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Original Contributions

A RANDOMIZED TRIAL COMPARING METERED DOSE INHALERS AND BREATH ACTUATED NEBULIZERS

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☐ **Abstract—Background: Despite little evidence for its effectiveness, the breath-actuated nebulizer (BAN) is the default albuterol delivery method in our pediatric emergency department. Objective: We compared the clinical efficacy of BAN and the metered-dose inhaler (MDI) in treating subjects patients 2 to 17 years of age who presented with mild to moderate asthma exacerbations. Methods: This is a randomized, nonblinded, noninferiority study conducted at a single pediatric tertiary care emergency department. Subjects presenting with a Pediatric Asthma Score ranging from 5 to 11 received albuterol by BAN or MDI via standard weight-based and symptom severity dosing protocols. Aerosolized ipratropium (via BAN) and intravenous magnesium sulfate were given when clinically indicated. The primary outcome was patient disposition. The noninferiority margin for the primary outcome was an admission rate difference ≤10%. Analyses were adjusted for confounders that were significant at $p \leq 0.10$. Results: We enrolled 890 subjects between October 2014 and April 2015. BAN and MDI groups were comparable for age, gender, and race but not for pretreatment symptom severity; 51% in the MDI group had a Pediatric Asthma Score of moderate severity (8–11) vs. 63% in the BAN group ($p < 0.003$). Unadjusted admission rates were 11.9% for MDI and 12.8% for BAN, for an unadjusted risk difference of −0.9% (95% confidence interval −5% to 3%). After adjusting for baseline confounder severity, the risk difference was 2% (95% confidence interval −4% to 7%), which met the criteria for noninferiority. Conclusions: Albuterol therapy by MDI is noninferior to BAN for the treatment of mild to moderate asthma exacerbations in children 2 to 17 years of age.** © 2018 Elsevier Inc. All rights reserved.

☐ **Keywords—asthma exacerbation; breath-actuated nebulizer; emergency department length of stay; intravenous magnesium sulfate; metered-dose inhaler; Pediatric Asthma Score; respiratory therapist; small volume nebulizer**

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INTRODUCTION

Breath-actuated nebulizers (BANs) are a relatively new method of treating pediatric asthma exacerbations (AEs) in the emergency department (ED). Like the small volume nebulizer (SVN), BANs aerosolize albuterol solution but use an air compressor rather than a nebulizer. Their use in the ED to treat AE may contribute to parents' lack of confidence in their home metered-dose inhalers (MDIs) (1). By treating acute AE with nebulized albuterol rather than with the MDI, we may be encouraging

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unnecessary repeat ED visits and contributing to the enormous national cost of treating asthma (2,3).

Acute AE can be effectively treated using BANs, MDIs, or SVNs (4). Both the MDI and the BAN are more effective than the SVN at reducing hospital admission rates and reducing ED length of stays (ED LOS) (5–8). To our knowledge, this is the first study comparing the effectiveness of the MDI and the BAN. We hypothesize that the MDI is as effective as the BAN in treating acute pediatric AE in the ED.

MATERIALS AND METHODS

This is a randomized, controlled, nonblinded, noninferiority trial comparing MDI to BAN conducted in children presenting with a first-time wheeze or a mild to moderate AE at a single, urban, pediatric ED in Memphis, Tennessee. The BAN, along with the MDI, became the standard of care for treatment of AE after an internal pilot study of 100 patients showed BAN to be superior to SVN resulting in fewer admissions (42% SVN vs. 28% BAN) and shorter ED LOS (mean SVN 344 min vs. mean BAN 225 min). An abbreviated consent form, one that could be reviewed in minutes, was approved by the institutional review board so that therapy for willing participants would not be delayed.

Subjects were identified for enrollment by respiratory therapists (RTs) and treating physicians. Eligible subjects ranged from 2 to 17 years of age and presented with either a first-time wheeze or an AE of mild to moderate severity as defined by a Pediatric Asthma Score (PAS) ranging from 5 to 11 (9). The PAS assigns points for respiratory rate, oxygen saturation, retractions, work of breathing, and findings on auscultation (Appendix). Subjects were excluded if they had initiated therapy at an outside medical facility or had a history of chronic lung disease, congenital heart disease, tracheostomy, or were receiving diuretic therapy. Patients who were diagnosed with bronchiolitis or pneumonia by the treating physician were excluded, along with children who were wards of the state or whose parents did not speak English.

One thousand numbers were generated and randomized using blocks of 20 to either MDI or BAN using online randomization software (www.randomization.com). Numbers were printed and placed in sealed, sequentially ordered opaque security envelopes that were stored in a secure location. Patients were enrolled in the study 24 hours per day, 7 days per week.

By protocol, all patients with a known history of asthma received oral dexamethasone (0.6 mg/kg, 16 mg maximum dose) at presentation, whereas those with first-time wheeze were assessed by a physician before dosing (10). Albuterol dosing was based upon the subject's randomized cohort, weight, and presenting asthma score (Appendix). Additional therapies including ipratropium, 0.5 mg via BAN, regardless of randomized cohort (ipratropium by MDI was too costly for routine use in the ED), or 50 mg/kg (max 2 g) of intravenous magnesium sulfate (IV $MgSO_4$) (11). Not infrequently, physicians may treat patients presenting with moderate severity AE with IV $MgSO_4$, especially if they received multiple doses of albuterol at home or have a history of pediatric intensive care unit admissions in hopes of discharging them home.

Albuterol administered via MDI was given through a spacer device fitted with an appropriately sized mask if needed. The RT was present for the entire treatment and either administered or supervised patient- or parent-administered doses. Subjects randomized to BAN were evaluated for proper breath actuation technique. For subjects unable to breath actuate, the RT attached an appropriately sized mask to the device, changed the setting to continuous nebulization, and returned to bedside after treatment completion.

This study was designed to reflect treatment of AE as is commonly practiced. Physicians could escalate care by increasing the dose of albuterol beyond the ED protocol. Physicians were discouraged from changing appliances but could do so if they felt that the child was not improving; however, all subjects remained assigned to their randomized cohort. Physicians could discharge a subject at any time, but the ED protocol suggests administering $\geq$3 treatments before admission. There were no strict criteria for admission, and each provider determined subject disposition. According to the intention to treat principle, all admissions counted against the cohort to which the subject was initially randomized.

The primary outcome was patient disposition defined as hospital admission or discharge from the ED. Secondary outcomes included: ED LOS, frequency of possible albuterol dose-related adverse events measured by age-adjusted tachycardia at the time of disposition, and ondansetron administration for nausea or vomiting (12). We also followed repeat ED visits within 7 days of presentation.

All information related to the subjects in the study was extracted from their electronic medical record and transferred to REDCap, a secure Web-based database (13). Measures of noninferiority were determined using chi-square tests for categorical variables, *t*-tests for continuous, normally distributed variables, and the Mann-Whitney *U* test for continuous nonparametric variables. Depending on the validity of normality assumption, Pearson or Spearman correlation was used to describe the association between two continuous variables. To adjust for possible confounding factors, we used a multivariate logistic regression analysis for patient disposition and a multiple linear regression analysis for