

Glucocorticoids in the treatment of croup: barking up the right tree

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Croup, a syndrome characterized by a barking cough, inspiratory stridor and respiratory distress, afflicts up to 3% of children less than 6 years of age each year.¹ The syndrome is usually caused by infection with a virus, most often parainfluenza 1 virus,² and this infection is believed to cause inflammation of the larynx and trachea, which results in the characteristic symptoms. Admission rates for patients with croup presenting to emergency departments have been documented at up to 30%.³

The optimal management of croup has been hotly debated for 40 years, with the dividing line at times falling between the “town” and “gown” groups^{4,5} (see box this page). However, the issue now appears to be resolved. Meta-analyses,⁶ which increase the power and precision of overall estimates,⁷ and recent randomized controlled trials (RCTs)⁸ (including our own⁹) have shown that steroids reduce both the frequency of complications of croup and the rates of visits to emergency departments and admissions to hospital.

Kairys and colleagues,⁶ in a meta-analysis on the effectiveness of glucocorticoids for inpatients with croup, found that there was a significant clinical improvement by 12 and 24 hours after administration of these agents, as well as a significant decrease in the probability of intubation. These results supported Coffin’s assertions from the early 1970s,⁴ an interesting paradox considering his abhorrence of double-blind studies. We performed a cumulative meta-analysis,⁸ which showed that there was evidence as early as 1966 for the effectiveness of glucocorticoids in producing a significant improvement in croup patients 12 hours after administration.

This evidence had been gathered from experimental work involving inpatients with croup and hence was not immediately generalizable to outpatients. An intriguing question has been whether intervening at an earlier stage in the child’s illness, while he or she is an outpatient, would lead to a reduction in hospital admission rates. Furthermore, would direct administration of budesonide, a nebulizable steroid, to the affected area — the larynx and trachea — be an effective method of administering glucocorticoid? One of our trials⁹ demonstrated that, relative to placebo, nebulized budesonide did indeed lead to faster clinical improvement, shorter stay in the emergency department and reduced probability of admission to hospital.

Earlier in the 1990s there was a dramatic increase in the number of croup trials, most involving outpatients. It was becoming evident that not only were glucocorticoids effective for inpatients, but they also offered significant benefits to children with croup who had



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Historical debate on the treatment of croup

The colourful debate that took place in the early 1970s is illustrated by the following excerpts from 2 letters to the editor that appeared in the journal *Pediatrics*. In one letter Dr. L.A. Coffin stated “unequivocally that I am strongly in favor of their [corticosteroids] use and feel certain that they contribute a great deal to the reduction of the morbidity and the necessity for tracheostomy or endotracheal intubation. . . . I must contest, then, the double blind studies which reveal no benefits of steroids in croup. . . . It is all very well for those who are practicing in the ivory tower atmosphere of pediatric departments to run their double blind studies caring little whether or not they are causing several croup patients to have unnecessary surgical procedures.”⁴ Dr. L. Menachof⁵ responded that “The letter by Dr. Coffin demonstrates very clearly unacceptable reasoning. His unequivocal endorsement of the use of steroids in viral croup is equally irrelevant to the issue as is my own 12 years’ experience demonstrating the failure of steroids to affect the outcome and excellent results using only supportive measures.”



Treatment recommendations for croup

- Nebulized budesonide (2 mg) or dexamethasone (0.6 mg/kg administered orally) should be given to children with mild to moderate croup (i.e., showing some degree of respiratory distress during assessment by a health care provider).
- Dexamethasone (0.15 mg/kg administered orally) can be considered for very mild cases.

not yet been admitted to hospital. The question then shifted from whether steroids were effective to which steroid, budesonide or dexamethasone, offered the greater benefit (or indeed whether a combination would prove even more effective).

Our group designed an RCT to address this question. A total of 198 children with mild to moderate croup were randomized to receive one of the following treatments: 2 mg nebulized budesonide (4 mL); 0.6 mg/kg of dexamethasone, administered orally; or a combination of the 2 drugs. We designed the trial to have adequate statistical power to detect important differences between the 3 groups. All but one of the patients were followed up 1 week after treatment. There were no significant differences between the 3 treatment arms.¹⁰ Because dexamethasone for oral administration is more widely available, easier to administer and cheaper, we feel it should be the preferred treatment option in most children with croup.

The croup story has shown how the results of RCTs can advance the treatment of children. Some hospitals where glucocorticoids have been widely adopted for treatment of croup in the emergency department have reported that the admission rates for this disease decreased 13-fold between 1991 and 1996 (Dr. Milton Tenenbein, Director, Emergency Services, Winnipeg Children's Hospital: personal communication, 1998). Some questions remain, for example, determination of the minimum dose of dexamethasone required. One study demonstrated that doses as low as 0.15 mg/kg were effective.¹¹ In addition, intramuscular administration of dexamethasone has never been compared directly with oral administration. Johnson and colleagues¹² recently showed that the intramuscular route is superior to placebo and appears more effective than nebulized budesonide.

What about children with very mild croup, those who display no respiratory distress when assessed by a physician? One small RCT suggested that a single oral dose of dexamethasone, at 0.15 mg/kg, decreases the need to the return to physician with problems related to croup.¹³

Despite these lingering questions, it is now obvious that administering some form of glucocorticoids to children with croup who have some degree of respiratory distress yields a better clinical outcome and reduces the utilization of health care resources. Perhaps the ivory tower has been dismantled, and all health care providers, whether they be in academic or private practice, can work together to ensure that the children who qualify for this treatment receive it (see box this page). The next major advance in this disease is unlikely to come from pharmacotherapy, but rather from the development of a vaccine effective against the parainfluenza virus. Such an effective vaccine would decrease the incidence of viral croup and obviate the need for drug therapy.

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