Effect of combined dexamethasone therapy with nebulized r-epinephrine or salbutamol in infants with bronchiolitis: A randomized, double-blind, controlled trial

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ABSTRACT

Background: This study investigated the effect of combining oral dexamethasone with either nebulized racemic epinephrine or salbutamol compared to bronchodilators alone for the treatment of infants with bronchiolitis. **Materials and Methods:** This was a double-blind, randomized controlled trial on infants (1 to 12 months) who were diagnosed in the emergency department with moderate-to-severe bronchiolitis. The primary outcome was the rate of hospital admission within 7 days of the first dose of treatment, and the secondary outcomes were changes in respiratory distress assessment instrument score, heart rate, respiratory rate, and oxygen saturation (O_2 Sat) over a 4-hour observation period. Infants ($n = 162$) were randomly assigned to four groups: A (dexamethasone + racemic epinephrine) = 45, B (placebo and racemic epinephrine) =39, C (dexamethasone and salbutamol) = 40, or D (placebo and salbutamol) = 38. **Results:** Patients who had received dexamethasone + epinephrine exhibited similar admission rates compared to placebo + epinephrine or salbutamol ($P = 0.64$). Similarly, no statistically significant difference was observed in the rate of hospitalization for patients who received dexamethasone + salbutamol compared to those who received placebo + epinephrine or salbutamol ($P = 0.51$). Clinical parameters were improved at the end of the 4-hour observation period for all treatment groups. Treatment with dexamethasone + epinephrine resulted in a statistically significant change in HR over time ($P < 0.005$) compared to the other groups. **Conclusions:** This study adds to a body of evidence suggesting that corticosteroids have no role in the management of bronchiolitis for young infants who are first time wheezers with no risk of atopy.

Key words: Bronchiolitis, dexamethasone, salbutamol, albuterol, beta2 agonist, racemic, epinephrine, efficacy, randomized trial

INTRODUCTION

Bronchiolitis is the most common lower respiratory tract infection among infants and the most common cause of hospitalization in this age group. It is characterized by acute inflammation, edema and necrosis of the epithelial cells lining the small airways, increased mucous production, and bronchospasms.[1]

The current treatments for bronchiolitis are controversial. The main stay of treatment is supportive care with supplemental oxygen, adequate hydration and mechanical ventilation as needed.[1,2] Bronchodilators and corticosteroids are widely used but not routinely recommended.[1] While a meta-analysis of the effects of nebulized selective beta2-agonists failed to show any consistent benefit,[3-5] a meta-analysis of the effect of nebulized epinephrine suggested a decrease in clinical symptoms compared with either placebo or albuterol.[6] Several published study on dexamethasone failed to show any difference in hospital admission rate or respiratory clinical score compared with placebo.[7] However, combination

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therapy using dexamethasone and epinephrine has been reported to produce an improvement in respiratory clinical score within the first hour and may significantly reduce hospital admissions.[8] Additionally, two small studies have reported beneficial outcomes by combining epinephrine with dexamethasone[9,10] or albuterol with dexamethasone.[9,10] In a similar population, there has been no benefit reported from the administration of dexamethasone alone, epinephrine alone or albuterol alone.[8-10]

Furthermore, although the mechanism of action is not known, synergism between corticosteroids and beta-agonists in the treatment of chronic asthma is well documented.[11-14] A small number of reports have demonstrated a possible synergistic effect for this combination in infants with bronchiolitis, resulting in clinical improvement.[8,11]

Because of the potential benefits of this combined therapy, this randomized double-blind controlled study was conducted to examine the clinical benefit of combining dexamethasone with either nebulized epinephrine or salbutamol compared to bronchodilators alone, in children younger than 12 months admitted to the emergency department (ED) with acute bronchiolitis. The clinical benefit was measured by assessing the rate of hospital admission within 7 days of illness (the natural course of the disease and the maximum time within which admission is expected to occur) and by monitoring changes in respiratory distress assessment instrument (RDAI) score, heart rate (HR), respiratory rate (RR), and oxygen saturation (O_2 Sat) from baseline during the first 4 hours of treatment following enrollment.

MATERIALS AND METHODS

This study was a randomized, double-blind, controlled clinical trial. Patients were recruited during the bronchiolitis season between November 2010 and March 2011 from the pediatric ED in King Abdulaziz Medical City (KAMC), King Fahad National Guard Hospital (KFNGH), Riyadh, KSA.

Participants
Infants with mild to moderate bronchiolitis, presented to the ED within 7 days of the onset of symptoms with RDAI score between 5 and 15 were recruited for the study.

Exclusion criteria
(1) infants who received a bronchodilator or steroids prior to admission to the ED (2) infants who had a prior wheeze or asthma or known chronic cardiopulmonary disease, neurological disease, or immunodeficiency (3) infants who experienced severe respiratory distress (4) infant who had an history of Varicella infection (5) if the infant exhibited

clinical or radiological evidence of bacterial pneumonia and require pediatric intensive care unit (PICU) admission or intubation or had been previously intubated.

Collection of demographic data and baseline assessment
The research coordinators obtained consent from the parents and assessed the patient for eligibility by completing an observation recording form that collected demographic data and the baseline assessment.

Intervention
Using a computer-generated randomization sequence, participants were assigned to one of the four study treatment groups: Nebulized epinephrine plus oral dexamethasone (group A), nebulized salbutamol plus oral dexamethasone (group B), nebulized epinephrine plus oral placebo (group C), and nebulized salbutamol plus oral placebo (group D). The three doses of nebulized treatments were administered at 0, 30 and 90 minutes apart by means of a Salter Labs nebulizer (REF 8900) with an oxygen flow rate of 8 liters per minute and 0.25 ml racemic epinephrine at 2.25% concentration or an equivalent volume of saline. Oral treatments were based on a study by Schuh *et al.*,[15] and consisted of 1.0 mg of dexamethasone per kilogram of body weight (maximum dose, 12 mg) or placebo given after the first nebulized treatment in the ED and were subsequently followed by two once-daily doses of dexamethasone (0.6 mg per kilogram; maximum daily dose, 12 mg) or placebo, to be taken at home. The dexamethasone suspension consisted of generic dexamethasone phosphate injection solution mixed with Ora-Plus and Ora-Sweet (Paddock Laboratories). The placebo consisted of Ora-Plus and Ora-Sweet. The research nurse administered all drugs in the ED and instructed parents in the administration of the oral drugs at home. The treating physician in the ED was allowed to provide co-interventions only after 90 minutes and independently determined whether to admit or discharge the infant. The study was terminated and the patient was excluded if mandated at any time by the clinical condition or if clinical deterioration occurred.

Randomization
Computer-generated, random sequences were used for randomization. Following enrollment, each subject was provided with a four-digit identification code, and this code was used as a label to identify the patient's group during and after completion of the study.

Patient code numbers were provided to the pharmacy department, where they were matched with study groups (A, B, C, and D) using a random list prepared prior to the start of the study. The pharmacist then provided study medications in envelopes labeled with

patient code numbers such that the nurse, physician and participants were unaware of group assignments. The research pharmacy prepared the study drugs in sequentially numbered, visually identical envelopes. The active drugs and placebos were identical in appearance, volume, weight, odor, and taste.

Participant assessments and follow-up

Eligible participants were randomly allocated to one of four groups. The research coordinator was provided with the patient's code numbers, and the coordinator then submitted the medication order to the pharmacy. Following administration of the medication by the ED nurse and respiratory therapist, the research nurse assessed the patient at 30, 60, 90, 120, 180, and 240 minutes for HR, RR, O_2 Sat, and RDAI score (based on two respiratory variables: Wheezing and retractions). The patient's temperature was recorded at 0, 120, and 240 minutes. Blood pressure was measured at 0 and 240 minutes.

Follow up telephone calls and chart reviews were performed at day 3 and day 7 following enrollment. Using a standard telephone follow-up form, a research coordinator obtained data about compliance with study medication following discharge; any additional visits to health care services; and details about the infant's feeding, sleeping, breathing, and coughing.

Outcome measures

The primary outcome was the rate of hospital admission attributable to bronchiolitis within seven days of the first dose of treatment. Outcome was determined through telephone follow-up and confirmed by chart review. The secondary outcomes were changes in RDAI score, HR, RR, and O_2 Sat from baseline within four hours of treatment and were determined by direct measurement by the research nurse.

Statistical analysis

To attain 80% power with a 5% type I error rate, the required sample size was 600 infants: 300 infants in the dexamethasone groups, including nebulized epinephrine plus oral dexamethasone (group A) and nebulized salbutamol plus oral dexamethasone (group C), and 300 infants in the placebo groups, including nebulized epinephrine plus oral placebo (group B) and nebulized salbutamol plus oral placebo (group D). This allowed the detection of a 9-10% absolute reduction in admission rates, equating to an approximately 33% relative reduction in admission rate. An interim analysis was planned and conducted at the end of the first season. All analyses were conducted and reported using SAS V9.2, SAS Institute, NC.

RESULTS

A total of 604 infants were screened for eligibility, and 162 were enrolled (45 failed to provide consent, and 394 did not meet eligibility criteria) [Figure 1]. Of the 394 ineligible infants, 161 (40.8%) had previous episodes of wheeze or received a bronchodilator prior to study enrollment, 67 (17%) had a history of bronchial asthma or received steroids within 2 weeks prior to emergency presentation, 46 (11.9%) had an RDIA score below 5, and 10 (2.5%) had an RDIA score above 15. A total of 45 patients were randomly assigned to the (dexamethasone + epinephrine) group, 40 patients were assigned to the (dexamethasone + salbutamol) group, 39 patients were assigned to the (placebo + epinephrine) group, and 38 patients were assigned to the (placebo + salbutamol) group.

There were 17 patients removed from the study: Six from the (dexamethasone + epinephrine) group, three from the (dexamethasone + salbutamol) group, five from the (placebo + epinephrine) group and three from the (placebo + salbutamol) group. Seven patients were removed by emergency department physicians due to deteriorations in their clinical conditions and increased oxygen requirement, while ten patients were removed by their families for social reasons. The stated reason was that the patient had improved and the family no longer wanted to remain in the ED to complete study observation [Table 1]. Despite these differences, the rate of patient removal did not differ significantly (*P*-value 0.33) among the study groups. All patients were included in the intention-to-treat analysis. Baseline clinical and demographic characteristics were similar among the groups [Table 1]. The additional use of bronchodilators 90 minutes after enrollment occurred in 4.5% of patients in the (dexamethasone + epinephrine) group, 10% in the (dexamethasone + salbutamol) group, 7.7% in the (placebo + epinephrine) group, and 23.7% in the (placebo + salbutamol) group, with a *P* value of 0.055. At follow up, the parents of 10 infants in the (dexamethasone + epinephrine) group, 5 in the (dexamethasone + salbutamol) group, 9 in the (placebo + epinephrine) group, and 10 in the (placebo + salbutamol) group reported that they had stopped the oral study medication. The study groups did not differ significantly with respect to oral study medication compliance (*P*-value 0.49).

Hospital admission

By the seventh day after treatment was initiated, 14 of 45 infants in group A (31.1%) had been admitted to the hospital, as had 10 of 40 infants in group B (25%),
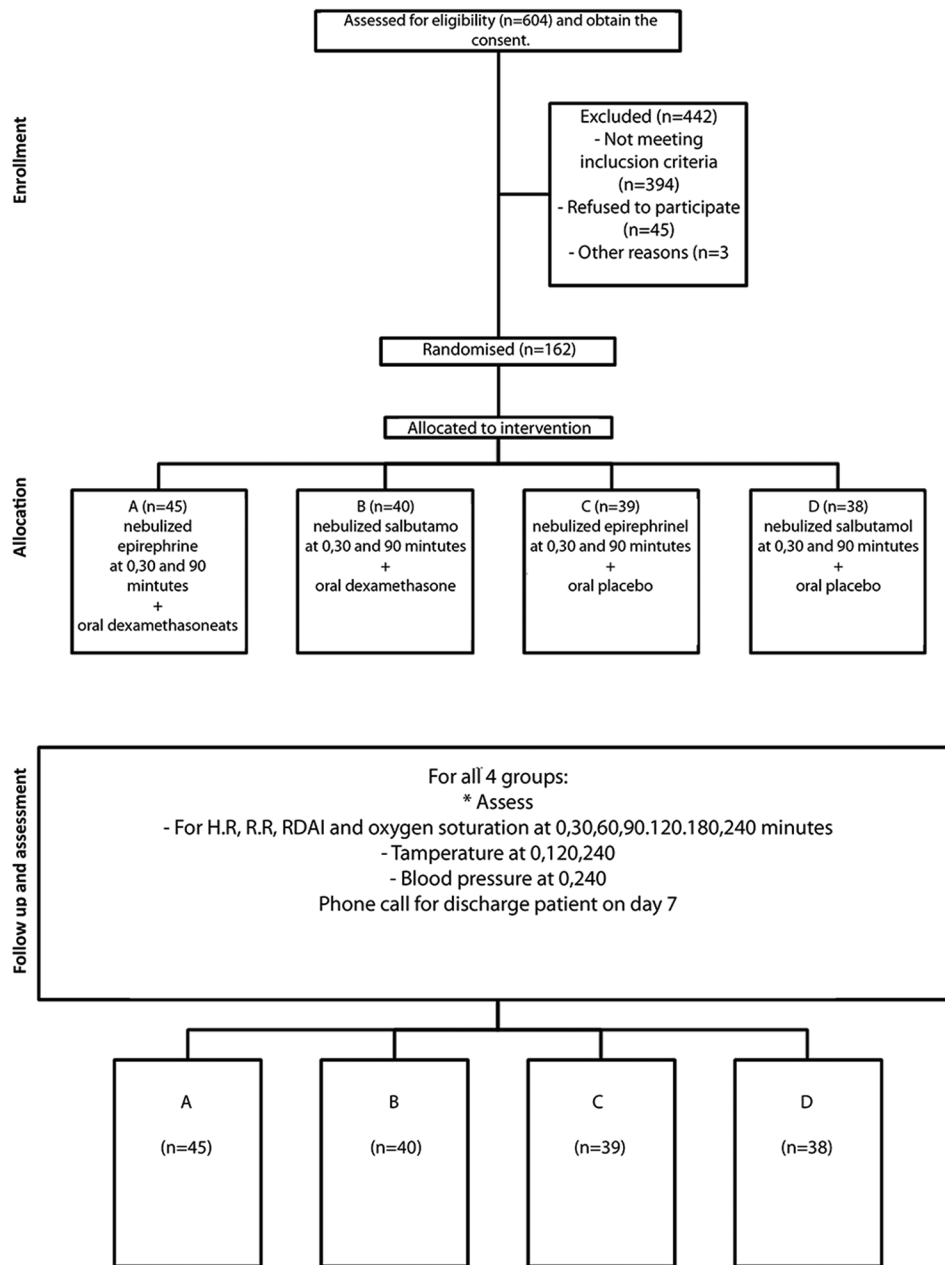
Figure 1: Flow diagram

12 of 39 infants in group C (30.7%), and 11 of 38 infants in group D (28.9%). The patients who had received dexa + epinephrine had similar admission rates compared to those who had received placebo [placebo + epinephrine and placebo + salbutamol] Odds ratio (OR 1.060, 95% confidence interval (CI 0.477–2.355) *P* value 0.642). Similarly, patients on dexa + salbutamol were not statistically and significantly different with regard to the likelihood of hospitalization compared to those on placebo [placebo + epinephrine and placebo + salbutamol] (OR 0.783, 95% CI (0.329-1.861) *P* value 0.5116). Within four hours of enrollment, and by day 7, there was no statistically significant difference in the likelihood of hospitalization between the different treatment groups [Table 2].

Changes in clinical parameters

Improvements in clinical parameters were observed by the end of the observation period (4 hours) in all treatment groups. However, across all treatment groups there was no statistically significant difference in RDAI score, RR, or O_2 Sat between the mean baseline and the mean end of observation, with *P* values of 0.8213, 0.3028, and 0.8312, respectively. A statistically significant difference was observed in HR between the mean baseline observation and the mean end of observation across all treatment groups, with a *P* value of 0.0414 [Table 3].

Table 1: Baseline demographics and clinical characteristics

Variables	Treatment groups				P value
	Dexa+ Epin (*n*=45)	Dexa+ Salb (*n*=40)	Placebo+ Epin (*n*=39)	Placebo+ Salb (*n*=38)	
Age (mean±(SD))	4.74±2.84	4.55±2.21	4.23±2.46	4.85±2.35	0.5839
Gender (N (%))					0.5093
Male	28 (62.22)	21 (52.50)	20 (51.28)	17 (45.95)	
Female	17 (37.78)	19 (47.50)	19 (48.72)	20 (54.05)	
Family history of asthma (N (%))					0.3430
Yes	18 (40.00)	14 (35.90)	10 (25.64)	17 (44.74)	
No	27 (60.00)	25 (64.10)	29 (74.36)	21 (55.26)	
Smoker at home (N (%))					0.7575
Yes	15 (33.33)	12 (30.00)	15 (38.46)	15 (40.54)	
No	30 (66.67)	28 (70.00)	24 (61.54)	22 (59.46)	
Number of people living in the same room (mean±(SD))	3.21±1.56	3.2±1.55	3.00±1.22	2.70±0.99	0.4365
Duration of illness (mean±(SD))	3.93±3.47	3.60±1.88	3.64±2.01	3.58±1.93	0.9783
Nasopharyngeal aspiration					0.9310
Not taken	35 (77.78)	32 (80.00)	28 (71.79)	29 (76.32)	
Negative	7 (15.56)	5 (12.50)	9 (23.08)	6 (15.79)	
RSV	3 (6.67)	3 (7.50)	2 (5.13)	3 (7.89)	
Study terminated by: (N (%))					0.33
Physician	3 (50.00)	2 (66.67)	2 (40.00)	0 (0.00)	
Family	3 (50.00)	1 (33.33)	3 (60.00)	3 (100)	
At 4 hr					0.3597
Admission	11 (24.44)	6 (15.00)	4 (10.26)	6 (15.79)	
Discharge	34 (75.56)	34 (85.00)	35 (89.74)	32 (84.21)	
At 3 Day					0.8252
Admission	14 (31.11)	9 (22.50)	10 (25.64)	11 (28.95)	
Discharge	31 (68.89)	31 (77.50)	29 (74.36)	27 (71.05)	
At 7 Day					0.9260
Admission	14 (31.11)	10 (25.00)	12 (30.77)	11 (28.95)	
Discharge	31 (68.89)	30 (75.00)	27 (69.23)	27 (71.05)	

SD: Standard deviation, RSV: Respiratory syncytial virus

Table 2: Dexamethasone effect modification analysis (within 4 hours of enrollment and by day 7)

	Within 4 hours of enrollment			By day 7		
	OR	P value	95% CI	OR	P value	95% CI
Dexa vs. Placebo	1.67	0.234	(0.71-3.92)	0.92	0.818	(0.46-1.82)
Placebo+Epin vs. Placebo+Salb	0.61	0.473	(0.15-2.35)	1.09	0.861	(0.41-2.89)
Dexa+Epin vs. Placebo+Epin	2.83	0.099	(0.82-9.76)	1.01	0.973	(0.40-2.57)
Dexa+Salb vs. Placebo+Salb	0.94	0.923	(0.27-3.22)	0.81	0.694	(0.30-2.22)

OR: Odds ratio, CI: Confidence interval

Moreover, a statistically significant interaction effect was identified with regard to changes in HR overtime when the dexa + epinephrine group was compared to the other groups, with a *P* value of 0.0047. Treatment with Dexa + epinephrine caused changes in HR over time from 0-240 minutes. However, no changes over time were observed for RR, O_2 Sat, or RDAI score following treatment with Dexa + epinephrine, with *P* values of 0.1522, 0.15428, and 0.809, respectively [Figure 2].

DISCUSSION

This randomized, double-blind, controlled study of the effect of dexamethasone given at the time of presentation to the ED and for two days afterwards on infants below 12 months of age with mild to moderate bronchiolitis identified no significant reduction in the primary outcome of hospitalization. The lack of effect on admission rate was observable after four hours and persisted for follow up at 3 days and 7 days. Furthermore, treatment had no positive effect on any of the secondary outcomes studied: RDAI score, HR, respiratory rate, and oxygen saturation. To the contrary, placebo was favored over dexamethasone in the epinephrine group after four hours, but this difference did not reach significance. Because of the concern that variations in the treatment of bronchiolitis might impact the outcome of the study, the use of B2 agonists and epinephrine was controlled in the first 90 minutes between the study arms. Similarly, in the subgroup analysis, dexamethasone had no positive effect when either nebulized salbutamol or epinephrine was used in the initial management. After the 90-minute mark, physicians were permitted to manage infants according to their clinical judgment. The use of and need for various nebulization therapies was monitored, and a trend towards a decreased need for nebulization therapy was observed in the dexamethasone group compared to placebo when combined with epinephrine (4.4% versus 7.6%) and when combined with salbutamol (10% versus 23.6%); however, this trend did not reach significance. To overcome the possible impact of atopy, all infants older than 12 months or who had any history of prior wheezing or previous use of inhalers/nebulizers were excluded from the study.

Many studies have examined the use of dexamethasone in bronchiolitis; however, despite a review of the evidence by the 2006 American Academy of Pediatrics (AAP) subcommittee on the diagnosis and management of bronchiolitis that recommended that corticosteroids shall not be used in the management of bronchiolitis, controversy remains.[1] Our study aimed to add to the body of evidence and to control the two most commonly used therapies for bronchiolitis. Controversy over the use of corticosteroids in bronchiolitis persists as a result of conflicting reports on the effect of corticosteroids on outcome, particularly with regard to hospital admissions and severity scores.[2,3] The results of our study are consistent with those that have failed to find a positive effect.[2,3,7,16,17] A large multi-center placebo controlled study found no reduction in hospital admission or clinical status upon administration of

Table 3: Change in clinical parameters from baseline to the end of the observation period (240 minutes)					
Variables (mean (SD))	Treatment groups				*P* value
	Dexa+Epinephrine	Dexa+Salbutamol	Placebo+Epinephrine	Placebo+Salbutamol	
RDAI score					
0 min	7.69 (1.36)	8.6 (1.66)	8.18 (2.05)	8 (1.58)	0.8312
240 min	4.41 (1.73)	5.14 (2.03)	4.79 (1.65)	5.03 (2.26)	
Respiratory rate					
0 min	50.6 (8.24)	53.95 (11.03)	51.49 (9.68)	48.76 (8.57)	0.3028
240 min	44.6 (8.48)	49.11 (8.94)	48.03 (9.06)	46.69 (6.63)	
Heart rate					
0 min	150.47 (19.55)	155.83 (19.82)	149.49 (22.89)	153.39 (19.74)	0.0414
240 min	146.7 (20.76)	163 (16.14)	152.09 (16.81)	165.4 (21.7)	
Oxygen saturation					
0 min	96.64 (2.64)	96.18 (2.84)	96.36 (2.99)	96.66 (2.72)	0.8312
240 min	96.83 (2.46)	97.06 (2.39)	96.88 (2.6)	96.77 (2.82)	

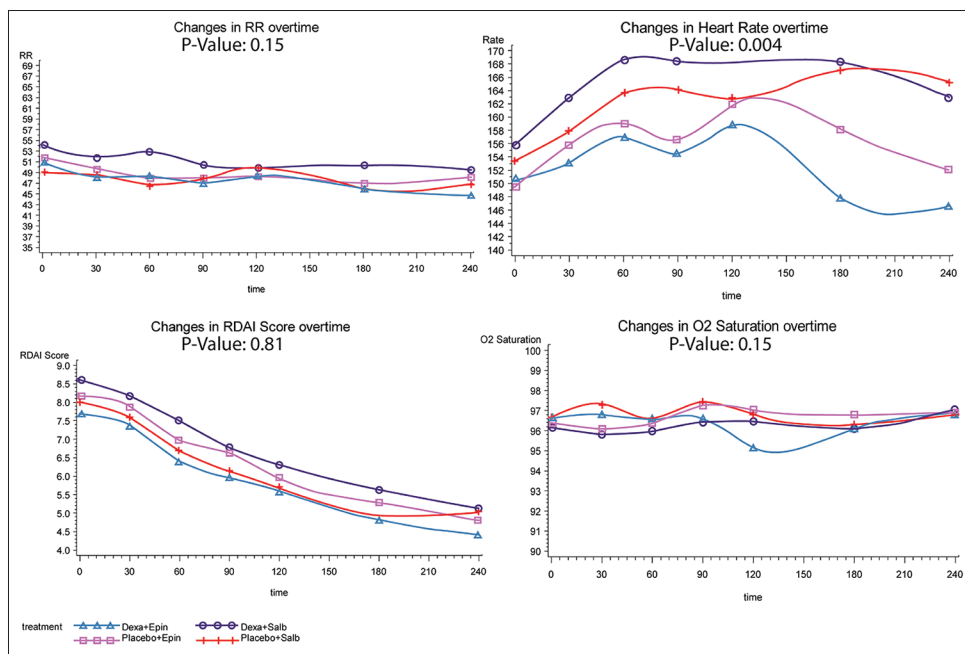SD: Standard deviation, RDAI: Respiratory distress assessment instrument

Figure 2: Changes in respiratory rate, HR, RDAI score and O$_2$ saturation over time

a single dose of dexamethasone, independent of a history of atopy. Although the authors of that study did not control for bronchodilator use, it was found to be utilized equally in both groups, and nebulized epinephrine was not reported to be a part of their therapy protocol. A 2003 Agency for Healthcare Research and Quality (AHRQ) report that reviewed several placebo controlled trials of corticosteroid use, including both oral and parenteral administration, identified only one study reporting a positive association.[15,18] In a meta-analysis by Garrison *et al.*, that included six controlled clinical trials of systemic corticosteroid use, a small but significant positive effect was identified; however, this effect was lost upon secondary analysis excluding those patients with a history of asthma.[19] In 2010, the Cochrane Collaboration performed a comprehensive review of 17 randomized, controlled trials comparing short-term systemic or inhaled glucocorticoids versus placebo or an alternate intervention in children <24 months of age with acute bronchiolitis. That review found that corticosteroids did not significantly reduce outpatient admissions by day 1 or day 7 when compared to placebo.[20] A bronchiolitis study by Schuh *et al.*,[21] identified a significant reduction in hospitalization and clinical scores within four hours of therapy when dexamethasone was compared to placebo in children up to two years of age who experienced symptoms for a brief duration. However, there was a high rate of family history of atopy favoring the dexamethasone group.[15] In a placebo controlled follow-up study on the efficacy of dexamethasone given at discharge from the ED to children up to two years of age with bronchiolitis, Shuh *et al.*, found no positive effect on admission rates or the need for bronchodilator or corticosteroid therapy after six days. The authors therefore concluded that there is no benefit of corticosteroids beyond the first dose.[21] Plint *et al.*,[8] found, in a randomized placebo controlled trial, that dexamethasone

combined with nebulized epinephrine led to a reduction in hospitalizations due to bronchiolitis within seven days of enrollment compared to nebulized epinephrine alone, dexamethasone alone or placebo.[8] It has been proposed that dexamethasone and epinephrine have a synergistic effect. The mechanism of action remains unclear, although the effect appears to be different from that observed for children with asthma. The positive effects reported in a number of studies are lost or diminished when children with asthma are excluded.[19,22] An alternative hypothesis suggested that dexamethasone has an anti-inflammatory effect. However, Somers *et al.*, found no effect for systemic steroids on the concentration of inflammatory cytokines in tracheal aspirates.[23] These conflicting outcomes regarding the efficacy of dexamethasone for the treatment of infants with bronchiolitis have led to confusion and variations in treatment regimens and protocols. These differences may be due to differences between the populations studied, differences in the timing of intervention, and differences in patient population such as age, history of bronchiolitis, or history of asthma.[21] A study by Plint *et al.*, in which the data were adjusted for multiple comparisons found no significant associations. The authors reported a reduction in admission by 9 percentage points: From 26% in the placebo group to 17% in the epinephrine-dexamethasone group. As such, 11 infants would have needed to be treated to prevent one hospital admission.[8]

Our study was limited by its small sample size and access to a single academic center. However, we did observe a trend towards positive effects. Because physicians were allowed to use therapies at their judgment after the 90 min mark, we were able to observe a trend toward a decreased need for nebulization therapy in the dexamethasone group compared to the placebo group for epinephrine (4.4% versus 7.6%) and for salbutamol (10% versus 23.6%). It is possible that additional power in the study may have identified a significant difference. In addition, we were unable to study the impact of positive respiratory syncytial virus (RSV) status on outcome, as the majority of our patients did not provide nasopharyngeal aspirates for viral studies.

In conclusion, our study adds to the body of data demonstrating that corticosteroids have no role in the management of bronchiolitis. This is particularly clear for younger infants who are first time wheezers with no risk of atopy. It is possible that a subpopulation of older children with a history of atopy who are presenting with a first episode of wheezing and who fit the clinical picture of bronchiolitis may benefit from corticosteroids; however the data presented here emphasize the overall need to minimize the use of these agents in this disorder.

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