

ORIGINAL ARTICLE

A Randomized Trial of a Single Dose of Oral Dexamethasone for Mild Croup

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ABSTRACT

BACKGROUND

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The benefits of dexamethasone treatment for moderate-to-severe croup are well established. However, most children with croup have mild symptoms, and it is unknown whether they would derive the same degree of benefit from dexamethasone treatment as children with more severe disease.

METHODS

We conducted a double-blind trial at four pediatric emergency departments in which 720 children with mild croup were randomly assigned to receive one oral dose of either dexamethasone (0.6 mg per kilogram of body weight) or placebo. The children had mild croup, as defined by a score of ≤ 2 on the croup scoring system of Westley et al. The primary outcome was a return to a medical care provider for croup within seven days after treatment. The secondary outcome was the presence of ongoing symptoms of croup on days 1, 2, and 3 after treatment. Other outcomes included economic costs, hours of sleep lost by the child, and stress on the part of the parent in relation to the child's illness.

RESULTS

Baseline clinical characteristics were similar in the two groups. Return to medical care was significantly lower in the dexamethasone group (7.3 percent vs. 15.3 percent, $P < 0.001$). In the dexamethasone group, there was quicker resolution of croup symptoms ($P = 0.003$), less lost sleep ($P < 0.001$), and less stress on the part of the parent ($P < 0.001$).

CONCLUSIONS

For children with mild croup, dexamethasone is an effective treatment that results in consistent and small but important clinical and economic benefits. Although the long-term effects of this treatment are not known, our data support the use of dexamethasone in most, if not all, children with croup.

CROUP (ACUTE LARYNGOTRACHEOBRONCHITIS) is common, occurring yearly in 3 percent of children under six years of age.¹ Less than 5 percent of such children are hospitalized, and of these, 1 to 2 percent receive endotracheal intubation.² Corticosteroids are effective in moderate-to-severe croup, resulting in reductions in the frequency and duration of intubation^{3,4} and hospitalization⁵⁻⁷ and the frequency of administration of nebulized epinephrine,^{5,7} a treatment reserved primarily for severe respiratory distress.

At least 60 percent of children who present for emergency care have mild symptoms (defined as the presence of a barking cough, no audible stridor at rest, and mild or no indrawing of the chest wall)⁸ and are routinely discharged without observation and often without treatment.⁸ Of these children with mild croup, most have transient symptoms; 15 percent or less seek additional medical care.^{8,9}

Only two published trials have focused on corticosteroid treatment of mild croup.^{10,11} One did not use clinical criteria to define mild croup clearly,¹⁰ and the other included children with audible stridor at rest and indrawing of the chest wall,¹¹ symptoms that most health care professionals consider to represent more severe disease. The first study was small (100 patients) and assessed only one outcome: return to medical care for croup.¹⁰ Though the second study showed that corticosteroid treatment was beneficial,¹¹ the inclusion of a substantial proportion of patients with more severe croup leaves the applicability to children with milder symptoms uncertain.

Since the majority of children with croup have mild symptoms and a transient, uncomplicated course, we thought it essential to have clearer evidence of benefit before advocating corticosteroid treatment for this large subgroup of children. Therefore, we conducted a multicenter, randomized, double-blind, placebo-controlled clinical trial of corticosteroid treatment for mild croup, defined by strict clinical criteria. The objectives of the study were to determine whether dexamethasone treatment of mild croup would reduce the incidence of a return to a medical care provider for croup and the associated economic costs. Other outcomes examined included the time to resolution of croup symptoms, hours of sleep lost by the child, and stress on the part of the parent due to the child's croup.

METHODS

STUDY PATIENTS

Enrollment occurred from September 24, 2001, to April 30, 2002, and from September 30, 2002, to February 28, 2003, at four Canadian pediatric emergency departments: Alberta Children's Hospital (Calgary), Stollery Children's Health Centre (Edmonton, Alta.), Winnipeg Children's Hospital (Winnipeg, Man.), and Children's Hospital of Eastern Ontario (Ottawa). Children were eligible if they had mild croup (defined as an onset within the previous 72 hours of a seal-like, barking cough and a score of 2 or less out of 17 points on the validated croup scoring system of Westley et al.^{6,12,13}) on an initial medical evaluation. Exclusion criteria were symptoms or signs of another cause of stridor (e.g., epiglottitis, bacterial tracheitis, or the presence of a supraglottic foreign body); history of congenital or acquired stridor, chronic pulmonary disease, asthma, severe systemic disease, exposure to varicella within the previous 21 days, or known immune dysfunction; treatment with corticosteroids within the preceding 2 weeks; treatment with epinephrine for respiratory distress before enrollment; enrollment in another clinical trial in the previous 4 weeks; inability of the parent to speak English or French; lack of a telephone in the home; and a prior visit to an emergency department due to croup during this episode of the disease. A database was maintained of eligible participants who did not participate for various reasons.

Written informed parental consent was obtained for all children enrolled. The study was approved by the scientific and ethics review board of each center.

BASELINE ASSESSMENT

Before treatment, we measured the croup score,^{6,12,13} the respiratory and heart rates, and the oxygen saturation percentage while the children were breathing room air. On the basis of previously described clinical definitions of the types of croup, we categorized children as having spasmodic croup, acute laryngotracheobronchitis, or a mixed presentation.⁵ Demographic information, associated symptoms, and the medical history were documented.

RANDOMIZATION

The computer-generated randomization scheme, stratified by center, used random permuted blocks of 6 to 10 children to ensure the comparable assign-

ment of eligible patients to dexamethasone or placebo during the study.¹⁴ Codes were secured at each center's pharmacy until enrollment and all decisions regarding data analysis had been finalized. Parents were unable to determine which preparation their child had received.

STUDY INTERVENTION

The dexamethasone suspension consisted of 12.5 ml of dexamethasone phosphate injection (Sabex) with 50 ml of wild-cherry-flavored syrup. The placebo consisted of 10 ml of distilled water and 50 ml of wild-cherry-flavored syrup. Preparations were not distinguishable by appearance, volume, weight, taste, or smell and were packaged in identical syringes in sequentially numbered, sealed, opaque bags.

Each child received a single oral dose of either dexamethasone (0.6 mg per kilogram of body weight; maximum dose, 20 mg) or placebo. Patients were observed for 30 minutes. If vomiting occurred, one additional dose was given.

Additional treatments, provided at the discretion of the attending physician, could include mist, antibiotics, and nebulized epinephrine or beta-agonists. Because none of these treatments alter croup symptoms for more than two hours, at most, they were not expected to interfere with the assessment of the effectiveness of dexamethasone.²

OUTCOME MEASURES

Using standardized telephone interviewing techniques, a trained assistant obtained data for the outcome measures from the parent on days 1, 2, 3, 7, and 21 after the day of treatment (day 0). Data were entered directly into a Microsoft Access 2000 database.

A return to a health care provider for croup within seven days after treatment was the primary outcome measure and was determined through an interview with the parent on day 7 and confirmed

when possible by chart review and review of the administrative database. The presence of ongoing croup symptoms on days 1, 2, and 3 after treatment was the secondary outcome and was determined through an interview with the parent on days 1, 2, and 3 with the use of a validated measurement tool (the telephone outpatient score) for determining the clinical status of children with croup by telephone (Table 1).¹⁵ To determine this score, the interviewer asked whether the child had had either a seal-like barking cough or stridor in the preceding 24 hours. To help the parent identify these pathognomonic sounds, an audiotape of a typical barking cough and stridor was played.

Data for the economic analysis included relevant costs for both the "payer" (the provincial government) and the "nonpayer" (the family of the child) during the 21 days after enrollment. The costs for the payer included the incremental cost of dexamethasone treatment, all physician-related billing (community and hospital), and the costs of all hospital visits during the follow-up period. The cost of treatment was obtained from data in the hospital pharmacy. The Alberta Health Care Insurance Plan schedule of medical benefits (list of procedures and prices) was used to estimate the cost of reported visits with a physician for all four centers.¹⁶ Per diem rates for visits to the emergency department and inpatient stays, on the basis of visits by patients with croup in 2000 and 2001, were obtained for Alberta Children's Hospital and applied to all four centers. Family costs included medication, equipment (e.g., humidifiers), parking and travel, ambulance service, day care, and lost productivity. Self-reported costs were used; in cases of partial data, a generic figure was applied consistently (e.g., \$50 for a humidifier). Lost productivity was calculated by multiplying reported days of missed work by the average daily wage, with the use of Statistics Canada data from 2000 and 2001 for the city in which the family lived.¹⁷ Figures are reported in Canadian

Table 1. The Telephone Outpatient Score for Clinical Status.

Clinical Status Question	Response	Score	Total Additive Score
For stridor: "In the past 24 hours, when your child breathed in did he or she make a noise?"	No	0	0
	Yes, when upset, active, or agitated	1	1
	Yes, at rest or when quiet	1	2
For cough: "In the past 24 hours, has your child had a cough?"	No (questionnaire complete)	0	0
	Yes (go to next question)		
For quality of cough: "Was the cough a barking cough or not?"	Not barking	0	0
	Barking	1	3

dollars (at the time of the study, 1 Canadian dollar was equivalent to 70 U.S. cents).

Two other outcomes were assessed on days 1, 2, and 3: hours of sleep missed by the child due to croup symptoms, and the degree of stress on the part of the parent due to the child's illness (rated on a seven-point Likert scale, with -3 denoting extreme stress and +3 denoting extreme calm). Adverse events were assessed by standardized questioning on day 21 and were confirmed by review of the medical chart if necessary. (See Table 1 in the Supplementary Appendix, available with the full text of this article at www.nejm.org.)

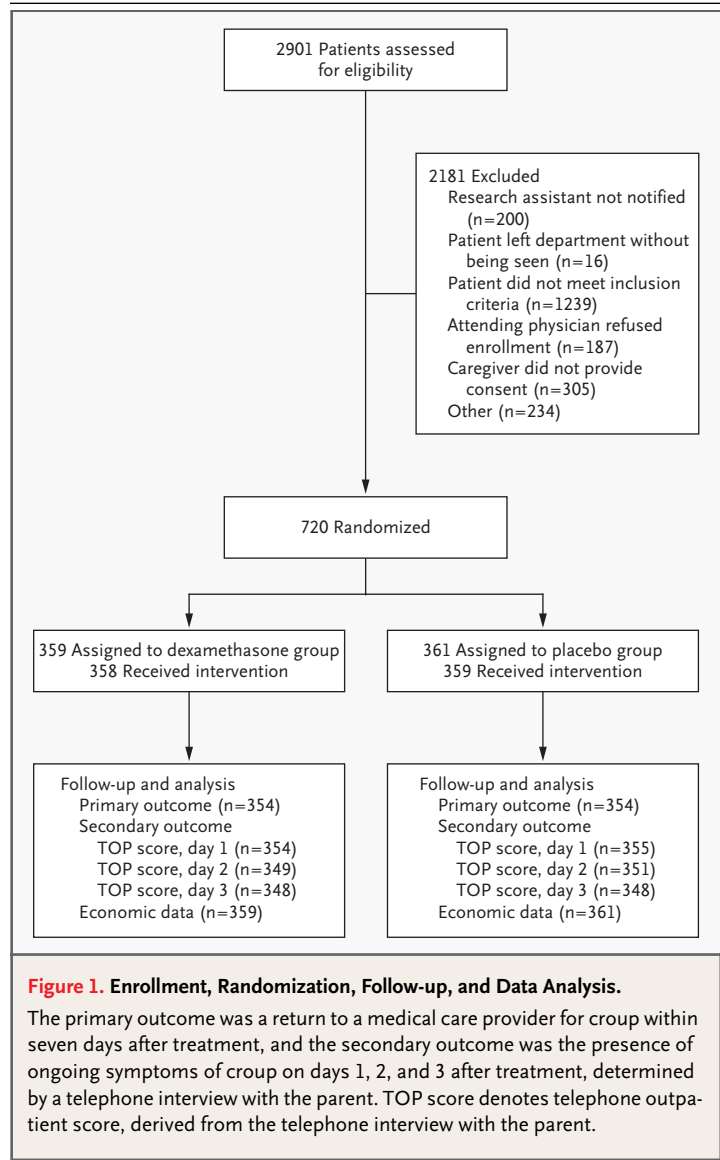
STATISTICAL ANALYSIS

A biostatistician who was not otherwise involved in the study performed the data analysis with the use of Stata software, version 7.0, and the R language (a programming language used for statistical computation and graphics), version 1.6.2.¹⁸ A sample of 350 patients per group provided 80 percent power to detect a difference in the rate of return to a medical care provider of 10 percent in the control group and 4.3 percent in the treatment group, allowing a two-sided type I error probability (that is, a probability of incorrectly showing that dexamethasone is effective) of 0.05. Two interim analyses of efficacy (both nonsignificant) were planned and conducted with the Haybittle-Peto method.¹⁹

Analysis of the primary outcome measure, a return to a medical care provider, was based on the uncorrected chi-square test and confidence intervals derived from the normal approximation to the binomial distribution. We used logistic-regression analysis to determine the potential heterogeneity of the effect of the study center and baseline characteristics on the primary outcome measure. Ordinal logistic regression for longitudinal outcomes was used to analyze the telephone outpatient scores for days 1, 2, and 3,²⁰ as well as the stress scores. Analogous methods of analyzing continuous data²¹ were applied to missed sleep.

For economic analyses, group differences were assessed with the use of a nonparametric, two-sample Wilcoxon rank-sum (Mann-Whitney) test (see Table 2 in the Supplementary Appendix). A sensitivity analysis examined the effect of including lost productivity as a variable.²²

The primary intention-to-treat analysis included all enrolled patients for whom data were available. To assess the implicit missing-at-random assumption, we performed a worst-case sensitivity analysis and assumed that children in the dexamethasone



group for whom outcome data were missing returned to care, whereas corresponding children in the placebo group did not. In addition, we performed a sensitivity analysis of data for all children who completed the study except those with deviations from the study protocol. All reported P values are two-sided, and statistical significance was assigned at the 5 percent level.

RESULTS

PARTICIPANTS

During the enrollment period, a total of 2901 children with croup were seen at the four study centers, 720 of whom met all the enrollment criteria; 361 of

these children were randomly assigned to receive placebo, and 359 to receive dexamethasone. Figure 1 summarizes enrollment, treatment allocation, follow-up, and data analysis of all study patients. Deviations from the protocol were uncommon (37 patients, or 5.1 percent) and equally distributed between the dexamethasone and placebo groups. (Ten children were already receiving corticosteroid treatment, 2 vomited their dose and the dose was not repeated, 3 received the wrong dose, 3 were given no study drug, 13 had incomplete follow-up, 2 were enrolled twice, and 4 had miscellaneous deviations from the protocol.) Only the primary analysis is reported, because the results are qualitatively similar to those of the two sensitivity analyses.

The baseline clinical severity was similar in the two groups (Table 2). Demographic variables were also similar. There were statistically significant but minor differences between the groups in the history of asthma in the child ($P=0.04$) and in the family history of croup ($P=0.03$).

Table 2. Baseline Characteristics of the Study Patients.*

Characteristic	Dexamethasone (N=359)	Placebo (N=361)
Male sex — no. (%)	219 (61)	222 (61)
Age — mo	35±23	35±23
Respiratory rate — breaths/min	28±6	29±8
Heart rate — beats/min	130±21	130±24
Oxygen saturation — %	98±2	98±2
Croup score — %†		
0	38	38
1	38	43
2	24	19
Spasmodic croup — %	44	43
Duration of symptoms before enrollment — days		
Prodromal fever	0.6±1.0	0.7±1.0
Rhinorrhea	1.6±4.1	1.7±3.3
Barking cough	0.7±2.5	0.8±2.4
History — %		
Croup	33	30
Asthma	8	13
Other medical problems	2	3
Prior hospitalization for croup — %	5	2
Prior intubation — %	0	0
Family history — %		
Croup	34	26
Asthma	44	42

* Plus-minus values are means ±SD.

† A score of ≤2 on the croup scoring system of Westley et al.^{6,12,13} indicates mild croup.

RETURN TO HEALTH CARE PROVIDER

Of the 354 patients in each group for whom data were available (708 of the 720 enrolled patients), 54 (15.3 percent) who received placebo as compared with 26 (7.3 percent) who received dexamethasone returned for care within seven days ($P<0.001$; 95 percent confidence interval for the difference, 3.3 to 12.5 percent). Regression-based adjustment for the baseline variables did not alter this finding or provide any indication of the heterogeneity of the relative effect among the prespecified subgroups (Fig. 2). The adjusted odds ratio was 2.4 (95 percent confidence interval, 1.4 to 3.9), after adjustment for study center, age, type of croup, baseline Westley croup score, and duration of barking cough before presentation. The number needed to treat in order to prevent one return visit is 13 (95 percent confidence interval, 8 to 31).

ONGOING SYMPTOMS

Figure 3 shows the distribution of the telephone outpatient score (derived from the telephone interview with the parent [Table 1]) according to treatment group and day. In the first 24 hours, the proportion of children with high scores was larger in the placebo group than in the dexamethasone group, indicating a greater severity of croup in the placebo group (odds ratio, 3.2; 95 percent confidence interval, 1.5 to 6.8; $P=0.003$). The odds ratio after adjustment for baseline variables was similar (3.4; 95 percent confidence interval, 1.6 to 7.4). By day 3, however, differences between the groups had largely disappeared, and symptoms had completely resolved in more than 75 percent of children in both groups. Thirty-four of the 348 children in the dexamethasone group (9.8 percent) and 33 of the 348 in the placebo group (9.5 percent) had an increase in the telephone outpatient score of one or more on either day 2 or 3 of follow-up.

ECONOMIC ANALYSIS

The total average societal cost in Canadian dollars (±SD) per case of croup treated with placebo was \$93±215, as compared with \$72±170 for treatment with dexamethasone, an average savings of \$21 per case ($z=2.46$, $P=0.01$). Payer (provincial government) costs and nonpayer (family) costs were significantly lower in the dexamethasone group than in the placebo group (payer cost, \$18±98 vs. \$25±134, $z=18.52$, $P<0.001$; nonpayer cost, \$54±127 vs. \$68±149, $z=-3.54$, $P<0.001$). More specifically, payer costs included a difference in physician costs

of \$4±12 versus \$5±14 (z=3.08, P=0.002), and a difference in Regional Health Authority costs of \$14±91 versus \$20±127 (z=20.69, P<0.001). Almost all of the overall difference was due to greater loss of productivity in the placebo group. However, even after lost productivity had been excluded from the analysis, the dexamethasone group still had significantly lower costs (\$31±112 vs. \$38±144; z=5.33, P<0.001).

OTHER OUTCOMES

Of children returning for care, 6 of 26 in the dexamethasone group and 24 of 54 in the placebo group were treated with corticosteroids (P=0.09), and 2 of 26 in the dexamethasone group and 7 of 54 in the placebo group were treated with epinephrine (P=0.71). By day 21, two patients in the dexamethasone group and none in the placebo group had been hospitalized.

Children treated with dexamethasone lost an average of 2.9±3.8 hours of sleep owing to their illness, as compared with 4.2±4.7 hours for those treated with placebo (P<0.001). The difference between the two groups was largest on day 1 (1.6±2.3 hours vs. 2.4±2.9 hours, P<0.001), though it persisted to a smaller degree to day 3. There was evidence of decreased mean stress on day 1 on the part of the parents of children receiving dexamethasone (P<0.001). However, the difference on the seven-point Likert scale was small (0.4; 95 percent confidence interval, 0.2 to 0.6), and there was no difference on days 2 and 3.

ADVERSE EVENTS

Among the 720 patients, there were no cases of gastrointestinal bleeding, complicated varicella, or bacterial tracheitis. There were seven cases of pneumonia (three in the dexamethasone group). All these cases were managed on an outpatient basis, without significant sequelae.

DISCUSSION

Though we found, as expected, that among untreated children with mild croup the disease burden was low, our trial showed small but consistent and important benefits of dexamethasone treatment, regardless of the clinical severity or day of illness at presentation. The proportion of children returning for medical care on account of croup was reduced by more than 50 percent in the dexamethasone group as compared with the placebo group, as was the

proportion with croup symptoms in the 24 hours after treatment; the average amount of sleep lost was reduced by 30 percent, and the amount of stress experienced in the first 24 hours by the parent was also reduced. In addition, dexamethasone treatment reduced costs to the family and the health care system as compared with placebo. And although the cost savings per patient were relatively small, mild croup is so common that treatment of all these children with dexamethasone would yield substantial societal benefits.

Our findings are consistent with the results of Geelhoed¹⁰ and Luria¹¹ and their colleagues. Geelhoed and colleagues reported a rate of return for medical care of 16 percent (8 of 50 patients) in the placebo group and 0 percent (0 of 50) in the dexamethasone group. Luria and colleagues reported a

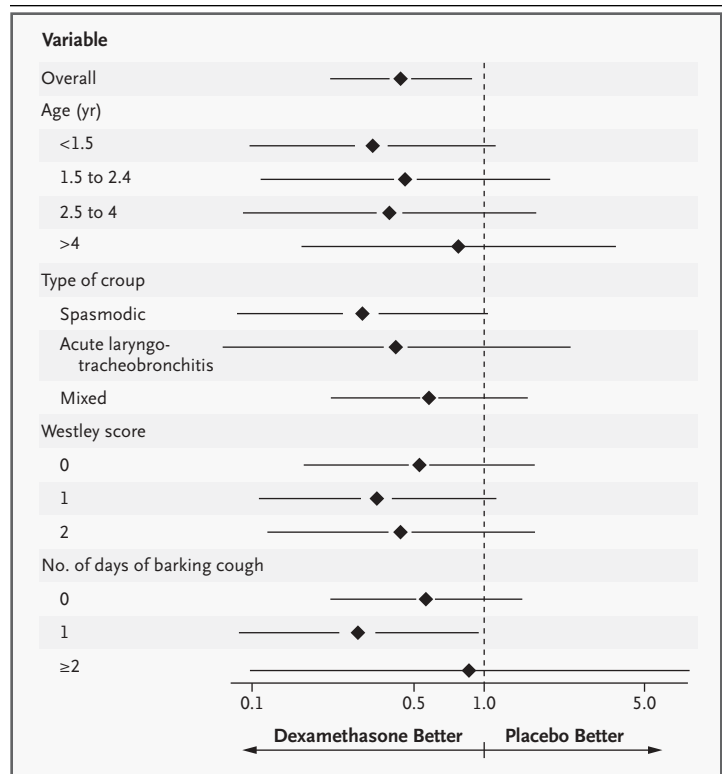
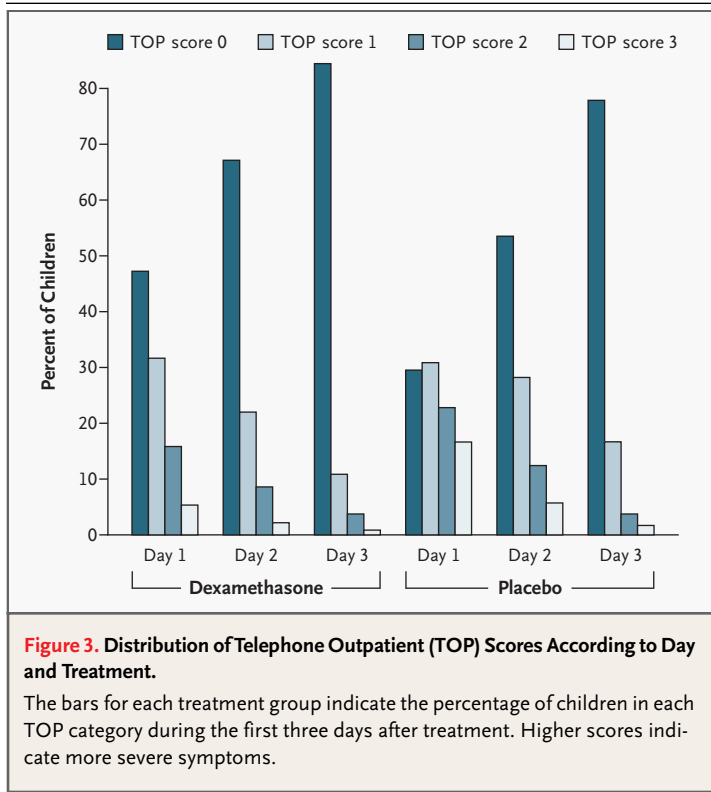


Figure 2. Odds Ratios for a Return for Care.

Estimated odds ratios (odds of a return for care in the dexamethasone group as compared with the placebo group) are plotted for the overall data set and separately by subgroups. The horizontal lines indicate 95 percent confidence intervals. Smaller odds ratios favor dexamethasone; the value 1.0 indicates equality between the dexamethasone and placebo groups. Mild croup was defined as an onset within the previous 72 hours of a seal-like, barking cough and a score of 2 or less out of 17 points on the validated croup scoring system of Westley et al.^{6,12,13}



rate of return of 31 percent (27 of 88 patients) in the placebo group, 30 percent (27 of 91) in the group receiving nebulized dexamethasone, and 12 percent (10 of 85) in the group receiving oral dexamethasone. Our strict clinical definition and enrollment of more than 700 children provide a more precise, unbiased estimate of the proportional reduction in return rates in children with mild symptoms than previous studies provide. Furthermore, we include data on outcomes not previously reported, including the severity of ongoing symptoms, lost sleep, stress on the part of the parent, and economic costs.

One way that our study differed from that of Geelhoed and colleagues¹⁰ was in the size of the dose. We chose the traditional dose of dexamethasone (0.6 mg per kilogram) because we were concerned that the study by Geelhoed and colleagues that compared three doses of dexamethasone (0.15, 0.3, and 0.6 mg per kilogram) in 120 children was inadequately powered to detect equivalence.²³ However, it is possible that a smaller dose of dexamethasone may be as effective as the dose of 0.6 mg per kilogram that we administered.

There were no serious adverse events attributable to therapy in any children in our study. Although our sample was large, the study was not sufficiently powered to exclude the possibility of rare adverse events. Therefore, we advise cautious use of dexamethasone in children with recent exposure to varicella or preexisting immunodeficiency.²⁴⁻²⁶

To our knowledge, no studies have examined the long-term effects of the use of oral corticosteroids in patients with croup. Though corticosteroid treatment for lung disease in premature neonates has been associated with long-term adverse effects on growth and neuromotor and cognitive function,²⁷ a more relevant comparison to our population may be children with exacerbations of asthma. In contrast to the findings in premature infants, repeated short courses of oral corticosteroids in children with asthma are not associated with long-term negative effects on bone metabolism, bone density, or adrenal function.²⁸

Some might argue that the use of dexamethasone in children with mild croup is unnecessary, since objectively, symptoms are mild and self-limited. But although mild croup can seem trivial to experienced medical personnel, the symptoms cause considerable anxiety in parents,²⁹ who may take their child to the emergency department for assessment and reassurance on more than one occasion during the same episode of the disease.

Others may be of the view that a treatment so clearly effective in moderate and severe croup must certainly be useful in mild croup as well. However, because the number of children with mild croup far exceeds those with more severe disease,⁸ we thought it essential to define clearly the degree of benefit and safety before recommending routine use of dexamethasone in this large population of children.

Our study shows small but important benefits of dexamethasone treatment for children with mild croup. The findings are consistent across a range of clinical, social, and economic outcome measures. Oral dexamethasone therapy is simple, inexpensive, and effective. Therefore, although the long-term effects are not known, we advocate dexamethasone treatment for essentially all children with croup.

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