In Vitro Comparison of Different Nebulizers Delivering 7% Hypertonic Saline

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BACKGROUND: Nebulized 7% hypertonic saline is used to treat patients with cystic fibrosis. Clinical trials supporting its use were conducted with breath-enhanced nebulizers (BEN). It is not uncommon for the specific nebulizer used in studies or prescribed by a physician to be unavailable to patients. The investigator compared the aerosol characteristics of hypertonic saline delivered by nebulizers of different operating principles. METHODS: A continuous-output nebulizer (CON), a breath-actuated (BAN) jet nebulizer, and 2 brands of BEN (Pari LC Plus and Sidestream Plus) were tested. Airway delivery and aerosol characteristics of nebulizers loaded with 7% hypertonic saline were determined with 3 breathing simulations (ie, infant, child, and adult breathing patterns) and cascade impaction, respectively. Solutes were analyzed with freezing point osmometry. RESULTS: Aerosols generated with the BEN and BAN had similar mass median aerodynamic diameters (3.43–3.67 μm), geometric standard deviations (2.12–2.34), percentage of particles < 5 μm (63.1–68.9%), and percentage of particles 1–3 μm (35.9–37%). The CON produced a larger aerosol than BEN and BAN. The 2 BENs had similar airway delivery values that were greater than those for both CON and BAN. CONCLUSIONS: Hypertonic saline aerosols generated with the BEN and BAN devices were similar, while that generated with the CON was different. Airway delivery was similar between the BEN devices, but higher than that observed with the BAN and CON devices. *Key words: breath-actuated jet nebulizer; breath-enhanced jet nebulizer; continuous output jet nebulizer; hypertonic saline; aerosol characteristics; cystic fibrosis.* [Respir Care 2021;66(10):1582–1587. © 2021 Daedalus Enterprises]

Introduction

Cystic fibrosis is a genetic condition characterized by the abnormal production/function of the cystic fibrosis transmembrane regulator protein.[1] This leads to a multi-organ involvement including the pulmonary system, which is responsible for most of the mortality in this disease. The pathophysiology includes depletion of airway surface liquid; therefore, therapies such as hypertonic saline have been investigated.[2-3] Several clinical trials have demonstrated improvement in lung function, reduction in exacerbations, and improvement in quality of life with the use on inhaled hypertonic saline.[3-5] Current guidelines for maintenance of lung health in patients with cystic fibrosis recommend its use in patients 6 y of age and older.[6-7]

During several clinical trials, the Pari LC Plus or the Pari LC Star nebulizer/Pari Proneb Turbo compressor were used (Pari Respiratory Equipment, Midlothian, Virginia).[3-5] In addition, some inhaled drugs have been approved for its use with a specific delivery devices.[8-9] For drugs not approved as part of a drug-device combination, practitioners tend to

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prescribe the device reported in the trials. However, if the specific device is not available, providers may resort to other devices. On many occasions, nebulizers are dispensed to patients as generic devices. Further, patients might not have individual devices for each medication and may reuse devices intended for other drugs. More recently, the COVID-19 pandemic created a combined health care and economic crisis with interruptions in distribution chains. Therefore, alternative supplies had to be used to deliver inhaled medication in patients with cystic fibrosis and other respiratory conditions.

Nebulizers are devices that convert a liquid solution or suspension into a mist (ie, aerosol).[10] There are several types of nebulizers, namely jet, ultrasonic, and vibrating mesh nebulizers, but jet nebulizers are the most commonly used. Jet nebulizers can be classified on the basis of the timing of aerosol release: continuous output jet nebulizers (CON) and breath-enhanced jet nebulizers (BEN) release the aerosol during inspiration and expiration, whereas breath-actuated jet nebulizers (BAN) release aerosol only during inhalation.[10] BEN devices incorporate a one-way valve that results in higher delivery during inhalation compared to exhalation. The aerosol characteristics and the patient's breathing pattern, among other factors, influence the site and amount of deposition of an inhaled aerosol.[11-13] Therefore, information on the particle size characterization of hypertonic saline aerosols produced by different devices is of importance to prescribing health care providers.

The investigator compared the aerosol characteristics and drug delivery of 7% hypertonic saline aerosolized by several jet nebulizers that operate under different principles. The investigator hypothesized that nebulizers of similar operating principles will produce aerosols of similar characteristics.

Methods

The experiments were performed at the Pediatric Aerosol Research Laboratory at Arkansas Children's Research Institute, Little Rock, Arkansas. Mean (95% CI) temperature and humidity during testing were 23.1°C (23–23.3°C) and 46% (45–48%), respectively. The experiments consisted of 2 parts using well established methodology: aerosol characterization by cascade impactor, and aerosol delivery measurement by simulated breathing.[14-16]

Materials used in this study included 4 new CON devices (Up-Draft II Optineb, Teleflex Medical, Research Triangle Park, North Carolina); 4 new Pari LC Plus (Pari GmbH, Starnberg, Germany) (Pari BEN) and 4 new Sidestream Plus BEN devices (Philips, Parsippany, New Jersey) (Sidestream BEN); and 4 new BAN devices (Aeroeclipse II, Monaghan, Plattsburg, New York) (Fig. 1). A 7% hypertonic saline solution was used (7% Hypersal, Pari GmbH). Nebulizers were operated for 6 min at 6 L/min of central air.

QUICK LOOK

Current knowledge

Use of inhaled 7% hypertonic saline has been studied in patients with cystic fibrosis using a specific nebulizer. However, the specific device might not be always be available. Therefore, knowing the characteristics of the aerosol generated by other devices is clinically relevant.

What this paper contributes to our knowledge

An in vitro evaluation using cascade impaction and breathing simulation techniques provided information about aerosol-producing devices in addition to the reference device. Breath-enhanced and breath-actuated jet nebulizers generated similar aerosols, whereas the continuous output jet nebulizer did not. Airway delivery was similar among breath-enhanced jet nebulizer devices and higher than the other devices.

Cascade Impaction

Aerosol characteristics were determined by cascade impaction using previously reported methodology.[14] Briefly, a Next Generation Impactor (MSP, Shoreview, Minnesota) was assembled with internal and external filters. The impactor was calibrated to 15 L/min using a mass flow meter (TSI 4043, TSI, Shoreview, Minnesota). The impactor was cooled at 4°C for 90 min before the first test and then for 60 min before each of the 3 remaining tests. This protocol minimizes evaporative losses to avoid undersizing of aerosols.[17] Impactor throat and stages were washed with double-distilled water. The solutions were analyzed with freezing point osmometry (Osmette II, PSI, Natick, Massachusetts) and with refractometry (Sodium Chloride Refractometer, HI 96821, Hanna Instruments, Woonsocket, Rhode Island); however, because both methods were similar, only the former is reported. Osmolality (mOsm/kg) is a measure of the number of dissolved particles in a fluid. Airway delivery was reported as the osmolality of the filter's washing. Mass median aerodynamic diameter (MMAD), geometric standard deviation (GSD), fine-particle fraction (percentage of particles < 5 μm, FPF), and 1–3 μm fraction (percentage of particles between 1 and 3 μm) were calculated with CITDAS 3.1 software (Copley Scientific, Nottingham, United Kingdom) according to United States and European Pharmacopeia recommendations.[14]

Simulated Breathing

A breathing simulator (Pari Compass, Pari Pharma, Munich, Germany) was programmed to deliver breathing patterns representative of infant (tidal volume 50 mL, frequency

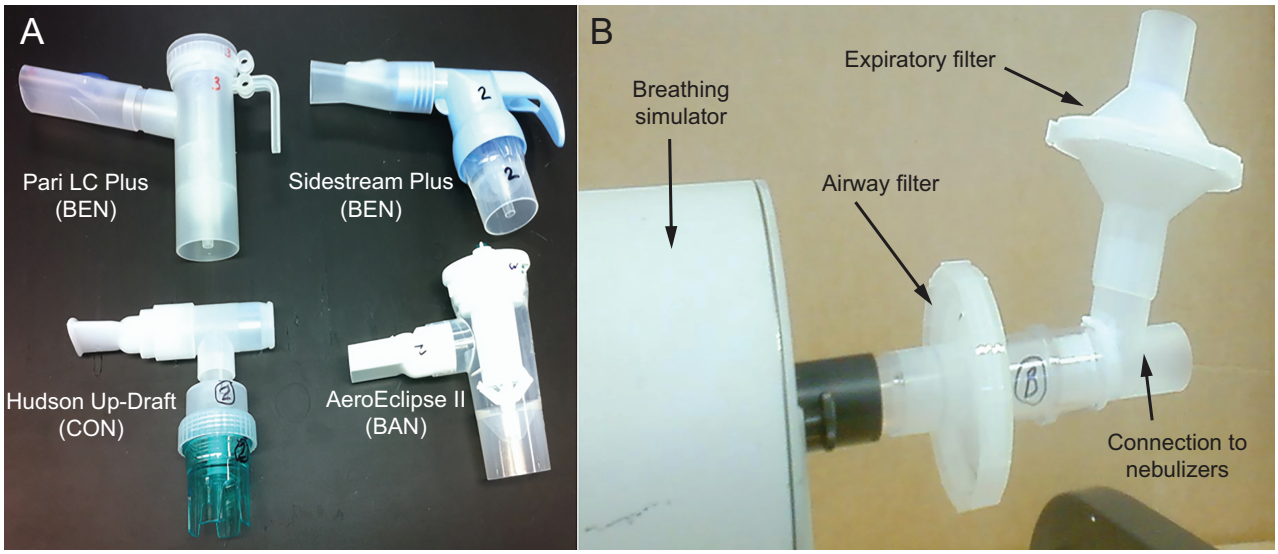

Fig. 1. A: Nebulizers tested. B: Experimental setup. BEN = breath-enhanced nebulizer; CON = continuous output nebulizer; BAN = breath-actuated nebulizer.

30 breaths/min, inspiratory time 0.5 s), child (tidal volume 155 mL, frequency 25 breaths/min, inspiratory time 0.8 s), and adult subjects (tidal volume 500 mL, frequency 15 breaths/min, inspiratory time 1.3 s).[16] Accuracy of flow and simulator tidal volume were verified before each experiment with the mass flow meter. The simulator was connected in series to a low dead space filter holder (airway filter) and the different nebulizers. A new disposable filter (Pari Respiratory Equipment) was used with each test. An expiratory extension with a one-way valve was interposed between the nebulizer and the filter (Fig. 1).[15] Each nebulizer was operated for 10 min at 6 L/min of central air. Nebulizers were weighed dry, after loading 4 mL 7% hypertonic saline, and after 10 min of operation. Solution output was calculated as the difference between loaded and post-operation weights. Solutes were eluted from the airway filter and analyzed as above. Airway delivery in the respirable range was calculated as the product of airway delivery and FPF. Delivery rate was calculated by dividing the airway delivery in the respirable range by the nebulization time. Consistency of airway delivery was assessed by calculation the coefficient of variation (SD/mean × 100). Results were reported as pooled data (ie, average of all breathing patterns).

Statistical Analysis

Results of each nebulizer test are expressed as mean ± SD of 4 measurements. The investigator utilized analysis of variance followed by Tukey test for multiple comparisons to compare outcomes from same device with different breathing patterns. The investigator utilized analysis of variance followed by Dunnet test to compare devices to the Pari BEN with each breathing pattern. Significance level was set at 0.05. The statistical software Kaleidagraph 4.5.4 was used for all calculations (Synergy Software, Reading, Pennsylvania).

Results

Aerosol Characteristics

The MMAD for the Sidestream BEN and the BAN were similar to that for the Pari BEN ($P = .39$ and $P = .89$, respectively), but MMAD for the CON was larger than that for the Pari BEN ($P < .001$). All aerosols were heterodisperse with a GSD > 1.2. The Sidestream BEN had a GSD similar to that of the Pari BEN ($P = .26$), and the CON and the BAN had a slightly smaller GSD than that for the Pari BEN ($P < .001$). The BAN and the Sidestream BEN had FPF similar to that for the Pari BEN ($P = .10$ and $P = .28$, respectively), but the FPF for the CON was lower ($P < .001$). The BAN and the Sidestream BEN had FPF similar to that of the Pari BEN ($P = .44$ and $P = .96$, respectively), but the FPF for the CON was lower ($P < .001$) (Table 1).

Airway Delivery

The Pari BEN had greater airway delivery than other devices with the infant breathing pattern ($P < .008$) (Table 2). The Pari BEN had airway delivery similar to that for the Sidestream BEN ($P = .41$) but greater than that for the BAN and the CON ($P < .001$). Airway delivery increased as the breathing patterns progressed from infant to adult for all nebulizers except for the CON during child and adult breathing patterns ($P = .98$). The Pari BEN had greater airway delivery than the BAN and the CON ($P < .001$), but this was lower than that for the Sidestream BEN ($P < .001$).

Table 1. Aerosol Characteristics of 7% Hypertonic Saline Aerosolized With Different Nebulizers

	Continuous Output	Pari BEN	Sidestream BEN	Breath-Actuated
MMAD, μm	4.52 ± 0.27*	3.50 ± 0.15	3.67 ± 0.13	3.43 ± 0.05
GSD	2.05 ± 0.05*	2.34 ± 0.04	2.28 ± 0.04	2.12 ± 0.06†
FPF, %	55.6 ± 3.5*	65.5 ± 1.9	63.1 ± 1.3	68.9 ± 0.6
1–3 μm fraction, %	24 ± 1.7*	35.9 ± 1.2	36.3 ± 0.8	37 ± 0.5

* $P < .001$ when compared to Pari breath-enhanced nebulizer.
† $P < .001$ when compared to Pari breath-enhanced nebulizer.
BEN = breath-enhanced nebulizer
MMAD = mass median aerodynamic diameter
GSD = geometric standard deviation
FPF = fine-particle fraction (< 5 μm)
1–3 μm fraction = percentage of particles 1–3 μm

Table 2. Airway Delivery (mOsm/kg) With Different Nebulizers and Breathing Patterns

	Infant	Child	Adult
Pari breath-enhanced nebulizer	177 ± 32	290 ± 25	394 ± 20
Sidestream breath-enhanced nebulizer	128 ± 13	271 ± 14	460 ± 14
Breath-actuated nebulizer	122 ± 9	203 ± 23	265 ± 22
Continuous output nebulizer	116 ± 12	151 ± 14	149 ± 17

Data are presented as mean ± SD.

Airway Delivery in the Respirable Range

The Pari BEN had greater airway delivery in the respirable range than the BAN and the CON for all breathing patterns ($P = .007$) (Fig. 2). The Pari BEN had greater delivery than the Sidestream BEN for the infant breathing pattern ($P = .007$), similar delivery for the child breathing pattern ($P = .13$), and lower delivery with the adult breathing pattern ($P = .006$).

Airway delivery in the respirable range increased as the breathing patterns progressed from infant to adult for all nebulizers except for the CON with the child and adult breathing patterns ($P = .98$). The Pari BEN had greater airway delivery than the BAN and the CON ($P < .001$), but lower delivery than the Sidestream BEN ($P = .006$). Results of drug delivery rate in the respirable range can be seen in Table 3.

The Sidestream BEN had the lowest pooled coefficient of variation for airway delivery in the respirable range (6%). The other nebulizers had a pooled coefficient of variation that ranged from 9% to 11%.

Solution Output

The Pari BEN and the Sidestream BEN had similar solution outputs for the child and adult breathing patterns ($P = .80$ and $P = .18$, respectively), while the BAN and the CON had lower solution outputs than the Pari BEN ($P < .001$) (Table 3). The CON and the Pari BEN had similar solution outputs for the infant breathing pattern ($P = .63$), while the BAN and the Sidestream BEN had lower solution outputs than the Pari BEN ($P < .0007$).

Solution output for the Pari BEN and the Sidestream BEN increased as the breathing patterns progressed: adult > child > infant ($P < .001$). The BAN had a similar solution output for the infant and child breathing patterns ($P = .53$), but both were lower than with the adult breathing pattern ($P < .02$). The CON nebulizer did not show difference among breathing patterns ($P < .05$).

Discussion

This study compared the aerosol characteristics and airway delivery of 7% hypertonic saline aerosolized by 4 different nebulizers. The Pari BEN nebulizer was considered the predicate device because it was used in the clinical trials that supported its use.[3-5] The investigator found that the Sidestream BEN and the BAN had aerosol characteristics similar to those of the Pari BEN, except for higher and lower airway delivery in the respirable range for the Sidestream BEN and the BAN, respectively. The CON had larger particle size and lower airway delivery in the respirable range than the Pari BEN.

The particle size characterization of 7% hypertonic saline for the CON and the BEN was similar to that obtained with an isotonic solution of albuterol in a previous study using similar methodology.[14] The MMAD, GSD, FPF, 1–3 μm fraction values were 4.67 μm, 2.14, 53%, and 21% for the CON and 3.50 μm, 2.32, 65%, and 34% for the Pari BEN. These values are consistent with the manufacturer's reported aerosol characteristics for the Pari BEN using a compressor (MMAD 3.8 μm, FPF 65%).[18] Similarly, the aerosol characteristics of 7% hypertonic saline for the Sidestream BEN were similar to those of isotonic solution of albuterol reported in a previous study.[19] The MMAD,

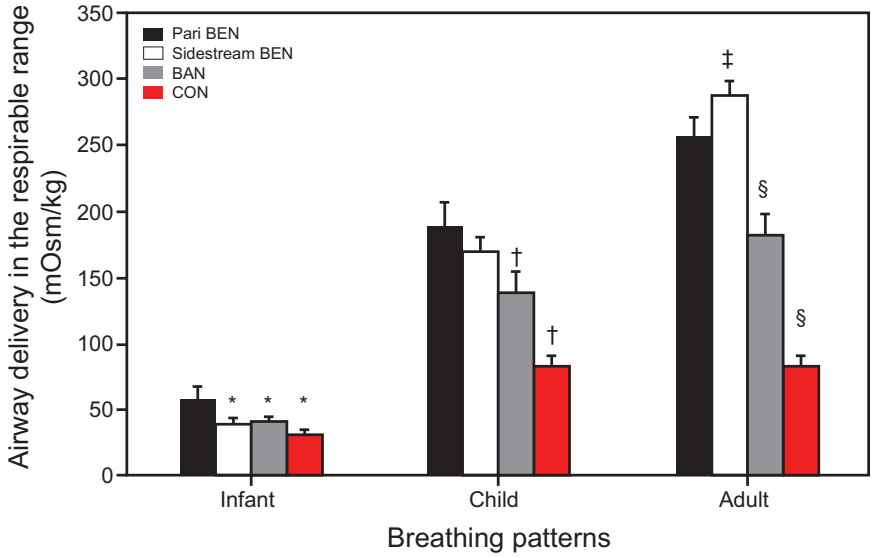

Fig. 2. Airway delivery in the respirable range for different devices and breathing patterns. *$P < .007$ when compared to Pari BEN. †$P < .004$ when compared to Pari BEN. ‡$P < .006$ when compared to Pari BEN. §$P < .001$ when compared to Pari BEN. CON = continuous output nebulizer; BEN = breath-enhanced nebulizer; BAN = breath-actuated nebulizer.

Table 3. Solution Output and Delivery Rate in the Respirable Range of 7% Hypertonic Saline

Nebulizer	Solution Output, mL			Drug Delivery Rate in the Respirable Range, mOsm/kg/min		
	Breathing Pattern			Breathing Pattern		
	Infant	Child	Adult	Infant	Child	Adult
Pari breath-enhanced nebulizer	2.24 ± 0.14	2.54 ± 0.14	2.82 ± 0.07	19	32	43
Sidestream breath-enhanced nebulizer	1.85 ± 0.06	2.47 ± 0.13	2.94 ± 0.04	13	29	48
Breath-actuated nebulizer	1.82 ± 0.07	1.90 ± 0.13	2.15 ± 0.09	14	23	30
Continuous output nebulizer	2.31 ± 0.13	2.08 ± 0.13	2.09 ± 0.12	11	14	14

Data are presented as mean ± SD.

GSD, and FPF were 3.80 μm, 1.9, and 60% while using a compressor.

The Sidestream BEN and the BAN had aerosol characteristics similar to those of the Pari BEN as determined by cascade impaction. Therefore, the aerosols generated by these 3 nebulizers are expected to have similar intrapulmonary deposition.[10] These data should help providers if the predicate device (ie, the Pari BEN) can't be secured due to any of myriad possible reasons. The aerosols generated by the CON are larger and therefore are expected to have more proximal deposition. Therefore, the CON does not appear to be a suitable replacement for the Pari BEN.

Although the aerosol characteristics of 7% hypertonic saline nebulized by the BEN and the BAN were similar, the airway delivery in the respirable range was different. The BAN had a ~ 30% lower delivery than the Pari BEN across all breathing patterns. The investigator speculates that a longer treatment time could improve drug delivery. The Sidestream BEN delivered 70%, 90%, and 113% of the drug delivered by the Pari BEN for the infant, child, and adult breathing patterns, respectively. Airway delivery did not improve when changing from the child breathing pattern to the adult breathing pattern. This is consistent with a previous study using the CON with a face mask and is most likely due to the fact that their time of aerosol exposure times (breathing frequency × inspiratory time) are similar, and their inspiratory flows is above the flow generated by the nebulizer.[16] Conversely, BEN and BAN devices showed an increase in airway delivery with increasing tidal volume. These findings are consistent with previous studies done with other solutions and with the mechanism of action of the nebulizers.[10,20] Solution output followed the patterns of airway delivery as expected. These data highlight once again that nebulizers are not necessarily interchangeable.

Limitations of the study include the limited number of nebulizer models studied, the use of only the 7% hypertonic saline (ie, not 3% or 3.5%), and the simulated nature of the tests (ie, the in vitro evaluation lacks the biological variability present in humans). However, the methodology used has been used previously and is accepted by regulatory agencies; it is also utilized for device selection during the drug development process. This study did not evaluate efficacy in humans, which may vary significantly in different muco-obstructive disease states.

Conclusions

Nebulizers of different operating principles are not interchangeable. The 2 brands of BEN devices generated aerosols with similar characteristics and delivery. The aerosol generated by the BAN was similar to that generated by the BEN devices, but the delivery was lower. These data should inform providers to find a suitable replacement nebulizer to deliver 7% hypertonic saline if the preferred nebulizer is not available.

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