**Objective**

To compare the efficacy of \(\beta\)-agonists given by metered-dose inhaler with a valved holding chamber (MDI+VHC) or nebulizer in children under 5 years of age with acute exacerbations of wheezing or asthma in the emergency department setting.

**Study design**

Published (1966 to 2003) randomized, prospective, controlled trials were retrieved through several different databases. The primary outcome measure was hospital admission.

**Results**

Six trials (n = 491) met criteria for inclusion. Patients who received \(\beta\)-agonists by MDI+VHC showed a significant decrease in the admission rate compared with those by nebulizer (OR, 0.42; 95% CI, 0.24-0.72; \(P = .002\)); this decrease was even more significant among children with moderate to severe exacerbations (OR, 0.27; 95% CI, 0.13-0.54; \(P = .0003\)). Finally, measure of severity (eg, clinical score) significantly improved in the group who received \(\beta\)-agonists by MDI+VHC in comparison to those who received nebulizer treatment (standardized mean difference, −0.44; 95% CI, −0.68 to −0.20; \(P = .0003\)).

**Conclusions**

The use of an MDI+VHC was more effective in terms of decreasing hospitalization and improving clinical score than the use of a nebulizer in the delivery of \(\beta\)-agonists to children under 5 years of age with moderate to severe acute exacerbations of wheezing or asthma. *(J Pediatr 2004;145:172-7)*

Wheezing-associated illnesses are a major cause of morbidity in infants and preschool children, with acute exacerbation of wheezing or asthma being a common reason for emergency department (ED) visits and hospital admissions. In general, nebulized short-acting \(\beta\)-agonists are the standard management for acute exacerbations.\(^1\)-\(^3\) However, nebulizers are more expensive (both in equipment cost and personnel time and equipotent drug cost), require a power source, need regular maintenance, represent a potential cause of cross-infection, and can be highly variable with respect to the rate of aerosol production and the nature of the aerosol.\(^4\)

A valved holding chamber (VHC) and metered-dose inhaler (MDI) combination is an alternative system for administration of \(\beta\)-agonists and is generally used for mild exacerbations of asthma or wheezing among young children.\(^5,^6\) The MDI+VHC combination has been evaluated in all ranges of severity in acute asthma among adults and is at least as effective as the nebulizer in outpatient, inpatient, ED and intensive care units.\(^5,^7-^9\) Moreover, compared with the nebulizer, the MDI+VHC combination provides a quicker and more cost-effective way to deliver aerosolized \(\beta\)-agonists, with fewer side effects in older children with acute wheezing or asthma.\(^10-^18\) as demonstrated by a recent meta-analysis.\(^5\) However, there are only a few studies comparing inhaled \(\beta\)-agonist therapy administered by MDI+VHC versus nebulizer in infants or children under 5 years of age with acute exacerbation of wheezing or asthma, and their conclusions have in some cases not been very well defined or were limited by small sample size (type II error). As a consequence, a systematic review with meta-analysis in this particular population will be useful and important. Thus, the objective of this systematic review was to compare the use of...
of β-agonists given by two different delivery methods (MDI+VHC or nebulizer) in infants or preschool children under 5 years of age with acute exacerbations of wheezing or asthma.

**METHODS**

A search was carried out by using three search strategies to identify potentially relevant trials without language restriction. First, we searched Medline (1966-2003) and Embase (1980-2003) databases by using the following MeSH, full text, and key word terms: (1) emergency or acute asthma or status asthmaticus or severe asthma or wheeze, (2) spacer or holding chamber or volumatic or nebulizer or aerochamber or fisonair or extension or spacing device or inspiire, and (3) nebulizer. Second, an advanced search of the Cochrane Controlled Trials Register was completed by using the above search strategy to identify any additional trials. Third, references from included studies, reviews, and texts were searched for citations.

Criteria for considering trials included (1) randomized, controlled trials conducted in an ED or equivalent care setting; studies involving admitted patients were excluded; (2) studies with infants or preschool children (<5 years of age) treated for acute exacerbation of wheezing or asthma; and (3) patients randomly assigned to receive any β-agonist given by MDI with any VHC versus the same β-agonist given by any nebulizer. The primary outcome measure was admission to the hospital. Secondary outcome measures were final clinical score, duration of treatment in the ED, respiratory rate, oxygen saturation, heart rate, and side effects. Agreement was measured by means of κ statistics.

Titles, abstracts, and citations were independently reviewed by two reviewers to assess 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, and 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.

Study methodological quality of each trial was evaluated through the use of the 5-point scale (0 = worst and 5 = best) described by Jadad et al. This instrument assesses the adequacy of randomization, blinding, and the handling of withdrawals and dropouts.

The data were combined in meta-analyses by means of random-effects models, using the DerSimonian and Laird method. Binary outcome (admission rate) was pooled by using the DerSimonian and Laird method. Binary outcome (admission rate) was pooled by using the DerSimonian and Laird method. The analysis showed that this variable differs on the basis of the β-agonist delivery method (Fig 1). At the end of treatment, patients who received β-agonists by MDI+VHC trial’s difference between the mean of the experimental and the control group, reported on the same scale. The SMD, reported in SD units, was calculated where different units were used to assess the change in symptom score scales: the weighted sum of each trial’s group mean difference divided by its pooled SD. The Cochran Q test was computed to test heterogeneity (examines the null hypothesis that all studies are evaluating the same effect), with a cutoff of 10% for significance. Because this test is known to be poor at detecting true heterogeneity, we used also P (percentage of total variation across studies that is due to heterogeneity). Values of 25%, 50%, and 75% represent low, moderate, and high heterogeneity, respectively. A P value of < .05, with the use of a 2-tailed test, was defined as significant.

Sensitivity analysis was conducted to explore the influence of the following factors on the results: (1) methodological quality (Jadad score of ≥3 vs 3 or <3); (2) baseline disease severity (moderate vs moderate-severe); and (3) disease (wheezing or asthma). The meta-analysis was performed by means of Review Manager 4.2 software (Cochrane Review Manager, Cochrane Collaboration, Oxford, UK, 2003).

**RESULTS**

Seventy-nine articles were identified in the initial search. Of these, reviewers found that 25 papers were potentially eligible. Reasons for subsequent exclusion were studies on children >5 years old (n = 12) and studies on nonacute exacerbations. Of a possible maximum of 5 points for quality, 3 studies scored 5, and 4 studies scored 4. Finally, 6 articles were selected for inclusion in the meta-analysis. One study was from Spain, one from New Zealand, one from Israel, one from France, one from Chile, and one from the United States. The κ statistic for interrater agreement on inclusion or exclusion of potential trials was 1.0. These studies were published between 1998 and 2003. The Table shows the characteristics of trials included in the review.

This systematic review enrolled 491 children, 1 to 60 months of age, who were treated in pediatric EDs. The studies included children with acute wheezing or asthma. Three studies consist of patients with moderate exacerbations and three with moderate to severe exacerbations. Of a possible maximum of 5 points for quality, 3 studies scored 5, and 3 studies scored 4. All studies used a multiple-dose β-agonist protocol, with 5 of the 6 studies analyzed through the use of salbutamol and only one through the use of terbutaline. Bronchodilators were administered at 20-minute intervals in 5 trials and at 10-minute intervals in 1 trial. The duration of treatment was between 40 and 120 minutes. Medication (β-agonists) was nebulized with jet nebulizers in 5 studies and an ultrasonic nebulizer in one study. All studies included in this review reported admission rates. The analysis showed that this variable differs on the basis of the β-agonist delivery method (Fig 1). At the end of treatment, patients who received β-agonists by MDI+VHC.
showed a significantly lower admission rate (OR, 0.42; 95% CI, 0.24-0.72; \( P = .002 \)). The number needed to treat was 10 (95% CI, 6.26), indicating that 10 children needed to be treated with \( \beta \)-agonists by MDI+VHC to prevent an admission. No significant heterogeneity was demonstrated (\( \chi^2 = 4.46, df = 5, P = .49, I^2 = 0% \)), which accepts the null hypothesis of similar treatment effects.

Five studies that recorded clinical scores from different scales through the use of means and standard deviations were analyzed. One study was excluded from this analysis because it reported a pulmonary score with the use of medians only.\(^42\)

The analysis showed a significant decrease of severity in the clinical score with the use of the MDI+VHC (SMD = \(-0.44\); 95% CI, \(-0.68\) to \(-0.20\); \( P = .0003 \)). No significant heterogeneity was demonstrated (\( \chi^2 = 5.43, df = 4, P = .25, I^2 = 24.3\% \)) (Fig 2).

The robustness of the findings to different assumptions was analyzed in sensitivity analyses. Three subgroup analyses were specified a priori: methodological quality (Jadad score), baseline disease severity, and disease. Hospital admission rate did not change when studies of lower methodological quality were excluded (OR, 0.34; 95% CI, 0.16-0.72; \( P = .005; I^2 = 17.9\% \)). The use of \( \beta \)-agonists through the MDI+VHC in children with moderate to severe exacerbations was associated with a significantly lower admission rate (OR, 0.27; 95% CI, 0.13-0.54; \( P = .0003; I^2 = 0\% \)) compared with the use of \( \beta \)-agonists through a nebulizer. On the contrary, there was no difference between both methods in children with moderate attacks (OR, 0.80; 95% CI, 0.34-1.91; \( P = .66; I^2 = 0\% \)). Finally, the analyses of children with acute wheezing also showed a significantly lower hospital admission rate (OR, 0.46; 95% CI, 0.23-0.91; \( P = .03; I^2 = 5.5\% \)).

Because there was insufficient information to pool outcomes such as heart rate, respiratory rate, oxygen saturation, or side effects, we present a narrative summary of individual studies. Two of three studies that reported heart rates showed a significant increase associated with the use of nebulizers.\(^43\) Finally, there were no significant differences in oxygen saturation.\(^40,42,44\)

**DISCUSSION**

The purpose of this systematic review was to compare the efficacy of \( \beta \)-agonists given by two different delivery methods (MDI+VHC or nebulizer) in infants or preschool children younger than 5 years of age with acute exacerbation of wheezing or asthma in the ED setting. Overall, the use of the MDI+VHC was more effective, in terms of hospitalizations and clinical score, than the use of a nebulizer. Our analysis strongly demonstrates that the administration of \( \beta \)-agonists by MDI+VHC significantly decreases hospital admission rate (>50%) compared with administration by nebulizer. This is a very relevant finding because visits to the ED and subsequent admissions count for the largest part of direct health care costs for asthma in most countries,\(^45\) and those children with more severe wheezing are more prone to be admitted to the hospital. Also, the present meta-analysis suggests that the decrease in hospital admission rate is even greater in those children with more severe asthma or wheezing exacerbations who receive \( \beta \)-agonists through the MDI+VHC system compared with the nebulizer. Admission rates could vary among different countries, depending on severity of patients and local practice. Although only three studies defined admission criteria,\(^40,42-43\) they were comparable (clinical symptoms and signs and hypoxia). In addition, a measurement of severity (eg, clinical score) significantly improved (nearly 40%) in the group that received the \( \beta \)-agonist by MDI+VHC in comparison to those by nebulizer. The results of this first systematic review in almost 500 infants or children under 5 years of age with acute wheezing or asthma exacerbation are in agreement with systematic reviews performed in adults and older children with asthma exacerbation who visit the ED\(^5,9,46\).

In our meta-analysis, we also looked at secondary outcomes of side effects (heart rate, respiratory rate, or oxygen saturation) that sometimes occur with \( \beta \)-agonist administration through different systems (eg, MDI+VHC or nebulizer).
However, this was difficult to analyze because of insufficient data. Despite this, two of three studies that reported heart rates showed a significant increase associated with the use of nebulizers.40,44 One study showed a significant increase in respiratory rate associated with the use of nebulizers as well.43 Finally, there were no significant differences in oxygen saturation.40,42,44 This lower incidence of side effects associated with MDI+VHC systems was recently reported in a meta-analysis comparing use of both systems in adults/infants presenting in either the ED or in the community setting.5 Differences in side effects may be because less systemic absorption of the drug occurs with the MDI+VHC system than with the nebulizer.

This study met most of the methodological criteria suggested for scientific reviews.47,48 Similar to all systematic reviews, this meta-analysis is limited by the quality and quantity of existing research and how the data are reported. A comprehensive search of the published literature for potentially relevant studies was conducted by using a systematic strategy to avoid bias. All of the six trials included were randomized, five were double-blinded, and one was placebo-controlled. However, there is a possibility of publication bias. For example, by missing unpublished trials, we may be providing an inaccurate estimation of the effects. Also, there is a possibility of study selection bias. Nevertheless, we employed two independent reviewers and feel confident that the studies were excluded for consistent and appropriate reasons. In addition, the assessment of the consistency of effects across studies is an essential part of the review to determine the generalizability of the findings. Thus, we obtained low values of heterogeneity (<25%) in all group and subgroup comparisons. Last, three of the six included trials were considered "high quality." Interestingly, these "high-quality studies" that include 60% of the total sample showed an even stronger effect in terms of lower hospital admission rate when β-agonists were administered through the MDI+VHC, compared with the nebulizer (OR, 0.34; 95% CI, 0.16-0.72; P = .005).
There is one issue that restricts the generalization of the results of this review. All reviewed studies excluded patients with life-threatening asthma (eg, those patients considered for ventilation), and the results of the review should not be extrapolated to this group. However, it is likely that in patients with life-threatening asthma, nebulizers become more inefficient because of waste of medication during exhalation and contribute increasingly to systemic adverse effects caused by increased oral deposition and systemic absorption. This is probable because of high inspiratory flows, short inhalation times, and increasing oral deposition as airflow obstruction increases.49

Another important potential limitation of this study would be the heterogeneity of wheezing or asthma exacerbation that a given population can have. For example, five of the six studies39,41-44 included in the meta-analysis grouped together subjects with a history of asthma or recurrent wheezing and infants with their first wheezing exacerbation; for many pediatric pulmonologists, the first episode of wheezing is called “bronchiolitis” and its management is controversial. The range of infants with their first wheezing exacerbation included in the studies was from 10% to 83% (see Table). In one study,43 the authors performed a subanalysis of those children with their first wheezing exacerbation, and the outcome (by clinical score) was similar to the rest of their population (in 72.7% with salbutamol by nebulizer and in 89.5% by MDI+VHC, P = .07). We recently developed an “asthma predictive index” (with major and minor criteria used) to identify those recurrent wheezy infants who are at high risk of development of asthma by the time they have reached school age50; however, the information for establishing those criteria are not completely available in the six studies.

Additional questions about the use of MDI+VHC include the use of different VHC and the optimal β-agonist dose and frequency of administration. Comparison of different devices was not possible from the available data; five studies used a plastic VHC39,40,42-44 with volume ranges from 140 mL to 500 mL; the remaining study39 using a metal VHC (volume 250 mL). However, because lung deposition of medication will depend on the degree of airflow obstruction, the method currently advocated in clinical practice consists of the administration of multiple treatments of β-agonists at short intervals titrated against individual patient clinical response (3-6 puffs every 10-20 minutes).13,40,41,44 Finally, we speculate that the administration of β-agonist by MDI+VHC is more effective than by nebulizer because a greater dose is delivered in a shorter period of time and/or a larger dose is delivered to the lungs as the result of greater targeting efficiency.

Overall, this meta-analysis supports the contention that infants and young children younger than 5 years of age with acute exacerbation of wheezing or asthma given β-agonists through the MDI+VHC have lower admission rates and clinical scores compared with patients receiving the same β-agonist through the nebulizer. Moreover, these differences are greater in the patients with more severe wheezing or asthma. Accordingly, we suggest that an MDI+VHC should be the delivery method of first choice to administer β-agonists in this age group of patients for treatment of acute exacerbation of wheezing or asthma in the ED setting.

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REFERENCES