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Bshayer R. Alhamad

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THE EFFECT OF AEROSOL DEVICES AND ADMINISTRATION TECHNIQUES ON
DRUG DELIVERY IN A SIMULATED SPONTANEOUSLY BREATHING PEDIATRIC
MODEL WITH A TRACHEOSTOMY

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ACCEPTANCE

This thesis, THE EFFECT OF AEROSOL DEVICES AND ADMINISTRATION TECHNIQUES ON DRUG DELIVERY IN A SIMULATED SPONTANEOUSLY BREATHING PEDIATRIC MODEL WITH A TRACHEOSTOMY, by Bshayer R. Alhamad was prepared under the direction of the Master’s Thesis Advisory Committee of the Respiratory Therapy department at Georgia State University. It is accepted by the committee in partial fulfillment of requirements for the Master’s of Science degree in Respiratory Therapy at Byrdine F. Lewis School of Nursing and Health Professions, Georgia State University. The Master’s Thesis Advisory Committee, as representatives of the faculty, certifies that this thesis has met all standards of excellence and scholarship as determined by the faculty.

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ABSTRACT

Background: Evidence on aerosol delivery via tracheostomy is lacking. The purpose of this study was to evaluate the effect of aerosol device and administration technique on drug delivery in a simulated spontaneously breathing pediatric model with tracheostomy.

Methods: Delivery efficiencies during spontaneous breathing with assisted and unassisted administration techniques were compared using the jet nebulizer (JN- MicroMist), vibrating mesh nebulizer (VMN- Aeroneb Solo) and pressurized metered-dose inhaler (pMDI- ProAirHFA). The direct administration of aerosols in spontaneously breathing patients (unassisted technique) was compared to administration of aerosol therapy via a manual resuscitation bag (assisted technique) attached to the aerosol delivery device and synchronized with inspiration. An in-vitro lung model consisted of an uncuffed tracheostomy tube (4.5 mmID) was attached to a collecting filter (Respirgard) which was connected to a dual-chamber test lung (TTL) and a ventilator (Hamilton). The breathing parameters of a 2 years-old child were set at an RR of 25 breaths/min, a Vt of 150 mL, a Ti of 0.8 sec and PIF of 20 L/min. Albuterol sulfate was administered with each nebulizer (2.5 mg/3 ml) and pMDI with spacer (4 puffs, 108 µg/puff). Each aerosol device was tested five times with both administration techniques (n=5). Drug collected on the filter was eluted with 0.1 N HCl and analyzed via spectrophotometry.

Results: The amount of aerosol deposited in the filter was quantified and expressed as inhaled mass and inhaled mass percent. The pMDI with spacer had the highest inhaled mass percent, while the VMN had the highest inhaled mass. The results of this study also found that JN had the least efficient aerosol device used in this study. The trend of higher deposition with unassisted versus assisted administration of aerosol was not significant ($p>0.05$).

Conclusions: Drug deposited distal to the tracheostomy tube with JN was lesser than either VMN or pMDI. Delivery efficiency was similar with unassisted and assisted aerosol administration technique in this in vitro pediatric model.

THE EFFECT OF AEROSOL DEVICES AND ADMINISTRATION TECHNIQUES
ON DRUG DELIVERY IN A SIMULATED SPONTANEOUSLY BREATHING
PEDIATRIC MODEL WITH A TRACHEOSTOMY

By

Bshayer R. Alhamad

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List of Abbreviations

BAN	Breath-actuated nebulizer
BEN	Breath-enhanced nebulizer
CINAHL	Cumulative Index to Nursing and Allied Health Literature
I:E	Inspiratory to expiratory ratio
JN	Jet Nebulizer
PEEP	Positive expiratory end pressure
PIF	Peak Inspiratory Flow Rate
pMDI	Pressurized metered dose inhaler
RR	Respiratory rate
Ti	Inspiratory Time
TT	Tracheostomy tube
VMN	Vibrating-mesh Nebulizer
Vt	Tidal volume
1/s rate	One time per second irrespective of timing with inspiration/expiration

CHAPTER I

INTRODUCTION

Over the years, aerosol therapy has come to play an integral role in the treatment of pediatric respiratory diseases. Inhaled aerosol agents such as bronchodilators, corticosteroids, antibiotics, and mucolytics are commonly delivered to spontaneously breathing pediatric patients with a tracheostomy. Administering therapeutic inhaled aerosols to pediatric patients is challenging. The pediatric population ranges in age, which means patients with different airway sizes, breathing patterns, and cooperation levels (Schüepf, Straub, Möller, & Wildhaber, 2004). These patient-related factors impact the deposition of aerosol drugs in the lungs (Ari & Fink, 2011; Schüepf et al., 2004). The presence of an artificial airway such as a tracheostomy tube (TT) or an endotracheal tube also influences the deposition of inhaled aerosols in the lungs (Ari, Harwood, Sheard, & Fink, 2012). Therefore, it is important to select an efficient aerosol delivery device and the proper administration technique to enhance aerosol deposition in pediatric patients with a tracheostomy.

Aerosol delivery devices, such as jet nebulizers (JN) and pressurized metered dose inhalers (pMDI) are the most common means of providing therapeutic inhaled aerosols to pediatric patients with a tracheostomy (Willis & Berlinski, 2012). In addition, the vibrating mesh nebulizer (VMN) is one of a group of new devices that has revolutionized the delivery of aerosol drugs. Each of these devices (JN, pMDI and VMN) can be used either alone (unassisted technique) or in conjunction with a manual resuscitation bag (assisted technique) to aid aerosol delivery. Health care providers need information about the best way to deliver aerosol drugs to pediatric patients who have a tracheostomy. Therefore, this study compares the amount of aerosol drugs deposited in the lungs by each of these three aerosol delivery devices when using

either the assisted or unassisted technique. This comparison can guide health care providers in selecting the optimum method for aerosol delivery to pediatric patients with a tracheostomy, which may result in a reduced drug dosage, a shorter treatment time, and a lower overall cost.

Few in vivo and in vitro studies have examined the delivery of aerosol therapy to spontaneously breathing pediatric patients with a tracheostomy. By contrast, many researchers have studied the administration of inhaled aerosols to either spontaneously breathing patients or to mechanically ventilated patients through endotracheal tubes (Dhand, 2000, 2004; Duarte, Fink, & Dhand, 2001; MacIntyre, 2002). To date, researchers have yet to determine which device should be used among the pediatric patient population to optimize aerosol deposition via a TT and no published study has evaluated the efficiency of a VMN as an aerosol delivery device in spontaneously breathing pediatric patients with TTs. More research is needed that compares assisted and unassisted administrative techniques on aerosol delivery to such patients. Therefore, this study examines the efficiency of three different types of aerosol devices— a JN, a VMN, and a pMDI— on aerosol deposition in a simulated spontaneously breathing pediatric model with a tracheostomy. This research is also designed to compare the influence of assisted and unassisted aerosol administration techniques on the amount of aerosol delivered to the pediatric model developed in this study.

The following research questions provide the structure for this study:

- 1) What is the most efficient device for administering inhaled bronchodilators through a pediatric TT (JN, VMN or pMDI)?
- 2) What is the best technique to administer inhaled bronchodilators via a pediatric TT (assisted or unassisted technique)?

CHAPTER II

LITERATURE REVIEW

This literature review presents articles focusing on the delivery of aerosol therapy through a pediatric TT. The following search terms were used to collect articles from the Cumulative Index to Nursing and Allied Health Literature (CINAHL) and PubMed databases: tracheostomy, pediatric, aerosol, nebulizer, breath-enhanced nebulizer, breath-activated nebulizer, metered dose inhaler and vibrating mesh nebulizer. Relevant articles are presented in two sections: (1) current practice for delivering aerosol through a pediatric tracheostomy and (2) aerosol generators, which describes and compares different aerosol delivery devices including a JN, a VMN, and pMDI. A discussion of in vitro comparison studies follows.

Current Practice for Delivering Aerosol Through a Pediatric Tracheostomy

There are no available recommendations for device and drug formulation selection for spontaneously breathing pediatric patients with a tracheostomy. Therefore, Willis and Berlinski (2012) developed a survey to describe patterns in current practice for delivering aerosol to this population. They surveyed pediatric pulmonologists at U.S. hospitals. The survey addressed institution characteristics, types of aerosol delivery devices and their administration technique, types of inhalation medication and factors influencing device selection. The researchers had an 81% response rate (38 out of 47 institutions surveyed responded). Of these institutions, 68% were freestanding children's hospitals. Results showed diversity among institutions in how aerosol to spontaneously breathing pediatric patients with a tracheostomy delivered. However, the authors found little variation in practice between the freestanding children's hospitals and the other types of institutions. Most of the institutions used a nebulizer or a pMDI (97% and, 92%, respectively). No institution reported using dry powder inhalers. Nebulizers were administered

using both assisted and unassisted techniques. Although there was a discrepancy in the article regarding the number of institutions using either technique, most of the institutions used the unassisted technique with the nebulizer. The types of nebulizers used by the institutions were the followings: JNs (34 institutions), breath actuated nebulizers (BAN, four institutions operated the BAN continuously), breath-enhanced nebulizers (BEN, two institutions, one of which removed the inspiratory valve), and VMNs (one institution). Furthermore, pMDIs were used with either an assisted technique (32%, all of which used a spacer) or an unassisted technique (34% with 83% of them using a valved holding chamber, while the remaining using spacer) or both techniques (34%). The assisted technique was used by 68% of the surveyed institutions with either a nebulizer or a pMDI. Of these, 38% used a flow-inflating bag only, 31% used a self-inflating bag only, and 31% used both types of bags. As stated earlier, this survey showed that there was a considerable variation among institutions in the practice of aerosol delivery to spontaneously breathing tracheostomized children. However, it did not provide information about the most efficient aerosol delivery method to this population. Thus, the authors stressed the need for studies that compare the effect of using different aerosol devices and techniques on aerosol deposition in this population.

Aerosol Generators

According to the Willis and Berlinski survey (2012) described above, several aerosol generators are used to deliver inhaled medications to spontaneously breathing pediatric patients with a tracheostomy, including JNs, BENs, BANs, VMNs and pMDIs with a spacer or valved holding chamber. This section only describes the JN, VMN, and pMDI because these are the aerosol generators that will be tested in this study. The advantages and disadvantages of these generators will be reviewed to help respiratory care providers select the proper device for each

individual patient. Finally, this section will examine in vitro studies that have compared the effects of these aerosol generators on aerosol deposition in a spontaneously breathing pediatric model with a tracheostomy.

Jet Nebulizer (JN)

A JN is used to convert an aqueous solution containing a medication into an aerosol form. It is pneumatically operated by directing a pressurized gas created from a compressed gas source through a restricted orifice called a jet. The high velocity of the gas flow creates a jet stream that causes a sub-atmospheric pressure zone. This sub-atmospheric pressure draws liquid up the capillary tube from the nebulizer reservoir and into the gas stream. In the gas stream, the liquid is sheared into filaments that break up into droplets. These droplets can be further broken into small particles by a baffle in the aerosol stream (Hess, 2008).

JNs can be used by any age group, including infants and small children, because they require minimal cooperation from the patient to deliver the medications (Ari, Hess, Myers, & Rau, 2009). They can be administered via either a mouthpiece or a face mask. The mouthpiece is recommended for use with spontaneously breathing children who have intact airways, who are more than three years old, and who are able to cooperate (Ari & Restrepo, 2012). The face mask is an appropriate interface to be used with young children, particularly those under three years old (Ari & Restrepo, 2012). A T-connector and tracheostomy collar are the interfaces that can be used with JNs for children with artificial airways such as a TT.

A JN is also able to nebulize more than one drug or solution containing many drugs (Ari et al., 2009). However, it requires a longer treatment time than other aerosol devices, a power supply, and routine cleaning. Also, it wastes medication during exhalation (Ari et al., 2009).

Vibrating Mesh Nebulizer (VMN)

VMNs use electricity to vibrate a mesh plate or aperture plate. The aperture plate contains multiple funnel-shaped holes with the wider cross-section facing towards the medication, and the narrower cross-section facing the place where the droplets emerge. The size of these funnel-shaped holes controls the size and flow of the nebulized particles. As the aperture plate begins to vibrate, the medication passes through the holes to generate aerosol. VMNs use either vibrating mesh (eg., Aerogen Aeroneb, Nektar, San Carlos, CA; eFlow, Pari, Richmond, Virginia) or a vibrating horn (eg., Omron, Omron Healthcare, Bannockburn, IL) to produce vibrations in the aperture plate (Ari et al., 2009; Dhand, 2002; Hess, 2008).

A VMN is small, portable, and compact and operates silently. Also, it has a minimal residual volume and a rapid nebulization rate, which means a faster nebulization time. On the downside, it is more expensive than a JN, and it cannot nebulize drug suspensions or viscous drugs, which can clog the holes. Moreover, it requires regular cleaning with gentle handling to the mesh to prevent blockage of the holes (Rubin, 2011).

Pressurized Metered Dose Inhaler (pMDI)

pMDI is a pressurized canister containing a mixture of drug and propellant that is fitted to a mouthpiece. Actuation of the canister opens a metering valve that releases a metered dose of drug in aerosolized form under the force of a pressurized propellant (Newman, 2005). The pMDI has many advantages. It is a small, portable, light, quiet, fast and relatively inexpensive device (Hess, 2008; Rubin & Fink, 2005). On the other hand, large amount of the emitted pMDI drug deposits in the oropharynx (Ari & Fink, 2011). In addition, many patients, especially young children, have trouble synchronizing the actuation and inhalation (Ari & Fink, 2011). To overcome the oropharynx deposition and/or synchronization issues, some patients use add-on

devices such as a spacer or a valved holding chamber. A spacer is simply a tube without a valve that captures aerosol from the pMDI (Hess, 2008). It reduces the amount of oropharynx deposition, but it still requires synchronicity between the actuation and the patient's inhalation (Rubin & Fink, 2005). By contrast, a valved holding chamber is a spacer device with a one-way valve that holds the medication until the patient's inhalation is initiated and the valve is opened, thus eliminating the need for synchronization between the actuation and patient's inhalation (Rubin & Fink, 2005).

In tracheostomized patients, Newhouse (1999) reported that frequent actuation of a pMDI directly into a long term tracheostomy leads to minor hemoptysis and accumulation of granulation tissue on the carina and the adjacent bronchi. However, after placing an AeroChamber attached to an infant mask between the pMDI and the tracheal stoma, the pathologic changes and hemoptysis were gradually resolved.

Several articles have described modifications to standard MDI spacers (Meeker & Stelmach, 1992; Mirza, Hopkinson, Malik, & Willat, 1999; Nakhla, 1997). All of these articles agree that current spacers do not easily fit onto a TT, which leads to inadequate drug delivery to the patients. Thus, simple modifications to standard MDI spacers are needed to make it easier to attach the spacer securely to the TT. All of the modifications to a standard pMDI presented in these articles were made to fit it to an adult TT. Monksfield (2008), in comparison, described the modification of a standard pMDI spacer for a pediatric TT. By using accessible materials such as a standard bladder irrigation syringe, he adapted a volumatic spacer (Allan and Hanburys) to fit firmly into a pediatric TT. After the center of the barrel's syringe had been cut, it snugly attached to the outflow end of the spacer because the barrel's diameter is appropriately the same size as the spacer's outflow end. Then, the end of the irrigation syringe was connected to the TT. When

Monksfield (2008) used this technique with his patient, compliance with bronchodilator therapy increased and the need for nebulized steroids in combination with bronchodilators decreased.

In Vitro Comparisons

Different types of nebulizers can be used to administer albuterol to pediatric patients with a tracheostomy. Berlinski and Hayden (2011) evaluated the effect of different aerosol devices on albuterol delivery in a spontaneously breathing pediatric tracheotomy model. The authors studied three different types of nebulizers: a continuous JN (Hudson), a BEN (Pari LC Plus) and a BAN (Aeroclipse II). All the nebulizers were tested with the following two TT sizes and two breathing patterns: tidal volume (V_t) = 80 ml, respiratory rate (RR) = 30 breaths/min, inspiratory to expiratory ratio (I:E) = 1:3 with a TT size of 3.5 mm and V_t = 310 ml, RR = 20 breaths/min, I:E = 1:2 with a TT size of 5.5 mm. For the continuous JN, the authors studied three different configurations: the JN alone, the JN with 15 cm of corrugated tubing attached to it, and a JN connected to the corrugated tubing and a resuscitation bag. In each configuration, a T-piece and a tracheotomy mask were tested. However, only the T-piece was tested with both the BEN and the BAN. The albuterol deposition was collected via a filter placed at the carinal level of the trachea/Trach model and was analyzed via a spectrophotometer at a wavelength of 276 nm. The authors found almost no difference in albuterol deposition among the different configurations of JN when the tracheostomy mask interface was used. The authors also reported that the highest albuterol deposition occurred with the JN and T-piece in conjunction with the resuscitation bag followed by the JN with the corrugated tubing; the lowest albuterol deposition occurred when the JN was used alone (61 ± 4 , 39 ± 8 , and 25 ± 3 μg , respectively, with a TT size of 3.5 mm; 71 ± 23 , 60 ± 12 and 43 ± 12 μg , respectively, with a TT size of 5.5mm). Berlinski and Hayden also concluded that the T-piece was generally more efficient than the tracheostomy mask.

Furthermore, the researchers reported that the BEN was more efficient when tested with a larger Vt and a larger TT size ($130 \pm 9 \mu\text{g}$ with Vt= 310 ml and a TT of 5.5 mm vs. $41 \pm 2 \mu\text{g}$ with Vt= 80 ml and a TT of 3.5 mm). However, the BAN was inefficient when tested with a low Vt ($4 \pm 2 \mu\text{g}$). Although the authors studied different types of nebulizers, they did not compare the efficiency of each aerosol device with the others. Comparing the efficiency of different types of nebulizers can help to determine which is the most efficient for delivering aerosol to this population.

Ari et al. (2010) conducted an in vitro study to assess the impact of the aerosol device (JN vs. VMN), position of the device on the ventilator circuit (prior to the humidifier vs. at the Y-piece) and bias flow (2 vs. 5 L/min) on aerosol drug delivery in simulated and mechanically ventilated pediatric and adult lung models. The adult ventilator settings were as follows: a Vt of 500 ml, a positive end expiratory pressure (PEEP) of 5 cmH₂O, a RR of 20 breaths/min, a peak inspiratory flow (PIF) of 60 L/min and a descending ramp flow pattern. The pediatric ventilator settings were a Vt of 100 ml, a PEEP of 5 cmH₂O, a RR of 20 breaths/min and an inspiratory time (Ti) of 1 second. The drug deposition was collected by an absolute filter distal to an 8 mm (adult) and 5 mm (pediatric) endotracheal tube. The amount of drug deposition was measured via spectrophotometry at a wavelength of 276 nm. Throughout this study, the VMN delivered the highest inhaled mass percentage ($23.8\% \pm 1.0$) in the adult lung model when it was placed prior to the humidifier with a 2 L/min bias flow. On the other hand, the JN delivered the least inhaled mass percentage ($3.8\% \pm 0.3$) in the pediatric lung model when it was placed at the Y-piece with a 5 L/min bias flow. In all positions, the inhaled mass of the VMN was two- to four fold greater than with the JN in both lung models. The authors also noted that using higher bias flow with both nebulizers tended to reduce aerosol drug delivery at both positions in the adult and pediatric lung models. Deposition of the aerosol was similar for both nebulizers when they placed the

devices at the Y-piece in the adult and pediatric lung models. When they placed the devices prior to the humidifier, they found that deposition of aerosol was higher for the VMN in the adult model than in the pediatric model.

Piccuito and Hess (2005) conducted an in vitro study to assess the impact of the aerosol delivery device, interface, bias flow and humidification on albuterol delivery through a TT in a spontaneous breathing adult model. The researchers conducted two experiments. The first experiment used a nebulizer (Hudson, Temecula, CA) and the second used a pMDI (Monaghan, Plattsburgh, NY). In the nebulizer experiment, four conditions of gas flow and humidification were used. For the first condition, heated aerosol was generated using the nebulizer and a heater with an outlet flow of approximately 30 L/min. The relative humidity was > 95%. The second condition was heated humidity generated using a concha-Therm heated humidifier. The oxygen outlet flow was approximately 30 L/min. The researchers set the heat of the humidifier to provide a gas temperature of approximately 30°C with a relative humidity > 95%. The third condition was high flow without added humidity (approximately 30 L/min). For the fourth condition, they attached the nebulizer to the TT without additional flow. In all four conditions, the nebulizer was filled with 4ml of 2.5 mg albuterol and tested with both a T- piece/flex tube and a tracheotomy mask. In the pMDI experiment, four conditions of gas flow and humidity were also used: (1) heated humidity with a T- piece, (2) heated humidity with a tracheostomy mask, (3) an AeroVent with a valved T-adaptor, and (4) an AeroVent with a valved T-adaptor and a one-way valve proximal to the AeroVent. In all of these four conditions, four actuations of the pMDI separated by ≥ 15 seconds were synchronized with the inhalation. In both experiments, the simulated adult breathing parameters were a RR of 20 breaths/min, a Vt of 400 ml, and an I:E of 1:2. A cuffed 8 mm TT was used. The aerosol delivered through the TT was captured by a

filter placed between the lung model and the distal end of the TT. This study had six major findings: (1) a measurable amount of albuterol aerosol was delivered through the TT with the use of either the nebulizer or the pMDI with a spacer; (2) the delivery of albuterol using the nebulizer with high gas flow was inefficient; (3) more albuterol was delivered when they used a T-piece than when they used a tracheostomy mask; (4) the pMDI with a valved holding chamber was more efficient than the nebulizer; (5) the pMDI was more efficient when a T-piece with a valve was placed proximal rather than distal to the spacer; and (6) the impact of humidity on aerosol delivery was not clear. In conclusion, albuterol delivery through a TT was affected by the device, the interface and the bias gas flow.

In an in vitro study, Ari et al. (2012) compared aerosol delivery through a TT and an endotracheal tube using different interfaces such as a tracheostomy mask, a T-piece and a manual resuscitation bag in a simulated spontaneously breathing adult model. They concluded that using the manual resuscitation bag increased lung dose by more than three- fold with either the TT or endotracheal tube ($45.75 \pm 1.8\%$ vs. $27.23 \pm 8.98\%$, $p = 0.038$ and $p = 0.025$, respectively). They also found that the tracheostomy mask had less inhaled dose than the T-piece with the TT ($6.92 \pm 0.81\%$, $p = 0.01$). Overall, the authors found that delivering aerosol through a TT was more efficient than through an endotracheal tube.

Aerosol delivery via a pMDI to spontaneously breathing tracheostomy pediatric patients can be affected by many factors. Chavez and Berlinski (2010) conducted an in vitro study to investigate whether the delivery device, the size of the TT and the patient's breathing pattern impact albuterol delivery via pMDI in a spontaneously breathing pediatric tracheostomy model. They examined several delivery devices: an AeroChamber MV™, an AeroChamber Mini™, an AeroTrach Plus™, a Medibag™, and a 6-inch tubing + Hudson™ adapter. These devices were

tested without bagging. With each device, two sizes of TT (3.5 and 4.5 mm) and three breathing patterns (16 months, 6 years old, and 12 years old) were tested. Furthermore, the Medibag™ and 6-inch tubing + Hudson™ adapter were also studied with synchronized bagging, and the AeroChamber MV™ was tested with both synchronized and asynchronized bagging. In all experiments, 10 pMDI actuations were delivered for six respiratory cycles each. The amount of albuterol was collected by a filter holder placed at the level of the carina. This amount was then measured via spectrophotometry at 276 nm. The authors reported that a smaller TT size, manual bagging and the breathing pattern of a younger child decreased the amount of albuterol reaching the carina. Moreover, the AeroTrach Plus™ was generally the most efficient delivery device.

The effect of using a resuscitation bag on the delivery of aerosol via pMDI was further studied by Chavez, Holt, Heullit, and Berlinski (2011). In an in vitro study, they evaluated the effect of using a resuscitation bag in conjunction with a pMDI with a spacer during albuterol delivery in a spontaneously breathing pediatric tracheostomy model. They studied two types of valved holding chambers, an Aerochamber MV™ and an AeroChamber Mini™. Both valved holding chambers were tested using different albuterol administration techniques via pMDI: unassisted, synchronized assisted, and asynchronized assisted (on expiration or 1/s rate). In all the tests, three different breathing patterns (16 months, 6 years old, and 12 years old) were simulated. In each test, 10 pMDI actuations were delivered for six repeated cycles through a 4.5 mm TT. The authors reported that when synchrony and asynchrony (1s/rate) techniques were used, albuterol delivery decreased for all the devices and breathing patterns. When the researchers used asynchrony during expiration, albuterol delivery decreased only for the 16 months old breathing pattern. The authors found that using a resuscitation bag with a pMDI

reduced the amount of aerosol delivered to the patients. This finding is similar to the previous study by Chavez and Berlinski (2010).

In conclusion, this literature review has shown that there are many factors affecting the delivery of albuterol through a TT, including the aerosol delivery devices, interfaces, bias flows, administration techniques, and TT sizes used as well as the patients' breathing patterns. Several findings from the research stand out. The most commonly used aerosol delivery devices with a tracheostomy are nebulizers and pMDIs. However, research shows that a pMDI with a valved holding chamber is more efficient than a nebulizer. The AeroTrach Plus is generally the most efficient valved holding chamber for tracheostomy. BANs are inefficient when tested with low Vt. BENs are more efficient when tested with large Vt. In terms of bias flow, nebulizers with bias flow decreases albuterol delivery. In regard to interfaces, a T-piece is generally better than a tracheostomy mask. When administering albuterol using the assisted technique with a nebulizer increases albuterol delivery. On the other hand, using the assisted technique with a pMDI decreases albuterol delivery. In regards to TT size, the amount of the albuterol delivery decreases as the size of the TT decreases. Finally, breathing patterns affect delivery, with albuterol delivery decreases among younger children.

CHAPTER III
METHODOLOGY
Experimental Setup

As shown in Figure 1, to simulate spontaneous breathing for a two-year-old child with a tracheostomy tube (TT), one side of a dual-chamber test lung with a lift bar (Training/test lung [TTL] PneuView Systems, Adult/infant lung simulator, Michigan Instruments, Grand Rapids, MI) was connected to the ventilator (Hamilton Medical AG, Rhäzüns, Switzerland). The other side of the test lung was connected to the TT. Breathing parameters were set at an RR of 25 breaths/min, a V_t of 150 ml, a T_i of 0.8 second, and a PIF of 20 L/min (Lin et al., 2012). An uncuffed TT (Shiley™, Covidien Inc, Mansfield, MA) with an inner diameter of 4.5 mm was used because previous research has found it to be suitable for a two-year-old child (Wyatt, Bailey, & Whiteside, 1999). The TT was attached to the collecting filter (Respirgard II, 303, vital signs, Brooklyn, NY). Another filter was placed between the collecting filter and the opposite side of the dual-chamber test lung to protect the test lung. The same experimental setup was used in each trial of this study.

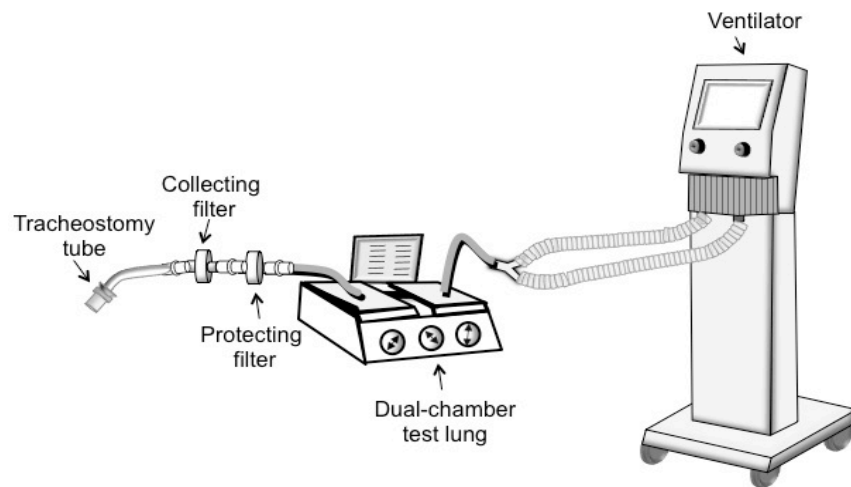


Figure 1. Experimental setup of the study.

Aerosol Devices types, Doses and Operation

Three types of aerosol devices were tested in this study: (1) a JN (Micro Mist, Hudson RCI, Temecula, CA), (2) a VMN (Aeroneb Solo, Aerogen, Galway, Ireland) and (3) a pMDI (ProAir HFA, Teva Specialty Pharmaceutical, Horsham, PA).

The nebulizers (JN and VMN) were filled with albuterol sulfate (2.5mg/3 ml) (Nephron Pharmaceuticals Corporation, Orlando, FL). The JN was operated with oxygen at 8 L/min, using a calibrated flow meter. The unit-dose of albuterol sulfate solution was aerosolized by the JN until the onset of sputter and by the VMN until no more aerosol was seen.

The pMDI canister, which contained albuterol sulfate (108 µg/actuation) was warmed to hand temperature, shaken well, and primed with four actuations before each experimental run. The pMDI was actuated at the onset of inspiration for a total of four puffs with more than 15 seconds between each. All actuations were activated by the same investigator to minimize inter-operator variability. Each experiment was repeated five times.

Administration Techniques

In this study, aerosol therapy was administered to the spontaneously breathing model using two techniques: 1) assisted technique using a manual resuscitation bag in conjunction with an aerosol device and 2) unassisted technique with direct administration from the aerosol device.

Unassisted Technique Setup

JN and VMN were administered as shown in Figure 2A and 2B, respectively. The T-piece of the nebulizers was connected to another T-piece which was attached to the TT. A 6-inch length of 22 mm ID corrugated tubing was placed on both open ends of the T-pieces.

The pMDI was removed from the actuator and inserted into the nozzle inlet of a spacer (Aerochamber HC MV, Trudell, London, Ontario, Canada). The pMDI + spacer was then connected to the proximal part 15 mm adapter of the TT (Figure 2C).

Assisted Technique Setup

In the assisted technique, both JN and VMN were attached to a manual resuscitation bag (Ambu SPUR II Disposable Resuscitator, Ambu Inc, Glen Burnie, MD) via a T-piece adaptor that was connected to the TT through a 6-inch length of corrugated tube (Figure 2D and 2E, respectively). The manual resuscitation bag was manually squeezed in synchrony with each inspiration of the model. To ensure consistency with the spontaneous breathing model, all breaths via the manual resuscitation bag were administered by a single investigator.

The pMDI + spacer was connected between the manual resuscitation bag and the TT. (Figure 2F). Each actuation was synchronized with the beginning of inspiration. To ensure consistency with the spontaneous breathing model, all pMDI actuations and the bagging were delivered by the same investigator.

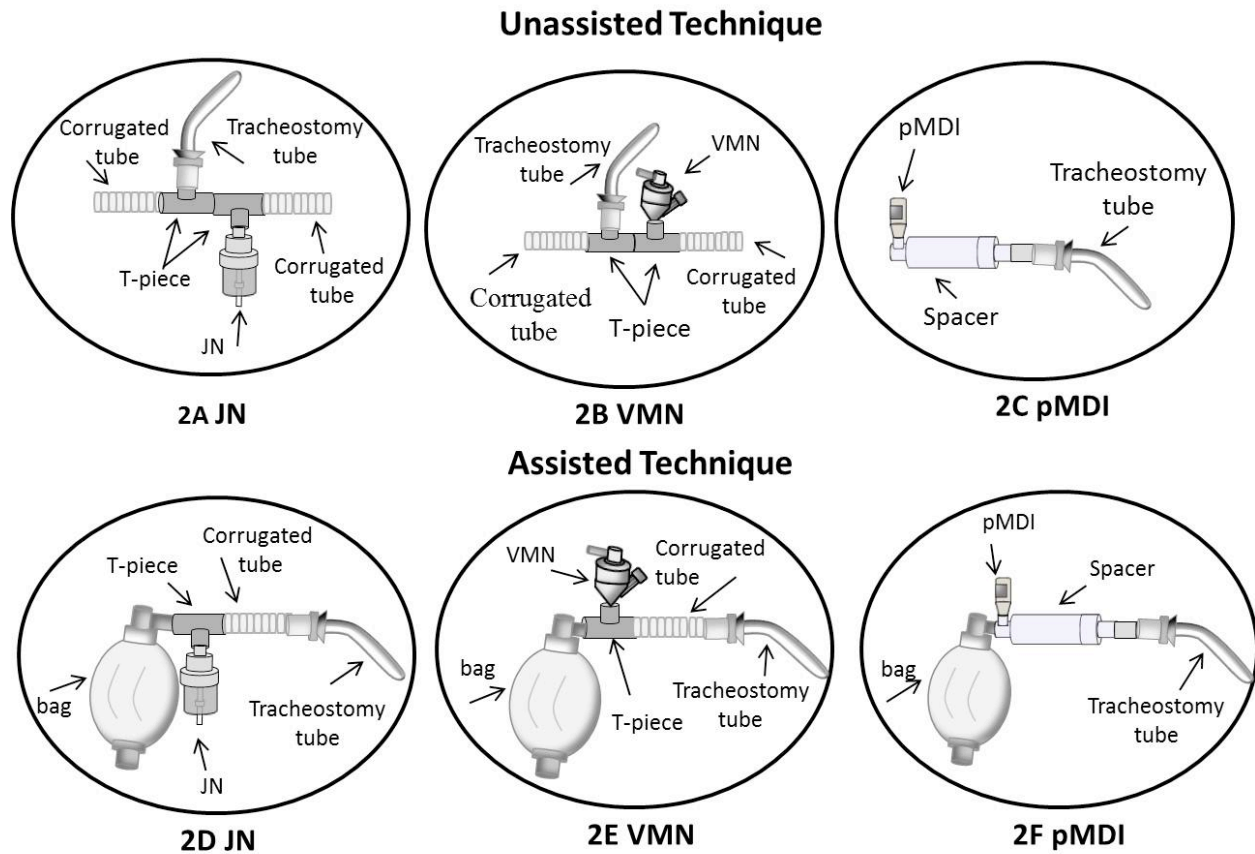


Figure 2. Experimental setup with each aerosol device using assisted and unassisted techniques. JN: Jet Nebulizer. VMN: Vibrating Mesh Nebulizer. pMDI: Pressurized Metered Dose Inhaler.

Measurement of Aerosol Deposition

Each aerosol device was tested five times using both administration techniques (n=5) (Figure 3). In each trial, the amount of aerosol exiting the TT was captured by an absolute filter. At the end of each trial, the deposited drug was eluted from the filter with 10 ml of 0.1 N hydrochloric acid (JT Baker Company, Phillipsburg, NJ) using gentle agitation for 1 minute to ensure proper mixing. The albuterol concentration was then analyzed with a spectrophotometry (Beckman Instruments, Fullerton, CA) using a quartz cuvette, at a wavelength of 276 nm. The spectrophotometer was calibrated prior to the trials via a holmium oxide filter (Beckman

Instruments, Fullerton, CA) to determine wavelength accuracy. It was then set to zero before the next trial by running only the solvent.

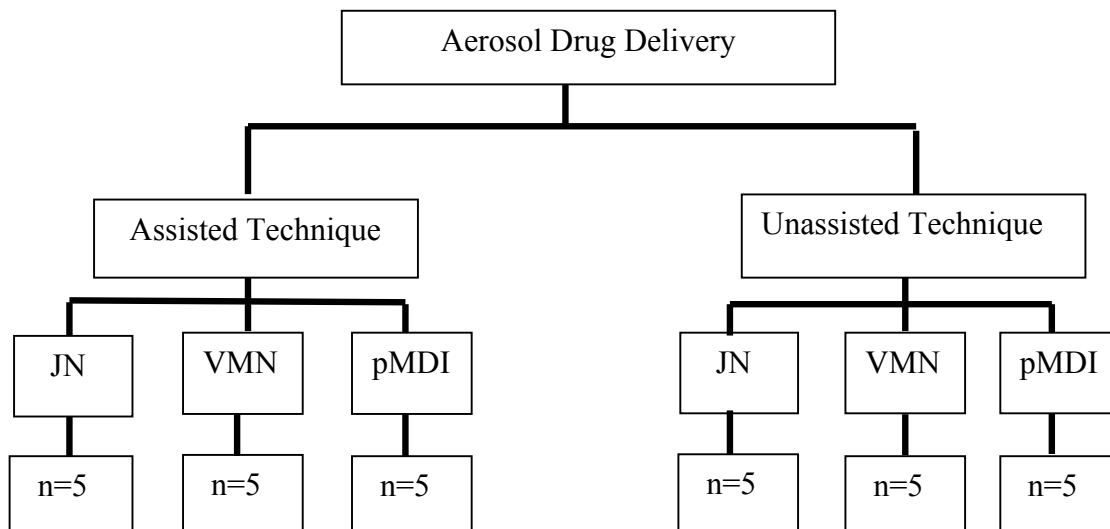


Figure 3. Organizational design of the study.

Data Analysis

The amount of drug deposited in the filter was quantified and reported as inhaled mass and inhaled mass percentage. Data analyses were performed using the Statistical Package for the Social Sciences (IBM SPSS, 18.0, Chicago, IL). Descriptive statistics including means and standard deviations were computed for each aerosol device (JN, VMN, pMDI) for both the assisted and unassisted techniques. A repeated measures test was performed to determine the difference in the inhaled mass and inhaled mass percentage among the JN, the VMN and pMDI, all together. Multiple comparisons were done to identify differences between aerosol devices tested in this study using the assisted and unassisted techniques. A paired *t*-test was used to

compare the assisted with unassisted techniques on inhaled mass and inhaled mass percentage for each aerosol device. In all comparisons, significance was defined as a p value < 0.05 .

CHAPTER IV

RESULTS

This study compared the amount of aerosol delivered to the TT (the inhaled mass) and the inhaled mass percentage of three devices—a JN, aVMN, and a pMDI— using both an assisted and unassisted techniques. Table 1 presents the means (\pm standard deviation) of albuterol mass deposited on the filter and percent of nominal dose for JN and VMN and emitted dose for 4 actuations from the pMDI using the assisted and unassisted techniques.

Table 1.

	Inhaled Mass (mg)			Inhaled Mass Percent (%)		
	JN	VMN	pMDI	JN	VMN	pMDI
Assisted Technique	0.13 \pm 0.03	0.43 \pm 0.03	0.18 \pm 0.05	5.31 \pm 1.59	17.45 \pm 1.26	43.32 \pm 12.38
Unassisted Technique	0.15 \pm 0.01	0.49 \pm 0.07	0.20 \pm 0.03	5.88 \pm 0.77	19.77 \pm 2.99	47.15 \pm 7.82

Efficiency of Aerosol Devices on Drug Delivery

This study found differences in the inhaled mass and inhaled mass percentage among the three aerosol devices ($p= 0.0001$). There was also a statistically significant difference in the inhaled mass and inhaled mass percentage between the JN and the VMN as well as between the VMN and the pMDI when using both the assisted ($p= 0.000$, and $p= 0.006$, respectively) and the unassisted techniques ($p= 0.002$, $p= 0.004$, respectively). The findings of this study showed no significant difference between the JN and the pMDI in terms of inhaled mass when using either

the assisted or unassisted technique ($p=0.481$, $p=0.080$, respectively). For inhaled mass percentage, however, the difference was statistically significant when using both the assisted and unassisted techniques ($p= 0.008$, $p= 0.001$, respectively). As shown in Table 1, the highest inhaled mass was with the VMN, while the inhaled mass efficiency was greatest with the pMDI. The JN was the least efficient device in both inhaled mass and inhaled mass percentage (Figure 4 and 5, respectively).

Efficiency of Aerosol Administration Techniques on Drug Delivery

While there was a trend towards higher inhaled mass and inhaled mass percentage with unassisted vs. assisted technique, the differences between the two techniques were not statistically significant for the JN, VMN and pMDI ($p= 0.46$, $p= 0.19$, and $p= 0.64$, respectively).

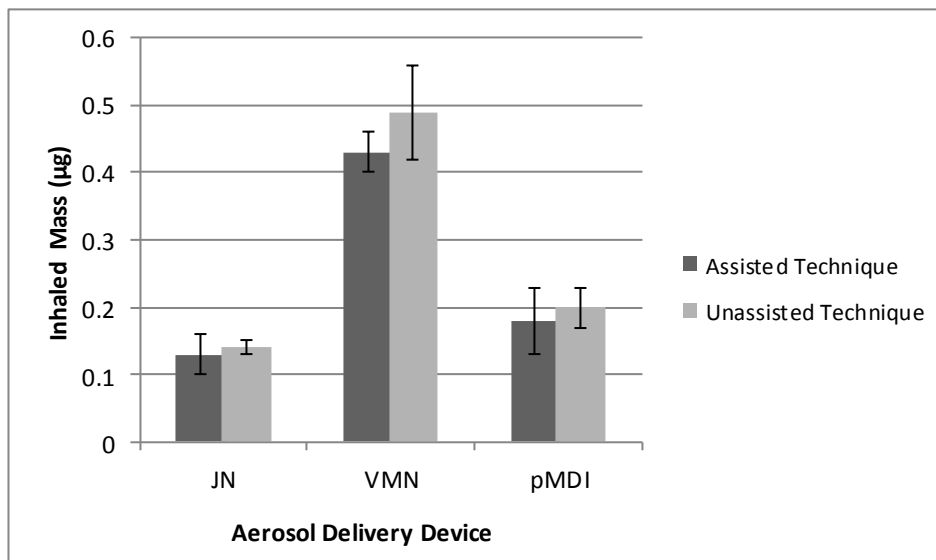


Figure 4. Differences in inhaled mass among aerosol delivery devices by delivery technique.

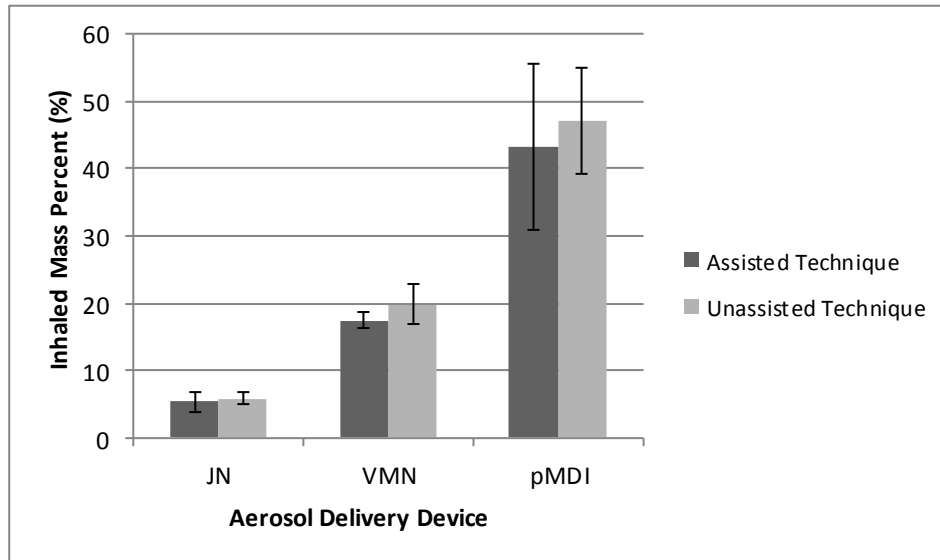


Figure 5. Differences in inhaled mass percentage among aerosol delivery devices by delivery technique.

CHAPTER V

DISCUSSION

The purpose of this study was to evaluate the efficiency of the aerosol devices and the administration techniques on the drug delivery to spontaneously breathing pediatrics with TT. The percent of albuterol deposited distal to the TT was greater with the pMDI than VMN or JN. The VMN was three fold more efficient than JN. In terms of administration technique, there was no statistically significant difference on aerosol deposition between assisted and unassisted techniques.

Efficiency of aerosol devices on drug delivery

When the pMDI was compared with the JN, we found that despite the smaller nominal dose of the pMDI (432 μ g) than the JN (2.5 mg), the amount of drug delivered to the TT was more with the pMDI than the JN. These data are supported by Piccuito and Hess (2005), who compared aerosol delivery between the JN and the pMDI in several conditions to the spontaneously breathing adult with tracheostomy. In their study, they found that pMDI is more efficient than JN in relation to the percentage of inhaled mass ($21 \pm 1\%$ vs. $15 \pm 3\%$, $p= 0.002$). However, they reported that the amount of inhaled mass was greater with JN than pMDI ($382 \pm 68 \mu$ g vs. $84 \pm 4\mu$ g, $p < 0.001$), while this study found the opposite. The difference in the amount of inhaled mass may attribute to the difference in the amount of fill volume in the JN given in each study. The amount of fill volume of their study was 2.5 mg/4ml, while in this study was 2.5mg/3ml. According to Hess, Fisher, Williams, Pooler, and Kacmarek (1996) study, increasing the amount of fill volume by adding more diluent volume will decrease the amount of drug remaining in the JN after treatment ends and will increase the amount of inhaled medication. Therefore, the higher fill volume in the JN of Piccuito and Hess study lead to an increase in the

amount of the inhaled mass obtained by using the JN than our study. Additionally, the administration setup of the JN was different between these two studies. Piccuito and Hess capped one end of the JN's T-piece, while the other end was attached to the T-piece interface via 15 cm flex tube. In this study, one end of the JN's T-piece was attached to the corrugated tube while the other was connected to the T piece interface (Figure 2A). Capping one end of the JN's T-piece will increase the amount of the inhaled medication. This difference in the setup of the JN administration contributes also to having higher inhaled mass with the JN in Piccuito and Hess than this study.

When the VMN is compared to the JN, this study found that VMN is three fold more efficient than JN. This result agrees with the findings of Ari et al. (2010), who evaluated aerosol drug delivery in pediatric mechanically ventilated lung model with endotracheal tube. They compared JN and VMN in different positions and bias flows. They found that drug delivery with VMN was 2-4 fold greater than JN in pediatric lung models regardless of position and bias flow. However, the inhaled mass percent of the JN and the VMN in their study was lower than this study. This difference is not surprising since the type of the population tested in this study is spontaneously breathing whereas mechanically ventilated in their study. Dolovich, Killian, Wolff, Obminski, and Newhouse (1977) reported that the mean of the amount of aerosol deposited in the lung with intermittent positive pressure ventilation was less than quite breathing by 32% despite having the same drug dose in the ultrasonic nebulizer. Another factor that may also attribute to the difference in the amount of aerosol deposition between these studies is the type of the artificial airway used. This study used TT, while they used endotracheal tube. The TT is shorter than the endotracheal tube which means lesser drugs will be lost in the tube. Ari et al. (2012) reported that the TT is more efficient than the endotracheal tube in terms of drug delivery.

Efficiency of aerosol administration techniques on drug delivery

This study found that adding a manual resuscitation bag to the aerosol device when administering bronchodilator (assisted technique) does not increase the amount of deposited drug on the TT with all the studied aerosol devices. This result differs from the findings of Ari et al. (2012). In an in vitro study, they evaluated the effect of using different patient interfaces such as T-piece, tracheostomy collar and manual resuscitation bag on aerosol drug delivery through TT and endotracheal tube. They concluded that using the manual resuscitation bag increased lung dose by more than three fold with either TT or endotracheal tube. This difference may account for the difference in breathing parameters, tracheostomy tube size and nebulizer type used in both studies. While Ari et al (2012) used adult breathing parameters ($V_t= 450$ mL, RR= 20 breaths/min, I:E ratio 1:2) with 8 mm TT size, this study used pediatric breathing parameters suitable for a 2 years old child (RR= 25 breaths/min, $V_t= 150$ ml, $T_i= 0.8$ second, and PIF= 20 L/min) with 4.5 mm TT size. The smaller V_t and higher RR with a smaller diameter TT would be expected to reduce the amount drug deposited distal to the airway. They also used evaluateMed nebulizer, while this study used Hudson MicroMist nebulizer. Having different brands of nebulizer may also account for the difference in the amount of deposited drugs.

Clinical Implications

This study provides good guidance to clinicians or caregivers regarding the relative efficiency of these three aerosol delivery devices and the two administration techniques used when administering aerosol therapy to spontaneously breathing pediatrics via TT. For the type of aerosol delivery devices, the pMDI or VMN should be the first selection, making the selection of the JN last option. However, there is no difference between assisted and unassisted aerosol administration techniques when using any one of the aerosol devices. Consequently,

administration technique selection can be determined by the patient comfort level, the need to augment ventilation with a manual resuscitation bag for the specific patient.

Limitations

This experiment was an *in vitro* study. Thus, the results should be validated by an *in vivo* study. In addition, the *in vivo* study provides more clinical responses in pediatric patients receiving aerosol therapy with different aerosol devices and administration techniques. This study only examined one type and size of the TT and resuscitation bag, as well as one set of breathing parameters.

Future Research

For future studies, we suggest studying the effect of administration technique on aerosol delivery to the pediatric patients by using other types of resuscitation bags, such as a flow inflating bag. Different breathing patterns should be also studied in order to determine how aerosol deposition would be affected by different diseases and patient conditions.

Conclusion

In this *in vitro* spontaneously breathing pediatric model, drug deposited distal to the TT was influenced by the type of aerosol device used. JN was the least efficient device than both VMN and pMDI. However, drug efficiency was similar with assisted and unassisted aerosol administration techniques. The findings of this study could provide clinical guidance to the health care providers or caregivers in selecting the best method to optimize drug delivery to pediatric patients with TT.

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