Nebulized Budesonide Is as Effective as Nebulized Adrenaline in Moderately Severe Croup

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ABSTRACT. Objective. Nebulized budesonide and nebulized adrenaline have been shown to be effective in the treatment of moderately severe croup. However, there has been no direct comparison of these therapies. We undertook a multicenter, randomized, double-blind, parallel group study in 66 hospitalized children with viral or spasmodic croup.

Methods. Children 0.5 to 6 years of age were assessed using a validated croup symptom score (stridor, 0 through 4; cough, 0 through 3; retractions, 0 through 3; dyspnea, 0 through 3; and color, 0 through 4) at 0.5, 1, 1.5, 2, 12, and 24 hours after nebulization. Patients received either budesonide (2 mg/4 mL) or L-adrenaline (4 mg/4 mL) via nebulization. The primary outcome measure was change in the total croup symptom score.

Results. Thirty-five children received budesonide and 31 received adrenaline. There was no significant difference in baseline features, including croup score (mean [95% confidence interval]: budesonide, 7.1 [6.7–7.5]; adrenaline, 7.7 [7.3–8.1]). All patients had significant improvement from baseline, and there was no significant difference between the two treatments, as measured by change in croup scores, change in oxygen saturation, duration of hospitalization, number of subsequent treatments with systemic steroids or adrenaline, and adverse events. No child required intubation.

Conclusion. This study does not show any difference in efficacy and safety between nebulized budesonide and nebulized adrenaline in the treatment of acute upper airway obstruction in patients with moderately severe croup. Pediatrics 1996;97:722–725; adrenaline, budesonide, croup.

ABBREVIATIONS. APT, all patients treated; PP, per protocol.

The majority of children with croup have mild upper airway obstruction and are treated at home without pharmacologic therapy.1-4 Hospitalized children with croup have been treated with close observation, nebulized adrenaline, and/or systemic steroids. Of those admitted to hospitals, only a small number (1% to 5%) require artificial airways. 1,5-7 Considerable debate has ensued regarding the efficacy of these treatments because of the variable and generally self-limiting course of the illness.6,9-11 Recently, nebulized budesonide has been shown to be superior to nebulized saline (placebo) in children presenting to hospitals with mild to moderate4 and moderate to severe12 croup. In both studies, the superiority of budesonide over the placebo was demonstrated within 2 to 4 hours.12,14 However, it is not known whether budesonide is as efficacious as nebulized L-adrenaline in children with moderately severe croup.

Therefore, we performed a randomized, double-blind, parallel group study of 24 hours’ duration in children hospitalized with viral or spasmodic croup to compare nebulized adrenaline with nebulized budesonide, using a validated croup symptom score.12

METHODS

Selection of Patients

Sixty-seven patients were recruited, and 66 patients received treatment with either nebulized budesonide (2 mg/4 mL) or nebulized L-adrenaline (4 mg/4 mL). The study was conducted in the emergency departments of three pediatric tertiary referral hospitals. Patients were eligible for this study if decisions to admit them to the hospitals because of croup severity had been made by the medical staff of the emergency departments. The medical staff in the emergency departments were aware of the study, although they did not use the total croup symptom score as a criterion for deciding on hospital admission.

Outcome Measures

Croup was defined as a clinical syndrome consisting of inspiratory stridor, barking cough, hoarseness, and signs of respiratory distress. Criteria for study entry included children 6 months to 6 years of age with a diagnosis of acute (viral) or spasmodic croup. A minimum score of 6 in a validated croup symptom scoring system (minimum, 0; maximum, 17; Table 1) was required.17 Exclusion criteria were significant past or present systemic disease, preexisting known airway abnormalities, confirmed hypersensitivity to budesonide or L-adrenaline, suspected epiglottitis, foreign body aspiration, bronchiolitis or asthma, the need for immediate intubation or transfer to intensive care, and treatment with glucocorticoids in the 4 weeks before enrollment. The study was approved by the ethics review committees of the three hospitals.

Study Design

Before randomization, the patient’s history was recorded, written informed consent was obtained from the child’s parent, and the croup symptom score was assessed by one of five clinical investigators. The same investigator again assessed the croup symptom score immediately before the patient received the study medication and then at 30, 60, 90, and 120 minutes after nebuli-
TABLE 1. Croup Symptom Scores*

<table>
<thead>
<tr>
<th>Symptoms and Signs</th>
<th>Grading</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inspiratory stridor</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Audible with stethoscope</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>When agitated</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>At rest</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>4</td>
</tr>
<tr>
<td>Cough</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>When agitated</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Croup-like at rest</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Severe croup-like at rest</td>
<td>3</td>
</tr>
<tr>
<td>Retractions</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>3</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Marked (obvious)</td>
<td>3</td>
</tr>
<tr>
<td>Color</td>
<td>Normal</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Cyanosed in air</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Cyanosis with oxygen</td>
<td>4</td>
</tr>
</tbody>
</table>

* Croup scoring system is as described by Husby et al. 
† Performed with patients seated when possible.

zation. Croup scores were also determined by the same investigator at 12 and 24 hours after nebulization. The pulse rate, respiratory rate, and oximetry were measured at these time points. Adverse events were recorded throughout the study. Additional medication was allowed 2 hours after administration of the study medication. The duration of the hospital stay and any doses of additional steroid or adrenaline therapy were recorded.

Patients were allocated to treatment according to a randomization list produced before commencement of the study. Patients were randomized in blocks of four. Randomization was separate for each of the treatment centers. To ensure blinding, the study medication was administered by nursing staff and the investigator was not present when the medication was placed in the opaque nebulizer bowl. Drug administration was via an Acorn nebulizer system (Medic-Aid, Ltd, West Sussex, UK) with oxygen at a flow rate of 6 L/min. Nebulization was continued for 5 minutes. A face mask was used, and the child’s face was washed after the treatment. Patients were able to be withdrawn from the study at any time by their parents or the investigators. Reasons for discontinuation before 24 hours were documented.

Estimate of Sample Size

Efficacy measures were calculated as means with SD and 95% confidence intervals. The level of significance was set at \( P \leq 0.05 \). The sample size was calculated to detect a difference in total croup symptom score between the two groups of two (minimum clinically significant difference) with an SD of 2.85 and a power of 80%. Under these conditions, a total of 66 patients (33 in each group) were required to complete the study.

Statistical Analysis

All patients who received the study medications were analyzed according to both the all patients treated (APT) principle and the per protocol (PP) analysis. A descriptive analysis of adverse event data was performed according to the intention to treat principle. The primary efficacy variable (total croup symptom score) was analyzed as the change from baseline using analysis of covariance with center and treatment as factors. Neither intraobserver nor interobserver variation between the five clinical investigators was calculated. The total croup symptom score at 0 hours was taken as the baseline measurement (rather than the −0.5-hour score) and was a covariate in the analysis. The “last observation carried forward” or “last value extended” principle was applied to the APT analysis of the total croup symptom score. This was applicable for patients who were discharged or withdrawn before the 24-hour assessment.

RESULTS

Sixty-seven patients were enrolled, and all were randomized to treatment. Sixty-six patients received medication (budesonide, 35 patients; adrenaline, 31 patients) and were included in the APT analysis. There was no statistically significant difference between the APT and PP analyses; therefore, the results are presented for the APT analysis only. One patient was withdrawn after randomization but before delivery of medication because of maternal fears that the nebulizer would upset her child. Sixty-six patients were included in the APT and PP analyses at baseline. In the PP analysis, 3 (1 adrenaline- and 2 budesonide-treated) patients were removed before 30 minutes, because the nebulizer mask was not used continuously for the 5-minute nebulization period. These 63 patients remained until after 2 hours but less than 24 hours, when a further 13 had discontinued. Consequently, 50 patients remained in the PP analysis, as opposed to 66 in the APT analysis. Thus, 13 patients who received study medications appropriately did not remain for the entire 24-hour period (budesonide, 8 patients; adrenaline, 5 patients). Of these, 10 were well and discharged from hospitals (budesonide, 6 patients; adrenaline, 4 patients). One patient who received budesonide remained in the hospital for 64 hours and received an additional dose of oral steroids, although her scores were not recorded at 12 and 24 hours. One patient who received budesonide remained in the hospital for 42 hours without additional treatment, although no 24-hour score was recorded. The remaining patient received adrenaline and was discharged before 24 hours at parental insistence. Consequently, 53 patients remained for the entire the 24-hour study period. No patient in the study was readmitted to our hospitals. A survey of other hospitals in Sydney for readmissions of patients from this study was not undertaken. Because the SD in the total croup symptom scores was less than the 2.85 anticipated (2.2), the resulting power of the study increased to 95% for the same sample size.

The demographic details were similar for the two treatment groups and are summarized in Table 2. Medical histories did not differ between groups.

The mean total croup symptom score was significantly reduced by both treatments. No statistically significant differences between treatments were demonstrated at any time point (Figure 1). Analysis of covariance demonstrated that the mean baseline (0-hour) total croup symptom score was a significant predictor of the mean total croup symptom scores at 0.5, 12, and 24 hours. Interobserver variation among the five clinical investigators was not calculated. There was no difference between the budesonide and adrenaline groups for any of the secondary efficacy

TABLE 2. Demographic Profile*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Budesonide (n = 35)</th>
<th>Adrenaline (n = 31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, yrs</td>
<td>20.9 (12.7)</td>
<td>24.9 (12.5)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>12.7 (3.2)</td>
<td>13.8 (3.4)</td>
</tr>
<tr>
<td>Duration of croup attack, h</td>
<td>31 (21)</td>
<td>26 (21)</td>
</tr>
<tr>
<td>Mean total croup symptom score at entry</td>
<td>7.1 (1.2)</td>
<td>7.7 (1.1)</td>
</tr>
</tbody>
</table>

* Values are mean (SD).
variables: heart rate, respiratory rate, and oxygen saturation at any time point. No patients required intubation. The number of patients receiving additional treatment with systemic steroids (14 vs 15) and the number of patients receiving subsequent adrenaline treatments (1 vs 3) were similar for the budesonide and adrenaline groups, respectively. The need for additional treatment of croup symptoms in any patient was determined by the clinical investigators on an individual basis. Baseline oxygen saturation was a significant predictor of oxygen saturation at 0.5 hours after treatment. Patients treated with nebulized budesonide were hospitalized for a mean of 5.8 (95% confidence interval, -11.2-22.8; \( P = .497 \)) hours longer than those patients who received nebulized adrenaline.

Six patients in each treatment group reported adverse events. These included vomiting, an erythematous rash, diarrhea, wakefulness, excessively active behavior, wheezing, and a nosebleed. These were minor and did not result in withdrawal from the study or require specific treatment.

**DISCUSSION**

In this study, we found no difference in efficacy and safety between nebulized budesonide and nebulized adrenaline in the treatment of children with moderately severe croup. Nebulized budesonide may have some effect within 30 minutes of nebulization, and this effect increases for up to 2 hours, a time course similar to that of nebulized adrenaline. A more rapid onset of action of adrenaline is suggested by the trends of the mean change in total croup symptom score from a higher baseline at 30 minutes [Figure; \( P = .0504 \)] and higher mean oxygen saturation at 30 minutes [Figure; \( P = .0503 \)], which favor adrenaline. These trends were not apparent subsequently. The majority of clinical improvement, as measured by a fall in the mean total croup symptom score, had occurred by 2 hours, before further treatment of croup symptoms with systemic corticosteroids (budesonide group, 40%; adrenaline group, 48%) or nebulized adrenaline (budesonide group, 3%; adrenaline group, 10%). It is possible that our therapies may have modified the course of the croup illness, although without a placebo treatment group, we cannot be certain of this. We did not think it ethically justifiable in patients with moderately severe croup to include a placebo treatment arm, because previous studies have clearly illustrated the efficacy of nebulized adrenaline, \(^{1,14,15}\) nebulized budesonide, \(^{4,12}\) and systemic steroids \(^{13,8}\) over a placebo in the treatment of croup of varying severity.

Because only 53 of our 66 patients who received treatment completed the 24-hour study, we used the last value extended principle in our analyses. \(^{13}\) This carries the last recorded croup score for those who discontinue through to the 24-hour score. We thought this was appropriate, inasmuch as 10 of the 13 patients who withdrew were discharged by attending medical staff because they were judged to have improved, suggesting a further fall in the croup score. The other patients were hospitalized for 42 hours (shorter than the mean hospital stay) and 64 hours without later scores being recorded. One patient was withdrawn because of parenteral insistence. Thus, patients with incomplete 24-hour data had evidence suggesting milder clinical courses as judged by the shorter-than-average duration of hospitalization (12 of 13) and the lack of need for additional treatment (9 of 13).

In clinical practice, our demonstration of sustained improvement after both treatments is important. Previous reports have suggested that the response to nebulized adrenaline is rapid but short lived, \(^{1,11,14,15}\) A meta-analysis \(^{10}\) of 10 randomized trials of systemic steroids in 1286 hospitalized patients with croup was able to demonstrate a beneficial effect over a placebo at 12 and 24 hours after treatment. Two recent studies have shown systemic steroids to be beneficial in spasmodic \(^{14}\) and viral \(^{17}\) croup. We agree that the distinction between viral and spasmodic croup may be artificial at presentation, \(^1\) and irrelevant in those with upper airway obstruction needing acute treatment. \(^{12}\) With equal efficacy of treatments in moderately severe croup, the choice between therapies may be influenced by cost, accessibility, and safety issues. Current wholesale costs do not differ greatly: budesonide (2 mg), Australian $2.20, United States $3.00; adrenaline (4 mg), Australian $1.88, United States $2.50. Both medications are readily available and safe when used as outlined. With adrenaline, there remain concerns about dosage confusion (particularly undertreatment with the use of a 1:10 000 concentration) and the theoretical risk of rebound or progression of proximal airway obstruction after nebulized adrenaline in severe croup. No episodes of rebound occurred in our 31 patients who received nebulized adrenaline. However, because nebulized budesonide and nebulized adrenaline are safe and inexpensive with different mechanisms of action, \(^{4,11,12}\) we speculate that, if given sequentially, they may have an additive effect, maximizing the acute response with greater sustained relief of upper airway obstruction. Further studies are required to clarify the issue of combining budesonide with adrenaline as initial therapy in moderately severe croup.

We conclude that nebulized budesonide at a dose of 2 mg should be considered as an alternative to 4 mg of nebulized adrenaline as first-line therapy in...
children presenting at hospitals with mild to moderately severe croup.

ACKNOWLEDGMENTS
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REFERENCES

GAG CLAUSES IN DOCTOR CONTRACTS

U.S. Healthcare, Inc. said it removed controversial provisions from its physician contracts that have prompted doctors to complain that they are hampered in treating patients.

Called “gag clauses” by critics, they are common in contracts of many managed-care companies. Doctors charge that such clauses prevent them from giving patients complete information about treatment options, for instance, or that they are forbidden from telling patients that health maintenance organization (HMO) financial arrangements may penalize doctors for making referrals to specialists.

HMOs counter that some doctors have waged campaigns against managed care with their patients, and that such clauses are intended to prevent such campaigns and any anxiety among patients about their care that may result.

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