

# Evidence for Clinicians: Nebulized epinephrine for croup in children

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For the current issue of the *Journal*, we asked Drs Atsushi Kawaguchi and Ari Joffe to comment on and put into context the Cochrane Review on nebulized epinephrine for reducing symptoms in children with severe croup.

## Background

Croup is a common childhood illness characterized by barking cough, stridor, hoarseness and respiratory distress. Children with severe croup are at risk for intubation. Nebulized epinephrine may prevent intubation.

## Methods

**Search strategy:** The authors searched CENTRAL 2013, Issue 6, MEDLINE (1966 to the third week of June 2013), EMBASE (1980 to July 2013), Web of Science (1974 to July 2013), CINAHL (1982 to July 2013) and Scopus (1996 to July 2013).

**Selection criteria:** Randomized controlled trials (RCTs) or quasi-RCTs involving children with croup evaluated in an emergency department (ED) or admitted to hospital were included. Comparisons were: nebulized epinephrine versus placebo, racemic nebulized epinephrine versus L-epinephrine (an isomer), and nebulized epinephrine delivered by intermittent positive pressure breathing (IPPB) versus nebulized epinephrine without IPPB. The primary outcome was change in croup score post-treatment. Secondary outcomes were rate and duration of intubation and hospitalization, croup return visit, parental anxiety and side effects.

## Data analysis

Two authors independently identified potentially relevant studies by title and abstract (when available), and examined relevant studies using a priori inclusion criteria, followed by methodological quality assessment. One author extracted data while the second checked accuracy. Standard methodological procedures outlined by the Cochrane Collaboration were used.

## Results

Eight studies (225 participants) were included. In general, children included in the studies were young (average age <2 years in the majority of included studies). Severity of croup was described as moderate to severe in all included studies. Six studies were performed in the inpatient setting, one in the ED and one setting was not specified. Six of the eight studies were deemed to have a low risk of bias and the risk of bias was unclear in the remaining two studies.

Nebulized epinephrine was associated with improvement in croup score 30 min post-treatment (three RCTs; standardized mean difference [SMD] -0.94 [95% CI -1.37 to -0.51];  $I^2$  statistic = 0%). This effect was not significant 2 h and 6 h post-treatment. Nebulized

epinephrine was associated with significantly shorter hospital stay compared with placebo (one RCT, MD -32.0 h [95% CI -59.1 to -4.9]). Comparing racemic and L-epinephrine, no difference in croup score was found after 30 min (SMD 0.33 [95% CI -0.42 to 1.08]). After 2 h, L-epinephrine showed significant reduction compared with racemic epinephrine (one RCT, SMD 0.87 [95% CI 0.09 to 1.65]). There was no significant difference in croup score between administration of nebulized epinephrine via IPPB versus nebulization alone at 30 min (one RCT, SMD -0.14 [95% CI -1.24 to 0.95]) or 2 h (SMD -0.72 [95% CI -1.86 to 0.42]). None of the studies sought or reported data on adverse effects.

## Conclusions

Nebulized epinephrine is associated with clinically and statistically significant transient reduction of symptoms of croup 30 min post-treatment. Evidence does not favour racemic epinephrine or L-epinephrine, or IPPB over simple nebulization. The authors note that data and analyses were limited by the small number of relevant studies and total number of participants and, thus, most outcomes contained data from very few or even single studies.

The full text of the Cochrane Review is available in The Cochrane Library (1).

## EXPERT COMMENTARY

### Importance of the topic

The annual incidence of croup is as high as 6% in children <6 years of age presenting to paediatricians' offices and EDs (2,3). Although usually self-limited, with symptoms resolving by 48 h in 60% of cases, up to 5% of children presenting for medical care are admitted to hospital, and up to 3% of these children are intubated (2,3). In clinical settings, severity is categorized as mild, moderate, severe and respiratory failure; at least two-thirds present with mild, and <1% with severe croup (4-6).

Children with croup should be kept as comfortable as possible; care must be taken not to frighten the child, and to avoid causing agitation, both of which can worsen the airway obstruction. Humidified air was traditionally used as a primary intervention; however, a Cochrane review concluded that it was ineffective (7). The benefits of corticosteroids and nebulized epinephrine have been evaluated in multiple well-designed prospective studies (1,8). In severe croup unresponsive to treatment, endotracheal intubation is indicated. Intubation can be difficult due to severe subglottic swelling. In addition, there are instances in which the symptoms of croup are due to other structural causes of upper airway obstruction, leading to a difficult airway. Thus, intubation of a child with croup should be performed by an anesthesiologist with the support of an ear, nose and throat specialist, ideally in the operating room.

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**When should nebulized epinephrine be initiated and at what dose?**

Given the evidence that the effects of a dose of corticosteroid can be expected only after 30 min, nebulized epinephrine should be initiated as early as possible for moderate to severe croup (7). We recommend a dose of 5 mL of 1:1000 L-epinephrine for nebulization because racemic epinephrine is often not available and one study found it to be less effective than L-epinephrine. This dose should have immediate effects and last for  $\geq 30$  min.

**Are there any cases for which nebulized epinephrine should not be used?**

We are not aware of any contraindications to nebulized epinephrine. A recently published RCT in intensive care assessing the effect of a single dose of L-epinephrine on postextubation stridor in children showed that patients receiving a 5 mL dose, compared with a 2.5 mL or 0.5 mL dose, experienced significantly increased blood pressure at up to 180 min, but by only a mild degree (systolic and diastolic blood pressure raised by a mean of  $< 7$  mmHg) (9). Acute angle-closure glaucoma is theoretically possible after nebulized epinephrine, although we are not aware of any reported cases (10). Severe events are likely very rare given the widespread use of nebulized epinephrine for several decades.

**Can nebulized epinephrine be repeated?**

The Cochrane review did not find studies that examined repeated doses of nebulized epinephrine. In our experience, clinicians often

use more than one dose of nebulized epinephrine in a short period. Although nebulized epinephrine appears to be safe, it is unclear how often it can be repeated. There is one case report of an 11-year-old child with croup receiving three doses of nebulized racemic epinephrine in 1 h, who experienced 5 min of spontaneously resolving ventricular tachycardia and a small myocardial infarction (11), and one reported case involving a 33-day-old infant with bronchiolitis who, after three doses of nebulized L-epinephrine in  $> 90$  min, experienced ventricular tachycardia with pulses, which was converted with lidocaine (12). The lack of other reports suggests that serious adverse events from repeat doses are very rare. Based on these considerations, we believe repeated doses of epinephrine are warranted for persisting severe croup while an increased level of observation is arranged, a paediatric intensivist is consulted or arrangements for intubation are being made (4,13).

**When can patients be sent home from the ED after nebulized epinephrine?**

When one dose of nebulized epinephrine is used with a good response, at least 2 h of observation under appropriate monitoring is recommended (4,13) because the action of nebulized epinephrine is short lived. All such children should also receive a corticosteroid. Discharge home requires resolution of stridor and respiratory distress.

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