Nebulized Budesonide and Oral Dexamethasone for Treatment of Croup

A Randomized Controlled Trial

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Context.—The effectiveness of glucocorticoids for patients with croup is well established but it remains uncertain which glucocorticoid regimen is most effective.

Objective.—To determine the effectiveness of 3 glucocorticoid regimens in patients with croup.

Design.—Randomized controlled trial with parallel design.

Setting.—Emergency departments of 2 Canadian pediatric tertiary care hospitals.

Participants.—Children with a clinical syndrome consistent with croup, aged 3 months to 5 years, with a croup score of 2 or greater following at least 15 minutes of mist therapy.

Interventions.—Oral dexamethasone, 0.6 mg/kg, and nebulized placebo; oral placebo and nebulized budesonide, 2 mg; or oral dexamethasone, 0.6 mg/kg, and nebulized budesonide, 2 mg.

Main Outcome Measures.—Westley croup score (primary outcome), hospital admission rates, time spent in the emergency department, return visits to the emergency department, or ongoing symptoms at 1 week.

Results.—The mean change in the croup score from baseline to the final study assessment was −2.3 (95% confidence interval [CI], −2.6 to −2.0) in the budesonide group (n = 65), −2.4 (95% CI, −2.6 to −2.2) in the dexamethasone group (n = 69), and −2.4 (95% CI, −2.7 to −2.1) in the budesonide and dexamethasone group (n = 64, *P* = .70).

Conclusions.—Based on the similar outcomes in the 3 groups, oral dexamethasone is the preferred intervention because of its ease of administration, lower cost, and more widespread availability.

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ALTHOUGH CROUP is usually a self-limited illness, it causes a significant health care burden through frequent emergency department visits and hospitalizations, as well as physician office visits.[1] By the early 1990s, evidence clearly supported the use of glucocorticoids for children with croup who required hospitalization.[2-5] This development created interest in examining the effectiveness of glucocorticoid treatment in outpatients with croup, in the hope that intervention at an earlier phase of their illness might lead to avoidance of hospitalization altogether.

Evidence from randomized controlled trials supports this notion, as the use of nebulized budesonide was shown to shorten emergency department visits, decrease the number of hospitalizations, and result in a faster resolution of croup symptoms.[6-10] One trial suggested that the benefit of budesonide was equivalent to that of oral dexamethasone and that either one was superior to placebo.[9] However, another trial seemed to suggest that a combination of budesonide and dexamethasone was superior to dexamethasone alone, although the benefit was small and limited to a change in the croup score.[6] Therefore, there is evidence to support the use of budesonide or dexamethasone over placebo, but no clear superiority of either glucocorticoid or a combination of both. Because dexamethasone is less expensive than budesonide, easier to administer, and more widely available, it is important to ascertain whether budesonide has any significant clinical advantages over dexamethasone, or whether a combination of the 2 would have an even greater clinical benefit.[11,12] In the context of this uncertainty, we designed a randomized, controlled, comparative trial to examine whether nebulized budesonide alone, oral dexamethasone alone, or a combination of both would result in the best clinical outcome in outpatients with mild-to-moderate croup.

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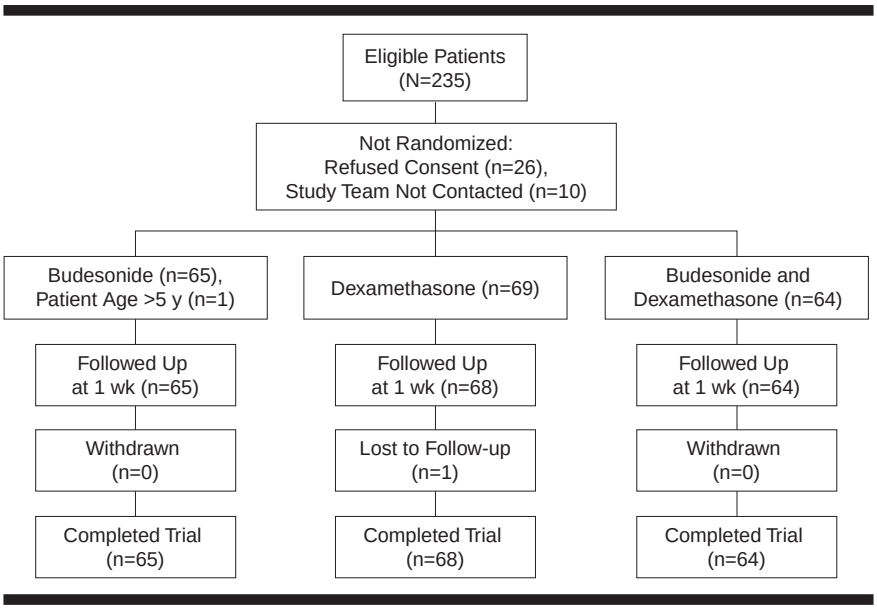
METHODS

Protocol

Children aged 3 months to 5 years presenting to the emergency departments of Children's Hospital of Eastern Ontario, Ottawa, from October 1995 to April 1996 and from October 1996 to January 1997 or the Winnipeg Children's Hospital, Winnipeg, Manitoba, from October 1996 to January 1997 were eligible if they presented with a croup syndrome consisting of hoarseness, inspiratory stridor, and barking cough, and had a croup score of 2 or greater following at least 15 minutes of mist therapy. In addition, parents had to be available for telephone follow-up 1 week after study enrollment. Patients were excluded if they had epiglottitis, chronic respiratory disease (excluding asthma), severe croup (defined as a croup score of 8 or greater), racemic epinephrine treatment on arrival in the emergency department, glucocorticoids within the preceding 2 weeks, a history of tuberculosis in either the patient or a member of the patient's household, chickenpox or exposure to chickenpox within the previous 21 days, or a known immunodeficiency.



Participant flowchart and follow-up diagram.

During the study period, research assistants were on call 24 hours a day (excluding holidays) and were notified whenever the emergency department staff identified a potential patient. After the patient's parents gave written informed consent, the patient was randomly assigned to 1 of 3 interventions: (1) budesonide solution, 2 mg (4 mL), and the appropriate volume of dexamethasone placebo (clear syrup solution); (2) budesonide placebo, 4 mL (saline solution), and dexamethasone solution, 0.6 mg/kg (clear syrup solution and dexamethasone sodium phosphate intravenous solution); or (3) budesonide, 4 mL, and dexamethasone solution, 0.6 mg/kg (clear syrup solution and dexamethasone sodium phosphate intravenous solution).

The primary outcome measure was the 17-point ordinal croup score initially developed by Westley et al,[13] which previously has been shown by our study team to be a valid, responsive, and reliable outcome measure in clinical trials of patients with croup.[14] Secondary outcome measures included oxygen saturation, heart rate, and respiratory rate. These outcome measures were evaluated by the research assistant at baseline and hourly until the patient had received epinephrine, the croup score had returned to 1 or lower, the physician had discharged the patient because of clinical improvement, or 4 hours had elapsed, whichever occurred first. Other secondary measures included time spent in the emergency department, number of hospital admissions, and number of cointerventions. Research assistants attempted to contact all study participants 1 week after enrollment to inquire about continuing croup symptoms, visits to physicians' offices or emergency departments, and further interventions.

Our sample size calculation was based on the desire to observe a difference among the 3 intervention groups of a croup score of 1 (the minimum clinically important difference).[14] This difference of 1 is also smaller than the minimum clinically important difference of 2 that we have used in sample size calculations for our previous trials.[6,8] It is our experience that clinicians would not be interested in detecting a smaller difference among treatment groups. Assuming a type I error (2-sided) of .05 and a type II error of .20 (ie, statistical power of 80%), the calculations, based on the Fleiss λ, resulted in a sample size of 62 participants per group.[15,16]

Our primary analysis was based on the intention-to-treat principle. All data were reported with 2-sided probability values. For normally distributed data, means with 95% confidence intervals (CIs) were used; for nonparametric data, the median and 25th to 75th percentile were used. The primary outcome of the croup score was analyzed using change from baseline (ie, final baseline assessment), hence, negative changes indicate improvement. An analysis of variance was used to relate the change from baseline to treatment group, treatment center, and supplemental glucocorticoid use. Least squares differences were calculated for treatment effect, adjusting for treatment center and supplemental glucocorticoid use. By our convention, a negative treatment difference of dexamethasone vs budesonide indicates that improvement in the croup score is better with dexamethasone than with budesonide.

Treatment differences were tested using the Kruskal-Wallis test for continuous variables where the normal assumption was untenable. Association between treatment and categorical data was tested using the Fisher exact test or the permutation test. One interim analysis was performed after the first croup season by a data monitoring committee external to the study team, with the stopping rules based on the Haybittle-Peto method,[17,18] which set the critical z score at 3.0. The committee's decision was to continue the trial at that time.

Assignment

A central pharmacy at the Children's Hospital of Eastern Ontario randomized individual patients to the 3 groups, using computer-generated random numbers in random blocks of 6 or 9 to help ensure equal distribution among the 3 groups during the different periods of the croup season. Randomization was stratified by study site and the list was kept in the central pharmacy until the end of the study to ensure allocation concealment. Because drugs were packaged identically and identified only by a sequential study number, the research assistant who administered the intervention remained unaware of the next group assignment.

Masking

Dexamethasone syrup and placebo dexamethasone syrup were identical in taste and appearance. Budesonide was slightly opaque, whereas its nebulized placebo was completely clear saline. All solutions were packaged in brown syringes and the research assistant instilled either solution directly into an opaque nebulizer reservoir. This technique has been successfully used to mask the allocation of patients in previous croup trials.[6,8]

After each patient had been enrolled and assessed, research assistants were asked to guess which intervention the patient had received. The research assistants identified the intervention correctly in 24 (35%) of 65 patients who received budesonide, 19 (28%) of 69 patients who received dexamethasone, and 21 (33%) of 64 patients who received both budesonide and dexamethasone (P = .30). Their responses were no greater than by chance alone, indicating that masking was successful. Parents were asked the same question and their responses also indicated no significant association with the actual intervention their child had received (P = .57).

RESULTS

Participant Flow and Follow-up

The Figure shows that 85% of eligible patients were randomized. The reasons for nonrandomization are listed. One pa-

tient was excluded after he was randomized because he was older than 5 years and was therefore ineligible and not included in the reported analysis (the results remained unchanged when he was included in the analysis). Follow-up at 1 week was excellent. Only 1 patient's parents (of 198 sets of parents) could not be contacted, because no one responded to numerous telephone messages.

Analysis

Table 1 indicates patient characteristics at baseline were comparable in the 3 groups. There was a male predominance in each of the groups, ranging from 62% to 77%. About 20% of the children in each group had experienced croup in the past, with about a third having a family history of asthma. The mean baseline croup score ranged from 3.5 to 3.8. The mean change from baseline for budesonide was –2.3 (95% CI, –2.6 to –2.0); for dexamethasone, –2.4 (95% CI, –2.6 to –2.2); and for budesonide and dexamethasone, –2.4 (95% CI, –2.7 to –2.1).

There were no differences between treatment groups ($P = .70$, $\chi^2 = 0.72$, $df = 2$), no treatment center effect ($P = .25$, $\chi^2 = 2.27$, $df = 2$), and use of supplemental glucocorticoids ($P = .21$, $\chi^2 = 1.57$, $df = 1$). The estimated treatment difference between dexamethasone vs budesonide was –0.12 (95% CI, –0.53 to 0.29) and for dexamethasone vs dexamethasone and budesonide was 0.02 (95% CI, –0.39 to 0.43). It is important to note that the 95% CIs for these comparisons were less than 1 in the croup score (the minimum clinically important difference). The estimated treatment difference between budesonide vs dexamethasone and budesonide was 0.14 (95% CI, –0.27 to 0.55).

The median time to discharge from the emergency department ranged from 127.5 minutes in the dexamethasone group to 155 minutes in the budesonide and dexamethasone group ($P = .65$) (Table 2). Only 3% of patients received epinephrine as a cointervention and this was evenly distributed among the 3 groups. Supplemental glucocorticoids were used in 14% of patients treated with budesonide and dexamethasone, 11% of patients treated with budesonide, and 4% of patients treated with dexamethasone ($P = .15$) (Table 2). During the initial emergency department visit only 1 patient was hospitalized. This patient was randomized to the dexamethasone group (Table 2).

Very few patients' parents reported croup symptoms persisting at the 1-week follow-up telephone call (range, 5%-8%; $P = .73$) (Table 3). About a third of patients in each group visited their physician after the initial study period. This was because of persisting croup symptoms in 60% of patients treated with budesonide, 38% of patients treated with budesonide and dexamethasone, and 27% of patients treated with dexamethasone ($P = .06$) (Table 3). Only 1 patient returned and was hospitalized after initial discharge from the emergency department. This patient was randomized to the dexamethasone group (Table 3).

All parents were asked about the presence of oral thrush and only 1 parent whose child was in the budesonide group reported this condition at the 1-week follow-up. Parents of 1 patient treated with dexamethasone reported hives, and parents of 1 patient treated with dexamethasone reported violent behavior. Parents of 1 patient who had received budesonide and dexamethasone reported their child to be more hyperactive than usual.

Table 1.—Patient Characteristics at Entry in Study

Characteristic	Budesonide	Dexamethasone	Budesonide and Dexamethasone
No. of patients	65	69	64
No. (%) of males	50 (77)	43 (62)	41 (64)
Age, y*	1.5 (1.0-2.2)	1.3 (0.8-2.1)	1.6 (1.0-2.5)
No. (%) with preceding upper respiratory tract infection	36 (54)	46 (67)	39 (61)
No. (%) with previous croup	13 (20)	11 (16)	15 (22)
No. (%) with family history of asthma	19 (29)	22 (32)	18 (28)
Croup score†	3.5 (3.2-3.7)	3.6 (3.3-3.8)	3.8 (3.5-4.0)
Heart rate, beats/min†	147 (142-153)	148 (144-153)	143 (139-148)
Respirations/min†	35 (33-37)	37 (35-39)	36 (34-37)
Oxygen saturation, %†	97 (96-97)	96 (94-98)	97 (96-98)
Temperature, °C†	37.6 (37.4-37.9)	38.8 (37.0-40.6)	37.7 (37.4-38.0)

*Data are given as median (25th-75th percentile).
†Data are given as mean (95% confidence interval).

Table 2.—Outcome Measures During Initial Emergency Department Visit

Variable	Budesonide	Dexamethasone	Budesonide and Dexamethasone	*P* Value
Croup score*	1.2 (0.9-1.5)	1.2 (1.0-1.4)	1.3 (1.0-1.6)	.89
Responders, No. (%)†	48/65 (74)	57/69 (83)	46/64 (72)	.31
Heart rate, beats/min*	131 (126-135)	131 (126-137)	131 (126-136)	.98
Respirations/min*	30 (29-32)	31 (29-33)	30 (28-31)	.58
Oxygen saturation, %*	98.2 (97.8-98.6)	98.1 (97.7-98.4)	98.0 (97.7-98.3)	.63
Time in emergency department, min‡	140 (95-255)	127.5 (91.5-201)	155 (87.5-210)	.65
Discharged home, No. (%)	52/65 (80)	55/69 (80)	49/64 (76)	.88
Hospitalization, No. (%)	0/65 (0)	1/69 (1)	0/64 (0)	1.00
Epinephrine, No. (%)	2/65 (3)	2/69 (3)	2/64 (3)	1.00
Supplemental glucocorticoids, No. (%)	7/65 (11)	3/69 (4)	9/64 (14)	.13

*Data are given as mean (95% confidence interval) at final study assessment.
†Responders are patients who had a 2-point improvement in their croup scores.
‡Data are given as median (25th-75th percentile).

Table 3.—Follow-up at 1 Week*

Variable	Budesonide	Dexamethasone	Budesonide and Dexamethasone	*P* Value
Croup symptoms	3/65 (5)	5/68 (7)	5/64 (8)	.77
Physician visits	25/65 (38)	22/68 (32)	29/64 (45)	.29
Physician visit because of croup	15/25 (60)	6/22 (27)	11/29 (38)	.07
Return to emergency department	5/65 (8)	3/68 (4)	4/64 (6)	.71
Hospitalization	0/65 (0)	1/68 (1)	0/64 (0)	1.00
Thrush	1/65 (2)	0/68 (0)	0/64 (0)	.65
Supplemental glucocorticoids	6/65 (9)	4/68 (6)	4/64 (6)	.78

*All data except *P* values are given as number (percentage).

COMMENT

The clinical outcome of mild-to-moderate croup patients is as good after treatment with oral dexamethasone as it is after nebulized budesonide alone or after a combination of budesonide and dexamethasone. All groups had a similar change in croup scores, length of stay in the emergency department, use of cointerventions, and persisting symptoms at the 1-week follow-up. We used guidelines proposed by Detsky and Sackett[19] that the minimum clinically important difference should be greater than the 95% CI around the measured treatment effect between the groups to safely conclude that a trial is negative. These results indicate with confidence that there is no clinically important dif-

ference in the croup score among the 3 glucocorticoid regimens.

With evidence for no significant differences between clinical outcomes of the different treatment groups, oral dexamethasone becomes the preferred intervention because it is less expensive (Can $0.50 per treatment) than budesonide (Can $6 per treatment). It is also easier to administer 1 dose of oral dexamethasone than to nebulize 1 dose of budesonide, which takes at least 10 minutes, during which a face mask must be held over the face of the child, who often resists. While oral dexamethasone is usually well tolerated, this study shows that in cases where children have difficulty tolerating dexamethasone, clinicians can be confident that nebulized budesonide is an adequate substitute.

The results of this trial are comparable to several recent trials involving patients with croup. In patients receiving a glucocorticoid, the rate of significant responders has ranged from 56% to 84%.[6,8] Geelhoed and Macdonald[9] showed that budesonide and dexamethasone had similar clinical outcomes and that either intervention was superior to placebo. While 1 trial did suggest that budesonide and dexamethasone were superior to dexamethasone alone, the magnitude of difference was small and convinced us that a larger, more definitive trial was needed to help resolve uncertainty.[6]

There is strong evidence that inpatients benefit from the administration of glucocorticoids,[2-5] but it is only recently that evidence has shown superior outcomes for outpatients with mild-to-moderate croup treated with a glucocorticoid as compared with placebo.[11,12] We have shown in an earlier study that patients who received budesonide spent significantly less time in the emergency department, had faster improvements in croup scores, and had significantly lower admission rates.[8] Geelhoed and Macdonald[9] showed that patients treated with either budesonide or dexamethasone spent significantly less time in the emergency department, required fewer epinephrine nebulizations, and had faster improvements in croup scores. Using intramuscular dexamethasone compared with placebo, Cruz and colleagues[7] demonstrated that patients treated with dexamethasone were significantly improved at follow-up compared with patients who received placebo. Evidence to support the use of glucocorticoids in patients with croup was available prior to our current trial, but the type of glucocorticoid best suited for this purpose required clarification. While recent work by Geelhoed and Macdonald[10] suggests that a lower dose of oral dexamethasone (0.15 mg/kg) may be equally effective, further evidence is required before any recommendation based on the lower dose can be made.

Based on the results of this trial, we recommend that mild-to-moderate croup patients presenting to the emergency department may receive oral dexamethasone or nebulized budesonide. The choice between oral dexamethasone or nebulized budesonide may be made based on availability of treatment, cost of the drugs, and ease of administration.

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