A Prospective, Comparative Trial of Standard and Breath-Actuated Nebulizer: Efficacy, Safety, and Satisfaction

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BACKGROUND: Nebulized drug delivery is a cornerstone of therapy for obstructive lung disease, but the ideal nebulizer design is uncertain. The breath-actuated nebulizer (BAN) may be superior to conventional nebulizers. This study compared the BAN to standard nebulizer with regard to efficacy, safety, and patient and respiratory therapist (RT) satisfaction. METHODS: Adults admitted to the hospital and for whom nebulizer therapy was prescribed were enrolled. Subjects were randomly assigned to either AeroEclipse II or standard nebulizer and were surveyed at the completion of each treatment. BAN delivered albuterol 2.5 mg or albuterol 2.5 mg plus ipratropium 0.25 mg. Standard nebulizer delivered albuterol 2.5 mg or albuterol plus ipratropium 0.5 mg. An RT assessed each subject's heart rate, respiratory rate, and peak expiratory flow rate prior to and following treatment. Treatment time and adverse events were recorded. Each RT was asked to assess his/her satisfaction with each of the nebulizers. RESULTS: Twenty-eight subjects were studied. The mean age was 69 years. Fifty-four percent of the subjects indicated that overall the BAN was superior to conventional nebulizer therapy; 68% indicated that duration was preferable with the BAN. RTs were more satisfied with the BAN, based on overall performance, treatment duration, and ease of use. There were no significant differences in heart rate, peak expiratory flow rate, or respiratory rate before or after nebulization therapy with either device. The duration of treatment was significantly lower with the BAN (4.1 min vs 9.9 min, $P < .001$). Additionally, the BAN was associated with a lower occurrence of adverse events. CONCLUSIONS: Patients and RTs expressed greater satisfaction with the BAN, compared with standard nebulizer. Pre- and post-treatment vital signs did not differ between groups, but use of the BAN was associated with a shorter duration and a lower occurrence of adverse events. Taken together, these data support the use of the BAN for nebulized medication delivery. *Key words: nebulizers; breath-actuated nebulizer; conventional nebulizer; breath-actuated nebulizer; patient satisfaction; adverse events.* [Respir Care 2012;57(8):1242–1247. © 2012 Daedalus Enterprises]

Introduction

The preferred route of drug therapy for obstructive lung diseases such as asthma and COPD is via inhalation.[1,2] Inhalation provides a more rapid onset of drug action while requiring smaller doses of the medication, compared with other routes.[3,4] Currently there are 3 major categories of dispensers for lung deposition of drugs: pressurized metered-dose inhaler, dry powder inhaler, and nebulizer.[5] Recent meta-analyses suggest equivalent clinical efficacy of different delivery systems if they are used correctly.[2] Nebulized therapy offers advantages over hand-held inhal-

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ers in those who cannot correctly utilize a metered-dose inhaler, such as infants, young children, and those with cognitive impairment or orthopedic or neuromuscular limitations.[6] In the hospital setting, nebulizers are widely used to overcome problems with inhaler techniques, especially in patients who are breathless.[7]

SEE THE RELATED EDITORIAL ON PAGE 1351

Nebulizers, which convert liquid into an aerosol, are typically either pneumatic (jet nebulizer) or ultrasonic.[8] With a pneumatic nebulizer, aerosol is generated throughout the patient's respiratory cycle, which wastes medication during exhalation. Ultrasonic nebulizer uses a high-frequency vibrating crystal to produce the aerosol.[6] To limit drug waste during exhalation, breath-enhanced nebulizers, breath-actuated nebulizers (BANs), and nebulizers with an attached storage bag and a one-way mouthpiece valve have been developed.[9] The breath-actuated AeroEclipse II nebulizer creates aerosol only during the inspiratory phase.[9-11] Several studies have reported reduced drug waste with BANs.[9-11]

As part of our hospital quality improvement project we performed a pilot exploratory study of the AeroEclipse II. This study was conducted independently of any industry support or input. We compared the AeroEclipse II to the standard nebulizer we used in our hospital with regards to patient and respiratory therapist (RT) satisfaction, efficacy, and safety.

QUICK LOOK

Current knowledge

Nebulized drug delivery is a cornerstone of therapy for obstructive lung disease, but the ideal nebulizer design is uncertain. Breath-actuated nebulizer may have advantages over conventional nebulizers.

What this paper contributes to our knowledge

Patients and respiratory therapists expressed greater satisfaction with a breath-actuated nebulizer than a standard jet nebulizer. Pre- and post-treatment vital signs did not differ between the groups, but the BAN was associated with a shorter treatment time and a lower occurrence of adverse events.

Methods

After institutional review board approval, eligible patients were asked to participate. Adults at least 18 years of age admitted to the hospital with obstructive airway disease for which nebulized albuterol sulfate, at a dose of 2.5 mg every 4–6 hours, or nebulized albuterol sulfate 2.5 mg combined with ipratropium 0.25 mg every 4–6 hours, had been prescribed were asked to participate in the study. Exclusion criteria included patients in the emergency department or ICU; patients on mechanical ventilation or noninvasive ventilation; those who were pregnant, allergic to albuterol or ipratropium; those prescribed other nebulizer drug therapy or therapy at a dose or frequency other than that stated above; and patients who were unable to use either standard nebulizer or BAN.

This randomized crossover study was designed to alternate between receiving BAN first or standard nebulizer first, so the order of nebulization was equally distributed, with half receiving BAN, then standard nebulizer, and the remainder in reverse order. Following treatment with both drug delivery devices, patients were surveyed about each device in regard to overall satisfaction and time it took to complete the treatment.

The 19 RTs involved in the study were all nationally board-certified registered RTs and licensed by the state of Florida. The mean age was 42.6 ± 2.6 years, with a mean working experience of 7.4 ± 1.4 years at our institution. Each RT recorded each subject's heart rate, respiratory rate, peak expiratory flow (PEF), and occurrence of adverse effects (AE) prior to and 15 min after treatment. Treatment time was recorded. Subjects were queried about AE with special attention to cough, nausea, vomiting, palpitations, and tremors after each nebulizer treatment. Each treating RT rated his/her satisfaction with the BAN compared to standard nebulizer, based on overall satisfaction, duration of treatment, and ease of use, utilizing a 5-point Likert scale. Both surveys were constructed as part of a quality improvement project. To achieve our aim, we constructed the questionnaire after consulting with both physicians and RTs. In addition, chart review for baseline characteristics such as age, sex, Sequential Organ Failure Assessment score, pulmonary function test within 2 years of the time of evaluation, oxygen usage, and steroid administration was performed.

Both the standard nebulizer (Micro Mist, Hudson RCI, Durham, North Carolina) and the BAN (AeroEclipse II, Monaghan Medical, Plattsburgh, New York) nebulizers were powered by 50-psi oxygen at 8 L/min. For the dosage and mixture of medication in the BAN we used a dosage that was based on the product insert and modeled by a hospital that utilizes the BAN. In the BAN, sole albuterol therapy was delivered using 2.5 mg albuterol (0.5 mL) plus 0.5 mL saline, to constitute a total delivery volume of 1 mL. For combined albuterol and ipratropium therapy, 2.5 mg albuterol (0.5 mL) and 0.25 mg ipratropium (1.25 mL), for a total delivery volume of 1.75 mL, was provided. For the conventional nebulizer, sole therapy with

Table 1. Demographics, Respiratory Therapist Satisfaction, Physiologic Effects, and Duration of BAN Compared to Standard Nebulizer ($n = 28$)

Demographics			
Age, y	69 ± 14.5		
Male, %	46		
SOFA score, median (IQR)	0 (0–1)		
Pulmonary Function Variables, median (IQR)			
FEV_1%	54 (43.25–69)		
FVC%	79 (61.75–89.75)		
TLC%	96 (87.5–106.25)		
D_{LCO}%	46 (38.75–58)		
FEV_1/FVC < 70%, %	86		
Oxygen usage, %	78		
Steroid usage, %	36		
RT Satisfaction (1–5 scale)*	BAN	Standard Nebulizer	P†
Overall	4.3 ± 0.94	3.6 ± 0.96	.02
Ease	4.5 ± 0.92	3.8 ± 0.79	.009
Duration	4.5 ± 0.84	3.3 ± 0.82	< .001
Physiologic Effects, post-treatment minus pre-treatment			
Heart rate, beats/min	0.72 ± 5.0	0.23 ± 5.9	.57
Respiratory rate, breaths/min	0 ± 1.1	0.27 ± 1.3	.84
Peak flow, mL	13.3 ± 21	24.8 ± 30.5	.13
Duration, min	4.1 ± 2.8	9.9 ± 1.7	< .001

± values are mean ± SD.
* Respiratory therapist (RT) satisfaction scale where 1 meant not satisfied at all and 5 meant extremely satisfied.
† Mean difference between breath-actuated nebulizer (BAN) and standard nebulizer analyzed using paired analysis with Wilcoxon signed-rank test.
SOFA = Sequential Organ Failure Assessment scale
TLC = total lung capacity
D_{LCO} = diffusing capacity of the lung for carbon monoxide

albuterol was provided with 2.5 mg albuterol (0.5 mL) and an additional 2.5 mL saline, for a total delivery volume of 3 mL. For combined ipratropium and albuterol therapy, albuterol 2.5 mg (0.5 mL) and 0.5 mg ipratropium (2.5 mL), for a total of 3 mL, were provided.

Statistical Analyses

Pair-wise analysis was performed with the Wilcoxon signed-rank test to compare the changes in the satisfaction scores, physiologic variables, ease of use, and the treatment time between the 2 groups. The mean difference of total AE between the BAN and standard nebulizer therapy were analyzed using paired analysis with Wilcoxon signed-rank test. The 95% confidence intervals of differences measured between the 2 groups are also reported, where appropriate. P values $\leq .05$ were considered statistically significant.

Results

A total of 30 patients participated in the study; however, 2 were excluded due to incomplete data collection, thus leaving 28 subjects for analyses. The mean age was 69 years, with nearly half (46%) being males, as shown in Table 1. The subjects evaluated were of mild severity, as calculated using the Sequential Organ Failure Assessment score, ranging from 0–4, with zero percent mortality. There were 22 (78%) subjects on oxygen at the time of evaluation, with a range of 2–6 L/min, via nasal cannula. Ten subjects or 36% were on steroid therapy at the discretion of the treating physician. Of those 10 subjects, 2 received intravenous solu-medrol, while the rest were given oral prednisone. The majority had an obstructive pattern on their pulmonary function test (86%) based on a FEV_1/FVC of < 70%. The average FEV_1 was 55.1% of predicted. The order of nebulization was equally distributed, with half receiving the BAN first, followed by standard nebulizer, and the remainder in reverse order. Eleven subjects received albuterol alone, and 17 received albuterol plus ipratropium.

Patient Satisfaction

Fifty-four percent (15/28) felt the BAN was superior with regards to overall satisfaction. Among the remaining

Table 2. Comparison of Heart Rate, Respiratory Rate, and Peak Flow Before and After Treatment With Each Device

	Pre-treatment	Post-treatment	P*
Breath-Actuated Nebulizer			
Heart rate, beats/min	81.9 ± 14.12	82.7 ± 15.41	.48
Respiratory rate, breaths/min	18.2 ± 2.3	18.2 ± 2.3	> .99
Peak flow, L/min	198.0 ± 69.01	211.35 ± 68.57	.003
Standard nebulizer			
Heart rate, beats/min	79.2 ± 13.6	79.0 ± 13.4	.89
Respiratory rate, breaths/min	19.2 ± 2.6	19.5 ± 3.1	.32
Peak flow, L/min	182.7 ± 84.1	207.5 ± 78.6	< .001

± values are mean ± SD.
* Mean difference analyzed using paired analysis with Wilcoxon signed-rank test.

Table 3. Number of Occurrences of Adverse Events

	Breath-Actuated Nebulizer	Standard Nebulizer
Cough	6	8
Nausea	1	2
Vomiting	0	0
Palpitation	1	4
Tremor	0	4
Total	8	18*

* The mean ± SD difference between the breath-actuated nebulizer and the standard nebulizer for total adverse events was −0.42 ± 1.0 ($P = .05$ analyzed using paired analysis with Wilcoxon signed-rank test).

46%, 62% (8 out of 13) could not tell the difference, and 5 out of 13 felt the conventional nebulizer was the preferred method. More subjects, 68% (19/28), favored the BAN with regards to drug delivery time.

Respiratory Therapist Satisfaction

Table 1 shows the RTs' satisfaction ratings on a scale of 1–5, where 5 meant extremely satisfied with a device and 1 not satisfied at all. RTs were more satisfied with the BAN, based on the overall performance (4.3 ± 0.94 vs 3.6 ± 0.96), ease of use of the device (4.5 ± 0.92 vs 3.8 ± 0.79), and duration of treatment (4.5 ± 0.84 vs 3.3 ± 0.82), when compared to standard nebulizer therapy ($P = .17$, $P = .009$, $P < .001$, respectively).

Safety and Efficiency

The heart rate, respiratory rate, and PEF were measured prior to and 15 min after use of each device. As shown in Table 2, in the BAN group and standard nebulizer group the mean heart rate and respiratory rate before and after the treatment were not significantly different. However, the PEF improved significantly from before to after treatment in the BAN group as well as the standard nebulizer group ($P = .003$ and $P < .001$, respectively). As in Table 1, there was a nonsignificant increase in heart rate between the BAN group and the standard nebulizer group, with a mean difference of 0.92 ± 7.2 beats/min ($P = .57$). Neither the respiratory rate ($P = .84$) nor the PEF ($P = .13$) differed between the 2 treatment modalities. The rate of occurrences of AE (cough, nausea, vomiting, palpitations, and tremors) after the use of each device was monitored and is shown in Table 3. AE following therapy occurred significantly less often with the use of the BAN, compared to the standard nebulizer group (8 vs 18, $P = .05$).

Duration of Therapy

The duration of each treatment was compared and is shown in Table 1. As anticipated, the BAN took significantly less time than standard nebulizer therapy, with a mean difference of almost 6 min ($P < .001$).

Discussion

This pilot exploratory crossover study was designed to evaluate the utility of a BAN compared to a standard nebulizer in our hospital. Overall, both patients and RTs favored the BAN. As already expected, the BAN duration of treatment was shorter; however, there was no difference in measured pre- and post-treatment vital signs and PEF, with a lower occurrence of AE.

Available evidence from systematic reviews and meta-analyses suggests that the efficacies of different aerosol delivery devices, nebulizers, metered-dose inhalers, and dry powder inhalers are equivalent, provided the device is used correctly.[2,7,12,13]

In both adults and children with acute asthma, and adults with COPD, there are equivalent bronchodilatory effects from hand-held inhalers and from nebulizers.[7] Although nebulizer therapy is often perceived as more inconvenient, cumbersome, and time consuming than inhaler use, it offers the advantages of decreased need for patient/device coordination, only normal tidal breathing rather than maximum inspiratory efforts, and no need for breath-holding.[14]

In a review of factors that guide the choice of delivery device for inhaled corticosteroids, Thorsson and Geller highlighted that nebulizers provide a useful alternative for patients of any age who cannot coordinate or activate a metered-dose inhaler or dry powder inhaler.[15] Because patient education is not required to achieve proper drug delivery with nebulizer therapy, it is often the preferable delivery method in hospitalized patients, especially those unaccustomed to hand-held inhaler use.

Although data are limited, patient tolerance and occurrence of AE appear similar between BAN and standard nebulizer therapy. Most previous studies of BAN tolerance have not reported heart rate or respiratory rate changes,

compared to conventional nebulizers. A study by Lin and Huang, comparing a BAN and a conventional nebulizer, reported a significantly higher pulse rate in the BAN group, beginning 5 min after treatment.[16]

Another study, by Sabato and colleagues, which evaluated children in an emergency department setting, comparing BAN and standard nebulizer, reported an insignificant change in heart rate and S_{pO_2} between the 2 groups. However, there was a significant drop in respiratory rate in the BAN group ($P = .002$). There were no differences in AE between each group in regard to coughing, nausea, tremors, vomiting, and/or hyperactivity before or after treatment.[17] Moreover, the study reported a significant improvement in clinical asthma score ($P = .01$) in the BAN group, and a lower admission rate ($P = .03$). Although well designed, their study is to be interpreted with caution, as pointed out in the editorial by Ari and Fink.[18] The distribution in their conventional group was further divided into continuous nebulizer treatment and small-volume nebulizer treatment, compared to subjects in the BAN group. The small number of subjects in the small-volume nebulizer group had indeed a lower initial asthma score, based on design, which may imply that it would be as effective as the BAN. But whether the BAN would be superior to small-volume nebulizer in patients with severe asthma would need further evaluation. Additional treatments may differ in each individual, as well as the evaluation for effectiveness, which may impact the decision for admission. Lastly, given the difficulties with nebulizer therapy in children, compared to adults, with either method the mask interface or compliance during therapy may impact effectiveness and would require further investigation.

As stated, the aim of the study was to examine the satisfaction of patients and RTs toward each device. In our study, both patients and RTs expressed their preference for the BAN, as opposed to the standard nebulizer. We found no significant differences in the change in heart rate, respiratory rate, or PEF between the 2 groups. Similar to other investigators, we found that use of the BAN was associated with lower occurrences of AE such as nausea, vomiting, palpitations, or tremors. However, this may be due in some part to the lesser amount of added mixture with normal saline or the overall total amount of delivered medication in the BAN group.

This study is not without its limitations. The study population was small, which limited statistical power. Additionally, the RTs could not be blinded to the delivery device used. This investigation studied only in-patients in a noncritical care setting. Even though the order of utilization of each device was balanced, the distribution of subjects receiving albuterol alone and albuterol plus ipratropium were not matched. The dosage of albuterol was the same in all subjects; however, the mixtures of normal saline and ipratropium were different. Thus, the time to deliver would be expected to be shorter, and one could consider this an unfair comparison. Larger studies and a controlled distribution of the medications could improve the balance of both elements. We cannot assure that these results, although probably applicable, could be extrapolated to patients in other settings. Further studies to include a larger population in various settings, as well as the use of different agents available on the market, but other than the ones utilized here, could provide more insight on its utility.

Finally, as part of the trial was to examine comparative efficacy, the only measurement of efficacy was change in PEF before and after treatment. Although there was a trend toward greater increase in PEF in those treated with standard nebulizer therapy, this difference was not statistically significant. Other patient centered outcomes assessing efficacy, including changes in subjective dyspnea scores with treatment, duration of hospitalization for obstructive lung disease, and need for intensification of bronchodilatory therapy, would be useful.

Conclusions

Both patients and RTs expressed a greater rate of satisfaction with the BAN, compared with standard nebulizer therapy. The magnitude of the preference was greater among RTs than patients. Tolerance of therapy was similar with both devices. Overall there were no differences in heart rate, respiratory rate, and PEF between the 2 devices. However, there were lower occurrences of AE and a significantly shorter treatment time with the use of the BAN. Our findings suggest that the BAN is an acceptable alternative to conventional nebulizer use. Its lower occurrence of AE may favor its use, and it may offer greater cost effectiveness due to reduced treatment duration.

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