

→What this article adds:

This double-blind randomized trial involving infants aged 1-6 months found that the addition of nebulized magnesium sulfate to standard bronchiolitis therapy did not improve primary clinical outcomes. Although the length of hospital stay appeared shorter in the intervention group, this finding was exploratory and not statistically robust, underscoring the necessity for larger confirmatory trials.

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Introduction

Acute bronchiolitis is the most prevalent lower respiratory tract infection in infants and young children, frequently caused by respiratory syncytial virus (RSV). It is a significant contributor to hospital admissions during the winter months and presents a considerable healthcare burden globally (1). Current management primarily involves supportive care, emphasizing the maintenance of adequate oxygenation and hydration, as no specific antiviral or bronchodilator therapy has consistently shown clinical efficacy (2, 3).

Magnesium sulfate, a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist and calcium channel blocker, has demonstrated bronchodilatory, anti-inflammatory, and smooth muscle relaxant properties. It is frequently utilized as an adjunct in the management of acute severe asthma (4, 5). These pharmacological actions suggest potential benefits in acute bronchiolitis, where airway obstruction and inflammation are prominent pathophysiological features.

Recent studies have investigated the use of nebulized magnesium sulfate as an adjunct therapy for infants with bronchiolitis, hypothesizing that it may reduce disease severity and shorten the length of hospital stay. However, the findings remain inconclusive. Some randomized controlled trials have reported modest improvements in clinical severity scores and oxygen requirements (6, 7), while others have found no significant reduction in hospitalization duration or the need for escalation of care (8).

Given the conflicting evidence and the absence of a clear consensus, further high-quality randomized clinical trials are warranted to evaluate whether the addition of nebulized magnesium sulfate to standard supportive therapy can significantly reduce hospital length of stay (LOS) and improve clinical outcomes in infants with acute bronchiolitis.

Methods

Study Design and Setting: A prospective, two-arm, double-blind, Phase 3 randomized controlled trial was conducted at Hazrat Ali Asghar Children's Hospital, affiliated with Iran University of Medical Sciences (IUMS), from August 2022 to February 2023. Data collection was finalized in February 2023, followed by several months dedicated to comprehensive data analysis, statistical verification, and manuscript preparation.

Participants

Inclusion criteria: (1) age 30–180 days; (2) first episode of clinically diagnosed bronchiolitis; (3) RDAI <9 (mild-to-moderate disease); (4) admission for supportive therapy. Exclusion criteria: prematurity <34 weeks; chronic cardiopulmonary disease; immunodeficiency; prior history of ≥2 wheezing episodes; need for immediate intensive care; respiratory rate (RR) > 100/min, pulse rate (PR) > 180/min; known hypersensitivity to study drugs.

Randomization and Blinding

An independent statistician, not involved in patient care, generated the randomization sequence using Random.org (www.random.org) with permuted blocks of four in a 1:1 ratio. Allocation concealment was ensured through sequentially numbered, opaque, sealed envelopes (SNOSE), which were prepared and secured by pharmacy staff not involved in clinical care. The envelopes were stored in a locked cabinet and opened sequentially only after the completion of written informed consent, enrollment, and baseline assessment. Treatment assignments were disclosed only after enrollment and the collection of baseline data.

Pharmacy staff prepared identical nebulization solutions in numbered syringes according to the allocation sequence. The solutions were indistinguishable in appearance, volume, and odor. All investigators, clinical staff, parents/guardians, and outcome assessors remained blinded to treatment allocation throughout the study. The pharmacy maintained the allocation code until the completion of data analysis. Unblinding procedures were available for medical emergencies but were not required during the trial.

Interventions

All infants received standard care, which included hydration, nasal suctioning, and O_2 to maintain $SpO_2 \geq 92\%$. Intervention arm: salbutamol (0.15 mg/kg, minimum 2.5 mg) + $MgSO_4$ 50% (40 mg/kg) + 4 mL 3% saline per nebulization. Control arm: the same salbutamol dose + 4 mL 3% saline + matching placebo. The placebo consisted of an equal volume of normal saline that was completely matched to the magnesium sulfate solution in appearance, color, and odor. Nebulizations were administered via a jet nebulizer with an oxygen flow of 6–8 L/min, consisting of three doses every 20 minutes (loading), followed by every 6 hours for up to 72 hours or until discharge.

Outcomes

Length of hospital stay (LOS) was evaluated as an exploratory outcome, defined as the duration (in hours) from randomization until the predefined discharge criteria were met ($SpO_2 \geq 94\%$ in room air for ≥ 12 hours, adequate oral intake, respiratory rate within age norms, RDAI ≤ 3). LOS was documented in hours and subsequently converted to days for analysis.

This operational definition differs from that of the trial registry, which specified LOS as the duration from admission to discharge. The current definition was adopted to standardize the measurement from the intervention's starting point.

The trial registration (IRCT20201122049461N1) initially designated physiological parameters (oxygen saturation, respiratory rate, and pulse rate) as the primary outcomes. During the early conduct of the trial (October 2022), LOS was prioritized internally due to its perceived

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clinical relevance and implications for resource utilization. However, this amendment was not reflected in the trial registry due to a protocol management oversight. Consequently, LOS findings should be interpreted as exploratory rather than confirmatory.

Physiological outcomes included daily assessments of the Respiratory Distress Assessment Instrument (RDAI) score, respiratory rate (RR), pulse rate (PR), and oxygen saturation (SpO_2). Additional clinical outcomes encompassed escalation of care (high-flow nasal cannula, ICU transfer, or mechanical ventilation) and adverse events.

Outcome assessments were performed at standardized time points: baseline (pre-intervention), 1 hour after the initial dose, and every 24 hours thereafter (± 2 hours), approximately at 8:00 AM, until either discharge or 72 hours, whichever occurred first.

All outcome assessments were performed by trained pediatric nurses and physicians who underwent standardized training in RDAI scoring and vital sign measurement before study initiation. All assessors remained blinded to treatment allocation throughout the study.

Safety outcomes encompassed adverse events monitored throughout hospitalization, including vomiting, hypotension (systolic BP < 70 mmHg), apnea (respiratory pause > 20 seconds), cardiac arrhythmia, and the need for escalation of care.

Sample Size

The trial was initially designed to evaluate changes in physiological outcomes, including oxygen saturation, respiratory rate, and heart rate, which were specified as the primary outcomes in the study protocol and trial registration. Based on available evidence at the time of study design, these outcomes were expected to demonstrate moderate between-group differences. Assuming a standardized effect size (Cohen's d) of 0.6, a two-sided significance level of 0.05, and 80% statistical power, G*Power version 3.1 estimated that 28 infants were required per group. To compensate for potential attrition, the target sample size was increased to 62 participants.

Length of hospital stay (LOS) was evaluated as a secondary clinical outcome. During the course of the study, its clinical importance became increasingly recognized, and the October 2022 protocol amendment identified LOS as an outcome of particular interest for subsequent analyses. This amendment did not alter the enrollment target or the original sample size determination, which had already been completed before participant recruitment commenced.

Statistical Analysis

Data were analyzed using SPSS version 26. Normality was assessed using the Shapiro-Wilk test. Length of stay (LOS) was compared using the Mann-Whitney U test, while categorical variables were analyzed using the χ^2 test or Fisher's exact test, as appropriate. Repeated-measures ANOVA was employed to examine longitudinal changes in vital signs and Respiratory Distress Assessment Instrument (RDAI) scores, with the treatment group as the between-subject factor and time as the within-subject factor. Sphericity was assessed using Mauchly's test; when violated ($p < 0.05$), the Greenhouse-Geisser correction was applied. The primary effect of interest was the group-by-time interaction. Missing data (< 5% of observations) were addressed using last observation carried forward (LOCF), acknowledging the limitations of this method compared with mixed-effects models. For post hoc pairwise comparisons involving repeated measures, Bonferroni correction was applied to adjust for multiple testing. Given the exploratory nature of secondary outcomes, nominal p-values are reported for analyses not subject to correction and should be interpreted with caution. A two-sided p-value < 0.05 was considered statistically significant unless otherwise specified by multiple-comparison adjustment. All analyses adhered to the intention-to-treat principle.

Results

Of the 94 screened infants, 32 were excluded (17 did not meet the inclusion criteria, 9 declined, and 6 were excluded for other reasons). All 62 randomized participants completed the study and were included in the analysis (Figure 1).

The study included 62 participants with comparable baseline characteristics across groups (Table 1). The mean age was 3.6 ± 1.25 months, with no significant difference between groups ($P = 0.612$). Males comprised 56.5% of the participants (35 infants). Baseline respiratory parameters exhibited no significant differences: respiratory rate (55.0 ± 8.7 breaths/min), pulse rate (145.7 ± 12.9 beats/min), and oxygen saturation (92.0 ± 3.6%). The mean baseline RDAI score was 6.45 ± 1.85, indicating mild-to-moderate respiratory distress.

The prospectively registered primary outcomes (oxygen saturation, respiratory rate, and heart rate) exhibited no statistically significant differences between groups at any time point (repeated-measures ANOVA; group × time interaction: all $P > 0.05$). An observed difference in length of stay (LOS)—an exploratory, unregistered secondary outcome—was noted: the mean LOS was 6.53 ± 1.57 days in the three-drug group compared to 6.98 ± 3.11 days in the two-drug group (Mann–Whitney U, unadjusted $p = 0.046$; difference = approximately 0.45 days). However, this difference did not achieve statistical significance after Bonferroni correction for the five outcome comparisons performed (corrected threshold: $P < 0.01$). Furthermore, the operational definition of LOS utilized in this manuscript differed from that in the trial registry. Accordingly, this LOS finding should be interpreted as exploratory only and does not constitute evidence of treatment efficacy.

For the registered primary outcomes, repeated-measures ANOVA revealed significant main effects of time for all physiological parameters ($P < 0.001$), indicating clinical improvement in both groups over the observation period. Notably, the group × time interaction effects were non-significant for respiratory rate ($F(4, 116) = 0.82$, $P = 0.51$), pulse rate ($F(4, 116) = 0.64$, $p = 0.63$), oxygen saturation ($F(4, 116) = 0.43$, $P = 0.78$), and RDAI ($F(4, 116) = 0.71$, $P = 0.58$). This suggests that the improvement tra-

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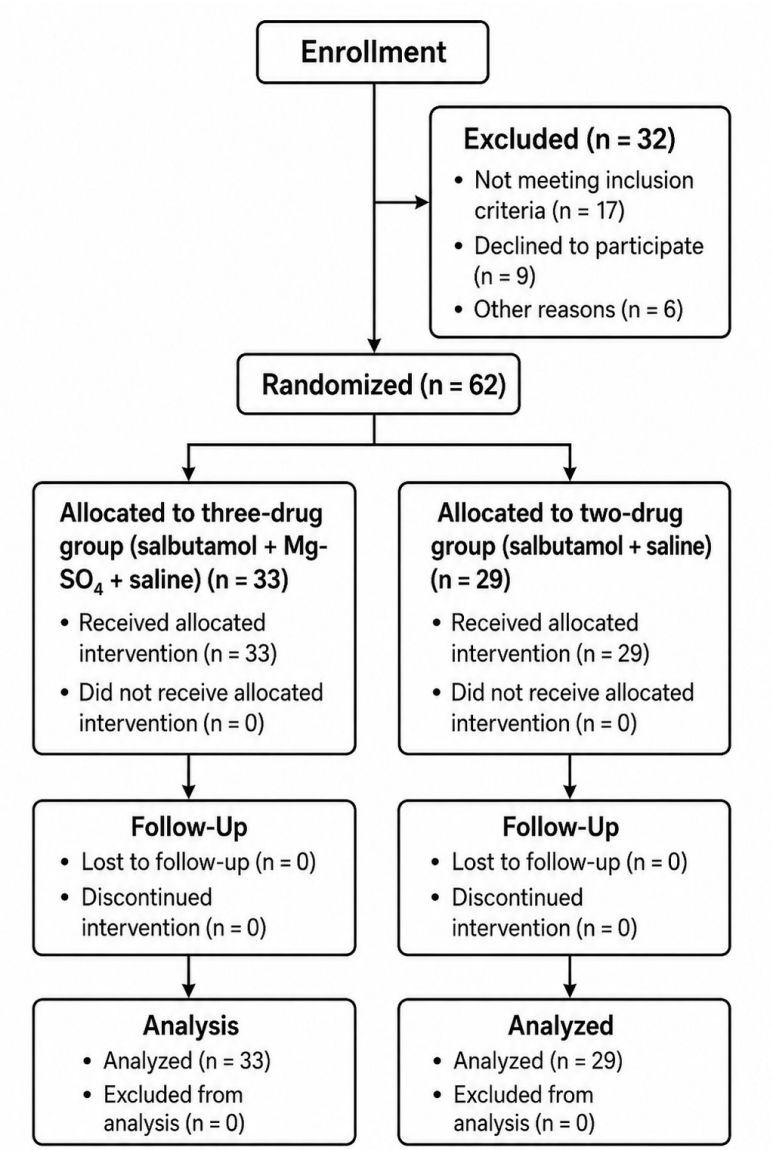

Figure 1. CONSORT Flow Diagram of participant enrollment, allocation, follow-up, and analysis.

Table 1. Baseline Demographic and Clinical Characteristics of Participants by Treatment Group.

Characteristic	Three-Drug Group (n=33)	Two-Drug Group (n=29)	Total (n=62)	*P*-value
Age (months, mean ± SD)	3.5 ± 1.2	3.7 ± 1.3	3.6 ± 1.25	0.612
Sex, n (%)				0.845
Male	19 (57.6%)	16 (55.2%)	35 (56.5%)	
Female	14 (42.4%)	13 (44.8%)	27 (43.5%)	
Respiratory Rate (RR, breaths/min, mean ± SD)	55.2 ± 8.4	54.8 ± 9.1	55.0 ± 8.7	0.912
Pulse Rate (PR, beats/min, mean ± SD)	145.3 ± 12.6	146.1 ± 13.2	145.7 ± 12.9	0.874
Oxygen Saturation (O_2 SAT, %, mean ± SD)	92.1 ± 3.5	91.8 ± 3.7	92.0 ± 3.6	0.765
Respiratory Distress Assessment Instrument (RDAI) Score (mean ± SD)	6.4 ± 1.8	6.5 ± 1.9	6.45 ± 1.85	0.821

jectories were similar between groups and that the addition of magnesium sulfate did not yield a differential effect on any registered primary outcome. No between-group difference reached statistical significance at any measured time point (all $P > 0.05$; Tables 2 and 3). The change in RDAI from baseline to Day 3 was −4.2 ± 1.1 in the three-drug group compared to −4.2 ± 1.2 in the two-drug group ($P = 0.912$).

No serious adverse events occurred in either group. Specifically, there were no cases of hypotension, cardiac arrhythmia, apnea, or allergic reactions observed. No participant required escalation to high-flow nasal cannula,

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Table 2. Changes in Clinical Parameters (RR, PR, O_2 SAT, RDAI) Over Time by Treatment Group.

Parameter / Time Point	Three-Drug Group (mean ± SD)	Two-Drug Group (mean ± SD)	*P*-value (Between Groups)
Respiratory Rate (RR, breaths/min)			
- Baseline	55.2 ± 8.4	54.8 ± 9.1	0.912
- 1 Hour	50.1 ± 7.2	49.8 ± 7.5	0.845
- Day 1	45.3 ± 6.1	45.6 ± 6.4	0.789
- Day 2	40.4 ± 5.3	40.9 ± 5.7	0.732
- Day 3	36.2 ± 4.8	36.7 ± 5.1	0.698
Pulse Rate (PR, beats/min)			
- Baseline	145.3 ± 12.6	146.1 ± 13.2	0.874
- 1 Hour	138.4 ± 11.5	139.2 ± 11.8	0.812
- Day 1	132.1 ± 10.3	132.7 ± 10.6	0.765
- Day 2	125.6 ± 9.4	126.3 ± 9.7	0.721
- Day 3	120.2 ± 8.7	120.8 ± 9.0	0.684
Oxygen Saturation (O_2 SAT, %)			
- Baseline	92.1 ± 3.5	91.8 ± 3.7	0.765
- 1 Hour	94.3 ± 2.8	94.0 ± 3.0	0.702
- Day 1	95.7 ± 2.1	95.4 ± 2.3	0.654
- Day 2	96.8 ± 1.6	96.5 ± 1.8	0.613
- Day 3	97.5 ± 1.2	97.2 ± 1.4	0.578
RDAI Score			
- Baseline	6.4 ± 1.8	6.5 ± 1.9	0.821
- 1 Hour	5.2 ± 1.5	5.3 ± 1.6	0.763
- Day 1	4.1 ± 1.2	4.2 ± 1.3	0.712
- Day 2	3.0 ± 0.9	3.1 ± 1.0	0.667
- Day 3	2.2 ± 0.7	2.3 ± 0.8	0.631

Table 3. Comparison of Exploratory, Secondary, and Safety Outcomes Between the Three-Drug and Two-Drug Treatment Groups

Outcome	Three-Drug Group (n=33)	Two-Drug Group (n=29)	Difference / Statistic	*P*-value
Exploratory Outcome				
Length of Stay in days (Median, IQR)	6.0 (5–7)	7.0 (6–9)	-	0.046
Secondary Outcomes (Change from Baseline to Day 3)				
Respiratory Rate (RR, breaths/min)	-19.0 ± 4.2	-18.1 ± 4.5	-0.9	0.412
Pulse Rate (PR, beats/min)	-25.1 ± 5.6	-25.3 ± 5.9	+0.2	0.876
Oxygen Saturation (O_2 SAT, %)	+5.4 ± 1.3	+5.4 ± 1.4	0.0	0.945
RDAI Score	-4.2 ± 1.1	-4.2 ± 1.2	0.0	0.912
Safety Outcomes				
Serious Adverse Events, n (%)	0 (0%)	0 (0%)	N/A	N/A
Withdrawals Due to Adverse Events, n (%)	0 (0%)	0 (0%)	N/A	N/A

continuous positive airway pressure, intensive care unit transfer, or mechanical ventilation. Mild transient adverse events, such as irritability during nebulization, occurred equally in both groups: intervention group reported 4 cases (12.1%); control group reported 3 cases (10.3%); $P = 0.83$. No withdrawals were attributed to adverse events.

Discussion

This double-blind randomized controlled trial evaluated the addition of nebulized magnesium sulfate to standard therapy (salbutamol and 3% hypertonic saline) in infants aged 1–6 months with mild-to-moderate acute bronchiolitis—a population that has been underrepresented in prior trials. The trial did not demonstrate a statistically significant effect on any of its prospectively registered primary outcomes (oxygen saturation, respiratory rate, or heart rate). An exploratory, unadjusted difference was observed in the secondary outcome of hospital length of stay (mean 6.53 vs. 6.98 days; unadjusted $P = 0.046$), which did not survive Bonferroni correction for multiple comparisons (corrected threshold: $P < 0.01$). Given these findings, this trial should be interpreted as null and inconclusive. The LOS observation is exploratory and insufficient to support a conclusion of efficacy.

The absence of significant differences in respiratory rate, pulse rate, oxygen saturation, or RDAI scores between groups aligns with the findings of Modaresi et al., who concluded that nebulized magnesium sulfate did not improve symptoms of acute bronchiolitis (12). Our study specifically focused on infants younger than 6 months—a demographic that is underrepresented in existing trials. Despite this targeted design, no between-group differences in the recorded primary physiological outcomes were detected, thereby reinforcing the overall null result.

The current evidence regarding the use of magnesium sulfate in bronchiolitis is still evolving. A recent Cochrane review emphasized the need for more high-quality data concerning the dosage and efficacy of nebulized magnesium sulfate (4). The debate surrounding the treatment of bronchiolitis continues, with most clinical practice guidelines advocating for supportive care due to a lack of robust evidence for specific effective treatments (13). Systematic reviews have demonstrated that bronchodilators, corticosteroids, and antibiotics provide limited to no clinical benefit (14, 15). Research conducted by Alansari et al. suggested that intravenous magnesium sulfate may not only be ineffective but could also be potentially harmful in cases of bronchiolitis (8).

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Previous studies have reported modest improvements with nebulized magnesium sulfate in cases of bronchiolitis (6, 7, 10, 11). These findings, along with our exploratory observation regarding LOS, may generate hypotheses for future trials. However, neither the prior studies nor the present investigation provides sufficient confirmatory evidence to recommend the routine use of nebulized magnesium sulfate in infants with acute bronchiolitis.

Limitations

This trial has several important limitations that must be considered when interpreting the findings. First, and most critically, the prospectively registered primary outcomes (physiological parameters: oxygen saturation, respiratory rate, heart rate) showed no statistically significant between-group differences, and the trial was insufficiently powered (post-hoc power <50%) to detect small-to-moderate effects on these outcomes. Consequently, this trial is considered negative regarding its registered primary endpoints. Second, length of hospital stay was not the prospectively registered primary outcome. Its introduction as a primary-level endpoint during the trial conduct represents an unregistered protocol change—an oversight in protocol management that substantially limits the confirmatory value of any LOS finding. Third, the operational definition of LOS in this manuscript (time from randomization to discharge criteria) differed from the registry definition (time from admission to discharge), introducing measurement inconsistency that further undermines reliability. Fourth, no minimum clinically important difference (MCID) for LOS was pre-specified, preventing the determination of whether the observed 0.45-day difference would be meaningful in clinical practice. Fifth, the unadjusted p-value for LOS ($p = 0.046$) does not withstand Bonferroni correction for the five comparisons performed (corrected threshold: $p < 0.01$), raising a substantial probability of Type I error. Sixth, the observed LOS reduction (~0.45 days) was substantially smaller than the 1.5-day difference used for power calculation, suggesting that the study was also underpowered to detect the effect that was ultimately observed. Seventh, the use of last observation carried forward (LOCF) for missing data is a limitation; mixed-effects models would be more appropriate for longitudinal data in future studies. Finally, the single-center design and three-day follow-up limit generalizability. Future multicenter, prospectively registered, adequately powered trials with a pre-specified primary outcome, MCID thresholds, and consistent outcome definitions are required before any clinical recommendations regarding nebulized magnesium sulfate in acute bronchiolitis can be considered.

Conclusion

This double-blind randomized controlled trial did not demonstrate a statistically significant benefit of adding nebulized magnesium sulfate to standard therapy (salbutamol and 3% hypertonic saline) in infants aged 1–6 months with mild-to-moderate acute bronchiolitis. The prospectively registered primary outcomes—oxygen saturation, respiratory rate, and heart rate—showed no between-group differences at any measured time point. The observed difference in length of stay (LOS) was borderline on unadjusted analysis ($p = 0.046$) and did not survive correction for multiple comparisons. This outcome was not prospectively registered, and its definition differed from the registry; no minimal clinically important difference (MCID) was pre-specified. Both treatment regimens demonstrated comparable safety profiles. This trial should be interpreted as null and inconclusive. The LOS observation is exploratory and hypothesis-generating only. Larger, adequately powered, prospectively registered confirmatory trials with pre-specified primary outcomes, MCID thresholds, standardized LOS definitions, and appropriate multiplicity control are necessary before any clinical recommendation regarding nebulized magnesium sulfate in acute bronchiolitis can be made.

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Conflict of Interests

The authors declare that they have no competing interests.

Authors' Contributions

PK: conceptualization, methodology, investigation, and writing—original draft. FD: investigation, data curation, and writing—original draft. FC: conceptualization, methodology, and writing—original draft, as well as supervision. HK: investigation, data curation, and writing—original draft. AJ: formal analysis, visualization, and writing—original draft. NM: formal analysis, data curation, and writing—original draft. SE: investigation, project administration, and writing—original draft. MAD: conceptualization, writing—review and editing, and supervision (corresponding author). All authors approved the final manuscript.

Ethical Considerations

Ethical approval was obtained from the IUMS Ethics Committee (IR.IUMS.FMD.REC.1400.215). Written informed consent was secured from parents/guardians. The trial adhered to the Declaration of Helsinki and was registered prospectively with IRCT (IRCT20201122049461N1).

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This study received no external funding.

Data Availability

Data is available upon reasonable request.

AI Use Statement

The authors did not use artificial intelligence or AI-assisted technologies in the preparation of this manuscript.

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