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ORIGINAL ARTICLE

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Randomized, Double-Blind, Controlled Trial of Nebulized Budesonide, Epinephrine and Salbutamol in Infants with Acute Bronchiolitis

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What is known on this subject?

Acute bronchiolitis remains a leading cause of pediatric lower respiratory tract infections, characterized by a highly variable clinical course. While it is a common diagnosis, the optimal management strategy is still a matter of significant debate. In particular, the clinical utility and therapeutic benefit of bronchodilators remain uncertain, leading to substantial variations in clinical practice.

What this study adds?

This study establishes that nebulized salbutamol, epinephrine, and budesonide provide no significant therapeutic advantage over normal saline in the management of infants with mild bronchiolitis. Comparative analysis reveals that while long-term outcomes remain unaffected, nebulized salbutamol may offer a modest clinical benefit in achieving short-term symptomatic improvement compared to other nebulized modalities.

ABSTRACT

Objective: Acute bronchiolitis is a leading cause of lower respiratory tract infections, and a wide range of clinical symptoms from mild cough to severe respiratory distress can be seen during the disease course. The optimal treatment for bronchiolitis has been controversial; the role of bronchodilators in the treatment of bronchiolitis is uncertain. The aim of this study was to evaluate the efficacy of nebulized therapies with control groups in the treatment of acute bronchiolitis.

Material and Methods: A prospective, randomized, and double blinded study was conducted among the infants diagnosed with acute bronchiolitis in a tertiary children's hospital. Heart rate, respiratory rate (RR), oxygen saturation by pulse oximetry, respiratory distress assessment instrument and side effects were recorded in the follow-up form.

Results: A total of 60 infants (66% male) diagnosed with acute bronchiolitis were included into the study. The median age of the patients at admission was 6.5 (3.5-9.5) months, and the median duration time of prodromal symptoms was 5.5 (3-7) days and wheezing symptoms was 3 (2-5) days. The baseline characteristics were similar in all groups ($p>0.05$). The outcome of patients at 120th minute was found to

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ABSTRACT

be significantly better than the baseline values ($p<0.05$). However, RR was improved statistically significantly at 30th minute in the salbutamol group ($p=0.031$). No serious side effects were observed in any patient during the follow-up.

Conclusion: The effectiveness of nebulized salbutamol, epinephrine, budesonide and normal saline treatments were not different in infants with mild bronchiolitis; however, nebulized salbutamol was found to be a little bit more effective in short-term improvement.

Keywords: Bronchiolitis, budesonide, epinephrine, infants, pediatrics, salbutamol

Introduction

Acute bronchiolitis is a major cause of lower respiratory tract infection in children under two years of age, with the highest incidence observed during infancy. The disease is characterized by inflammation of the small airways, resulting in airflow limitation due to mucosal edema, increased mucus production, and epithelial cell injury. A distinct seasonal pattern has been described, with case numbers rising predominantly in the winter and early spring months (1,2,3). Viral pathogens account for the majority of cases, with respiratory syncytial virus (RSV) identified as the leading causative agent in infants (3,4).

Bronchiolitis is among the most frequent reasons for presentation to pediatric emergency departments (EDs) due to respiratory distress in this age group (5). Although the clinical course is often self-limiting, some patients may develop severe, potentially life-threatening respiratory compromise. After an initial prodromal phase lasting approximately two to four days and characterized by fever, rhinorrhea, and nasal congestion, affected infants may experience progressive respiratory symptoms, including cough, wheezing, and tachypnea. Current management strategies are primarily supportive and focus on ensuring adequate oxygenation, maintaining hydration, and providing appropriate nutritional support (6,7).

Despite the absence of definitive evidence demonstrating a clear clinical benefit, inhaled pharmacological therapies such as salbutamol, epinephrine, and corticosteroids have been widely used in the treatment of acute bronchiolitis. However, clinical trials and meta-analyses evaluating these interventions have produced inconsistent findings regarding their efficacy and comparative advantages (8).

Although acute bronchiolitis can result in significant morbidity, no therapeutic intervention has been conclusively shown to reduce disease severity, shorten symptom duration, or decrease hospital length of stay. Nevertheless, nebulized treatments remain frequently employed in clinical practice. Accordingly, the present study aimed to compare the clinical effectiveness and potential adverse effects of nebulized salbutamol, epinephrine, and budesonide to those observed in a control group among infants admitted to the pediatric ED with a diagnosis of acute bronchiolitis.

Material and Methods

Study Population

This study was conducted in the pediatric ED of Bakırköy Maternity and Children's Diseases Training and Research Hospital, where the participating physicians had previously been employed. That study was a prospective, randomized, double-blind, controlled trial; all patients enrolled in the study had a first or second episode of acute bronchiolitis. Sixty children aged between 1 and 24 months who were diagnosed with acute bronchiolitis were admitted to our pediatric ED and recruited to the study during a two-month period from November to December. The Ethics Committee of Bakırköy Maternity and Children's Training and Research Hospital was approved the study (approval number: 147 date: 11.07.2008), and verbal informed consent was obtained from the parents of patients.

Exclusion Criteria

- >2 attacks of bronchiolitis
- Any prior symptoms or documented history of atopic diseases (atopic dermatitis, asthma)
- Family history of asthma
- Presence of two of the following criteria: Allergic rhinitis, presence of wheezing and cough between attacks (with effort), eosinophilia (4%), specific immunoglobulin E (IgE) positivity and male gender
- Patients with congenital heart disease, chronic lung disease or immunodeficiency
- History of preterm birth
- Presence of cough more than 7 days or pneumonia
- Presence of any of the following criteria: Oxygen saturation by pulse oximetry (SaO_2, on admission ≤91%) and/or respiratory rate (RR) >100/minute and/or heart rate (HR) >200/minute and/or fever >38.5 °C (axillary)

- Patients who require mechanical ventilation
- Patients who received nebulizer treatment prior to admission
- Parents who refused to be a participant for the study.

Study Design

Age, gender, weight, and other demographic information of the patients (duration of prodromal symptoms and wheezing, tobacco exposure, gestational age, presence of prior treatment etc.), and physical examination findings, HR, RR, presence of retraction and wheezing, SaO_2, clinical RDAI (respiratory distress assessment instrument) (Table 1) were recorded on the study follow-up form.

The selected patients were randomly assigned to four groups to receive blinded treatment with nebulized budesonide, epinephrine, salbutamol, or 0.9% saline (control group). Randomization of the participants to receive each treatment was performed using a table of random numbers prepared by the ED physician, and codes were assigned to each drug. Both parents and the attending physician were absent during the preparation of the drugs. The attending physician who completed the follow-up forms and assigned the clinical scores was blinded to the patients received to avoid bias.

The ED physician calculated the drug doses for each patient: budesonide 0.5 mg/dose (9), salbutamol 0.15 mg/kg/dose (minimum 1.25 mg/dose) (10), and epinephrine 3 mg/dose (11). All drugs were diluted to a 5 mL dose with normal saline (NS), and the control group received 5 mL/dose of NS. Because all study drugs were colorless and odorless, the study drugs were similar in appearance and smell. The study drugs were prepared by the ED nurse and were administered in two nebulized doses at 30-minute intervals under the supervision of the ED physician.

Measurements

Viral etiology testing for RSV antigen was performed on nasopharyngeal specimens. Complete blood count and specific IgE tests for cow's milk and egg white were also obtained.

The RDAI scoring system was developed by Lowell et al. (12) (Table 1). The scores range between 0 and 17 and are based on wheezing and respiratory retractions. Patients RDAI scores fewer than 3 were considered clinically mild bronchiolitis, whereas patients RDAI scores greater than 15 were regarded as severe bronchiolitis and excluded from the study (12).

The attending physician examined the infants initially and at 30th, 60th, and 120th minutes, assessed HR, RR (breaths/minute), SaO_2, RDAI score and the presence of side effects (hyperactivity, muscle tremor, vomiting) that may occur during drug administration and recorded at the follow-up form. At the second hour of the study period if the patient's clinical score was ≤3, SaO_2 >%95 without supplemental O_2 and those without any signs of respiratory distress and feeding difficulty were discharged from the emergency room. Patients who did not meet these criteria continued to receive supportive treatment in the ED, outside the study.

Statistical Analysis

Statistical analyses were conducted using SPSS® software (version 22.0 for Windows). Descriptive statistics were applied to summarize the data. Continuous variables were presented as mean ± standard deviation for normally distributed data or as median with interquartile range (IQR) for non-normally distributed data. Categorical variables were reported as frequencies and percentages with corresponding 95% confidence intervals (95%), and group comparisons were performed using the chi-square test. Univariate analyses were carried out to examine the associations between demographic and clinical variables and clinical outcome scores, using the Mann–Whitney U test with Bonferroni correction, the chi-square test, or the Kruskal–Wallis test, as appropriate. Repeated measurements were analyzed using the Wilcoxon signed-rank test. A p value <0.05 was considered statistically significant.

Table 1. Respiratory distress assessment instrument (12)

	0	1	2	3	4	Maximum points
Wheezing						
Expiration	None	End	1/2	3/4	All	4
Inspiration	None	Part	All	-	-	2
Location	None	Segmental	Diffuse	-	-	2
Retractions						
Supraclavicular	None	Mild	Moderate	Marked		3
Intercostal	None	Mild	Moderate	Marked	-	3
Subcostal	None	Mild	Moderate	Marked	-	3
Total	-	-	-			17

Results

Characteristics of the Study Population

A total of 60 children (66% male) who were diagnosed with acute bronchiolitis were enrolled in the study. The median (IQR) age of the patients at admission was 6.5 (3.5-9.5) months. The median (IQR) durations of the prodromal period and of wheezing symptoms were 5.5 (3-7) and 3 (2-5) days, respectively.

There was no difference among the groups in terms of gender, age, weight, tobacco exposure, previous treatments (symptomatic treatments such as antipyretics and nasal cleansing), RSV positivity, the duration of the prodromal period, and wheezing symptoms ($p>0.05$) at enrollment. The demographic and general characteristics of the patients, with comparisons between groups are depicted in Table 2.

Initial values of RDAI scores, HR, SaO_2, and RR on admission are shown in Table 3. There were no significant differences among the groups before the initial nebulized treatment ($p>0.05$), indicating that the treatment groups were similar.

Time-Dependent Changes in Clinical Scores

The treatment groups were compared with each other to assess time dependent changes in terms of HR, SaO_2, RDAI values, and no significant difference was found. The values also did not differ among the groups at 30, 60, and 120 minutes.

When we compared the groups after administration of nebulized salbutamol, epinephrine, budesonide, and NS at the 30th, 60th, and 120th minutes, RR improved significantly at the 30th minute in the salbutamol group ($p=0.031$). However, there were no statistically significant differences at the 60th and 120th minutes among the study groups (Table 3).

The time-dependent curve of RDAI, HR, SaO_2, and RR values among the groups at the beginning, 30th minute, 60th minute, and 120th minute of the treatment is depicted in Figure 1a-d.

The treatment groups were compared with their baseline values and with the values at the 30th, 60th, and 120th minutes in terms of RDAI scores, HR, and RR. A statistically significant difference was found in the improvement of RDAI scores and RR across all the treatment groups between baseline and 120 minutes after nebulized treatment. In contrast, were no differences between SaO_2 and HR values at any time (Table 4).

Comparison of the Treatment Groups

The treatment groups were compared pairwise with each other and with the placebo group; RR was significantly lower in the salbutamol group than in the placebo group at the 120th minute ($p=0.01$) (Figure 1c). However, there were no statistically significant differences in RDAI scores, HR, or SaO_2 at 30, 60, and 120 minutes.

Side Effects

Patients in the study were also monitored for side effects during the nebulized treatment. No serious side effects were observed in any patient during the follow-up. Oxygen and intravenous (IV) fluid treatment were required for seven patients in the budesonide group, and one patient experienced vomiting. One patient in the salbutamol group also had vomiting. Five patients in the epinephrine group needed supplemental O_2 and IV fluid therapy. Supplemental O_2 and IV fluid requirements were observed in seven cases in the NS group.

Table 2. Comparison of the clinical features of nebulized budesonide, salbutamol, epinephrine and control groups

	Budesonide (n=16)	Salbutamol (n=15)	Epinephrine (n=15)	Control (n=14)	p
Gender (male; n, %)	11 (68)	11 (73)	8 (54)	10 (72)	0.643
Age, months*	6 (3-12)	8.5 (3-12)	5.5 (4-11)	7.5 (3-13)	0.733
Weight, kg*	7.25 (4-13)	8 (4.5-10)	7.5 (4-11)	7.7 (5-10)	0.457
Hospitalization rate	8 (50)	5 (33)	3 (20)	5 (35)	0.378
Tobacco exposure	4 (25)	6 (40)	3 (20)	5 (35)	0.619
Duration of prodromal symptoms*	5.5 (3-25)	7 (4-12)	5 (2-15)	4.5 (2-15)	0.662
Duration of wheezing symptoms*	3 (2-6)	3 (2-6)	3 (1-7)	3 (2-7)	0.701
Previous treatments	5 (30)	2 (12)	4 (26)	3 (21)	0.678
Eosinophilia (4%)	-	-	-	2 (14)	0.079
Specific IgE positivity	1 (6)	2 (13)	1 (6)	-	0.347
RSV positivity	5 (31)	4 (26)	5 (33)	1 (7)	0.349
WBC	9950 (6000-13500)	9800 (7400-15000)	12100 (6900-13300)	8700 (5800-14100)	0.465

**Median (IQR). RSV: Respiratory syncytial virus, WBC: White blood cell, IgE: Immunoglobulin E, IQR: Interquartile range*

Table 3. **Comparison of RDAI score, respiratory rate, heart rate and SaO_2 among the treatment groups at 0, 30, 60 and 120 minutes**

	Budesonide (n=16)	Salbutamol (n=15)	Epinephrine (n=15)	Control (n=14)	p
RDAI scores					
0 min	10 (9-12)	12 (9-12)	11 (9-12)	11 (8.75-13)	0.928
30 min	10 (8-11.75)	9 (6-10)	10 (7-10)	10 (8.75-12.25)	0.397
60 min	9.5 (6.25-11)	8 (5-10)	8 (6-10)	10 (8.75-12)	0.146
120 min	8 (5.25-9.25)	7 (3-9)	6 (3.5-10)	9 (7.5-10.5)	0.090
RR					
0 min	60 (49-67)	58 (48-60)	60 (52-60)	56 (52-61)	0.351
30 min	56 (52-60)	52 (40-56)	56 (48-60)	56 (48-61)	**0.031**
60 min	52 (49-60)	50 (40-52)	56 (44-56)	54 (44-60)	0.197
120 min	52 (43-56)	48 (40-50)	50 (38-56)	52 (48-56)	0.100
HR					
0 min	129 (120-140)	132 (120-136)	132 (124-140)	132 (120-137)	0.905
30 min	132 (124-136)	132 (120-136)	132 (128-136)	132 (124-136)	0.890
60 min	130 (128-136)	128 (127-140)	136 (124-140)	132 (124-136)	0.805
120 min	130 (124-136)	130 (125-135)	130 (120-137)	132 (124-138)	0.463
SaO_2					
0 min	98 (96-98)	98 (96-98)	98 (96-98)	97 (96-98)	0.950
30 min	97 (96-98)	98 (96-98)	97 (96-98)	97 (96-98)	0.780
60 min	97 (96-98)	98 (96-98)	98 (96-98)	98 (96-98)	0.840
120 min	98 (96-99)	99 (97-99)	98 (96-98)	98 (96-98)	0.870

Median (IQR). HR: Heart rate, RDAI: Respiratory distress assessment instrument, RR: Respiratory rate, SaO_2: Oxygen saturation by pulse oximetry, IQR: Interquartile ranges, min: Minute

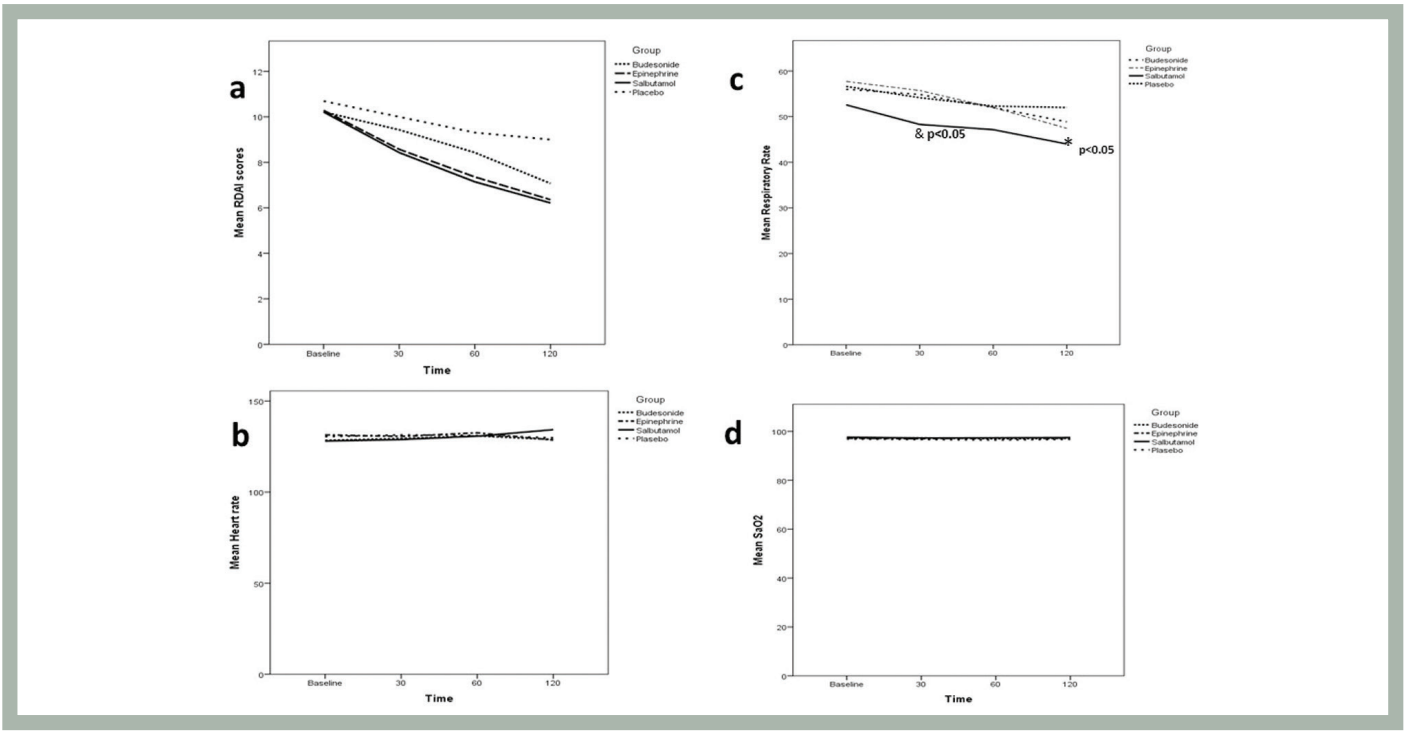

Figure 1. (a-d) Comparison of the time dependent changes among the treatment groups in terms of RDAI scores, RR, HR and SaO_2. &: p=0.031, *p=0.01

HR: Heart rate, RDAI: Respiratory distress assessment instrument, RR: Respiratory rate, SaO2: Oxygen saturation by pulse oximetry

Table 4. Comparison of baseline RDAI scores, respiratory rate, heart rate, SaO_2 and the values at the second hour

	Budesonide			Salbutamol			Epinephrine			Control		
	Before	After	p	Before	After	p	Before	After	p	Before	After	p
RDAI*	10 (9-12)	8 (5.25-9.25)	0.001	12 (9-12)	7 (3-9)	0.001	11 (9-12)	6 (3.5-10)	0.001	11 (8.75-13)	9 (7.5-10.5)	0.003
RR*	60 (49-67)	52 (43-56)	0.005	58 (48-60)	48 (40-50)	0.001	60 (52-60)	50 (38-56)	0.002	56 (52-61)	52 (48-56)	0.003
HR*	129 (120-140)	130 (124-136)	0.719	132 (120-136)	130 (125-135)	0.120	132 (124-140)	130 (120-137)	0.507	132 (120-137)	132 (124-138)	0.810
SaO_2*	98 (96-98)	98 (96-99)	0.859	98 (96-98)	99 (97-99)	0.608	98 (96-98)	98 (96-98)	0.891	97 (96-98)	98 (96-98)	0.660

**Median (IOR). HR: Heart rate; RDAI: Respiratory Distress Assessment Instrument; RR: Respiratory rate; SaO_2: Oxygen saturation by pulse oximetry*

Discussion

Acute bronchiolitis is the most common lower respiratory tract infection in children under 2 years of age, often caused by viral agents, and the underlying pathogenesis is mostly inflammatory contractions of small airways (1,2). Several treatment options used during the disease course have been reported. There are controversies about the use of bronchodilator drugs in the treatment; pros and cons have been reported. Although there is a high incidence of bronchiolitis in infants, no consensus has been established on a common effective treatment, yet (5).

We evaluated sixty infants diagnosed with acute bronchiolitis who were followed in the ED. RR and RDAI scores showed significant improvement at the 120th minute compared to baseline in all treatment groups. When comparing RR at baseline and at the 30th minute across all groups, the salbutamol group showed a statistically significant improvement. In addition, the study groups were compared with the control group, and a statistically significant difference in RR at the 120th minute was observed in the salbutamol group.

Despite bronchodilators not being recommended for the treatment of routine bronchiolitis, physicians were found to use them. Salbutamol was the most preferred treatment for bronchodilator treatment (10). There are some studies that demonstrated the effectiveness of salbutamol in terms of SaO_2, respiratory distress, and clinical improvement (13,14).

A meta-analysis depicted the ineffectiveness of salbutamol in terms of improvement of SaO_2, reducing hospital admission and shortening the duration of hospitalization in the treatment of acute bronchiolitis, also the authors warned for the small sample sizes and lack of standardized treatment groups (15). Moreover, Cai et al. (16) found salbutamol had no effect on bronchiolitis of infants based on the results of their systematic review. They also warned of the side effects of salbutamol treatment particularly on high HR (16). In our study, nebulized salbutamol was found to be slightly more effective for short-term improvement. However, no evidence was found to recommend it for the treatment of bronchiolitis with respect to its long-term effects.

In the current study, we used nebulized epinephrine instead of racemic epinephrine due to its unavailability in our country. However, there are studies reporting that nebulized adrenaline is as effective as the racemic form in the treatment of croup and bronchiolitis (17,18). A significant improvement in RDAI score and RR was observed at the 120th minute compared with baseline in both the epinephrine and control saline groups. Therefore, nebulized epinephrine has not been shown to be a more effective treatment than that in the control group.

Five randomized controlled trials have been published that evaluated the effect of nebulized epinephrine treatment and reported clinical improvement in infants with acute bronchiolitis. In addition, nebulized epinephrine treatment was found to be safe in terms of side effects (17,19,20,21,22). Nevertheless, Anil et. al. (23) compared nebulized salbutamol, epinephrine, normal and 3% saline treatments in infants with mild bronchiolitis, and they concluded there were no significant different clinical outcomes among the study groups.

In a clinical trial conducted in children with bronchiolitis requiring admission to the intensive care unit, the combination of repeated doses of systemic steroids and nebulized epinephrine, in addition to standard treatment, has been shown to shorten the duration of positive pressure support, especially in RSV-positive cases. However, the

authors stated that there may be bias due to the design of the study and the lack of blinding (24).

On the other hand, in a systematic review, evaluating the use of nebulized epinephrine for acute bronchiolitis suggested that comparing with placebo no differences were found for length of hospital stay, and emphasized the insufficient evidence to support the use for the treatment of bronchiolitis (25). Considering this information, there is no direct evidence to recommend nebulized epinephrine for the treatment of acute bronchiolitis because clinical outcomes are inconsistent.

Steroids have been used as a maintenance treatment because of their potential effects on inflammation, which underlies the pathogenesis of acute bronchiolitis. There are several studies which evaluate the efficacy of steroids in the treatment of acute bronchiolitis (9,26). In a multicenter, randomized, double-blind, placebo-controlled study in infants who were hospitalized for first-line RSV bronchiolitis, nebulized budesonide was compared to placebo. The result of this study depicted that the use of nebulized corticosteroids during the acute period of RSV bronchiolitis did not provide clinical benefit either in the acute or long-term (27).

Nebulized budesonide was administered at 0.5 mg/dose in this study, and a significant improvement was observed compared with the baseline scores in both RDAI scores and RR at the 120th minute, similar to the control group. There is insufficient evidence that glucocorticoids, whether systemic or nebulized, are beneficial in the treatment of acute bronchiolitis. Therefore, it is not recommended for routine use in bronchiolitis (28).

Study Limitations

The most important limitation of this study is the lack of long-term results due to the study design.

NS was selected as the placebo in most comparative trials. However, subsequent studies conducted after the completion of our study have suggested that nebulized NS may exert measurable physiological effects and therefore should not be considered an inert placebo (29,30). Additionally, the use of NS in the control group—as well as in other treatment arms for dilution—may have attenuated the observable differences between groups, representing another limitation of our study.

Furthermore, the prospective, randomized, double-blind study design with a control group is a strength of our study.

Conclusion

In our study, all the nebulized treatment groups showed improvements in RR and RDAI scores at the second hour compared with baseline. However, the salbutamol group was slightly more efficacious for short-term improvement in RR. Also, when we compared the treatment groups with the control group, we observed an improvement in RR during the second hour in the salbutamol group.

Bronchiolitis is an emerging health issue, particularly in infants. Large sample sizes with long-term follow-up and multicenter, placebo-controlled clinical trials are needed to evaluate the efficacy of bronchodilator therapy in the treatment of acute bronchiolitis.

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Ethics

Ethics Committee Approval: The Ethics Committee of Bakırköy Maternity and Children's Training and Research Hospital was approved the study (approval number: 147 date: 11.07.2008).

Informed Consent: The informed consent was obtained from the parents of patients.

Footnotes

Authorship Contributions

Surgical and Medical Practices: B.K., M.A., D.Y.Ö., R.Ş., Concept: M.A., R.Ş., Design: M.A., R.Ş., Data Collection or Processing: B.K., M.A., D.Y.Ö., R.Ş., Analysis or Interpretation: B.K., M.A., D.Y.Ö., Literature Search: B.K., M.A., Writing: B.K., M.A.

Conflict of Interest: No conflict of interest was declared by the authors.

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