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Original

Rational drug use for acute bronchiolitis in emergency care

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Despite the large variety of inhaled treatment options of acute bronchiolitis, there is no generally agreed treatment regime. This study aimed to determine the most appropriate treatment option. This was a double-blind randomized prospective clinical trial and has been performed in emergency department. The mean age of the 378 infants included in the study was 7.63 ± 4.6 months, and 54.8% (207) were boys. Patients were randomized by using the lottery method for simple random sample into 5 different treatment options; 3% hypertonic saline, nebulized adrenaline, nebulized adrenaline mixed with 3% hypertonic saline, nebulized salbutamol, and as control group; normal saline (0.9% NaCl). From the first treatment time until discharge time; treatment durations, adverse events and readmission rates within the first fifteen days were recorded for each patient. Nebulized adrenaline mixed with 3% hypertonic saline, as compared with other options, were associated with a significantly higher discharge rate at 4th hours ($p<0.001$) and shorter length of hospital stay ($p=0.039$). However, there was no significant difference between options with regard to adverse events, discharge rates at 24th hours, and readmission rates within the first fifteen days. The superiority of discharge rates at 4 hours of nebulized adrenaline mixed with 3% hypertonic saline, was evaluated as 'better acute response' and can be helpful to reduce hospitalization needs. Additionally, this option seems to be more effective to reduce length of hospital stay.

Key words: bronchiolitis, epinephrine, patient discharge, patient readmission, adverse effects.

Acute bronchiolitis is one of the most common causes of emergency room admissions in the first year of life.

Most infants with acute bronchiolitis (AB) have mild, self-limiting illness and recover completely[1]. Although it has a benign clinical course, bronchiolitis seems an important disease among infants and is the leading cause of hospitalization in infancy[2]. The hospitalization rate varies between 1% and 20% among children less than 24 months of age during seasonal epidemics[3-5].

The American Academy of Pediatrics (AAP) recommendations do not support use of bronchodilators, corticosteroids, antibiotics, and diagnostic testing for patients with bronchiolitis[6]. There is great variation in the clinical management of AB[7]. The optimal pharmacological therapy in AB is still controversial[8]. The mainstay of therapy is supportive care such as adequate hydration, management of secretions, supplementary oxygen, and mechanical ventilatory support as needed[9]. In addition to supportive care, nebulized bronchodilators (salbutamol, adrenaline, ipratropium bromide) and corticosteroids are commonly used in clinical practice. Even if there is no exact evidence for administration of nebulized epinephrine to infants with a diagnosis of AB; according to AAP guidelines, more studies are needed to consider for treatment of outpatients[6]. Multiple comparisons of symptomatic therapies in varying doses have been undertaken and outcomes have varied widely even within

the same country[10-14]. There is no agreed therapeutic standard of care worldwide. The management of disease differs greatly also in our country, Turkey.

We had two aims in this study. The primary aim was to determine the most appropriate therapy for patients with AB in the emergency department that provides the earliest discharge, reduces length of hospital stay (LOS) hours, and cause less readmission rates (RR). The secondary aim was to determine if there were any significant adverse events (AE) during medication. We tested the hypothesis that there is no significant difference between inhaled treatment options with regard to LOS, discharge rates (DR), RR, and AE in the treatment of AB in infancy.

Material and Methods

Patients and Study Design

This was a randomized double-blind prospective study in the Pediatric ED of Istanbul University Istanbul Faculty of Medicine, between October 2011 and April 2012. The study protocol was approved by the Institutional Ethics Committee of Istanbul Faculty of Medicine The recommendations of the Declaration of Helsinki for biomedical research involving human subjects were followed. Children with AB aged between 2-24 months with a score as moderate (4-8) in the bronchiolitis clinical score (BCS) system were included[15]. Infants who had symptoms of viral respiratory tract infections such as coryza, cough, fever, and clinical findings of bronchiolitis like tachypnea, respiratory distress with chest recession, wheezing and/or crackles were studied. Exclusion criteria were being younger than 2 months old, prematurity (less than 36th gestational week), low birth weight (less than 2,500 g), history of admission in neonatal intensive care unit due to respiratory distress, history of intubation in the intensive care unit, congenital heart/lung/neurologic or immunologic disease, history of atopic disease or recurrent wheezing, clinical or radiologic findings of bacterial infections, atelectasis or consolidations on X-ray and refusal to consent by parents.

Based on mean and standard deviation values of LOS in a previous study of Tal et al.[16], a power analysis revealed that, for detection of this significant LOS difference between the five treatment groups, with an α of 0.05, power of 90% and standardized effect size of 0.55, we required at least 350 patients (70 per group). The study was not powered to detect differences in secondary outcome measures.

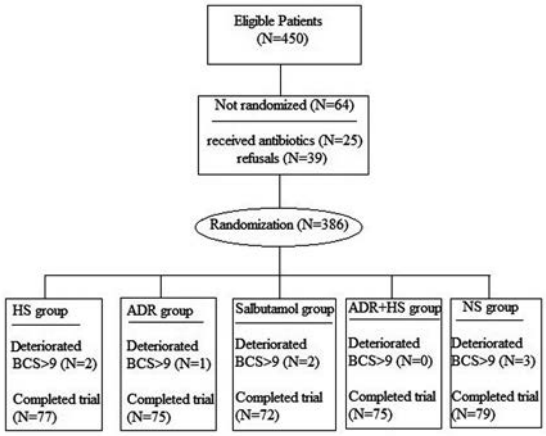

Fig. 1. Selection and randomization of patients

Informed consents were obtained from parents of children included in the study. The patients were evaluated according to the inclusion and exclusion criteria. The patients enrolled in the study were randomized by using the lottery method for simple random sample into treatment options (Fig. 1).

The first 4 hours of the study passed in the observation unit (OU). At the end of 4 hours, the patient's discharge status was decided. Non-responders were admitted to the emergency observation unit (EOU). Discharge status was evaluated after 24 hours. Patients who were not discharged received continued treatment in the pediatric emergency service (PES).

Data Collection

Clinical data and demographic information were collected by the same pediatrician. The patients were divided into five treatment groups: 3% hypertonic saline (HS), nebulized adrenaline (ADR), nebulized adrenaline mixed with 3% hypertonic saline (ADR+HS), nebulized salbutamol and as control group normal saline (0.9% NaCl) (NS) among children presenting to the Emergency Department (ED) with AB. Infants were examined at 0–240 minutes for respiratory rate, pulse, SaO_2, AE, and BCS were recorded in the case report form. Infants were evaluated using BCS at 4-hour intervals

Table I. Demographic and Clinical Characteristics of the Patients at Admission According to Treatment Groups.

Characteristics	Treatment Groups					P
	HS (n: 77)	ADR (n: 75)	Salbutamol (n: 72)	ADR+HS (n: 75)	Normal saline (n: 79)	
Age (month)*	7 (4-10)	7 (4-10)	7 (4-10)	7 (4-10)	7 (4-10)	1.00
Weight (kg)*	8.5 (7-10)	8.2 (7-10)	8.25 (7-11)	8.2 (...)	8.3 (7-10)	0.99
Male/Female (%/%)	55.8/44.2	54.7/45.3	54.2/45.8	54.7/45.3	54.4/45.6	1.00
Temperature (^{O}C)*	37.5 (36.4-38.2)	37.5 (36.4-38.2)	37.65 (37.5-38.2)	37.5 (36.4-38.2)	37.5 (36.3-38.1)	0.763
Duration of URTI symptoms (days)*	5 (4-5)	5 (4-5)	5 (4-5)	5 (4-5)	5 (4-5)	0.964
Duration of wheezing (days)*	2 (2-3)	2 (1-3)	2 (2-3)	2 (1-3)	2 (2-3)	0.935

*Data is presented as median (25^{th}-75^{th} percentile)
HS: 3% hypertonic saline; ADR: nebulized adrenaline; ADR+HS: nebulized adrenaline mixed with 3% hypertonic saline.

and a score less than 3 were considered for discharge decision.

Length of hospital stay hours were considered between first treatment and discharge time. Adverse events (tachycardia, pallor, tremor, nausea, vomiting) were recorded within the LOS. Readmission to the hospital within first 15 days was recorded. The primary outcomes of the study were DR and LOS, and the secondary outcomes were RR and AE to evaluate efficacy and safety of the treatment.

Infants aged younger than 2 months (n=13), with low birth weight (n=7), and those born before the 36th gestational week (n=9) were excluded before randomization. 450 patients were eligible for the study. However, 25 patients had bacterial infection findings and received antibiotics and informed consents were refused by parents of 39 patients. Therefore 386 patients were randomized. During the study, infants whose BCS have deteriorated worse than 9 were excluded from the study (2 in HS group, 1 in ADR group, 2 in salbutamol group and 3 in NS group). At the end, 378 patients were able to complete the trial (Fig. 1).

Treatments

Drugs were administered by means of standard hospital nebulizers through a firmly applied face mask with an oxygen flow of 6 liters per minute within 6-8 minutes. Group HS was given 4 ml HS, group ADR received 4 ml NS with ADR 0.1 mg/kg, group Salbutamol had nebulized salbutamol 0.15 mg/kg with 4 ml NS, group ADR+HS received 4 ml HS with 0.1 mg/kg/dose ADR, and as control group; group NS was administered 5 ml NS at 0, 30, and 60 minutes, and every 4 hours thereafter if needed to a maximum of 24 h (Fig. 1).

Statistical Analysis

The statistical analysis was performed using SPSS for Windows, version 16.0 (SPSS Inc., Chicago, IL). One-way analysis of variance (ANOVA) was used to measure the distribution of demographic and clinical variables such as age, weight, temperature, duration of URTI and duration of wheezing. Because of gender is a dichotomous event, Pearson chi-square test was performed to measure distribution among infants. Pearson chi-square test was performed also for evaluating of outcomes of the study such as DR at 4 hours, DR at 24 hours, RR and AE. LOS is not a dichotomy event; it is intermittent variable. Thus, to evaluate LOS; ANOVA was used. To detect the cause of significant difference; in DR at 4 hours, binary logistic regression test was performed and in LOS, as post hoc method, Tukey analysis was performed. Statistical significance was defined as $p < 0.05$.

Results

The study included 378 patients with a mean

Table II. Outcome Measures of the Study According to Treatment Groups

Outcomes	Treatment Groups						p
	HS (n: 77)	ADR (n: 75)	Salbutamol (n: 72)	ADR+HS (n: 75)	Normal saline (n: 79)	Total (n: 378)	
Discharge rate at 4 hrs, n (%)	37/77 (48.1)	42/75 (56.0)	27/72 (37.5)	52/75 (69.3)	29/79 (36.7)	187/378 (49.5)	0.001
Discharge rate at 24 hrs, n (%)	69/77 (89.6)	66/75 (88.0)	63/72 (87.5)	71/75 (94.7)	66/79 (83.5)	335/378 (88.6)	0.294
Readmission rate within first 15 days, n (%)	14/77 (18.2)	14/75 (18.7)	19/72 (26.4)	14/75 (18.7)	20/79 (25.3)	81/378 (21.4)	0.571
Adverse events (tachycardia, pallor, tremor, nausea, vomiting), n (%)	0 (0)	7/75 (9.3)	7/72 (9.7)	5/75 (6.7)	2/79 (2.5)	21/378 (5.6)	0.079
Length of stay (hours), median (IQR)	8 (12)	4 (12)	16 (20)	4 (8)	16 (20)	10 (16)	0.039

HS: 3% hypertonic saline; ADR: nebulized adrenaline; ADR+HS: nebulized adrenaline mixed with 3% hypertonic saline.

age of 7.63 ± 4.6 months. Male sex ratio was 54.8% within the study population. There were no significant differences between treatment groups in terms of age, sex, clinical parameters (weight, body temperature, duration of upper respiratory tract infection (URTI) symptoms and duration of wheezing at admission to hospital (Table I).

Discharge Rates

Discharge rates (DR) of treatment options were compared at 4th and 24th hours. At the end of 4 hours, 187 patients (49.5%) were discharged and DR at 4th hour were found statistically significant ($p<0.001$). ADR+HS treatment option had the highest DR at 4th hour with 69.3% (Table II). To Compare DR at 4th hour of treatment options, NS group was defined as control group and binary logistic regression test was performed; in ADR group ($p=0.017$) and in ADR+HS group ($p<0.001$) discharge rates at 4th hour were significantly higher (Table III). At the end of 24 hours, 335 of 378 patients were discharged (88.6%). Within the treatment options there was no statistically significant difference in terms of DR at 24th hour (Table II).

Length of Hospital Stay

Length of hospital stay was statistically different between the treatment options ($p=0.039$). ADR+HS group had the shortest LOS values with a median of 4 hours (IQR: 8) (Table II). To compare LOS of treatment options, NS group was defined as control group Kruskal-Wallis analysis was performed and adjusted for treatment group numbers ($p<0.01$; paired group analysis is performed with Mann Whitney. In ADR+HS group LOS were significantly lower ($p<0.001$).

Readmission Rates

Readmission rates between treatment options within the first 15 days were evaluated and were not different ($p=0.571$) (Table II).

Adverse Events

As adverse events; tachycardia, pallor, tremor, nausea and vomiting were observed within the LOS. The total frequency was 5.5% and the frequencies were not different when compared between treatment options ($p=0.079$) (Table II).

Discussion

The short-term benefits in clinical response are more valuable to physicians in pediatric ED. Managing patient circulation with outpatient treatments and reducing the need for hospitalization especially comes into prominence in crowded cities such as Istanbul. For our ED, the EOU includes many types of patients. Therefore, discharging patients from the OU provides us enough logistic facilities

for hospitalization and prevents close patient-to-patient interactions, which reduces the risk of contagion.

To evaluate the short-term clinical benefits, outcomes of patients who were discharged before 24 hours were considered. Additionally, to evaluate acute response differences, outcomes of patients who were discharged within the first 4 hours were considered. Our other primary outcome has shown that clinical benefits in acute response provided with ADR+HS and/or ADR treatment was significantly superior to the other treatment options. This statistical data may be helpful to reduce hospitalization rates in infants with AB. In the study of Grewal et al.[17]; clinical score from baseline to 120 minutes demonstrated no improvement in respiratory distress in ADR+HS group compared with ADR group. A study from Iran demonstrated that ADR treatment provides better recovery in infants with AB compared to nebulized salbutamol[18]. In the study of Sanchez et al.[19], clinical score and pulmonary mechanics of patients were evaluated just 30 minutes after the initial treatment and ADR was found superior to nebulized salbutamol. In a study from India, nebulized salbutamol and L-epinephrine were compared with regard to clinical responses in first three hours and significantly more children in ADR group could be sent home after the emergency treatment[20].

For measuring the efficacies, LOS hours were also used. The mean LOS was significantly shorter for children in the group receiving ADR+HS than in the groups receiving treatment HS, NS, nebulized salbutamol or ADR. According to a review prepared by Chen et al.[21]; HS significantly decreased both the rate and the duration of hospitalization. A study from Spain has demonstrated that ADR+HS significantly shortens LOS in hospitalized infants with acute moderate bronchiolitis compared to HS[22]. In the study of Miraglia et al.[23]; ADR+HS was found significantly superior to ADR with regard to LOS. The superiority of ADR+HS over ADR and HS may be a consequence of a synergistic or additive effect.

In infants with AB there was no statistically significant difference for long-term efficacy between the treatment options. To consider this, RR within first fifteen days were evaluated and we found that no treatment was superior to another (p=0.571). Similar to ours; in the study of Anil et al.[24]; NS, HS, ADR and nebulized salbutamol options were compared and no significant difference was found with regard to RR.

As much as efficacy, drug safety is also important for rational use. To evaluate drug safety, we considered AE. For our secondary outcome, the frequency of AE in our study groups was within acceptable limits, none was clinically significant and there were no statistically significant differences between treatment options (p=0.079). Furthermore, the detected AE may have been reflexes not true symptoms, a natural infantile agitated behavior response to any intervention. In a study from Israel, AE and benefits on clinical response of ADR+HS were observed and no AE were detected[25]. Another double-blind trial with 46 patients who received ADR+HS reported AE in four patients[17] (vomiting in 3 patients, diarrhea in 1 patient).

The number of patients assessed eligibility was decreased because we excluded infants aged younger than 2 months (13 infants), with low birth weight (7 infants), and those born before

Table III. Comparison of Discharge Rates at 4 Hours of Treatment Options (Reference Group: Normal saline)

Treatment options	Odds ratio	Confidence interval %95		P value
		Lower	Upper	
Hypertonic saline	1.595	0.841	3.024	0.153
Adrenaline	2.194	1.150	4.186	0.017
Salbutamol	1.034	0.534	2.004	0.920
Adrenaline mixed hypertonic saline	3.898	1.993	7.625	<0.001

the 36th gestational week (9 infants) before randomization. Many studies have shown that LOS is longer and these infants are more likely to be admitted to the intensive care unit with severe disease[26-27]. Therefore, including such infants is considered to be harmful for the homogeneity of study patients. Furthermore, although not previously shown, the possibility that NS may have a bronchoconstrictive effect in infants (aged younger than 2 months) should not be ignored[26]. In order to be able to observe clinical recovery in patients faithfully, similar to the study of Jacob et al.[28]; ones had mild symptoms (1-3 score in BCS) were not included. Additionally, ones had severe symptoms (9-12 score in BCS) may be resistant to inhaled treatment regimes, may require more aggressive supportive care and all these disadvantages may prevent to get reliable results. Therefore, similar to the study of Grewal et al[17], they were also not included in the study.

A randomized double-blind trial from Norway showed that LOS was significantly shorter for children in the on-demand treatment group than in the group that received treatment on a fixed schedule[26]. While considering the clinical responses in our study groups, the use of a fixed schedule may have decreased the clinical recovery in all patients. However, it seems to have had no effect on recovery. Even if the recovery was affected, there was no significant difference in hospitalization between the fixed schedule and on-demand schedule comparisons in the Norwegian study[26]. Thus, our clinically and statistically significant 'acute response' (4 hours) data may not have been affected by the fixed schedule option. However, a study that includes a five by two factorial design may be needed in the future.

This study showed that for the treatment of infants with AB, ADR+HS is superior to other inhaled treatment options (HS, NS, ADR and salbutamol) with regard to LOS and DR in the first 4 hours. Reduced LOS and increased DR are important outcomes for emergency care settings when limited capacity and other risk factors are considered. Furthermore, rates and severity of AE with ADR+HS were similar to the other treatments and there was no statistically significant difference between them. However, this combination treatment was not associated with a lower RR. Although it has been evaluated for considering long-term efficacy, longer observation periods will be necessary in the future.

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