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IN-VITRO COMPARISON OF AEROSOL DRUG DELIVERY IN PEDIATRICS  
USING PRESSURIZED METERED DOSE INHALER, JET NEBULIZER, AND  
VIBRATING MESH NEBULIZER

By

Huriah H. Al Sultan

A Thesis

Presented in Partial Fulfillment of Requirements for the

Degree of

Master of Science

In

the Division of Respiratory Therapy

in

Byrdine F. Lewis School of Nursing and Health Professions

Georgia State University

Atlanta, Georgia

2012

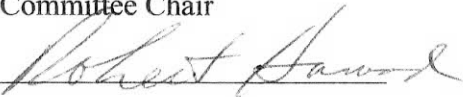
ACCEPTANCE

This thesis IN-VITRO COMPARISON OF AEROSOL DRUG DELIVERY IN PEDIATRICS USING PRESSURIZED METERED DOSE INHALER, JET NEBULIZER, AND VIBRATING MESH NEBULIZER, by Huriyah H. Al Sultan 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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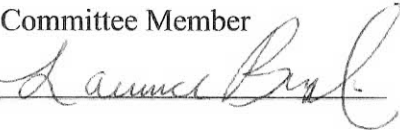
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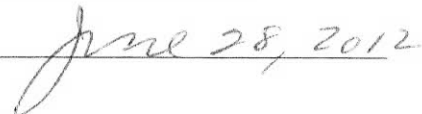
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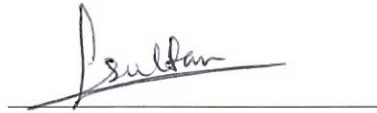
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## ABSTRACT

### IN-VITRO COMPARISON OF AEROSOL DRUG DELIVERY IN PEDIATRICS USING PRESSURIZED METERED DOSE INHALER, JET NEBULIZER, AND VIBRATING MESH NEBULIZER

By

Huriah H. Al Sultan

**Background:** Aerosol therapy has been established as an efficient form of drug delivery to pediatric and adult patients with respiratory diseases; however, aerosol delivery to the pediatric population is quite challenging. While some studies compare jet nebulizer (JN), vibrating mesh nebulizer (VMN), or JN and pMDI, there is no study comparing these three devices in pediatric and young children. The aim of this study quantifies aerosol deposition using JN, VMN, and pMDI/VHC in a simulated pediatric with active and passive breathing patterns.

**Methods:** Each aerosol generator was placed between manual resuscitator bag (Ambu SPUR II Disposable Resuscitator, Ambu Inc, Glen Burnie, MD) and infant facemask (Mercury Medical, Cleanwater, FL), which was held tightly against the SAINT model. Breathing parameters used in this study were  $V_t$  of 100 mL, RR of 30 breaths/min, and I:E ratio of 1: 1.4. Active and passive breathing patterns were used in this study with aerosol device; active breathing pattern was created using a ventilator (Esprit Ventilator, Respironics/Philips Healthcare, Murrysville, PA) connected to a dual chamber test lung (Michigan Instruments, Grand Rapids, MI), which was attached to an absolute filter (Respirgard II, Vital Signs Colorado Inc, Englewood, CO), to collect aerosolized drug, connected to the SAINT model. Pediatric resuscitator bag was run at 10 L/min of oxygen and attached to aerosol generator with facemask. In passive breathing pattern, SAINT model was attached to test lung and ventilated using the resuscitator bag with the same breathing parameters. Each aerosol device was tested three times ( $n=3$ ) with each breathing patterns. Drug was eluted from the filter and analyzed using spectrophotometry. The amount of drug deposited on the filter was quantified and expressed as a percentage of the total drug dose. To measure the differences in the inhaled drug mass between JN, VMN, and pMDI/VHC in active or passive breathing, one-way analysis of variance (one-way ANOVA) was performed. To quantify the difference in aerosol depositions between the two breathing patterns, independent t-test was performed. A  $p < 0.05$  was considered to be statistically significant.

**Results:** Although the amount of aerosol deposition with the JN was the same in passive and active breathing without any significant difference, the VMN was more efficient in active breathing than the JN ( $p = 0.157$  and  $p = 0.729$ , respectively). pMDI/VHC had the greatest deposition in the simulated spontaneous breathing ( $p=0.013$ )

**Conclusion:** Aerosol treatment may be administered to young children using JN, VMN, or pMDI/VHC combined with resuscitator bag. Using pMDI/VHC with resuscitator bag is the best choice to deliver albuterol in spontaneously breathing children. Further studies are needed to determine the effectiveness of these aerosol generators with different type of resuscitator bag and different breathing parameters.



## TABLE OF CONTENTS

	Page
List of Tables	iii
List of Figures	iv
Abbreviations	v
Chapter	
I. INTRODUCTION	1
Significance	3
Hypothesis	4
Purpose	4
Research Question	4
II. REVIEW OF THE LITERATURE	5
In Vivo Aerosol Research	5
In Vitro Aerosol Research	12
III. METHODOLOGY	19
Types of Aerosol Generator, Doses, and Operation	19
In Vitro Lung Model	20
Active Breathing	20
Passive Breathing	21
In Vitro Measurements	22
Data Analysis	23
IV. RESULTS	24
V. DISCUSSION	26
References	31

## LIST OF TABLES

Tables		Page
1.	Mean inhaled mass percent $\pm$ SD of albuterol sulfate using JN, VMN, and pMDI/VHC in passive and active breathing	24

## LIST OF FIGURES

Figures		Page
1.	Diagram of lung model for simulated active and passive breathing	21
2.	Organizational design of the study	22
3.	Mean aerosol percent in JN, VMN, and pMDI/VHC in passive and active breathing patterns	25

## ABBREVIATIONS

BPD	Bronchopulmonary dysplasia
CF	Cystic fibrosis
DPI	Dry Powder Inhaler
GSD	Geometric Standard Deviation
JN	Jet Nebulizer
MMAD	Mass Median Aerodynamic Diameter
MMD	Mass Median Diameter
pMDI	Pressurized Metered-Dose Inhaler
SVN	Small Volume Nebulizer
SAINT	Sophia Anatomical Infant Nose-Throat
SPECT	Single Photon Emission Computed Tomography
VHC	Valved Holding Chambers
VMN	Vibrating Mesh Nebulizer
USN	Ultrasonic Nebulizer

## **CHAPTER I**

### **INTRODUCTION**

Aerosol therapy has been established as an efficient form of drug delivery to pediatric and adult patients with respiratory diseases. However, aerosol delivery to the pediatric population is quite challenging. When dealing with infants, healthcare providers face different factors than the adult population. For instance, factors such as anatomical and physiological differences, choosing the right aerosol delivery device, and minimizing stress and facemask leak are some of that affect aerosol delivery to small children.

One of the challenging factors is anatomical and physiological differences between adults and children. Children are obligatory nose breathers until age 18 months. According to Chua et al. (1994a), delivery of aerosol through the nose to the lower airways is less effective than through the mouth and this might be explained by high velocity and turbulent flow in the nose and nasopharynx area. Moreover, aerosol deposition is influenced by children's breathing pattern. High respiratory rate (RR) with variable inspiratory flow, low tidal volume (Vt), and smaller airway diameter can diminish deposition of inhaled aerosols to the lower airways in children (Fok et al., 1996).

One of the most important challenges during aerosol treatment is the child's acceptance and tolerance of the aerosol device and its interface. Crying, squirming, and facemask leak can affect the total dose delivered to the lungs. A study done by Tal et al. (1996) showed that the total lung deposition delivered by pMDI-VHC-facemask was decreased by 6 fold in crying children (0.3%) compared to quietly breathing children (2%). Another in-vivo study done by Schuepp et al. (2009) showed that mean lung

deposition was higher in quietly breathing children (48.6%) than in children crying during inspiration (20.0%). During crying, most of the drug is deposited in the upper airways and the pharynx, which is then swallowed.

Choosing the right aerosol device with its interface is vital for optimizing aerosol treatments in young children. Aerosol generators used for the treatment of infants can be categorized into nebulizers, pressurized metered-dose inhalers (pMDI), and dry-powder inhalers (DPI). There are three types of nebulizers; jet nebulizers (JN), vibrating mesh nebulizers (VMN), and ultrasonic nebulizers (USN). JN and pMDI/spacer are commonly used for aerosol drug delivery to children. However, lung deposition in young children inhaling from conventional nebulizers is low and has been shown to be between 0.1% and 8% (Schuepp et al., (2009). Another in-vivo study done by Fok et al. (1996), showed less than 2% of aerosol was deposited in the lungs by pMDI with spacer and JN in spontaneously breathing and ventilated infants with bronchopulmonary dysplasia (BPD).

Vibrating mesh nebulizer is a novel device that generates a higher dose of uniformed small particles, has negligible residual volume, and faster rate of nebulization than traditional nebulizers, which consequently improves drug deposition (Dolovich et al. (2011)). Ari et al. (2010) compared JN and VMN in two different positions in mechanically ventilated adult and pediatric models. They found that VMN had higher deposition than JN at all positions (2-4 fold). An in-vitro study compared two different types of VMNs, Aeroneb Go/Idehaler and MicroAir, to JN PARI LC Star. Aeroneb Go VMN showed the greatest performance in terms of pulmonary aerosol delivery and optimal particle size (Coates et al. (2011).

Facemasks, blow-by, hood, high-flow nasal cannula, mouthpiece, and spacer or valved-holding chambers (VHC) are different interfaces used with aerosol devices in infants. A facemask is the most common interface used in infants; however, facemask seal and leak around the facemask is a common problem that affects drug delivery. Esposito-Festen et al. (2004) and Erzinger et al (2007) showed that even a small leak around the facemask could cause significant reduction in aerosol delivery to infants. Therefore, an optimal seal with light pressure on the face could minimize the leak and improve aerosol delivery. In some clinical settings manual resuscitator bag is being used to deliver aerosol treatments in an effort to improve aerosol deposition. For instance, some pediatric hospitals in the southeast use resuscitator bag with jet nebulizer to provide continuous positive pressure (CPAP) in order to open collapsed lungs and relieve bronchospasm.

Aerosolized drug delivery is more challenging in the pediatric population. Identification of factors of efficient drug delivery and challenges of delivering aerosol to children can optimize aerosol delivery to this age group. Thus, extensive research needs to be conducted to identify the most effective delivery device and the best way to deliver medical aerosol therapy in infants.

**Significance:**

Different types of aerosol devices have been used to administer aerosolized drugs for children with pulmonary diseases such as asthma, cystic fibrosis (CF), and BPD. JNs, pMDIs, and VMNs are the most common type of aerosol devices used in children. Even though there are some studies comparing either JNs and VMNs or JN and pMDI, there is no study comparing these three devices in pediatric and young children.

Any new device or intervention introduced into clinical practice should be supported by strong research evidence. For example, manual resuscitator bag combined with aerosol devices is being used in some clinical settings even though the effect of this combination on aerosol deposition is unknown. Therefore, more information is needed to determine the effect of using resuscitator bag on aerosol delivery.

Since this study also determines the difference in aerosol deposition between active and passive breathing, it would help health care providers to select the best aerosol delivery device to use with manual resuscitator bag in pediatrics.

**Hypothesis:**

Aerosol deposition with each aerosol generator varies in active and passive breathing patterns. Simulated active breathing pattern would have different aerosol deposition than a passive breathing pattern.

**Purpose:**

The aim of this study is to quantify aerosol deposition using pMDI, jet nebulizer, and vibrating mesh nebulizer in a simulated pediatric model with active and passive breathing patterns.

**Research Questions:**

1. What is the efficiency of aerosol therapy through manual resuscitator bag used with jet nebulizer, vibrating mesh nebulizer, and pMDI?
2. What is the difference in delivery efficiency of aerosol therapy between simulated active and passive breathing patterns?



## **CHAPTER II**

### **REVIEW OF THE LITERATURE**

#### **Introduction:**

This is a review of the literature for the articles published in the area of aerosol therapy for pediatrics. Literature was obtained using different terms such as aerosol delivery, aerosol deposition, nebulizers, vaporizers, metered dose inhaler, pMDI, jet nebulizers, small volume nebulizers, SVN, and vibrating mesh nebulizers in pediatrics. For aerosol delivery through facemask, terms such as facemask, facemask leak, and facemask in pediatrics were used. For manual resuscitator bag terms such as ambu bag, flow-inflating bag, self-inflating bag, and resuscitation bag for pediatrics were used. All research was obtained from PubMed, CINAHL Plus with Full Text, and MEDLINE with Full Text. The articles included in the review of the literature ranged from 1990 to 2011. All articles were written in English and peer-reviewed.

#### **In-Vivo Aerosol Researches:**

Mallol et al. (1996) conducted a study on 20 asymptomatic infants aged between 3 and 24 months with CF. They used radiolabelled aerosols generated by jet nebulizer to quantify the amount of deposited aerosol in the pulmonary system. Group A, which consisted of 10 infants, was sedated while receiving aerosol with 7.7  $\mu\text{m}$  mass median diameter (MMD) using Bennet-Twin jet nebulizer with air flow of 5.5 L/min. Group B, consisted of 5 infants, used the same type of nebulizer while they were awake. Group C (N=5), infants were awake; they inhaled aerosol with 3.6 $\mu\text{m}$  MMD administered by

Hudson Up-Draft II jet nebulizer with airflow of 8 L/min. The aerosol deposition was evaluated using gamma camera with closed system upon completion of nebulization. They found that the total lung depositions for the 3 groups A, B, and C were  $0.97 \pm 0.35\%$ ,  $0.76 \pm 0.36\%$ , and  $2.0 \pm 0.71\%$ , respectively. In group C most deposition occurred in the lung region while in group A and B the aerosol deposited in the trachea and main bronchi. In addition, they found that the most important determinant of aerosol deposition in the lung region was the particle size rather than demographic features and sedation.

Amirav et al. (2002) studied 12 children, aged between one month and 14 months, diagnosed with acute respiratory syncytial or bronchiolitis to evaluate aerosol deposition and distribution in the lower respiratory tract. Radiolabelled albuterol was administered through a Micromist jet nebulizer (Hudson Respiratory Care Inc.) with a facemask connected to oxygen at 8 L/min. They used scintigraphy to evaluate the total lung and body deposition and distribution of aerosolized medication in the lungs. They found that 10% – 12% of the drug dose exiting from the nebulizer deposited on the face with  $7.8\% \pm 4.9\%$  deposited in the upper respiratory and gastrointestinal tracts. In addition, they found that  $1.5\% \pm 0.7\%$  of the drug dose reached to the right lung and 0.6% penetrating to the peripheral lung zone. There was no relationship found between demographic data such as height, weight, or body surface area, and deposition indices or clinical response.

Tal et al.(1996) performed a study on fifteen children with obstructive airway diseases, aged between 2.5 and 5 years (mean of age 20.9 months), to examine the amount of drug deposition in the pulmonary and gastrointestinal tracts. Seven children were diagnosed with asthma, four children have CF, and four diagnosed with BPD.

Gamma camera was used to assess the drug deposition immediately after administering 1 puff of radiolabelled salbutamol through pressurized metered dose inhaler (pMDI), spacer (Aerochamber), and facemask. They found that the mean aerosol deposition was  $1.28\% \pm 0.77\%$  in the oropharynx,  $1.97\% \pm 1.4\%$  in the lungs, and  $1.11\% \pm 2.4\%$  in the stomach with the remaining was trapped in the spacer.

Wildhaber et al. (1999) conducted a study to compare lung deposition between pMDI with holding chamber (Aerochamber, Trudell Medical) and nebulizer (PARI Baby and PARI LC Star, PARI GmbH). They examined seventeen stable asthmatic children aged between 2 and 9 years. Treatment was administered randomly with 4 puffs of radiolabelled salbutamol (Ventolin,  $100\mu\text{g}/\text{actuation}$ ) via pMDI/holding chamber or 2 ml radiolabelled nebulized salbutamol (Ventolin, 1 mg/ml). By scanning body and lungs with a gamma camera, they found that the mean total lung deposition for the pMDI was 5.4% ( $21.6\mu\text{g}$ ) in children less than 4 years old and 9.6% ( $38.4\mu\text{g}$ ) in children older than 4 years old. For nebulized treatment, mean lung deposition was 5.4% ( $108\mu\text{g}$ ) in younger children and 11.1% ( $222\mu\text{g}$ ) in older children.

Salmon, Wilson, & Silverman (1990) studied sixteen children, nine infants were wheezy and 7 adults were healthy, to assess the delivery of aerosol by using sodium cromoglycate as a non-toxic marker. They delivered the drug via pMDI, facemask, and spacer or facemask and nebulizer (an Acorn nebulizer). They measured the concentration of sodium cromoglycate in urine to estimate the dose of drug that deposited in the lung. They found that only 0.13% - 0.61% of the 20 mg nominal dose was found in the urine, which represents 0.3% - 1.5% deposited in the pulmonary system.

Fok et al. (1996), conducted a study to evaluate drug deposition in ventilated versus non-ventilated infants, who either had BPD or at high risk of BPD, by using radiolabelled salbutamol via pMDI or jet nebulizer. Twenty-three infants enrolled in a randomized, crossover study; thirteen infants were spontaneously breathing and ten infants were mechanically ventilated. For non-ventilated babies, inhaled aerosol treatments were given through facemask attached to a nebulizer or pMDI and spacer (Aerochamber, Trudell Medical). While in ventilated babies, treatment received through either pMDI + spacer (MV15, Aerochamber) or a nebulizer attached to the ventilator circuit. They found that the mean of the mass median aerodynamic diameters (MMADs) and geometric standard deviation (GSD) of pMDI for ventilated infants were 1.88 $\mu$ m and 1.45 $\mu$ m, respectively after passing the MV15; for the spontaneously breathing infants MMAD and GSD were 1.83 $\mu$ m and 1.50  $\mu$ m, respectively after exiting the Aerochamber with the mask. In addition, they found that the mean MMAD and GSD for the jet nebulizer with the ventilated babies were 0.83 $\mu$ m and 1.69 $\mu$ m, respectively, and MMAD of 1.01 $\mu$ m and GSD of 1.64 $\mu$ m for non-ventilated babies. For spontaneously breathing infants, aerosol deposition in the lungs using pMDI was between 0.12 % and 2.26% 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 reservoir.

Chua et al. (1994b) performed a study on 12 infants (median age 0.8 yrs) and 8 older children (median age 10.8 yrs) with asymptomatic CF to evaluate the effect of age on aerosol deposition in the lungs. A Turret nebulizer with compressed air at 9 L/min was used to administer radiolabelled normal saline via facemask for infants and facemask and

mouthpiece for older children. Planar and single-photon emission computed tomography (SPECT) scans were used to evaluate the deposition in the pharynx and lungs for all children after inhalation therapy. When they used a facemask, they found that the total lung deposition for infants was (median 1.3%, range 0.3–1.6%) and for the older children was (median 2.7%, range 1.6–4.4%). In addition, they found that there is no difference between mouthpiece and facemask in older children.

Ploin et al. (2000) conducted a randomized double-blinded, parallel group equivalence trial on 64 children (range 2 -5 yrs old) with acute recurrent wheezing and a history of at least one episode of wheezing. The aim was to determine the clinical equality for albuterol administration between pMDI and spacer devices and nebulizer. Sixty four children were divided into two groups of 32; one group was received pMDI albuterol and nebulized placebo and the other group has albuterol solution through nebulizer and then pMDI placebo. Treatment was repeated three times with an interval of twenty minutes. Pulmonary index, hospitalization, pulse oximetry saturation, ease of use, and acceptability were measured. They found that pMDI/spacer has the same efficacy as the nebulizer; however, parents considered administration of albuterol by pMDI/ spacer is easier and accepted by children.

Coates et al.(2011) performed a study on eight children and eight adults diagnosed with CF to determine if equivalent levels of pulmonary deposition could be achieved in shorter time using 1.5 ml of 100 mg/ml tobramycin solution delivered by a vibrating mesh nebulizer (PARI eFlow nebulizer). All subjects instructed to inhale one of the two formulations of radiolabeled tobramycin, in which approximately 150 – 250 mBq were added to either 5ml of tobramycin solution (60 mg/ml, TOBI1) with the PARI LC

PLUS1 nebulizer or for the investigational PARI e-Flow (PARI GmbH), charged with 1.25 ml (six initial subjects) or 1.5 ml (all subjects) of tobramycin solution (100 mg/ml). Blood samples were taken after 60 min to measure the amount of tobramycin in the serum. The PARI LC PLUS delivered 45.4 mg (mean) to the lungs in  $17.0 \pm 2.5$  min (mean  $\pm$ SD) with serum levels of  $1,089 \pm 388$   $\mu$ g/L. e-Flow delivered 46.3 mg in  $4.0 \pm 1.0$  min with blood levels of  $909 \pm 458$   $\mu$ g/L.

Rotta et al. (2010) conducted a randomized clinical trial on 46 children (1–5 years of age) to determine if the plasma concentrations of salbutamol, obtained during inhalation treatment of acute asthma, are influenced by age range or by the aerosol system used. Twenty five children received salbutamol using a pMDI with spacer (50  $\mu$ g/kg), and 21 children received salbutamol by nebulization (150  $\mu$ g/kg), three times during a 1-hour period. At the end of the treatment, one blood sample was drawn and the plasma was stored for later determination of salbutamol concentration (liquid chromatography). Salbutamol plasma concentrations were compared in two age groups ( $\leq 2$  years and  $>2$  years of age). The type of device used (pMDI or nebulizer) and the need of hospitalization were also tested. No differences were detected regarding either the aerosol delivery system used or the need for hospitalization in relation to the plasma concentrations of salbutamol. However, higher plasma levels were found in children  $>2$  years vs. children  $\leq 2$  years.

Schuepp et al. (2009) recruited 10 asymptomatic asthmatic children (mean age of 20.3 months and range between 6 and 41 months) to determine lung deposition and its ratio to oropharyngeal deposition. They used radiolabelled budesonide (Budesol 200 $\mu$ g/ml with MMD 2.6  $\mu$ g) delivered through a modified vibrating membrane

nebulizer (e-Flow® Baby, PARI GmbH). Each child inhaled 2 puffs of Ventolin (Salbutamol, 100µg/actuation, Glaxo Smithkline, Australia) through a holding chamber (Babyhaler®, Glaxo Smithkline, Australia) prior to nebulization. Nebulized treatment administered using a tightly fitting facemask (Sure Seal®, 1237 pediatric, Hudson RCI.), a round shaped facemask with an inflatable rim. All patients were scanned using scintigraphy and lung deposition was measured, which was expressed as a percentage of the emitted dose, and its ratio to oropharyngeal deposition were calculated. Mean lung deposition (SD) was higher in quietly breathing children 48.6% (10.5) than in children crying during inspiration 20.0% (10.9). Mean lung deposition to oropharyngeal deposition ratio (SD) in quietly breathing children was 1.0 % (0.3) and in crying children was 0.3 % (0.2).

Erzinger et al.(2007) conducted an in vivo study on eight asymptomatic children with recurrent wheezes aged between 18 and 36 months. Their aim was to verify that a small air leak in the facemask can significantly reduce the efficiency of aerosol drug delivery. Four children inhaled 2 mL of radiolabeled salbutamol solution (Ventolin, 1 mg/ mL) from an open vent-assisted nebulizer (Pari Baby with Pari facemask no.2); and four children inhaled 4 puffs radiolabeled pMDI (Ventolin, 100 µg/puff) via a plastic spacer (Aerochamber with an Aerochamber 2<sup>nd</sup> generation facemask, Trudell Medicine). Drug deposition was quantified with a gamma camera and lung deposition was expressed as percentage of the total dose. They found that in 2 children with a facemask leak, lung deposition for pMDI and nebulizer were 0.2% and 0.3%, respectively. In another 2 children, who were screaming and without facemask leak, lung deposition for pMDI and nebulizer were 0.6% and 1.4%, respectively. In addition, they found that in quietly

breathing children (n =4) without facemask leak was 4.8% for pMDI and 8.2% for nebulizer. Moreover, face deposition ranged between 2.6% and 8.4% with mask deposition ranged between 0.8% and 5.2%.

Esposito-Festen et al.(2006) conducted a study to investigate the feasibility of aerosol administration by means of pMDI-spacer in sleeping young children. Thirty children (age range, 6 to 23 months) with recurrent wheeze over a period of 3 weeks were recruited. They inhaled 1 puff of budesonide aerosol (Pulmicort, 200 µg; AstraZeneca) while awake and 1 puff during sleep. Filters positioned between the chamber and the facemask trapped the budesonide aerosol. Parents scored the child's asthma symptoms, degree of cooperation, and feasibility of administration on diary cards. They found that, the mean filter dose, which was expressed as the percentage of the nominal dose, while awake was 47%, and during sleep was 16%. The median within-subject dose variability while awake was 50%, and during sleep it was 110%.

#### **In-Vitro Aerosol Researches:**

Coates et al.(2011) conducted an in vitro study to select the best nebulizer system for delivering magnesium sulfate ( $MgSO_4$ ) that would be effective over the entire age range. They compared different types of vibrating mesh nebulizers such as MicroAir vibrating-mesh nebulizer (Omron) and the Aeroneb Go (Aerogen) with the Idehaler valveless holding chamber to jet nebulizer the Pari LC Star (Pari). They diluted 2 ml of  $MgSO_4$  in 7 ml sterile water then added 1 ml of albuterol (5mg/ml) and they put 6 ml in each nebulizer from that solution. They found that the Pari LC Star had an appropriate particle size distribution but a very slow aerosol output rate. Omron MicroAir has the



slowest output rate with the largest particle size while Aeroneb Go/Idehaler system demonstrated the superior performance with optimal particle size.

Johnson et al. (2008) performed an in vitro study to evaluate the efficiency of vibrating mesh nebulizers and jet nebulizer in delivering inhaled recombinant human DNase I (rhDNase). They compared vibrating mesh nebulizer (MicroAir, Omron) to a jet nebulizer (Pari LC+ with the Pari ProNeb Ultra compressor). They used a respirator pump (Harvard Apparatus) connected to simulated human lung system to determine the total amount of nebulized rhDNase. In addition, they used an exhalation valve, such that aerosol samples were collected onto a bacteria/virus filter (Respirgard, Marquest Medical Products). The total aerosol delivered from both nebulizers was collected at the filters (5 of each), respiratory rate of 12/min, and tidal volume of 500 ml. For MicroAir the MMAD was 4.3 $\mu$ m and GSD was 2.8 $\mu$ m, which was equivalent to Pari LC (MMAD 4.2 $\mu$ m, GSD 2.7 $\mu$ m). However, MicroAir was 88% more efficient than Pari LC with less nebulization time (6.1 min vs. 7.2 min).

Laube et al. (2010) conducted a study to quantify deposition and distribution of aerosolized albuterol in the nose and lungs by a pneumatic nebulizer using 4 copies of the Sophia Anatomical Infant Nose-Throat (SAINT) model of a nine month old child. In addition, they aimed to measure the amount of aerosol that escaped into the environment, which represents the possible exposure to the care providers. They used radiolabelled albuterol that was generated by an IP nebulizer (IPI Medical Products) at flow of 10.5 L/min from air compressor. A funnel shaped facemask was connected to 15 cm long corrugated tube, which was attached to the nebulizer. Aerosol was delivered over a thirty seconds period. A computer operated breathing simulator (PARI breath simulator, PARI

GmbH) was used to control the breathing process with respiratory rate of 15 breaths over 30 seconds. The duty cycle was 0.45 seconds. Inspiratory time of 0.90 seconds and expiratory time of 1.1 seconds were used. They used three different tidal volumes 50 ml, 100 ml, and 200 ml. Each model was surrounded with a bag to quantify the amount of aerosolized medication that escaped into the environment. They found that lung deposition was the same for all tidal volumes with an average of  $7.17 \pm 0.01\%$ ,  $9.34 \pm 0.01\%$ , and  $9.41 \pm 0.02\%$  at tidal volumes of 50 ml, 100 ml, and 200 ml, respectively. However, with increasing tidal volume from 50 ml to 200 ml, nose deposition increased significantly. Aerosol escaped into the environment was higher with tidal volume of 50 ml ( $71.99 \pm 0.02\%$ ) compared to 200 ml ( $53.81 \pm 0.04\%$ )

Schüepf, et al., (2005) conducted an in vitro study to investigate the interaction between infant's airway anatomy, breathing patterns, and particle size on deposition of nebulized aerosol to determine the optimal particle size for infants. They used budesol (nebulizer solution of budesonide) delivered using a perforated vibrating membrane nebulizer (e-Flow Baby functional prototype) through an upper airway cast of a 9-month-old infant (SAINT-model). Particle size was measured at a fixed RR of 30 breaths/min and different Vt of 50, 100, and 200 ml, and at a fixed Vt of 100 mL and different RR of 30, 60, and 78 breaths / min, respectively. Lung deposition, expressed as a percentage of the nominal dose (range 5.8 - 30.3%), decreased with increasing Vt and with increasing RR. MMAD (range, 2.4-3.4 $\mu$ m) after passage through the upper airway showed a negative correlation with increasing Vt and with increasing RR. Particles available as lung region for all simulated breathing pattern showed a particle size distribution with a MMAD of 2.4 $\mu$ m and GSD of 1.56 $\mu$ m.

Janssens et al. (2004) performed a study to measure the influence of tidal volume (Vt) respiratory rate (RR) and pMDI/spacer combination on aerosol deposition of 4 types of infants' pMDI/spacer combinations. A SAINT model was connected to a breathing simulator with infant breathing parameters of duty cycle: 0.42, Vt: 25, 50, 75, 100, 150, 200 ml (RR: 30 breaths/min); and RR: 20, 30, 42, 60, 78 breaths/min (Vt: 100 mL). pMDI/spacers used were: budesonide 200 µg/Nebuchamber®, fluticasone 125 µg/Babyhaler® and both budesonide and fluticasone with Aerochamber®. Spacer output was measured by placing a filter (Vital Signs®) between facemask and spacer and lung dose was assessed by a filter positioned between the model and breathing simulator. Particle size distribution of lung dose was measured with impactor (Graseby Anderson) using three-way glass connection. Spacer-output was significantly increased with increasing Vt for all pMDI/spacers; however, there was no significant influence of RR on spacer types. Lung doses initially increased from Vt = 25 to 50 mL (Nebuchamber, Aerochamber) or to 100 mL (Babyhaler) and then decreased, with increasing Vt and RR. Lung doses of fluticasone were 1.5–6-fold higher compared with budesonide, irrespective of spacer type. MMAD decreased with increasing Vt and RR.

Esposito-Festen et al. (2004) performed an in vitro study to investigate the relation between size and position of a mask leak on spacer output and lung dose. They used an upper-airway model (SAINT model, Erasmus MC), which was attached to an infant breathing simulator with Vt 100 ml, RR 30 breaths/min, and duty cycle of 0.42. 200µg budesonide (Pulmicort®, AstraZeneca) was administered via spacer (NebuChamber®, AstraZeneca), which was connected to a round-shaped resuscitation facemask (Galemed®). Facemasks with different leaks, were located close to the nose or

to the chin, ranging from 0.05, 0.1, 0.16, 0.2, 0.3, 0.4, 0.5, 1, to 1.5 cm<sup>2</sup> were examined. Spacer output was measured by placing a filter (MQ303, Marquest®) between pMDI/spacer and facemask. Lung dose was measured by placing another filter between the SAINT model and breathing simulator. Budesonide was quantified by high-performance liquid chromatography (HPLC), and expressed as percentage of the nominal dose. They found that for leaks from 0 to 1.5 cm<sup>2</sup>, mean spacer output doses for the nose and the chin position ranged between 50% and 0%; leak position did not affect the spacer output. For leaks from 0 to 1.5 cm<sup>2</sup>, mean lung doses for the nose and chin position ranged between 10% and 0. However, lung deposition for leaks in the chin position was greater compared to the nose position.

Sangwan et al. (2004) performed an in vitro study to quantify facial and eye aerosol drug deposition in a two-year-old child's face model facsimile (Massachusetts Institute of Technology) with breathing parameters of: Vt 50 mL, RR 25 breaths/min, and duty cycle of 0.40. Aerosol delivery and facial deposition of radiolabeled saline test aerosols were delivered through jet nebulizer with a filter placed in the oropharynx. A child's face facsimile was attached to a piston pump (Harvard Pump). Seven commercially available facemasks (Laerdal, Laerdal Medical Corp.; Sealflex, Caradyne Ltd. Ferraris Panda, Ferraris Medical Ltd. PARI Baby & PARI Bubble, PARI Respiratory Equipment, Inc.; Salter, Salter Labs, A Hudson, Hudson Respiratory Care, Inc.) in combination with three jet nebulizers (Pari LC Plus, PARI Respiratory Equipment, Inc. MistyNeb, Allegiance, and AeroTech II, CIS-US, Inc.), were used for aerosol delivery and found that there was a leak around all types of facemask. In addition they found that,

from the nominal dose 2.24–5.96% of nebulizer charge was inhaled with facial deposition of 0.44 to 2.34%, and eye deposition of 0.09 to 1.78%.

Ari et al. (2010) performed an in-vitro study to determine the influence of nebulizer position and bias flow on aerosol drug delivery in simulated and mechanically ventilated pediatric and adult patients. Using a jet nebulizer and vibrating-mesh nebulizer, 2.5 mg in 3 mL of albuterol sulfate were aerosolized in different positions. The first position was 15 cm from the Y-piece for the jet nebulizer and vibration-mesh nebulizer (VMN) was placed directly to the Y-piece. In position two, jet nebulizer attached prior to the heated humidifier with 15 cm of large corrugated tube, and the VMN placed at the humidifier inlet. In adult and pediatric simulations a ventilator with heated humidifier was used. Adult ventilator parameters include Vt 500 mL, RR of 20 breaths/min, peak inspiratory flow of 60 L/min, PEEP of 5 cmH<sub>2</sub>O, and descending ramp flow waveform. For the pediatric simulation ventilator settings were Vt of 100 mL, RR of 20 breaths/min, inspiratory time (Ti) of 1 second, and PEEP of 5 cmH<sub>2</sub>O. Two different bias flows of 2 and 5 L/min were used. Endotracheal tube with 8-mm inner diameter was used for adult and 5-mm for pediatric. Each aerosol device was run three times at both positions then the drug was eluted from the filter and analyzed using spectrophotometry. The amount of drug deposited on the filter was measured and expressed as a percentage of the nominal dose. They found that higher bias flow reduced drug delivery and placing the nebulizer prior to the humidifier increased drug delivery with both nebulizers. Moreover, VMN was more efficient than jet nebulizer at all positions and in both lung models ( $P < 0.05$ ).

**Summary:**

Effective aerosol delivery to infants and children is challenging. Several considerations should be taken into account when selecting the administration device. JN is as efficient as pMDI with spacer. Nevertheless, some in-vitro studies advocate that VMN is more efficient than JN or pMDI with spacer. In addition, facemask is the most common interface to use for aerosol administration for infants and children less than 3 years old. Many studies suggest that even a small amount of leak around the facemask could lower the aerosol deposition in the lungs.

## **CHAPTER III**

### **METHODOLOGY**

#### **Types of Aerosol Generators, Dose, and Operation**

Three types of aerosol generator (JN, pMDI, or VMN) were placed between manual resuscitator bag (Ambu SPUR II Disposable Resuscitator, Ambu Inc, Glen Burnie, MD) and infant facemask (Mercury Medical, Clearwater, FL). In all runs, the facemask was held firmly against the SAINT model, to minimize facemask leak.

Jet nebulizer (Misty-neb, Allegiance Healthcare, McGaw Park, Illinois) is a pneumatic Bernoulli type nebulizer. The nebulizer was connected to a pediatric facemask with a T-piece adaptor, which was attached to the manual resuscitator bag. The jet nebulizer was operated with air at a flow of 8 L/min. During nebulization, the SAINT model was kept in a supine position. Albuterol sulfate (2.5 mg) (Nephron Pharmaceuticals Corporation, Orlando, FL) in 3 ml normal saline was placed in the medication reservoir of the jet nebulizer. In each experiment, the jet nebulizer was run continuously until sputter (5 minutes).

Vibrating mesh nebulizer (Aeroneb Solo, Aerogen, Galway, Ireland) uses electricity to vibrate an aperture plate (containing 1,000 funnel-shaped holes) at 128 kHz. The vibrating-mesh produces aerosol through the holes by means of a micro-pumping action. The emitted dose of the vibrating mesh nebulizer can exceed 90% of the dose, with a residual drug volume of 0.1– 0.3 mL. The aerosol plume from the vibrating mesh is relatively low velocity, compared to the plume from a jet nebulizer or metered-dose inhaler.

pMDI albuterol sulfate (ProAir HFA, Teva Specialty Pharmaceutical, Atlanta, Georgia) with a manufacture estimated dose of 108 µg/ puff was actuated into VHC (Aerochamber MV, Trudell Medical International, London, Canada) with a pediatric facemask. pMDI/VHC with facemask was attached to SAINT model, which was kept in upright position by an elbow adapter to keep the pMDI in upright position during the administration. Each pMDI canister was warmed to hand temperature, well shaken, and primed using the standard boot supplied by the manufacturer before each experimental run. A total of 4 puffs were actuated at the beginning of inspiration with an interval of 30 seconds.

#### **In Vitro Lung 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 (Amsallem et al., 2008; Stick, 1996). These breathing parameters were based on the reference values for a 10 Kg 9 months old (Amsallem et al., 2008; Stick, 1996).

Two breathing patterns were used in this study active and passive breathing patterns. Active breathing pattern is placing the mask firmly over the model while it is spontaneously breathing (with no mechanical assistance). Passive is using the same model but manually assisting ventilation with the resuscitator bag.

#### **Active Breathing:**

As shown in Figure 1, pediatric spontaneous breathing was created using a ventilator (Esprit Ventilator, Respironics/Philips Healthcare, Murrysville, PA) connected to a dual chamber test lung (Michigan Instruments, Grand Rapids, MI), which was attached to an absolute filter (Respirgard II, Vital Signs Colorado Inc, Englewood, CO),



to collect aerosolized drug, which was connected to SAINT model. Pediatric resuscitator bag was run at 10 L/min of oxygen and attached to aerosol generators with facemask.

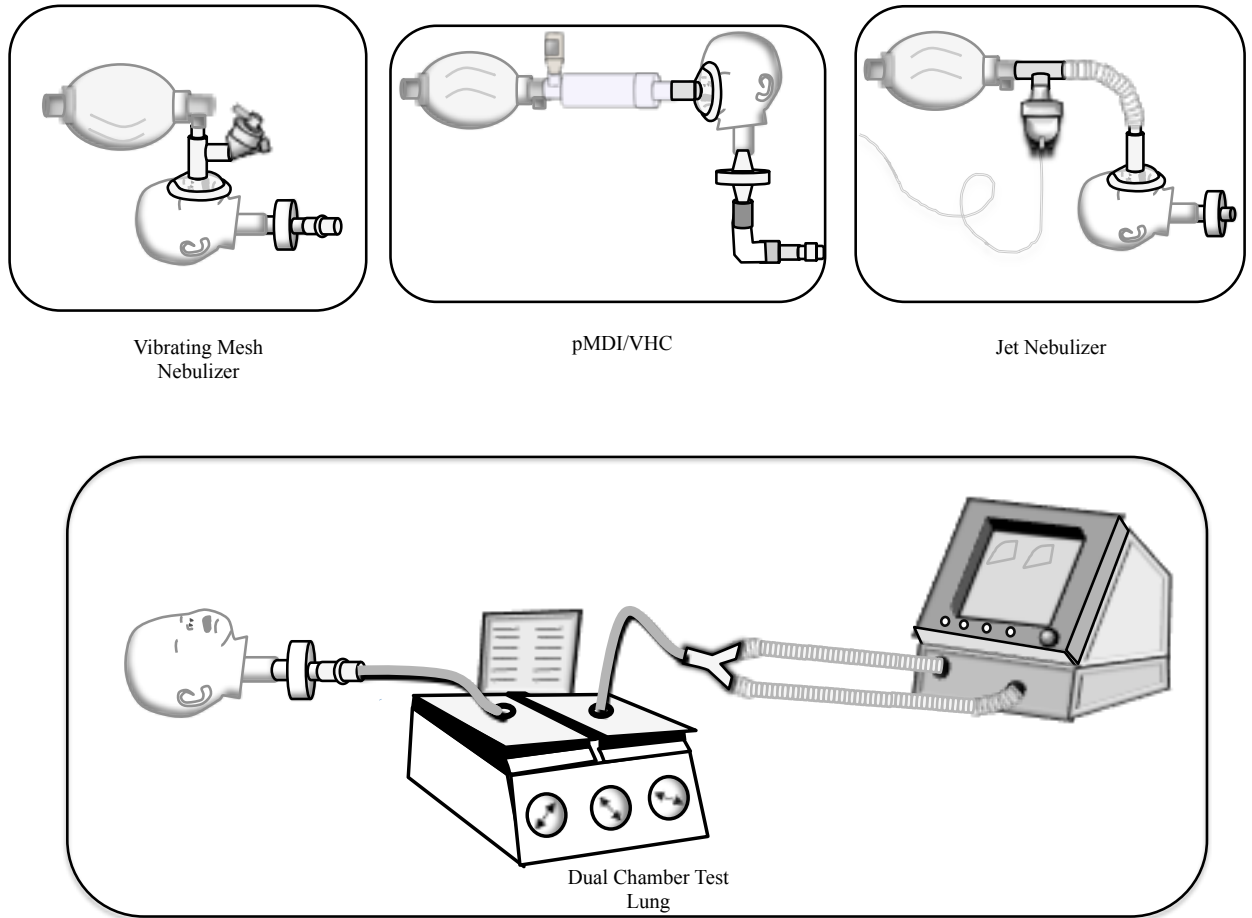


Figure 1. Diagram of lung model for simulated active and passive breathing patterns

**Passive Breathing:**

After the ventilator was disconnected, the SAINT model, connected to the test lung (Michigan Instruments, Grand Rapids, MI), was manually ventilated with the resuscitator bag during aerosol administration. The same breathing parameters were used.

**In Vitro Measurements:**

As shown in Figure 2, each aerosol device was tested three times (n=3) with each breathing pattern. The deposited drug was collected and measured using an absolute filter. On completion of each experiment the filter was removed, labeled, and capped. The drug was eluted from the filter with 0.1 M normal hydrochloride acid with gentle agitation for 3 min. Drug concentration was analyzed using spectrophotometry (Beckman Instruments, Fullerton, CA) at a wavelength of 276 nm. Wavelength accuracy was determined by calibrating the spectrophotometry before the trials and set to zero, using the solvent alone before each analysis. Albuterol eluted from the filter, measured, and expressed as a percent from the original dose. In order to minimize interoperator variability, the same operator performed all pMDI actuations and ambu bagging.

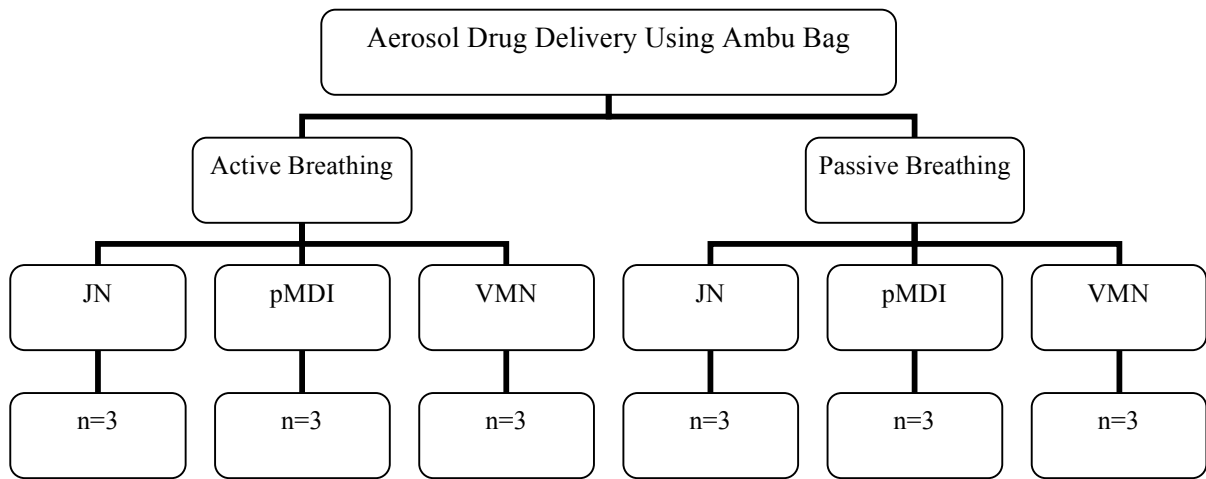


Figure.2 Organizational design of the study

## **Data Analysis**

The amount of drug deposited on the filter was quantified and expressed as a percentage of the total drug dose. The means and standard deviations were calculated for each component of the total inhaled drug mass percent. One-way analysis of variance (one-way ANOVA) was performed to measure the differences in the inhaled drug mass between JN, VMN, and pMDI/VHC in active or passive breathing. Independent t-test was performed to quantify the difference in aerosol depositions between the two breathing patterns. A  $p < 0.05$  was considered to be statistically significant.

## CHAPTER IV

### RESULTS

The mean  $\pm$  SD percent of the nominal dose of inhaled albuterol sulfate deposited on the filter for each aerosol device are shown in Table 1.

Table 1. Mean inhaled mass percent  $\pm$  SD of albuterol sulfate using JN, VMN, and pMDI/VHC in passive and active breathing

Aerosol Device	Passive Breathing	Active Breathing	<i>p</i> -values
JN (%)	2.57 $\pm$ 0.34	2.45 $\pm$ 0.46	0.729
VMN (%)	5.99 $\pm$ 1.28	7.62 $\pm$ 1.01	0.157
pMDI/VHC (%)	19.55 $\pm$ 1.60	27.84 $\pm$ 2.52	0.013
<i>p</i> -values	0.0001	0.0001	

#### Effect of aerosol Device on Drug Delivery Efficiency

In both breathing patterns, passive and active, the mean inhaled percent of albuterol delivered by pMDI/VHC was superior to the other aerosol device, JN and VMN ( $p = 0.0001$ ). Aerosol delivery efficiency of VMN was  $> 2$  fold greater than the JN ( $p = 0.0001$ ); however, pMDI/VHC had a greater proportion of lung deposition than VMN in both passive and active breathing.

#### Effect of Breathing Pattern on Aerosol Delivery

Although the percent of aerosol deposition with the JN was the same in passive and active breathing without any significant difference, the VMN was more efficient in active breathing than the JN ( $p = 0.157$  and  $p = 0.729$ , respectively). pMDI/VHC had the

greatest deposition percent in the simulated spontaneous breathing ( $p = 0.013$ ). However, VMN delivered more drug mass as shown in Figure 3.

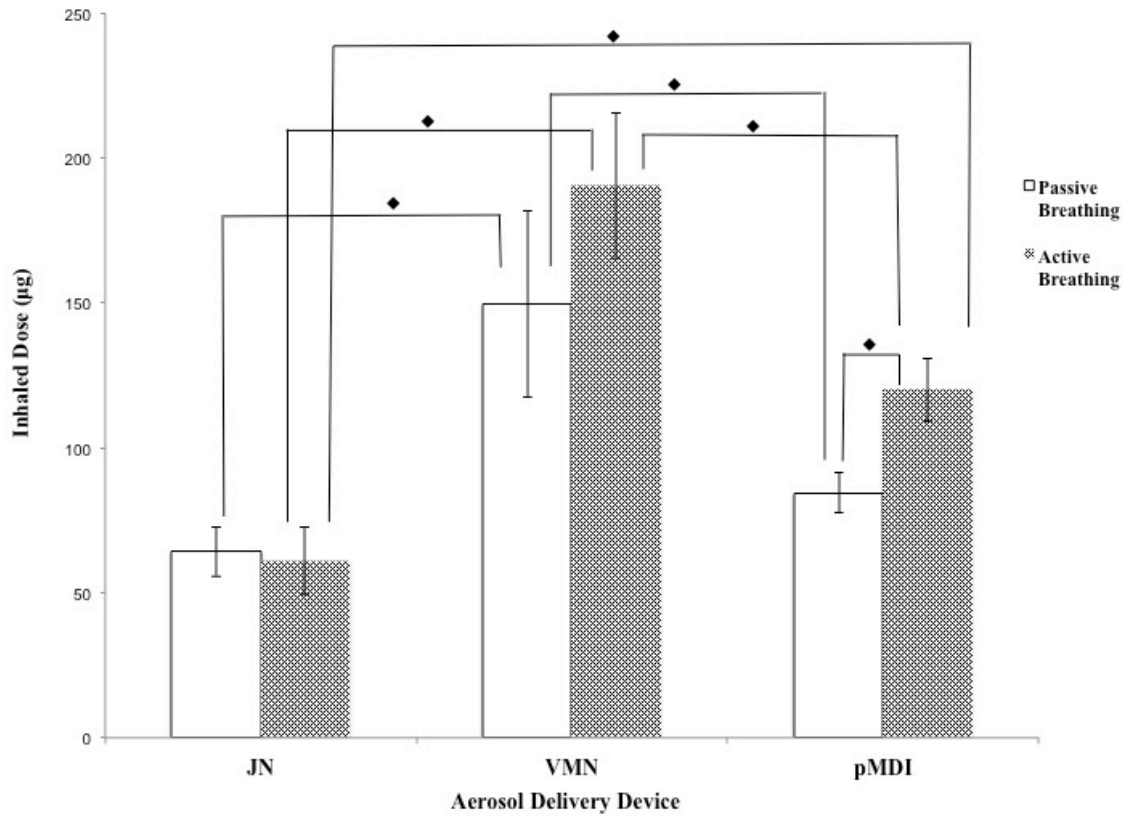


Figure 3. Mean aerosol inhaled mass in JN, VMN, and pMDI/VHC in passive and active breathing. ♦ indicates significant difference ( $p > 0.05$ )

## **CHAPTER V**

### **DISCUSSION**

Aerosol therapy has been established as a common form of drug delivery to pediatric and adult patients with pulmonary diseases; however, aerosol delivery is more challenging in the pediatric population. According to the findings of this study, albuterol delivery as percent of dose was significantly higher with pMDI/VHC in both breathing patterns. In addition, the type of breathing pattern, passive versus active, has an impact on aerosol drug delivery even though it was not significant in JN and only a trend with VMN.

#### **Effect of aerosol Device on Drug Delivery**

The most surprising finding of this experiment was the magnitude of aerosol deposition efficiency with the pMDI/VHC. The percent of dose deposited with the pMDI/VHC was consistently greater than either VMN or JN with both breathing patterns. In terms of drug mass delivered distal to the trachea of the model, the VMN was 2-4-fold greater than the JN; and 50% greater than pMDI with VHC. Unlike the JN, the VMN delivered more drug with active rather than passive breathing.

The results of JN and VMN from this study were consistent with Ari et al. (2010) who studied delivery via endotracheal tube during pediatric mechanical ventilation. They reported that the JN (3.8 – 5.2%) was less efficient than VMN (8.4 – 13.6%) in their mechanically ventilated pediatric model, however the absolute inhaled percent of albuterol delivered by VMN and JN were higher than our findings. The  $V_t$  used in both

studies was the same; however, they used a RR of 20 breaths/min, Ti of 1 second, and I:E of 1:2 as opposed to RR of 30 breaths/ min, Ti of 0.9 second, and I:E of 1:1.3 used in this study. Their I:E ratio and not passing through an airway model may account for substantial increase in efficiency.

The inhaled mass percent of JN of  $2.57 \pm 0.34\%$  and  $2.45 \pm 0.46\%$  of nominal dose in passive and active breathing were lower than those reported by Laube et al. (2010). They reported a percent of inhaled dose of  $9.39 \pm 0.01\%$  of the emitted dose. They used the same breathing parameters; however, aerosol was administered using IP JN through a 15-cm corrugated tube attached to a funnel-shaped facemask and run by air at 10.5 L/min. In the present study, the MistyNeb JN was directly attached to a pediatric facemask from one side and resuscitator bag from the other side and run by air at 8 L/min until sputter. It is difficult to compare % of emitted dose to % of nominal dose, as jet nebulizers may have > 1 mL of residual drug volume remaining at end of dose. If Laube timed the dose, the emitted dose may be much smaller than running the nebulizer to sputter, so deposition as a % of emitted dose might be even greater.

The results of this study were different than the results of Janssens et al. (2004) reporting a maximum percent of inhaled fluticasone HFA pMDI with AeroChamber of 16% at Vt of 50 mL and RR of 30 breaths/min. ProAir HFA combined with AeroChamber MV was used in this study with inhaled mass percent of  $19.55 \pm 1.60$  and  $27.84 \pm 2.52$  in passive and active breathing, respectively.

### **Effect of Breathing Pattern on Drug Delivery**

In this study albuterol delivery was lower in passive breathing pattern than active breathing. According to Dolovich et al. (1977), intermittent positive pressure breathing

(IPPB) delivered a mean of 32% less aerosol to the lung than did quiet breathing caused by rapid flow rate delivered by IPPB in contrast to a continuous steady flow rate delivered with quiet breathing. Fink et al (1996), compared albuterol delivery between controlled mechanical ventilator breaths and spontaneous breaths through the ventilator circuit and reported 30% greater aerosol delivery during simulated passive spontaneous breaths than during controlled breaths at equivalent tidal volumes. The mechanism of reduced aerosol delivery with passive breathing is unclear. A possible rationalization could be that spontaneous breathing, which pulls gas through the upper airway produces more laminar flow toward the bronchi, as opposed to the ventilator pushing air into the lungs.

Using a manual resuscitator bag with aerosol delivery may improve drug deposition in the lungs. According to Lugo et al. (2004) the reduction of the duration of manual ventilation after pMDI actuation significantly reduces albuterol delivery in neonatal ventilator lung model. For instance, they used a cone-shaped ACE spacer, and placed it horizontally between the endotracheal tube and a bag-valve-mask, and pMDI, which was actuated prior to the inspiration, followed by 5, 15, or 30 manual breaths/min. Albuterol delivery was  $2.3 \pm 0.5\%$ ,  $3.6 \pm 1.8\%$ , and  $5.1 \pm 1.3\%$  after 5, 15, and 30 manual breaths, respectively. The results of this study, using pMDI/VHC with passive and active breathing patterns, were higher than the aforementioned study. They used chlorofluorocarbon (CFC) pMDI with spacer to administer aerosol to mechanically ventilated neonatal lung model, as opposed to using HFA pMDI/VHC, JN, and VMN with passive and active breathing in this study. The results of their study apply to extremely-low-birth-weight infants, who weigh 1 Kg and who have Vt of approximately



7 mL/Kg, and may not apply to larger infants. In contrast, the parameters used were within the reference values appropriate for a 9-month-old 10-kg baby.

### **Clinical Implication**

For a spontaneously breathing infant administration of aerosol with the assistance of manual resuscitator bag does not increase drug delivery. When applying aerosol by mask to small children with spontaneous breathing and manual ventilation pMDI/VHC was more efficient than other devices tested. Not only is aerosol administration via pMDI quick, which consists of two or more inhalations at 15 to 30 second intervals requiring seconds rather than minutes as with nebulizers, but also it is more efficient than other nebulizers. Moreover, albuterol administration via pMDI is a very common medication used practice. According to Ballard et al. (2002), 57% of 80 institutions used pMDI to administer albuterol to intubated newborns.

### **Limitations and Future Research**

Although this study provides an insight into the best device to deliver aerosol to young children when using a manual resuscitator bag, findings may vary with different breathing patterns. For example, when children are in stress or crying, this may further reduce drug deposition. Different age or different type of resuscitator bag such as flow inflating bags may also have effects on aerosol delivery. Further studies with different breathing patterns would help to provide additional guidance to clinicians in evaluating the best method to optimize aerosol delivery with pediatric patients. In addition, an in-vivo model may provide more clinical information such as clinical response.

**Conclusion:**

Aerosol treatment may be administered to young children using JN, VMN, or pMDI/VHC combined with resuscitator bag. Using pMDI/VHC is the most efficient method to deliver albuterol via resuscitator bag in spontaneously breathing children. However, administration of aerosol therapy with assistance of a manual resuscitator bag does not increase drug delivery for spontaneously breathing children. Further studies are needed to determine the effectiveness of these aerosol generators with different type of resuscitator bag and different breathing parameters.

## References

- Amirav, I., Balanov, I., Gorenberg, M., Luder, A. S., Newhouse, M. T., & Groshar, D. (2002). Beta-agonist aerosol distribution in respiratory syncytial virus bronchiolitis in infants. *Journal of Nuclear Medicine*, *43*(4), 487–491.
- Amsallem, F., Gauthier, R., Ramonatxo, M., Counil, F., Voisin, M., Denjean, A., & Matecki, S. (2008). EFR du nourrisson: le point sur les valeurs normales. [Respiratory function testing in infants: Recommendations on normal values]. *Revue des Maladies Respiratoires*, *25*(4), 405–432.
- Ari, A., Atalay, O. T., Harwood, R., Sheard, M. M., Aljamhan, E. A., & Fink, J. B. (2010). Influence of nebulizer type, position, and bias flow on aerosol drug delivery in simulated pediatric and adult lung models during mechanical ventilation. *Respiratory care*, *55*(7), 845–851.
- Chua, H. L., Collis, G. G., Newbury, A. M., Chan, K., Bower, G. D., Sly, P. D., & Le Souef, P. N. (1994a). The influence of age on aerosol deposition in children with cystic fibrosis. *European Respiratory Journal*, *7*(12), 2185–2191.
- Coates, A. L., Denk, O., Leung, K., Ribeiro, N., Chan, J., Green, M., Martin, S., et al. (2011). Higher tobramycin concentration and vibrating mesh technology can shorten antibiotic treatment time in cystic fibrosis. *Pediatric Pulmonology*, *46*(4), 401–408.
- Coates, A. L., Leung, K., Vecellio, L., & Schuh, S. (2011). Testing of nebulizers for delivering magnesium sulfate to pediatric asthma patients in the emergency department. *Respiratory Care*, *56*, 314–318.

- Dolovich, M. B., & Dhand, R. (2011). Aerosol drug delivery: developments in device design and clinical use. *The Lancet*, 377(9770), 1032–1045.
- Dolovich, M. B., Killian, D., Wolff, R. K., Obminski, G., & Newhouse, M. T. (1977). Pulmonary aerosol deposition in chronic bronchitis: intermittent positive pressure breathing versus quiet breathing. *The American Review of Respiratory Disease*, 115(3), 397–402.
- Erzinger, S., Schuepp, K. G., Brooks-Wildhaber, J., Devadason, S. G., & Wildhaber, J. H. (2007). Facemasks and aerosol delivery in vivo. *Journal Of Aerosol Medicine: The Official Journal Of The International Society For Aerosols In Medicine*, 20 Suppl 1, S78.
- Esposito-Festen, J. E., Ates, B., van Vliet, F. J. M., Verbraak, A. F. M., de Jongste, J. C., & Tiddens, H. A. W. M. (2004). Effect of a facemask leak on aerosol delivery from a pMDI-spacer system. *Journal of Aerosol Medicine*, 17(1), 1–6.
- Esposito-Festen, J., Ijsselstijn, H., Hop, W., van Vliet, F., de Jongste, J., & Tiddens, H. (2006). Aerosol therapy by pressured metered-dose inhaler-spacer in sleeping young children: To do or not to do? *Chest*, 130(2), 487–492.
- Fink, J. B., Dhand, R., Duarte, A. G., Jenne, J. W., & Tobin, M. J. (1996). Aerosol delivery from a metered-dose inhaler during mechanical ventilation. An in vitro model. *American Journal of Respiratory and Critical Care Medicine*, 154(2 Pt 1), 382–387.
- Fok, T. F., Monkman, S., Dolovich, M., Gray, S., Coates, G., Paes, B., Rashid, F., et al. (1996). Efficiency of aerosol medication delivery from a metered dose inhaler

- versus jet nebulizer in infants with bronchopulmonary dysplasia. *Pediatric Pulmonology*, 21(5), 301–309.
- Janssens, H. M., Krijgsman, A., Verbraak, T. F. M., Hop, W. C. J., De Jongste, J. C., & Tiddens, H. A. W. M. (2004). Determining factors of aerosol deposition for four pMDI-spacer combinations in an infant upper airway model. *Journal of Aerosol Medicine*, 17(1), 51–61.
- Johnson, J., Waldrep, J., Guo, J., & Dhand, R. (2008). Aerosol delivery of recombinant human DNase I: In vitro comparison of a vibrating-mesh nebulizer with a jet nebulizer. *Respiratory Care*, 53(12), 1703–1708.
- Laube, B. L., Sharpless, G., Shermer, C., Nasir, O., Sullivan, V., & Powell, K. (2010). Deposition of albuterol aerosol generated by pneumatic nebulizer in the sophia anatomical infant nose-throat (SAINT) model. *Pharmaceutical Research*, 27(8), 1722–1729.
- Lugo, R. A., & Ballard, J. (2004). Albuterol delivery from a metered-dose inhaler with spacer is reduced following short-duration manual ventilation in a neonatal ventilator-lung model. *Respiratory Care*, 49(9), 1029–1034.
- Mallol, J., Rattray, S., Walker, G., Cook, D., & Robertson, C. F. (1996). Aerosol deposition in infants with cystic fibrosis. *Pediatric Pulmonology*, 21(5), 276–281.
- Ploin, D., Chapuis, F. R., Stamm, D., Robert, J., David, L., Chatelain, P. G., Dutau, G., et al. (2000). High-dose albuterol by metered-dose inhaler plus a spacer device versus nebulization in preschool children with recurrent wheezing: A double-blind, randomized equivalence trial. *Pediatrics*, 106(2 Pt 1), 311–317.

- Rotta, E. T., Amantéa, S. L., Froehlich, P. E., & Becker, A. (2010). Plasma concentrations of salbutamol in the treatment of acute asthma in a pediatric emergency. Could age be a parameter of influence? *European Journal of Clinical Pharmacology*, *66*(6), 605–610.
- Salmon, B., Wilson, N., & Silverman, M. (1990). How much aerosol reaches the lungs of wheezy infants and toddlers? *Archives of Disease in Childhood*, *65*(4), 401.
- Sangwan, S., Gurses, B. K., & Smaldone, G. C. (2004). Facemasks and facial deposition of aerosols. *Pediatric Pulmonology*, *37*(5), 447–452.
- Schuepp, K. G., Devadason, S. G., Roller, C., Minocchieri, S., Moeller, A., Hamacher, J., & Wildhaber, J. H. (2009). Aerosol delivery of nebulised budesonide in young children with asthma. *Respiratory Medicine*, *103*(11), 1738–1745.
- Schüep, Karen G., Jauernig, J., Janssens, H. M., Tiddens, H. A. W. M., Straub, D. A., Stangl, R., Keller, M., et al. (2005). In vitro determination of the optimal particle size for nebulized aerosol delivery to infants. *Journal of Aerosol Medicine*, *18*(2), 225–235.
- Stick, S. (1996). Measurements during tidal breathing. In J. Stocks, P. Sly, R. Tepper, & W. Morgan (Eds.), *Infant Respiratory Function Testing* (p. 134). New York, NY: Wiley-Liss.
- Tal, A., Golan, H., Grauer, N., Aviram, M., Albin, D., & Quastel, M. R. (1996). Deposition pattern of radiolabeled salbutamol inhaled from a metered-dose inhaler by means of a spacer with mask in young children with airway obstruction. *The Journal of pediatrics*, *128*(4), 479–484.

Wildhaber, J. H., Dore, N. D., Wilson, J. M., Devadason, S. G., & LeSouëf, P. N. (1999).  
Inhalation therapy in asthma: Nebulizer or pressurized metered-dose inhaler with  
holding chamber? In vivo comparison of lung deposition in children. *The Journal  
of Pediatrics*, 135(1), 28–33.