CJEM Journal Club

Combination therapy with epinephrine and dexamethasone for bronchiolitis

Reviewed by: Sara Ahronheim, MDCM

Clinical question
Does the use of nebulized epinephrine (NE) alone, oral dexamethasone (OD) alone or a combination of both reduce hospital admissions of infants with bronchiolitis?
Article chosen
Plint AC, Johnson DW, Patel H, et al. Epinephrine and dexamethasone in children with bronchiolitis. *N Engl J Med* 2009; 360:2079–89.
Study objective
The study authors sought to assess whether hospital admissions can be reduced in infants with bronchiolitis treated in an emergency department with OD and/or NE.

BACKGROUND

Although bronchiolitis is the most common acute infection of the lower respiratory tract and the leading cause of morbidity in infants in North America and Europe,[1,2] the optimal therapy is controversial. Although practice guidelines do not recommend using either epinephrine or dexamethasone, both are widely used.[1]

Nebulized epinephrine (NE) is used in bronchiolitis as a bronchodilator and to decrease airway edema.[3] A Cochrane review found small, short-term benefit from the use of bronchodilators in bronchiolitis, but did not recommend their routine use given cost, adverse effects and uncertain efficacy.[4] Oral dexamethasone (OD) was thought to reduce the inflammation associated with bronchiolitis, but a large randomized controlled trial showed no clinically significant benefit.[5]

The study by Plint and colleagues was undertaken to assess whether NE and OD, either alone or in combination, could significantly reduce hospital admissions among infants with a first episode of bronchiolitis.

POPULATION STUDIED

All infants 6 weeks to 12 months of age presenting to 8 Canadian pediatric emergency departments (EDs) for bronchiolitis, during the period from December to April in 2004–2007, were eligible if their Respiratory Distress Assessment Index (RDAI) score lay between 4 and 15 (< 4 = very mild; > 15 = very severe). Infants were excluded if there was recent prior use of a study drug, prior history of wheezing, certain comorbidities, severe distress or insurmountable communication barriers with caregivers.

STUDY DESIGN

The study was a multicentre, randomized, double-blind, placebo-controlled clinical trial with a factorial design. A sample population of 800 infants (80% power, 5% type I error) was randomly assigned in blocks to one of 4 groups: 1) NE (2 treatments 30 minutes apart of oxygen at 8 L/min with 3 mL epinephrine in 1:1000 solution) plus OD (1.0 mg/kg, maximum 10 mg in ED, and 0.6 mg/kg/d for 5 more days), 2) NE plus oral placebo (OP), 3) OD plus nebulized placebo (NP), 4) NP plus OP. The treatments and placebos (identical in appearance, volume, weight, odour and taste) were administered in the ED by the research nurse and at home by parents. After 90 minutes the treating physician could give co-interventions, and thereafter independently decide which infants to discharge or admit. The research nurse followed up by telephone daily until 7 days after discharge, every 2 days until 14 days after discharge and then every 3 days until 22 days after discharge, at which time a review of the hospital chart was performed.

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OUTCOMES MEASURED

The primary outcome was hospital admission up to 7 days after the initial ED visit; also assessed were rates of admission at time of enrolment and up to 22 days after discharge. Secondary outcomes included change in vital signs and respiratory distress at 30, 60, 120 and 240 minutes, duration and severity of symptoms, time to discharge and return for symptoms of bronchiolitis within 22 days.

RESULTS

A total of 3556 infants were assessed; 2756 were excluded (e.g., criteria not met, no parental consent) and 800 were enrolled. Each arm of the study had 199–201 patients, and each lost 0–1 to follow-up. Baseline patient characteristics were similar among groups, and a similar number of patients across groups (1 in 5) received additional bronchodilators after the first 90 minutes.

Hospital admissions 7 days after discharge were 17% in the combination therapy group, 23.7% in the epinephrine group, 25.6% in the dexamethasone group and 26.4% in the placebo group. Relative risk of admission (using the placebo group as the reference standard) at time of enrolment, and at 7 and 22 days after discharge (95% confidence interval [CI]) were as follows: 0.65 (0.37–1.15), 0.65 (0.45–0.95 unadjusted, 0.41–1.03 adjusted) and 0.69 (0.48–0.99 unadjusted, 0.44–1.07 adjusted) for NE plus OD; 0.79 (0.47–1.34), 0.88 (0.59–1.32) and 0.92 (0.62–1.36) for NE plus OP; and 0.85 (0.51–1.43), 0.96 (0.65–1.42) and 0.98 (0.66–1.44) for OD plus NP (adjusted CIs unless otherwise stated). Combination therapy as compared with placebo reduced the relative risk of admission by 35% at enrolment and at 7 days after discharge ($p = 0.02$ unadjusted, $p = 0.07$ adjusted for multiple comparisons). The number of infants that would need to be treated with NE and OD to prevent 1 admission was 11 (95% CI 6–84), with most apparent effects seen during the first 3 days. Results were not affected by presence of respiratory syncytial virus, history of atopy, presentation less than 2 days after onset of symptoms, severe illness (RDAI score > 6) or by a pharmacy error in which 80% of the dose of OD was given to 23 (11.5%) patients in each of groups 1 and 3 (included in the analysis).

Clinically, RDAI score and respiratory rates improved in all groups; however, infants in the group receiving NE and OP and in the group receiving NE and OD showed significantly lower RDAI scores but higher heart rates during the first hour than infants in the other 2 groups. Median time to discharge from the ED was slightly lower in the group receiving NE and OD (4.6 h) compared with the group receiving NP and OP (5.3 h). Similar numbers of patients sought care for ongoing symptoms.

Adverse events were uncommon and mild (pallor, tremor, vomiting) with 2 infants (both admitted and in each of groups 2 and 3) experiencing transient hypertension.

STUDY CONCLUSION

The study suggests that in infants with bronchiolitis, combined treatment with epinephrine and dexamethasone reduces hospital admissions and shortens both time to discharge and recovery from symptoms; however, this study needs to be confirmed by a larger one powered to directly compare the combination therapy with placebo.

COMMENTARY

This study was undertaken rigorously with appropriate concealment and blinding. Recruitment occurred only 16 hours per day so a proportion of patients was missed, possibly introducing an element of bias. Intention-to-treat analysis was used; only 3 patients were lost to follow-up. Follow-up was too short to assess for possible long-term adverse effects of 6 days of OD; studies have indicated that adverse effects (e.g., growth retardation) do exist, but over a much longer term (i.e., weeks to months of use).[6,7]

The study found an unexpected synergy between dexamethasone and epinephrine with an absolute risk reduction of 9% (number needed to treat = 11) for hospital admissions in the first 7 days compared with placebo, without major adverse effects. The infants treated with combination therapy normalized their feeding patterns and were discharged earlier; neither therapy when given alone differed from placebo. However, the adjusted CIs for risk of admission and return to normal breathing cross 1, and the 95% CI for the number needed to treat of 11 is quite broad. This suggests that the study sample may have been underpowered to detect a statistically significant effect of the combination therapy (although a clinically significant effect is seen).

Perhaps the most important question is, Are these results applicable to my practice? This study is general-

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izable to the average Canadian ED, despite having taken place in academic centres, because the patients are representative of the average healthy infant with acute viral bronchiolitis, given that strict exclusion criteria ensured that those with complex medical issues were not included. One limitation is the exclusion criterion of insurmountable communication barriers; given the diversity of Canada, language is often a problem, but usually translators can be found. A second limitation is that there was no way to distinguish with certainty bronchiolitis from asthma in these infants. It may be that the positive result in this study as opposed to the negative results published elsewhere can be explained by infants with unidentified first-time asthma being enrolled and responding to bronchodilators and steroids.

The clinically observed, if not statistically significant, treatment benefits appear to be worth the demonstrated short-term risks seen in a minority of cases, but long-term health effects are unknown in this otherwise healthy population. The cost of treatment is minimal when compared with the cost of an average hospital admission; 3 mL of 1:1000 epinephrine for nebulization costs US$13.99, and in a 10-kg infant, the course of OD used in this study would cost US$26.65.[8,9]

CONCLUSION

Although the findings of this study are not statistically significant and need to be confirmed by a study with more power that directly compares only the combination therapy with placebo, the results suggest that the combination of NE and OD for the treatment of acute viral bronchiolitis is safe for use by the average ED physician. No major adverse effects were seen with the combination therapy, and the cost of treatment is minimal for clinical, if not statistically significant, benefit in a well-done moderately sized randomized controlled trial.

Competing interests: None declared.

Keywords: bronchiolitis, epinephrine, dexamethasone, pediatrics

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