Comparison between nebulized adrenaline and $\beta_2$ agonists for the treatment of acute asthma. A meta-analysis of randomized trials

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Abstract

Objective: To evaluate the efficacy of aerosolized adrenaline compared to inhaled $\beta_2$ agonists in the treatment of acute asthma in the emergency setting.

Data sources: MEDLINE, EMBASE, CINAHI, and Cochrane databases, review articles, and references of included trials.

Review methods: Published (1966-2005) randomized controlled trials with pulmonary function as primary outcome.

Results: Six studies met the criteria for inclusion in the meta-analysis. They included 161 adults and 121 children and adolescents. Patients who received inhaled adrenaline showed a nonsignificant improvement in pulmonary function (standardized mean difference = 0.20, 95% confidence interval −0.22 to 0.63, $P = .35$) compared to patients getting inhaled $\beta_2$ agonists. Moderate heterogeneity was identified between studies ($I^2 = 47.2\%$). Homogeneity was achieved when studies that reported pulmonary function were stratified by intensity of adrenaline treatment. The use of more than 2 mg of adrenaline per dose was equivalent to 5 mg of salbutamol or terbutaline per dose. On the contrary, 2 mg or less of adrenaline per dose was inferior to 2.5 or 5 mg of salbutamol per dose. In addition, there were no differences in heart rate and $Pao_2$ between treatments.

Conclusions: There was no statistically significant benefit of nebulized adrenaline over salbutamol or terbutaline in the treatment of children and adults with moderate-severe acute asthma.

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1. Introduction

Inhaled selective $\beta_2$ agonists, systemic corticosteroids, and supplemental oxygen are the treatment of choice for acute severe asthma [1,2]. In the past, adrenaline has been considered as a first-line treatment for severe acute asthma and is still used when patients do not respond to standard...
treatment [3]. However, when administered parenterally, it may have major adverse effects [4]. More recently, adrenaline has been used in a nebulized form [5]. Its inhalation would allow delivery of the drug on the airway mucosa, optimizing its bronchodilator effect and reducing cardiopulmonary side effects. Nebulized adrenaline offers potential theoretical advantages when compared with \( \beta_2 \) agonists: (1) it may act more rapidly; (2) it may increase bronchial caliber, reducing bronchial mucosal edema through its \( \alpha \) agonist effects; (3) it may also reduce the parasympathetic tonus, allowing a larger bronchodilation; and (4) the stimulation of the \( \alpha \) receptors of lung vasculature might reduce the hypoxemia induced by selective \( \beta_2 \) agonists because of diminished ventilation/perfusion mismatch. On the other hand, potential disadvantages include bronchoconstriction due to the \( \alpha \) agonist properties and the need for more frequent administration of the drug according to its shorter half-life. One study to date demonstrated the efficacy of inhaled adrenaline in the treatment of acute asthma [5]. Nevertheless, there is no published systematic review comparing nonselective agonists to \( \beta_2 \) agonists in the treatment of acute asthma. Thus, this review was designed to compare the efficacy of inhaled adrenaline with selective \( \beta_2 \) agonists for the ED treatment of children, adolescents, and adults with acute asthma.

2. Methods

2.1. Search strategy and selection criteria

The search was conducted using 5 strategies to identify potentially relevant trials. Firstly, we queried the MEDLINE (1966–September 2005), EMBASE (1974–September 2005), and CINAHL (1982–September 2005) databases using the following MeSH, full-text, and keyword terms: emergency OR acute asthma OR status asthmaticus OR severe asthma OR wheeze, AND epinephrine OR adrenaline. Secondly, an advanced search of the Cochrane Controlled Trials Register (third quarter 2005) was completed using the above search strategy to identify any additional trials. Thirdly, references from included studies, reviews, and texts were searched for citations. Fourthly, a manual search of the top 10 respiratory and emergency journals was completed. Finally, unpublished data were requested from the primary authors when necessary. Trials published solely in abstract form were excluded.

Included studies met the following criteria: (1) Target population: children (18 months–17 years) and adults (≥18 years) with acute exacerbations of asthma presenting to an ED or equivalent care setting. All study participants had a clinical diagnosis of acute asthma exacerbation (according to accepted criteria such as those published by the American Thoracic Society [6]. (2) Intervention: single or repeated doses of inhaled adrenaline compared with inhaled \( \beta_2 \) agonists. (3) Design: randomized and placebo-controlled trials without language restriction. (4) Primary outcomes: changes in peak expiratory flow rate (PEFR; absolute and percent of predicted [% PEFR]) and forced expiratory volume in the first second (FEV\(_1\); absolute and percent of predicted [% FEV\(_1\)] from baseline 5 to 45 minutes after the last adrenaline or \( \beta_2 \)-agonist inhalation. Secondary outcome measures were admission to hospital, heart and respiratory rates, oxygen saturation, PaO\(_2\), and side effects/adverse effects.

2.2. Data abstraction and validity assessment

Titles, abstracts, and citations were independently reviewed by 2 reviewers (GJR and LJN) to assess the potential relevance for full review. From the full text, both reviewers independently assessed studies for inclusion based on the criteria for population, intervention, study design, and outcomes. Data extraction included the following items: (1) population: age, sex, number of patients studied, patient demographics, withdrawals; (2) intervention: agent, dose, route of delivery, and duration of therapy; (3) control: concurrent treatments; (4) outcomes; and (5) design: method of randomization and allocation concealment. Any disagreement over study inclusion was resolved by consensus. The methodological quality of each trial was evaluated using the 5-point scale (0 = worst and 5 = best) as described by Jadad et al [7]. This instrument assesses the adequacy of randomization, blinding, and the handling of withdrawals and dropouts.

2.3. Data analysis

The data were combined in meta-analysis by means of random-effects models [8]. For continuous outcomes, the weighted mean difference (for variables using the same unit of measure) or the standardized mean differences (SMD) (reported in SD units, where different units were used) and 95% confidence interval (CI) were calculated. Binary outcomes were pooled using common relative risk and 95% CIs. We tested for heterogeneity by using the DerSimonian and Laird \( Q \) statistic. We also measured heterogeneity by using the \( I^2 \) test [9]. Values of 25%, 50%, and 75% represent low, moderate, and high heterogeneity, respectively. Otherwise, a \( P \) value of less than .05 using a 2-tailed test was taken as being of significance. When heterogeneity was found, subgroup analyses were carried out in an attempt to explain the findings. Sensitivity analysis was performed to identify sources of heterogeneity. These subgroups included intensity of protocol, baseline severity, cotherapies, and methodological quality of the studies. The meta-analysis was performed with the Review Manager 4.2.8 software (Cochrane Review Manager, Cochrane Collaboration, Oxford, UK, 2005).

3. Results

Fig. 1 gives a flow chart of studies assessed and excluded at various stages of the review. Finally, a total of
6 randomized controlled trials (1 including children and adolescents [10], and 5 including adults [5,11-14] were selected). Table 1 gives details of extracted data. Data for 282 subjects (121 children and adolescents, and 161 adults) were available for analysis. There was total agreement between the 2 independent reviewers on inclusion of studies and the Jadad study quality grading. All eligible reports were described as randomized, controlled trials. One study was from Canada [10], 1 from France [14], 1 from Great Britain [11], 1 from Morocco [13], and 2 from Tunisia.

**Table 1** Characteristics of trials included in the review^a^

<table>
<thead>
<tr>
<th>Trial</th>
<th>Design</th>
<th>No. of patients (age range)</th>
<th>Mean baseline severity</th>
<th>Jadad score</th>
<th>Adrenaline dose</th>
<th>β-Agonist dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coupe et al [11]</td>
<td>R, DB</td>
<td>18 (21-57 y)</td>
<td>22% predicted PEFR</td>
<td>2</td>
<td>1 mg × 1</td>
<td>S, 2.5 mg × 1</td>
</tr>
<tr>
<td>Abroug et al [5]</td>
<td>R, DB</td>
<td>22 (&gt;18 y)</td>
<td>&lt;150 L/min PEFR</td>
<td>3</td>
<td>2 mg × 1</td>
<td>S, 5 mg × 1</td>
</tr>
<tr>
<td>Elatrous et al [12]</td>
<td>R, CO</td>
<td>39 (&gt;18 y)</td>
<td>46% predicted FEV1</td>
<td>2</td>
<td>2-5 mg × 1</td>
<td>S, 5 mg × 1</td>
</tr>
<tr>
<td>Plint et al [10]</td>
<td>R, DB</td>
<td>121 (1-17 y)</td>
<td>&gt;5 PIS</td>
<td>5</td>
<td>9 mg × 3</td>
<td>S, 2.25 mg × 3</td>
</tr>
<tr>
<td>Zeggwagh et al [13]</td>
<td>R</td>
<td>44 (&gt;18 y)</td>
<td>&lt;150 L/min PEFR</td>
<td>2</td>
<td>3 mg × 4</td>
<td>S, 5 mg × 4</td>
</tr>
<tr>
<td>Adoun et al [14]</td>
<td>R, DB, CO</td>
<td>38 (16-55 y)</td>
<td>&lt;200 L/min PEFR</td>
<td>3</td>
<td>3 mg × 1</td>
<td>T, 5 mg</td>
</tr>
</tbody>
</table>

^a^ CO indicates cross-over; DB, double blind; PIS, pulmonary index score; R, randomized; S, salbutamol; T, terbutaline.
[5,12]. They were published between 1987 and 2004. One study tested 2 different doses of adrenaline [12]. One study presented patients with moderate exacerbations (baseline predicted FEV1 or PEFR ≥ 50% but < 80%) [12] and 4 with severe exacerbations (baseline predicted FEV1 or PEFR ≤ 50%) [5,11,13,14]. Finally, only 1 study provided clinical scores and admission rates [10]. Measures of pulmonary function were made between 5 and 45 minutes after the last treatment. β2 Agonists and adrenaline were nebulized using jet nebulizers in all studies. In 2 studies, patients were treated with systemic corticosteroids [5,13].

3.1. Pulmonary function

Four studies reported PEFR [5,11,13,14] and 1 FEV1 [12]. When we pooled all studies, patients receiving inhaled adrenaline did not show any significant difference in pulmonary function compared with patients getting inhaled β2 agonists (SMD = 0.20, 95% CI −0.22 to 0.63, P = .35). Moderate heterogeneity was identified between studies ($I^2 = 47.2\%$). However, homogeneity was achieved when studies were stratified by intensity of adrenaline treatment (Fig. 2). Thus, the use of more than 2 mg of adrenaline per dose was equivalent to 5 mg of salbutamol or terbutaline per dose. On the contrary, 2 mg or less of adrenaline per dose (3 studies) was inferior to 2.5 or 5 mg of salbutamol per dose (SMD = 0.66, 95% CI 0.16 to 1.17, $P = .009$).

3.2. Other outcomes

There was no significant difference between groups in the 6 studies [5,10-14] that reported heart rate (SMD = −0.10, 95% CI −0.33 to 0.13, $P = .37$, $I^2 = 0\%$) (Fig. 3). Similar pattern was seen in 3 studies that reported PaO$_2$ [11,13,14] (SMD = −0.09, 95% CI −0.49 to 0.32, $P = .68$). However, in this comparison, there was significant heterogeneity ($I^2 = 79.4\%$). Finally, nebulized β2 agonists showed a marginal significant reduction in PaCO$_2$ compared to adrenaline (SMD = 0.37, 95% CI −0.02 to 0.76, $P = .06$, $I^2 = 0\%$) [5,13,14].

There was insufficient information to pool outcomes such as respiratory rate, blood pressure, oxygen saturation, or side effects. All studies reported that there were no serious side effects. The pediatric study reported that the adrenaline group had a significantly higher incidence of nasal symptoms than the salbutamol group [10].
4. Discussion

The purpose of this systematic review was to examine the efficacy of nebulized adrenaline compared to inhaled $\beta_2$ agonists in the treatment of children and adults with acute asthma in the ED setting. The pooled data showed no significant difference in pulmonary function between both drugs. Moderate heterogeneity was identified between studies, but homogeneity was achieved when studies were stratified by intensity of adrenaline treatment. Then, it was shown that there was a significant difference favoring $\beta_2$ agonists in the stratified category of lower dose (1 or 2 mg) of adrenaline. When the dose of nebulized adrenaline was greater than 2 mg, no difference was achieved in comparison with 2.5 or 5 mg of inhaled $\beta_2$ agonists.

Adrenaline is the drug that most completely activates a $\beta$ receptor, so it is referred to as a full agonist. This pharmacological action results from the temporary occupancy of only a fraction of the total receptor population to exert its maximum effect or intrinsic activity. It has high efficacy [15]. In contrast, the intrinsic efficacy of salbutamol is only 5% of that of adrenaline [16]. Stated otherwise, epinephrine will activate 20 times more $\beta_2$ adrenoceptors than salbutamol when both drugs occupy the same number of receptors. In view of these striking differences in intrinsic efficacy, it is worth considering the clinical implications. The question is why nebulized adrenaline would not be superior to salbutamol in a clinical setting? The short half-life of adrenaline is not a convincing explanation because 4 trials used only 1 dose of inhaled adrenaline and the effect persisted along the trials. However, the duration of adrenaline was significantly shorter in 1 trial [14]. An alternative explanation could be that edema may predominate in smaller airways, and the beneficial effect of adrenaline may have been ignored because PEFR only reflects the response of larger airways [1]. Finally, the positive effect of adrenaline may have been counterbalanced by a bronchoconstriction induced by the stimulation of $\alpha$ airway receptors.

As with any class of drugs, the therapeutic goal with $\beta$-agonist use is achievement of maximal therapeutic effect with minimal undesirable side effects. Thus, data from this review did not show any significant difference in heart rate between groups. Also, the use of inhaled $\beta_2$ agonists has been associated with a fall in PaO$_2$ because of the increase in V/Q mismatching, particularly when they are used by intravenous route [17]. In clinical practice, the fall in PaO$_2$ is small, of short duration, and generally of negligible clinical significance [18,19]. On the other hand, adrenaline was expected to achieve a better PaO$_2$ because of the stimulation of the $\alpha$ receptors of lung vasculature. In agreement with this, patients treated with adrenaline and $\beta_2$ agonists displayed increases in PaO$_2$ without any difference between both groups.

This study met most of the methodological criteria suggested for scientific reviews [20]. A comprehensive search of the published literature for potentially relevant studies was conducted using a systematic strategy to avoid bias. All of the 6 selected trials were randomized, mostly (4) double blind. We did not impose restrictions by language or year of publication, and the search results were complemented by manual searching of relevant journals. In addition, we assessed the consistency of effects between studies to determine the generalizability of the findings; thus, we obtained low or null values of heterogeneity in almost all group comparisons. However, we cannot fully exclude publication bias because we did not evaluate by means of formal statistical analysis [21], as these tests have very low power in meta-analysis of only 6 trials. Short-term trial design precluded obtaining data regarding hospitalization rates, adverse events, and withdrawals. The pharmacoeconomic issue might be contemplated in future trials. Thus, 1 study reported that racemic epinephrine is available at a cost from 2 to 10 times the cost of salbutamol [10]. From the review of the 6 studies included in our systematic review, the use of nebulized adrenaline (despite theoretical advantages) did not produce any advantages over $\beta_2$ agonists in the treatment of moderate to severe acute asthma attacks.

References


