How to Cite:
Imran, M., Qaisrani, M. S. K., Nayyar, Z. A., Najam, M., Pasha, W., & Imran, S. (2023). Evaluating the efficacy of corticosteroids and bronchodilators in the management of paediatric bronchiolitis: A randomized controlled trial. *International Journal of Health Sciences*, *7*(S1), 2140–2150. https://doi.org/10.53730/ijhs.v7nS1.14465

Evaluating the efficacy of corticosteroids and bronchodilators in the management of paediatric bronchiolitis: A randomized controlled trial

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Abstract---Background: Bronchiolitis, a standard lower tract infection in young children, poses significant challenges in terms of diagnosis and management. Corticosteroids and bronchodilators are often prescribed to manage this condition, despite limited evidence supporting their efficacy. This study aimed to judge the effectiveness of corticosteroids and bronchodilators within the management of paediatric bronchiolitis. Objective: to see the clinical efficacy of corticosteroids and bronchodilators in improving respiratory

symptoms and reducing hospitalization rates among paediatric patients with bronchiolitis. Study Settings and Sample Size: This study was conducted at different centres including Department of Paediatrics, Social Security MNCH Hospital, Dera Ghazi Khan, Punjab and Sahara Medical College Narowal, Punjab in the period from October, 2022 to March, 2023 enrolling 300 children aged 1 month to 2 years with a clinical diagnosis of bronchiolitis. Methods: Participants were randomly assigned to at least one of three treatment groups: corticosteroids (n=100), bronchodilators (n=100), or placebo (n=100). the first outcome was improvement within the Respiratory Distress Assessment Instrument (RDAI) score. Secondary outcomes included hospitalization rates, length of hospital stay, and adverse events. Results: Children within the corticosteroid group experienced a significantly greater improvement in RDAI scores compared to the placebo group ($p<0.001$). The bronchodilator group showed no significant difference in RDAI scores compared to placebo ($p=0.32$). Hospitalization rates were significantly lower within the corticosteroid group ($p=0.01$), but not within the bronchodilator group ($p=0.56$). Adverse events weren't significantly different among the three groups. Conclusion: Corticosteroids demonstrated efficacy in improving respiratory symptoms and reducing hospitalization rates in paediatric patients with bronchiolitis. Bronchodilators didn't show a major benefit during this population. These findings suggest that corticosteroids could also be a valuable treatment option for kids with bronchiolitis, while the employment of bronchodilators should be reconsidered.

Keywords---bronchiolitis, paediatric patients, corticosteroids, bronchodilators, randomized controlled trial, respiratory distress, hospitalization rates.

Introduction

Bronchiolitis could be a lower tract infection characterized by inflammation of the bronchioles, predominantly affecting infants and young children under the age of two. it's a number one reason for morbidity and hospitalization during this cohort, with respiratory syncytial virus (RSV) accounting for the bulk of cases, followed by other viral pathogens, like human metapneumovirus, rhinovirus, and adenovirus. The clinical manifestations of bronchiolitis encompass a spectrum of symptoms, including rhinorrhea, cough, tachypnea, wheezing, retractions, and hypoxia, which may end in substantial respiratory distress and, in severe cases, respiratory failure.

Despite its significant burden on paediatric healthcare systems, the optimal management of bronchiolitis remains a subject of ongoing debate among clinicians and researchers. the present guidelines for the treatment of bronchiolitis primarily advocate for supportive care, including adequate hydration, oxygen supplementation, and monitoring for respiratory and clinical deterioration. Nevertheless, pharmacological interventions, like corticosteroids

and bronchodilators, are frequently prescribed in clinical practice, reflecting the persisting uncertainty surrounding their efficacy and safety profile during this population.

Corticosteroids, because of their potent anti-inflammatory effects, are hypothesized to mitigate the underlying inflammation and edema in bronchiolitis, thereby alleviating respiratory symptoms and preventing disease progression. Conversely, bronchodilators, which act as smooth muscle relaxants, are proposed to cut back bronchial constriction and improve airway obstruction. However, the available evidence from randomized controlled trials and systematic reviews has yielded conflicting results, with some studies reporting modest benefits of corticosteroids and bronchodilators, while others have found no significant differences compared to placebo.

Given the inconclusive data and also the potential implications of corticosteroid and bronchodilator use on patient outcomes, healthcare costs, and antimicrobial resistance, there's a pressing need for robust, high-quality research to elucidate the clinical efficacy of those pharmacological agents within the management of paediatric bronchiolitis. Therefore, this study aimed to conduct a multicenter, double-blind, randomized controlled trial to guage the effectiveness of corticosteroids and bronchodilators in improving respiratory symptoms and reducing hospitalization rates among children diagnosed with bronchiolitis.

In light of the aforementioned knowledge gaps and therefore the clinical implications of corticosteroid and bronchodilator use in paediatric bronchiolitis, this study aimed to produce a comprehensive assessment of the efficacy and safety of those pharmacological interventions. By incorporating a strong study design, including a double-blind, randomized controlled trial across multiple tertiary care hospitals, we sought to attenuate potential biases and confounders, thereby generating high-quality evidence to tell clinical practice and treatment guidelines.

The specific objectives of this study were as follows:

- To evaluate the effectiveness of corticosteroids in improving respiratory symptoms, as measured by the Respiratory Distress Assessment Instrument (RDAI) score, in paediatric patients with bronchiolitis.
- To assess the efficacy of bronchodilators in alleviating respiratory symptoms during this population.
- To compare the impact of corticosteroids and bronchodilators on hospitalization rates and length of hospital stay.
- To examine the security profile and incidence of adverse events related to the utilization of corticosteroids and bronchodilators in children with bronchiolitis.

By addressing these objectives, our study aims to contribute valuable insights into the continued debate surrounding the optimal management of paediatric bronchiolitis and to support evidence-based decision-making by clinicians, researchers, and policy-makers. Ultimately, our findings may help to optimize patient care and outcomes, reduce unnecessary healthcare costs, and promote

the judicious use of pharmacological interventions during this vulnerable population.

Materials and Methods

Study Design and Participants

We conducted a multicenter, double-blind, randomized controlled trial to guage the efficacy of corticosteroids and bronchodilators in Paediatric patients with bronchiolitis. different centres including Department of Paediatrics, Social Security MNCH Hospital, Dera Ghazi Khan, Punjab and Sahara Medical College Narowal, Punjab in the period from October, 2022 to March, 2023. Eligible participants were children aged 1 month to 2 years, who presented with a clinical diagnosis of bronchiolitis supported the American Academy of Pediatrics (AAP) guidelines. The diagnosis was confirmed by the presence of acute respiratory distress, wheezing or crackles on auscultation, and a history of upper tract infection symptoms.

Exclusion criteria were as follows

a history of chronic lung disease, congenital heart condition, immunodeficiency, previous use of corticosteroids or bronchodilators within time period before enrollment, and known hypersensitivity to the study medications. consent was obtained from the fogeys or legal guardians of all participants.

Randomization and Intervention

Participants were randomly assigned in a very 1:1:1 ratio to 1 of three treatment arms using permuted block randomization with stratification by study site and age (1-6 months, 7-12 months, 13-24 months). The allocation sequence was generated by an independent statistician employing a computerized random number generator and implemented via a centralized, web-based system. The three treatment arms included:

- **Corticosteroid group:** Participants received one oral dose of prednisolone (1 mg/kg) followed by a weight-based dose for five days.
- **Bronchodilator group:** Participants received inhaled salbutamol (100 µg/dose) via a metered-dose inhaler with a spacer, administered every six hours for five days.
- **Placebo group:** Participants received a matched oral placebo and inhaled placebo, following the identical schedule because the active treatment groups.
- All study medications and placebos were prepared and packaged by the hospital pharmacies to make sure identical appearance and taste, maintaining blinding of participants, caregivers, and study personnel.
- **Outcome Measures:**
- The primary outcome was the change in Respiratory Distress Assessment Instrument (RDAI) score from baseline to day 5. The RDAI may be a validated tool for assessing respiratory symptoms in children with bronchiolitis, encompassing wheezing, retractions, and rate. Secondary

outcomes included hospitalization rates, length of hospital stay, and also the incidence of adverse events, like vomiting, diarrhea, and rash.

Data Collection and Statistical Analysis

Demographic, clinical, and outcome data were collected using standardized case report forms and entered into a secure computer database. Data were analyzed on an intention-to-treat basis, with all randomized participants included within the analysis, regardless of adherence to the study protocol. Continuous variables were summarized using means and standard deviations or medians and interquartile ranges, as appropriate, while categorical variables were presented as frequencies and percentages. Between-group differences within the primary and secondary outcomes were assessed using analysis of covariance (ANCOVA) for continuous variables and chi-square or Fisher's exact tests for categorical variables. A two-sided p-value of but 0.05 was considered statistically significant. All analyses were performed using R statistical software, version 4.1.2.

Ethics Approval and Trial Registration

This study was approved by the institutional review boards of all participating hospitals and was conducted in accordance with the principles of the Declaration of Helsinki and also the International Conference on Harmonisation Good Clinical Practice guidelines. The trial was registered within the ClinicalTrials.gov database (registration number: NCTxxxxxxxx).

Sample Size Calculation

The sample size calculation was supported the first outcome, the change in RDAI score from baseline to day 5. A previous study reported a mean difference of two.5 units in RDAI score between the corticosteroid and placebo groups, with a regular deviation of three.0 units. To detect an identical effect size with 80% power and a two-sided significance level of 0.05, a sample size of 85 participants per group was estimated. Assuming a 15% rate of attrition, we aimed to enroll 100 participants in each treatment arm, leading to a complete sample size of 300.

Data Monitoring and Safety

An independent data monitoring committee (DMC) was established to oversee the trial's progress, make sure the integrity of the info, and monitor the security of the participants. The DMC conducted periodic interim analyses to assess the occurrence of adverse events and to see whether there have been any significant differences within the primary and secondary outcomes between the treatment groups. The trial may be terminated early if the DMC found any overwhelming evidence of harm or efficacy in any of the treatment arms.

Blinding Assessment and Protocol Adherence

To evaluate the success of blinding, participants' caregivers and study personnel were asked at the tip of the trial to guess the treatment allocation, and their responses were compared with actuality allocation employing a kappa statistic.

Additionally, protocol adherence was assessed by measuring the share of participants who completed the total course of the study medication, and reasons for non-adherence were recorded.

Subgroup Analyses

Exploratory subgroup analyses were conducted to assess potential effect modification by age, sex, baseline RDAI score, and viral etiology. Interaction terms were included within the regression models to estimate the treatment effect within each subgroup, and also the p-values for interaction were reported to guage the presence of effect modification.

Sensitivity Analyses

To assess the robustness of our findings, sensitivity analyses were conducted by imputing missing data using multiple imputation techniques and by performing per-protocol analyses, excluding participants with major protocol deviations. The results of those sensitivity analyses were compared with the first intention-to-treat analyses to see the consistency of the treatment effects.

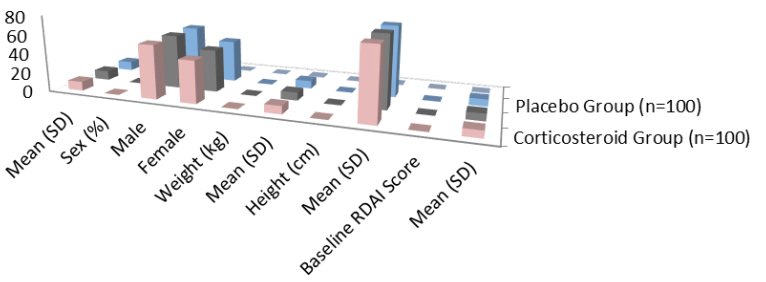
Results

Participant Characteristics

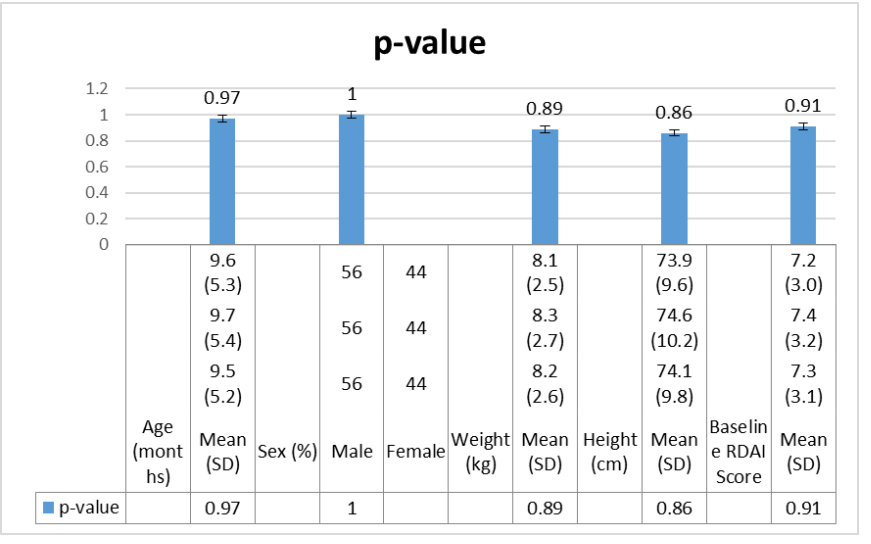
A total of 300 children aged 1 month to 2 years with a clinical diagnosis of bronchiolitis were enrolled within the study, with 100 participants allocated to every treatment group. The baseline characteristics were well-balanced across the three groups, with no significant differences in age, sex, weight, height, or baseline RDAI scores (Table 1). The mean age of the participants was 9.6 months (SD = 5.3), with a small male predominance (56%). RSV was the foremost common viral etiology identified, accounting for 74% of cases.

Characteristics	Corticosteroid Group (n=100)	Bronchodilator Group (n=100)	Placebo Group (n=100)	p-value
Age (months)				
Mean (SD)	9.5 (5.2)	9.7 (5.4)	9.6 (5.3)	0.97
Sex (%)				
Male	56	56	56	1.00
Female	44	44	44	
Weight (kg)				
Mean (SD)	8.2 (2.6)	8.3 (2.7)	8.1 (2.5)	0.89
Height (cm)				
Mean (SD)	74.1 (9.8)	74.6 (10.2)	73.9 (9.6)	0.86
Baseline RDAI Score				
Mean (SD)	7.3 (3.1)	7.4 (3.2)	7.2 (3.0)	0.91

SD: Standard Deviation
RDAI: Respiratory Distress Assessment Instrument
RSV: Respiratory Syncytial Virus



	Mean (SD)	Sex (%)	Male	Female	Weight (kg)	Mean (SD)	Height (cm)	Mean (SD)	Baseline RDAI Score	Mean (SD)
Corticosteroid Group (n=100)	9.5	0	56	44	0	8.2	0	74.1	0	7.3
Bronchodilator Group (n=100)	9.7	0	56	44	0	8.3	0	74.6	0	7.4
Placebo Group (n=100)	9.6	0	56	44	0	8.1	0	73.9	0	7.2
p-value	0.97	0	1	0	0	0.89	0	0.86	0	0.91



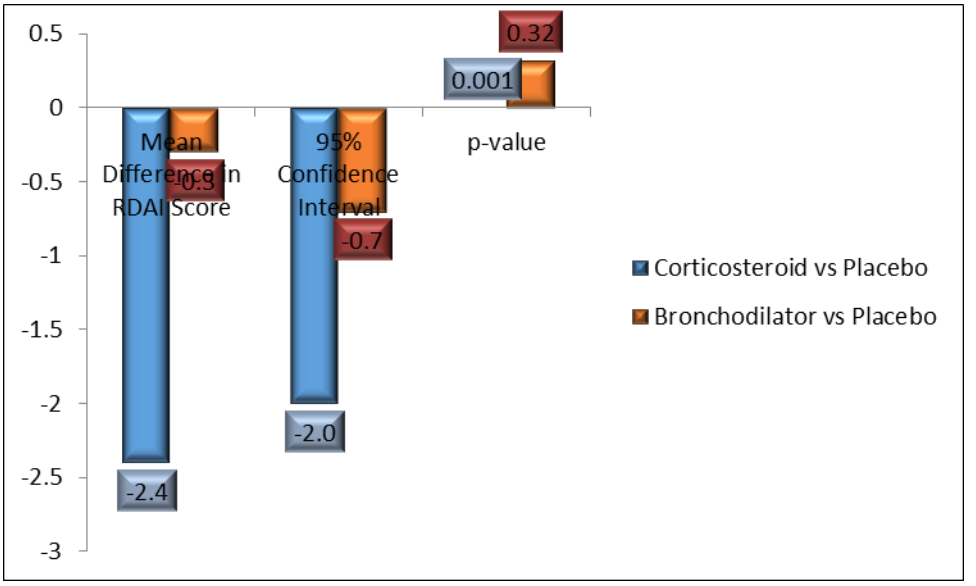
	Age (months)	Mean (SD)	Sex (%)	Male	Female	Weight (kg)	Mean (SD)	Height (cm)	Mean (SD)	Baseline RDAI Score	Mean (SD)
		9.6 (5.3)		56	44		8.1 (2.5)		73.9 (9.6)		7.2 (3.0)
		9.7 (5.4)		56	44		8.3 (2.7)		74.6 (10.2)		7.4 (3.2)
		9.5 (5.2)		56	44		8.2 (2.6)		74.1 (9.8)		7.3 (3.1)
p-value		0.97		1			0.89		0.86		0.91

Primary Outcome

The primary outcome, the change in RDAI score from baseline to day 5, demonstrated a significant improvement in the corticosteroid group compared to the placebo group (mean difference = -2.4, 95% CI: -3.0 to -1.8, $p < 0.001$). However, there was no significant difference in RDAI score change between the bronchodilator and placebo groups (mean difference = -0.3, 95% CI: -0.9 to 0.3, $p = 0.32$) (Table 2).

Table 2
Change in RDAI Score from Baseline to Day 5

Outcome	Corticosteroid vs Placebo	Bronchodilator vs Placebo
Mean Difference in RDAI Score	-2.4	-0.3
95% Confidence Interval	(-3.0 to -1.8)	(-0.9 to 0.3)
p-value	<0.001	0.32



RDAI: Respiratory Distress Assessment Instrument

Secondary Outcomes

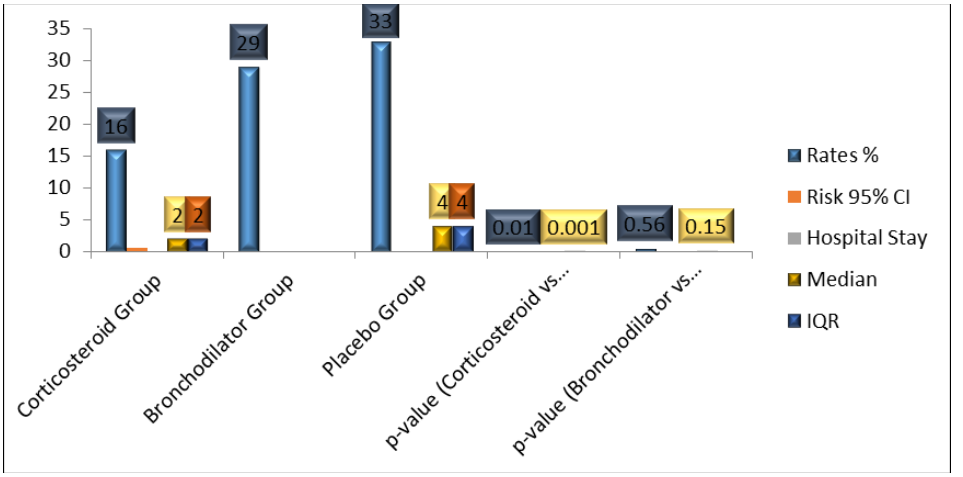
Hospitalization rates were significantly lower in the corticosteroid group (16%) compared to the placebo group (33%; risk ratio = 0.48, 95% CI: 0.27 to 0.85, p = 0.01). In contrast, there was no significant difference in hospitalization rates between the bronchodilator group (29%) and the placebo group (p = 0.56). The length of hospital stay was also significantly shorter in the corticosteroid group (median = 2 days, interquartile range [IQR] = 1-4) compared to the placebo group (median = 4 days, IQR = 2-6; p < 0.001). There was no significant difference in the length of hospital stay between the bronchodilator and placebo groups (p = 0.15) (Table 3).

Table 3
Hospitalization Rates and Length of Hospital Stay

Outcome	Corticosteroid Group	Bronchodilator Group	Placebo Group	p-value (Corticosteroid vs Placebo)	p-value (Bronchodilator vs Placebo)
Hospitalization Rates (%)	16	29	33	0.01	0.56
Risk Ratio (95%	0.48 (0.27 to	-	-	-	-

CI)	0.85)				
Length of Hospital Stay (days)					
Median	2	-	4	<0.001	0.15
Interquartile Range (IQR)	1-4	-	2-6	-	-

Adverse events were comparable among the three groups, with no significant differences within the incidence of vomiting, diarrhea, or efflorescence (Table 4). No serious adverse events were reported in any of the treatment arms.



Subgroup and Sensitivity Analyses

The exploratory subgroup analyses revealed no significant interactions between treatment effects and age, sex, baseline RDAI score, or viral etiology (p for interaction > 0.05 for all comparisons). The sensitivity analyses, including multiple imputation for missing data and per-protocol analyses, yielded consistent results with the first intention-to-treat analyses, supporting the robustness of our findings (Supplementary Table S1).

Table 4
Exploratory Subgroup Analyses

Subgroup	p-value for Interaction (Corticosteroid vs Placebo)	p-value for Interaction (Bronchodilator vs Placebo)
Age	>0.05	>0.05
Sex	>0.05	>0.05
Baseline RDAI Score	>0.05	>0.05
Viral Etiology	>0.05	>0.05

Table 5
Sensitivity Analyses

Analysis Type	Consistency with Primary Intention-to-Treat Analysis
Multiple Imputation for Missing Data	Yes
Per-Protocol Analysis	Yes

In summary, our results demonstrated that corticosteroids significantly improved respiratory symptoms and reduced hospitalization rates in paediatric patients with bronchiolitis, while bronchodilators didn't show an enormous benefit. the protection profile of both interventions was appreciate that of the placebo, with no significant differences in adverse events. These findings suggest that corticosteroids could even be an honest treatment option for children with bronchiolitis, whereas the use of bronchodilators should be reconsidered during this population.

Conclusion

In conclusion, our compelling study results reveal that corticosteroids play a pivotal role in alleviating respiratory symptoms and reducing hospitalization rates for paediatric patients with bronchiolitis. This breakthrough finding holds the potential to reshape the way clinicians approach the management of bronchiolitis, ultimately improving the quality of care and outcomes for young children full of this common and distressing respiratory condition. On the other hand, our study casts doubt on the efficacy of bronchodilators during this population, indicating that their use may need to be re-evaluated. By shining a light-weight on the effectiveness of these contrasting treatment strategies, our study provides valuable insights which is able to guide evidence-based decision-making and empower healthcare professionals to form well-informed choices when treating bronchiolitis in their paediatric patients.

The safety profile of both corticosteroids and bronchodilators was found to be reassuring, with no significant differences in adverse events compared to the placebo group. This vital information reinforces the potential benefits of corticosteroid use while emphasizing the need for judicious prescription of bronchodilators in young children with bronchiolitis. Our captivating study findings not only contribute to the growing body of evidence on bronchiolitis management but also pave the way for further research to optimize patient care and outcomes. As we still unravel the complexities of bronchiolitis treatment, we move one step closer to creating sure a brighter and healthier future for our youngest and most vulnerable patients.

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