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In Vitro Evaluation oF Aerosol Drug Delivery With And Without High Flow Nasal Cannula Using Pressurized Metered Dose Inhaler And Jet Nebulizer in Pediatrics

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IN VITRO EVALUATION OF AEROSOL DRUG DELIVERY WITH AND WITHOUT HIGH FLOW NASAL CANNULA USING PRESSURIZED METERED DOSE INHALER AND JET NEBULIZER IN PEDIATRICS

By

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ACCEPTANCE

This thesis, IN VITRO EVALUATION OF AEROSOL DRUG DELIVERY WITH AND WITHOUT HIGH FLOW NASAL CANNULA USING PRESSURIZED METERED DOSE INHALER AND JET NEBULIZER IN PEDIATRICS, by Mahmood Ahmed Alalwan was prepared under the direction of the Master's Thesis Advisory Committee of Respiratory Therapy department at Georgia State University. It is accepted by the committee members 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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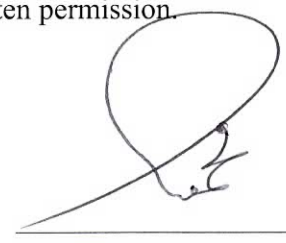

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ABSTRACT

IN VITRO EVALUATION OF AEROSOL DRUG DELIVERY WITH AND WITHOUT HIGH FLOW NASAL CANNULA USING PRESSURIZED METERED DOSE INHALER AND JET NEBULIZER IN PEDIATRICS

By

Mahmood Ahmed Alalwan

Background: HFNC system is a novel device used with aerosol therapy and seems to be rapidly accepted. Although there are some studies conducted on HFNC and vibrating mesh nebulizer, the effect of HFNC on aerosol delivery using jet nebulizer or pressurized metered-dose inhaler (pMDI) has not been reported. In an effort to examine the effect of HFNC on aerosol deposition, this study was conducted to quantify aerosol drug delivery with or without a HFNC using either pMDI or jet nebulizer.

Methodology: The SAINT model, attached to an absolute filter (Respirgard II, Vital Signs Colorado Inc., Englewood, CO, USA) for aerosol collection, was connected to a pediatric breathing simulator (Harvard Apparatus, Model 613, South Natick, MA, USA). To keep the filter and the SAINT model in upright position to collect aerosolized drug, an elbow adapter was connected between the absolute filter and the breathing simulator. An infant HFNC (Optiflow, Fisher & Paykel Healthcare LTD., Auckland, New Zealand) ran at 3 l/min O_2 was attached to the nares of the SAINT model. Breathing parameters used in this study were Vt of 100 mL, RR of 30 breaths/min, and I:E ratio of 1: 1.4. Aerosol drug was administered using: 1) Misty-neb jet nebulizer (Allegiance Healthcare, McGaw Park, Illinois, USA) powered by air at 8 l/min using pediatric aerosol facemask (B&F Medical, Allied Healthcare Products, Saint Louis, MO, USA) to deliver albuterol sulfate (2.5 mg/3 mL NS), and 2) Four actuations of Ventolin HFA pMDI (90 µg/puff) (GlaxoSmithKline, Research Triangle Park, NC, USA) combined with VHC (AeroChamber plus with Flow-Vu, Monaghan Medical, Plattsburgh, NY, USA). Aerosol was administered to the model with and without the HFNC and another without (n=3). Drug was collected on an absolute filter, eluted and measured using spectrophotometry. Independent t tests were performed for data analysis. Statistical significance was determined with a p value of <0.05.

Results: The mean inhaled mass percent was greatest for pMDI with ($p = 0.0001$) or without HFNC ($p = 0.003$). Removing HFNC from the nares before aerosol treatment trended to increase drug delivery with the jet nebulizer ($p = 0.024$), and increased drug delivery by 6 fold with pMDI ($p = 0.003$).

Conclusions: Aerosol drug may be administered in pediatrics receiving HFNC therapy using either jet nebulizer or pMDI. However, using pMDI, either with or without HFNC, is the best option. When delivering medical aerosol by mask, whether by jet nebulizer or pMDI, removing HFNC led to an increase in inhaled mass percent. However, the benefit of increased aerosol delivery must be weighed against the risk of lung derecruitment when nasal prongs are removed.

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ABBREVIATIONS

BPD	Bronchopulmonary dysplasia
CF	Cystic fibrosis
HFNC	High flow nasal cannula
pMDI	Pressurized metered-dose inhaler
SVN	Small volume nebulizer
SAINT	Sophia Anatomical Infant Nose-Throat
VHC	Valved-holding chambers
NCPAP	Nasal continuous positive airway pressure
CPAP	Continuous positive airway pressure
WOB	Work of breathing
MMD	Mass median diameter
MMAD	Mass median aerodynamic diameters
GSD	Geometric standard deviation

CHAPTER I

INTRODUCTION

Childhood respiratory diseases such as asthma, bronchopulmonary dysplasia (BPD), and cystic fibrosis (CF) require aerosolized drug therapy as a part of the disease management. However, infants pose unique challenges for efficacious aerosol delivery (Ahrens, 2005; Ari & Fink, 2011; Everard, 2004; Rubin et al., 2001). Some of the challenges that face clinicians during aerosol administration are infant distress, poor cooperation, and achieving optimum facemask seal.

Distress and poor cooperation during aerosol administration is one of the recurrent and challenging factors that face clinicians when dealing with pediatrics. For instance, a study showed that in 69% of the sleep administrations of aerosol to infants aged between 6 and 23 months, the children woke up and 75% of them were distressed during the treatment. Moreover, poor cooperation was reported in 29% of the awake administrations (Esposito-Festen et al., 2006). The level of infant distress is directly correlated to lung deposition. Amirav et al. (2003) reported an increase in the amount of extrathoracic deposition with increased infant distress. Furthermore, lung deposition was reduced significantly to 0.3% in 2 crying infants compared to 2.0% during their quiet breathing (Tal et al., 1996).

Another factor that plays an important role in determining the lung deposition during aerosol administration is facemask leak. The facemask, a common alternative to mouthpiece in infants and small children, functions as an interface between the patient

and the aerosol delivery device. Not only does lung deposition significantly depend on the size of the facemask leak, but also the leak position. Different studies reported that there was a strong correlation between the size of the leak and lung deposition (Esposito-Festen et al., 2004; Amirav et al., 2001; Smaldone et al., 2005). Even a leak as small as 0.5 cm could result in greater than 50% reduction of the inhaled mass of the drug (Esposito-Festen et al., 2004; Amirav et al., 2001; Smaldone et al., 2005). Moreover, leaks around the nose were associated with less lung deposition than leaks around the chin (Esposito-Festen et al., 2004). Those factors and challenges clearly emphasize that aerosol administration in this age group is profoundly different.

In an effort to reduce infant distress, recent aerosol research suggested the use of high flow nasal cannula (HFNC) as an aerosol delivery device. They proposed that an aerosol drug could be administered using a vibrating mesh nebulizer with HFNC (Ari et al., 2011; Bhashyam et al., 2008). Traditionally, HFNC is utilized to avoid mechanical ventilation, maintain patent airways, and improve gas exchange (Campbell et al., 2006; Saslow et al., 2006; Shoemaker et al., 2007). There is a rapid increase in the use of the HFNC in the neonatal and pediatric population. One study revealed a 64% increase in HFNC usage after its introduction in infants of all gestational ages (Shoemaker et al., 2007). In addition, 95% of infants born at less than 30 weeks gestation received HFNC at some point during their hospital stay (Shoemaker et al., 2007).

Significance:

HFNC system is a novel device used with aerosol therapy and seems to be rapidly accepted. Although there are some studies conducted on HFNC and vibrating mesh nebulizer, the effect of HFNC on aerosol delivery using jet nebulizer or pressurized

metered-dose inhaler (pMDI) has not been reported. Also, there is no evidence to support keeping or removing the HFNC when a facemask is used during aerosol drug delivery. Thus, more research is required to detect the effects of the presence of HFNC systems on lung deposition during aerosol administration. In an effort to examine the effect of HFNC on aerosol deposition, this study is to quantify aerosol drug delivery with or without a HFNC using either pMDI or jet nebulizer. It would establish a guideline for the clinicians to make an informed decision in determining the most efficient way to administer aerosol drug in concurrence with the HFNC therapy.

Hypothesis:

Keeping HFNC in the nares of pediatrics during aerosol therapy with pMDI or jet nebulizer would decrease drug delivery to the lungs.

Purpose:

The purpose of this study is to quantify aerosol drug delivery in pediatrics with or without a HFNC using either pMDI or jet nebulizer.

Research Question:

During HFNC therapy in pediatrics, what is the most efficient way to administer inhaled medications using jet nebulizer or pMDI with or without HFNC?

CHAPTER II

REVIEW OF THE LITERATURE

Introduction:

This is a literature review of the articles published in the area of aerosol research and high flow nasal cannula in the pediatric population. Literature was obtained using PubMed, MEDLINE with Full Text, and CINAHL Plus with Full Text. Different terms were used for the term aerosol such as nebulizer, aerosols, vaporizers, bronchodilator, nebulization, inhalation therapy, aerosol therapy, metered dose inhaler, MDI, small volume nebulizer, SVN, jet nebulizers, and inhalers in pediatrics. For the research on aerosol delivery via facemask, terms used were facemask, facemask leak, facemask effects; they were combined with aerosol search terms. For the research on high flow nasal cannula, search terms used were high flow nasal cannula, HFNC, nasal cannula, and heated high flow nasal cannula; they were also combined with aerosol search terms. Articles were divided into four sections: in vivo aerosol research, in vitro aerosol research, high flow nasal cannula, and aerosol delivery via HFNC. This research incorporated twenty years of references, ranging from 1991 to 2011. All references were peer-reviewed and written in English.

In Vivo Aerosol Research:

Chua et al. (1994) conducted a study on 20 asymptomatic children with CF. Twelve were sleeping infants aged between 0.3 and 1.4 years (median age 0.8 years), and eight older children aged between 6.3 and 18.0 years (median age 10.8 years). The aim

was to quantify aerosol deposition in children of wide age range. They used a nebulizer to administer radiolabelled normal saline with a flow of 9 l/min. Planar and single-photon emission computed tomography scans were obtained after aerosol administration. They found that the total lung deposition in the infants who were asleep (median 1.3%) and for older children (median 2.7%).

Amirav et al. (2003) conducted a study on 14 wheezy infants (mean age 8 months) to compare aerosol lung deposition using a small volume nebulizer (SVN) with facemask and prototype hood. Radiolabelled salbutamol was administered to the subjects randomly by SVN at a flow of 8 l/min with either hood or facemask. Salbutamol delivery was evaluated using gamma scintigraphy. They found that there was no significant difference in total lung deposition; mean total lung deposition was 2.4% with the mask and 2.6% with the hood.

Amirav et al. (2005) conducted a randomized, double-blinded, controlled trial on 49 infants (mean age ± SD, 2.75 mo ± 2.2 mo) diagnosed with viral bronchiolitis to compare aerosol drug delivery using Aeroneb Go Nebulizer (Aerogen, Inc) with either hood or facemask. Subjects were divided into 2 groups, hood group and facemask group. To use both devices on all subjects, half of each group received 1.5 mg epinephrine in 4 mL of 3% saline via one of the devices (hood or facemask) followed immediately by placebo treatment (normal saline) via the other device, while the other half received the opposite order. Therapy was repeated 3 times daily until discharge. Outcome measures included clinical scores and parental preference. They found a significant improvement in clinical severity scores after the aerosol treatment in both groups on day 1, 2, and 3 after admission (hood group: 15%, 15.4%, and 16.4%, respectively; facemask group: 17.5%,

12.1%, and 12.7%, respectively); no significant difference between the two groups was observed. In addition, 80% of parents preferred the hood over the facemask.

Tal et al. (1996) conducted a study on 15 infants and children (mean age 21 months) with chronic airway obstruction (asthma, BPD, and CF) to assess aerosol deposition in the lower respiratory tract and gastrointestinal tract. One puff of radiolabelled salbutamol was administered by pMDl via an Aerochamber spacer combined with mask. Immediately after administration subjects were scanned with a gamma camera. They found that mean aerosol deposition was 1.28% ± 0.77% in the oropharynx, 1.97% ± 1.4% in the lungs, and 1.11% ± 2.4% in the stomach. In addition, lung deposition was reduced significantly to 0.3% in 2 crying infants compared to 2.0% during their quiet breathing.

Mallol et al. (1996) conducted a study on 20 asymptomatic children with CF to quantify aerosol deposition in the respiratory system. They used 2 different jet nebulizers, Bennett Twin which produces 7.7 μm mass median diameter (MMD) and Hudson Up-Draft II which produces MMD of 3.6 μm, to administer radiolabelled normal saline. Subjects were divided into 3 groups: group A consisted of 10 children that received aerosol using Bennett Twin jet nebulizer while sedated. Group B consisted of 5 children that received aerosol via Bennett Twin jet nebulizer while awake. Group C consisted of 5 children that received aerosol using Hudson UpDraft 11 jet nebulizer while awake. Subjects and equipment were scanned using a gamma camera on completion of nebulization. They found that total lung deposition in group A was 0.97 ± 0.35%, group B 0.76 ± 0.36%, and group C 2.0 ± 0.71%. In groups A and B, the deposition occurred mainly in the trachea and main bronchi. Deposition in the pharynx, mouth, and nose was

least in group C. No correlation was detected between aerosol deposition in the respiratory system and with age, weight, height, or sedation. Aerosol deposition was influenced mainly by aerosol particle size.

Amirav et al. (2002) conducted a study on 12 children (mean age ± SD, 8 mo ± 4 mo) with acute respiratory syncytial virus bronchiolitis to evaluate the distribution characteristics of aerosolized bronchodilators to the lower respiratory tract. They used the Micromist jet nebulizer (Hudson Respiratory Care Inc.) attached to a facemask operated at 8 l/min oxygen to administer radiolabelled albuterol to the subjects. Total body and lung deposition and pulmonary distribution of the aerosol were measured using scintigraphy. They found that 1.5% ± 0.7% of the drug dose leaving the nebulizer deposited in the right lung, with just about 0.6% penetrating to the peripheral lung zone. 7.8% ± 4.9% deposited in the upper respiratory tract and gastrointestinal tract and 10%–12% remained on the face. No correlation was detected between aerosol deposition and clinical response (e.g. SO_2, HR, RR), height, weight, or body surface area.

Salmon et al. (1990) conducted a study on 9 wheezy children aged between 9 months and 3 years (median 16 months) and 7 healthy adults to evaluate aerosol delivery to the lungs. They used an Acorn nebulizer (Medic Aid) with Hudson oxygen facemask (Henleys Medical Supplies) to deliver sodium cromoglycate to the children and adults. In addition, they delivered the same medication by pMDI, spacer, and mask to the children. The medication concentration was evaluated in urine samples collected in a timely manner to estimate lung deposition. In all subjects tested, they found that merely 0.13% - 0.61% of the nominal dose was detected in the urine, which represents an estimated 0.3% - 1.5% deposited in the lung.

Wildhaber et al. (1999) conducted a study on seventeen children (2-9 years) with stable asthma to compare aerosol deposition in the lungs from a nebulizer and a pMDI with nonstatic holding chamber. The subjects were divided into two groups: group A 2-4 years and group B 5-9 years. They administered radiolabelled salbutamol with the nebulizer and pMDI randomly to the subjects. Lung deposition was evaluated with a gamma camera. With the nebulizer, they found that the mean total aerosol deposition was 5.4% and 11.1% for group A and group B, respectively. With the pMDI and holding chamber, they found that the mean total aerosol deposition was 5.4% and 9.6% in group A and group B, respectively.

Fok et al. (1996) conducted a study on 23 preemies, 10 intubated and 13 spontaneously breathing infants, with or at high risk of developing BPD to evaluate aerosol deposition in the lungs. They administered radiolabelled salbutamol to every infant twice on separate occasions. Spontaneously breathing infants received aerosol using a tightly sealed facemask (Laerdal Resuscitation Mask; Laerdal) with either a jet nebulizer or pMDI and Aerochamber spacer (Aerochamber, Trudell Medical). Intubated infants received aerosol using either a jet nebulizer or a pMDI and Aerochamber (MV15 Aerochamber, Trudell) connected to the ventilator circuit. After administration, imaging was obtained using a gamma camera. Only data from 18 infants (11 spontaneous and 7 intubated) were available for the analysis of regional deposition. They found that the mass median aerodynamic diameters (MMAD) was 1.88 μm and geometric standard deviation (GSD) was 1.45 μm of the pMDI aerosols after passing the endotracheal tube (ETT) for the intubated infants; the spontaneously breathing infants had MMAD of 1.83 μm and GSD of 1.50 μm after exiting the mask. The MMAD and GSD of the aerosols of

the jet nebulizer were 0.83 μm and 1.69 μm, respectively, for the intubated infants, and 1.01 μm and 1.64 μm for the spontaneously breathing infants. In addition, they found that aerosol deposition in the lungs of spontaneously breathing infants was between 0.12 % and 2.26% using the pMDI and between 0.12% and 0.66% of the initial nebulizer reservoir. For the intubated infants, aerosol deposition in the lungs was between 0.35% and 2.12% using the pMDI, and 0.22% of the initial nebulizer charge.

Esposito-Festen et al. (2006) conducted a study on thirty infants aged between 6 and 23 months with recurrent wheeze to examine the possibility of aerosol administration via a pMDI and spacer (NebuChamber, 250 mL, AstraZeneca) in sleeping infants in daily life setting. Over a period of 21 days, parents were instructed to administer 2 extra puffs of budesonide (Pulmicort, 200 ug; AstraZeneca) to the children's regular treatment; 1 puff while awake and another while asleep. Parents also added a new filter between the chamber and the facemask before each administration to measure aerosol deposition. Scoring of the children's asthma symptoms, degree of cooperation, and feasibility of administration on diary cards was done by the parents. They found that administration of aerosol to most of the infants while asleep was not superior to administration while awake. The mean filter dose ± SD % of the nominal dose for the sleep administration was 16 ± 13%, and that for the awake administration was 47 ± 26% ($p = 0.007$). During sleep administration, 69% of the children woke up during the treatment with distress. Poor cooperation was reported in twenty nine per cent of the administrations while awake.

Erzinger et al. (2007) conducted a study on 8 asymptomatic children aged between 18 months and 3 years with recurrent wheeze. They hypothesized that a minor air leak in the facemask can significantly reduce lung deposition. They administered

radiolabelled salbutamol with either vent-assisted nebulizer (PariBaby with Pari facemask no. 2) or a pMDI attached to a holding chamber (Aerochamber with an Aerochamber 2nd generation face mask; Trudell Medical). Aerosol deposition was measured using a gamma camera and expressed as a percentage of the nominal dose. They found that lung deposition in 2 subjects with a facemask leak was 0.2% (pMDI) and 0.3% (nebulizer). In 2 subjects who were screaming and without facemask leak, lung deposition was 0.6% (pMDI) and 1.4% (nebulizer). In 4 subjects who were quietly breathing and without facemask leak, lung deposition was between 4.8% and 8.2%. In addition, mask deposition ranged between 0.8% and 5.2%, and face deposition ranged between 2.6% and 8.4%.

In Vitro Aerosol Research:

Sangwan et al. (2004) conducted an in vitro study to quantify facial and eye aerosol delivery in a model simulating an average 2-year-old child's face facsimile (Massachusetts Institute of Technology, Cambridge, MA). They used a jet nebulizer to administer radiolabelled normal saline; which was inhaled using a piston pump (Harvard Pump, South Natick, MA) attached to facsimile. A pediatric tidal volume (Vt) of 50 mL, respiratory rate (RR) of 25 breaths/minute, and duty cycle (inspiratory time/total respiratory cycle time) of 0.4 were used. To quantify aerosol deposition at the mouth, a filter was placed between the piston pump and the mouth opening. Seven commercially available facemasks (Laerdal, Laerdal Medical Corp.; Sealflex, Caradyne Ltd; Ferraris Panda, Ferraris Medical Ltd; PariBaby&Pari Bubble, Pari Respiratory Equipment, Inc; Salter, Salter Labs; Hudson, Hudson Respiratory Care, Inc.) in combination with three jet nebulizers (Pari LC Plus, PARI Respiratory Equipment, Inc.; MistyNeb, Allegiance; AeroTech II, CIS-US, Inc), which produce different sizes of particles, were tested for aerosol deposition in the lungs, on the face and in the eyes. They found that 2.24–5.96% of the nominal dose was inhaled; 0.44–2.34% deposited on the face; 0.09–1.78% deposited in the eyes. There was a leak with all facemasks with substantial facial and eye deposition. Additionally, aerosol deposition in the eyes and face was affected by the facemask design and aerosol particle size.

Laube et al. (2010) conducted an in vitro study using four copies of a 9-month-old infant model, the Sophia Anatomical Infant Nose-Throat (SAINT), to measure the aerosol deposition of albuterol within the nose and lungs. The model was connected to a computer-operated breathing simulator (PARI Breath Simulator, PARI GmbH). They

administered radiolabelled albuterol to the four copies of the SAINT model continuously over thirty seconds by an IPI nebulizer (IPI Medical Products, Inc.). The nebulizer was run by an air compressor (Thomas Model 1020) at 10.5 l/min. a 15-cm corrugated tube with a plastic funnel-shaped facemask was used to deliver aerosol; the mask was not held tightly against the face. The simulator's RR, inspiratory time, expiratory time, and duty cycle were 30 breaths/min, 0.9 sec, 1.1 sec, and 0.45, respectively. Three different Vt's (50, 100, and 200 mL) were used. Aerosol deposition was measured using a gamma camera as percentage of discharged dose. They found that the mean MMD for the nebulizers used was 4.78± 0.18 μm. Lung deposition was alike for the different Vt's; it was 7.17± 0.01% at 50 mL, 9.34±0.01% at 100 mL, and 9.41±0.02% at 200 mL. On the contrary, nose deposition increased when Vt was increased; it was 4.40±0.02% at 50 mL, 11.39±0.02% at 100 mL, and 22.12± 0.02% at 200 mL. Aerosol lost in the environment was significantly higher at 50 mL Vt (71.99± 0.02%), compared to 200 mL (53.81±0.04%).

Esposito-Festen et al. (2004) conducted an in vitro study using a SAINT model (SAINT model, Erasmus MC) that was connected to a computer-controlled breathing simulator; the study was to investigate the relationship between size and position of a mask leak on spacer output and lung dose. The simulator's set parameters were duty cycle of 0.42, Vt of 100 mL, and RR 30 breaths/min. They administered budesonide pMDI (Pulmicort 200 mg, AstraZeneca) to the model via a metal spacer (NebuChamber, AstraZeneca) with a round-shaped resuscitation facemask (Galemed). Nine facemask leaks (0-1.5 cm^2) close to the nose (nose position) or the chin (chin position) were tested. The spacer output was trapped by a filter placed between spacer and facemask; the lung

dose was trapped by a filter placed between model and breathing simulator. Quantification was done by a validated high-performance liquid chromatography (HPLC), and expressed as percentage of the nominal dose. They found that the nose position leaks and their corresponding spacer output (mean output%) were 0 (50%), 0.05 (38%), 0.1 (28%), 0.16 (12%), 0.2 (10%), 0.3 (6%), and greater than 0.4 (0%). The chin position leaks and their corresponding spacer output (mean output%) were 0 (50%), 0.05 (40%), 0.1 (31%), 0.16 (11%), 0.2 (9%), 0.3 (4%), and greater than 0.4 (0%). The nose position leaks and their corresponding lung doses (mean dose%) were 0 (10%), 0.05 (8%), 0.1 (6%), 0.16 (3%), 0.2 (3%), 0.3 (1%), 0.4 (0%), 0.5 (0%), 1.0 (0%), and 1.5 (0%). The chin position leaks and their corresponding lung doses (mean dose%) were 0 (10%), 0.05 (9%), 0.1 (8%), 0.16 (6%), 0.2 (6%), 0.3 (5%), 0.4 (1%), 0.5 (1%), 1.0 (0%), and 1.5 (0%).

Smaldone et al. (2007) conducted an in vitro study to determine the effect of facemask seal, mask vents and nebulizer flow on aerosol drug deposition in the lungs in children using nebulizers and facemasks. They used a pediatric face facsimile and piston pump to simulate breathing with Vt 50 mL, RR 25 breaths/min, and duty cycle 0.4 for all of the tests. They administered radiolabeled saline using Pari LC jet plus nebulizer run at 4 or 8 l/min with front-loaded and bottom-loaded masks. A gamma camera was used to assess deposition in the face and eyes. A filter was placed between the face and piston pump to measure drug delivery to the lungs and expressed as a percentage of the nominal dose. Nebulizer flows of 4 and 8 l/min were tested. In their preliminary experiments, they tested different facemasks including original Laerdal Facemask (A), a bottom-vented Laerdal Facemask (B), and eye-cutouts Laerdal Facemask (C) to study the effects of

vents and nebulizer flow. These observations led to the design of a mask prototype; a front-loaded modified Pari Bubbles facemask with a vent and eye cutouts (D). This prototype was compared to a bottom-loaded Salter I-Guard facemask (E) combined with NebuTech HDN nebulizer. They found that the inhaled mass (Mean ± SE%) with its corresponding mask were 6.38 ± 0.42% (A), 6.55 ± 1.42% (B), 7.69 ± 1.68% (C), 8.78 ± 0.98% (D), and 2.33 ± 0.22% (E). At the flow of 8 l/min, the inhaled mass was reduced by nearly a half. Facial depositions were 1.76 ± 0.17% (A), 0.72 ± 0.07% (C), 0.66 ± 0.07% (D), and 1.43 ± 0.16% (E). Eye depositions were 1.14 ± 0.15% (A), 0.15 ± 0.02% (C), 0.09 ± 0.01% (D), and 0.31 ± 0.03% (E). At 8 l/min nebulizer flow, facial and eye deposition remained approximately the same.

Janssens et al. (2004) conducted an in vitro study using the SAINT model connected to a simulator to evaluate the effect of Vt, RR, and pMDI/spacer combination on aerosol deposition of 4 pMDI/spacer combinations, which are used for infants. Spontaneous breathing patterns were simulated with duty cycle 0.42, Vt's of 25, 50, 75, 100, 150, 200 mL were tested with RR of 30 breaths/min; and RR's of 20, 30, 42, 60, 78 breaths/min were tested with Vt of 100 mL. pMDI's used were Budesonide (Pulmicort 200 mg, AstraZeneca) and Fluticasone HFA (Flixotide 125 mg, GlaxoWellcome). Spacers used were Babyhaler (polycarbonate), Nebuchamber (metal), and Aerochamber (plastic). pMDI's were combined with the spacers as the following: budesonide/Nebuchamber, fluticasone/Babyhaler, budesonide/Aerochamber, and fluticasone/Aerochamber. To reduce electrostatic charge, plastic spacers were detergent coated. A filter positioned between spacer and facemask to measure spacer-output dose or between model and breathing simulator to measure aerosol deposition in the lungs. An

impactor was used to determine aerosol particle size. They found a significant positive correlation between spacer output and Vt but not RR. There was an initial increase in lung deposition with increased Vt from 25 to 50 mL (Nebuchamber, Aerochamber) or to 100 mL (Babyhaler). However, lung deposition was decreased, with further increase in Vt and RR. Maximum lung doses, expressed as percentage of nominal dose, at Vt of 50 mL were 11%, 9%, and 16% for budesonide/Nebuchamber, budesonide/Aerochamber, and fluticasone/Aerochamber, respectively. Maximum lung dose at Vt of 100 mL was 19% for fluticasone/Babyhaler. Irrespective of spacer type, aerosol deposition in the lungs generated by fluticasone was 1.5–6-fold higher compared with budesonide. MMAD decreased with increasing Vt and RR. Aerosol particles <2.1 mm was independent of Vt and RR for deposition in the lungs. Lung dose decreased with increasing inspiratory flow (increasing Vt or RR) by increasing impaction of coarse particles in the upper airways. Deposition of particles <2.1 mm is relatively flow independent. If electrostatic charge of spacers is minimized, lung dose is pMDI dependent and relatively spacer independent.

Smaldone et al. (2005) conducted an in vitro study to measure the effect of the facemask on aerosol drug delivery using a pediatric breathing simulator connected to a face. For aerosol administration, they used Budesonide (0.25 mg) with 2 nebulizer brands: Hudson Up-draft II with standard pediatric facemask, and breath enhanced Pari LC Plus with Bubbles the fish facemask; a fluticasone propionate (220 μg) pMDI with 2 valved-holding chambers (VHCs) brands were used: AeroChamber Plus with medium ComfortSeal facemask, and OptiChamber with medium facemask. VHCs were tested in non-detergent-coated and detergent-coated conditions. A filter was positioned between the simulator and the face. The simulator's Vt, RR, and duty cycle for breathing pattern

(1) were 207 mL, 37 breaths/min, 0.41 and breathing pattern (2) 75 mL, 25 breaths/min, 0.40. The delivery systems described above were tested in three conditions; the first condition with a constant flow to deliver all generated aerosol to the filter; the second condition with applied breathing pattern with tight seal; the third condition with applied breathing pattern with possible facemask leak. They found that in the first condition the drug output was 45.8 ± 4.4% and 46.0 ± 7.2% for Hudson and Pari nebulizers, respectively; 35.5 ± 1.0% and 18.2 ± 3.3% for non-detergent coated AeroChamber and OptiChamber, respectively; 50.8 ± 4.7% and 38.8 ± 4.4% for detergent coated AeroChamber and OptiChamber, respectively. In the second condition, they found that the inhaled mass ranged between 9.6 ± 0.7 and 24.3 ± 3.1% for the nebulizers, 0.7 ± 0.5% and 7.7 ± 1.6% for the non-detergent coated VHCs, and 27.2 ± 1.4% and 53.3 ± 6.2% for the detergent coated VHCs. In the third condition, they found that the inhaled mass ranged between 4.1 ± 0.8% and 19.3 ± 2.3% for the nebulizers, 1.0 ± 0.2% and 3.1 ± 2.4% for the non-detergent coated VHCs, and 4.0 ± 1.6% and 28.6 ± 2.5% for the detergent coated VHCs.

Amirav et al. (2001) conducted a preliminary in vitro study followed by an in vivo study to evaluate whether parents can keep a good facemask seal in children. They studied NebuChamber mask (Astra Draco AB), BabyHaler mask (infant size 2; Glaxo), and AeroChamber mask (child mask; Trudell Medical), combined with frequently used pediatric VHCs and compared them with the seal obtained with the Hans Rudolph mask (#2; Hans Rudolph, Inc.). The preliminary in vitro study was conducted using albuterol pMDI, the NebuChamber VHC, electrostatic filter inserted between the NebuChamber and the mask, a screen pneumotachograph from a portable spirometer (Flowscreen; E.

Jaeger) inserted between the mask and the filter holder, and a cooperative healthy adult to simulate breathing. In vivo studies were conducted on 30 asymptomatic children (mean age 3.2 ± 1.4 years) with asthma to evaluate facemask leak for the 4 masks by measuring ventilation with a pneumotachograph connected to the outlet of the mask. The facemask was held in place by experienced parents who were not given any instructions. Maximal voluntary ventilation (MVV) was measured. Ten patients repeated the tests, however, unlike the first time, the parents were instructed continuously and encouraged to maintain a tight facemask seal against the child's face. The in vitro studies showed that there was a positive linear relationship between the measured ventilation and the dose deposited in the filter. They found that MVV's (mean ± SD) were 4.22 ± 0.93, 2.89 ± 0.81, 4.24 ± 0.85, and 3.82 ± 1.19 l/min for the Hans Rudolph, NebuChamber, AeroChamber, BabyHaler masks, respectively. Intraindividual variability ranged between 24% and 45% but the greatest variability was found with the NebuChamber mask. MVV's during coached sessions were significantly higher than the uncoached sessions.

High Flow Nasal Cannula (HFNC):

Saslow et al. (2006) conducted a study on 18 preterm infants weighing less than 2 kg at birth to compare their work of breathing (WOB) with HFNC and nasal continuous positive airway pressure (NCPAP). Infants were studied on both devices and received NCPAP at 6 cm H_2O with nasal prongs through a ventilator and HFNC via Vapotherm at 3, 4, and 5 l/min randomly. Infants served as their own control. Vt was obtained using respiratory inductance plethysmography coupled with facemask pneumotachography for calibration. Changes in end distending pressure were calculated using an esophageal balloon to estimate pleural pressure. Elastic, resistive, and inspiratory WOB and

respiratory parameters were calculated. They found that there were no differences in the WOB for all settings. Compliance was increasing with increased HFNC flow but it was only statistically significant at flow of 5 l/min. Changes in end distending pressure was statistically significantly only with HFNC at 5 l/min.

Spence et al. (2007) conducted an observational study over one year on a convenience sample of 14 stable infants who required either HFNC or NCPAP. The aim of the study was to measure the intrapharyngeal pressure (IPP) generated by HFNC at different flow rates using IPP manometry. They found that flow rates of 1, 2, 3, 4 and 5 $l.min^{-1}$ (l/min) generated an IPP of 1.70 ± 0.34, 1.75 ± 0.2, 2.62 ± 0.28, 3.78 ± 0.44, and 4.84 ± 0.51 cm H_2O respectively. No correlation was found between the size of the baby and the IPP generated.

Shoemaker et al. (2007) conducted a retrospective database review composed of two parts. The first part of the study was to assess the frequency of usage, safety and clinical utility of HFNC in two tertiary neonatal intensive care units. The second part compares outcomes of premature infants, born at less than 30 weeks gestation, who received either NCPAP or HFNC as an early respiratory support mode. The first part of the study revealed a 64% increase in HFNC usage after its introduction in infants of all gestational ages while the usage of NCPAP dropped from 19% to 4%. Ninety five per cent of infants born at less than 30 weeks gestation received HFNC at some point during their hospital stay whereas only 12% received NCPAP. There were no differences in death or BPD, but ventilator-days per patient were decreased from19.4 to 9.9 days following introduction of HFNC. The second part of the study revealed no differences in

deaths, ventilator-days, BPD, blood infections or other outcomes. 40% of infants were intubated for failing early NCPAP compared to 18% with early HFNC.

Campbell et al. (2006) conducted a study on 40 intubated preterm infants weighing less than or equal to 1250 g at birth to compare the feasibility of continuous positive airway pressure (CPAP) support generated by HFNC with conventional CPAP for prevention of reintubation. The infants were randomized to HFNC or 5 to 6 cm H_2O NCPAP (VIASYS) at extubation. HFNC system consisted of a gas source, air-oxygen blender and a nonheated bubble humidifier delivering air/oxygen via standard nasal cannula; a formula was used to calculate the flow required to generate a CPAP level of 4.5 cm H_2O. Primary outcome was the incidence of reintubation within 7 days. Secondary outcomes included change in O_2 use and frequency of apnea and bradycardia postextubation. They found 12 of 20 infants randomized to HFNC were reintubated compared to 3 of 20 using NCPAP. The HFNC group had increased oxygen use and more apneas and bradycardias postextubation.

Aerosol Delivery Via HFNC:

Bhashyam et al. (2008) conducted an in vitro study to evaluate the possibility of delivering aerosols through adult, pediatric, and infant nasal cannulas. They used an aerosol delivery system composed of an Aeroneb Solo nebulizer (Aerogen, Inc.) which was positioned downstream of a Fisher Paykel humidifier (Fisher & Paykel Healthcare Inc.), followed by nasal cannula driven by 3 l/min O_2. A corrugated tube was placed over, and sealed around, the prongs of the cannula as a collection system. A single cartridge HEPA filter (HEPA-Lites, Teleflex Medical) was placed at the end of the collection system. They tested this delivery system with and without inhalation-only flows using a

Harvard Lung. Vt, RR, and I:E ratio were 150 mL, 25 breaths/min, 1:1; 300 mL, 18 breaths/min, 1:1; and 550 mL, 15 breaths/min, 1:1 for the infant cannula, pediatric cannula, and adult cannula, respectively. They administered 4 mL radiolabelled deionized water by the nebulizer. Total cannula output in the HEPA filter and losses were measured as a percentage of the nominal dose using a nuclear medicine dose calibrator (Radioisotope Calibrator CRC-4, Capintec, Inc.). Aerosol particle size was measured using laser-diffraction techniques (Malvern Instruments) at three different points. They found that total cannula output was 8.4-25.1% and 18.6–26.9% without and with the Harvard Lung, respectively. The pediatric cannula output was 18.1 ± 4.2 and 25.4 ± 1.7 without and with the Harvard Lung, respectively. Volume median diameters were 2.2 ± 0.2 μm and 1.9 ± 0.3 μm from the adult and pediatric cannulas, respectively. 90% of the aerosol volume was in sizes smaller than 4.2 ± 0.4 μm and 3.8 ± 0.5 μm for the adult and pediatric cannulas, respectively. On the one hand, system losses were highest in the nebulizer–humidifier connectors, heated tube, and humidifier. On the other hand, losses in the nebulizer were the lowest.

Ari et al. (2011) conducted an in vitro study to measure aerosol deposition using two different gases; one is 100% oxygen (O_2) and the other is heliox (80/20%) in a pediatric-breath simulator. The pediatric-breath simulator was composed of a ventilator (Galileo, Hamilton, Inc., Reno, NV), a dual chamber test lung (Michigan Instruments, Grand Rapids, MI), and an absolute filter. A simulated inhalation and exhalation was created in one of the chambers when the positive pressure applied by the ventilator displaced the other chamber. From one side, the absolute filter was attached to the chamber that simulated breathing. The other side was connected to a t-piece with two

openings to simulate the nares. Breathing parameters were Vt 100 mL, RR 20 breaths/min, and Itime of 1 sec. They used a vibrating mesh nebulizer (Aeroneb Solo, Aerogen) to administer albuterol sulfate (2.5 mg/3 mL) via a pediatric HFNC. The nebulizer was positioned on the inspiratory inlet of a heated humidifier and heated wire circuit attached to a pediatric nasal cannula (Optiflow, Fisher & Paykel). They tested this system at two different flow rates, 3 and 6 l/min, for each gas for a total of 12 runs. Drug was collected, eluted and measured through spectrophotometry (Beckman Instruments, Fullerton, CA) and expressed as a percentage of the nominal dose. They found that the mean drug deposition at 3 l/min was 11.41 ± 1.54 and 10.65 ± 0.51 with heliox and O_2, respectively. At 6 l/min, drug deposition was 5.42 ± 0.54 and 1.95 ± 0.50 with heliox and O_2, respectively.

Summary:

Aerosol delivery to infants and small children is significantly different. For instance, facemask leak, even a small one, could cause a substantial reduction in aerosol delivery. Aerosol delivery using a combination of pMDI and spacer is at least as effective as a jet nebulizer. Traditionally, HFNC is utilized to avoid mechanical ventilation, maintain patent airways, and improve gas exchange. There is a rapid increase in the use of the HFNC in the neonatal and pediatric population. Recent bench studies suggested that the nasal route is a viable option for aerosol administration. It was reported that aerosol administration via vibrating mesh and HFNC may provide a relatively high inhaled mass.

CHAPTER III

METHODOLOGY

In Vitro Lung Model:

The SAINT model used in this study is an anatomically correct model of the upper airways of a young child. It was reproduced from CT scans of the upper airways of a 9-month-old infant. The nasal airway was open for air passage with the oral passage closed (Janssens et al., (2001).

The SAINT model, attached to an absolute filter (Respirgard II, Vital Signs Colorado Inc., Enlgewood, CO, USA) for aerosol collection, was connected to a pediatric breathing simulator (Harvard Appartus, Model 613, South Natick, MA, USA). To keep the filter and the SAINT model in upright position to collect aerosolized drug, an elbow adapter was connected between the absolute filter and the breathing simulator. An infant HFNC (Optiflow, Fisher & Paykel Healthcare LTD., Auckland, New Zealand) was attached to the nares of the SAINT model.

The HFNC setup was composed of wick humidifier (MR850JHU, Fisher & Paykel Healthcare LTD., Auckland, New Zealand), heated-wire circuit, and infant HFNC. It was operated at a flow of 3 l/min O_2. Figure 1 illustrates the experimental setup of the study.

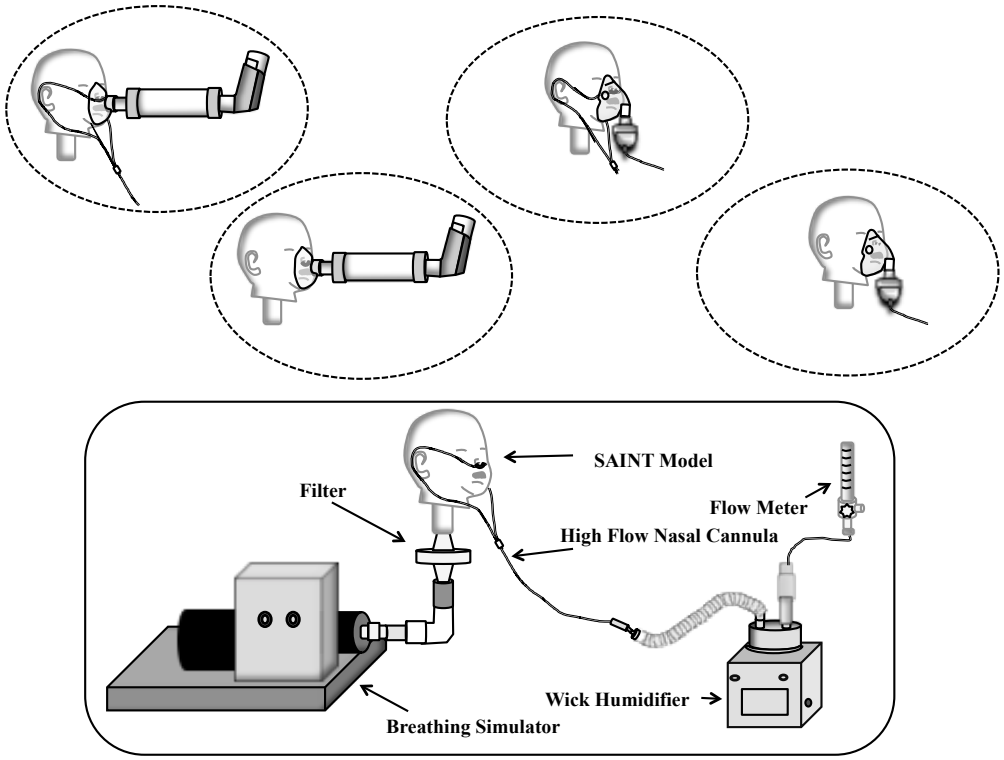

Figure 1. The experimental setup of the study

Breathing Parameters:

Breathing parameters used in this study were Vt of 100 mL, RR of 30 breaths/min, and I:E ratio of 1: 1.4. The breathing parameters were verified using NICO 2 monitor (Respironics California Inc., Carlsbad, CA, USA). The 9-month-old baby that the SAINT model was based on was 10 kg (Janssens et al., 2001). The parameters used are within the reference values appropriate for a 9-month-old 10-kg baby (Amsallem et al., 2008; Stick, 1996)

Aerosol Generator Types, Doses, and Operation:

Two types of aerosol devices were used in this study: (1) Jet Nebulizer (2) pMDI.

Jet nebulizer: Misty-neb jet nebulizer (Allegiance Healthcare, McGaw Park, Illinois, USA) is a traditional pneumatic Bernoulli type nebulizer combined with pediatric aerosol mask (B&F Medical, Allied Healthcare Products, Saint Louis, MO, USA) was

used to deliver aerosol. In this study, the jet nebulizer was operated with air; the flowmeter was set at 8 l/min and albuterol sulfate (2.5 mg/3 mL NS, Nephron Pharmaceuticals Corporation, Orlando, FL, USA) was placed in the nebulizer medication reservoir. All of the nebulizers were run continuously until sputter, which took about 5 minutes.

pMDI: Albuterol sulfate pMDI (Ventolin HFA, GlaxoSmithKline, Research Triangle Park, NC, USA) combined with VHC (AeroChamber plus with Flow-Vu, Monaghan Medical, Plattsburgh, NY, USA) were used for aerosol administration. Four puffs of Ventolin HFA (90 μg/puff) were administered into VHC. Each pMDI canister was well shaken, warmed to hand temperature, and primed using the standard actuator provided by the manufacturer before each experimental run. During testing, 4 puffs were actuated at the beginning of inspiration at periods of 20 seconds. To reduce interoperator variability, the same operator actuated all pMDI doses. The VHC was held horizontally, with the pMDI in a vertical position during actuation.

Study Design:

A total of 12 runs were conducted with albuterol sulfate administered using the jet nebulizer and pMDI in two different conditions; one with the HFNC and another without the HFNC. Figure 2 illustrates the organizational design of the study.

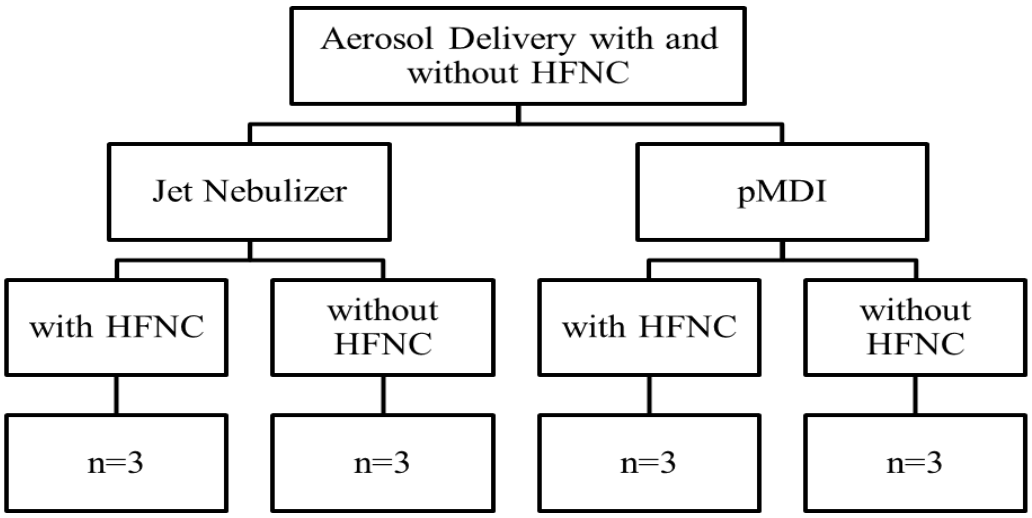

Figure 2 Organizational design of the study

In Vitro Measurements:

The absolute filter placed between the breathing simulator and the SAINT model was used to collect aerosolized albuterol with each run. Elution of the drug from the filter was performed with 0.1 M normal hydrochloric acid for 3 min with gentle agitation, and analyzed via spectrophotometry (Beckman Instruments, Fullerton, CA), at a wavelength of 276 nm. Calibration of the spectrophotometer was performed using only the solvent before the trials to determine wavelength accuracy and it was set to zero before every analysis. Albuterol eluted from the filter was quantified and expressed as a per cent of drug delivered from the nominal dose.

Data Analysis:

The amount of drug deposited in the filter was expressed as a percentage of the drug delivered from the nominal dose (jet nebulizer) and emitted dose (pMDI) during each trial experiment. Descriptive statistics were calculated for the means and standard deviations of each aerosol generator type with the presence or absence of HFNC. Independent samples t tests were performed to determine significant differences between

the percent inhaled dose measured with or without the HFNC, using the jet nebulizer and the pMDI. Statistical significance was determined with a p value of <0.05.

CHAPTER IV

RESULTS

Deposition of albuterol on the filter (inhaled mass) was expressed as percent of the nominal dose inhaled by the model. In addition to the *p* values, Table 1 shows the mean and standard deviation of inhaled mass obtained with each aerosol device with or without HFNC.

Table 1. Mean percent deposition of albuterol on the filter (Inhaled mass) using jet nebulizer and pMDI with the pediatric simulated breathing pattern

Aerosol Device	With HFNC	Without HFNC	*p*-value
Jet Nebulizer	2.91 ± 0.23	6.05 ± 1.53	0.024
pMDI	6.04 ± 0.28	39.54 ± 8.98	0.003
p-value	0.0001	0.003	

The mean inhaled mass percent was greatest for pMDI with ($p = 0.0001$) or without HFNC ($p = 0.003$). Removing HFNC from the nares before aerosol treatment trended to increase drug delivery with the jet nebulizer ($p = 0.024$), and increased drug delivery by 6 fold with pMDI ($p = 0.003$). Figure 3 shows the mean inhaled mass (μg) using both devices with or without HFNC. While the jet nebulizer delivered more drug than the pMDI with HFNC ($p<0.05$), there was no difference without HFNC.

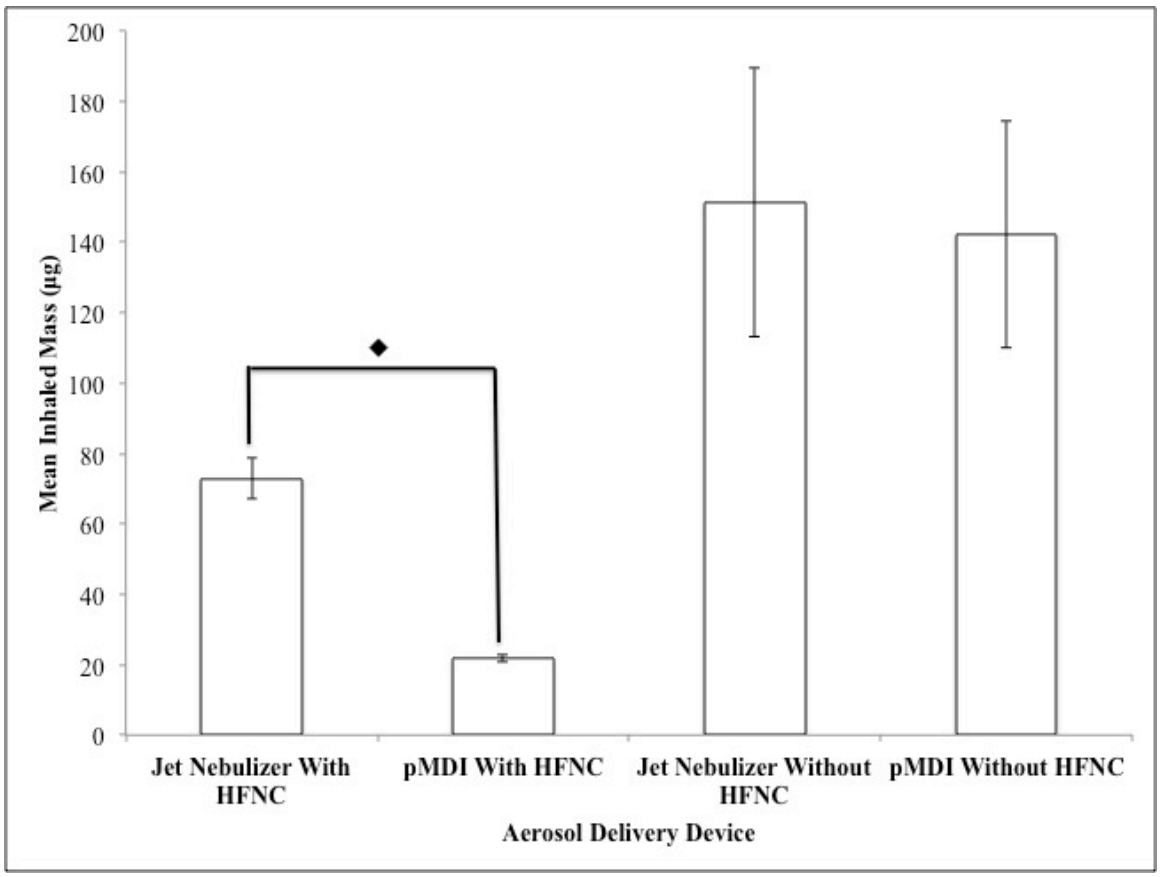

Figure 3. Mean inhaled mass using the jet nebulizer and pMDI with or without HFNC. ◆ indicates significant difference (p value < 0.05).

CHAPTER V

DISCUSSION

There are some recent studies conducted on aerosol delivery via HFNC and vibrating mesh nebulizer. However, the effect of HFNC on aerosol delivery using the jet nebulizer or pMDI has not been reported. To examine the effect of HFNC on aerosol deposition, this study quantified aerosol drug delivery with or without HFNC using either pMDI or jet nebulizer.

The administration of aerosol via facemask with a HFNC in place reduced the mean percentage of inhaled dose with either jet nebulizer or pMDI, compared to administration by mask alone. Using the jet nebulizer, inhaled dose was nearly doubled when HFNC was removed. With pMDI, removing HFNC increased inhaled dose by 6 folds.

The findings of this study using pMDI without HFNC were different from Janssens et al. (2004). Using similar breathing parameters, Janssens et al. reported a maximum percent of inhaled dose of 19% while this study found 39.54 ± 8.98% inhaled mass percent. A similar model was used in both studies, which was composed of a SAINT model in upright position connected to an absolute filter distal to the trachea attached to a breathing simulator. Two key differences between the two studies were the drug/device formulation tested and the valved holding chamber used. They used a combination of fluticasone HFA pMDI with Babyhaler, while we used Ventolin HFA pMDI combined with Aerochamber plus with Flow-Vu.

The inhaled mass as percent of nominal dose (6.05 ± 1.53) using jet nebulizer without HFNC in this study was similar to that reported by Laube et al. (2010) as the percent of emitted dose inhaled (9.34 ± 0.01%). Similar breathing parameters and model were used in both studies. However, different jet nebulizer (IPI nebulizer) powered by air at 10.5 l/min to administer albuterol sulfate for 30 seconds was used in their study, as opposed to Misty-neb jet nebulizer powered by air at 8 l/min till sputter was used in this study. While aerosol was administered through a 15-cm corrugated tube connected to a funnel-shaped plastic facemask in their study, the jet nebulizer was directly connected to a commercial pediatric facemask in this study. The reported deposition as the percent of emitted dose that reached the filter does not account for the residual drug remaining in the nebulizer, which may overestimate efficiency by 2 – 6 folds compared to percent of inhaled nominal dose.

Fok et al. (1996), reported differences in lung deposition between pMDI and jet nebulizer in an infant population between 1 - 4 kg. They administered radiotagged aerosol drug to spontaneously breathing infants with jet nebulizer and pMDI/Aerochamber with mask. Using the nebulizer with facemask the lung deposition was 1.74 ± 0.21% of the nebulized dose and 0.28 ± 0.04% of the initial dose placed in the reservoir. Actual lung deposition with the pMDI was 0.67 ± 0.17% of the emitted dose. While deposition was lower with both aerosol generators, so was the range of tidal volumes (6- 24 mL) in this infant population.

In our study, HFNC appears to reduce aerosol delivery due to the physical obstruction created by the HFNC, as opposed to unobstructed nasal openings without HFNC. In addition, the flow of O_2 delivered through HFNC represents a significant

proportion of the model's minute ventilation, so that flushing gas into the nares acts to reduce the entry of aerosol into the nasopharynx.

An obvious answer to increasing the aerosol deposition would be to remove the HFNC during administration of drug. However, there are some clinical consequences of interrupting the HFNC therapy for aerosol administration. Some of these consequences may include lung derecruitment and delivery of lower percentage of inspired O_2.

The findings of this study, using the jet nebulizer or pMDI applied via mask with HFNC, were different from studies reporting administration of aerosol via HFNC. Bhashyam et al. (2008) reported an inhaled dose of 18.6 ± 4% using 3 LPM flow with infant cannula. The breathing parameters for the infant population used in their study were Vt of 150 mL, RR of 25 and I:E ratio of 1:1; the higher Vt may overestimate the inhaled dose. They used a vibrating mesh nebulizer to administer aerosol drug through infant HFNC system with inhalation-only Harvard lung. Vibrating mesh nebulizers are reported to have a higher efficiency than jet nebulizers in terms of particles size, low residual drug volumes and aerosol output. In their study, they used a collection system composed of a corrugated tube to measure inhaled dose from the cannula as opposed to an upper airway model. Aerosol losses are expected in the SAINT model between the nares and trachea.

The results of this study, using jet nebulizer or pMDI with HFNC, were also different from Ari et al. (2011) reporting a percent of inhaled dose of 10.65 ±0.51 with flow rates of 3 l/min. They administered albuterol using a vibrating mesh nebulizer through a pediatric HFNC system run at 3 and 6 l/min O_2 while in this study aerosol was administered using facemask with HFNC. Inhaled dose efficiency of aerosol was reduced

to < 2% as flow through the HFNC increased to 6 l/min when delivering aerosol through the HFNC. They expressed the theory that as flow of oxygen increased, the aerosol was diluted, so the "model" inhaled lower percentage of dose. Vibrating mesh nebulizer has been reported to be more efficient than jet nebulizer, which could result in a higher deposition. They used a simulated nares/pharynx in their study, as opposed to an upper airway model used in this study. Aerosol losses are expected in the SAINT model between the nares and trachea, resulting in a lower dose. In addition, the I:E of 1:2 used by Ari et al. as opposed to I:E of 1:1.4 in this study would report a lower inhaled dose of drug deposited.

Aerosol delivery via HFNC appears to be more efficient option than using facemask for administration with HFNC in place. Aerosol delivery via HFNC avoids the obstruction faced when aerosol is delivered using facemask with HFNC. It also maintains the lung recruitment and percentage of inspired O_2, which may reduce infant distress.

Clinical Implications

During HFNC therapy in pediatrics, jet nebulizer is a less efficient device for aerosol delivery than pMDI. If the patient is stable enough to take the HFNC off for a short period, the best condition is to administer aerosol using pMDI without HFNC. Even during HFNC therapy, pMDI is superior to jet nebulizer. Aerosol administration using pMDI is faster and more effective than jet nebulizer during HFNC therapy. However, clinical consequences of interrupting HFNC therapy may include lung derecruitment and delivery of lower percentage of inspired O_2.

Limitations

Only one breathing pattern was examined in this study. Different breathing patterns would generate more understanding of the variables that affect aerosol drug delivery with HFNC. In addition, vibrating mesh nebulizer was not tested in this study. Vibrating mesh nebulizers are reported to have a higher efficiency. This is an in-vitro study; therefore, an in-vivo study is required to assess the clinical response in pediatrics receiving aerosol therapy with HFNC therapy.

Future Research Questions

How would different breathing patterns affect aerosol deposition in pediatrics receiving HFNC therapy? How efficient is the vibrating mesh nebulizer in pediatrics receiving HFNC therapy? What would the clinical response of aerosol administration be in pediatrics receiving HFNC therapy?

Conclusions

Aerosol drug may be administered in pediatrics receiving HFNC therapy using either jet nebulizer or pMDI. However, using pMDI, either with or without HFNC, is the best option. In both devices, removing HFNC led to an increase in inhaled mass percent. However, the benefit of increased aerosol delivery, when delivering medical aerosol by mask, must be weighed against the risk of lung derecruitment when nasal prongs are removed. Further studies are needed to determine the effect of aerosol delivery devices and other breathing patterns on drug delivery to pediatrics receiving HFNC therapy.

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