*Archives of Disease in Childhood* 1993; **68**: 352–355

# Treatment of croup with nebulised steroid (budesonide): a double blind, placebo controlled study

S Husby, L Agertoft, S Mortensen, S Pedersen

**Abstract**

**The aim of this prospective, randomised, double blind study was to evaluate whether nebulised local steroid treatment is effective in the treatment of croup. Thirty six infants and children (0·4–4·9 years of age) admitted to hospital with moderate to severe croup were allocated to receive either 2 mg nebulised budesonide (20 children) or saline (16 children). Disease severity was assessed by a clinical total croup score based on stridor, cough, retractions, dyspnoea, and cyanosis. In addition the overall clinical impression was evaluated (0–100). Two hours after treatment there was a significant improvement in the total croup score in the group treated with budesonide (8 to 4·5), but not in the group treated with saline (8 to 8). Furthermore, the overall clinical impression assessment score decreased significantly (50 to 25) in the group treated with budesonide, whereas it remained constant in the placebo group (60 to 62). The total croup score and overall clinical severity were significantly better in the group treated with budesonide than in the placebo group. No side effects were observed. The results indicate that nebulised budesonide can be used as a safe and effective alternative treatment in children and infants with moderate to severe croup.**

(*Arch Dis Child* 1993; **68**: 352–355)

Croup may be defined as a clinical syndrome consisting of inspiratory stridor, a barking cough, hoarseness, and signs of respiratory distress.[1] The disorder is common in infants and young children.[1] Racemic epinephrine has been shown to be an effective treatment, but the effect is short and transient.[2,3] Treatment with systemic corticosteroids has been studied extensively and a meta-analysis of 10 studies[4] concluded that this treatment was effective. This has been confirmed in two double blind, placebo controlled studies,[5,6] showing a significant effect of systemic dexamethasone and of systemic dexamethasone in combination with epinephrine. The management of croup still seems controversial, however.[7]

Theoretically, inhaled steroid treatment should be advantageous in croup, as the active substance can reach the inflamed laryngeal and tracheal tissue in a rapid and efficient way. To test the clinical effectiveness of such treatment we undertook a double blind, placebo controlled study of nebulised budesonide in infants and young children with croup, evaluating the effect two hours after treatment.

In this study we showed a clinical effect of treatment with inhaled budesonide in children with croup. Further studies are needed to clarify the time of onset and the duration of effect and the question of whether inhaled budesonide has any additional advantages over systemic steroid treatment and nebulised epinephrine.

**Department of Paediatrics, Kolding Hospital, Denmark**
S Husby
L Agertoft
S Mortensen
S Pedersen

Correspondence to:
Dr S Husby, Department of Paediatrics, Aarhus University Hospital, DK-8000 Aarhus, Denmark.

Accepted 25 October 1992

## Patients and methods

Infants and young children with croup admitted to the department of paediatrics, Kolding Hospital from 1 October 1990 to 31 December 1991 were evaluated for inclusion in the study. The criteria for croup included inspiratory stridor, cough, and respiratory distress. Patients were eligible if their age was between 3 months and 4·9 years, their total croup score (see later) was higher than 5, and informed consent was obtained from their parents. Patients were excluded if their clinical condition was consistent with epiglottitis, foreign body aspiration, bronchiolitis or asthma, or if they had received local or systemic steroid treatment or epinephrine. No attempt was made to separate laryngotracheobronchitis from spasmodic croup, as this distinction was not considered to be of any major importance in the acute clinical situation. No viral examinations were performed in this study. The study was approved by the regional eithical committee for medical research.

### CLINICAL SCORE

The croup score was modified from the score of Westley *et al*,[2] based on inspiratory stridor (0–4), cough (0–3), retractions (0–3), dyspnoea (0–3), and colour (0–4). Scoring was always performed with the infant or child in the sitting position. Stridor was assessed with and without the aid of a stethoscope, retractions were assessed at four sites (jugulum, supraclavicular, intercostal, and subcostal), and colour was scored as central cyanosis in air (2) or after the administration of oxygen (4).

In addition, clinical disease severity was assessed as the observer's clinical impression on a scale from 0 (no disease) to 100 (maximum illness).

### PATIENT CHARACTERISTICS

A total of 37 infants and children entered the study. One of these patients did not receive the treatment (placebo) due to technical problems and was omitted, leaving 36 participants. All were white and all the patients but two had a fever (maximum temperature 38·5–40·5°C). Of 33 patients six had had croup before, but only

*Table 1 Clinical characteristics of patients with croup on admission to hospital. No variable (including separate clinical scores) showed any significant difference between the budesonide and the placebo group (Mann-Whitney U test) on admission*

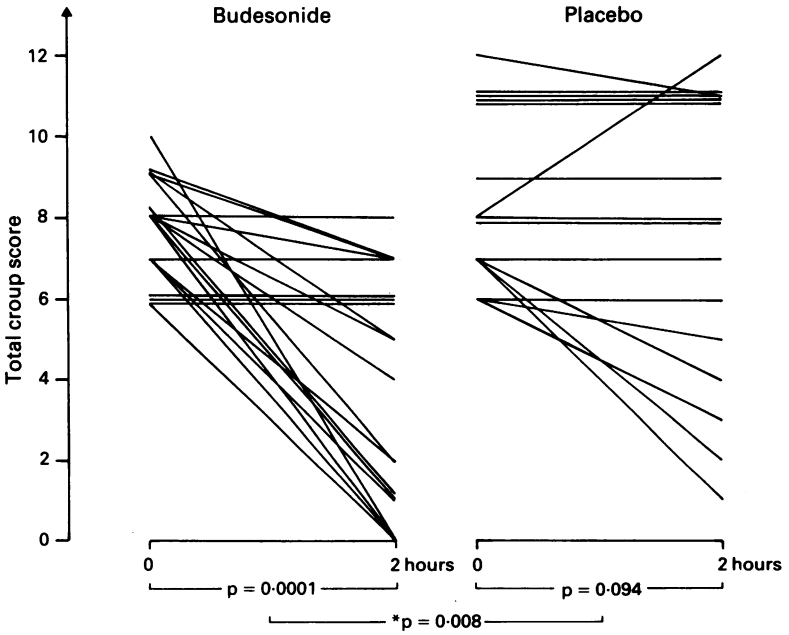
| | *Budesonide (n=20)* | *Placebo (n=16)* |
|---|---|---|
| Median (range) age (years) | 1·6 (0·6–4·9) | 1·1 (0·4–4·2) |
| Boys/girls | 16/4 | 12/4 |
| Total croup score (range) | 8 (6–10) | 8 (6–12) |

one had been previously admitted to hospital for this disorder.

Treatment with budesonide or placebo was allocated by random numbers under double blind conditions. Twenty patients were allocated to active and 16 to placebo treatment. The two groups did not differ with regard to age, sex, or severity of disease at entry (table 1). Three subjects, two in the active group and one in the placebo group, received antibiotics during the study.

TREATMENT AND EVALUATION

After admission the patients received general supportive measures and were evaluated by the clinical croup score. The patients fulfilling the inclusion criteria and none of the exclusion criteria then received either budesonide (Astra) at a dose of 1000 µg (2 ml 500 µg/ml) or placebo treatment (2 ml 0·9% saline) two times 30 minutes apart. The treatment was given with a Parinebuliser driven by a CR 60 compressor with a dynamic flow rate of 8 l/min. No additional treatment was given during the study period. Two hours after the first administration the clinical croup score was assessed again by the observer who made the initial score. The records at these two time points included remarks on possible side effects, but no specific side effects were formally asked for.




*Total croup score of the budesonide (n=20) and the placebo (n=16) groups assessed at admission (zero hours) and after two hours. The statistical significance (*p value) was calculated from the difference in the croup scores (initial minus two hour scores).*

The evaluation after two hours was chosen based on the clinical impression in a few previous patients with croup, who responded favourably within two hours. After the two hour evaluation additional treatment was allowed if necessary.

STATISTICAL ANALYSIS

Non-parametrical statistical tests were used for comparisons as two tailed tests. The Mann-Whitney U test was used for comparison between groups and the Wilcoxon matched pair signed rank test for paired data. The level of statistical significance was chosen as $p<0·05$.

To calculate the necessary sample size[8] a change of total score of 2 was considered to be the minimum relevant difference. To provide a significance level of 0·05 the necessary sample size was calculated to be 15, corresponding well to the patient numbers obtained.

## Results

At study entry the budesonide and the placebo groups were comparable with regard to age, sex, and total croup score (table 1). This was also true for the separate entities of the score (stridor, cough, retractions, dyspnoea, and cyanosis) and for the overall disease severity (table 2). A predominance of boys was observed in the two groups.

The change in the assessment (initial value minus two hour value) within the separate study groups was statistically significant for the budesonide group with regard to respiratory rate ($p=0·0009$), stridor ($p=0·001$), cough ($p=0·0002$), retractions ($p=0·002$), dyspnoea ($p=0·0005$), overall disease severity ($p=0·0002$), as well as for the total croup score ($p=0·0001$). The figure shows the latter. None of the variables showed any significant changes in the placebo groups. Six of 16 subjects in the placebo group did show a spontaneous decrease in total croup score, however (figure).

A comparison of the changes (initial value minus two hour value) in the various clinical variables between the budesonide and the placebo groups did not show statistically significant differences between the two groups in changes in heart rate, respiratory rate, retractions, dyspnoea, and colour (table 2). Only two subjects were cyanotic at any time. The differences between the two groups in the overall disease severity, stridor, cough (table 2) and in the total croup score (figure) were statistically significant in favour of the treatment with budesonide. No side effects were reported.

## Discussion

Croup is a disease caused by acute obstruction of the laryngeal area. Croup has been divided into laryngotracheobronchitis mainly caused by a viral infection such as parainfluenza virus,[9,10] and acute spasmodic croup, which usually occurs recurrently as a mild disorder without a viral prodrome and fever.[11] Spasmodic croup has been related to hyperreactivity of the upper airway[12] and allergic disease,[13–15] though this view has been challenged.[16] It has been suggested that the

*Table 2 Clinical characteristics and croup scores at admission to hospital and within subject changes in the variable (ΔS) initial value minus two hour value. The data are shown as median (range). A positive ΔS value for the croup scores indicates a clinical improvement*

| | *Budesonide* | | *Placebo* | | |
|---|---|---|---|---|---|
| *Variable* | *0 hours* | *ΔS* | *0 hours* | *ΔS* | *p Value** |
| Heart rate | 140 (88 to 196) | +10 (−20 to +40) | 140 (100 to 200) | 0 (−20 to +30) | 0·524 |
| Respiratory rate | 36 (20 to 54) | +6 (−12 to +27) | 40 (20 to 60) | +2 (−9 to +14) | 0·139 |
| Overall severity† | 50 (25 to 75) | +25 (0 to +75) | 60 (25 to 100) | 0 (−25 to +25) | 0·007 |
| Stridor | 3·0 (2 to 4) | +1 (0 to +4) | 3·0 (3 to 4) | 0 (−1 to +2) | 0·039 |
| Cough | 2·0 (0 to 3) | +1 (0 to 3) | 2·0 (0 to 3) | 0 (0 to +2) | 0·016 |
| Retractions | 2·0 (0 to 2) | 0 (0 to +2) | 2·0 (0 to 3) | 0 (−1 to +2) | 0·131 |
| Dyspnoea | 1·0 (0 to 2) | +1 (0 to +2) | 1·0 (0 to 3) | 0 (0 to +1) | 0·074 |
| Cyanosis | 0·0 (0 to 2) | 0 (0 to +2) | 0·0 (0 to 2) | 0 (0 to +2) | 0·438 |
| Total croup score | 8·0 (6 to 10) | +4 (0 to +10) | 8·0 (6 to 12) | 0 (−4 to +6) | 0·008 |

*p Value calculated by comparison of the ΔS after the two treatments. †Assessed blindly as the clinical value (0–100) of disease severity.

two entities represent two ends of a broad spectrum in the clinical presentation of a single disease.[17]

Two studies of systemic steroids in the treatment of croup were based on a patient selection for laryngotracheobronchitis[5] and spasmodic croup[6] respectively. In the two studies a significant effect of systemic steroid treatment with dexamethasone was observed. In the present study we decided not to make any distinction between laryngotracheobronchitis and spasmodic croup, as local steroid treatment in principle should have the same effect on the inflammatory process in the two disease entities and as the distinction has no major value in the acute clinical situation. Most of the subjects in the present study seemed to have laryngotracheobronchitis, however, as they presented with a prodrome with fever and had experienced no previous attacks of croup.

This double blind, placebo controlled study shows that nebulised budesonide can be used as a rapidly effective treatment of croup in infants and children. To our knowledge no previous studies of this treatment modality have been reported. The treatment was assessed over a two hour period and compared with the control group the effect was mainly observed in inspiratory stridor and cough. The lack of effect on heart rate, respiratory rate, and colour was probably due to the moderate disease severity in the patients. A similar lack of change in respiratory rate and heart rate was observed in a study showing the effect of systemic dexamethasone.[5]

The natural history of croup is variable, as illustrated by the fact that four subjects in our control group showed a spontaneous improvement in the croup score of more than one point. The placebo group as a whole did not show any significant changes in the croup score variables. The finding that the differences in score change between the two treatments was not significant for all parameters does not weaken the conclusions of the study. The scoring system has been developed for the assessment of total score and not the individual parameters of which it is composed, and the difference in change between the two treatments was marked and highly significant.

The mechanism of action of corticosteroids is mainly anti-inflammatory, reducing inflammation and oedema, and systemic steroid treatment has been advocated in croup.[4] The effect of systemic treatment is probably not apparent until six hours after the treatment, however.[6] Theoretically, inhaled treatment should have several advantages over systemic administration including a more rapid onset of action due to the direct access to the affected tissues and fewer systemic side effects. We do not know the exact time of onset of action for treatment with budesonide as the assessment was made after two hours when highly significant changes were observed. Such a rapid effect raises the question of the mode of action of budesonide. Studies in experimental animals have shown a rapid effect of budesonide on the mucosal permeability in acute inflammation of the trachea.[18] Steroids in general may have numerous rapidly induced effects of different tissues, including the induction of increased α and β adrenergic activity.[19] The rapid therapeutic action in the present study may possibly be ascribed to an α adrenergic vasoconstriction. If such an effect is associated with a later anti-inflammatory effect, inhaled budesonide may be ideal for the treatment of croup, combining a rapid and more sustained mode of action.


1 Couriel JM. Measurement of croup. *Arch Dis Child* 1988; **63**: 1305–8.
2 Westley CR, Cotton EK, Brooks JG. Nebulized racemic epinephrine by IPPB for the treatment of croup. *Am J Dis Child* 1978; **132**: 484–7.
3 Fogel JM, Berg IJ, Gerber MA, Sherter CB. Racemic epinephrine in the treatment of croup: nebulization alone versus nebulization with intermittent positive pressure breathing. *J Pediatr* 1982; **101**: 1028–31.
4 Kairys SW, Olmstead EM, O'Connor GT. Steroid treatment of laryngotracheitis: a meta-analysis of the evidence from randomized trials. *Pediatrics* 1989; **83**: 683–93.
5 Super DM, Cartelli NA, Brooks LJ, Lembo RM, Kumar ML. A prospective randomized double-blind study to evaluate the effect of dexamethasone in acute laryngotracheitis. *J Pediatr* 1989; **115**: 323–9.
6 Kuusela A-L, Vesikari T. A randomized, double-blind, placebo-controlled trial of dexamethasone and racemic epinephrine in the treatment of croup. *Acta Paediatr Scand* 1988; **77**: 99–104.
7 Anonymous. Steroids and croup [Editorial]. *Lancet* 1989; ii:1134–6.
8 Sokal RR, Rohlf FJ. *Biometry*. New York: Freeman, 1981.
9 Foy HM, Cooney MK, Maletzky AJ, Grayston JT. Incidence and etiology of pneumonia, croup and bronchiolitis in preschool children belonging to a prepaid medical care group over a four-year period. *Am J Epidemiol* 1973; **97**: 80–92.
10 Korrpi M, Halonen P, Kleemola M, Launiala K. The role of parainfluenza viruses in inspiratory difficulties in children. *Acta Paediatr Scand* 1988; **77**: 105–11.
11 Bass JW, Wehrle PF. Croup and epiglottitis. In: Nussbaum B, Galant SP, eds. *Pediatric respiratory disorders. Clinical approaches*. New York: Saunders, 109–16.
12 Zach M, Schnall RP, Landau LI. Upper and lower airway hyperreactivity in recurrent croup. *Am Rev Respir Dis* 1980; **121**: 979–83.
13 Konig P. The relationship between croup and asthma. *Ann Allergy* 1978; **41**: 227–31.
14 Zach M, Erben A, Olinsky A. Croup, recurrent croup, and airways hyper-reactivity. *Arch Dis Child* 1981; **56**: 336–41.
15 Cohen B, Dunt D. Recurrent and non-recurrent croup: an

epidemiological study. *Australian Paediatric Journal* 1988; **24**: 339–42.
16 Dirdal M. Is croup an allergic condition? *Ugeskr Laeger* 1988; **150**: 164–5.
17 Skolnik NS. Treatment of croup. A critical review. *Am J Dis Child* 1989; **143**: 1045–9.
18 Miller-Larsson A, Brattsand R. Topical anti-inflammatory activity of the glucocorticoid budesonide on airway mucosa. Evidence for a 'hit and run' type of activity. *Agents Actions* 1990; **29**: 127–9.
19 Duval D, Durant S, Homo-Delarche F. Non-genomic effects of steroids. Interactions of steroid molecules with membrane structures and functions. *Biochem Biophys Acta* 1983; **737**: 409–42.

## Steroids in croup

The debate about whether or not children with croup benefit from being given steroids has gone on for many years. James Tibballs and colleagues (*Lancet* 1992; **340**: 745–8) quote a meta-analysis of nine trials involving 1126 patients[1] which gave support to the use of steroids for patients in hospital and two trials[2,3] in which a single intramuscular injection of dexamethasone (0·6 mg/kg body weight) was given, both of which showed benefit for the treated group. The recent *Lancet* paper concerned patients with severe croup nursed on an intensive care unit and needing endotracheal intubation. The diagnosis of croup (acute laryngotracheobronchitis) was made on clinical grounds – coryzal symptoms, barking cough, hoarse voice, inspiratory stridor, retraction, or cyanosis, developing over several days. They performed a randomised, double blind, placebo controlled study of prednisolone in a dose of 1 mg/kg body weight given via a nasogastric tube after intubation and continued every 12 hours until 24 hours after extubation. Thirty two children received placebo and 38 prednisolone. The duration of intubation was less in the treated group (mean duration 98 hours (95% confidence intervals 85 to 113) in the prednisolone group and 138 hours (118 to 160) in the placebo group ($p<0·003$).

The children in this study were not sedated and 17% extubated themselves. Otherwise extubation was done electively when there was an audible air leak round the tube. After extubation, either planned or not, reintubation was necessary in 11 out of 32 (34%) in the placebo group and two out of 38 (5%) in the prednisolone group ($p=0·004$).

The authors conclude that treatment with prednisolone reduced the duration of intubation and the need for reintubation in their children. They suggest that a higher dose might have been even more effective and their present policy when they need to intubate a child with croup is to give first dexamethasone 0·6 mg/kg by intramuscular injection and then prednisolone 1 mg/kg every 12 hours by nasogastric tube. The durations of intubation quoted in this paper seem rather long to me. Could their tendency to continue with intubation for such lengths of time have influenced the results? For how long should intubation be continued? This paper does not answer that question, although the authors suggest that with prednisolone treatment routine extubation after two or three days might be preferable to waiting for an air leak. Would the effect of prednisolone have been as marked if earlier routine extubation had been done? Again the data given do not provide an answer.

ARCHIVIST

1 Kairys SW, Olmstead EM, O'Connor GT. Steroid treatment in laryngotracheitis: a meta-analysis of the evidence from randomised trials. *Pediatrics* 1989; **83**: 683–93.
2 Super DM, Cortelli NA, Brooks LJ, Lembo RM, Kumar ML. A prospective randomised double-blind study to evaluate the effect of dexamethasone in acute laryngotracheitis. *J Pediatr* 1989; **115**: 323–9.
3 Kuusela AL, Vesikari T. A randomised double-blind placebo-controlled trial of dexamethasone and racemic epinephrine in the treatment of croup. *Acta Paediatr Scand* 1988; **77**: 99–104.