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Effect of Previously Administered Medication on Length of Hospital Stay in Patients with Moderate Acute Bronchiolitis

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Abstract

Background: Bronchiolitis is a leading cause of hospitalization in infants and the most common lower respiratory infection of infancy, yet optimal treatment is still debated. Most inpatients with bronchiolitis have been referred to hospitals by their primary care providers, and are usually prescribed inhaled bronchodilators and/or oral corticosteroids despite current recommendations.

Aim: To assess the efficacy of inhaled salbutamol and oral corticosteroids received prior to admission in patients with acute bronchiolitis.

Methods: Prospective study in the context of a randomized, controlled, double-blind clinical trial. In total, 185 patients with moderate bronchiolitis were included and categorized into 4 groups: patients who received 1) no medication, 2) inhaled salbutamol, 3) oral corticosteroids or 4) a combination of these therapies, prior to admission for more than 24 hours. Patients who received corticosteroids during hospitalization and patients with risk factors for severe bronchiolitis were excluded. Length of stay (LOS) was recorded as the main variable. Secondary variables were clinical status, respiratory rate, and oxygen saturation on admission.

Results: Demographic and clinical data were similar in all 4 groups except age, which was lower in the groups that received no medication ($p<0.0001$). The group that received combined therapy with salbutamol and corticosteroids before admission had a shorter mean LOS compared to the group that did not receive any medication at all (3.76 ± 1.6 *vs*. 4.66 ± 2.1; $p=0.007$). There were, however, no differences in any secondary outcomes: clinical severity score, respiratory rate or oxygen saturation.

Conclusion: Hospital stay is shorter in outpatients with moderate acute bronchiolitis receiving oral corticosteroids and inhaled salbutamol for more than 1 day before admission than in untreated patients. More studies are needed to confirm these results and to help identify which groups benefit from this treatment.

Keywords: Bronchiolitis; Corticosteroids; Salbutamol; Outpatients; Length of stay

Introduction

Bronchiolitis is a leading cause of hospitalization in infants [1,2]. It is also one of the most common conditions for which infants are evaluated in outpatient and emergency departments [3]. Although it is self-limiting, and testing and therapies offer little or no benefit for most previously healthy infants, millions of dollars are still spent each year in treating this disease [4,5].

Although bronchiolitis is the most common lower respiratory infection in children, the optimal treatment is still unclear. There is good evidence that many commonly used therapies, such as bronchodilators and corticosteroids, are ineffective or have no proven efficacy in the treatment of inpatients with acute bronchiolitis [6-10]. Evidence-based guidelines for bronchiolitis management recommend supportive care with oxygen and supplemental hydration (when necessary), and discourage routine use of bronchodilators, corticosteroids, and antibiotics [11-14]. Despite these recommendations, the management of these patients still varies significantly, especially in primary care but also in emergency departments and after admission, and bronchodilators and corticosteroids are still commonly used [15-21].

Most patients with bronchiolitis do not need hospital admission [22], but little is known about possible variations in the treatment of children who are treated at the primary care stage [3]. One potential cost saving strategy in primary care is to reduce the use of bronchodilators and corticosteroids; however, it should be noted that there might be yet unidentified subsets of children with bronchiolitis for whom bronchodilators and/or corticosteroids may prove helpful [3].

It seems that combined therapy with a corticosteroid and a bronchodilator may significantly reduce hospital admission when given in the emergency department [23], but to our knowledge, there are no studies evaluating the effectiveness of prescribing this combination in primary care, prior to admission, and the possible impact on length of stay.

Patients and Methods

Patients were recruited during 3 bronchiolitis seasons (from October 2011 to May 2014) at Puerta del Mar University Hospital in Cádiz. The study was approved by the hospital ethics committee.

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Informed consent was obtained from the parents or legal guardians of all infants included in the study.

Eligible patients included infants aged under 24 months who were brought to the emergency department with a clinical diagnosis of moderate acute bronchiolitis, defined as the first episode of respiratory distress with wheezing and/or crackles, preceded by an infection of the upper airways, and a Wood-Downes clinical score modified by Ferres (WDF) of 4 to 7 (Table 1) [24]. We excluded infants with risk factors (premature birth in infants with an adjusted age of less than 6 weeks, chronic respiratory disease, hemodynamically significant coronary heart disease, immunodeficiency, and neuromuscular disease), previous episodes of wheezing, physician's diagnosis of asthma, or infants treated with systemic or inhaled corticosteroids during hospitalization. Infants who subsequently developed severe bronchiolitis that required admission to the pediatric intensive care unit were also excluded from the primary analyses.

At enrollment, once a pediatrician had confirmed the diagnosis and parental consent had been signed, research assistants performed a full physical examination to calculate the WDF score and a medical history was obtained from the parents or legal representatives, including questions about family history of atopy (including asthma, rhinitis or eczema), parental smoking, personal history of atopy, type of feeding (breastfeeding *vs*. formula or a combination of both), number of siblings, attendance at a nursery school, auscultation findings, and medication prior to admission (medications (inhaled salbutamol or oral corticosteroids) and duration of therapy).

On admission, a test for respiratory syncytial virus in nasopharyngeal aspirate was performed, and infants with an oxygen saturation of 94% or less received oxygen supplementation via a nasal cannula with the appropriate fraction of inspired oxygen (FIO_2) to achieve a saturation level >94%.

Intervention

This is an observational study derived from the results of a randomized, double-blind, placebo-controlled trial which aimed to compare the efficacy of nebulized epinephrine in 3% hypertonic saline in reducing the length of hospital stay in infants with moderate acute bronchiolitis [25].

In this study, we classified patients into 4 groups according to the medication administered prior to admission for more than 24 hours: no medication, inhaled salbutamol, oral corticosteroids, or a combination of these. The corticosteroid used in all cases was prednisolone steaglate (and the patients were only included in this group if they had had at least 3 doses).

Patients in all groups received the same standard support during hospital stay (elevation of head of bed and supplemental oxygen when oxygen saturation dropped below 94%, paracetamol for fever, and saline nasal lavage before and after administration of the nebulized solution). Pediatricians were free to choose the infant's diet according to the degree of respiratory distress and oral tolerance. All patients were monitored with a pulse oximeter (Nellcor, Oximax N-600x) until oxygen saturation remained above 94% without supplemental oxygen. According to current recommendations, no patients received corticosteroids in any form during hospital stay.

Assessments and Efficacy Outcome

The primary efficacy outcome was length of hospital stay, defined as the number of days from admission to the time the patient was discharged by the pediatrician or fulfilled the study discharge criteria: WDF score of 3 or less, oxygen saturation of 97% or more whilst breathing ambient air, adequate oral tolerance, and no need for nebulization.

Secondary efficacy variables (respiratory rate, heart rate, oxygen saturation and WDF score) were recorded 3 times a day (morning, afternoon, and night) throughout the hospital stay. Respiratory rate was measured over a period of 1 minute. The lowest Fio2 required to maintain oxygen saturation above 94% was used in all cases. Admission to intensive care and need of mechanical ventilation were also recorded.

Statistical analysis

We conducted a descriptive analysis using means, standard deviations, medians, and ranges for quantitative variables, and frequencies and percentages for qualitative variables. Categorical variables were analyzed in both groups using the Mantel-Haenszel chi-square method or, where applicable, Fisher's exact test.

The Kolmogorov–Smirnov test was used to check for normality, and Student's t-test and the Mann-Whitney U test were used to compare means for parametric and non-parametric data, respectively.

Results

A total of 208 infants with moderate bronchiolitis who were seen in the emergency department during 3 epidemic seasons (from October 2011 to May 2014), met the enrolment criteria, and 185 were finally enrolled. Of the 23 ineligible infants, 13 required admission to the pediatric intensive care unit, 3 parents withdrew informed consent, 3 did not meet criteria, and 4 were excluded for other reasons.

110 (59.5%) out of the 185 patients enrolled, had not received any medication or had received medication for less than 24 hours prior to admission, 26 (14.1%) had received inhaled salbutamol, 7 (3.8%) oral corticosteroids, and 42 (22.7%) combined inhaled salbutamol and oral corticosteroids. Mean duration of inhaled salbutamol administration before admission was 2.82 ± 4.11 days (P25, 1 day; P75, 3 days) and mean duration of oral corticosteroid administration was 2.16 ± 1.41 days (P25, 1 day, P75, 3 days).

	0	1	2	3
Wheezing	None	End expiration	Entire expiratory phase	Inspiration and expiration
Retractions	None	Subcostal or lower intercostal	1 + supraclavicular + nasal flaring	2 + suprasternal + lower intercostal
Respiratory rate, breaths/min	<30	31-45	46-60	>60
Heart rate, beats/min	<120	>120		
Inspiratory breath sounds	Normal	Regular, equal	Markedly silent, equal	Silent thorax, no wheezing
Cyanosis	No	Yes		
*A score of 1-3 points denotes mild bronchiolitis; 4-7 moderate bronchiolitis; and 8-14 severe bronchiolitis.				

Table 1: Wood-Downes Clinical Scoring System Modified by Ferres*

Of the 185 patients included, 94 would receive epinephrine in 3% hypertonic saline, while 91 only hypertonic saline. Baseline clinical and demographic characteristics were similar among the groups (Table 2) except for age: patients in the untreated group were significantly younger.

We found significant differences in length of hospital stay between the untreated group and the group that received the combination of salbutamol and corticosteroids (4.66 ± 2.1 *vs.* 3.76 ± 1.6, p=0.007). No significant differences were detected among the other groups, possibly due to the differences in sample size (Figure 1). With respect to vital signs (clinical score, respiratory rates, cardiac rate, oxygen saturation FiO_2), there were no differences between the groups at admission or during hospitalization (Figure 2).

Hospital stay was shorter for patients in the 3% hypertonic saline + adrenaline group, RR=1.49 (95% CI: 1.1-2.01; p=0.01), and for those who had received combined treatment before admission, RR=1.42 (95% CI: 1.02-1.97; p=0.04).

In the multivariate analysis of hospital stay calculated using the Cox regression model, statistically significant associations were only found with the variables "previous combined treatment" and "treatment group" (proportionate among the groups), while the interaction term of the model was not statistically significant.

Discussion

The use of corticosteroids in the treatment of bronchiolitis remains

	No medication (N=110)	Inhaled salbutamol (N=26)	Oral corticosteroids (N=7)	Combined medication (N=42)	P value
Mean age, months	1.24 ± 1.26	2.92 ± 1.87	3.42 ± 3.95	3.66 ± 2.93	P<0.0001
Male sex, n (%)	54 (49.1%)	15 (57.7%)	2 (28.6%)	21 (50%)	P=0.587
Personal history of atopic dermatitis, n (%)	13 (11.8%)	4 (15.4%)	0 (0%)	7 (16.7%)	P=0.612
Personal history of cow's milk protein allergy, n (%)	2 (1.8%)	0 (0%)	0 (0%)	2 (4.8%)	P=0.545
Premature birth†, n (%)	8 (7.3%)	6 (23.1%)	0 (0%)	3 (7.1%)	P=0.060
Parental history of smoking, n (%)	42 (38.2%)	11 (42.3%)	5 (71.4%)	17 (40.5%)	P=0.383
Family history of atopy, n (%)	31 (28.2%)	7 (26.9%)	2 (28.6%)	17 (40.5%)	P=0.494
Breastfed, n (%)	64 (58.2%)	12 (46.2%)	6 (85.7%)	19 (45.2%)	P=0.136
Disease severity score‡ on admission	5.05 ± 1.01	5.08 ± 0.97	5.57 ± 1.13	5.45 ± 1.06	P=0.144
Respiratory syncytial virus positivity, n (%)	69 (63.3%)	13 (50%)	4 (57.1%)	26 (61.9%)	P=0.586
HS3%+A vs HS3%+P (%) ****	49.1%/50.9%	50%/50%	57.1%/42.9%	54.8%/45.2%	P=0.916
WDF on admission	5.05 ± 1.01	5.08 ± 0.97	5.57 ± 1.13	5.45 ± 1.06	0.144
Hospital stay	4.66 ± 2.1	4.27 ± 1.56	3.86 ± 1.3	3.76 ± 1.6	0.051

*Plus–minus values are means ±SD. No significant differences in baseline characteristics were found among the 2 groups;† Premature infant older than 6 weeks; ‡ Defined using the Wood-Downes scale modified by Ferres;**** Patients treated with HS3%+P: nebulized 3% hypertonic saline plus placebo or with HS3%+A: nebulized 3% hypertonic saline plus adrenaline.

Table 2: Baseline clinical and demographic characteristics of study patients *

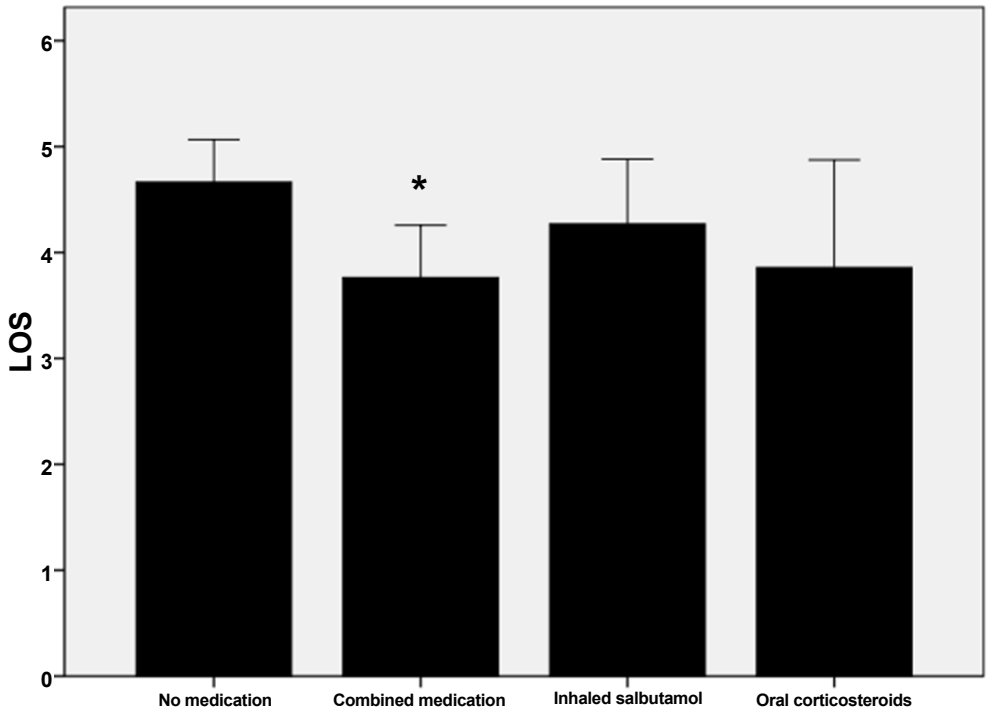
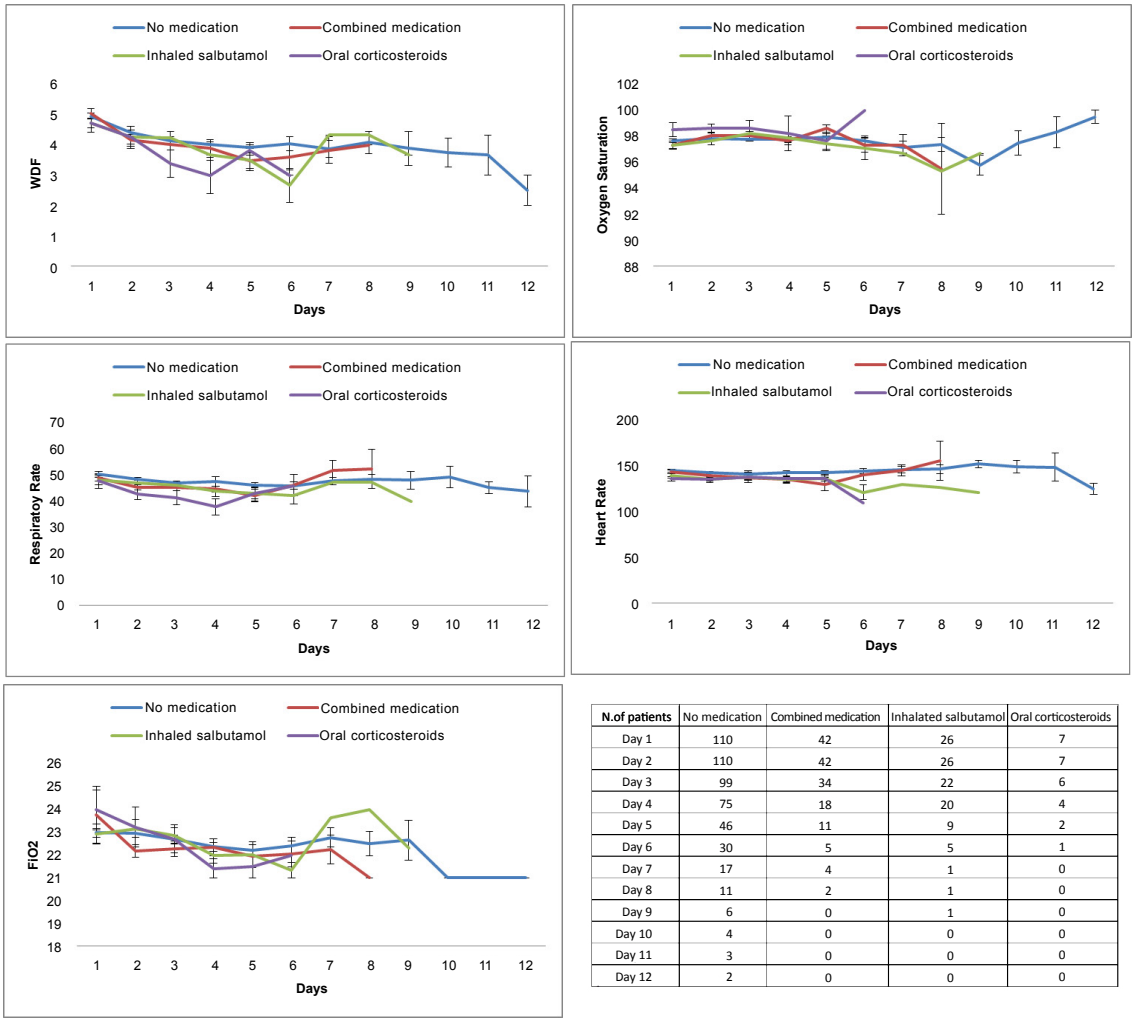


Figure 1: Significant difference in hospital stay between the untreated group and the group that received inhaled salbutamol plus oral corticosteroids is indicated with an asterisk.



N.of patients	No medication	Combined medication	Inhalated salbutamol	Oral corticosteroids
Day 1	110	42	26	7
Day 2	110	42	26	7
Day 3	99	34	22	6
Day 4	75	18	20	4
Day 5	46	11	9	2
Day 6	30	5	5	1
Day 7	17	4	1	0
Day 8	11	2	1	0
Day 9	6	0	1	0
Day 10	4	0	0	0
Day 11	3	0	0	0
Day 12	2	0	0	0

Figure 2: Vital signs during hospital stay

controversial. Successive systematic reviews performed to date show that systemic corticosteroids do not provide a clear benefit in acute viral bronchiolitis [6,26]. Despite this negative evidence, they are still commonly used and a considerable number of articles have appeared on this practice. The variables most commonly examined in these studies are the rate of admission in patients receiving corticosteroids on an outpatient basis, and hospital stay in patients receiving corticosteroids during hospitalization. These studies have found that the administration of systemic corticosteroids in the outpatient setting does not reduce the rate of admission [6,27,28], and that administration of systemic corticosteroids to hospitalized patients does not reduce the length of stay [6,29-31]. To our knowledge, the benefit of systemic corticosteroids administered to outpatients in reducing length of hospital stay has not yet been explored.

In our study, most patients were untreated before admission, as recommended in the latest guidelines of the American Academy of Pediatrics [10]. When primary care pediatricians did decide to start treatment, they generally chose the combination of an oral corticosteroid (prednisolone steaglate) and an inhaled bronchodilator (salbutamol). Some studies have reported a synergic effect when these 2 treatments are combined, showing that administration before admission (generally to the emergency room) reduces clinical severity and the rate of admission [32-34].

According to our results, hospital stay is significantly reduced by approximately 1 day in patients who receive oral corticosteroids plus inhaled salbutamol on an outpatient basis for more than 1 day before admission (p=0.007), as confirmed by the multivariate analysis. Both groups had similar severity scores and vital sign values on admission, but patients in the group that did not receive medication before admission were younger. Thus, the shorter hospital stay of the group that did receive combined treatment may be age-related. Although an age of less than 12 weeks is considered a criterion for hospital admission and a risk factor for severity [10], we do not believe this is a limitation, for 2 reasons. Firstly, in our study, the severity scores determined on admission and then 3 times daily throughout the stay were similar in the untreated group and the group that received combined treatment, ruling out the possibility of a difference in clinical severity between the younger and older patients. Vital signs determined on admission and then once a day during hospitalization (respiratory rate, heart rate, oxygen saturation, and FiO_2 required to maintain saturations >94%) were also similar in both groups throughout their stay, despite the differences in age. Secondly, younger infants might be kept longer in the hospital for reasons that are not strictly medical, including anxiety on the part of parents faced with the discharge of a patient who may still be coughing, or peace of mind of the pediatrician who prefers to discharge a completely cured child, etc. This was ruled out by the use

of a study protocol with well-defined, independent criteria for hospital discharge applied to all patients.

This is an observational study of a clinical trial conducted to compare length of hospital stay in patients with bronchiolitis treated with nebulized 3% hypertonic saline + placebo compared to 3% hypertonic saline + adrenaline [35,36]. The trial concluded that the hospital stay of patients treated with nebulized 3% hypertonic saline plus adrenaline was significantly shorter. This does not represent a limitation to our study because the distribution of patients treated with both types of nebulization was the same in all 4 groups (Table 2).

Similarly, we observed a homogeneous distribution of patients with predisposing factors for a possible first asthma attack (such as personal history of atopic dermatitis and family history of asthma, allergic rhinitis or atopic dermatitis) who might benefit from early treatment with oral corticosteroids and inhaled salbutamol.

Prednisolone is an intermediate-acting glucocorticoid with a biological half-life of 12-36 hours, so the effect of administration before admission will not persist throughout the hospital stay, but early administration of a potent anti-inflammatory could inhibit or reduce the bronchiolitis inflammatory cascade and improve progress in treated patients, even though this effect has not been demonstrated in patients receiving these agents after admission [37]. Few of the articles, which assess the effect of corticosteroids administered before admission evaluate the impact on hospital stay among patients who are finally hospitalized.

One hypothesis that might explain the shorter hospital stay among patients admitted with moderate bronchiolitis who were prescribed combined medication in primary care is that they had had the disease for a longer period on admission, and therefore required a shorter hospital stay. In the absence of data, we cannot rule out this possibility, but we find it unlikely, because if the medication administered were having a beneficial effect, all those patients would systematically have been kept at home with moderate bronchiolitis without being referred to the hospital, while the untreated (younger) patients would have been systematically referred for admission without delay.

In our study, we cannot rule out the potential role of epigenetic modifiers affecting individual response to therapies of respiratory diseases such as bronchiolitis. It has been recently shown that alteration of DNA methylation in many respiratory disorders, including asthma, COPD and IPF and the aberrant established DNA methylation affects a great number of signaling pathway associated factors, such as STAT5A, PTEN and Nrf2 [39-41]. This made the inhibitors of DNA methyltransferases (DNMTs) serve as the novel therapies of respiratory diseases [42,43]. Interestingly, since many histone modifiers, such as H3K9 histone methylase G9A and GLP, also interact with DNMTs and maintain DNA methylation at particular loci [44], inhibitors of the histone modifiers might also function for the treatment of respiratory diseases. Actually, inhibitors of several histone modifiers, such as histone deacetylase HDAC and acetylase p300, have been found to play a role in the therapies of respiratory diseases [45,46]. Therefore, it is interesting to investigate the underlying mechanisms that involved in the initiation and development of lung diseases and generate the associated inhibitors for the treatment of these disorders.

In conclusion, the results of our study suggest that the combination of inhaled salbutamol and oral corticosteroids prescribed in primary care may improve progress in infants hospitalized with moderate bronchiolitis. More studies are needed to confirm our results and to help identify which groups benefit from this treatment.

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