THE USE OF METERED-DOSE INHALER VERSUS NEBULIZATION FOR THE DELIVERY OF SALBUTAMOL IN PEDIATRIC SEVERE ASTHMA EXACERBATIONS: A SYSTEMATIC REVIEW

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ABSTRACT

BACKGROUND: Recent guidelines for the management of asthma have advocated the use of a pressurized metered-dose inhaler (MDI) and spacer in the delivery of salbutamol. However, there is a dearth of research in children with severe exacerbation.

OBJECTIVES: To compare the effectiveness of MDI with spacers versus nebulizers in drug delivery of salbutamol for the management of pediatric severe asthma exacerbations

METHODOLOGY: A systematic search of the Pubmed, Cochrane library, Herdin, WPRIM, ClinicalTrials and reference review databases was conducted for studies containing "severe asthma" using MDI and spacer as an intervention with nebulization as a comparator.

RESULTS: Of 220 articles, 4 met the criteria. In the subgroup analysis, children who received salbutamol through MDI showed no significant difference in hospital admission, pulmonary score, heart and respiratory rate, oxygen saturation, and lung function.

CONCLUSION: In severe asthma exacerbations, there is evidence to support that MDI compared with nebulizer is statistically equal in terms of hospital admission, pulmonary scores, clinical improvement, and side effects

RECOMMENDATIONS: Further randomized controlled trials are suggested to explore the intricacies of drug delivery in management of severe asthma. A meta-analysis may be made possible in the future with more evidence.

KEYWORDS: severe asthma, metered-dose inhaler, nebulizer, salbutamol

INTRODUCTION

Asthma exacerbation is one of the more common reasons for emergency department consult for children. In acute asthma exacerbations, the drug of choice for management is salbutamol (1). In the pediatric population, these are more commonly delivered through a metered-dose inhaler with a holding chamber or spacer or using a nebulizer. The Global Initiative for Asthma (GINA) released interim guidelines for asthma management this 2020 which advocates the use of a pressurized metered-dose inhaler (MDI) and spacer in the delivery of salbutamol, a short-acting beta-agonist (1). Recent randomized controlled trials and reviews have supported the use of the metered-dose inhaler as more effective and cost-effective (2,6). However, there has been some resistance to this movement.

Although latest guidelines have advocated the use of metered-dose inhaler for infection-control purposes, nebulizers have historically been preferred in the management of asthma exacerbation. This may have been due to the difficulty of younger patients to coordinate inhalation and demonstrate proper technique when using the MDI. Studies have shown that some institutions demonstrated a "nebulizer culture' (3,4). Many parents and physicians still prefer to use nebulizers with diverse reasons, among which is the assumption that the nebulizer has a better delivery of medication compared with salbutamol (3). The lack of available information contributed to this misperception. Furthermore, patients with severe asthma were excluded in systematic reviews determining effectiveness. Therefore, this research aims to answer the question: For managing pediatric severe asthma exacerbations, is using a metered-dose inhaler with spacer as effective as using a nebulizer? Asthma remains to be a major cause of morbidity and mortality in the Philippines with a prevalence of 12% in children (4). Theoretically, MDI with spacers can improve drug distribution to the lower airways by

delivering smaller particles and by decreasing side effects by lessening deposition in upper airways by 80% (5). This is supported by systematic reviews that have already concluded that the use of MDI with spacer is as effective as delivery by nebulizer for the treatment of acute illness with lower side effects of tachycardia or tremor (1). However, people with life-threatening disease were excluded from the study thus limiting the applicability in severe cases (1). There is limited information said about using MDI for severe life-threatening disease. As such, this leaves an impression for some physicians that nebulizers may be more appropriate in severe or life-threatening disease. This systematic review aims to analyze available data to resolve conflicts in management and promote physician champions for change who can help with the cultural change.

Asthma is a chronic airway inflammatory disease resulting to hyperresponsiveness, airflow limitations, and disease chronicity (1,4). An asthma exacerbation is an episode characterized as progressive increase in wheezing, chest tightness, cough, or shortness of breath sufficient to require a change of treatment. This is often triggered by viruses, allergens, pollution, or poor adherence with controllers. Diagnostically, this would present as a decrease in peak expiratory flow (PEF) and forced expiratory volume in the first second (FEV1) from baseline. Severe exacerbations would present as a patient who can only talk in words, sits hunched or agitated, with respiratory rate > 30 mins and a pulse rate more than 120, with use of accessory muscles, desaturation, and PEF 50% predicted. Life-threatening exacerbations present with drowsiness or changes in sensorium (1). In circumstances wherein spirometry is not readily available such as in the emergency room or there is difficulty performing expiratory maneuvers such as with younger children, a scoring system can be used to measure severity. The pulmonary score is a validated severity measure for acute asthma

exacerbation that assesses respiratory rate, wheezing, and accessory muscle use on a scale of 0 to 3. A score of more than seven generally connotes severe asthma exacerbation. A decrease in the pulmonary score signifies response to treatment (8). Salbutamol is a short-acting beta-agonist (SABA) that allows rapid reversal of airflow limitation during exacerbation. A good response to initial treatment is described as an increase of PEF to more than 60 to 80% of predicted or personal best a few hours after administration. Clinically, this will present with increasing oxygen saturation, decreased respiratory rate and pulse rate, and less effort in breathing (1). However, the most common identified side-effects of the same drug include fine tremors and tachycardia with a dose-dependent presentation. Evidence also suggests that delivery through MDI with spacer had lesser side-effects compared with nebulizer (2,7).

General objective

To determine the effectiveness of MDI with spacers compared to nebulizers in drug delivery of salbutamol for the management of pediatric severe asthma exacerbations

Specific objectives

1. To compare the rate of hospital admission and pulmonary scores in patients who were given salbutamol through nebulization versus those who were given through MDI and spacer.

2. To compare oxygen arterial saturation, heart rate, respiratory rate, and lung function test in patients who were given salbutamol through nebulization versus those who were given through MDI and spacer.

3. To compare the most common adverse side effects including tachycardia between MDI with spacer and nebulization

METHODOLOGY

This was a systematic review guided by the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA)

guidelines for systematic reviews. A literature search from various search engines and electronic databases such as The Cochrane Library, PubMed®, Herdin, and WPRIM was done by the primary investigator. Databases of unpublished trials such as Clinicaltrials.gov were utilized. The search strategy: (metered-dose inhaler OR spacer OR holding chamber) AND (nebuli*) AND (asthma) AND ((pedia*) or (child*)) AND (salbutamol OR albuterol) was used. The Medical Subject Headings (MeSH) was employed when searching a database when available. The bibliographies of included studies were also reviewed to identify other relevant trials. Field experts were asked for reference articles or unpublished studies. After reviewing the results of the search, duplicate studies were removed, and a review of titles and abstracts were done. Two reviewers independently evaluated the abstracts generated by the search strategy for inclusion. Those that met the inclusion criteria as seen in table 1 were retrieved as full text articles. Full text copies of studies included were saved in a Google drive accessible to the investigators. The full text articles were screened again based on the inclusion and exclusion criteria. The two reviewers then compared their list of included studies. Discrepancies were compared and disagreements were resolved through discussion. The studies included in the systematic review was assessed for methodological quality using the Cochrane Collaboration Risk of Bias Tool. Risk of bias scorings and extracted data from the studies was managed using Review Manager (RevMan) 5.4 software. All included randomized trials were evaluated based on randomization, concealment of allocation, blinding, treatment of incomplete outcome data, selective reporting, and other bias. Table 2 demonstrates how rating of 'low risk of bias,' 'high risk of bias' or 'unclear risk of bias' was scored for each category. Two investigators independently assessed each study. Discrepancies were compared and discussed until a consensus among the

investigators was reached. Two investigators independently extracted data from the full-text articles. The information needed included descriptive data (author, year published, age range, number of patients studied), details in the administration of salbutamol (agent, dose, delivery method, duration of therapy, and concurrent treatments) and outcomes assessed, and study details required for appraising the methodological quality of the document. After data collection, the two investigators verified information extracted. A narrative synthesis of all included research based on identified outcomes was done. If possible, pooled estimate of Mean Difference (MD) for continuous variables and Risk Ratio (RR) for categorical variables is planned to be computed along with 95% confidence intervals (CIs). We used RevMan 5.4 for statistical analysis.

RESULTS

The search of articles through databases and other sources yielded 216 references. After deduplication, fifty-seven articles were reviewed based on their title and abstract for eligibility. Out of the fifty-seven, seven articles were found to meet the inclusion criteria and full-text studies were retrieved. Of the seven articles, one article was excluded due to incomplete data as it was an ongoing clinical trial. A total of six studies were included in the analysis. However, one study was also excluded due to difficulty in retrieving an English translation. Another study was excluded since the study population also included adults. A flowchart of study selection is discussed in figure 1.

Four studies are included in this systematic review as seen in table 3. The study of Leversha et al. (2000) is a randomized, double-blind, placebo-controlled trial consisting of 60 children aging one to four years old with moderate to severe exacerbation and a known history of asthma. The study of Vilarinho (2003) was a randomized, single-blinded trial among children presenting with wheezing

crises at the walk-in section of a hospital in Brazil. A total of 54 children with moderate wheezing crisis ages 22 days to 11.7 years were included. On the other hand, Jamalvi et al. (2006) conducted a cross sectional study in the Emergency Room (ER) of National Institute of Child Health (NICH) on a total of 50 children, with ages six months to fifteen years old, and with a history of wheeze and presenting with an acute asthma exacerbation. They were later categorized into mild, moderate, and severe asthma based on medical scoring system. Finally, the most recent among the four studies is the randomized clinical trial conducted by Iramain et al. (2019), The study includes 103 children with severe asthma exacerbations treated in the ED. In total there were 267 children with moderate to severe asthma included in this review. All four studies randomly assigned patients between a spacer group and a nebulizer group. Leversha et al., (2000) divided his study population into the Spacer group (n=30, mean age: 36.0 ± 11.5 months) and the Nebulizer Group (n=30, mean age: 32.3 ± 13.5 months). The spacer group were given 600 ug salbutamol via MDI by spacer (AeroChamber) then placebo by nebulizer, while the Nebulizer Group were given placebo MDI by spacer then salbutamol (2.5 mg) by nebulizer. The treatments were repeated by an interval of 20 minutes up to a maximum of 6 treatments. Until the attending physician decides that the patient does not need further doses of bronchodilator (10). In 2003, Vilarinho et al. after equally dividing his study population between the two groups administered 3 doses of salbutamol (100 mcg/3 kg in the spacer group and 250 mcg/3 kg in the nebulizer group) every 20 minutes until the child was considered to have improved significantly and no longer required any further treatment, or until three doses were done (11). On the other hand, Jamalvi et al (2006), compared effectiveness of administration of salbutamol by Metered Dose inhaler (MDI) with accessory device (AD) by giving 100 mcg for 2 puffs for 3 times versus administration of

salbutamol by small volume nebulizers (SVN) using 0.3 ml/kg as asthma treatment (12). Finally, Iramain et al. (2018) gave salbutamol for two puffs every 10 minutes for 2 hours and subsequently by every 30 minutes for 2 hours through MDI with valved-holding chamber and mask in conjunction with oxygen through a separate cannula (n=52) for his intervention group. For his control group (n=51) nebulization was done with oxygen and salbutamol and ipratropium (1 puff every 20 minutes for 2 hours and subsequently 30 minutes for an additional 2 hours) (13). Outcomes for each study varied. Most studies used clinical outcomes such as heart rate, respiratory rate, oxygen saturation, and effort of breathing to measure effectivity. Measures of cost-effectivity such as hospital admission rate and duration of admission were also measured. Different pulmonary scores were used to measure clinical responsiveness and asthma severity post-treatment. Only Jamalvi et al. (2006) was able to utilize pulmonary function tests such as PEFR to measure asthma response. Side effects of drug administration were measured through presence of tachycardia and hyperactivity. Majority of studies were of low risk of bias as shown in figure 2. Three were double-blinded studies and four had randomize treatment allocation. Only the study of Jamalvi et al. (2003), demonstrated high risk for bias as there was no mention of blinding done in the study for both the participant and the outcome assessment. Participants were also aware of treatment group whether by MDI with spacer or nebulizer. Leversha et al. (2000) found that there was a significantly less admission rate in children treated using MDI with spacer (33% spacer versus 60% nebulizer, p-value = 0.04, adjusted for sex). This is consistent with the findings of Iramain et al. (2018) who found that children who were nebulized had a higher risk for admission versus those who used MDI with spacer (RR 0.21 [0.6-0.69], P=0.003). In contrast, Vilarinho et al. (2003) and Jamalvi et al (2006) both saw no significance in the rate of admission (p-value = 0.19, p-value =

0.185). Table 4 shows that for all studies only mean hospital admission rate was reported and standard deviation was not computed for hence a pooled analysis was not made possible.

While pulmonary scores were used more often to assess response to treatment, different standards were used. The study of Leversha et al. (2000) utilized clinical severity score to determine effect of MDI and spacer versus nebulizer and found that the absolute change in score was similar (-2.9 spacer vs -2.7 nebulizer, P-value = 0.55). This was consistent with a study by Vilarinho et al. (2003) and Jamalvi et al. (2006) which showed no clinical significance between the use of MDI and nebulization in clinical severity scoring. However, of the four included studies, one study demonstrated that the pulmonary score index of children in the spacer group showed significantly better improvement than those in the nebulizer group after 4 hrs. of treatment (2.5±1.0 spacer vs 4.15±0.9 nebulizer, $p<0.00001$) (1,3). The clinical criteria for pulmonary scores used per study were different as demonstrated in table 5 hence pooling cannot be done.

With regards to effect on vital signs, the evidence from available studies also showed varying results. In terms of heart rate, only Leversha et al. (2000) and Iramain et al. (2019) demonstrated a higher heart rate in the nebulizer group compared with the MDI group. In contrast, Jamalvi et al. found no significant difference. In comparison, all studies showed no significant difference in respiratory rate change. Finally, only one study by Iramain et al. (2019) showed that significant improvement in oxygen saturation after treatment with MDI with spacer compared with the nebulizer group. In a study by Leversha et al. (2000), while the 2 groups had similar outcomes for oxygen saturation, respiratory rate, the spacer group developed greater decrease in wheezing (p-value= 0.030). This is consistent with the study of

Vilarinho et al. (2006) and Jamalvi et al. (2003) who both reported that there were no significant differences in outcome measures between the 2 groups in terms of vital signs and related outcomes (respiratory rate: p-value= 0.133; heart rate; p-value= 0.188; dyspnea: p-value= 0.082; cyanosis: p-value= 0.236). On the other hand, the study of Iramain et al. (2019) observed that the metered-dose inhaler group had significantly increased oxygen saturation 90 minutes post-treatment than the nebulizer group (90.5 ± 1.7 vs 88.43 1 ± 1, respectively, p-value< 0.00001). In table 6, only 2 studies published data on standard deviation thus limiting our ability to acquire a collected result.

Only one study utilized lung function tests to measure outcome. The study of Jamalvi et al. (2003) showed that the Peak Expiratory Flow Rate (PEFR) in children more than 5 years old increased significantly in both groups after treatment completion, but it was not statistically significant when compared in between groups (p-value of 0.10 each after 10 minutes, 20 minutes and 2 hours of treatment) (1,2).

Tachycardia was noted to be significantly greater in the nebulizer group within the first treatment compared with the spacer group (p-value< 0.010), based on the study of Leversha et al. (2000). Furthermore, this was found to be continuously higher throughout the rest of the study period (p-value = 0.03). This was supported by the study of Iramain et al. (2018) which found that heart rate was significantly higher in the nebulization group from 30 minutes of treatment until the end of the study (p-value < 0.00001). However, the studies of Vilarinho et al. (2003) and Jamalvi et al (2006) showed no significant difference. The differences in table 7 may lie in the study population wherein Leversha et al (2000) and Iramain et al (2019) both had a baseline mean heart rate of 149 bpm to 156 bpm whereas Vilarinho et al (2003) and Jamalvi et al. (2006) had a mean heart rate of 125 bpm to 136 bpm.

DISCUSSION

Overall, results in this study were consistent with previous research. It has been found that comparisons between spacer and nebulizer treatment show that they are equally effective in the delivery of salbutamol to children with mild to moderate asthma in shortening hospital stay (MD: -33.48 minutes; 95% CI:-43.43 to -24.65 minutes, $p<0.001$) with a tendency but without statistical significance on decreasing hospital admission (RR: 0.71, 95% CI: 0.47 to 1.08, $p=0.11$) (2,14). For children with severe asthma, two of the four studies showed no statistical significance in terms of hospital admission rate and pulmonary scores to measure response to treatment between the two study groups in severe asthma.

In terms of secondary outcomes, the result of this study builds on the current recommendations for bronchodilator delivery on MDI use. Outcomes measured included heart rate, respiratory rate, oxygen saturation, lung function tests, and adverse outcomes. Leversha et al. (2000) concluded that a combination of MDI and spacer is as effective as a nebulizer in delivering salbutamol to young children with moderate and severe acute asthma. In the study population, the MDI-spacer combination was the preferred option for treatment for its lower hospital admission rates and lower costs. The spacer offers an effective choice to the nebulizer routine use in the acute setting (10). In Vilarinho et al. (2003), their study revealed that outcomes in the groups do not differ significantly (p-value> 0.05), except for air entering, which scored lower in the MDI group. Furthermore, both the spacer and the nebulizer were equally beneficial when it comes to improving clinical scores and oxygen saturation levels. They were proven to be clinically equal at different doses (100 microg/3 kg with the spacer and 250 microg/3 kg with the nebulizer). It was then concluded that the use of a homemade spacer with a metered-dose inhaler is a more cost-effective option to the use of a jet nebulizer in the

delivery of salbutamol to children experiencing mild wheezing attacks (11). Jamalvi et al. (2003) also observed comparable discharge outcomes in both groups and concluded that the use of MDI in the ER is an effective alternative to nebulizer for the treatment of children with acute asthma exacerbation (12). Finally, one study (Iramain et al., 2019) concluded that MDI was more effective than nebulization in relation to reducing hospital admission, enhanced oxygen saturation and clinical score. However, further studies are needed to support these new outcomes (13).

Remarkable in this systematic review is the differences in salbutamol dosage given between MDI with spacer and nebulizer. In general, a higher dose was provided during nebulization as per clinical guidelines. This was justified by a study done on a model of a neonatal lung on mechanical ventilation which showed that albuterol at 100 mcg given through MDI with a spacer is equivalent to 2500 mcg to 3700 mcg via nebulizer (15). In all studies, uncertainty over the dosage was overcome by repeating treatments at short intervals until a clinical response was observed. Another factor that should be taken into consideration when interpreting this study is that children with severe asthma were further classified to those requiring advanced airway such as mechanical ventilation and those who do not. Some studies excluded those who required advanced airway since decision-making to use an MDI versus nebulization is influenced by other factors such as feasibility and tolerance of the patient. However, a study conducted on twelve intubated infants and children showed no significant difference in respiratory mechanics or hemodynamics between those treated with nebulizer versus MDI plus spacer (p-value = 0.56) (16). It is theorized that small diameter endotracheal tubes influence drug delivery due to deposition of medication but can be overcome with higher doses. Finally, this study also does not take into account the individual preferences of

children in terms of nebulization and use of a spacer. Some children find difficulty in sitting for 5 to 10 minutes during nebulization and find the noise produced by the device as frightening. Whereas some children may have difficulty with maneuvering the valve in some spacers. These factors should be considered by the clinician during decision-making

To summarize, we showed that the metered-dose inhaler (MDI) can be used as an alternative to the nebulizer for the delivery of salbutamol in pediatric severe asthma exacerbations. In majority of studies, it was shown to be comparable in outcomes with nebulization while study authors recommend it because it is convenient to use. The results with respect to lack of significant difference in outcomes was consistent with previously published systematic reviews and meta-analysis (14). Apart from the clinical response, the physician should also consider different individual factors that may influence the choice between the use of MDI with spacer and nebulization.

CONCLUSION AND RECOMMENDATIONS

This study shows that there appears to be no major differences in terms of efficacy and side effects between MDI and nebulization with salbutamol. However, we acknowledge the limitations in the review due to the limited quality of evidence available to come up with a meta-analysis. Furthermore, different standards were used among studies to define asthma severity. It was difficult to compare effects of medication due to the variety of treatment protocols and doses used in the studies included. The lower dose needed in MDI delivery may support favorability due to cost effectivity and efficiency. Also, it may have led us to underestimate the clinical effect of MDI with spacer. In conclusion, despite the lack of evidence showing the superiority of MDI in the treatment of severe asthma, there may be some evidence to support that they are

statistically equal in terms of hospital admission, pulmonary scores, clinical improvement, and side effects. This should guide the clinician in decision making when treating severe asthma amongst other factors such as feasibility, availability, and applicability. Clinical trials have been found underway to provide more evidence in support of the best delivery method for bronchodilators in management of severe asthma. Once enough research is made available, the author recommends revisiting this study for a possible meta-analysis. In addition, parental and child acceptance and tolerance are also factors that influence physician decision-making and may be worth exploring.

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TABLE 1: INCLUSION AND EXCLUSION CRITERIA FOR INCLUDED STUDIES

Inclusion Criteria	Exclusion Criteria
Target population Children 0 to 18 years old diagnosed with asthma in moderate to severe exacerbation consulting at a primary or tertiary care institution **Type of intervention** Salbutamol delivery through MDI with spacer Comparator: Salbutamol delivery through nebulizer **Type of studies** Randomized controlled study **Types of outcomes** Hospital admission rate, pulmonary score, change in respiratory rate, pulse rate, and oxygen saturation, immediately after intervention, incidence of tachycardia, and lung function.	Articles published in non-English language Observational studies or randomized trials which are cross-over in design

TABLE 2. RISK OF BIAS JUDGEMENT FOR A SPECIFIC OUTCOME

Overall risk of bias judgment	Criteria
Low risk of bias	The study is judged to be at low risk of bias for all domains for this result
Unclear risk of bias	The study is judged to be at some concerns in at least one domain for this result
High risk of bias	The study is judged to be at high risk of bias in at least one domain for this result OR the study is judged to have some concerns for multiple domains in a way that substantially lowers confidence in the result

TABLE 3. CHARACTERISTICS OF STUDIES INCLUDED

STUDY ID (Author, year, location)	Study title	Population	Method/Design	Comparator	Intervention	Study outcomes
A Leversha A.M., Campanella, S.G., Aickin, R.P., Asher, M.I. 2000 Starship Children's hospital in Auckland, New Zealand	Costs and effectiveness of spacer versus nebulizer in young children with moderate and severe acute asthma	Inclusion 1 to 4 yrs. old in moderate to severe exacerbation, known history of asthma Exclusion -Received inhaled bronchodilator 1 hr. prior to admission - coexisting pneumonia	Randomized, double-blind, placebo-controlled trial	Nebulizer of 600 mcg salbutamol + NSS	MDI with spacer of 2.5 mg salbutamol	Heart rate, respiratory rate, oxygen saturation, clinical severity score, wheezing, tremor, hyperactivity, admitted or discharged
B Vilarinho, L.C.S, Mendes, C.M.C, Souza, L.S.D 2003 Centro Pediatrico Prof Hossana de Oliveira, Brazil	Metered-dose inhalers with home-made spacers versus nebulizers to treat moderate wheezing attacks in children	Inclusion Children up to 12 yrs. of age, with moderate wheezing crisis Exclusion Use of bronchodilators or corticosteroids, severe chronic disease such as GERD, cystic fibrosis, cardiopathy, immune deficiency	Randomized, single-blinded trial	Nebulizer with 250 mcg/3kg in 5ml saline solution	MDI with spacer of 100mcg/ /3kg weight of salbutamol	Level of consciousness, skin color, intensity of dyspnea and retractions of the chest muscles, expiratory period, air entry, wheezing, o2saturation
C Jamalvi, S.W., Raza, S.J., Naz, F., Shamim, S., Jamalvi, Z. 2006 National Institute of Child Health, Pakistan	Management of acute asthma in children using metered dose inhaler and small volume nebulizer	Inclusion 6 months to 15 years with acute asthma exacerbation Exclusion ICU requiring, PEFR <20% or >70%, O2 saturation < 90%, received daily treatment with corticosteroids	Cross-sectional study	Nebulization of salbutamol (0.3 mg/kg) with 2ml normal saline	MDI with spacer of salbutamol 100mcg, 2 puffs for 3 times	Dyspnea and retractions, respiratory rate, heart rate, wheeze, blood pressure, o2 saturation, PEFR, pulmonary score
D Iramain, R., Castro-Rodriguez, J.A., Jara, A., Cardozo, L., Bogado, N., Morinigo, R., De Jesus, R. 2018	Salbutamol and ipratropium by inhaler are superior to nebulizer in children with severe acute asthma exacerbation: randomized clinical trial	Inclusion 2-18 yrs. old with severe acute asthma exacerbation Exclusion Radiologic pneumonia, pulmonary and or cardiac congenital malformations,	Randomized, double-blinded	Nebulization of salbutamol (0.15 mg/kg) in 5ml Normal saline, 7mins every 20 mins for 2h then every 30 mins for 2 more hrs.	MDI with spacer of salbutamol 100mcg, 2 puffs every 10 mins for 2 hrs. then every 30 mins for 2 hrs.	Pulmonary score, oxygen saturation

Hospital Clinicas and Instituto Privado del Nino, Paraguay		chronic pulmonary disease, foreign body aspiration, neurologic alteration, very severe acute asthma exacerbation requiring intubation				

TABLE 4. SUMMARY OF OUTCOMES FOR HOSPITAL ADMISSION

Study	Outcome	p-value
A (Leversha et al.)	33% required hospital admission with MDI and spacer 60% required admission with nebulizer	=0.04
B (Vilarinho et al.)	9% required hospital admission with MDI and spacer 15 % required hospital admission nebulizer	=0.19
C (Jamalvi et al.)	4.8% required hospital admission with MDI and spacer 10.6% required hospital admission with nebulizer	=0.185
D (Iramain et al.)	Higher hospitalization in the nebulization group versus the NBI group (RR 0.21 [0.6-0.69])	=0.003

TABLE 5. SUMMARY OF OUTCOMES FOR PULMONARY SCORES

Study	Outcome	p-value
A (Leversha et al.)	Clinical severity score based on wheeze, heart rate, and accessory muscle use Less 2.9 in MDI with spacer group Less 2.7 in nebulizer group	0.55
B (Vilarinho et al.)	Global score based on level of consciousness, skin color, retraction, dyspnea, expiratory period, air entry, wheezing, and oximetry Less 3.68 for MDI with spacer group Less 3.15 for nebulizer group	0.55
C (Jamalvi et al.)	Medical scoring system based on heart rate, respiratory rate, pulsus paradoxus, dyspnea, accessory muscle use, wheeze Less 3.8 for MDI with spacer group Less 3.7 for nebulizer group	n/a
D (Iramain et al.)	Pulmonary score based on wheeze, heart rate, and accessory muscle use Less 4.54 for MDI with spacer group Less 2.91 for nebulizer group	<0.00001

TABLE 6. SUMMARY OF OUTCOMES FOR VITAL SIGNS

STUDY	OUTCOME	P-Value
	Heart rate change compared with baseline	
A (Leversha et al.)	Higher 2.4 bpm in MDI with spacer group Higher 10.5 bpm in nebulizer group	<0.01
B (Vilarinho et al.)	Not reported	
C (Jamalvi et al.)	Lesser 18 bpm in MDI with spacer group Lesser 17 bpm in nebulizer group	=0.188
D (Iramain et al.)	Lesser 11.86 bpm in MDI with spacer group Higher 15.66 bpm in nebulizer group	<0.00001
	Respiratory rate change compared with baseline	
A (Leversha et al.)	Higher 0.3 cpm in MDI with spacer group Lesser 0.9 cpm in nebulizer group	insignificant
B (Vilarinho et al.)	Lesser 7.4 cpm in MDI with spacer group Lesser 8.8 cpm in nebulizer group	=0.93
C (Jamalvi et al.)	Lesser 22 cpm in MDI with spacer group Lesser 21 cpm in nebulizer group	=0.133
D (Iramain et al.)	Not reported	
	Oxygen saturation percent change compared with baseline	
A (Leversha et al.)	Higher 0.7% in MDI with spacer Higher 1% in nebulizer group	insignificant
B (Vilarinho et al.)	Higher 2.52% in MDI with spacer Higher 1.3% in nebulizer group	=0.29
C (Jamalvi et al.)	Not reported	
D (Iramain et al.)	Higher 10% in MDI with spacer Higher 6.75% in nebulizer group	<0.00001

TABLE 7. SUMMARY OF SIDE EFFECTS

Study	Outcome	p-value
A (Leversha et al.)	HR higher by 0.17 bpm with MDI group HR higher by 11 bpm with nebulizer group	<0.010
B (Vilarinho et al.)	Not reported	<0.06
C (Jamalvi et al.)	HR 110 bpm with MDI group HR 107 bpm with nebulizer group	=0.188
D (Iramain et al.)	HR 144.7692 bpm with MDI group HR 172.2 bpm with nebulizer group	<0.00001

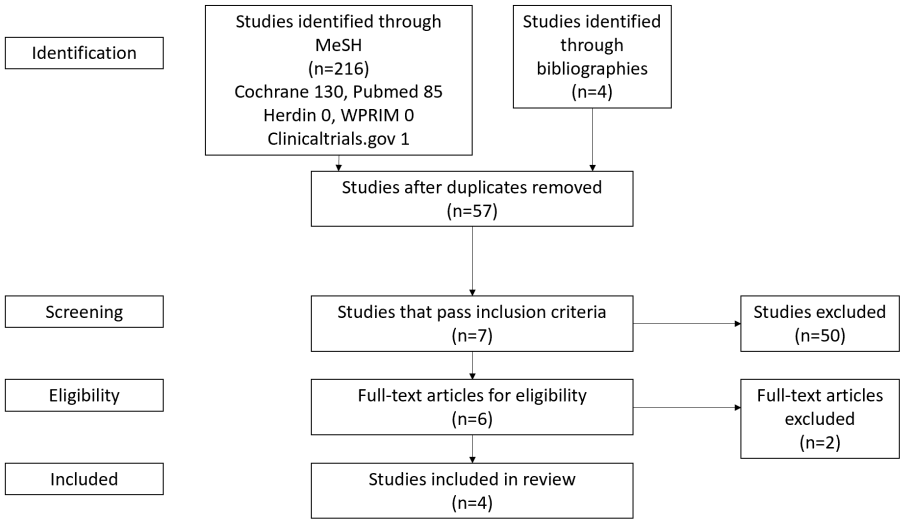

FIGURE I: PRISMA FLOW DIAGRAM OF STUDY SELECTION PROCESS

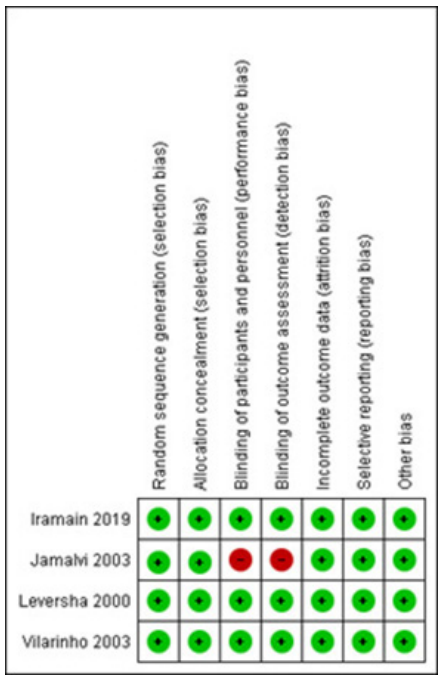

FIGURE II: RISK OF BIAS ASSESSMENT