Clinical Efficacy of Vibrating Mesh and Jet Nebulizers With Different Interfaces in Pediatric Subjects With Asthma

Gerald B Moody, Peter M Luckett, Courtney M Shockley, Rong Huang, and Arzu Ari

BACKGROUND: Nebulizers are commonly used in emergency departments to deliver bronchodilators to children with asthma exacerbations. However, no clinical study comparing a vibrating mesh nebulizer with a jet nebulizer is available in this patient population. The purpose of this study was to compare the clinical efficacy of a vibrating mesh nebulizer to a jet nebulizer combined with a mouthpiece or mask in children with asthma exacerbations admitted to the emergency department. METHODS: We conducted a single-blinded randomized clinical trial of 217 children (2–18 y old) with a moderate to severe asthma exacerbation in the emergency department. Assessment of severity was defined by our acute asthma score, adapted from the Pediatric Asthma Score. Subjects were randomized to receive bronchodilator treatment via vibrating mesh nebulizer (n = 108) or jet nebulizer (n = 109) and were treated until they achieved a mild asthma score and were discharged or until a decision to admit was made. All subjects were treated per our acute asthma clinical pathway algorithm for the emergency department with modifications to allow for blinding, assessment of treatment, and data collection. Outcome variables included hospital admission rate, number of treatments, and time to mild asthma score. RESULTS: There was a significant difference in baseline asthma score between subjects treated with the vibrating mesh nebulizer and those treated with the jet nebulizer (P = .042), but no other significant differences in demographics existed between groups. To adjust for effect of baseline asthma score, a multiple logistic regression model was used to model admission. The vibrating mesh nebulizer group had a lower probability of being admitted to the hospital (P = .062), and they required significantly fewer treatments (P < .001) and less time to reach a mild asthma score (P = .004) than those in the jet nebulizer group. In subjects with a mask interface, the vibrating mesh nebulizer significantly reduced the probability of admission (P = .032). CONCLUSIONS: Subjects treated with a vibrating mesh nebulizer required significantly fewer treatments and less time to achieve a mild asthma score. In subjects with a mask interface, the vibrating mesh nebulizer significantly reduced the probability of admission compared to jet nebulizer. (ClinicalTrials.gov registration NCT02774941.) Key words: aerosols; jet nebulizer; vibrating mesh nebulizers; pediatric asthma; moderate; severe; children; emergency department; albuterol.

Introduction

Asthma is a common childhood disease affecting approximately 6.1 million children in the United States. AAcute asthma exacerbation leads to > 680,000 emergency department visits and > 70,000 hospitalizations for children each year. The first-line treatment for children presenting in the emergency department with an asthma exacerbation is timely administration of oral corticosteroids and aerosolized short-acting β-agonists (SABAs). While

Mr Moody is affiliated with the Department of Respiratory Care, Children’s Health – Children’s Medical Center, Dallas, Texas. Dr Luckett is affiliated with the Department of Pediatrics, Division of Critical Care Medicine, University of Texas Southwestern Medical Center, Dallas, Texas. Dr Shockley is affiliated with the Department of Emergency Medicine, Division of Pediatric Emergency Medicine, UT Health Science Center at San Antonio, San Antonio, Texas. Mr Huang is affiliated with the Research Administration, Children’s Health – Children’s Medical Center, Dallas, Texas. Dr Ari is affiliated with the Department of Respiratory Care, Texas State University, Round Rock, Texas.
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QUICK LOOK

Current knowledge

Advancements in technology have led to the development of newer nebulizers, such as vibrating mesh nebulizers. Multiple in vitro and in vivo studies indicate that vibrating mesh nebulizers are more efficient and deliver more medication compared to jet nebulizers. There have been no randomized clinical trials comparing the clinical efficacy of vibrating mesh nebulizers versus jet nebulizers with different interfaces.

What this paper contributes to our knowledge

Among pediatric subjects who presented to the emergency department with moderate to severe asthma exacerbations, those who were randomized to receive bronchodilator treatment with a vibrating mesh nebulizer required significantly fewer treatments and took less time to reach discharge criteria compared to those who were randomized to treatment with a jet nebulizer. For subjects treated with a face mask interface, the vibrating mesh nebulizer significantly reduced the probability of admission compared to the jet nebulizer.

Methods

Subject Population

The study was conducted in the emergency department of Children’s Medical Center, a 490-bed not-for-profit tertiary pediatric hospital in Dallas, Texas, between August 2016 and March 2019. Subjects were children between the ages of 2 and 18 years who had a known history of asthma and presented to the emergency department with moderate to severe asthma exacerbation. Eligible subjects were enrolled when the study investigator was available to obtain consent and collect study data. Assessment of severity was defined by the Children’s Medical Center’s acute asthma score, adapted from the Pediatric Asthma Score, which rates the

short-term systemic corticosteroid dosing and administration are well established, variations in terms of dosing, frequency, and devices used to deliver inhaled SABAs still exist. Current recommendations for the initial treatment of mild to moderate asthma in the emergency department are to administer up to 3 SABA treatments via nebulizers or pressurized metered-dose inhalers (pMDIs) over 1 h in 20-min increments. For severe asthma exacerbations, the current recommendation is 3 high doses of SABA plus ipratropium bromide administered every 20 min or an equivalent dose administered continuously over 1 h. pMDIs and nebulizers can be used to administer intermittent therapy, but nebulizers must be used to deliver continuous treatment. Although pMDIs with valved holding chambers have been shown to be just as effective as nebulizer treatments, nebulizers are often preferred in moderate to severe exacerbations due to the ability to deliver single or multiple medications continuously.

A variety of patient interfaces, such as masks and mouthpieces, are available to administer aerosol therapy regardless of device used. Interface selection is usually based on patient size, age, and adherence. Nebulizers are more efficient when used with a mouthpiece, but younger children and acutely dyspneic patients may not be able to use a mouthpiece properly.

Nebulized SABA dosing recommendations are based on the use of jet nebulizers, which are commonly used in hospitals and emergency departments due to their low cost and ease of use. Advancements in technology have led to the development of newer nebulizers, such as vibrating mesh nebulizers. In vivo and scintigraphy data indicate that vibrating mesh nebulizer are more efficient and deliver higher concentrations of medication compared to jet nebulizers. In a recent study using a pediatric lung model, the combination of a vibrating mesh nebulizer and valved mask delivered a >2-fold increase in drug delivery compared to a jet nebulizer with an aerosol mask, dragon mask, or valved mask. There have been no randomized clinical trials comparing vibrating mesh nebulizers with jet nebulizers in terms of clinical outcomes in pediatric subjects with moderate to severe asthma exacerbations in the emergency department.

The primary purpose of this study was to compare the effect of using a jet nebulizer versus a vibrating mesh nebulizer with different interfaces on clinical outcomes in treating children with acute moderate to severe asthma. The secondary purpose of the study was to determine the clinical efficacy of mouthpiece and face mask combined with a vibrating mesh nebulizer or a jet nebulizer in children with asthma admitted to the emergency department. The effect of disease severity on the hospital admission rate was also explored. We hypothesized that using a vibrating mesh nebulizer would result in fewer hospital admissions, fewer treatments, and decreased time to achieve a mild asthma score compared to our current practice of using a jet nebulizer.

This study was supported by an unrestricted educational grant by Aerogen. Mr Moody has disclosed a relationship with Aerogen. Dr Ari has disclosed relationships with the CHEST Foundation, Bayer Pharmaceuticals, ARC Medical, Aerogen, and Sunovion Pharmaceuticals. The other authors have disclosed no conflicts of interest.

Correspondence: Gerald B Moody RRT RRT-NPS, Department of Respiratory Care, Children’s Health – Children’s Medical Center, Dallas, TX. E-mail: gerald.moody@childrens.com.

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severity of exacerbation based on breathing frequency, oxygen requirement, retractions, and findings on auscultation (mild: 1–4; moderate: 5–8; severe: 9–12) (Table 1). The score has been utilized in our in-patient and emergency department acute asthma clinical pathway algorithm since 2013. Initial asthma score was obtained by an emergency department respiratory therapist after initial nursing assessment in triage. Patients were excluded if they had any comorbid/complex medical conditions (eg, cardiovascular disease, cystic fibrosis, chronic lung disease, airway anomalies, or immunodeficiency syndromes), coexisting medical conditions such as pneumonia, or if they were in impending respiratory failure as determined by treating physician. Patients who received oral corticosteroids in the previous 24 h or bronchodilator treatment within 1 h of the emergency department admission were also excluded.

Subject Enrollment

Eligible subjects were approached for enrollment by a study investigator after receiving permission from the attending physician. Prior to enrollment, informed consent was obtained from the parent, legally authorized representative, or subject if they were 18 y of age. All subjects received a corticosteroid (1–2 mg/kg prednisone or prednisolone, maximum 60 mg; 0.3–0.6 mg/kg oral dexamethasone, maximum 16 mg; or 1–2 mg/kg intravenous methylprednisolone, maximum 60 mg) as soon as possible per standard of care, but no SABAs were administered prior to obtaining consent. Once enrolled, subjects were randomized in a single-blinded fashion (from study investigator) to receive aerosol treatments via jet nebulizer with aerosol mask or mouthpiece or via vibrating mesh nebulizer with valved mask or mouthpiece.

Online randomization software (https://www.graphpad.com, Accessed May 12, 2016) was used to assign subjects to a treatment group. Sequentially numbered envelopes were assigned to the jet nebulizer and vibrating mesh nebulizer groups (in a 1:1 ratio) with a corresponding card placed inside to indicate jet nebulizer or vibrating mesh nebulizer. Envelopes were sealed and stored in a secure location, and then assigned to study subjects in numerical order as enrolled. This study was approved by the hospital’s institutional review board.

Nebulizers

The control group used our standard single-use, small-volume jet nebulizer (AirLife Sidestream High-Efficiency Nebulizer, CareFusion, Yorba Linda, California) operated at 7 L/min per the manufacturer’s guidelines. The jet nebulizer is operated with pressurized oxygen to aerosolize liquid drugs. The study group used a vibrating mesh nebulizer (Aerogen Solo with Ultra adapter, Aerogen, Galway, Ireland), which is an electronically powered nebulizer with a mesh consisting of 1,000 precision-formed holes vibrating at 128,000 times per second to generate aerosol by pumping liquid through the holes. The Ultra adapter is an accessory to the vibrating mesh nebulizer that allows intermittent or continuous nebulization for pediatric and adult patients via a valved mouthpiece or a valved mask. It was operated per manufacture’s guidelines with 2 L/min of supplemental flow with a valved mask, and without supplemental flow with the valved mouthpiece unless subjects had an oxygen requirement (Figure 1).

Table 1. Acute Asthma Score*

<table>
<thead>
<tr>
<th>Score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breathing frequency by subject age, breaths/min</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2–3 y old</td>
<td>≤ 26</td>
<td>27–34</td>
<td>35–39</td>
<td>≥ 40</td>
</tr>
<tr>
<td>4–5 y old</td>
<td>≤ 24</td>
<td>25–30</td>
<td>31–35</td>
<td>≥ 36</td>
</tr>
<tr>
<td>6–12 y old</td>
<td>≤ 20</td>
<td>21–26</td>
<td>27–30</td>
<td>≥ 31</td>
</tr>
<tr>
<td>&gt; 12 y old</td>
<td>≤ 18</td>
<td>19–23</td>
<td>24–27</td>
<td>≥ 28</td>
</tr>
<tr>
<td>Oxygen requirement</td>
<td>≥ 98% on room air</td>
<td>95–97% on room air</td>
<td>90–94% on room air</td>
<td>&lt; 90% on room air or any oxygen</td>
</tr>
<tr>
<td>Auscultation</td>
<td>Normal with good aeration throughout</td>
<td>Normal to end-expiratory wheezes</td>
<td>Expiratory wheezing</td>
<td>Inspiratory and expiratory wheezing to diminished breath sounds</td>
</tr>
<tr>
<td>Retractions†, no.</td>
<td>None (0)</td>
<td>Intercostals (1)</td>
<td>Intercostals, substernal (2)</td>
<td>Intercostal, substernal, supraclavicular (3)</td>
</tr>
</tbody>
</table>

* Severity of exacerbation based on breathing frequency, oxygen requirement, retractions, and findings on auscultation (mild: 1–4; moderate: 5–8; severe: 9–12).
† Our acute asthma score captures the types of retractions to define severity; however, it is common practice in our institution to score based on the number of retractions, and not necessarily on the type of retraction because children of different ages and anatomy present differently. To be consistent with common practice, the number of retractions was used for scoring in this study.
Interfaces

As our standard care, the jet nebulizer was used in conjunction with one of 2 face masks, either a dragon aerosol mask (KidsMED Pediatric Aerosol Dragon Mask, KidsMED, Hinsdale, Illinois) or an AirLife aerosol mask (adult size, CareFusion), or a mouthpiece utilizing a T-piece and 6-inch flexible tube as a reservoir. The vibrating mesh nebulizer was used with a pediatric or adult valved face mask (Salter Labs I-Guard Aerosol Mask, Arvin, California) or a valved mouthpiece (Aerogen). The selection of the interface for both aerosol devices was made at the discretion of the treating respiratory therapist and based on the subject’s age, size, and ability to follow instructions or comply with mouthpiece application.

Study Procedure

All subjects were treated per the Children’s Medical Center’s acute asthma clinical pathway algorithm with modifications to allow for blinding, treatment assessment, and data collection. Per the algorithm initial treatment of moderate to severe asthma (asthma score 5–12) consists of 3 treatments of albuterol and ipratropium delivered intermittently in 20-min increments or combined and given continuously over 1 h. For this study, 3 intermittent treatments were ordered instead of continuous aerosol therapy to allow for the assessment of response after each dose. Two personnel were used for study procedures, an emergency department respiratory therapist to administer treatments and the blinded study investigator to perform assessments after treatment. To eliminate inter-rater variability, all posttreatment assessments were performed by the blinded study investigator. The asthma score was used to determine the severity of the exacerbation and the need for additional treatments. If the subject received an asthma score of 5–12, a subsequent treatment was administered. If the subject received an asthma score of 1–4 (mild), they did not receive a subsequent treatment and were reassessed every 20 min. If after 40 min the subject still demonstrated a mild asthma score, treating physicians were notified to evaluate subjects for discharge. Subjects receiving an asthma score of 5–12 during any reassessment received subsequent treatment. This procedure was repeated until the subject received a mild asthma score or there was a decision to admit. In our institution, patients who have not progressed after 2 h of treatment (ie, 6 treatments) are commonly admitted. See Figure 2 and Figure 3 for the study procedure, medication, and dosages for the first, second, and third hours.

Blinding was achieved when the emergency department respiratory therapist placed a randomized nebulizer in an opaque bag hanging from an intravenous pole after each treatment. Considering that the vibrating mesh nebulizer operates via electricity, the controller box used to power the vibrating mesh nebulizer was attached to an intravenous pole and placed bedside for each enrolled subject regardless of assigned nebulizer to maintain blinding. Because subjects, parents, and legal guardians were not blinded to the nebulizer used, they were instructed not to comment or discuss the nebulizer with the blinded study investigator during posttreatment assessments. Any questions, concerns, or comments were directed to the emergency department.
To compensate for different treatment times between the jet nebulizer and vibrating mesh nebulizer, posttreatment assessments were completed 15–20 min after initiation of treatment to ensure blinding of the investigator. In addition, a sign was posted outside the subject’s treatment room to indicate when the randomized nebulizer was hidden so that blinded investigator could safely enter the room.

If, at any time or any phase, a subject was deemed to be in impending respiratory failure by treating physicians, the subject was removed from the study and managed by the clinical team. The study procedure stopped as soon as a decision to discharge or admit was made by the treating physicians. The decision to admit or discharge was at the sole discretion of treating physicians regardless of asthma score or number of treatments administered. Physicians’ requests for additional treatments despite meeting mild asthma score were noted to track total treatments to discharge. Any adjuvant therapies were ordered at the treating physician’s discretion.

*Adjuvant therapies ordered at physician discretion:
- Magnesium sulfate - IV
- Terbutaline - IV
- Epinephrine - IV
- Heliox
- Noninvasive ventilation

Study protocol ends if heliox or NIV ordered.

1st Neb treatment

- <10 kg: 2.5 mg albuterol/250 μg ipratropium
- ≥10 kg: 5 mg albuterol/500 μg ipratropium

20 min post assessment and AS

- Mild; AS 1-4
- Moderate; AS 5-8
- Severe; AS 9-12*

2nd Neb treatment

- <10 kg: 2.5 mg albuterol/250 μg ipratropium
- ≥10 kg: 5 mg albuterol/500 μg ipratropium

20 min post assessment and AS

- Mild; AS 1-4
- Moderate; AS 5-8
- Severe; AS 9-12*

3rd Neb treatment

- <10 kg: 2.5 mg Albuterol/250 μg Ipratropium
- ≥10 kg: 5 mg Albuterol/500 μg Ipratropium

20 min post assessment and AS

- Mild; AS 1-4
- Moderate; AS 5-8
- Severe; AS 9-12*

Advance to phase 1b

*Mild; AS 1-4 Moderate; AS 5-8 Severe; AS 9-12*

Mild; AS 1-4

- If subject scores moderate to severe (5-12) at any 20 min re-assessment, administer subsequent treatment or advance to next phase depending on number of treatments given

Fig. 2. Flow chart of the first hour of the study procedure, medication, and dosages for the first, second, and third hours. AS = asthma score.
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Fig. 3. Flow chart of the second hour of the study procedure, medication, and dosages for the first, second, and third hours. AS = asthma score.

Statistical Analysis

The initial sample size was based on another previously published study comparing pMDIs with a spacer versus jet nebulizers in children with moderate to severe asthma exacerbations.13 The hospital admission rate was estimated to be 60% in the jet nebulizer group and 33% in the vibrating mesh nebulizer group. The overall admission rate was estimated to be 60% in the jet nebulizer group and 33% in the vibrating mesh nebulizer group. The overall admission rate was
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estimated to be 45%. A sample size of 60 subjects per group (ie, 120 subjects in total) was initially calculated to be adequate to provide 80% power to detect a statistically significant difference in hospital admission rates between the 2 groups (significance level = 0.05, 2-sided). After the 108th subject was enrolled, an independent, third-party, blinded, interim power analysis was performed because the overall rate of hospitalization was considerably lower than the rates anticipated in the original design. Using the same power calculation as before, it was determined the study would require an additional 50 subjects per group. Institution review board approval was granted, and the sample size was increased to 220 subjects.

The primary outcome variable was the rate of hospitalization between the 2 treatment groups. Hospitalization was defined as admission to a general pediatric unit or ICU. Secondary outcome variables were the number of treatments to mild asthma score and the time to mild asthma score. Time to mild asthma score was defined as the time elapsed from the start of the initial treatment to the time of mild asthma score as documented in the electronic medical record. The maximum recorded posttreatment heart rate was noted as the posttreatment heart rate. All outcome variables were compared to identify differences between mouthpiece and mask combined with the jet nebulizer and the vibrating mesh nebulizer.

Descriptive analyses of categorical and continuous variables were performed using proportions, frequencies, medians, and interquartile ranges, respectively. Statistical methods to test 2 independent groups included the chi-square test, Fisher exact test, and Wilcoxon rank sum test, as appropriate to the variable’s level of measurement and distribution. Log transformation was used to make independent variables with highly skewed distributions less skewed. The adjusted effect of different types of nebulizers was estimated with a multiple logistic regression model for a binary outcome, or with multiple linear regression analysis for a continuous outcome. The other independent variables in the regression models included the unbalanced variable (ie, log-transformed asthma score) and significant predictive variable (ie, log-transformed subject weight). P values ≤ .05 or less were considered statistically significant. The statistical analyses were performed with SAS 9.4 (SAS Institute, Cary, North Carolina).

Results

Initially, 220 children were enrolled and randomized to the jet nebulizer and vibrating mesh nebulizer groups. Two children were excluded when they were discharged after an initial decision to admit was made and they were treated off of study protocol, and one child was excluded after the diagnosis of pneumonia was made. Of the remaining 217 children, 108 were treated with a vibrating mesh nebulizer and 109 were treated with a jet nebulizer (Fig. 4). Table 2 shows demographic and baseline characteristics. The median (interquartile range) baseline asthma score was significantly higher in the vibrating mesh nebulizer group [9.0 (8.0–10.0) vs 8.0 (7.0–10.0), P = .042], but no other significant differences existed between groups.

Effect of Nebulizers and Disease Severity on Admission and Discharge

Figure 5 shows overall admission rates in the vibrating mesh nebulizer and jet nebulizer groups. Admission rates were 31% lower (6.3 percentage point difference) in the vibrating mesh nebulizer group (15 of 108 children) than in the jet nebulizer group (22 of 109 children), but this did not reach significance (P = .22). Although there was no significant difference in admission rate between groups based on severity, the absolute reduction with vibrating mesh nebulizer remained even when analyzed by subgroup: 7.2% for moderate and 8.4% for severe. One child in the jet nebulizer group was transferred to the ICU after initially being admitted to general care, while all other subjects were admitted to general care. Additionally, it is important to note that simple randomization failed to balance the baseline characteristics between the 2 groups because the baseline asthma score was significantly higher in the vibrating mesh nebulizer group.

To adjust for the effect of significant differences in baseline asthma score, multiple logistic regression models were used to model admission. The predictors included vibrating mesh nebulizer, log-transformed asthma score, and log-transformed subject weight. Based on the sign of regression coefficients, subjects with a higher asthma score and body weight were positively associated with the risk of admission (P < .001, P < .001, respectively). After the adjustment of log-transformed asthma score and weight, subjects treated with a vibrating mesh nebulizer had a higher probability of being discharged overall (P = .062).

Effect of Nebulizers on Subject Treatments and Progress

Overall, the median number of treatments required to achieve a mild asthma score was significantly less in the vibrating mesh nebulizer group than in the jet nebulizer group (2 vs 3 treatments, respectively, P < .001), regardless of baseline asthma score (Fig. 6). As shown in Table 3, there was a 28.4% decrease in median (IQR) time of 58 (33–103) min to reach mild asthma score in the vibrating mesh nebulizer group compared a time of 81 (56–133) min in the jet nebulizer group (P = .004). None of the discharged subjects received adjuvant therapies; however, in
subjects who were admitted, 2 subjects received magnesium sulfate and 3 subjects received magnesium sulfate plus terbutaline in the jet nebulizer group versus 2 subjects who received magnesium sulfate in the vibrating mesh nebulizer group. There was no significant difference between groups in the overall mean pretreatment heart rate (vibrating mesh nebulizer 122 ± 6 17.28 beats/min vs jet nebulizer 122 ± 20.62 beats/min) and posttreatment heart rate (vibrating mesh nebulizer 153 ± 19.91 beats/min, jet nebulizer 152 ± 22.72 beats/min).

Effect of Mask and Mouthpiece on Subject Outcomes

There was no significant difference between mask and mouthpiece interface in terms of hospital admission and number of treatments to mild asthma score when combined with vibrating mesh nebulizer (P = .15 and P = .40, respectively) or jet nebulizer (P = .97 and P = .80, respectively). However, in subjects with a face mask, using the vibrating mesh nebulizer combined with a valved mask reduced hospital admission rate by a relative 48% (10% absolute reduction) compared to jet nebulizer with aerosol mask: vibrating mesh nebulizer 10.7% (9 of 84) versus jet.

Fig. 4. Flow chart for subject enrollment and treatment. VMN = vibrating mesh nebulizer; JN = jet nebulizer.

Table 2. Demographics and Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Vibrating Mesh Nebulizer</th>
<th>Jet Nebulizer</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>73 (67.6%)</td>
<td>73 (67.0%)</td>
<td>.92</td>
</tr>
<tr>
<td>Female</td>
<td>35 (32.4%)</td>
<td>36 (33.0%)</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>45 (41.7%)</td>
<td>48 (44.0%)</td>
<td>.80</td>
</tr>
<tr>
<td>Black</td>
<td>62 (57.4%)</td>
<td>59 (54.1%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1 (0.9%)</td>
<td>2 (1.8%)</td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>42 (38.9%)</td>
<td>46 (42.2%)</td>
<td>.62</td>
</tr>
<tr>
<td>Non-Hispanic</td>
<td>66 (61.1%)</td>
<td>63 (57.8%)</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>7.0 (5.0–9.5)</td>
<td>6.0 (5.0–10.0)</td>
<td>.61</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>27.3 (20.2–42.8)</td>
<td>25.7 (20.0–44.9)</td>
<td>.66</td>
</tr>
<tr>
<td>Baseline asthma score</td>
<td>9.0 (8.0–10.0)</td>
<td>8.0 (7.0–10.0)</td>
<td>.042</td>
</tr>
<tr>
<td>Baseline asthma score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate (5–8)</td>
<td>46 (42.6%)</td>
<td>63 (57.8%)</td>
<td>.03</td>
</tr>
<tr>
<td>Severe (9–12)</td>
<td>62 (57.4%)</td>
<td>46 (42.2%)</td>
<td></td>
</tr>
<tr>
<td>Interfaces</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mask</td>
<td>84 (77.8%)</td>
<td>87 (79.8%)</td>
<td>.71</td>
</tr>
<tr>
<td>Mouthpiece</td>
<td>24 (22.2%)</td>
<td>22 (20.2%)</td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as n (%) or median (interquartile range). Vibrating mesh nebulizer group: n = 108 subjects; jet nebulizer group: n = 109 subjects.
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![Graph showing rate of admission](image)

**Discussion**

In children presenting to the emergency department with acute moderate to severe asthma exacerbations, we observed a relative reduction in overall admission rate by 31% (6.3% absolute) when delivering medication through the vibrating mesh nebulizer. Although this difference did not reach statistical significance, we believe that it is clinically important. The reduction in admission rate was similar regardless of exacerbation severity. In children treated with a face mask, we noted that the vibrating mesh nebulizer reduced hospital admission by 48% (10% absolute reduction) and significantly reduced the probability of admission compared to treatment with the jet nebulizer. In children who were discharged, those who received bronchodilator therapy with the vibrating mesh nebulizer required significantly fewer treatments and took less time to reach a mild asthma score compared to treatment with the jet nebulizer. Whereas multiple studies have reported that the vibrating mesh nebulizer delivers more medication compared to the jet nebulizer, this is the only randomized clinical trial to examine the clinical efficacy of the vibrating mesh nebulizer versus the jet nebulizer in children with moderate to severe asthma exacerbations using a face mask or mouthpiece.

The motivation for our research was based on a previous bench study by Ari et al\textsuperscript{20} that compared aerosol delivery between a jet nebulizer and a vibrating mesh nebulizer in a simulated spontaneously breathing pediatric lung model using 3 different mask interfaces: an aerosol mask, a dragon mask, and a valved mask. Although the authors found no significant difference between masks when combined with a jet nebulizer, the delivery efficiency of a vibrating mesh nebulizer with the valved mask was greater than with the dragon or the aerosol mask. The authors also noted that, when combined with a valved mask, a vibrating mesh nebulizer delivered significantly more medication (11.11 ± 0.66%) than a jet nebulizer regardless of mask interface used (5.33 ± 0.75% with a valved mask, 4.67 ± 0.94% with a dragon mask, and 4.08 ± 0.27% with an aerosol mask). We designed this study to test whether the difference in drug delivery between a vibrating mesh nebulizer and a jet nebulizer, as reported by Ari et al,\textsuperscript{20} would lead to improved clinical outcomes compared to our current practice of using jet nebulizers combined with the dragon or aerosol masks. Whereas Ari et al\textsuperscript{20}...
**Table 3. Time to Achieve Mild Asthma Score**

<table>
<thead>
<tr>
<th>Outcome by Subjects</th>
<th>Vibrating Mesh Nebulizer</th>
<th>Jet Nebulizer</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall, min</td>
<td>58 (33–103)</td>
<td>81 (56–133)</td>
<td>.004</td>
</tr>
<tr>
<td>Moderate baseline</td>
<td>45 (25–92)</td>
<td>71 (52–95)</td>
<td>.01</td>
</tr>
<tr>
<td>Severe baseline</td>
<td>74 (42–127)</td>
<td>105.5 (68–162)</td>
<td>.02</td>
</tr>
</tbody>
</table>

Data are presented as median (interquartile range).

Fig. 7. Admission rate between groups stratified by mask interface. In subjects with face mask, overall admission rate was 48% lower (10% absolute reduction) in the vibrating mesh nebulizer group compared to the jet nebulizer group (P = .07). After adjustment for significant difference in baseline asthma score, logistic regression model showed that vibrating mesh nebulizer combined with a valved mask could significantly reduce the probability of admission (P = .032) compared to jet nebulizer with aerosol mask. JN = jet nebulizer; VMN = vibrating mesh nebulizer.

Prior to this study, there has been only one project comparing clinical outcomes between a vibrating mesh nebulizer and a jet nebulizer. Dunne and Shortt evaluated a quality improvement project that substituted a vibrating mesh nebulizer for a jet nebulizer in all subjects (adults and pediatrics) receiving bronchodilator therapy in the emergency department for 30 d. For all age groups, the authors reported a 32% decrease in admissions, significantly less administered albuterol, and a 37-min decrease in the median stay in the emergency department with the vibrating mesh nebulizer group compared to the jet nebulizer group. Although our findings are similar, it is important to note that in patients 3–18 y old, Dunne and Shortt reported no difference in admission rates between those treated with a vibrating mesh nebulizer and those treated with a jet nebulizer (4.72% absolute reduction, 12.1% with a vibrating mesh nebulizer vs 12.7% with a jet nebulizer). In contrast, we observed a 31% relative reduction (6.3% absolute) in overall admission rate with the vibrating mesh nebulizer compared to the jet nebulizer, and a 48% reduction (10% absolute) with the vibrating mesh nebulizer in children who used a face mask. Differences in specific patient inclusion and exclusion criteria could have contributed to the difference in the admission rates between these studies. For example, Dunne and Shortt evaluated all subjects prescribed nebulized albuterol regardless of primary diagnosis or severity of respiratory disease, and their results may have been diluted with subjects with mild asthma exacerbations or without a known history of asthma or reactive airway disease, as only 23% of subjects in the jet nebulizer group and no subjects in the vibrating mesh nebulizer group required > 5 mg albuterol.

Our asthma scoring system is a modified version of the scoring system used previously by Qureshi et al. They conducted a randomized, double-blind, placebo-controlled study of children with severe asthma, with the final score assigned to the most severe category. Our scoring system used a modified version of the scoring system used previously by Qureshi et al. They conducted a randomized, double-blind, placebo-controlled study of children with severe asthma, with the final score assigned to the most severe category.
study of 434 children with acute moderate to severe asthma exacerbations in the emergency department. The aim of their study was to determine whether the addition of ipratropium bromide to standard albuterol therapy would reduce hospital admission rates. The authors reported that the overall admission rate was lower in the ipratropium group (27.4%) compared to the control group (36.5%) ($P = .05$). However, when stratified based on severity, they reported that the addition of ipratropium made no difference in hospitalization rates for children with moderate asthma (10.7% control vs 10.1% ipratropium), although admissions for those with severe exacerbations were reduced significantly (52.6% control vs 37.5% ipratropium, $P = .02$). Whereas they demonstrated that the addition of ipratropium to standard albuterol therapy delivered with jet nebulizer and face mask significantly reduced hospitalization in children with severe asthma, we found further reductions in admission by delivering albuterol and ipratropium with a vibrating mesh nebulizer and a face mask (10.7% overall admission rate), as well as an absolute reduction in overall admission rate with the vibrating mesh nebulizer when analyzed by subgroup (7.2% for moderate, 8.4% for severe).

Although we observed clinically meaningful reductions in hospital admission rate with the vibrating mesh nebulizer compared to the jet nebulizer, it is important to note that there are multiple factors that determine whether children may be safely treated as out-patients or if hospital admission is indicated. Decisions regarding the most appropriate disposition for children with asthma exacerbations can be challenging, and there is no clear consensus regarding either symptom severity at presentation or intensity of the emergency department management that should serve as a threshold for admission. Undoubtedly, children with tachypnea, accessory muscle use, or hypoxia after treatment will require hospitalization. Assessment of posttreatment peak flow may provide valuable data to emergency physicians and has been reported to correlate with hospitalization; however, these measurements are inconsistently performed and may not be feasible in younger patients.32 Each patient’s history and socioeconomic status must also be carefully considered prior to disposition. Children who respond well to the emergency department management may still be at risk of poor outcomes if they have comorbid conditions or concurrent pulmonary infection, or if they have previously required endotracheal intubation or ICU admission for asthma exacerbation. Physicians may also consider hospitalization for children with poor access to out-patient follow-up, insufficient caregiver availability or understanding, or limited access to prescribed medication.

The current protocol in our institution for the initial treatment of acute moderate to severe asthma exacerbations is based on current National Institutes of Health guidelines.5 It consists of 3 treatments of albuterol and ipratropium bromide delivered intermittently in 20-min increments or combined and given continuously over 1 h using a jet nebulizer with a dragon or aerosol mask or mouthpiece. Combining treatments and administering continuously over 1 h is the preferred method because it reduces the time spent by the emergency department respiratory therapist.33 Results of our study support this practice because the median number of treatments required to achieve a mild asthma score in the jet nebulizer group was 3; however, this commits patients to an hour of initial treatment, whereas use of the vibrating mesh nebulizer allowed fewer intermittent treatments and a 28.4% reduction in time to realize the same clinical response. In a busy pediatric emergency department, a decrease in required treatments may result in more efficient utilization of resources including physician, nurse, and respiratory therapist time, as well as respiratory equipment and medications. Additionally, improvements in patient throughput may occur, resulting in decreased wait times and patients leaving without being seen, fewer delays in diagnosis and intervention, shorter length of stay, and improved patient experience, all of which are factors affecting hospital reimbursement.34

Although the results of this study indicate improved clinical outcomes associated with using a more efficient nebulizer, it is not unreasonable to question whether the same outcome might be achieved by increasing the loading dose of the jet nebulizer compared to using a more expensive nebulizer. However, multiple variables affect the performance of pneumatic nebulizers,35,36 and it is unknown whether increasing the loading dose alone would lead to similar results without increasing cardiopulmonary side effects. Future studies are needed to assess dose-equivalent outcomes based on performance differences between nebulizers.

**Limitations of the Study**

The primary limitation of this study was that it was underpowered for the primary end point of admission rates. The initial sample size was based on a previous study with an overall admission rate of 45%. Our overall admission rate was 17%, much lower than the anticipated rate. Post hoc analysis based on actual admission rates demonstrated that admission rate as a primary end point would have required a larger number of subjects, ie, 560 per arm (total sample size of 1,120 subjects) for an 80% power. We did not proceed with the larger sample size for a few reasons. Such a study would have been cost- and time-prohibitive. Furthermore, we believe that the study as designed demonstrated improved outcomes with the vibrating mesh nebulizer. Multiple secondary end points were significant, including the number of treatments and time to mild asthma.
score. In addition, a constant trend toward lower admission rates with the vibrating mesh nebulizer regardless of severity and lower probability of admission associated with the vibrating mesh nebulizer and a valved mask suggested clinically important differences in treatment arms.

The unequal sample sizes of the groups using different interfaces was another limitation of this study. Although unequally sized groups are common in research, it can affect the statistical power of the study. Because the sample size of the patient population using the mouthpiece was smaller than the groups with the face mask, the mouthpiece group may have a general loss of power that leads to the superiority of the face mask over the mouthpiece in clinical outcomes of this study. Also, the aerosol and aerosol masks were combined in the jet nebulizer group, whereas only the valved mask was used with the vibrating mesh nebulizer. Due to the protocol of the hospital and the purpose of this study to compare the vibrating mesh nebulizer and the valved mask with the current protocol, the valved mask was not tested with the jet nebulizer in this study.

Randomization did not account for the severity of asthma score, which led to an imbalance in the groups for the baseline asthma score. Future studies should stratify randomization for severity to prevent these imbalances. Nevertheless, there is evidence that this does not impact the validity of the study because the results demonstrated improved outcomes with the vibrating mesh nebulizer notwithstanding the imbalance.

Our study population was based on convenience sampling. Screening and enrollment occurred during the morning and afternoon hours when the study investigator was available to consent and collect study data. No subjects were enrolled during the evening hours. This may have led to sampling bias assuming children with moderate to severe asthma respond to therapy differently depending on the time of day.

Conclusions

There are many different types of aerosol devices and interfaces used in the treatment of children with asthma exacerbations. Selecting the right device and interface is important for effective aerosol drug delivery to this patient population. Subjects treated with a vibrating mesh nebulizer required significantly fewer treatments and less time to achieve a mild asthma score. In subjects with a mask interface, the vibrating mesh nebulizer reduced the probability of admission compared to the jet nebulizer. The lower admission rates in the vibrating mesh nebulizer group was constant, regardless of the severity of asthma exacerbation.

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REFERENCES

NEBULIZER EFFICACY FOR PEDIATRIC SUBJECTS IN THE ED