Role of glucocorticoids in treating croup

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Ausejo M, Saenz A, Pham Ba', Kellner JD, Johnson DW, Moher D, Klassen TP. The effectiveness of glucocorticoids in treating croup: meta-analysis. *BMJ* **1999;319:599-600.**

Research question

Are glucocorticoids effective at treating croup?

Type of article and design

Systematic review with a meta-analysis consisting of 24 studies.

Relevance to family physicians

Croup, a syndrome characterized by a barking cough, inspiratory stridor, and respiratory distress, afflicts about 1.5% to 6% of children younger than 6 years. Croup is a considerable burden on the health care system due to the frequent visits made to family doctors and emergency departments, which might result in hospitalization. Admission rates for children with croup brought to emergency departments have been documented at up to 30%.[1]

Conventional treatment for croup includes humidified air or mist, but there is very little evidence that this is effective. Parents are advised to remain calm (easy for doctors to say), to give their children fluids to loosen the mucus, to raise the head of the bed to ease breathing, and to give acetaminophen if children develop a fever. These measures are largely supportive and tend not to resolve the croup any faster. Adrenaline has also been used for treating croup. It provides temporary, but not sustained, relief.

Treating croup with glucocorticoids has been controversial since the early 1970s. A series of double-blind studies had shown that glucocorticoids were ineffective at treating croup and that supportive measures only were required to provide relief. Many front-line clinicians think glucocorticoids have a role and "feel they contribute a great deal to the reduction of the morbidity and the necessity for tracheostomy or endotracheal intubation."[2] Ever since the debate in the 1970s, researchers have tried to determine whether glucocorticoids are effective at treating croup.

An optimal medication would target inflammation to relieve the obstruction governing croup. Glucocorticoids have been proposed to fill this role and, as such, they would provide some clinical benefit to children with croup. The possible side effects of steroids and the mode of delivery must also be considered, however, before glucocorticoids are used as standard treatment for croup.

Some questions need to be answered. Are glucocorticoids effective at treating croup? Are they safe? And if so, which mode of delivery is most efficacious? Given the lack of consensus on treating croup, what should we recommend?

Overview of study and outcomes

The study searched MEDLINE from January 1966 to August 1997, exploring the headings "glucocorticoid treatment" and "croup." The search was restricted to randomized controlled trials in any language and was also applied to *Excerpta Medica*, EMBASE, and the Cochrane library. Letters were sent to authors of trials published during the previous 5 years to see whether they knew of other published or unpublished trials. The search found 97 studies, which were then reviewed by two independent examiners.

To be included in the meta-analysis, the studies had to meet the following criteria: to have studied patients with croup; to have compared glucocorticoid treatment with placebo or other treatment; to have had relevant outcome measures, such as croup score and hospitalization rate; and to have randomly assigned patients to the treatment groups.

Once studies were identified, author names and instructions, location of the study, reference lists, and any other potential identifiers were concealed. Each study was examined by one of the reviewers to identify patient status (inpatient or outpatient), the intervention used, and its control. The drug's name, route of administration, and dose and the primary outcome measure of the study were also identified. This could

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include a clinical croup score at baseline and at other subsequent times; length of stay in hospital or emergency department; whether patients had improved; and whether additional interventions, such as adrenaline and adjunct glucocorticoids, had been used. Once data extraction was complete, the second reviewer checked accuracy.

Quality of the trials was assessed using the Jadad 5-point scale.[3] Score was given according to whether randomization or double-blinding were performed and whether there were withdrawals or drop-outs.

During data analysis, comparisons were made between treatment and control groups. Main outcome of interest was croup score at baseline, and at 6, 12, and 24 hours after treatment with glucocorticoids compared with placebo or other treatment. Croup score was used to assess air entry, stridor, intercostal retractions, cyanosis, and level of consciousness. Treatment differences were defined using the trial effect size, which looked at mean change in croup score from baseline.

Results

Of 97 studies identified, 24 met the inclusion criteria. Inter-rater reliability between the two reviewers was high, indicating substantial agreement. Dexamethasone was evaluated in 17 trials, budesonide in nine, and methylprednisolone in three. Five trials compared active treatments; 19 were placebo controlled. Mean age of children in the studies ranged from 13 months to 45 months.

For croup severity, the most common scoring system used in the trials (and the only validated tool) was a scale developed by Westley.[4] Westley scores use a 17-point scale to assess air entry (2 points), stridor (2 points), intercostal retractions (indrawing of the chest wall between the ribs on inspiration) (3 points), cyanosis (5 points), and level of consciousness (5 points). Differences in Westley scores were calculated in place of effect sizes to provide an approximate conversion between the two scales. Differences between estimates derived from Westley and other scores were assessed.

At 6 hours after treatment with glucocorticoids, risk reduction was 15% (95% confidence interval [CI] 2 to 28), number needed to treat (NNT) was 7 (95% CI 4 to 50), and baseline rate of clinical improvement was 41% (95% CI 32 to 50). At 12 hours, risk difference was 21% (95% CI 9 to 33), NNT was 5 (95% CI 1 to 11), and baseline rate of clinical improvement was 68% (95% CI 58 to 77). At 24 hours, risk difference was 12% (95% CI 3 to 22), NNT was 8 (95% CI 5 to 33), and baseline rate of improvement was 83% (95% CI 75 to 91).

Overall, children spent less time in emergency when they were treated with glucocorticoids compared with placebo. Across five studies (596 patients), the weighted mean difference was –11 (range -18 to 4) hours for outpatients compared with –16 (range -31 to 1) hours for inpatients.

Across 11 studies (1150 patients), when glucocorticoids were compared with placebo, there was no significant difference in rates of intubation or tracheotomy: –2% (range -14% to 10%), baseline rate 3.2% (range 2.9% to 3.5%).

The study was unable to compare route of administration of glucocorticoids among the various studies due partly to lack of standardization of scores. An NNT of 5 to 7 would be sufficient to support use of glucocorticoids over placebo. Hence, glucocorticoids were found to be effective at 6 and 12, but not 24, hours after treatment. Because fewer patients were evaluated at 24 hours, statistical power could have been limited.

Glucocorticoid treatment was also associated with a decrease in number of adrenaline treatments needed: 9% (95% CI 2 to 16) with budesonide and 12% (95% CI 4 to 20) with dexamethasone. There was also a decrease in length of time spent in emergency (11 hours, 95% CI 18 to 4) and in hospital (16 hours, 95% CI 31 to 1).

Analysis of methodology

The meta-analysis was well performed and evaluated both the quality and the heterogeneity of the studies. The authors did entertain the possibility of publication bias, stating that their analysis likely did not include smaller studies that had statistically negative results. This bias could result in overestimation of the effectiveness of glucocorticoids. Although the authors broke down the Westley score, it would have been helpful to have more insight into the clinical meaning of risk reduction and more discussion of the efficacy of oral medications that are more likely to be prescribed in the community. As well, although concerns might be unfounded compared with benefits, it would have been reassuring to some readers to see some data or commentary on safety.

Application to clinical practice

This meta-analysis provides good evidence that treatment with glucocorticoids is effective at improving symptoms of croup in children as early as 6 hours and for up to at least 12 hours after treatment. The efficacy of glucocorticoids has been demonstrated by a significant improvement in croup severity, shorter hospital stays, and a decreased need for additional treatments, such as adrenaline. The paper suggested that five to

seven patients would need to be treated with glucocorticoids for one patient to have a noticeable improvement in symptoms.

An important concern here is whether these trials can be replicated because they used mainly inhaled or intravenous budesonide and dexamethasone and were conducted in emergency rooms. Obviously, these routes are not available to every community-based clinician. Primary care physicians have been reluctant to prescribe glucocorticoids for croup, but, considering their safety, low cost, and effectiveness at relieving croup symptoms, it might be warranted. Further studies looking at the optimal mode of administration might help to alleviate physicians' concern about using steroids to treat croup.

Bottom line

- Glucocorticoids are effective at improving symptoms of croup in children as early as 6 hours after treatment. There was a very slight advantage to dexamethasone (12%; 95% CI 4 to 20) over budesonide (9%; 95% CI 2 to 16), but actual efficacy needs to be further evaluated to declare a winner.
- Most of the trials reviewed took place in emergency rooms and, therefore, used less common routes of administration (eg, inhaled or intravenous). Studies show that administration of oral steroids (0.15 to 0.6 mg/kg) in the office reduces the number of children needing to attend primary care facilities for ongoing treatment.[5] There is no evidence that steroids administered with metered-dose inhalers are beneficial.[6]
- Use of glucocorticoids would result in fewer additional interventions, such as adrenaline administration, and would decrease length of time spent in hospital.

Points saillants

- L'administration de glucocorticostéroïdes est efficace pour améliorer les symptômes du croup chez les enfants dans un délai aussi rapide que six heures après le traitement. Le dexaméthasone présentait un léger avantage (12%; IC à 95% de 4 à 20) par rapport au budésonine (9%; IC à 95% de 2 à 16), mais leur efficacité respective réelle mérite une évaluation plus approfondie pour déclarer le gagnant.
- La majorité des essais analysés se déroulaient en salle d'urgence et ne portaient donc pas sur les modes d'administration les plus courants (p.ex. l'inhalation ou par voie intraveineuse). Les études font valoir que l'administration de stéroïdes par voie orale (0,15 à 0,6 mg/kg) en cabinet réduit le nombre d'enfants devant fréquenter des établissements de soins de première ligne pour un traitement continu[5]. Il n'est pas prouvé que les stéroïdes administrés par aérosol-doseur soient bénéfiques[6].
- Le recours aux glucocorticostéroïdes se traduirait par un nombre moins grand d'interventions additionnelles, comme l'administration d'adrénaline, et réduirait la durée des séjours à l'hôpital.

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