



The safety of nebulization with 3 to 5 ml of adrenaline (1:1000) in children: an evidence based review

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Abstract

Objective: To present the evidence regarding the safety of nebulization with 3-5 ml of adrenaline (1:1000) for the treatment of children with acute inflammatory airway obstruction.

Sources of data: An electronic search was undertaken, using mainly Medline databases (January of 1949-July of 2004). The study inclusion criteria for this review were: 1) randomized clinical trial; 2) Patients (up to 12 yrs) with diagnosis of bronchiolitis or laryngotracheobronchitis; 3) use of adrenaline (1:1000) by nebulization. The principal data extracted from the trials included adrenaline dosages and their effects on heart rate and blood pressure and any other side effects.

Summary of the findings: Seven clinical trials with a total of 238 patients were included for this review. Two of the five trials in which larger dosages (≥ 3 ml) of adrenaline were used demonstrated a significant increase in heart rate. The mean increase in heart rate varied from seven to 21 beats per minute, up to 60 minutes after treatment. The highest incidence of pallor was observed in one trial with 21 children treated by nebulization with 3 ml of adrenaline (47.6% in the adrenaline group vs. 14.3% in the salbutamol group, 30 minutes after treatment). Two clinical trials failed to observe a significant effect on blood pressure from nebulization with adrenaline (4 and 5 ml).

Conclusion: Evidence shows that nebulization with 3 to 5 ml of adrenaline (1:1000) is a safe therapy, with minor side-effects, for children with acute inflammatory airway obstruction.

J Pediatr (Rio J). 2005;81(3):193-7. Adrenaline, nebulization, laryngotracheobronchitis, bronchiolitis, side effects.

Introduction

Adrenaline (epinephrine) is a potential stimulant of α - and β -adrenergic receptors. In addition to its widespread use in cardiopulmonary resuscitation, adrenaline has been administered, via inhalation, to children with acute obstructions of the airways, caused by inflammatory processes such as laryngotracheobronchitis (croup) and bronchiolitis.¹⁻³ It is believed that the clinical benefits of adrenaline in acute airway obstruction treatment are the result of the following pharmacological effects: a reduction in respiratory secretions and respiratory mucosa edema (α -adrenergic effects) and a relaxation of airway smooth muscle and inhibition of the inflammatory process

(β -adrenergic effects).^{1,4} Despite these theoretical pharmacological properties, a recent meta-analysis did not demonstrate significant effects from the use of adrenaline with infants admitted to hospital for bronchiolitis.⁵ Nevertheless, the benefits of inhaled adrenaline to children with laryngotracheobronchitis were fully confirmed. Initially, the effects of racemic adrenaline were explored,⁶⁻⁹ however, two recent clinical trials have demonstrated efficacy and safety when nebulizing children with laryngotracheobronchitis using 4 and 5 ml of standard adrenaline (1:1000).^{10,11} Based on the results of these studies, the international literature on management of children with laryngotracheobronchitis recommends nebulization with 0.5 ml racemic adrenaline at 2.25%, diluted in 2-3 ml of saline, or with 3 to 5 ml of standard adrenaline (1:1000).¹⁻³ In Brazil only standard adrenaline is available. There is great variation in terms of the adrenaline dosages recommended in Brazilian literature for children with laryngotracheobronchitis.¹²⁻¹⁶ The majority of authors recommend lower doses, varying from 0.5 to 3 ml of adrenaline, diluted in 2 ml of saline.^{12,13,15} However,

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efficacy of nebulization with adrenaline at lower doses has not yet been adequately assessed in children with laryngotracheobronchitis. We have observed that nebulization with smaller doses of adrenaline can often result in incomplete relief of the airway obstruction caused by laryngotracheobronchitis, giving rise to repeated nebulizations with adrenaline, which are rarely necessary when dosages are adequate. Potential side effects, such as tachycardia, hypertension, arrhythmia and pallor, are the main concerns about the use of adrenaline.¹² It is likely that such concerns lead physicians to nebulize children with laryngotracheobronchitis with lower doses of adrenaline.

The objective of this review is to present the evidence on the safety of nebulization with 3 to 5 ml of adrenaline (1:1000) for the treatment of children with acute inflammatory obstruction of the airways.

Methods

Identification of studies

The MEDLINE electronic database (January 1949 to July 2004) was used to identify studies. The keyword search string used was: (adrenaline OR epinephrine) AND (larynx* OR croup OR bronchiolitis) AND (nebul* OR inhal*). Search limits set were: All child: (0-18 years), Clinical trial and Humans. Additional searches were performed on the LILACS and Cochrane Controlled Clinical Trials Register databases. The bibliographical references cited by the articles found were also investigated to identify further studies.

Study selection

The selection of studies was performed in two stages. First two authors independently examined the title, abstract and keywords of the articles identified by the electronic databases in order to select potentially relevant studies with a view to a more detailed reading of the full text. After reading the full texts, the two authors independently decided whether or not to include each article in the review. Studies were included when, in the opinion of the authors, all of the following criteria were met: 1) randomized clinical trial; 2) patients diagnosed with bronchiolitis or laryngotracheobronchitis, aged 18 or less; 3) using adrenaline (1:1000) via nebulization. Interobserver agreement between the two authors was assessed (Kappa: 0.89) and disagreements resolved by consensus.

Extraction and management of data

The two authors independently extracted data from the selected studies, using a predefined table. Data collated included number and age group of patients studied, doses of adrenaline given, effects of adrenaline on heart rate and arterial pressure systemic, in addition to any other side effects of adrenaline. This data, extracted by the two authors, was then compared to check for errors. Side effects of 3 to 5 ml nebulized adrenaline and also of smaller doses of the drug were listed comparatively.

Results

Seven clinical trials were selected for the review. Five trials evaluated the effects of adrenaline on bronchiolitis,^{4,17-20} and two on laryngotracheobronchitis.^{10,11} Table 1 shows the characteristics of the seven clinical trials. A total of 238 patients were given nebulization with adrenaline (1:1000), of whom 184 (77.3%) were given doses greater than or equal to 3 ml. The adrenaline nebulization scheme was similar for the two clinical trials with laryngotracheobronchitis (4 and 5 ml, in a single dose). There was, however, a large variation between the adrenaline doses given to bronchiolitis patients in the other five clinical trials. No severe adverse effects from adrenaline were recorded in any of the seven clinical trials and no patients abandoned studies because of adrenaline side effects.

The effects of inhaled adrenaline on heart rate

The effects of adrenaline on heart were assessed in all seven of the clinical trials. Two of the five trials that used adrenaline doses greater than or equal to 3 ml^{4,10,11,17,19} demonstrated a significant increase in heart rate.^{17,4} In the first study, 99 children admitted for bronchiolitis were given three consecutive nebulizations with 4 ml of adrenaline (1:1000), at 4-hour intervals.¹⁷ The average increase in heart rate, compared with the base rate prior to nebulization, was 13 to 21 beats per minute (bpm), 30 minutes after each nebulization, and 10 to 15 bpm 60 minutes after each nebulization. These increases were statistically significant, compared with a control group (nebulization with saline) (p values between 0.02 and < 0.001). Sixty minutes after the last nebulization, the mean heart rate was 151 bpm (95% CI: 147 to 156) for the adrenaline group, and 138 bpm (95% CI: 134 to 142) for the control group ($p < 0.001$). In the second study 19 children admitted for bronchiolitis received nebulization with 3 ml of adrenaline (1:1000) in a single dose.⁴ The mean increase in heart rate was approximately seven bpm, 40 minutes after nebulization ($p < 0.05$). In contrast with these two studies, Waisman et al. demonstrated a reduction in heart rate after nebulization with 5 ml of adrenaline (1:1000) in 14 children treated in the emergency room for laryngotracheobronchitis.¹⁰ Compared with base heart rate, the mean reduction was five and ten bpm, 30 and 60 minutes after nebulization respectively. There was no data on the statistical significance of this reduction. There were no significant difference in heart rate between groups given standard adrenaline and racemic adrenaline.

Two clinical trials, in which lower doses of adrenaline were administered, did not demonstrate any significant increase in heart rate.^{18,20}

The effect of inhaled adrenaline on systemic arterial pressure

Two clinical trials evaluated the effects of adrenaline on systemic arterial pressure. The dose of adrenaline (1:1000) was greater than 3 ml in both of them. Wainwright et al. showed an increase of 5 mmHg both in systolic arterial pressure and diastolic arterial pressure, 30 minutes after

Table 1 - Characteristics of the seven clinical trials included

Author, place (year)	Patient	Interventions	Adrenaline side effects
Wainwright et al., Australia (2003) ¹⁷	Patients (age < 12 months) admitted to hospital for acute bronchiolitis.	Three consecutive nebulizations with 4 ml of adrenaline (1:1000), at 4-hour intervals. Control group (nebulization with saline), 4 ml, three nebulizations at 4-hour intervals (n = 95).	Mean increase in HR from 13 to 21, and from 10 to 15 bpm, 30 and 60 minutes after each nebulization with adrenaline (p < 0.05). Mean increase of 5 mmHg in systolic arterial pressure and diastolic arterial pressure, 30 minutes after nebulization with adrenaline (p > 0.05). Other side effects not reported.
Hariprakash et al., Great Britain (2003) ¹⁸	Patients (age between 1 and 12 months) admitted to hospital for acute bronchiolitis.	Nebulization with 3 ml of adrenaline (1:1000) diluted in 3 ml of saline, two nebulizations in 30 minutes (n = 38). Control group (nebulization with saline), 5 ml, two nebulizations in 30 minutes (n = 36).	No increase in HR. Pallor, tachycardia, arrhythmia and vomiting not observed.
Abul-Ainine & Luyt, Great Britain (2002) ⁴	Patients (age between 1 and 12 months) admitted to hospital for acute bronchiolitis.	Nebulization with 3 ml of adrenaline (1:1000), single dose (n = 19). Control group (nebulization with saline), 3 ml, single dose (n = 19).	Mean increase in HR of about 7 bpm, 40 minutes after nebulization with adrenaline (p < 0.05). Pallor, tachycardia, arrhythmia, shivers and vomiting not observed.
Bertrand et al., Chile (2003) ²⁰	Patients (age < 12 months) admitted to hospital for acute bronchiolitis.	Nebulization with adrenaline (1:1000), 0.5 ml diluted in 3.5 ml of saline, repeated at each 2-4 hours (n = 16). Nebulization with salbutamol (0.5%), 0.5 ml diluted in 3.5 ml of saline, repeated at each 2-4 hours (n = 14).	No increase in HR. Other side effects were not observed.
Fitzgerald et al., Australia (1996) ¹¹	Patients (age between 6 months and 6 years) admitted to hospital for croup.	Nebulization with adrenaline (1:1000), 4 ml, single dose (n = 31). Nebulization with budesonide (0.05%), 4 ml, single dose (n = 35).	No increase in HR. Six patients in each group presented adverse effects, such as hyperactivity, vomiting, erythema, diarrhea, wheezing and epistaxis.
Menon et al., Canada (1995) ¹⁹	Patients (age between 6 and 12 months) admitted to hospital for acute bronchiolitis.	Nebulization with adrenaline (1:1000), 3 ml, two doses in 30 minutes (n = 21). Nebulization with salbutamol (0.5%), 0.3 ml, diluted in 2.7 ml of saline, two doses in 30 minutes (n = 21).	No increase in HR. Higher incidence of pallor in the group of nebulization with adrenaline, 30 minutes (47.6% versus 14.3%, p < 0.05) and 60 minutes after treatment (38.1% versus 14.3%, p > 0.05). No other side effects were reported.
Waisman et al., United States (1992) ¹⁰	Patients (age between 6 months and 6 years) admitted to emergency room for croup (laryngo-tracheobronchitis).	Nebulization with adrenaline (1:1000), 5 ml, single dose (n = 14). Nebulization with racemic adrenaline (2.25%), 0.5 ml, diluted in 4.5 ml of saline, single dose (n = 14).	Mean decrease in HR of about 5 to 10 bpm, 30 and 60 minutes after nebulization with adrenaline (1:1000). Mean decrease of 6 mmHg in the systolic arterial pressure and diastolic arterial pressure, 60 minutes after nebulization with adrenaline (1:1000).

HR = heart rate; bpm = beats per minute.

nebulization with 4 ml of adrenaline (1:1000) in children with bronchiolitis.¹⁷ These increases were not, however, statistically significant (*p* values: 0.06 and 0.83). Waisman et al. also failed to detect significant effects on the systemic arterial pressure of children with laryngotracheobronchitis after nebulization with 5 ml of adrenaline (1:1000).¹⁰ Mean values for systolic arterial pressure were 115, 114 and 109 mmHg, before and 30 and 60 minutes after nebulization, respectively. Mean values for diastolic arterial pressure were 75, 71 and 68 mmHg, before and 30 and 60 minutes after nebulization respectively.

Other side effects of inhaled adrenaline

The presence of pallor was evaluated in three clinical trials.^{4,19,18} In the first two the adrenaline dose was greater than or equal to 3 ml. Only one demonstrated a greater incidence of pallor in the adrenaline group (3 ml, two doses in 30 minutes), compared with the control group (salbutamol), at 30 minutes (47.6 *versus* 14.3%, *p* < 0.05) and 60 minutes (38.1 *versus* 14.3%, *p* = 0.06) after nebulization.¹⁹ Fitzgerald et al. described other adverse effects, such as a hyperactivity, vomiting, erythema, diarrhea, wheezing and epistaxis, in six patients in each treatment group (adrenaline 1:1000, 4 ml *versus* budesonide 0.05%, 4 ml).¹¹

Discussion

In this review we chose to use the Cochrane protocol to identify and select randomized clinical trials. This strategy guarantees the best evidence on a subject, avoiding errors in the conclusions, which frequently occur in traditional review articles.²¹

Overall, the evidence presented in this review demonstrates a safe profile of nebulization with 3 ml or more of adrenaline (1:1000) in children with acute inflammatory obstruction of the airways. Among the 184 children treated with these doses no adverse effects were observed and no patients had to abandon the studies because of side effects.

Tachycardia is a common side effect of adrenaline administered subcutaneously or intravenously.^{12,15,22} All seven clinical trials evaluated the potential effects of inhaled adrenaline on heart rate. Just two of the five clinical trials that used the larger dose (≥ 3 ml) of adrenaline demonstrated a small, but statistically significant, increase in heart rate. From a clinical point of view, however, these increases can be considered tolerable and without clinical relevance. Furthermore, a tendency was even observed to reduced heart rate in children treated with larger adrenaline doses via nebulizer.¹⁰ It is not surprising that inhaled adrenaline slightly increases or even reduces heart rate in children with acute inflammatory obstructions of the airways. In this case, the potent vasoconstrictive effects of adrenaline on the respiratory mucosa limit its systemic absorption and consequently its β_1 -adrenergic (tachycardia producing) effects.^{2,4} The vasoconstrictive and bronchodilatory effects of adrenaline reduce the inflammatory airway obstruction,

regulate the ventilation-pulmonary perfusion ratio and, thus improve hypoxemia, which is an important cause of tachycardia and arrhythmia.⁴

Another concern about the use of adrenaline is the increase in systemic arterial pressure caused by its α -adrenergic effects. This article reviewed two clinical trials with 113 children that evaluated the effects of inhaled adrenaline on systemic arterial pressure. Neither study demonstrated significant increases, either in systolic pressure or diastolic pressure. The small quantity of systemic adrenaline absorption after inhalation is probably the factor responsible for the absence of significant effects on systemic arterial pressure.

Pallor is another common side effect of the systemic use of adrenaline. The phenomenon is also caused by adrenaline's α -adrenergic effects. Just one of the seven clinical trials that evaluated the side effects of adrenaline, demonstrated an increased frequency of pallor.¹⁹ These data indicate that pallor is uncommon in children treated with inhaled adrenaline.

Summing up, the evidence presented in this review shows that nebulization with 3 to 5 ml of adrenaline (1:1000) is a safe treatment with few side effects. Based on this evidence, we recommend nebulization with 3 to 5 ml of adrenaline (1:1000) for children suffering from acute inflammatory obstructions of the airways.

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