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REVIEW ARTICLE

MDI versus Nebulizers for Acute Asthma

Hengameh H. Raissy, PharmD and H. William Kelly, PharmD

Department of Pediatrics, The University of New Mexico, Health Sciences Center, Albuquerque, New Mexico

OBJECTIVE: To evaluate studies comparing metered dose inhalers with holding chambers to nebulizers in the emergency department for the treatment of asthma exacerbation.
DATA SOURCE: Primary articles and systematic review provided by the Cochrane Airways Review Group of the Cochrane Library identified by MEDLINE search (1966-February 2004) and through secondary sources.
DATA SYNTHESIS: The Cochrane review included 21 randomized clinical trials conducted in hospital emergency departments comparing clinical outcomes following β_2 agonist administration via a nebulizer or a metered dose inhaler with holding chamber. Although the relative risk ratio of hospital admission with metered dose inhaler and holding chamber did not differ in children or in adults compared to the nebulizer delivery, none of the individual studies reviewed were powered to detect a difference in the rate of hospital admission. Specific factors in the treatment of acute asthma such as assessment of severity, appropriate outcome selection, appropriate dose selection, and appropriate delivery systems need to be considered to critically evaluate the literature.
CONCLUSION: Although available randomized clinical trials suggest equivalency of metered dose inhaler plus holding chambers and nebulized delivery of inhaled β_2 agonists, these trials are biased to show no difference in response. There is no data to support the advantage of one method over the other in mild to moderate asthmatic patients either clinically or economically.

KEYWORDS: asthma exacerbation, β_2-agonists, emergency department, metered dose inhaler, nebulizer

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The National Institutes of Health, National Asthma Education and Prevention Program's (NAEPP), Expert Panel Report 2 (EPR 2), Guidelines for the Diagnosis and Management of Asthma defines asthma exacerbations as "acute or subacute episodes of progressively worsening shortness of breath, cough, wheezing, and chest tightness or some combination of these symptoms." Viral respiratory tract infection and environmental exposures, such as tobacco smoking, air pollution, atmospheric ozone and sulfate levels and aeroallergens, are the precipitants of asthma exacerbations.[1]

From 1997 to 2000, the prevalence of asthma exacerbation in children remained the same at 55.3 per 1000 children in 2000.[2] There are about 1.6 million emergency department (ED) visits and 477,000 hospitalizations yearly with a total estimated direct medical expenditure for asthma for inpatient hospital and ED services reaching almost $2.6 billion in 1998. Although not all the patients with asthma exacerbation are hospitalized, hospital inpatient care counted for almost 30% of

ABBREVIATIONS: ED, emergency department; EPR 2, Expert Panel Report 2; FEV_1, forced expiratory volume in one second; MDI, metered dose inhaler; NAEPP, National Asthma Education and Prevention Program; PEF, peak expiratory flow; RR, relative risk ratio; VHC, valved holding chamber

Address correspondence to: Hengameh H. Raissy, PharmD, The University of New Mexico, Health Sciences Center, Ambulatory Care Center 3rd Floor, Pediatric Department, 2211 Lomas Blvd NE, Albuquerque, New Mexico 87131, e-mail: hheidarian-raissy@salud.unm.edu

the total direct medical cost of asthma in 1998.[3] Thus, efforts have been targeted to both decrease the risk of hospitalization, through decreasing the risk of exacerbations, as well as to decrease the cost of the asthma exacerbations by improving therapy of exacerbations. Interestingly, the cost of hospitalization for asthma decreased to 29.5% from 1985 to 1994 because of a shorter length of stay rather than a decrease in rate of admission to the hospital.[4] This suggests that improving the therapy of an exacerbation can produce a significant reduction in cost of care.

Management of asthma exacerbations includes inhaled short-acting β_2 agonists, systemic corticosteroids, inhaled ipratropium, and supplemental oxygen.[1] The EPR 2 recommends albuterol nebulizer solution, 2.5–5 mg every 20 minutes for 3 doses, then 2.5–10 mg every 1 to 4 hours as needed. If a patient is able to coordinate inhalation of medication from a metered dose inhaler (MDI), albuterol MDI 4 to 8 puffs every 20 minutes up to 4 hours, then every 1–4 hours as needed, is recommended.[1] Although aerosolized short-acting β_2 agonists are the mainstay of therapy for asthma exacerbations, the dose, dosing frequency, and method of delivery remain controversial. The aerosolized b_2 agonists can be delivered by either a nebulizer or an MDI with a valved holding chamber (MDI+VHC) type of spacer device. Traditionally, patients who present to an ED with an asthma exacerbation are treated with nebulized β_2 agonists. Results of several studies in adult and children suggest that MDI+VHC is as efficacious as nebulization in the treatment of asthma exacerbation and therefore presents a more cost-effective therapy. Indeed, two recently published systematic reviews have concluded that delivery of short-acting β_2 agonists by MDI+VHC is at least as effective as delivery by nebulizer for the treatment of non life-threatening severe acute asthma exacerbations in children.[5,6] An additional systematic review with a meta-analysis found that in children under 5 years of age the use of an MDI+VHC was superior to nebulizer delivery of β_2 agonists for improving outcomes.[7]

Response to an aerosolized β_2 agonist in severe acute asthma is dependent on the amount of drug delivered to the lung β_2 receptors, as well as the distribution of the aerosol throughout the conducting airways (site of bronchoconstriction).[6,8] On the other hand, systemic effects are due to both the amount of drug delivered to the lung as well as the amount of drug delivered to the mouth and throat and swallowed. As absolute lung delivery and distribution are dependent upon particle size generated by the aerosol device and inhalation rate and airway patency of the patient, greater delivery from one device is dependent on two controllable factors (particle size and inhalation technique). Therefore, an MDI+VHC might improve outcomes by increasing lung delivery and/or distribution by providing a greater number of small particles in the respirable range.[8,9] In addition, delivery via MDI+VHC might produce fewer systemic effects due to the lower oropharyngeal deposition of larger particles that would be swallowed and then absorbed. The first factor would be easily overcome by starting with a higher dosage in the nebulizer, but this may contribute to greater systemic effects. It is with these basic concepts that we critically review the studies that have compared the use of MDI+VHC and nebulizers in the ED for the treatment of asthma exacerbations in children.

LITERATURE REVIEW

Because this is a topic of recent systematic reviews,[5-7] a MEDLINE search of English language publications since the last review was completed up to January 2005. No new study was found when the search was limited to randomized, placebo-controlled, double-blind clinical trials in children with acute asthma exacerbation in ED.

The Cochrane review consisted of 18 trials including 1076 children ≥ 2 years with 4 inpatient trials including 184 children. The trials compared administration of a short-acting β_2 agonist via a nebulizer or an MDI+VHC.[5] For the meta-analysis of ED studies, the primary outcome measure was rate of hospital admission. The relative risk ratio (RR) of hospital admission with MDI+VHC versus nebulizer did not differ in children (RR = 0.65, 95% CI: 0.4 to1.06) which was similar to the adult studies that were reviewed (RR = 0.88; 95% CI: 0.56 to 1.38). Interestingly, the duration in ED for children who were treated with an MDI+VHC was shorter by 37 minutes compared to those who were treated with a nebulizer (95% CI: -50.4 to -24.0 minutes). Pulmonary function as measured by peak expiratory flow (PEF) and forced expiratory volume in one second (FEV_1) at 30 minutes and at the end of the study did not differ between the treatment groups. A lower heart rate was re-

ported in children who used MDI+VHC compared to nebulizer (–7.6% of baseline, 95% CI: –9.9 to –5.3%) but not in the adults. There were no differences in change in respiratory rate, tremor, or the number of patients who received systemic corticosteroids. The authors concluded that there may be some advantages of MDI+VHC over nebulizers in children.

The systematic review recently published by the American College of Chest Physicians and the American College of Asthma, Allergy and Immunology utilized 4 studies included in the Cochrane review and 2 additional trials (1 that was not included in the Cochrane review because of age range).[6] The authors concluded that there was no difference between MDI+VHC and nebulization for improving symptom scores or affecting heart rate in children or adults. Finally, the meta-analysis specific for children less than 5 years reported decreased risk of hospitalization and decreased effect on heart rate for MDI+VHC compared to nebulization.[7] These authors included 2 of the studies assessed by the Cochrane review plus 4 additional studies. In addition, 5 of the studies included first-time wheezers that may or may not have represented asthma. So, we are left with 3 systematic reviews with meta-analyses (including some of the same trials) that report disparate results. Some of this is because of the outcomes assessed and some due to the inclusion criteria for the systematic reviews (age range, asthma versus viral wheezing, etc.). We will attempt to reconcile these differences by reviewing the literature on the issues associated with the studies.

Hospitalization rate

Numerous studies in children 3–18 years of age indicate that the rate of hospitalization with standard care using inhaled β_2 agonists and systemic corticosteroids is 20%–40% of those patients presenting to an ED.[10,11] These rates were taken from control groups of additional interventions so they represent those rates associated with a protocol in place. This is important as instituting a protocol can improve outcomes from ED therapy.[12] The hospitalization rate can be reduced by 30% with the addition of multiple dose ipratropium bromide to the regimen.[10,11,13] Thus, when evaluating studies of alternative therapies, these background hospitalization rates need to be considered. In addition, admission rate varies with age, ethnicity, socioeconomic status and type of insurance. However, the most significant variables are the severity of obstruction upon presentation and initial response to the inhaled β_2 agonist.[6] Therefore, the studies need to be either stratified for severity, or baseline severity should be controlled for in the final analysis. Due to the potential confounding effect of age, the Cochrane review analyzed pediatric and adult studies separately.[5] None of the studies in the Cochrane review were powered to detect a difference in hospital admissions.

Of interest, the 2 trials in the meta-analysis in young infants that provided over 56% of the weight of the analysis and were the only individual studies that favored MDI+VHC over nebulizers, recorded admission rates outside of the range expected.[14,15] Delgado et al. reported a 5% admission rate for the MDI+VHC group versus 20% admissions for the nebulizer group—an incredible 75% reduction.[14] However, they also reported a significantly greater severity as measured by Pulmonary Index score in the group that received nebulized drug, and their analysis demonstrated a significant interaction between baseline severity and admission rate. In contrast, Leversha et al. reported a very high admission rate in the nebulizer group (60%) that was reduced almost by 50% (to 33%) in the MDI+VHC group.[15] However, there was no significant difference in baseline severity between the groups.

Study methodology

The table summarizes the results from the blinded pediatric ED studies in the Cochrane review.[15-18] Nine of the fourteen trials included in the Cochrane review were not blinded.[5] Five of the trials included children less than 2 years of age, the stated cutoff by the Cochrane group. Although patients were randomly assigned to different treatment groups and received the alternative placebo treatment, the order of receiving the treatment was not randomized in all of the studies.[15,16] As a result, there is a bias toward the first treatment, which was MDI+VHC in these studies. When treating young children it is important to administer the drug when the patient is calm and cooperative. Only one of the studies addressed this factor.[15] In one of the studies, patients were instructed to discharge all the puffs (6–10) of the medication in the VHC once and to take deep breaths from the spacer for one minute.[16] Previous studies have shown that this technique decreases the lung deposition of medication.[19]

Although instruction on how to breathe from the VHC was given by one of the studies,[16] no instruction was noted regarding the use of nebulizer. Delgado et al. reported that the principal investigator assisted with the administration of the MDI+VHC to the infants but made no mention of assistance with nebulizer administration.[14]

Additional factors required for critical review of ED studies

In addition to assessing study quality by assigning Jadad[20] criteria for randomized clinical trials, factors specific to the treatment of acute asthma and the delivery of aerosolized medication are required to critically evaluate the literature. These include assessment of severity, appropriate outcome selection, appropriate dose selection, and appropriate delivery systems. Obviously, some of these are interconnected, such as the dose and delivery system.

Dose

A primary assumption of the studies comparing MDI+VHC with nebulizer is that equivalent dosages of the β_2 agonists can be delivered with both methods. Sufficient literature comparing deliveries of the two methods, including dose-response curves in adults and children with stable asthma or mild exacerbations, is available to validate that assumption.[21] Most of the studies utilize a fixed dose and schedule that assumes a fixed dose-response to the inhaled b_2 agonists in acute bronchospasm. Unfortunately, this is not true and studies have clearly demonstrated a variable dose-response that is particularly evident in the more severely obstructed patients.[21] However, even in the less severe patients with a good response to inhaled β_2 agonists, there is a significant variation in response. Strauss et al. reported that up to 36% of adults presenting to an ED required only a single 2.5 mg nebulized dose of albuterol with an additional 20% requiring two doses and the rest requiring a third dose (cumulative total of 7.5 mg) to achieve the optimal response.[22] This 3-fold variation in response combined with the potentially 3- to 4-fold differences in lung delivery from patient to patient is likely to result in a bias towards no significant difference in comparative studies, particularly in patients with mild to moderate exacerbations. This has been confirmed in a comparative clinical trial in children with mild asthma exacerbations (FEV_1 between 50% and 79% of predicted normal) presenting to an ED. The children received single doses of low dose albuterol (2 puffs by MDI+VHC) or high dose albuterol (either as 6–10 puffs by MDI+VHC or 0.15 mg/kg by nebulizer).[23] Although the two high dose regimens produced somewhat greater mean improvements in FEV_1 than the low dose, the differences were not significant ($P = 0.12$). They also looked at good responders (≥ 15 % of predicted improvement) versus poor responders (< 5% improvement) and found 21% excellent responders without a significant difference between treatment groups.

Since most of the studies were designed to demonstrate equivalence, an attempt was made to give equivalent dosages by the two different methods. However, this has resulted in significant differences in the doses compared among the studies (see below) to the point where it appears they are comparing apples to oranges. Just comparing the two major trials in infants, we see that Delgado et al. gave 3 puffs of albuterol in the MDI+VHC while Leversha et al. administered 6 puffs of albuterol.[14,15] Nebulized doses also differed; Leversha et al. administered a fixed dose of 2.5 mg while Delgado et al. used a weight-based dose of 0.15 mg/kg that resulted in a dose range of 0.75 mg–1.8 mg based on mean weights of infants 2–24 months old.[14,15]

Device

The relative dose of β_2 agonist delivered to the airways is dependent on the device and patient cooperation. Most studies have demonstrated more efficient dose delivery from an MDI+VHC versus nebulization.[6,21] However, in comparisons in stable and acute severe asthma, the dose ratio of MDI+VHC to nebulizer has ranged from 1:1 to 1:10.[24] This wide range may be explained by use of different spacers and nebulizers in the trials as well as differences in technique and disease severity. Reduced airway caliber may alter lung deposition,[25] while discharging all of the puffs into the holding chamber before inhaling reduces the amount of drug delivered compared to inhaling each dose separately.[16,19]

Different VHCs have been used in many of the trials (Table 1). While all VHCs decrease deposition of aerosolized drug in the oropharyngeal cavity, their effect on delivery to the lungs varies.[26] In patients who cannot coordinate the actuation and inhalation of MDIs, especially in young chil-

Table 1. Pediatric Emergency Department Double-Blinded Studies Included in Cochrane Review

REF	AGE (N)	DOSE	DEVICE	OUTCOMES	CONCLUSION
16	6–14 yrs (33)	**Albuterol** Neb: 0.15 mg/kg MDI: < 25 kg, 6 puffs 25-35 kg, 8 puffs > 35 kg, 10 puff once	Jet nebulizer (Whisper Jet nebulizer) or VentAHaler	Vital signs, clinical score, arterial oxygen saturation and FEV_1	No difference in efficacy Hospitalization: 6/16 in nebulizer and 5/17 in MDI group
15	1–4 yrs (60)	**Albuterol** Neb: 2.5 mg MDI: 6 puffs every 20 min, repeated at physician discretion (max 6 treatments)	Nebulizer with a Marquest bowl and Hudson facemask or Aerochamber	Heart rate, oxygen saturation, clinical severity score, assessment of wheezing and side effects	MDI was as effective as nebulizer for all the outcomes but produced a greater reduction in wheezing (P = 0.03) Hospitalization:33% in MDI and 60% in Nebulizer group
17	1–5 yrs (64)	**Albuterol** Neb: 0.15 mg/kg MDI: 1 puff/kg (Max 10 puffs) given 3 times at 20 min intervals	Ultrasonic nebulizer or Babyhaler	Pulmonary index	No difference in efficacy Hospitalization: 3 patients in MDI and 3 patients in nebulizer group
18	4–12 yrs (155)	**Albuterol** Neb: < 25 kg, 2.5 mg > 25 kg, 5 mg MDI: < 25 kg, 6 puffs > 25kg, 12 puffs Once	AVA-NEB Hudson or Volumatic	Withdrawal to further treatment, PEF, pulse, blood pressure, tremor and symptom score	No difference in efficacy

dren, delivery is generally enhanced with a VHC. However, using a facemask in young children (necessary in children < 5 years old) decreases lung delivery by one-half compared to inhalation through a mouthpiece for both VHCs and nebulizers.[27] Interestingly, investigators found no difference in delivery efficiency between MDI+VHC (Aerochamber) and nebulization (Pari Baby and Pari LC Star) using radiolabeled albuterol in children with stable asthma. The Pari nebulizers are among the most efficient jet nebulizers.[28] Finally, VHCs can develop static electricity that can result in loss of drug onto the spacer walls and diminished delivery, particularly in young children and infants that require multiple breaths to empty a VHC.[21] This issue was addressed in the study by Leversha et al. but not in the others.[15]

The principal advantage voiced for nebulizers is that they do not require coordination of inhalation and actuation of the device.[29] However, like spacers, different types of nebulizers have been used in different trials. Hess and colleagues compared output and respirable aerosol for 17 nebulizers using a spontaneous breathing lung model.[30] They demonstrated that the dose delivered by the nebulizers varies depending on the brand used, fill volume, and flow. Loffert and colleagues compared 17 jet nebulizers using the same initial fill volume, flow and air compressor.[28] The nebulizers varied significantly in the total delivery of fluid, the time required to deliver the fluid, and percent of the respirable fluid. Interestingly, compared to the trial by Wildhaber[27] that demonstrated equivalent delivery efficiency, the trial by Kerem[16] (Table 1) suggested the MDI+VHC was more efficient, in a 1:5 ratio, despite inappropriate use of the VHC (multiple actuations into the holding chamber prior to inhalation). However, Kerem et al. utilized a large volume (750 mL) VHC compared to the 150 mL volume VHC used by Wildhaber et al., and the nebulizer used by Kerem et al. was one of the least efficient nebulizers, which probably explains the apparent discrepancy.[15,27-29] Interestingly, the trials by Delgado et al. and Leversha et al. used two of the least efficient nebulizers for producing respirable particles.[14,15,28-30] These findings emphasize the importance of the type of nebulizers used in the trials when comparisons are made. Both nebulizer

treatment and MDI+VHC require a certain technique for optimal drug delivery.[8,9] Trained personnel are necessary to coach the patients through the procedure. All comparative studies should state the time for assembly, instruction and administration of each aerosol.

Severity of illness

Some of the issues of disease severity, particularly surrounding mild exacerbations, have been discussed above. Adequate comparisons of delivery methods have not been completed in patients with the most severe exacerbations presenting to the ED (FEV_1 < 30% of predicted) or admitted to intensive care units. A recent review of clinical evidence for treatment of acute severe asthma stated that "As studies excluded people with life-threatening asthma, results may not generalize to such people."[31] It is interesting to note that continuous albuterol nebulization has been shown to be more effective than intermittent nebulization in this more severe subset of patients.[32] In addition, a number of studies of adjunctive therapy to standard doses of the inhaled β_2 agonists suggest that the greatest effect of the adjunctive therapies is found in this severe subset. Indeed, meta-analyses focusing on the addition of multiple doses of inhaled ipratropium bromide to inhaled β_2 agonists found a significant difference in hospitalization primarily in patients with the most severe obstruction.[10,11]

Pharmacoeconomic studies

Cost-effectiveness studies are based on the assumption that the outcomes are equivalent when different delivery methods of β_2 agonists are used. If that is true, then the least costly method is the most favorable one for managing asthma exacerbation in ED. Economic studies should include medication costs, labor costs, equipment costs and startup costs. Labor costs are the most important determinants of the total cost of care.[33,34] Medication costs only account for 6% of ED costs and 11% of hospital costs for acute severe asthma.[33] As both forms of inhaled albuterol (MDI and nebulizer solution) are available as generic drugs, it is highly unlikely that any alteration of drug cost will significantly alter cost-effectiveness. Leversha et al. reported that the cost of the nebulizer equipment and drug was actually much less than that of the MDI+VHC (NZ$3.52 versus NZ$30.60).[15] Their reported cost benefit was from the 50% reduction in hospital admissions. Use of emergency supplies (53%) and respiratory therapy (11%) are the majority of costs for care in the ED, and nursing care (44%) and respiratory therapy (14%) are the major costs in hospitalized patients.[33] As such, improving outcomes through system-wide strategies to improve delivery of both outpatient and ED care is more likely to have a significant financial impact than lowering the cost of medication.[1,12] A few studies suggest substantial cost savings to hospitals with use of MDI+VHC.[35-38] Unfortunately, these studies misclassify labor cost as a variable cost which results in overestimation of nebulizer treatment cost. Labor cost is a fixed cost, meaning that it does not vary with the volume of patients or time spent on patients. Institution costs would decrease only if a switch from one delivery method to the other resulted in elimination of salaries.

As both nebulizer treatment and MDI+VHC require a certain technique for optimal drug delivery, trained personnel are necessary to coach the patients through the procedure. Numata and colleagues measured the teaching time for use of MDI+VHC in ED in adults.[39] The measured teaching time began with giving instruction and placebo administration by a trained nurse followed by patients' self-administration of β_2 agonists. The teaching was completed in 94% of the patients. Median teaching time was 6.2 minutes for asthmatic patients. The teaching time for patients with no previous MDI instruction was 8.4 minutes (66% of the patients). The teaching time was reduced in patients with previous MDI instruction and VHC use at home and use of β_2 agonists before the randomization. When healthy volunteers were instructed on use of MDI+VHC, the teaching time was 17–20 minutes.[40,41] Currently no adequate pharmacoeconomic studies have been completed.[32]

COMMENT

Most summaries of available information suggest that there is sufficient data to support equivalent efficacy of inhaled β_2 agonists whether administered by MDI+VHC or jet nebulizer for patients presenting to the ED with mild to moderate asthma exacerbations. We do not refute that conclusion, nor do we disagree that equivalency has not been established in more severe exacerbations. However, taking the position of the "Devil's advocate," we would like to reformulate

the conclusion as the following: Available data suggests that delivery of inhaled β_2 agonists by MDI plus spacer is no more effective for improving outcomes in acute severe asthma exacerbations than delivery of inhaled β_2 agonists by nebulizer. Equality to a standard that has not been shown to produce an improvement in outcomes for the last 20 years is hardly a finding worth changing the standard of care.[4,42] As long as sufficient inattention is paid to dose, delivery system, and outcomes, we will be wading in a quagmire of data without direction. Critically looking at all of these factors that can affect the study outcomes suggests that there is sufficient grist for debate without resolution. Each side of the debate has either sufficient data to change or resist change.

SUMMARY

Available randomized clinical trials suggest equivalency of MDI+VHC or nebulized delivery of inhaled β_2 agonists. However, numerous factors can create such a large variability in response in the patients that even in those trials that did not use optimal aerosol delivery techniques, the results show equivalency. Thus, trials in mild to moderate asthma are intrinsically biased to show no difference in response. Adequate cost-effectiveness trials have yet to be performed. There is no data (clinical or economic) to support one method over the other in mild to moderate patients. MDI+VHC administration has not been adequately evaluated in patients with life-threatening asthma exacerbations.

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