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Effect of nebulizer type, delivery interface, and flow rate on aerosol drug delivery to spontaneously breathing pediatric and infant lung models

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Abstract

Background: Different types of nebulizers, interfaces, and flow rates are used to deliver aerosolized medications to children. The purpose of this study was to determine the effect of nebulizer type, delivery interface, and flow rate on aerosol drug delivery to spontaneously breathing pediatric and infant lung models.

Methodology: A teaching mannequin was attached to a sinusoidal pump via a collecting filter at the bronchi to simulate a spontaneously breathing child (Vt: 250 mL, RR: 20 bpm and Ti: 1 second) and infant (Vt = 100 mL, RR = 30 bpm, Ti: 0.7 seconds). Albuterol sulfate was nebulized with jet (Misty Max 10; Cardinal Health) and mesh (Aerogen Solo; Aerogen) nebulizers using a low-flow nasal cannula (LFNC; Hudson), a high-flow nasal cannula (HFNC; Fisher & Paykel), face mask (FM; Hudson), and mouthpiece (MP; Cardinal Health). While all interfaces were used in the pediatric study, only LFNC, HFNC, and FM were tested in the infant study. The mesh nebulizer was tested at 2, 4, and 6 L/min with LFNC, 4 and 6 L/min with HFNC, and 6 L/min with FM and MP. The jet nebulizer was operated at 6 and 8 L/min with FM and 6 L/min with LFNC, HFNC, and MP (n = 5). The drug was eluted from the filter and analyzed by spectrophotometry. Factorial analysis of variance and post hoc comparisons were used for data analysis. $P < .05$ was considered statistically significant.

Results: Delivery efficiency of mesh nebulizers is two to fourfold more than jet nebulizers used with HFNC, FM, and MP. No statistical difference was found between jet and mesh nebulizers used with LFNC in infants ($P = .643$) and pediatrics ($P = .255$). Aerosol delivery with MP was the best compared to other interfaces used in pediatrics ($P < .05$). As the second-best interface in aerosol drug delivery, the delivery efficiency of FM was greater than HFNC ($P = .0001$) and LFNC ($P = .0001$). Increasing flow rate with LFNC and HFNC decreased aerosol delivery with the mesh nebulizer in both infants and pediatrics.

Conclusion: The type of nebulizer, delivery interface, and flow rate used in the treatment of children affect aerosol drug delivery.

KEYWORDS

aerosols, face mask, flow rate, high-flow nasal cannula, interfaces, mouthpiece, nebulizers, pediatrics and infants

1 | INTRODUCTION

Jet and mesh nebulizers are commonly used for aerosol drug delivery to children. Jet nebulizers (JN) are traditional nebulizers generating aerosols throughout the subject's respiratory cycle, wasting aerosol during expiration.[1-3] There are several issues associated with JNs during aerosol therapy. For instance, they have a bulky nebulizer design requiring a compressor or pressurized gas to operate. More preparation is required to set up the device and they are inefficient in aerosol drug delivery. Previous research reported that the delivery efficiency of JNs among different brands and units of the same brands also varies.[4-7] Therefore, new nebulizer technologies, such as mesh nebulizers, were designed to increase the efficiency of aerosol therapy. Mesh nebulizers are portable handheld nebulizers that are used to deliver suspensions, solutions, proteins, and liposomal formulations. Since they produce aerosols with a high fine-particle fraction and have minimal residual medication volume, mesh nebulizers are more efficient than JNs in aerosol delivery. Both jet and mesh nebulizers are combined with an interface such as a mouthpiece (MP), face mask (FM), or high-flow nasal cannula (HFNC) to deliver aerosolized medications to children.[8]

The interface used for aerosol drug delivery may impact the efficiency of jet and mesh nebulizers.[9-11] Because small children cannot use a MP effectively, a FM is commonly utilized as a patient interface during aerosol therapy. Previous studies have noted the importance of the FM seal for efficient drug delivery to children.[12-16] However, when the FM is used to deliver aerosolized medications, clinicians may fail to achieve a good FM seal. Further, when clinicians attempt to have a tight seal between the face and the mask, young children may fuss and cry during therapy. Crying causes either high variability in drug delivery or no aerosol deposition in the lungs.

Given these challenges, drug delivery to children and infants needs to be improved. Although young children tend to be preferential nose breathers, little attention has been focused on the nasal delivery of aerosols to this patient population. Clearly, choosing the right type of nebulizer, interface, and flow rate play an important role in the efficiency of aerosol therapy in children. Since there is no study quantifying aerosol drug delivery with jet and mesh nebulizers using different interfaces in children, the purpose of this study was to determine the effect of nebulizer type, delivery interface, and flow rate on aerosol drug delivery to spontaneously breathing pediatric and infant lung models.

2 | METHODS

2.1 | Experimental design

Figure 1 shows the experimental design of this study tested jet and mesh nebulizers with a HFNC, a low-flow nasal cannula (LFNC), FM, and MP at different flow rates using simulated, spontaneously breathing pediatric and infant lung models.

2.2 | Lung models and breathing parameters

An in vitro lung model was constructed to simulate spontaneously breathing pediatrics and infants using teaching mannequins with anatomical face and upper airways that were attached to a collecting filter at the level of the bronchi to a breathing simulator (Figure 2). The breathing parameters that were used in this study included: Vt: 250 mL, RR: 20 bpm, and Ti: 1 second for a simulated spontaneously breathing pediatric and Vt = 100 mL, RR = 30 bpm, Ti: 0.7 seconds for the infant lung model.

2.3 | Nebulizers

Jet (Misty Max 10; CareFusion) and mesh (Aerogen Solo; Aerogen Ltd, Galway, Ireland) nebulizers were compared in terms of aerosol drug delivery in infants and pediatrics. While the JN was run until sputter, the mesh nebulizer was operated until the end of nebulization.

2.4 | Interfaces

The HFNC (Fisher & Paykel, Auckland, New Zealand), LFNC (Hudson RCI; Teleflex Medical, Research Triangle, NC), FM (Devilbiss Healthcare, Port Washington, NY), and MP (CareFusion, Yorba Linda, CA) were tested with jet (Misty Max 10; Carefusion, Yorba Linda, CA) and mesh (Aerogen Solo; Aerogen, Galway, Ireland) nebulizers using the pediatric lung model. Since infants cannot use MP, only HFNC, LFNC and FM (OxyKid Mask; SouthMedic, Barrie, Ontario, Canada) were compared in the infant lung model. Figure 3 shows the experimental setups used with LFNC and HFNC.

2.5 | Flow rates

Regardless of the lung model used in this study, aerosol delivery with the mesh nebulizer was quantified with LFNC at 2, 4, and 6 L/min; HFNC at 4 and 6 L/min; and FM and MP at 6 L/min. Delivery efficiency of the JN was determined with LFNC, HFNC, and MP at 6 L/min, as well as with FM at 6 and 8 L/min using the infant and pediatric lung models.

2.6 | Data collection

Albuterol sulfate is the most commonly used drug in children as it represents up to 90% of treatments in the hospital and has been shown to be a good surrogate for other approved drug solutions. Therefore, albuterol sulfate (2.5 mg/3 mL) was delivered with jet and mesh nebulizers to the infant and pediatric lung models used in this study. After each treatment, aerosol delivery was measured through a collecting filter, which was placed at the distal tip of the bronchi of the mannequin. The inhaled dose was collected on a filter during each experiment and analyzed via spectrophotometry (276 nm). The sample size of this study is five (n = 5).

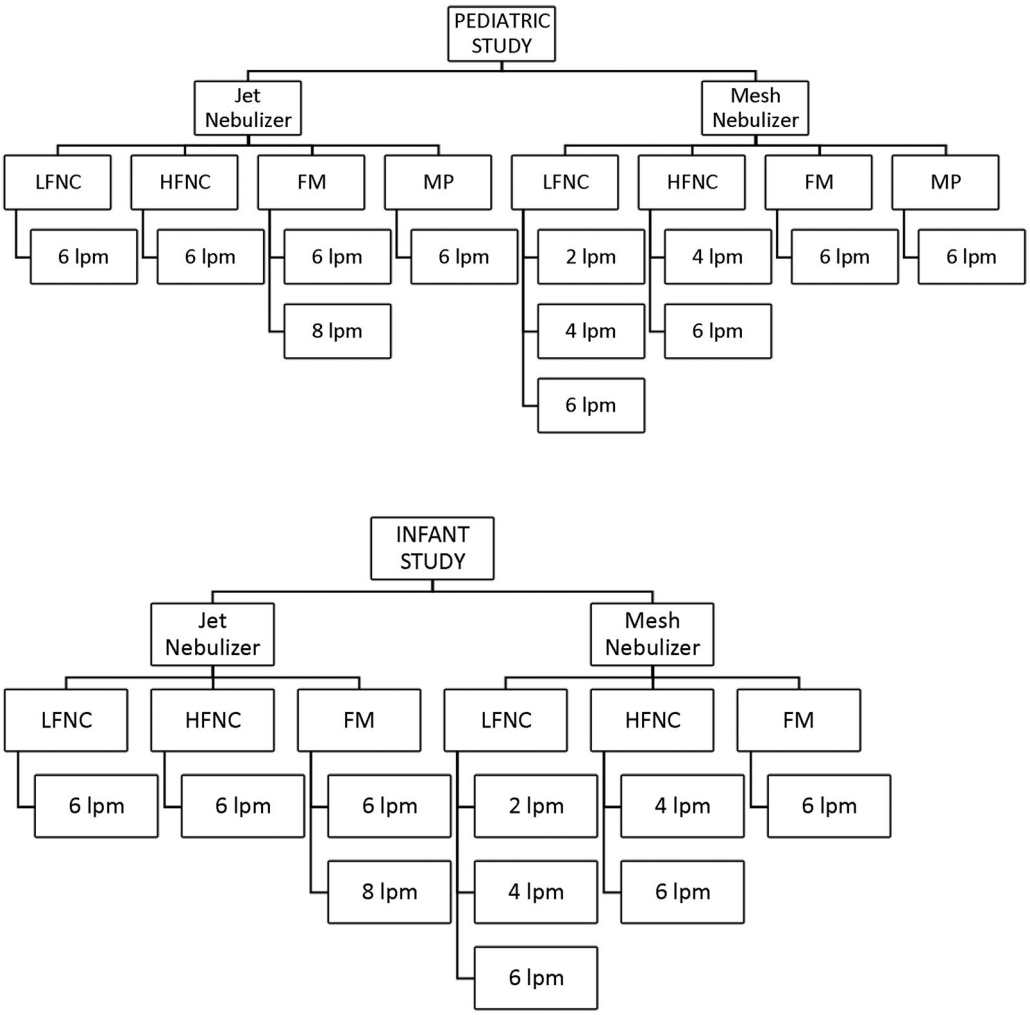

FIGURE 1 Experimental design of the study using jet and mesh nebulizers with different interfaces in spontaneously breathing pediatric and infant lung models. FM, face mask; HFNC, high-flow nasal cannula; LFNC, low-flow nasal cannula; MP, mouthpiece

2.7 | Data analysis

The amount of drug depositing in the filter was expressed as the total fraction of the nominal dose placed in each nebulizer. Differences in means between inhaled dose for the interfaces used in jet and mesh nebulizers at various flow rates were compared with the factorial analysis of variance and post hoc comparisons. The significance level was set at .05.

3 | RESULTS

3.1 | Aerosol delivery to pediatrics and infants

Table 1 and Table 2 show percent of the nominal dose delivered distal to the trachea of the pediatric and infant lung models, respectively. Aerosol delivery ranged from 1.49% to 29.67% in the pediatric lung model while it was between 1.0% to 7.2% in the infant lung model depending on the nebulizer, interface, and flow rate used in this study. Differences on aerosol drug delivery to pediatrics and infants were statistically significant with the mesh nebulizer using LFNC at 2 L/min ($P = .001$), 4 L/min ($P = .004$), 6 L/min ($P = .007$), HFNC at 4 L/min ($P = .002$), 6 L/min ($P = .003$), and the FM at 6 L/min ($P = .023$). While no significant difference was found between pediatrics and infants using JN with LFNC at 6 L/min ($P = 0.178$), the findings of this study showed that aerosol drug delivery to pediatrics was up to twofold greater than infants when HFNC ($P = .0001$) or the FM ($P = .004$) is utilized for aerosol therapy.

3.2 | Delivery efficiency of jet and mesh nebulizers

There was no significant difference between the jet and mesh nebulizers when LFNC is used for aerosol drug delivery to the pediatric ($P = .255$) and infant lung model ($P = .643$). Delivery efficiency of JNs was significantly less than mesh nebulizers using HFNC, FM, and MP ($P = .001$, $P = .007$, and $P = .0001$, respectively) in pediatrics. According to the findings of the infant study, aerosol deposition obtained with JNs were significantly less efficient than

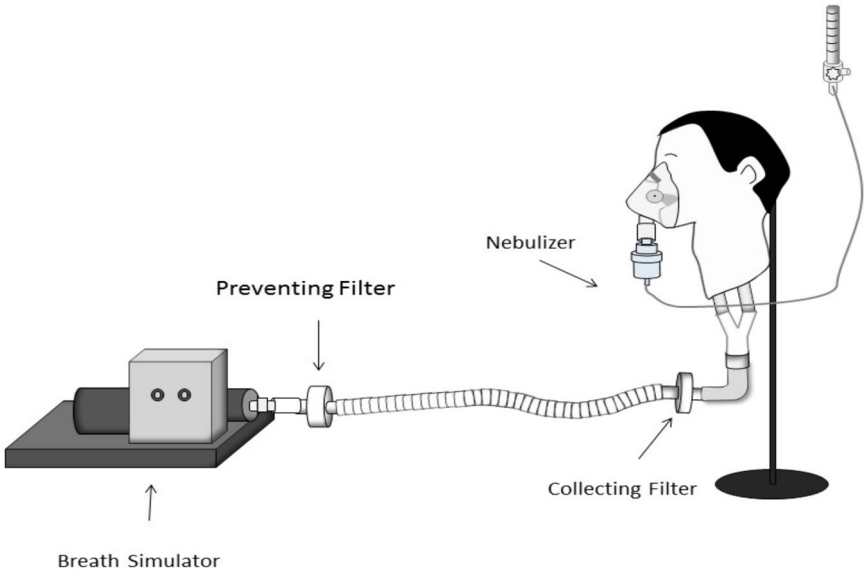

FIGURE 2 Lung model used in this study [Color figure can be viewed at wileyonlinelibrary.com]

mesh nebulizers when they are combined with HFNC ($P = .012$) and FM ($P = .002$) at 6 L/min.

3.3 | Delivery efficiency of different interfaces at 6 L/min

When the mesh nebulizer is used with the pediatric lung model, aerosol delivery with the MP was significantly greater than LFNC ($P = .0001$), HFNC ($P = .0001$), and the FM ($P = .0001$). Similarly, the delivery efficiency of the JN was better with the MP than LFNC ($P = .0001$), HFNC ($P = .0001$), and the FM ($P = .021$) used with the pediatric lung model. The FM was the second-best interface in terms of aerosol drug delivery compared to LFNC and HFNC in jet ($P = .0001$ and $P = .001$, respectively) and mesh nebulizers ($P = .0001$ and $P = .0001$, respectively). The findings of this study showed that aerosol delivery to infants significantly increased with the FM compared to LFNC and HFNC using jet ($P = .0001$ and $P = .0001$, respectively) and mesh nebulizers ($P = .0001$ and $P = .0001$, respectively). Aerosol deposition obtained

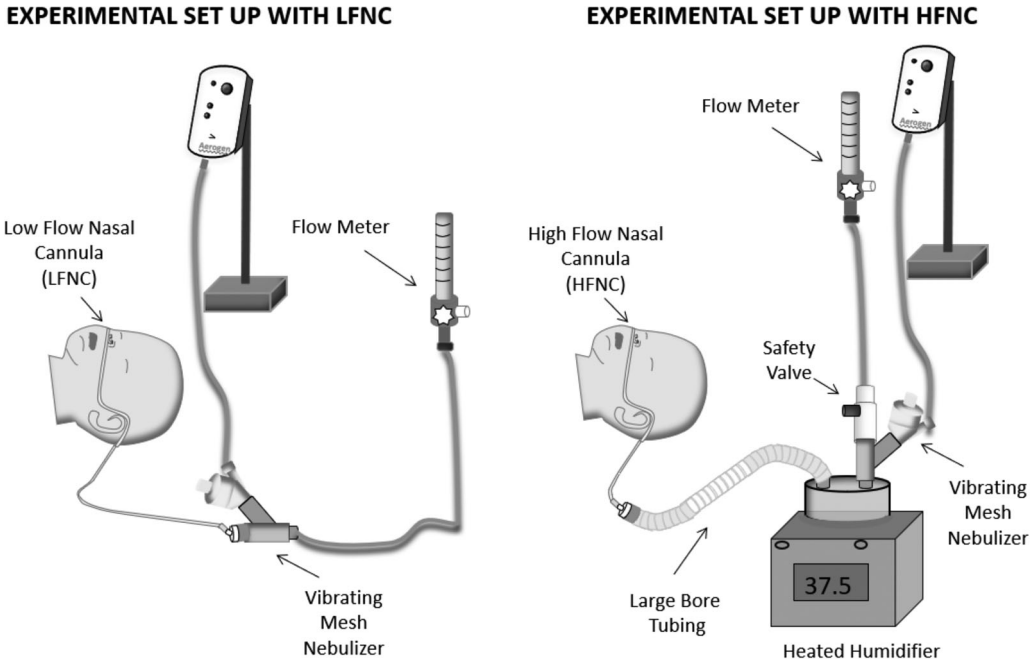

FIGURE 3 Experimental set up used with LFNC and HFNC. HFNC, high-flow nasal cannula; LFNC, low-flow nasal cannula

TABLE 1 Percent of the nominal dose delivered distal to the trachea of pediatric lung model using jet and mesh nebulizers with a low-flow nasal cannula (LFNC), a high-flow nasal cannula (HFNC), face mask, and mouthpiece

Interfaces	LFNC			HFNC		Face mask		Mouthpiece
Flow rates	2 L/min	4 L/min	6 L/min	4 L/min	6 L/min	6 L/min	8 L/min	6 L/min
Mesh nebulizer	3.38% ± 0.3%	2.41% ± 0.3%	1.87% ± 0.2%	8.64% ± 1.2%	5.37% ± 0.7%	11.26% ± 1.9%	–	29.67% ± 0.1%
Jet nebulizer	–	–	1.49% ± 0.5%	–	2.46% ± 0.1%	5.76% ± 0.1%	6.70% ± 0.2%	6.67% ± 0.2%

TABLE 2 Percent of the nominal dose delivered distal to the trachea of infant lung model using jet and mesh nebulizers with a low-flow nasal cannula (LFNC), a high-flow nasal cannula (HFNC), face mask, and mouthpiece

Interfaces	LFNC			HFNC		Face mask	
Flow rates	2 L/min	4 L/min	6 L/min	4 L/min	6 L/min	6 L/min	8 L/min
Mesh nebulizer	1.77% ± 0.2%	1.20% ± 0.2%	1.1% ± 0.1%	3.27% ± 0.4%	2.35% ± 0.3%	7.20% ± 0.6%	6.72% ± 0.4%
Jet nebulizer	–	–	1.0% ± 0.2%	–	1.45% ± 0.1%	3.83% ± 0.5%	4.49% ± 0.3%

with HFNC was significantly greater than LFNC used with jet and mesh nebulizers in infants ($P = .035$ and $P = .002$, respectively) and pediatrics ($P = .019$ and .014, respectively).

3.4 | Aerosol delivery at different flow rates

Regardless of the type of lung model used in this study, increasing flow rate with LFNC and HFNC decreased aerosol delivery with the mesh nebulizer. Drug delivery with LFNC at 2 L/min was significantly greater than 4 and 6 L/min using mesh nebulizers in pediatrics ($P = .031$ and $P = .015$, respectively) and infants ($P = .010$ and $P = .001$, respectively). There was no significant difference between 4 and 6 L/min using LFNC in the pediatric ($P = .104$) and infant ($P = .790$) lung model. Aerosol delivery with HFNC significantly decreased ($P = .007$) when the flow rate increased from 4 to 6 L/min with mesh nebulizers both in pediatrics ($P = .008$) and infants ($P = .007$). While aerosol deposition obtained with the FM at 6 and 8 L/min were not statistically significant with jet ($P = .209$) and mesh ($P = .452$) nebulizers used with the infant lung model, drug delivery with a FM at 8 L/min was significantly higher than 6 L/min ($P = .002$) in the pediatric lung model when using JNs.

4 | DISCUSSION

Although aerosolized medications are commonly used in the treatment of children, there is no consensus about which device and interface to use at which flow rates in this patient population. The findings of this study showed that the type of nebulizer, delivery interface, and flow rate used in the treatment of pediatrics and infants affect aerosol drug delivery. While delivery efficiency of the MP was best compared to the other interfaces used in pediatrics, aerosol deposition obtained with the FM was greater than LFNC and HFNC in infants. Regardless of the type of nebulizer and flow rate used in this study, drug delivery with LFNC was less than other interfaces tested in the infant and pediatric lung models. Decreasing flow rate increased aerosol delivery with HFNC and LFNC in infant and pediatric lung models and aerosol delivery with mesh nebulizers was two to fourfold more compared to JNs in all conditions tested in this study except when LFNC was used with the infant lung model.

Aerosolized medications can be delivered via different interfaces such as the MP, FM, or HFNC. Previous research reported that delivery efficiency of a JN with the MP was greater than the FM[10,17] For instance, Nikander et al[17] showed that aerosol delivery with a MP ranged from 8.9% to 12.2% as opposed to a FM that has a delivery efficiency between 5% and 6.9% in pediatrics. The findings of this study are consistent with Nikander's. Kishida et al[18] evaluated the clinical efficacy of the FM compared to the MP in children with asthma and found that aerosol therapy with the MP results in significant improvement in forced expiratory volume in the first second compared to FM. Therefore, using a MP for aerosol drug delivery to pediatrics may be a good choice if the child can use the MP comfortably and reliably during aerosol therapy.

While the MP is to be more efficient than a FM, it is hard to use it in infants, small children less than 3 years of age, and pediatrics who are uncooperative due to dyspnea or illness during treatment. In this case, aerosolized medications are administered via a FM. However, it is important to have a tight seal between the face and mask to avoid aerosol loss and drug deposition in the eyes when a FM is used during aerosol therapy.[14,16,19-22] Also, aerosol delivery to children varies based on the type of FM used during therapy.[9-11] Previous evidence showed that front-loaded FM configuration was more efficient than the bottom-loaded mask configuration[15] and using a valved mask substantially increases aerosol drug delivery to children due to one-way valves that keep aerosols in the mask during inhalation and allow the exit of exhaled gas during expiration.[10,11] In this study, we used a standard aerosol mask with the pediatric and infant lung models. We found that aerosol deposition with a FM attached to a JN operated at 6 and 8 L/min was 5.76% and 6.70% in pediatrics, respectively, while it was 3.83% at 6 L/min and 4.49% at 8 L/min in infants. Restrepo et al[23] quantified aerosol delivery with T-piece and aerosol mask at different distances (0, 1, and 2 cm) away

from the collecting filter. The mean inhaled mass as a percentage of nominal dose at 0 cm was 2.88% in the Restrepo et al[23] study as opposed to 3.83% in our study. Lin et al[24] compared the effect of different designs of FM such as the dragon, aerosol, and fish masks at 0, 1, and 2 cm away from the face of the infant lung model. Similar to Restrepo et al,[23] they also reported 2.18% with the aerosol mask at 0 cm. Both studies used a tidal volume of 60 ml and a respiratory rate of 20 bpm, while the breathing parameters that were used in our study, including a tidal volume of 100 mL and respiratory rate of 30 bpm that explain differences in our findings. Lower tidal volume and minute ventilation lead to a decrease in aerosol drug delivery to patients.

For children who cannot tolerate the FM during therapy, using HFNC for aerosol drug delivery may be a good alternative. For instance, delivery of aerosolized medications via HFNC can achieve good cooperation during treatment, which in turn will lead to improved drug delivery and more efficacious treatment in children. Therefore, the administration of aerosolized medications via HFNC is a promising therapy for the management of young children with pulmonary diseases. Everard et al[25] found approximately 50% reduction in lung deposition with nasal inhalation, which is consistent with the findings of this study. Aerosol drug delivery through HFNC has gained popularity over the years and the performance of HFNC on aerosol delivery has been investigated in previous research.[9,26-31] Similar to previous evidence,[28,30,32] we also found that decreasing flow rate with HFNC and LFNC increases aerosol drug delivery in infants and pediatrics because of a reduction in turbulent and transitional flow. The findings of this study also showed LFNC is the least efficient delivery interface compared to the MP, FM, and HFNC in children. No studies investigating the impact of LFNC on aerosol drug delivery to children were found to compare with the data in this study.

According to previous evidence, mesh nebulizers are more efficient than JNs.[10,33-38] Due to their small residual volume, silent operation, easy to use and clean, use of mesh nebulizers for aerosol therapy has gained popularity over the years. In our previous research, we compared aerosol delivery with jet and mesh nebulizers using different FMs in the infant lung model and showed that drug delivery with the aerosol mask was 4.08% and 4.56% with jet and mesh nebulizers, respectively.[10] Although we found similar efficiency (3.83%) with the JN attached to an aerosol mask, delivery efficiency of the mesh nebulizer (6.72%) that we obtained in this study is greater than our previous research. Differences in our findings are due to variation in configurations used with the mesh nebulizer in both studies.

This study illustrates the effects of nebulizer type, delivery interface, and flow rate on aerosol drug delivery to infants and pediatrics. The primary limitation of this study is that only one set of breathing parameters was used despite children having a wide range of breathing parameters. Although the mannequins we used in this study have anatomically accurate nasal airways, several researchers put extensive effort into developing accurate anatomical infant and pediatric nasal airways that will be appropriate to use in future studies.[39-43] While the use of LFNC is not a common practice in aerosol therapy, it was tested in this study to better understand its impact on aerosol deposition in infant and pediatric lung models used. As an in vitro study, the findings of this study may overestimate aerosol drug delivery in vivo. Therefore, further research is needed to determine the clinical efficacy of different delivery interfaces and their impact on patient outcomes.

5 | CONCLUSION

Type of nebulizer, delivery interface, and flow rate used in the treatment of children affect aerosol drug delivery. Delivery efficiency of mesh nebulizers is two to fourfold more than the JNs used with HFNC, FM, and MP. While aerosol delivery with FM was greater than HFNC and LFNC in infants, the delivery efficiency of MP was the best compared to other interfaces used in pediatrics. Increasing flow rate with LFNC and HFNC decreased aerosol delivery with the mesh nebulizer in infants and pediatrics.

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CONFLICT OF INTEREST

Dr. Ari discloses her relationship with the CHEST Foundation, Bayer Pharmaceuticals, Aerogen Ltd, ARC Medical, and Sunovion Pharmaceuticals.

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