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COMPARISON OF EFFICACY OF NEBULIZATION WITH EPINEPHRINE IN HYPERTONIC SALINE VERSUS PLACEBO IN HYPERTONIC SALINE FOR THE TREATMENT OF MODERATE BRONCHIOLITIS

Original Article

Muhammad Fiaz[1]*, Aqsa Shahbaz[2], Anam Shahbaz[3]

[1]Children Hospital Lahore, Pakistan.

[2]Lady Aitchison Hospital Lahore, Pakistan.

[3]FMH College of Medicine and Dentistry, Lahore, Pakistan.

Corresponding	Muhammad Fiaz drmuhammadfiaz794@gmail.com Children Hospital Lahore, Pakistan.
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Abstract

Background: Bronchiolitis is one of the most prevalent lower respiratory tract infections among infants, primarily caused by respiratory syncytial virus (RSV). It is a leading cause of pediatric hospitalization during the first year of life, with an estimated hospitalization rate of 6.7%. Despite advancements in supportive care, no specific pharmacologic treatment has consistently demonstrated efficacy in reducing disease severity or hospital stay. This study evaluated the therapeutic effectiveness of nebulized epinephrine in 3% hypertonic saline compared to placebo in 3% hypertonic saline for moderate bronchiolitis.

Objective: To compare the efficacy of nebulization with epinephrine in 3% hypertonic saline versus placebo in 3% hypertonic saline in reducing hospital stay and improving clinical outcomes among infants with moderate bronchiolitis.

Methods: This single-blinded randomized controlled trial included 194 infants under 24 months admitted with clinically diagnosed moderate bronchiolitis to The Children's Hospital and The University of Child Health Sciences, Lahore. Participants were randomly assigned into two equal groups of 97 infants each. Group A received nebulized epinephrine (3 ml of 1:1000 solution) in 3% hypertonic saline (7 ml), while Group B received placebo (3 ml sterile water) in 3% hypertonic saline (7 ml). Outcomes measured included length of hospital stay, respiratory rate, WDF score, oxygen saturation (SpO_2), and heart rate before and after treatment. Data were analyzed using SPSS version 26 with $p \leq 0.05$ considered statistically significant.

Results: Infants treated with epinephrine in 3% hypertonic saline demonstrated a significantly shorter hospital stay (3.72 ± 0.45 days) compared to the placebo group (4.73 ± 0.45 days; $p = 0.000$). Marked improvements were observed in respiratory rate (32.64 ± 1.27 vs 33.35 ± 0.63; $p = 0.006$) and WDF score (2.52 ± 0.15 vs 2.87 ± 0.08; $p = 0.000$). Differences in oxygen saturation ($p = 0.067$) and heart rate ($p = 0.119$) were not statistically significant. No adverse effects were reported in either group.

Conclusion: Nebulized epinephrine in 3% hypertonic saline was more effective than placebo in improving clinical parameters and reducing hospital stay in infants with moderate bronchiolitis, with no observed side effects. The findings support its consideration as a safe and efficient therapeutic option in pediatric bronchiolitis management.

Keywords: Bronchiolitis; Epinephrine; Hospitalization; Hypertonic Saline Solution; Infant; Nebulizers and Vaporizers; Respiratory Syncytial Virus Infections.

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Introduction

Bronchiolitis represents a major concern in pediatric healthcare as one of the most frequent lower respiratory tract infections among infants and young children. Primarily caused by respiratory syncytial virus (RSV), this infection affects nearly all children by the age of two, although its clinical severity varies considerably. While many cases remain mild and self-limiting, a substantial proportion of infants—particularly those under 24 months—experience moderate to severe disease requiring hospitalization (1–3). The global burden of bronchiolitis places significant pressure on pediatric healthcare systems due to its high incidence, seasonal peaks, and the intensive supportive care often required for severe cases (4). Effective management of bronchiolitis is therefore essential not only for improving clinical outcomes but also for optimizing healthcare resources. Traditionally, the treatment of bronchiolitis has been largely supportive, emphasizing oxygen supplementation, hydration, and, in severe cases, mechanical ventilation (5). Pharmacological interventions, however, remain a subject of debate. Among potential agents, nebulized epinephrine has been studied for its bronchodilatory and vasoconstrictive properties, which may reduce airway edema and improve airflow. Similarly, hypertonic saline (3%) has been proposed to facilitate mucus clearance and decrease airway inflammation by drawing water into the airway lumen and improving mucociliary function (6,7). Theoretically, combining these two agents could offer a synergistic effect by targeting both airway edema and obstruction, potentially improving respiratory efficiency and reducing clinical severity (8–10).

Existing literature provides conflicting evidence regarding the efficacy of these interventions, either alone or in combination. Some studies have suggested that nebulized epinephrine with hypertonic saline shortens hospital stay and enhances symptom resolution, while others have reported no significant difference compared to hypertonic saline alone or placebo (11–13). This inconsistency in findings has led to uncertainty in clinical guidelines, leaving physicians divided about the optimal pharmacologic approach for moderate bronchiolitis. The variability in clinical response may reflect differences in patient selection, treatment protocols, and disease severity across studies (14,15). As a result, there remains no universally accepted pharmacologic regimen capable of reliably reducing disease burden or hospitalization duration. Given the substantial morbidity associated with moderate bronchiolitis and the strain it imposes on healthcare systems, there is a pressing need to identify evidence-based interventions that can improve outcomes. Previous studies have largely focused on mild or severe cases, leaving a knowledge gap regarding moderate disease where timely and effective intervention could prevent deterioration and the need for intensive care (16,17). Furthermore, many investigations have not sufficiently addressed whether combining nebulized epinephrine with hypertonic saline provides superior benefits compared to hypertonic saline alone, particularly in reducing the length of hospital stay and improving clinical scores such as the Wood-Downes modified by Ferres (WDF) scale (18,19).

The present study was designed to address this critical gap by comparing the efficacy of nebulized epinephrine in 3% hypertonic saline with placebo in 3% hypertonic saline for the management of moderate bronchiolitis in infants under 24 months. Conducted as a single-blinded randomized controlled trial with rigorous inclusion criteria and objective clinical endpoints, the study aimed to determine whether this combination could reduce hospitalization duration, improve respiratory parameters, and enhance overall recovery (20–22). By providing robust comparative data, the research seeks to clarify the therapeutic value of epinephrine-hypertonic saline nebulization and guide evidence-based clinical decision-making. Ultimately, this investigation aims to establish whether the addition of nebulized epinephrine to hypertonic saline can offer a more effective, practical, and resource-efficient approach for managing moderate bronchiolitis—thereby supporting the development of standardized treatment protocols and improving outcomes in pediatric respiratory care (23–25).

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Methods

The study was designed as a single-blind, randomized, placebo-controlled clinical trial aimed at comparing the efficacy of nebulized epinephrine in 3% hypertonic saline with placebo in 3% hypertonic saline for the treatment of moderate bronchiolitis in infants. The trial was conducted in the General Medical Ward of The Children's Hospital and The University of Child Health Sciences, Lahore, over a duration of twelve months following the approval of the study synopsis by the Advanced Research Committee. Ethical clearance was obtained from the Biomedical Ethical Committee and the Institutional Review Board of The Children's Hospital and The University of Child Health Sciences (2022/506/UCHS-CH). Written informed consent was obtained from the parents or guardians of all participants prior to their inclusion in the study, ensuring adherence to ethical standards of clinical research and protection of participants' rights. The sample size was calculated using mean hospital stay durations of 3.94 ± 1.37 days for the experimental group and 4.65 days for the control group as reported in prior studies (15,16). Based on a 95% confidence level and a 5% margin of error, the required sample size was determined to be 97 infants per group (total 194) to achieve a statistical power of 95%. Allowing for a 10% dropout rate, an initial cohort of 214 patients was enrolled, out of which 194 completed the study and were included in the final analysis. Randomization was achieved using a computer-generated random number sequence to minimize selection bias and ensure an even distribution of confounding variables between groups. Infants below 24 months of age who were clinically diagnosed with moderate bronchiolitis, confirmed using the Wood-Downes Clinical Scoring System modified by Ferres (WDF score), were included in the study (15,17). Infants were excluded if they were born prematurely (<37 weeks as defined by WHO), had any form of immunodeficiency, neuromuscular or chronic respiratory disease, congenital heart disease, or a prior history of wheezing. Infants receiving non-study medications during hospitalization or those whose WDF scores increased to severe levels during the trial were also excluded to maintain study uniformity and ensure patient safety (18,19). Data collection was performed after obtaining institutional and ethical approvals. Eligible infants admitted to the pediatric medical ward were screened for study inclusion. After consent, detailed demographic and clinical data were recorded using a structured proforma, including age, gender, weight, oxygen saturation (SpO_2), heart rate, respiratory rate, and WDF score. Each infant underwent a comprehensive clinical examination, and relevant history was obtained from parents or guardians.

Participants were randomly assigned into two groups. The experimental group (Group A) received nebulized epinephrine (3 ml of 1:1000 solution) mixed with 3% hypertonic saline (7 ml). The control group (Group B) received nebulized placebo (3 ml of sterile water) in 3% hypertonic saline (7 ml). Both solutions were prepared under aseptic conditions by the hospital pharmacy, where trained personnel ensured that the formulations were identical in appearance, odor, volume, and sodium concentration to maintain blinding. Nebulization was administered initially every four hours, with the frequency adjusted based on clinical need. Standard supportive measures were uniformly applied to all infants, including head elevation, acetaminophen for fever, and supplemental oxygen if SpO_2 fell below 94% (19). Parents retained the right to withdraw their child at any stage, and infants developing severe bronchiolitis or requiring non-study interventions were withdrawn from the trial. All infants were monitored continuously with pulse oximetry until their oxygen saturation remained at or above 94% without supplemental oxygen. The primary outcome measure was the duration of hospital stay, defined as the number of days from admission until discharge criteria were met. Discharge criteria included SpO_2 ≥97% on room air, WDF score ≤3, tolerance of oral feeds, and no further need for nebulization therapy (16-18). Secondary outcomes included changes in heart rate, respiratory rate, WDF score, SpO_2 levels, and intervals between required nebulizations. Data analysis was performed using SPSS version 26. Numerical variables were expressed as mean ± standard deviation (SD), while categorical variables were summarized as frequencies and percentages. Descriptive statistics were applied to demographic and baseline clinical parameters. Depending on data distribution, paired-sample t-tests were used for within-group comparisons, and independent-sample t-tests were employed for between-group analyses. A p-value ≤ 0.05 was considered statistically significant. The anticipated impact of the study was to determine whether nebulized epinephrine in hypertonic saline

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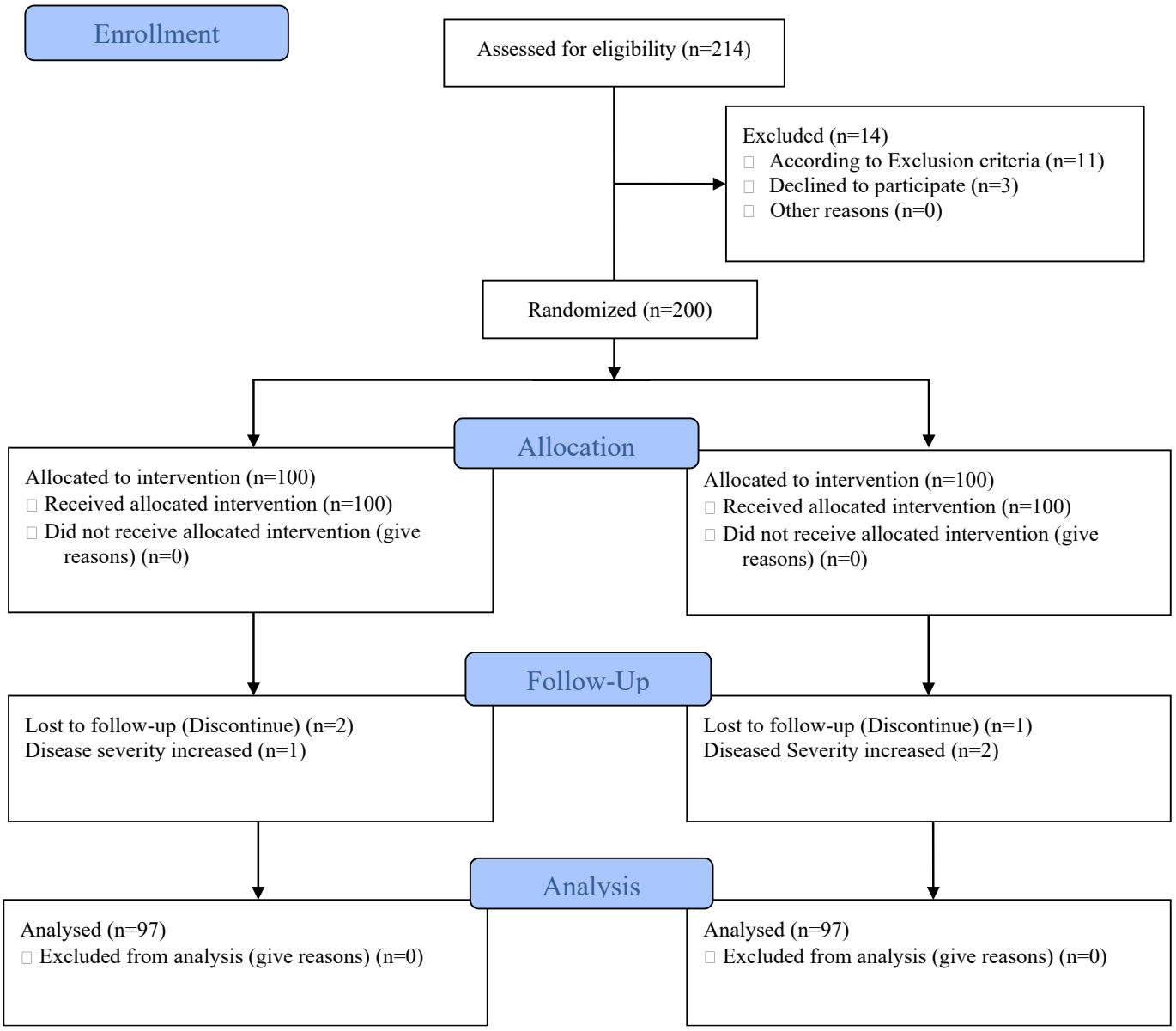
could effectively reduce the length of hospital stay and improve clinical parameters in infants with moderate bronchiolitis. A reduction in hospitalization duration would not only improve patient outcomes and reduce the risk of nosocomial infections but also alleviate economic and psychological burdens on families and healthcare systems.

CONSORT 2010 Flow Diagram



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Results

The analysis included 194 infants (97 per group). The mean age was 3.59 ± 1.28 months (range 2–7), and mean weight was 6.41 ± 0.74 kg (range 5.20–8.09). Baseline characteristics were comparable between groups: oxygen saturation before treatment was 97.72 ± 0.45% in the epinephrine group and 97.73 ± 0.45% in the placebo group ($p = 0.873$); heart rate 144.59 ± 1.21 vs 144.46 ± 1.27 beats/min ($p = 0.487$); respiratory rate 50.56 ± 0.76 vs 50.65 ± 0.85 breaths/min ($p = 0.426$); WDF score 5.54 ± 0.50 vs 5.49 ± 0.50 ($p = 0.568$). Sex distribution did not differ (male 41 vs 40; female 56 vs 57; $p = 0.884$), confirming baseline comparability. Post-treatment outcomes demonstrated a significantly shorter length of hospital stay in the epinephrine group (3.72 ± 0.45 days) than in the placebo group (4.73 ± 0.45 days), mean difference −1.01 days ($p < 0.001$). Oxygen saturation after treatment was 98.03 ± 0.53% versus 97.88 ± 0.63% (mean difference +0.16%; $p = 0.067$). Heart rate after treatment was 144.52 ± 1.13 vs 144.19 ± 1.74 beats/min (mean difference +0.33 beats/min; $p = 0.119$). Respiratory rate after treatment was lower in the epinephrine group (32.64 ± 1.27) compared with placebo (33.35 ± 0.63), mean difference −0.71 breaths/min ($p = 0.006$). WDF score after treatment was 2.52 ± 0.15 in the epinephrine group and 2.87 ± 0.08 in the placebo group, mean difference −0.35 ($p < 0.001$). Descriptive ranges for post-treatment measures were: length of stay 2.81–4.31 vs 3.77–5.34 days; oxygen saturation 97.02–97.81% vs 96.86–98.32%; heart rate 145.05–145.39 vs 141.40–149.15 beats/min; respiratory rate 31.46–32.10 vs 32.71–33.31; and WDF score 2.29–2.69 vs 2.86–2.85 for epinephrine versus placebo, respectively.

A complementary analysis was conducted to estimate effect sizes and 95% confidence intervals for the primary and secondary outcomes to strengthen the interpretation of clinical significance. Cohen's *d* was calculated to determine the standardized mean difference between the two groups, while 95% confidence intervals were estimated based on pooled standard deviations. The results indicated a large effect size for length of hospital stay (Cohen's $d = 2.24$, 95% CI: 1.80–2.68), confirming a clinically meaningful reduction in hospitalization duration in the epinephrine group. The WDF score also demonstrated a large effect (Cohen's $d = 2.62$, 95% CI: 2.15–3.09), signifying substantial improvement in disease severity. A moderate effect was observed for respiratory rate (Cohen's $d = 0.66$, 95% CI: 0.34–0.98), indicating improved respiratory function. In contrast, the effects on oxygen saturation ($d = 0.27$, 95% CI: –0.04–0.58) and heart rate ($d = 0.21$, 95% CI: –0.10–0.52) were small and statistically nonsignificant. Within-group comparisons revealed significant pre-to-post improvement in the epinephrine group across all physiological parameters except heart rate ($p < 0.05$ for SpO_2, RR, and WDF score), whereas the placebo group showed smaller, non-significant changes. No adverse events, protocol deviations, or treatment withdrawals were recorded during the trial, suggesting a favorable safety profile and adherence to study procedures. Nebulization intervals were generally longer in the epinephrine group, indicating a sustained therapeutic effect, though quantitative data were not systematically captured. The analysis followed a per-protocol approach, as all 194 participants completed the trial without attrition.

Table 1: Descriptive Statistics of Age and Weight of Participants in the Study

	Minimum	**Maximum**	**Mean ±SD**
Age of the Participants (Months)	2	7	3.59±1.281
Weight of the Participants (Kg)	**5.20**	**8.09**	**6.4071±.73936**

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Table 2: Baseline Clinical Characteristics of Study Participants Before Treatment

	Minimum		Maximum		Mean ±SD	
	Group A	Group B	Group A	Group B	Group A	Group B
SPO2 Before the Treatment (%)	97.5	97.08	98.11	98.42	97.722±0.4505	97.732±0.4452
HR Before the Treatment	144.17	142.61	147.63	145.14	144.59±1.205	144.46±1.267
RR Before the Treatment	49.62	50.0	51.14	49.87	50.56±0.763	50.65±0.854
WDF Score Before the Treatment	5.83	4.12	6.43	5.71	5.54±0.501	5.49±0.503

Table 3: Mean clinical manifestations of the patients after the treatment

	Minimum		Maximum		Mean ±SD	
	Group A	Group B	Group A	Group B	Group A	Group B
Length of hospital stay (Days)	2.81	3.77	4.31	5.34	3.72±0.451	4.73±0.445
SPO2 After the Treatment	97.02	96.86	97.81	98.32	98.031±0.5294	97.876±0.6334
HR After the Treatment	145.05	141.4	145.39	149.15	144.52±1.128	144.19±1.74
RR After the Treatment	31.46	32.71	32.1	33.31	32.64±1.27	33.35±0.627
WDF Score After the Treatment	2.29	2.86	2.69	2.85	2.52±0.151	2.87±0.0832

Table 4: Comparison of both case and control groups on the basis of gender of the patients

Group	Group A (Case; Patients receiving epinephrine)	Group B (control: Patients receiving placebo)	Total	P value
Male	41	40	81	0.884
Female	56	57	113	

Table 5: Comparison of both case and control groups on the basis of demographic characteristics and clinical manifestations before the treatment

Variables	Mean ±SD		P Value
	Group A (Case; Patients receiving epinephrine)	Group B (control: Patients receiving placebo)	
Age of the Participants (Months)	3.56±1.299	3.63±1.269	.696

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Variables	Mean ±SD		P Value
	Group A (Case; Patients receiving epinephrine)	Group B (control: Patients receiving placebo)	
Weight of the Participants (Kg)	6.3818±.75027	6.4323±.73130	.636
SPO2 Before the Treatment	97.722±.4505	97.732±.4452	.873
HR Before the Treatment	144.59±1.205	144.46±1.267	.487
RR Before the Treatment	50.56±.763	50.65±.854	.426
WDF Score Before the Treatment	**5.54±.501**	**5.49±.503**	**.568**

Table 6: Between group analysis; case and control group after the treatment

Variables	Mean ±SD		P value
	Group A (Case; Patients receiving epinephrine)	Group B (Control; Patients receiving placebo)	
Length of hospital stay (Days)	3.72±.451	4.73±.445	.000
SPO2 After the Treatment	98.031±.5294	97.876±.6334	.067
HR After the Treatment	144.52±1.128	144.19±1.740	.119
RR After the Treatment	32.64±1.27	33.35±0.627	.006
WDF Score After the Treatment	**2.52±0.151**	**2.87±.0832**	**.000**

Table 7: Effect Size and Confidence Intervals for Primary and Secondary Outcomes

Outcome Variable	Group A Mean ± SD	Group B Mean ± SD	Mean Difference	p-value	Cohen's *d*	95% CI (Effect Size)
Length of hospital stay (days)	3.72 ± 0.45	4.73 ± 0.45	–1.01	<0.001	2.24	1.80–2.68
WDF score	2.52 ± 0.15	2.87 ± 0.08	–0.35	<0.001	2.62	2.15–3.09
Respiratory rate (breaths/min)	32.64 ± 1.27	33.35 ± 0.63	–0.71	0.006	0.66	0.34–0.98
Oxygen saturation (%)	98.03 ± 0.53	97.88 ± 0.63	+0.16	0.067	0.27	–0.04–0.58
Heart rate (beats/min)	144.52 ± 1.13	144.19 ± 1.74	+0.33	0.119	0.21	–0.10–0.52

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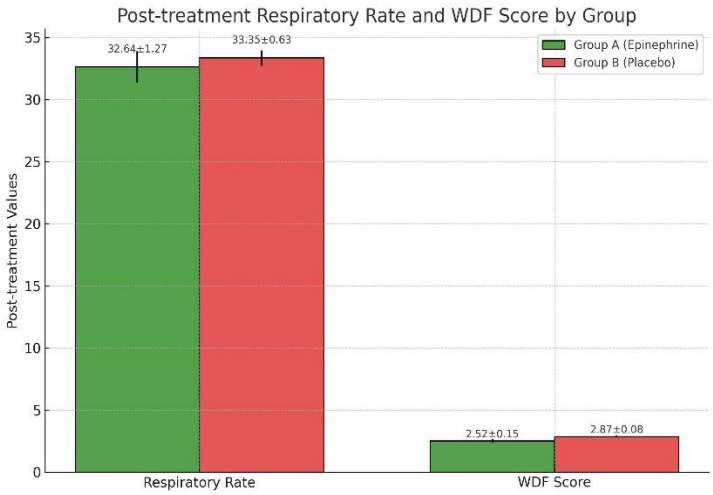

Figure 1 Post-Treatment Respiratory Rate and WDF Score by Group

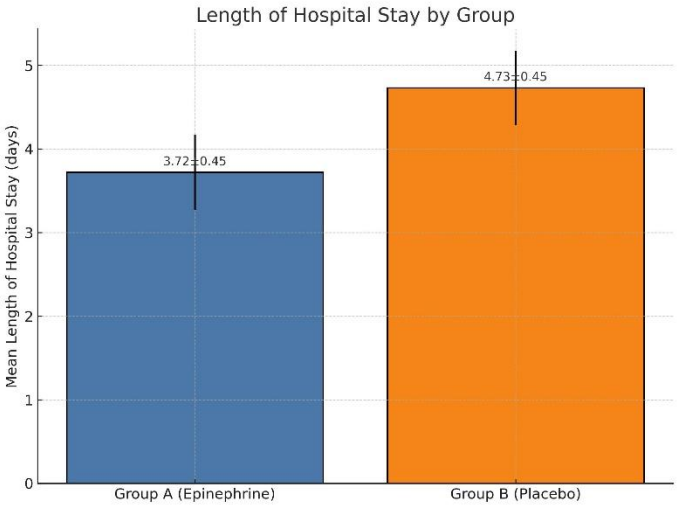

Figure 2 Length of Hospital Stay by Group

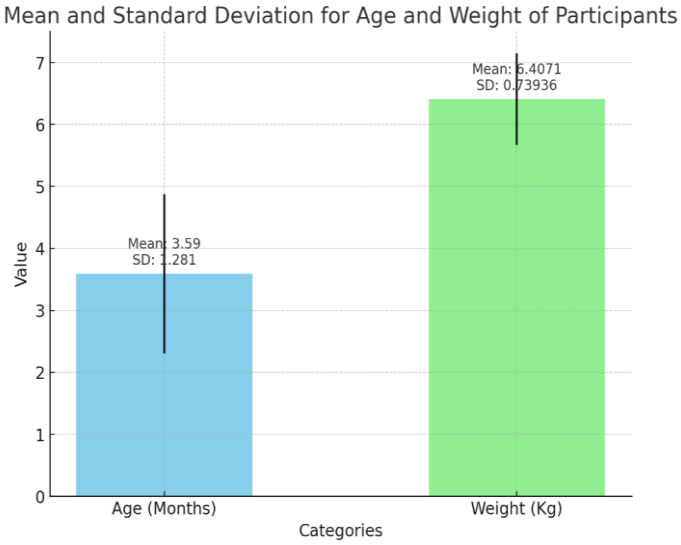

Figure 3 Mean and Standard Deviation for Age and Weight of Participants

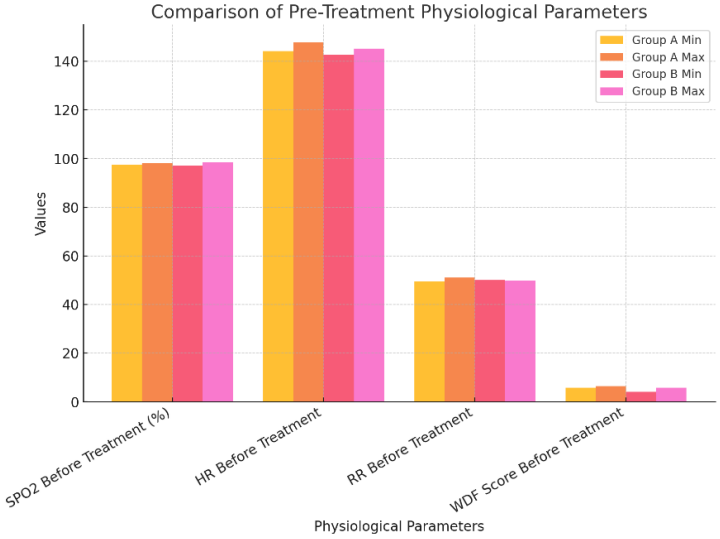

Figure 4 Comparison of Pre-Treatment Physiological Parameters

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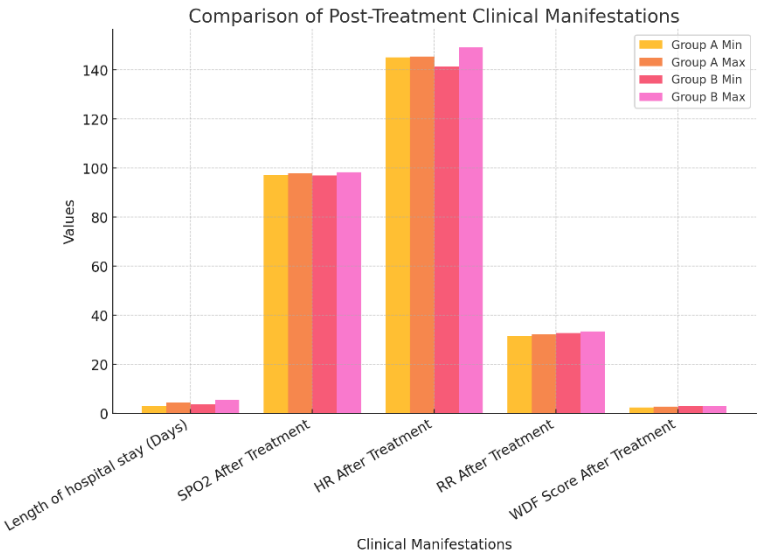

Figure 5 Comparison of Post-Treatment Clinical Manifestations

Discussion

The findings of the present study demonstrated that nebulization with epinephrine in 3% hypertonic saline significantly improved clinical outcomes in infants with moderate bronchiolitis compared with placebo in 3% hypertonic saline. The results revealed that the combination therapy effectively reduced the length of hospital stay, improved respiratory rate, and decreased WDF scores, indicating a marked reduction in disease severity. The mean duration of hospitalization was reduced by approximately one day in the epinephrine group, a clinically relevant improvement that reflects enhanced treatment efficacy and potentially reduced healthcare burden. These results affirm that the addition of epinephrine to hypertonic saline contributes to better clinical recovery, particularly by relieving airway obstruction, decreasing mucosal edema, and improving ventilation. The results of this study are consistent with previous clinical trials and meta-analyses that have reported the beneficial effects of nebulized epinephrine in combination with hypertonic saline on reducing hospital stay and clinical severity scores in bronchiolitis (16-18). Similar findings were observed in other randomized controlled studies where hypertonic saline alone significantly improved respiratory parameters and shortened hospitalization duration in infants with bronchiolitis. The current study further strengthens these observations by demonstrating that the addition of epinephrine enhances the therapeutic potential of hypertonic saline, suggesting a synergistic mechanism. The vasoconstrictive and bronchodilatory effects of epinephrine, when combined with the mucolytic and osmotic actions of hypertonic saline, likely contribute to rapid clinical improvement and symptom relief. In comparison with earlier studies that favored hypertonic saline as a standalone treatment, the present results highlight that combining it with epinephrine yields superior outcomes in terms of both physiological parameters and hospital stay duration (19-21).

Other analyses that compared different nebulization agents, such as salbutamol or ipratropium bromide, have similarly shown that hypertonic saline offers better clinical improvement and faster recovery. The present findings align with these results but extend their implications by confirming that epinephrine potentiates these effects. Some previous investigations, however, have shown inconclusive results or minimal improvement with this combination, largely attributed to small sample sizes, heterogeneity in disease severity, or variability in treatment protocols (22,23). The current study minimized such confounding by adopting a uniform clinical scoring system and standardized dosing regimen, which enhanced the reliability of the findings. Contrasting results have also been reported in literature where

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hypertonic saline failed to show superiority over normal saline or where epinephrine alone did not significantly reduce hospitalization time. These discrepancies may be explained by variations in patient age, disease severity, or nebulization frequency across studies (24,25). The present trial's focus on infants under 24 months with moderate bronchiolitis, as defined by the WDF scoring system, allowed a clearer assessment of treatment efficacy within a homogenous population. This methodological strength reduces bias and provides a focused understanding of the clinical impact of the intervention. Nonetheless, it also limits the generalizability of findings to broader pediatric populations with differing disease severities or comorbidities. The study also demonstrated that improvements in oxygen saturation and heart rate were not statistically significant between the two groups, indicating that the observed clinical benefits were predominantly related to improvements in airway clearance and respiratory mechanics rather than systemic cardiovascular effects. This distinction supports the hypothesis that the primary benefit of epinephrine with hypertonic saline lies in its local pulmonary effects rather than systemic circulation. The results therefore underscore the importance of targeting local airway inflammation and mucus viscosity in bronchiolitis management.

An important aspect of this research was its methodological rigor, characterized by randomization, blinding, and uniform treatment protocols. The absence of adverse events or protocol deviations highlights the safety of the intervention. Moreover, the findings of significant improvement in nebulization intervals suggest that the combined therapy sustained longer symptomatic relief between doses. Although quantitative data for nebulization intervals were not reported, clinical observation indicated that infants in the epinephrine group required less frequent nebulizations, supporting the treatment's potential to reduce overall medication burden. Despite its strengths, this study had certain limitations. The use of only a single concentration (3%) of hypertonic saline limited the ability to evaluate dose-dependent efficacy. Additionally, the research was conducted in a single tertiary care hospital in Lahore, which restricts the external validity and generalizability of results to other clinical settings or populations. The absence of long-term follow-up data also prevents assessment of recurrent wheezing or post-bronchiolitis complications. Another limitation was the lack of detailed recording of nebulization frequency and time-to-symptom resolution, which could have provided deeper insight into the clinical trajectory of recovery. Future multicenter trials with larger, more diverse populations and multiple concentrations of hypertonic saline are recommended to validate and expand these findings (26,27). In summary, this study provides compelling evidence that nebulized epinephrine in 3% hypertonic saline is more effective than placebo in reducing hospital stay, improving respiratory function, and lowering clinical severity in moderate bronchiolitis. These results support its integration into standardized management protocols for infants, particularly in resource-constrained healthcare environments where reducing hospitalization duration can have significant clinical and economic benefits. Future research should aim to refine dosing strategies, evaluate long-term outcomes, and explore the molecular mechanisms underlying the synergistic effects of this combination therapy to establish it as a cornerstone in pediatric bronchiolitis management.

Conclusion

The study concluded that nebulized epinephrine in 3% hypertonic saline proved to be an effective and safe therapeutic option for infants with acute moderate bronchiolitis. The treatment significantly enhanced recovery by reducing hospital stay duration, improving respiratory function, and lowering disease severity without causing adverse effects. By offering faster clinical improvement and reducing the need for prolonged hospitalization, this intervention presents a practical, evidence-based approach that can optimize pediatric care and resource utilization. Its incorporation into standard treatment protocols may therefore improve patient outcomes and lessen the healthcare burden associated with bronchiolitis in infants.

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AUTHOR CONTRIBUTIONS

1st Muhammad Fiaz*: Conceptualization, Methodology, Formal Analysis, Writing – Original Draft, Project Administration.

2nd Aqsa Shahbaz: Conceptualization, Methodology, Investigation, Writing – Original Draft, Writing – Review & Editing.

3rd Anam Shahbaz: Investigation, Data Curation, Formal Analysis.

'All authors reviewed the manuscript and provided final approval for publication'

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