Emergency room management of acute bronchiolitis: a randomized trial of nebulized epinephrine

Pelin Özlem Şimşek-Kiper[1], Nural Kiper[2], Gülşen Hasçelik[3], Anıl Dolgun[4], Ebru Yalçın[2], Deniz Doğru-Ersöz[2], Uğur Özçelik[2]

[2]Pediatric Pulmonology Unit, [1]Department of Pediatrics and Departments of [3]Microbiology and Clinical Microbiology, and [4]Biostatistics, Hacettepe University Faculty of Medicine, Ankara, Turkey

SUMMARY: Şimşek-Kiper PÖ, Kiper N, Hasçelik G, Dolgun A, Yalçın E, Doğru-Ersöz D, Özçelik U. Emergency room management of acute bronchiolitis: a randomized trial of nebulized epinephrine. Turk J Pediatr 2011; 53: 651-660.

Acute bronchiolitis is a common, potentially life-threatening condition with few therapeutic options. In the present randomized study, we compared the clinical efficacies of nebulized epinephrine and salbutamol in the emergency room management of acute bronchiolitis. Primary outcome measures were improvement in mean respiratory rate, mean oxygen saturation value and severity score. Secondary outcome measures were length of hospital stay, hospitalization and relapse rates. A total of 75 patients were analyzed (36 epinephrine, 39 salbutamol). Both groups experienced a similar pattern of clinical improvement. Hospitalization rates were 8.3% for epinephrine and 5.1% for salbutamol ($p>0.05$), whereas relapse rates were 80% for epinephrine and 20% for salbutamol groups ($p<0.001$). Respiratory syncytial virus was the most common virus identified (41%). We did not find a difference between salbutamol and epinephrine in terms of clinical improvement, but salbutamol can be a drug of choice due to its lower relapse and hospitalization rates compared to epinephrine.

***Key words:** acute bronchiolitis, respiratory syncytial virus, epinephrine, salbutamol, wheezing.*

Acute bronchiolitis, first described as a distinct clinical entity in 1941[1], is defined as a constellation of clinical symptoms and signs including a viral upper respiratory prodrome followed by increased respiratory effort and wheezing in children less than two years of age[2]. Today, it is not only one of the most common causes of hospital admissions in the first 12 months of life, but also one of the most common respiratory tract illnesses with a great deal of variation in its clinical management[3]. It is generally seasonal and associated with a growing number of respiratory viruses, most commonly respiratory syncytial virus (RSV)[4-7]. Annual outbreaks typically occur between October and May, with the peak effect falling in January and February[8]. Most infants have a mild, self-limiting illness and recover completely, although subtle pulmonary abnormalities and respiratory symptoms may persist for weeks[9]. Around 1-3% of all infants require admission to a hospital for more aggressive management and monitoring, and almost half of them will have recurrent episodes of wheeze[9-11]. The disease accounts for a substantial morbidity, with a mortality of less than 1%[12]. The mortality increases substantially with pre-existing medical conditions[13]. The optimal pharmacological therapy in bronchiolitis is controversial. The role of bronchodilators has been subject to many studies and systematic evidence-based reviews of the literature since the late 1950s[14,15]. Although bronchodilator therapy is in common use today, its efficacy is not universally accepted. Multiple studies have documented wide variation in management, hospitalization rates and length of hospital stay, suggesting a lack of consensus and an opportunity to improve care for this common disorder[14]. Conflicting results have been obtained, with some studies favoring treatment while others show no benefit over placebo.

Epinephrine, with its combined alpha and beta receptor agonist activity, is suggested to be an ideal bronchodilator[16]. There has been some evidence suggesting that the use of epinephrine may be favorable over salbutamol for short-term clinical benefits[3,17,18]. Some, but not all, small studies also suggest that epinephrine may decrease admissions in outpatients[17,19,20]. However, a Cochrane review of these studies was inconclusive[21]. In our hospital, nebulized salbutamol has almost been a standard drug of choice in the treatment of children with acute bronchiolitis. The objective of the present study was to compare the clinical efficacies of nebulized epinephrine and nebulized salbutamol in the emergency room management of acute bronchiolitis.

Material and Methods

The study was conducted in the Emergency Department (ED) of İhsan Doğramacı Children's Hospital, a tertiary-care pediatric hospital in Turkey. The study was performed in accordance with the Declaration of Helsinki protocols. Informed consent was obtained from the legal representatives of all patients included in the study, in accordance with the protocols of our institution. The procedures used were in accordance with the ethical standards of the national and institutional committees on human subject research. Patients could be withdrawn from the study at any time at the parents' request. Recruitment occurred from September 2003 to May 2004 and from September 2004 to December 2005. A clinical diagnosis of acute bronchiolitis was made by the physician in the ED if the patient had a history of upper respiratory tract infection and clinical findings consistent with acute bronchiolitis at admission, including tachypnea, wheezing, wheezing with crackles, or respiratory distress with recessions. Patients were scored according to Respiratory Distress Assessment Instrument (RDAI)[22]. Patients diagnosed with acute bronchiolitis were considered eligible for the study if they met the following criteria: (1) aged 2-24 months old, (2) first incidence of wheeze, and (3) a severity score of either 'mild' or 'moderate' according to RDAI as shown in Table I. Patients were excluded from the study if they: (1) had a chronic cardiopulmonary or immunodeficiency disease, (2) were ever diagnosed with asthma or any other comorbidities, (3) were recurrent wheezers, and (4) had taken bronchodilators or corticosteroids during the 24 hours prior to admission. Patient heterogeneity was minimized by including previously healthy patients with first-time wheezing with no underlying comorbidities, thus reducing the risk of including patients with true bronchial asthma who would benefit from beta$_2$ agonist therapy and may therefore bias the results.

Table I. Calculation of the Severity Score

Respiratory-effort score: Patients are examined for intercostal recession, subcostal recession, substernal recession, tracheal tug, and nasal flaring, and assigned a score of 0 (not present), 1 (mild to moderate), or 2 (severe) for each factor. Each score was then multiplied by a weighting factor, as follows: intercostal recession (1), subcostal recession (1), substernal recession (1), tracheal tug (1.5), and nasal flaring (1.5). The weighted scores were then totaled to obtain a score for respiratory effort. Finally, infants with respiratory-effort scores of 0 to 4.9 were given a severity score of 1 (mild); those with respiratory-effort scores of 5.0 to 8.9 were given a score of 2 (moderate); and those with respiratory-effort scores of 9.0 to 12.0 were given a score of 3 (severe).

Oxygen saturation score: The patients received scores of 0, 1 or 2 for oxygen-saturation values of 95-100%, 90-94%, and less than 90%, respectively.

Respiratory rate score: The patients whose respiratory rates were within 2 SD of the mean for their age received a score of 0; those whose rates were 2 to 3 SD above or below the mean for their age received a score of 1; and those whose rates were more than 3 SD from the mean for their age received a score of 2.

SEVERITY SCORE: The above three scores were totaled for each patient, and the patient's condition was classified as mild (total score <2), moderate (total score 2-3), or severe (total score >3).

There were two drug groups. One group received two doses of nebulized epinephrine, applied 30 minutes apart (L-epinephrine 1:1000, 2.5 mg/dose combined with 0.9% saline solution). The other group received two doses of salbutamol, applied 30 minutes apart (salbutamol 0.15 mg/kg/dose combined with 0.9% saline solution). Participants were randomly assigned into one of the two drug groups, using computer-generated randomization within blocks with six subjects. The patients received the medication under the supervision of pediatricians in the ED who remained blinded to the identity of the medication throughout the study. Treatment was allocated by a trained nurse from the Pediatric Pulmonology Unit who had no contact with the study participants. All other study personnel and participants were blinded to the treatment assignment. All study solutions were clear, colorless and odorless. Equal volumes of medication (either salbutamol or epinephrine) were prepared in advance daily. Medication was dispensed in aluminum wrapped syringes, numerically coded for use in the ED. The trained nurse from the Pediatric Pulmonology Unit who handled the treatment allocation was the only person who knew the numerical codes assigned to the two medications. In order to evaluate the process of blinding, parents, nurses and all study personnel in the ED were asked which therapy they believed the patient received. The nebulizations were administered for 10-15 minutes with a standard hospital jet nebulizer, with continuous flow of 100% oxygen at 6 liters/minute. All patients with a mean oxygen saturation value of <92% received continuous supplemental oxygen. The principle investigator (who remained blinded to the drug groups) observed the patients prior to treatment (baseline), one hour after the delivery of the drugs, and four hours after the delivery of the drugs. The followings were assessed and recorded while the patient was resting: body temperature, respiration rate, heart rate, respiratory effort, oxygen saturation while breathing room air, severity score, and blood pressure. The respiration rate was scored by comparing with data from age-matched healthy infants[23]. Severity score was mild, moderate, or severe, as indicated by the RDAI[22]. The primary outcome measures included improvements in mean respiration rate, mean oxygen saturation values and severity scores. The secondary outcome measures included the length of hospital stay, hospitalization (after the initial 4 hours following the treatment) and relapse rates. The length of hospital stay was defined as the time between study entry and patient discharge (either from the ED or inpatient ward). A nasopharyngeal aspiration sample was obtained from all patients for detection of the etiologic agent including RSV, adenovirus, influenza A, influenza B, parainfluenza 1, parainfluenza 2, and parainfluenza 3 (Bartels Respiratory Kit). Serum total immunoglobulin (Ig)E levels and absolute eosinophil counts were analyzed. The possible effect of RSV status on primary outcome measures in both drug groups was also assessed. The admitting medical officer and nurse recorded detailed clinical histories, including current and previous medications, duration of the symptoms, the infant's ability to feed, history of breastfeeding, parental smoking, and history of atopic dermatitis. The patients were observed in the ED for four hours after they were given medication. After this time, they were either discharged or admitted to the hospital, depending on their symptoms and severity scores. Hospitalization criteria were defined as: (1) severity score of 'severe' assessed by RDAI, (2) oxygen saturation <92%, and (3) requirement of additional bronchodilators and supplemental oxygen. Discharge criteria from the ED were defined as: (1) no sign of respiratory distress, (2) oxygen saturation >92%, and (3) lack of further requirement of additional bronchodilators and supplemental oxygen. The patients who were discharged were asked to return one week later for reevaluation in the Pediatric Pulmonology outpatient clinic. They were then checked for any respiratory symptoms and further need for readmission. This study was supported by Hacettepe University Faculty of Medicine Scientific Research Unit (project number: 04 T05 101 002).

Statistical Analysis

A sample size of 32 patients per group would be sufficient to detect an important treatment effect, using a two-tailed test, type I error of 0.05, and power of 90%, assuming a standard deviation of 10 breaths/minute in respiration rate. A reduction of 6 breaths/minute in respiration rate was regarded as clinically important. The results are expressed as mean

± standard deviation (SD), frequency and percent, where appropriate, throughout the article. Repeated measures analysis of variance was used to analyze mean oxygen saturation, mean respiration rate, mean heart rate, and blood pressure for the effects of drug group (epinephrine, salbutamol), time (baseline prior to treatment, 1 hour after medication, 4 hours after medication), and interaction between drug group and time. In addition, a chi-square test was used to analyze the improvement in severity scores among the two drug groups. All statistical analyses were performed using the SPSS program (version 15 for Windows). Statistical significance was set at $p<0.05$.

Results

A total of 150 patients were assessed for eligibility in the study (Fig. 1). Eighty of them were randomly assigned to one of the drug groups. Seventy-five patients were taken into consideration in the main analysis. Of these, 39 (52%) received salbutamol and 36 (48%) received epinephrine. Demographic characteristics of patients at admission and the degree of illness at study enrollment are shown in Table II.

Primary Outcome Measures

The clinical conditions of patients in both drug groups improved over time from their baseline. Mean respiration rates decreased, mean oxygen saturation increased and severity scores decreased (Table III) (Fig. 2). Repeated measures analysis of variance showed that there was a significant effect of time for mean respiration rate ($p<0.001$) and mean oxygen saturation ($p<0.001$), but there was no significant interaction between time and drug groups ($p>0.05$) (Table IV). Baseline mean heart rates were not statistically different between drug groups ($p=0.115$), but the difference from baseline was significantly higher in the salbutamol group compared to the epinephrine group at the end of the first hour after the delivery of the drugs ($p=0.019$) (Table III, Fig. 2). Repeated measures analysis of variance did not show a statistically significant effect of time for systolic and diastolic blood pressures during the study ($p>0.05$) (Table IV). At the end of the four hours of observation in the ED, 5 patients progressed to a severity score of 'severe' and were admitted to the hospital. Among them, 2 patients from the epinephrine group and 1 patient from the salbutamol group progressed to a severity score of 'severe' at the end of the first hour, and 1 patient from the salbutamol group and 1 patient from the epinephrine group progressed to a severity score of 'severe' at the end of the fourth hour following the delivery of drugs (Table III). The effect of drug group on hospital admittance was not statistically significant ($p=0.666$). We observed an improvement in the severity scores of 19 (53%) patients in the epinephrine group and of 23 (59%) patients in the salbutamol group. This difference was not statistically significant ($p=0.589$).

Secondary Outcome Measures

The hospitalization rate was 8.3% in the epinephrine group and 5.1% in the salbutamol group. This difference was not statistically significant ($p>0.05$). Mean hospital stay length was 18.5 hours in the epinephrine group and 14.5 hours in the salbutamol group. This difference was also not statistically significant ($p=0.577$). Seventy (93%) patients were discharged successfully from the ED. They were not given any additional bronchodilators and were told to return one week later for reevaluation in the Pediatric Pulmonology outpatient clinic. Of these 70 patients, 61 (87%) returned one week later for reevaluation (Fig. 1). It was revealed that 10 (16.3%) of these 61 patients were readmitted to the ED with respiratory symptoms and required additional nebulizations, while 51 (83.7%) patients did not show any symptoms. Among patients returning for reevaluation, there were no statistically significant differences between the patients who were readmitted and those who were not readmitted in terms of age, gender, RSV status, serum total IgE levels, absolute eosinophil counts, family history of atopy, and exposure to cigarette smoking ($p>0.05$). Among 10 patients with respiratory symptoms, 8 (80%) were from the epinephrine group and 2 (20%) were from the salbutamol group ($p<0.001$) (Fig. 1). The patients who were readmitted ($n=10$) were followed to determine whether subtle pulmonary abnormalities and respiratory symptoms would persist. Among these 10 patients, 7 had recurrent bronchiolitis

Table II. Demographic Characteristics of Patients at Admission and Degree of Illness at Study Enrollment

Characteristic	Epinephrine (n=36)	Salbutamol (n=39)	p value
Age (Mean±SD), months	7.7±4	7.6±5.1	0.937
Gender, n (%)			
Male	25 (69%)	23 (59%)	0.345
Female	11 (31%)	16 (41%)	
Parental smoking, n (%)	22 (61%)	25 (64%)	0.789
Duration of symptoms (Mean±SD) days	4.8±3.4	6.4±4.9	0.115
Breastfeeding positive, n (%)	34 (94%)	37 (95%)	0.934
History of atopic dermatitis, n (%)	7 (19%)	9 (23%)	0.701
History of atopy in the family, n (%)	-	2 (6.7%)	0.492
History of bronchial asthma in the family, n (%)	4 (13.3%)	9 (30%)	0.117
RSV status positive, n (%)	15 (41.7%)	16 (41%)	0.955
Other viruses, n (%)			
Influenza A	1 (3%)	1 (3%)	
Influenza B	2 (6%)	2 (5%)	
Parainfluenza 1	-	-	
Parainfluenza 2	-	-	NA
Parainfluenza 3	1 (3%)	-	
Adenovirus	-	1 (3%)	
Total	4 (11.1%)	4 (10.2%)	
Absolute eosinophil count (/mm3) (Median, Min-Max)	111.6 (9.5-514.8)	181 (0-597.8)	0.289
Serum total IgE (IU/ml) (Median, Min-Max)	7 (2-465)	6 (0-305)	0.615
Respiratory rate, breaths/min (Mean±SD)	54.6±11.6	54.6±10.8	0.999
Heart rate, beats/min (Mean±SD)	151.2±21.8	143.7±18.9	0.115
Oxygen saturation, % (Mean±SD)	96.1±2.9	95.7±2.4	0.610
Severity score, n (%)			
Mild	13 (36%)	11 (28%)	
Moderate	23 (64%)	28 (72%)	0.463
Severe	-	-	

SD: Standard deviation. NA: Statistical analysis is not available.

in the follow-up. Among these 7 patients, 1 had gastroesophageal reflux detected by scintigraphy and 1 had RSV pneumonia and needed to be hospitalized. Skin prick tests and reflux scintigraphy of the remaining 5 patients were negative. The number of wheezy episodes decreased in time, and they have been symptom-free for the last two years.

Respiratory syncytial virus (RSV) was found to be the most common (41%) etiologic agent in the nasopharyngeal aspiration samples, followed by influenza B, influenza A, adenovirus, and parainfluenza type 3 (Table II). In the epinephrine group, 15 (42%) patients were RSV- positive and 21 (58%) patients were RSV-negative. In the salbutamol group, 16 (41%) patients were RSV-positive and 23 (59%) patients were RSV-negative. The RSV status did not have an effect on the primary outcome measures of the patients in either drug group (data not shown). In terms of adverse effects, oxygen desaturation was observed in both drug groups (3 patients from the epinephrine group and 2 patients from the salbutamol group). No other adverse effects (such as pallor, hypertension or tremor) were observed in either drug group. Double-blinding was maintained throughout the study. When the participants

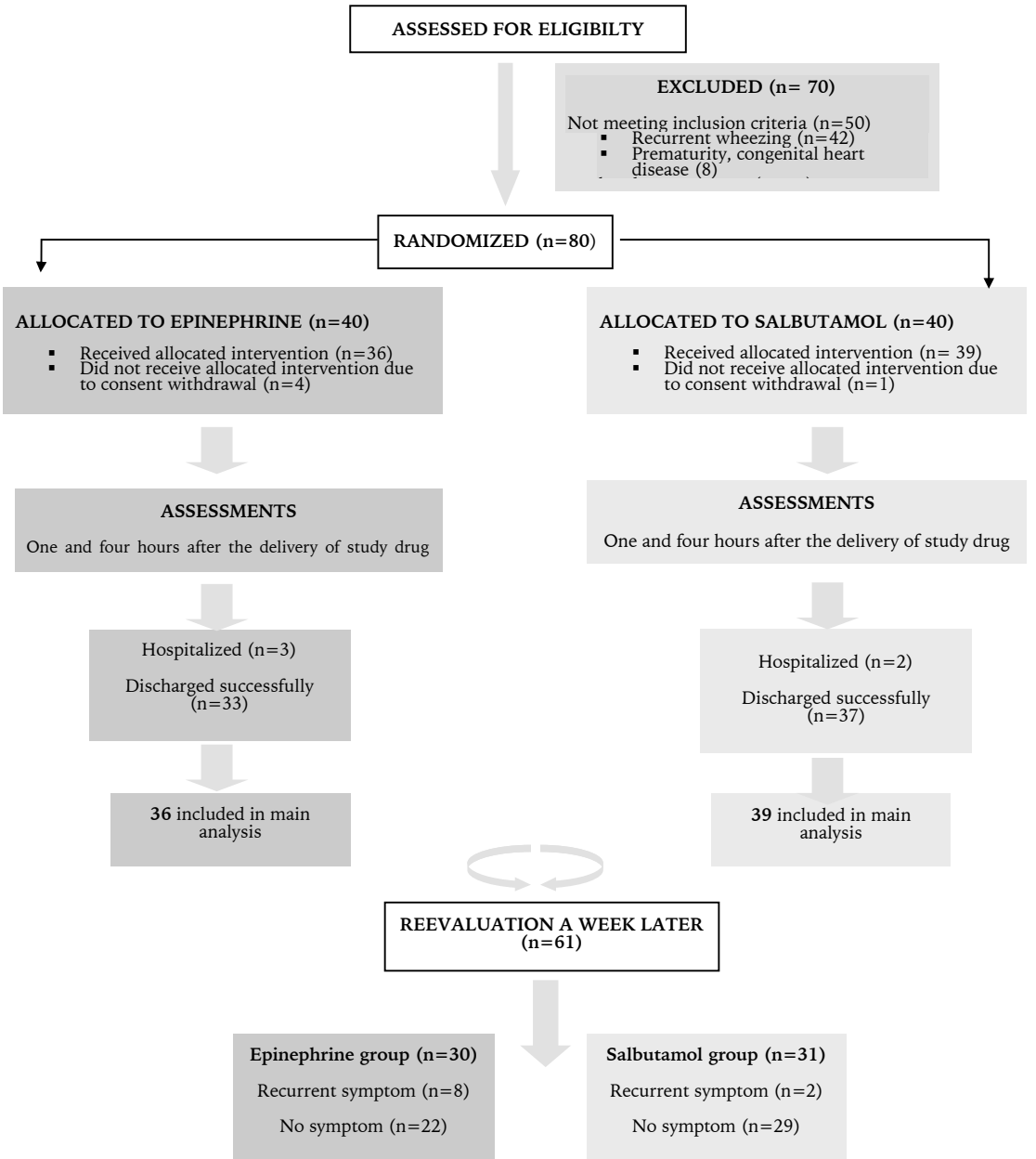

Fig. 1. Flow diagram of patient allocation.

and the medical staff were asked to guess the allocation group, the majority (99%) replied that they did not know which study drug the patient had received; 1% were able to guess the allocation correctly. There was no difference in the proportion of correct guesses by the drug groups ($p>0.05$).

Discussion

The present study did not show a statistically significant difference between nebulized salbutamol and epinephrine in terms of clinical effects, including mean respiration rate, mean oxygen saturation and severity score in the emergency room management of acute bronchiolitis. It was also found that salbutamol had lower hospitalization and relapse rates compared to epinephrine and can therefore be a drug of choice in the emergency room management of acute bronchiolitis.

Management of acute bronchiolitis is highly variable with respect to therapeutic measures.

Table III. Respiratory Rate, Oxygen Saturation Value, Heart Rate Measurements, and Severity Score Distribution of Patients at Baseline, and One and Four Hours after the Delivery of Study Drugs

	Epinephrine	Salbutamol
Respiratory rate (/min)	Mean±SD	Mean±SD
Baseline	54.6±11.6	54.6±10.8
1st hour	52.3±11.8	52.1±10.8
4th hour	48 ±8	49.7±7.6
Oxygen saturation (%)	Mean±SD	Mean±SD
Baseline	96.1±2.9	95.7±2.4
1st hour	95.8±2.7	95.7±2.4
4th hour	97.3 ±2.1	96.7±2.5
Heart rate (/min)	Mean±SD	Mean±SD
Baseline	151.2±21.8	143.7±18.9
1st hour	152.8±22.5¥	155±17.9¥
4th hour	145.4 ±15.3	149.2±17.6
Severity score (RDAI)	n, %	n, %
Baseline		
Mild	13 (36%)	11 (28%)
Moderate	23 (64%)	28 (72%)
Severe	-	-
1st hour		
Mild	21 (58%)	19 (49%)
Moderate	13 (36%)	19 (49%)
Severe	2 (6%)	1 (2%)
4th hour		
Mild	30 (83%)	32 (82%)
Moderate	3 (8.5%)	5 (12.8%)
Severe	3 (8.5%)	2 (5.2%)

Systematic analyses of recent literature have yielded contradictory results on the clinical use of current therapies and offer limited benefit in the treatment[3]. Short-acting $beta_2$ agonists like salbutamol are widely considered among the first-line agents, although little evidence supports their efficacy[21,24-26]. A small but statistically significant improvement in clinical score in response to short-acting $beta_2$ agonists is demonstrated, but heterogeneity of the reported studies makes it difficult to determine the clinical importance of this short-term benefit[21]. Two meta-analyses that addressed the efficacy of $beta_2$ agonists in bronchiolitis showed a modest impact in the evolution of the disease[25,27]. A systematic review including 22 clinical trials with 1,428 children with acute bronchiolitis administered salbutamol, ipratropium bromide or adrenergic agents reported evidence of small, short-term improvements in clinical scores of doubtful clinical importance[28]. The present study demonstrated statistically significant improvements in short-term effects like clinical score, oxygen saturation and respiratory rate in response to salbutamol over time from baseline. Nebulized epinephrine, which has both $beta_2$ agonist and alpha agonist activities, has also been studied in the management of acute bronchiolitis. The potential advantage of epinephrine over salbutamol is probably associated with its alpha-adrenergic activity causing vasoconstriction and thereby reducing edema and secretions of the airways involved in the pathophysiologic changes[16]. A meta-analysis revealed that epinephrine may be favorable compared to placebo and albuterol for short-term benefits among outpatients[28]. Another randomized study found that inhaled epinephrine significantly improved oxygenation and reduced hospitalizations as compared with salbutamol[17]. Similarly, a randomized trial of nebulized epinephrine and albuterol revealed that patients treated with epinephrine were discharged significantly earlier than the patients treated with albuterol[29]. All of these studies suggest that clinical improvements observed probably represent the short-term benefits. On the other hand, a multicenter clinical trial of epinephrine revealed that epinephrine had

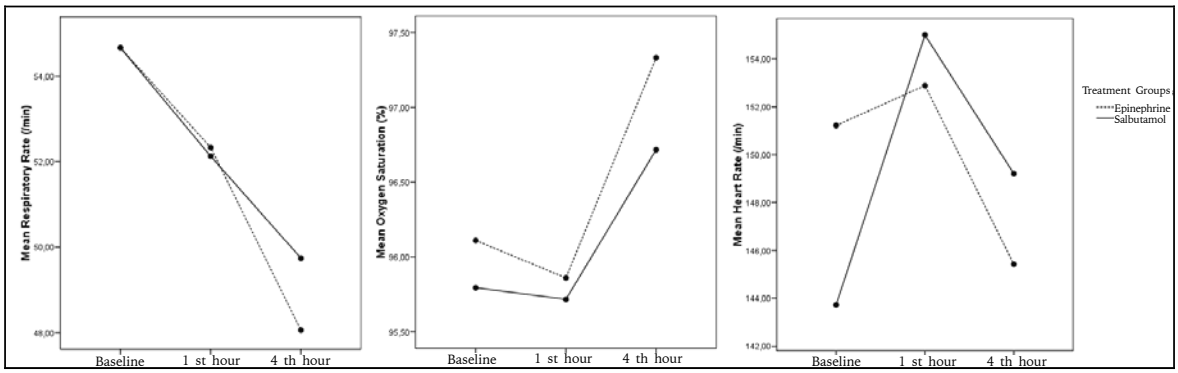

Fig. 2. The effect of time on mean respiratory rate, mean oxygen saturation value and mean heart rate in treatment groups.

no effect on duration of hospitalization[22]. The present study also demonstrated statistically significant improvements in short-term effects like clinical score, oxygen saturation and respiratory rate in response to epinephrine over time from baseline. However, regarding longer-term outcomes such as hospital admission and relapse rates, epinephrine failed to demonstrate significant improvements. It was observed that patients in both drug groups experienced a similar degree of improvement in respiratory rate, oxygen saturation and severity scores. The improvements observed in both drug groups may be related to the minute-to-minute variability that is typical of the disease process.

We used epinephrine in our study because it is more readily available and less costly than racemic epinephrine. However, while there seems to be no agreement on the optimal dose schedules of nebulized epinephrine, it is believed that the dose of epinephrine has to be similar for each patient regardless of weight[30]. Several randomized placebo-controlled trials have shown that nebulizations of epinephrine at a dose of 2-5 ml of 1:1000 have significant effects on clinical scores and pulmonary resistance, enabling a more rapid discharge of bronchiolitis patients from the emergency room[31]. Moreover, nebulization with 3-5 ml of epinephrine (1:1000) is considered to be a safe treatment with few side effects[32]. In the present study, a dose of 2.5 mg/dose of 1:1000 epinephrine was considered to be safe and appropriate, as it would be a good therapeutic dose for the infants between one and two years of age. We used two nebulizations of epinephrine with a 30-minute interval and observed no deleterious effects on the cardiorespiratory status of infants with acute bronchiolitis. Salbutamol was applied 30 minutes apart with a dose of 0.15 mg/kg/dose, which is the preferred dose in most of the studies and daily practice. We believed that more and frequent nebulizations would unlikely create a significant difference in our outcomes

Table IV. The Results of Repeated Measures Analysis of Variance of Vital Signs of Patients Over Time

	Factor	MSE	F	p value
Respiratory rate	Time effect	647.013	15.45	<0.001
	Time and group interaction	20.83	0.498	0.603
Oxygen saturation	Time effect	38.1	6.854	0.002
	Time and group interaction	1.206	0.217	0.779
Heart rate	Time effect	1072.614	7.758	0.001
	Time and group interaction	695.120	5.028	0.008
Systolic blood pressure	Time effect	21.251	1.297	0.276
	Time and group interaction	26.140	1.595	0.206
Diastolic blood pressure	Time effect	14.792	1.418	0.246
	Time and group interaction	1.307	0.125	0.852

MSE: Mean square error. F: F test statistic.

and could possibly produce more undesirable cardiovascular effects. There is evidence that multiple doses of nebulized bronchodilators can have deleterious effects[33]. Some adverse effects such as tachycardia, agitation and oxygen desaturation are relatively more common among patients receiving $beta_2$ agonists, mainly salbutamol[17]. In the present study, five of 75 patients had oxygen saturation values <92%, and their severity scores progressed to 'severe' during the clinical course. The arterial desaturation of these patients could be a reflection of the worsening of the already disturbed ventilation-perfusion balance in the lungs with the use of bronchodilators[34]. Thus, bronchodilators should only be continued in a portion of patients who show clinical improvement upon nebulization, and the clinician should decide on a case-by-case basis. Their use should be continued only if clinical improvement can be documented by objective endpoints such as severity scores or vital signs[3,13,26]. Baseline mean heart rates were not statistically different between drug groups, but the difference from the baseline was significantly higher in the salbutamol group compared to the epinephrine group at the end of the first hour after the delivery of drugs. Salbutamol is known to cause tachycardia as a result of $beta_2$-mediated vasodilation, subsequent reflex tachycardia and also some degree of $beta_1$ receptor stimulation. Epinephrine, on the other hand, is known to cause tachycardia as a result of alpha receptor stimulation. In the present study, the finding of tachycardia in the salbutamol group was statistically significant, but clinically it was self-limited, transient and irrelevant. Clinically obvious tremor, hyperactivity, hypertension, and pallor, which can be seen after salbutamol or epinephrine applications, were not observed in the present study.

Among the patients presenting one week later for reevaluation, the majority with recurrent respiratory symptoms (80%) were from the epinephrine group. The higher relapse rate observed in epinephrine group may be related to the shorter duration of action of epinephrine compared to salbutamol and minute-to-minute variability that is typical of the disease. There is also some evidence that patients treated with epinephrine had a more rapid discharge rate from the ED, probably reflecting the transient reductions in edema and improving pulmonary mechanics and clearance of secretions[31]. Lung function that is reduced in acute bronchiolitis shows a significant improvement after immediate inhalation of epinephrine. However, studies collecting data beyond this initial treatment did not usually reveal a persistent improvement as was the case in the present study. Finally, the present study involved patients with a severity score of mild-moderate acute bronchiolitis; therefore, the findings presented here cannot be extrapolated to patients with a severity score of severe acute bronchiolitis. Further conclusions on the clinical efficacy of nebulized epinephrine and salbutamol will require large and multicentric trials involving patients with heterogeneous clinical severity.

In conclusion, epinephrine and salbutamol can both be considered as an option for patients with acute bronchiolitis, provided the clinical presentation is mild or moderate. These medications should only be continued if there is clinical improvement. Further studies are needed before routine use of bronchodilators among outpatients can be strongly recommended.

REFERENCES

1. Hubble D, Osborn GR. Acute bronchiolitis in children. Br Med J 1941; 1: 107-110.
2. American Academy of Pediatrics, Subcommittee on Diagnosis and Management of Bronchiolitis. Diagnosis and management of bronchiolitis. Pediatrics 2006; 118: 1774-1793.
3. Seiden AJ, Scarfone RJ. Bronchiolitis: an evidence-based approach to management. Clin Pediatr Emerg Med 2009; 10: 75-81.
4. Glezen WP, Taber LH, Frank AL, et al. Risk of primary infection and reinfection with respiratory syncytial virus. Am J Dis Child 1986; 140: 543-546.
5. Hall CB, Weinberg GA, Iwane MK, et al. The burden of respiratory syncytial virus infection in young children. N Engl J Med 2009; 360: 588-598.
6. Henrickson KJ, Hoover S, Kehl KS, Hua W. National disease burden of respiratory viruses detected in children by polymerase chain reaction. Pediatr Infect Dis J 2004; 23: 11-18.
7. Wolf DG, Greenberg D, Kalkstein D, et al. Comparison of human metapneumovirus, respiratory syncytial virus, and influenza A lower respiratory tract infections in hospitalized young children. Pediatr Infect Dis J 2006; 25: 320-324.
8. Steiner RW. Treating acute bronchiolitis associated with RSV. Am Fam Physician 2004; 69: 325-330.

9. Fjaerli H-O, Farstad T, Rod G, et al. Acute bronchiolitis in infancy as a risk factor for wheezing and reduced pulmonary function by seven years in Akershus County, Norway. BMC Pediatrics 2005; 5: 31.
10. Thompson W, Shay D, Weintraub E, et al. Mortality associated with influenza and respiratory syncytial virus in the United States. JAMA 2003; 289: 179-186.
11. Hall CB. Respiratory syncytial virus and parainfluenza virus. N Engl J Med 2001; 344: 1917-1928.
12. Willson DF, Horn SD, Hendly JO, Smout R, Gassaway J. Effect of practice variation on resource utilization in infants hospitalized for viral lower respiratory illness. Pediatrics 2001; 108: 851-855.
13. Zorc JZ, Hall CB. Bronchiolitis: recent evidence on diagnosis and management. Pediatrics 2010; 125: 342-349.
14. Behrendt CE, Decker MD, Burch DJ, Watson PH. International variation in the management of infants hospitalized with respiratory syncytial virus. Eur J Pediatr 1998; 157: 215-220.
15. Henderson FW, Clyde WA, Collier AM, et al. The etiologic and epidemiologic spectrum of bronchiolitis in pediatric practice. J Pediatr 1979; 95: 183.
16. Whol ME, Chernick V. State of the art: bronchiolitis. Am Rev Respir Dis 1978; 118: 759-781.
17. Menon K, Sutcliffe T, Klassen TP. A randomized trial comparing the efficacy of epinephrine with salbutamol in the treatment of acute bronchiolitis. J Pediatr 1995; 126: 1004-1007.
18. Wright M, Mullett CJ, Piedimonte G. Pharmacological management of acute bronchiolitis. Ther Clin Risk Manag 2008; 4: 895-903.
19. Lowell DI, Lister G, Von Koss H, McCarthy P. Wheezing in infants: the response to epinephrine. Pediatrics 1987; 79: 939-945.
20. Ray MS, Singh V. Comparison of nebulized adrenaline versus salbutamol in wheeze associated respiratory tract infection in infants. Indian Pediatr 2002; 39: 12-22.
21. Gadomski AM, Brower M. Bronchodilators for bronchiolitis. Cochrane Database Syst Rev 2010; (12): CD001266.
22. Wainwright C, Altamirano L, Cheney M, et al. A multicenter, randomized, double-blind, controlled trial of nebulized epinephrine in infants with acute bronchiolitis. N Engl J Med 2003; 349: 27-35.
23. Rusconi F, Castagneto M, Gagliardi L, et al. Reference values for respiratory rate in the first 3 years of life. Pediatrics 1994; 94: 350-355.
24. Dobson JV, Stephens-Groff SM, McMahon SR, Stemmler MM, Brallier SL, Bay C. The use of albuterol in hospitalized infants with bronchiolitis. Pediatrics 1998; 101: 361-368.
25. Kellner JD, Ohlsson A, Gadomski AM, Wang EE. Efficacy of bronchodilator therapy in bronchiolitis: a meta-analysis. Arch Pediatr Adolesc Med 1996; 150: 1166-1172.
26. Newcomb RW. Use of adrenergic bronchodilators by pediatric allergists and pulmonologists. Am J Dis Child 1989; 143: 481-485.
27. Flores G, Horwitz RI. Efficacy of beta2 agonists in bronchiolitis: a reappraisal and meta-analysis. Pediatrics 1997; 100: 233-239.
28. Hartling L, Wiebe N, Math M, Russel K, Patel H, Klassen TP. A meta-analysis of randomized controlled trials evaluating the efficacy of epinephrine for the treatment of acute viral bronchiolitis. Arch Pediatr Adolesc Med 2003; 157: 957-964.
29. Mull CC, Scarfone RJ, Ferri LR, et al. A randomized trial of nebulized epinephrine vs albuterol in the emergency department treatment of bronchiolitis. Arch Pediatr Adolesc Med 2004; 158: 113-118.
30. Bertrand P, Araníbar H, Castro E, Sánchez I. Efficacy of nebulized epinephrine versus salbutamol in hospitalized infants with bronchiolitis. Pediatr Pulmonol 2001; 31: 284-288.
31 Klassen TP. Recent advances in the treatment of bronchiolitis and laryngitis. Pediatr Clin North Am 1997; 94: 249-261.
32. Zhang L, Sanguebsche LS. The safety of nebulization with 3 to 5 ml of adrenaline (1:1000) in children: an evidence based review. J Pediatr (Rio J) 2005; 81: 193-197.
33. Butte MJ, Nguyen BX, Hutchison TJ, et al. Pediatric myocardial infarction after racemic epinephrine administration. Pediatrics 1999; 104: 9.
34. Ho L, Collis G, Landau Ll, LeSouef PN. Effects of salbutamol on oxygen saturation in bronchiolitis. Arch Dis Child 1991; 60: 1061-1064.