The Impact of Aerosol Devices and Delivery Interfaces on Aerosol Deposition in Children Receiving Noninvasive Ventilation

Malak Obaid Alshlowi

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THE IMPACT OF AEROSOL DEVICES AND DELIVERY INTERFACES ON AEROSOL DEPOSITION IN CHILDREN RECEIVING NONINVASIVE VENTILATION

Malak Alshlowi
malshlowi1@student.gsu.edu
ACCEPTANCE

This thesis, THE IMPACT OF AEROSOL DEVICES AND DELIVERY INTERFACES ON AEROSOL DEPOSITION IN CHILDREN RECEIVING NONINVASIVE VENTILATION, by Malak Obaid S. Alshlowi was prepared under the direction of the Master’s Thesis Advisory Committee of the Respiratory Therapy department at Georgia State University. It is accepted by the committee in partial fulfillment of requirements for the Master of Science degree in Respiratory Therapy at Byrdine F. Lewis College 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.

Douglas S. Gardenhire, EdD, RRT-NPS, FAARC
Committee Chair

Ralph D. Zimmerman, PhD, RRT-NPS
Committee Member

Shi huh Samuel Shan, MS, RRT-NPS-ACCS
Committee Member
AUTHOR’S STATEMENT

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All these deposited in the Georgia State University library must be used in accordance with stipulation prescribed by the author in the preceding statement. The author of this thesis is:

Malak Obaid Alshlowi

771 Lindbergh Drive NE

Atlanta, GA 30324

The director of this thesis is:

Douglas S. Gardenhire, EdD, RRT-NPS, FAARC

Chair and Clinical Associate Professor, Governor’s Teaching Fellow

Department of Respiratory Therapy

Byrdine F. Lewis College of Nursing and Health Professions

Georgia State University

P. O. BOX 4019

Atlanta, GA 30303
VITA

Malak Obaid Alshlowi

ADDRESS:
771 Lindbergh Drive NE
Atlanta, GA 30324

EDUCATION:
BS. RT 2012 Dammam University
College of Applied Medical Sciences
Dammam, Saudi Arabia

PROFESSIONAL EXPERIENCES:
2013- Present Assistant lecturer and Clinical instructor
At Imam Abdulrahman Bin Faisal University for Respiratory Care
Dammam, Saudi Arabia
2012-2013 Respiratory Therapist
Security Forces Hospital
Dammam in king Saudi Arabia
2011-2012 Internship in Respiratory Care
King Faisal specialist hospital &research center
Al- Riyadh, Saudi Arabia

PROFESSIONAL SOCIETIES AND ORGANIZAIONS:
2011-presnt Saudi Society of Respiratory Care
2017-present COPD Educator from American Association for Respiratory Care
2017-Present American Association for Respiratory Care
ABSTRACT

**Background:** Selecting optimal aerosol device and interface of noninvasive ventilation (NIV) to children is a challenge. The purpose of this study is to measure the delivery efficiency of two nebulizers with three interfaces in a simulated spontaneously breathing pediatric lung model.  

**Methods:** A ventilator (Trilogy 202, Philips) with single limb circuit (S/T mode, inspiratory pressure: 18 cmH\(_2\)O, expiratory pressure: 8 cmH\(_2\)O, respiratory rate: 30 and I:E ratio 1:2) was connected to a pediatric upper airway manikin via the standard oronasal mask (AF 541, Respironics), the oronasal mask with nose cushion (AF541, Respironics), and the nasal mask (PN 831 Respironics). A collecting filter was placed between the bronchi and a passive test lung (QuickLung, Ingmar Medical) with compliance of 20 mL/cmH\(_2\)O and resistance of 20 cmH\(_2\)O/L/s. Albuterol sulfate (2.5mg/3 ml) was administered with jet (Micro Mist, Hudson RCI, Temecula, CA) and mesh (Aerogen Solo, Aerogen Ltd, Galway, Ireland) nebulizers during noninvasive ventilation (n=5). Drug was eluted from filters and analyzed with spectrophotometry (276 nm). Descriptive statistics, Kruskal Wallis one way analysis of variance, and Mann Whitney U test were used for data analysis (p<0.05). **Results:** The result shows inhaled mass and inhaled dose % delivered (mean±SD) distal to the trachea. The mesh nebulizer delivered significantly greater drug deposition than the jet nebulizer with the standard oronasal mask (p=0.0001), the oronasal mask with nose cushion (p=0.0001), and nasal mask (p=0.047). Aerosol deposition with the standard oronasal mask was greater than the oronasal mask with nose cushion and the nasal mask using both jet and mesh nebulizers. **Conclusion:** Type of nebulizer and masks had an impact on aerosol drug delivery to this simulated passive pediatric lung model receiving noninvasive ventilation. Both oronasal masks were more efficient than the
nasal mask by 15 – 20 fold, with either type of nebulizer. The Mesh delivered 2-3 folder more drug distal to the tracheal than the Jet Nebulizer.
The Impact of Aerosol Devices and Delivery Interfaces on Aerosol Deposition in Children Receiving Noninvasive Ventilation

By
Malak Obaid S. Alshlowi
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Presented in Partial Fulfillment of Requirements for the
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in
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The Department of Respiratory Therapy
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Georgia State University
Atlanta, Georgia
2018
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After an intensive period of eleven months, today is the day: writing this acknowledgement is the finishing touch on my dissertation. It has been a period of intense learning for me, not only in the scientific arena, but also on a personal level. Writing this dissertation has had a big impact on me. I would like to reflect and give gratitude to the people who have supported and helped me throughout this process.

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DISCUSSION

The Effect of Aerosol Mask Type on Aerosol Drug Delivery
The Effect of Nebulizer Type on Aerosol Drug Delivery
Delivery technique
Limitation
Clinical Implications
Future Research
Conclusion

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Table 1. Gantt Chart

Table 2. presents the means (± standard deviation) of albuterol mass deposited on the inspiratory filter for each type of aerosol mask and percent of the nominal dose for (the standard oronasal mask, the oronasal mask with nose cushion and the nasal mask) using the jet and vibrating mesh nebulizer.
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<tr>
<td>JN</td>
<td>Jet Nebulizer</td>
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<td>VMN</td>
<td>Vibrating-mesh Nebulizer</td>
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<td>NIV</td>
<td>Noninvasive ventilation</td>
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<td>CINAHL</td>
<td>Cumulative Index to Nursing and Allied Health Literature</td>
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<tr>
<td>HFNC</td>
<td>High flow nasal cannula</td>
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<tr>
<td>PEFR</td>
<td>Peak expiratory flow rate</td>
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<tr>
<td>BIPAP</td>
<td>Bilevel positive airway pressure</td>
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<tr>
<td>SVN</td>
<td>Small-volume nebulizer</td>
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<td>PSV</td>
<td>Pressure support ventilation</td>
</tr>
<tr>
<td>VC</td>
<td>Vital capacity</td>
</tr>
<tr>
<td>FEV₁</td>
<td>Forced expiratory volume in 1 second</td>
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<tr>
<td>VT</td>
<td>Tidal volume</td>
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<tr>
<td>ETT</td>
<td>Endotracheal tube</td>
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<tr>
<td>RR</td>
<td>Respiratory rate</td>
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<tr>
<td>COPD</td>
<td>Chronic obstruction pulmonary disease</td>
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<tr>
<td>IPAP</td>
<td>Inspiratory pressure</td>
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<tr>
<td>EPAP</td>
<td>Expiratory pressure</td>
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<tr>
<td>FiO₂</td>
<td>Fractional concentration of inspired oxygen</td>
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<td>SpO₂</td>
<td>Oxygen saturation</td>
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<td>CPAP</td>
<td>Continues positive airway pressure</td>
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<td>Data Management Advisory Team</td>
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Aerosol therapy plays an essential role in the management of respiratory diseases. It is an effective way to deliver aerosolized medications to patients who suffer from pulmonary diseases, and one of its advantages is that it can deliver smaller doses of medication directly to the lungs. Aerosolized medications are generally administered through several devices such as Jet Nebulizer (JN) and Vibrating Mesh Nebulizer, and different interfaces such as nasal mask and oronasal mask which can be used in children of all ages.

In some situations, health care providers need to deliver aerosol therapy to pediatric patients receiving noninvasive ventilation (NIV). The presence of delivery interfaces as nasal mask or oronasal mask will interrupt the path of medication particles, which may affect the deposition of inhaled aerosol’s medications in the lung. The pediatric population ranges in age, which means patients present with different airway sizes, breathing patterns, and cooperation levels (Schüepp, Straub, Möller, & Wildhaber, 2004). These patient related characteristics influence the delivery and deposition of aerosolized medications in the lung. Therefore, the selection of the perfect device and interface to use to deliver aerosolized medications in line with NIV in a pediatric patient is a challenge.

Choosing the optimum device and interface is crucial in aerosol medication delivery via NIV. The proper choice will help health care providers make better choices. Previous studies showed that the Vibrating Mesh Nebulizer is superior to the Jet Nebulizer in medication delivery, but little is known about which interface yields greater medication delivery via NIV. Health care providers need more information about the optimum delivery interface to deliver
aerosolized medication in pediatric patients receiving NIV. In this study, the purpose is to measure the delivery efficiency of different aerosol devices, and interfaces that are used with pediatric patients who receive NIV. This is a basic experimental research where authors hypothesize that there is an impact on how aerosol therapy is delivered to patients in treatment deposition.

The main question that will drive this research is:

- What is the most efficient delivery interface to deliver aerosolized medication via NIV in a simulated pediatric lung model receiving NIV?
CHAPTER II
LITERATURE REVIEW

This literature review presents articles focused on the delivery of aerosolized medications in children receiving noninvasive ventilation. The articles in this study were collected from the Cumulative Index to Nursing and Allied Health Literature (CINAHL), Science Direct, Web of Science, and PubMed databases using the following terms: Children, aerosol, nebulizer, noninvasive ventilation (NIV), high flow nasal cannula (HFNC), breath-enhanced nebulizer, jet nebulizer, and vibrating mesh nebulizer. Relevant articles are divided into three categories: (1) aerosol drug delivery through NIV versus nebulization alone, (2) different type of interfaces, and (3) aerosol deposition with different devices.

Aerosol Drug Delivery Through NIV versus Nebulization Alone

Many researchers have tried to investigate a good way to deliver aerosolized medications into the lungs of patients receiving NIV. Pollack et al. (1995) used peak expiratory flow rate (PEFR) as a measurement tool to see how much patients improved after received aerosol therapy. In this study, they looked for the most effective way to deliver inhaled β-adrenergic agonist in acute bronchospasm either by delivering aerosolized medications during nasal positive airway pressure (BiPAP) or using small-volume nebulizer (SVN) alone without BiPAP. Patients’ age included in this study ranged from 18 to 40 years of age. All patients were admitted to the emergency room with acute bronchospasm and a history of asthma. Before delivering aerosol therapy, researchers measured oxygen saturation of arterial blood, pulse,
respiratory rate, and PEFR. Patients were randomly assigned into two groups. The first group of 40 patients received two aerosol therapies with 2.5 mg albuterol in 3 mL normal saline by small-volume nebulizer (SVN) and the second group of 60 patients had two therapies by BiPAP through a nose mask or face mask. The authors reported an improvement in PEFR from 211±89 to 357±108 L/minute after the second treatment in the first group of patients as opposed to patients who received the treatment by SVN alone and whose PEFR improved from 183± 60 to 280±87 L/minute (p = 0.0001). However, the pulse, oxygen saturation, and respiratory rate improved in similar ranges between the two groups.

Fauroux et al. (2000) evaluated the efficacy of pressure support ventilation (PSV) in improving aerosol deposition within the lungs of children with cystic fibrosis using in vitro and in vivo studies. In the in vitro study, the nebulizer alone was used as a control group and PS group received aerosols with a nebulizer through PSV. A different action triggered the nebulizer in the study. In the control group, the nebulizer was triggered by the inspiratory flow of the patient as opposed to the PSV group, in which nebulization was initiated by the positive pressure generated by PS ventilator. The solution used in the nebulizer was 2.5% KCl, and aerosol medication was captured by the filter attached to the carina. The PS ventilator was connected to a two chamber test lung, one was connected to a test lung, and another chamber was connected to the ventilator. The compliance of the test lung was at 50 mL/cm H2O with a resistance of 17 cm H2O at 1 L/s. Ventilator settings used in this study are RR of 20 breaths/minute, Ti of 1 second, inspiratory flow rate of 10 L/min, inspiratory trigger at -0.7 cm H2O, inspiratory pressure of 8 to 10 cm H2O, and exhalation at 30% of peak inspiratory flow. The authors reported that the mass KCl was greater in the filter of the PS group than in the control group, but the results were not statistically significant. Also, they calculated the ratio of the amount of KCl by the number of
inhalations and the amount of KCl in the capture filter. Both system ratios were stable from 50 to 400 inhalations, and was 75% and 70% for PSV group and the control group, respectively. The in vivo study was on 18 children with cystic fibrosis aged 12±4 years with a vital capacity (VC) of 77±21% and a forced expiratory volume in 1 second (FEV₁) of 72 ±26%. Every child received aerosol therapy with both SVN alone and PSV via nasal mask. The study shows aerosol deposition in the lung was 30% greater when using aerosol therapy with PSV than with SVN via a perfusion scan. Also, Fauroux et al. reported no relationship between aerosol deposition in the lung and age or height of the patients. But there was an inverse relationship between aerosol deposition and the percent predicted FEV₁ in control and PSV groups (p=0.0025 and p<0.0001, respectively). The findings show that reduced lung function (measured by FEV₁) had more asymmetric and more heterogeneous aerosol distribution.

Dai and colleagues (2014) examined the effect of different types of the exhalation valves (single-arch exhalation port, plateau exhalation valve, and whisper swivel) and the different positions of the nebulizer in the ventilator circuit such as proximal position (near the ventilator outlet) and distal position (between exhalation valve and lung model). In this study, the authors used a Michigan dual-chamber test lung and lung compliance was set to 0.05 L/ cm H₂O with an airway resistance of 4.3 cm H₂O L⁻¹ sec⁻¹ at a flow rate of 60 L/minute. NIV was connected to the test chamber without a humidifier. The ventilator settings included VT of 500 mL, flow rate of 50 L/min, waveform is square-wave, RR of 20 breaths/min, and pressure rising slope of 3. The inspiratory and expiratory pressures were set at different levels (15/5, 15/10,25/5 and 25/10 cm H₂O). 1 mL of 0.5% albuterol in 3 mL of normal saline was nebulized with the jet nebulizer. The aerosol was measured by spectrophotometry at 276 nm. Authors found an increase in the amount of the air leak with the single-arch exhalation port from 13.85 ± 0.32 L/min to
28.93±0.75 L/min as inspiratory pressure increased. However, the amount of air leak with plateau exhalation valve was constant at different pressure levels (24.01±0.68 L/min). Findings suggest that the single-arch exhalation port had the best aerosol delivery compared to any of the exhalation valves tested in this study when the nebulizer was placed distally (p<0.05), and had the lowest efficiency at proximal location (p<0.05). However, aerosol delivery at the proximal location was better than at the distal location when used with a plateau exhalation valve or whisper swivel. In addition, a direct relationship was found between inspiratory pressure and aerosol delivery (p<0.05) but the expiratory pressure was difficult to calculate.

White et al. (2013) looked at how aerosol delivery through NIV was affected by different positions of exhalation leak valves in the ventilator circuit in the pediatric population. In this study, researchers used a pediatric resuscitation manikin (5.5 mm inner diameter ETT and lung model of a child with severe static asthmatics; a compliance of 20 mL/cm H2O, resistance of 15 cm H2O/L/s, and expiratory muscle of 5 cm H2O) connected to NIV. They used two bacterial filters in the lung model; one filter was used to capture aerosols and another filter was used to protect the lung model. NIV was attached to a heated wire circuit and the settings were BiPAP S/T mode with an inspiratory pressure of 16 cm H2O, expiratory pressure of 8 cm H2O, FiO2 0.50, rise time of 2 second, and Autotrack trigger. Albuterol (5 mg with 2.5 mL of the normal saline) was delivered by mesh nebulizers (Areoneb solo) set at three different positions in the circuit: before the humidifier and leak valve; between the humidifier and leak valve; and integrated within the mask and after the leak. Albuterol was measured by HPLC and detector wavelength (278 nm). The researchers reported that there was more albuterol delivered on pediatric NIV when the vibrating-mesh nebulizer was combined into the mask than any other positions (p<0.001). When the nebulizer was placed prior to the exhalation leak valve, greater
aerosol delivery was noted than the nebulizer position between the humidifier and the leak valve (p=0.002).

In a crossover clinical trial, Galindo-Filho et al. (2015) used mesh and jet nebulizers during NIV to compare radio-aerosol pulmonary index, and radio-aerosol mass in pulmonary and extra pulmonary settings. The study included 10 healthy adults (between 18 and 60 years of age) who were assigned to two groups. The first group of 10 subjects received aerosol therapy by the jet nebulizer and the second group received aerosol by the mesh nebulizer. Both groups received 2.5 mg of salbutamol, 0.25 mg of ipratropium bromide with 3 mL of technetium-99m diethylenetriaminpedntaacetic acid, and 0.9% saline solution via nebulizer during NIV (inspiratory pressure of 5 cm H2O and expiratory pressure of 12 cm H2O) with a facemask. After inhalation, researchers used the gamma camera to measure radio-aerosol. Authors reported that the mesh nebulizer produced >2-fold more aerosols than the jet nebulizer (972.013±214.459 vs.386.025±130.363, p=0.005).

Michotte and colleagues (2014) analyzed inhaled and exhaled doses of three types of nebulizers (mesh, jet, and ultrasonic nebulizers) combined with bi-level ventilator. They assessed the effect of nebulizer placement on these doses. The test lung had two chambers. The first chamber was aping the adult respiratory muscles with obstructive disease (VT=400 mL, RR=15 breaths/min, I/E ratio=1:3, inspiratory time=5% of respiratory cycle) and attached to a ventilator. The second chamber was mimicking the lung and attached the bi-level ventilator (BiPAP). The ventilator settings included PS mode with inspiratory pressure of 20 cm H2O, expiratory pressure of 5 cm H2O, flow trigger of 9 L.m⁻¹, inspiratory rise time at level 1, and inspiratory cycle-off 30%. The authors tested each nebulizer at two different positions, before and after the exhalation port in an adult lung model receiving NIV. They measured the inhaled
dose, the exhaled dose, and the total lost dose by using the residual gravimetric method. The results from the study showed a benefit for the use of the mesh nebulizer before the exhalation valve (p<0.001). This position demonstrated the greatest deposition of medication. The mesh nebulizer delivered the highest inhaled dose compared to other nebulizers tested in this study. The placement of the mesh nebulizer after the exhalation port delivered the highest inhaled (p<0.001) and expiratory wasted dose (p<0.001). The jet nebulizer had highest exhaled dose when it is placed before the exhalation valve (p<0.001). The ultrasonic nebulizer is not recommended because of its maximum total lost dose compared with mesh and jet nebulizers (p<0.001).

Calvert et al. (2006), evaluated the delivery of nebulized aerosol during non-invasive ventilation by using a lung model simulating COPD adult respiration. The breathing simulator was set with a VT of 600 mL, RR of 12 breaths/min, and Ti of 40%. The bi-level ventilator was set in spontaneous mode at an inspiratory pressure (IPAP) of 20cmH2O and expiratory pressure (EPAP) of 5cmH2O. The nebulizer alone was used as a control group and NIV group received aerosols with a nebulizer through NIV. Nebulizer solution was Salbutamol 5mg in 2.5 mL normal saline using jet nebulizer. The nebulizer location was different within the ventilator circuit. The spaces between the nebulizer and the breathing simulator were 10cm, 19cm, and 204cm for locations A, B, and C, respectively. In the control study, the nebulizer was connected straight to the facemask via a T-piece without NIV. The aerosol was measured by spectrophotometry at 276 nm. There was significant output of salbutamol to the filter when placing the nebulizer at position B in the circuit (P > 0.05) than position A (544 ± 85 mg) or position C (267 ± 26 mg) (P < 0.001). Also, the nebulizer at position B was significantly better than nebulization without the ventilator (424 ± 61 mg; p < 0.01).
Abdelrahima et al. (2010), examined effective ventilation during Non-invasive ventilation (NIV) with nebulized bronchodilators in chronic obstructive pulmonary disease. In this study, a breathing simulator was used and the settings were a VT of 500 mL, RR of 15 breaths per minute, and I: E ratio of 1:3. The bi-level ventilator was set in spontaneous mode at an inspiratory pressure of 20 cm H2O and expiratory pressure of 5 cm H2O. Authors used the Aeroneb Professional (AERO) and the Sidestream (SIDE) nebulizer. AERO is a vibrating mesh nebulizer and SIDE is a jet nebulizer. Nebulizer solution was two mL of 5 mg of terbutaline sulfate respiratory solution (Bricanyl Respules containing a nominal dose of 2.5 mg/mL; AstraZeneca, UK). They used three electrostatic filters. The first electrostatic filter was used as an inhalation filter which connected to a breathing machine to measure the total inhaled aerosol dose. The second electrostatic filter was used as a ventilator filter which connected to a ventilator to check if aerosol reaches the ventilator. The third electrostatic filter was used as an expiration filter which was connected 4 cm above the outlet of the expiration port of the NIV system. A vacuum of 25 l/min was drawn through the circuit which ensured the capture of the entire dose that was expelled from the NIV system. The nebulizers were tested on two positions; in position A, the nebulizer was direct to the breathing simulator and in position B, the expiration port was direct to the breathing simulator. The researchers reported higher concentration of terbutaline on the inhalation filter than the expiration port in position A than in position B (p<0.001) for both nebulizers. The mesh nebulizer on positions A was captured leaving the expiration port than was entrained on the inhalation filter (p<0.001). The jet nebulizer on positions A and B was captured leaving the expiration port than was entrained on the inhalation filter (p<0.001). There were similarities of residual volumes left in the chambers for mesh nebulizer in both positions, as well as jet nebulizer in both positions.
In a prospective randomized controlled study, Brandão et al. (2009) assessed the effect of jet nebulization administered to spontaneous breathing patients, suffering an acute asthmatic episode, on NIV. They select 36 patients (18-65 years) diagnosed with severe asthma. Criteria for inclusion were patients with an \( \text{FEV}_1 \) less than 60% of predicted, history of asthma for at least one year, and present asthma catastrophe lasting less than 7 days. Criteria for exclusion were if patients smoked, used anti-inflammatory drugs, had chronic obstructive pulmonary disease, were hemodynamically unstable (defined as having a heart rate over 150 bpm or systolic pressure below 90 mmHg), had congestive heart failure, altered consciousness, facial deformity, or were pregnant. Patients were randomized into three groups: control group (nebulization alone), experimental group 1 (nebulization and NIV with inspiratory positive airway pressure [IPAP] = 15 cm H2O and expiratory positive airway pressure [EPAP] = 5 cmH2O), and experimental group 2 (nebulization and NIV with IPAP = 15 cm H2O and EPAP = 10 cm H2O). The nebulization solution was 2.5 mg of fenoterol bromidrate, 0.25 mg of ipratropium bromide, and 4 mL of physiological saline (NaCl at 0.9%). Aerosol was administered with a jet nebulizer for all three groups. The researchers recorded respiratory rate (RR), heart rate (HR), oxygen saturation (SpO2), peak expiratory flow (PEF), forced expiratory volume in 1 second (\( \text{FEV}_1 \)), forced vital capacity (FVC), and forced expiratory flow between 25% and 75% (\( \text{FEF}_{25-75} \)). Data was collected before and after 30 minutes of each intervention. The authors reported that the RR lower (\( p = 0.04 \)) 30 minutes after treatment compared with before treatment with Experimental group 1. No changes were witnessed for either HR or SpO2. There was no difference in HR, RR, and SpO2 collected 30 minutes after treatment compared with before treatment between the control group and experimental group 2. There was significant higher PEF (\( p < 0.03 \)), FVC (\( p < \))
0.03), FEV$_1$ (p < 0.03), and FEF$_{25-75}$% (p < 0.00) in experimental group 2, however for experimental group 1, just the PEF (p < 0.04) was higher.

Françaa et al. (2005) assessed pulmonary radioaerosol deposition during jet nebulization with noninvasive ventilation against spontaneous breathing nebulization (SB). The study was done in 13 healthy volunteers (nine females and four males) with normal spirometry. Their age was 23.4 ±1.49 (SD) years and body mass index (BMI) was 21.2±2.3 kg/m2. Criteria for exclusion were if patients smoked or have respiratory problems, pregnancy, breathing rate >20 bpm, heart rate <50 or >100 bpm, oxygen saturation (SpO2) ≤ 90%, maximal inspiratory pressure ≤ 50 cm H2O, Vt ≤ 6 mL/kg, forced vital capacity (FVC) < 81%, and forced expiratory volume on the 1 s (FEV$_1$) < 82% of predicted values. All volunteers underwent nebulization in two phases, one in SB and another with bi-level NV. There were 7 days of washout period between two phases. The nebulization solution was technetium (Tc99m) and diethylene triamine penta acetic acid, produced by a jet nebulizer. After the radioaerosol radioactive inhalation, the volunteers stayed in the scintigraphy camera. Authors observed that pulmonary deposition of radioaerosol when connected to bi-level NIV was less when compared to SB (p<0.001). There was lower significance of radioaerosol deposition in upper, middle, and lower thirds of the lung when nebulization was carried out connected to bi-level NIV than with SB nebulization (p<0.001). There was a significant relationship between Vt and radioaerosol deposition (r. = 0.565, p< 0.05) in spontaneous breathing nebulization, and between inspiratory flow and radioaerosol deposition in the lungs (r =0.141, p< 0.05). During bi-level NIV nebulization, there was no relationship between Vt and pulmonary deposition of radioaerosol (r = 0.082).

Mukhopadhyay et al. (2009) assessed the effects of disconnecting noninvasive ventilation (NIV) used during acute exacerbation of chronic obstructive pulmonary disease for the delivery
of aerosolized medications on physiologic factors and dyspnea sensation. The study was done in 19 patients. Criteria for inclusion were patients with COPD (2) requiring NIV for type 2 respiratory failure with pH of 7.25 to 7.35 and raised PaCO2 while maintaining oxygen saturation between 88% and 92%; (3) mentally alert and able to answer simple questions on breathlessness. Criteria for exclusion were if pneumonia was noticed by chest radiography, they were hemodynamically unstable, or unable to answer questions because of drowsiness or disorientation. All volunteers underwent 4 phases in this study; NIV1 phase, oxygenation phase, nebulization phase, and NIV2 phase. NIV1 phases. Patients were placed on NIV for 10 minutes and ventilation settings were peak inspiratory pressure 19 (±4) cm H$_2$O, PEEP 4 (±1.5) cm H$_2$O, and FiO2 32% ±6%. Before the removal NIV, researcher recorded the following parameters: peak inspiratory pressure, positive end-expiratory pressure (PEEP), tidal volume (Vt), respiratory rate (RR), fractional concentration of inspired oxygen (FiO2), oxygen saturation (SpO2), heart rate (HR), and blood pressure (BP). The subjects were then asked questions in the language of their best understanding (English, Malay, or Mandarin) to indicate their level of breathlessness on the modified Borg score. A clinician then indicated by “yes” or “no” whether the subject was using accessory muscles to breathe. Finally, an ABG sample was drawn and analyzed. In the oxygenation phases, the patients were removed from the NIV and put on oxygen via nasal cannula to maintain an oxygen saturation of 88% to 92%. This phase helped to avoid overlapping effects of NIV and nebulization on physiologic parameters. After 10-minute oxygen therapy, the vital signs, accessory muscles usage, and the Borg score were again recorded. In the nebulization phases, the patients received bronchodilator nebulization treatment with salbutamol 5 mg and ipratropium 500 µg administered via small volume nebulizer. Following the end of the nebulizer treatment, the vital signs, the Borg score, and use of accessory muscles were again recorded.
Finally, ABG sample was drawn and analyzed. In the NIV2 phase, the patients were then put back on NIV with the same ventilation settings. After 10 minutes, the vital signs, accessory muscles usage, and the Borg score were again recorded. Authors reported there were no significance different between two phases of NIV in all parameters. Between NIV and nebulization phases there were no significant changes in physiologic parameters and oxygenation. Only physiologic changes were seen and the result show an increase in systolic BP (SBP, p = .012) and HR (p = .003) after nebulization. More patients were assessed to be using the accessory muscles of respiration after discontinuation of NIV (22% vs. 44%, P = NS). There was a significant decrease in oxygen saturation (P = .009) and increase in SBP (P = nonsignificant) between NIV and oxygenation phases.

In a prospective study, Nava et al. (2001) examined clinical response of salbutamol delivered through metered dose inhaler (MDI) during noninvasive mechanical ventilation (NIMV-MDI), during spontaneous breathing using a spacer (MDI-Spacer), and during intermittent positive pressure ventilation (IPPB). They selected 18 patients (age < 75 years) diagnosed with COPD. Criteria for inclusion were patients with an FEV₁/FVC less than 60%, and FEV₁ < 1.5 or 50% predicted. Another criteria were patient who used short- or long- acting β2-agonist as chronic therapy. Arterial blood gas sampling, pulmonary function test, and vital signs were recorded. This study has two sets of experiments. The first set of experiments has 10 patients. Before the start of the study, all medication except oxygen were stopped at least 24 h. The study was conducted on four consecutive days. 1) placebo via spacer chamber; 2) 400 mg dose of salbutamol via MDI-Spacer; 3) 400 mg dose of salbutamol via NIMV-MDI, and 4) 5 mL of saline solution with 5 mg of salbutamol via IPPB. Authors measured FEV₁ prior to the test to checked the patients’ clinical stability. During NIMV, ventilation setting was volume-assured
pressure support; pressure support 14.3 ± 1.8 cmH₂O and VT guarantee of 10 mL/kg. The inspiratory trigger was set at -0.5 cmH₂O. All patients were breathing room air and used a full-face mask. During IPPB, the setting was a pressure of 15 cmH₂O, a flow rate of 50 l/min, and no oxygen supplementation. All the measurements were recorded 10 min before the start of aerosol therapy and then repeated 15 min and 30 min after aerosol therapy. The second set of experiments had 8 patients. The study was conducted on two consecutive days. 1) 400 mg of salbutamol via NIMV-MDI, 2) placebo via NIMV-MDI. The ventilator setting as described above. Authors report that there was a significant improvement in FEV₁ salbutamol compared to placebo. ∆FVC significantly increased with NIMV-MDI. In the second set of the experiment, the researchers found improvements in FVC in both trials (placebo or salbutamol via NIMV-MDI) (+206 ± 147 mL and 208 ±145, respectively). However, there was a significant increase in FEV₁ after salbutamol.

Reychler et al. (2007) evaluated lung deposition of amikacin produced by jet nebulizer (SideStream) used alone (SST) or combined with a CPAP machine. They recruited six non-smoking healthy male volunteers with a normal lung function. Their mean age = 27.3 ± 2.2; height = 179± 3 cm; and weight = 77± 4 kg. All volunteers underwent nebulization in two phases, one in (SST) and another in connection to CPAP. There was one week of washout period between each nebulization. The solution was amikacin sulfate dissolved in 4 mL 0.9% NaCl solution to a concentration of 250 mg mL⁻¹. The CPAP setting was 6 cm H₂O. The researchers requested the urine sample to be collected before nebulization and after 24 h from therapy. They assessed urinary amikacin concentration by fluorescent polarization immunoassay. Also, they measured residual volume by pipetting after a 5-minute rest period. Authors reported that the amount of amikacin excreted in the urine was 2.5-fold lower with CPAP than with SST. There
was significantly higher level of amikacin excreted in the urine with SST than with CPAP (4.88% initial dose versus 1.97% initial dose, p<0.001). The residual amount of amikacin in the nebulizer was lower with SST than with CPAP (541 mg versus 607 mg), but the results were not significant (p = 0.35).

In a laboratory study, Chatmongkolchart (2002) studied the effect of ventilator parameters and nebulizer position on aerosol delivery during NIV. In this study, the authors used a Michigan adult dual-chamber test lung and lung compliance was set to 0.064 L/cm H 2O with an airway resistance of 4.3 cm H 2O L -1 sec -1 at a flow rate of 60 L/minute. NIV was connected to the test chamber without a humidifier. The ventilator settings (BiPAP S/T) included a flow rate of 25% duty cycle, the waveform is sinusoidal-wave, and RR of 10 and 20 breaths/min. The inspiratory and expiratory pressures were set at different levels (10/5, 15/5, 20/5, 15/10, 20/10, and 25/10 cm H 2O). One mL of 0.5% albuterol in 3 mL of normal saline was nebulized with the jet nebulizer. The nebulizer was placed in either a proximal (ventilator outlet) or distal position (between circuit leak and the collecting filter). The aerosol was gathered by filter located at the inlet of lung model. Authors found an increase in the amount of the aerosol delivery with nebulizer placed at the distal position and RR of 20 breaths/min. There was a significant effect in aerosol deposition by nebulizer position, RR, and the BiPAP setting (p<0.001). Furthermore, there was a significant effect between RR and the BiPAP setting (p<0.001), nebulizer position and the BiPAP setting (p<0.001), and nebulizer position and RR (p<0.001).
Different Type of Interface

Clinicians should select the most appropriate interface for NIV for the best clinical outcome. Ramirez et al. (2011) evaluated the best interface for long-term NIV in children. The study was done in 97 children with neuromuscular or thoracic scoliosis (35 patients), obstructive sleep apnea (32 patients), maxillofacial deformity (21 patients), and lung disease (9 patients). The author selected the interface based on age, disease, patient tolerance, absence of skin injury, pain, and leak. During the study, authors changed the interface due to discomfort (16 patients), leaks (4 patients), facial growth (3 patients), skin injury (2 patients), and changes in the ventilator mode (2 patients). The result was 50% of children fitted to the nasal mask, 16% to face mask, and 2% to nasal prongs. Noise during NIV is considered one of the important factors of cooperative patients with NIV.

Cavaliere and colleagues (2004) assessed noise during NIV with three types of interfaces (helmet, nasal, and face mask) in 10 healthy adults (23-49 y). They received NIV at a pressure support of 10 and 15 cm H$_2$O. The three masks were tested randomly, and each test took 15 minutes to complete. They measured sound by putting the microphone close to the right ear. The result was helmet noise registered more than 100dB, but nasal and facial masks did not exceed 70dB.

Urbüz et al. (2015) compared helmet with face mask in 50 COPD patients receiving NIV. Participants of the study were divided into two groups. The first group of 25 patients used the helmet while the second group of 25 patients were connected to NIV with the face mask. Settings of NIV included FiO$_2$ 0.40, PEEP 5-7 cm H$_2$O, PS 10 cm H$_2$O, and trigger -2 cm H$_2$O. Authors measured demographic data, FEV$_1$, hemodynamics, vital signs, arterial blood gases, and FiO$_2$ before starting the test. Then, they documented these parameters in 30 min intervals of NIV
until 120 min, 24 h, and 48 h. Researchers reported that there was no difference between the two groups based on the parameters measured in this study (p>0.05) except the CO₂ that decreased with the full-face mask compared to the helmet.

Branconnier et al. (2005) tested delivery efficiency of different aerosol devices such as the nebulizer or the metered-dose inhaler (MDI) by using two different types of masks during NIV. The Spectrum mask that has the leak port in the circuit and Mirage mask with the leak port in the mask were tested in this study. They used a lung model connected to the ventilator (BiPAP mode) with 15/5 cmH₂O, RR 20 breaths/minute, and tidal volume 0.4 L. The amount of aerosol captured on the filter was analyzed from the absorption-concentration and the stander, and then measured with the spectrophotometer using a 1mL quartz cuvette at the wavelength of 276 nm. The results of this study showed that the nebulizer delivered more albuterol than the MDI (p<0.01). There was significantly more albuterol delivered with the Spectrum mask (p=0.001). Delivery efficiency of the nebulizer and MDI was similar with the Spectrum mask (p=0.57), while albuterol delivery was better on MDI with the Mirage mask (p=0.001).

Lin et al. (2012) studied the impact of nebulizer types and different aerosol masks on drug deposition in pediatrics by using a lung simulator with settings for a spontaneously breathing child (2-4 years old). The study set a tidal volume of 150 mL, inspiratory time 0.8 sec, flow rate 20 l/min, and RR 25 breaths/min. They used three different types of nebulizers (constant-output, breath-enhanced, and breath actuated nebulizers) and three types of masks (standart face mask, Fish mask, and valved mask). The inhaled aerosol was salbutamol sulfate (5.0 mg/2.5 mL with distilled water). The total nebulizer fill volume of 4 mL was used in this study. The amount of aerosol was collected by the filter placed distal to the trachea. Inhaled dose was measured via spectrophotometry at 276 nm. The nebulization time of each nebulizer was
measured. The result showed that the breath actuated nebulizer had lower aerosol deposition and longer treatment times compared to other nebulizers (p=0.001). Constant aerosol generation had the highest aerosol deposition and shortest times of nebulization (p=0.025). The Fish mask had higher aerosol deposition than the others (p=0.001).

**Aerosol Deposition with Different Devices**

Ari et al. (2015) evaluated the efficiency of mesh nebulizer (MN) with proprietary adapter and a jet nebulizer (JN) using different interfaces in adult and pediatric models. In this study, the authors used adult and pediatric models attached to a sinusoidal pump via a collecting filter at a level of the bronchi. A spontaneously breathing adult settings (TV of 500 mL, RR of 15 breaths/min and I: E ratio of 1:2) and a spontaneously breathing Pediatric settings (TV of 150 mL, RR of 25 breaths/min and I: E ratio of 1:2) were used. The adult interfaces tested in this study included the mouthpiece, the aerosol mask, and the valve-mask. The pediatric interfaces tested were the dragon mask, the aerosol mask, and the valve-mask. Albuterol sulfate (2.5 mg/3 mL) was collected in the filter and analyzed by spectrophotometry. The researchers reported that the delivery efficiency of JN was two-fold less than MN when a mouthpiece or valve–mask was used for aerosol therapy using the adult lung model (p=0.013 and p=0.014, respectively). However, drug delivery by an aerosol mask with MN was less efficient than the mouthpiece or valve-mask (p=0.001 and p=0.0001, respectively). There was no significant difference in an aerosol deposition by using mouthpiece or valve-mask with JN and MN (p=0.0 121 and p=0.951, respectively). The inhaled dose with adult lung model was greater than a pediatric model with both JN and MN (p<0.05). Also, aerosol deposition was significantly greater in an adult lung
model than the infant lung model used with JN (p=0.001 and p=0.002, respectively) and MN (p=0.001 and p=0.005, respectively).

Pitance et al. (2010) evaluated the efficacy of a mesh nebulizer and a jet nebulizer by measuring inhaled mass and urinary drug concentration of amikacin using in vitro and in vivo studies. Authors used three different nebulizer delivery structures: jet nebulizer alone, jet nebulizer with 110 mL corrugated tube, and a vibrating mesh nebulizer. In the in vitro study, they used adult lung model set at RR of 20 breath/min, VT of 440 mL, 10% inspiratory pause, and 33% I/E ratio. Every nebulizer was filled with 4 mL of amikacin (125 mg/mL) and was weighted unfilled when filling, and at the end of nebulization. The in vivo study was on six non-smoking healthy male aged 28±4.4 years. Volunteers were randomly selected to the three nebulizer configurations. Every volunteer received a single therapy from each nebulizer. There was 48 hours of washout period between each nebulization. The researchers requested the urine should be collected before nebulization and after 24 h from therapy. They assessed urinary amikacin concentration by fluorescent polarization immunoassay. They showed that the mesh nebulizer had higher inhaled mass than another device. The percentage of amikacin increased with corrugated tubing by 2-3 fold compared to without it. The jet nebulizer had significantly higher drug mass than two jet nebulizers (p<0.05). However, the amount of amikacin in the reservoir at the end of nebulization was significantly higher with two jet nebulizers than the mesh nebulizer (p<0.001).

In a crossover clinic trial, Dugernier et al. (2016) compared a vibrating mesh nebulizer with a valved holding chamber and a conventional jet nebulizer with a corrugated tube for lung deposition. The study was performed on six healthy male subjects (18 or older), who were non-smokers with no evidence of respiratory disease, and who had normal lung function tests. The
diethyleneteriaminepentaaccetic acid labeled with technetium-99 m was measured by single-photon emission computed tomography combined with a low-dose CT-scan (SPECT-CT). Every volunteer received a single therapy from each nebulizer. There was 60 hours of washout period between each nebulization. Authors reported that aerosol delivery with the vibration mesh nebulizer was >6-times greater than the jet nebulizer (43.1±6.0% versus 5.2±1.1%, p<0.001).

In conclusion, this literature review has shown that there are many factors affecting the aerosol delivery through a NIV, including the nebulizer types, interfaces, types and position of exhalation valve, tidal volume used, and pressure used in NIV. The most commonly used nebulizer devices with the NIV are jet and vibrating mesh nebulizer. Research shows that the mesh-nebulizer delivered the highest inhaled dose when used after the exhalation port. However, the jet nebulizer had the highest exhaled dose before the exhalation valve. The ultrasonic nebulizer is not recommended because of the maximum total lost dose compared with mesh and jet. Regarding interfaces, a nasal mask is generally superior than a face mask or nasal prongs. In terms of types of exhalation valve, the single-arch exhalation port had the best aerosol delivery than plateau exhalation valve or whisper swivel. The used of low Vt when administering aerosol with a nebulizer increases aerosol delivery. On the other hand, greater inspiratory pressure correlated with increased aerosol delivery. Finally, breathing patterns affect delivery, and aerosol delivery decreased in the pediatric population.
CHAPTER III

Methods

Research Design

This is an experimental study in which the delivery efficiency of different aerosol devices and interfaces that are used in children receiving NIV will be determined. The method of sampling will be non-probability purposive sampling based on literature review and commonly used interfaces and devices for aerosol drug delivery in clinical practice.

Lung Model

This study will use a pediatric teaching mannequin and an in vitro lung model will be prepared to conduct this study. The upper airway of the teaching mannequin will be attached to a collecting filter at the level of bronchi connected to a passive single chamber test lung (QuickLung, IngMar Medical, Pittsburgh, USA) to represent the breathing parameters of a 5 year-old child. The target tidal volume will be 180 mL, the respiratory rate will be 30 breaths/min, and I:E ratio of 1:2 will be used. Both the tidal volume and leak will be monitored continuously during each experiment. A collecting filter (Respirgard II, Vital Signs, San Antonio, TX) will be placed between the bronchi of a pediatric upper airway manikin (child airway management trainer IF03609U, Nasco) and the test lung (QuickLung, Ingmar Medical) with compliance of 20 mL/cmH\textsubscript{2}O and resistance of 20 cmH\textsubscript{2}O/L/s. This filter will be used to collect the aerosolized drug. A vibrating mesh nebulizer (Aerogen Solo, Aerogen Ltd, Galway, Ireland) and jet nebulizer (Micro Mist, Hudson RCI, Temecula, CA) will be placed between the leak port and the interface that will be tested in this study. A ventilator (Trilogy 202, Philips) with single limb circuit (S/T mode, inspiratory pressure: 18 cmH\textsubscript{2}O, expiratory pressure: 8
cmH₂O, respiratory rate: 30, and I:E ratio 1:2) will be connected to a pediatric upper airway manikin via mask.

Variables

Two independent variables will be examined in this research. The first independent variable is the interfaces, including the standard oronasal mask (AF 541, Respironics), the oronasal mask with nose cushion (AF541, Respironics), and the nasal mask (PN 831 Respironics). The second independent variable is the nebulizer: (1) Jet Nebulizer (Micro Mist, Hudson RCI, Temecula, CA) and (2) Vibrating Mesh Nebulizer (Aerogen Solo, Aerogen Ltd, Galway, Ireland) (Alhamad, Fink, Harwood, Sheard, & Ari, 2015). The measured dependent variable will be aerosol drug delivery distal to the trachea.

Figure 1. Experimental set-up of the study using the jet nebulizer

Figure 2. Experimental set-up of the study using the mesh nebulizer

Figure 3. Three interfaces tested:
(A) the standard oronasal mask,
(B) the oronasal mask with nose cushion,
(C) the nasal mask
Settings

The study will be conducted in the Aerosol Research Laboratory in the Department of Respiratory Therapy at Georgia State University (GSU).

Procedures

Albuterol sulfate (2.5mg/3 ml) will be administered with jet and mesh nebulizers during NIV. Oxygen flow of 8 L/min will be used to operate the jet nebulizer until sputter, while the drug solution will be aerosolized by the vibrating mesh nebulizer until no more aerosol is seen. The same experimental setup will be used in five nebulization sessions (n=5). After each session, albuterol sulfate deposited on the filter will be measured by rinsing the filter with 10 ml of 0.1 N hydrochloric acid (JT Baker Company, Phillipsburg, NJ) using a gentle stirring for 3 minutes to ensure proper mixing. A calibrated spectrophotometry device (Beckman Instruments, Fullerton, CA) will measure albuterol concentration in the solution.
Table 1. Gantt Chart

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Data Collection

As shown in Figure 4, a total of 30 runs, 15 using the vibrating mesh nebulizer and 15 using the jet nebulizer will be conducted with each interface (n=5).

Figure 4. A scheme of variables and experiments plan in the study

Statistical Analysis

Variables conducted in this research are interfaces and nebulizers. As a result, the amount of albuterol sulfate deposited on the filter will be calculated as a percentage of the total inhaled drug mass delivered distal to trachea after each experiment. In comparison, significance is defined as a $p$ value < 0.05. Analysis will be performed by a Statistical Package for the Social Sciences (IBM SPSS, 24.0).

Data management and storage

Prior to data entry into a computer database (Microsoft Excel), a codebook will be created to describe each variable and how information will be entered. Data security will be
ensured by protecting computer files with a password for restricted access and use. The Data Management Advisory Team (DMAT) in the university library will be available for assistance in managing the data.

CHAPTER IV

RESULTS

This study compared the amount of aerosol delivered to the trachea (the inhaled mass) and the inhaled mass percentage of the three-aerosol mask (Standard Oro-nasal Mask, Oronasal Mask with Nose Cushion, and Nasal Mask) using both jet nebulizer and vibrating mesh nebulizer.

Table 2. presents the means (± standard deviation) of albuterol mass deposited on the inspiratory filter for each type of aerosol mask and percent of the nominal dose for (the standard oronasal mask, the oronasal mask with nose cushion, and the nasal mask) using the jet and vibrating mesh nebulizers.

Table 2. Needs a title (n=5)

<table>
<thead>
<tr>
<th></th>
<th>Mesh Nebulizer</th>
<th>Jet Nebulizer</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Standard Oronasal Mask</td>
<td>Oronasal Mask with Nose Cushion</td>
</tr>
<tr>
<td>Inhaled Mass (mcg)</td>
<td>506.5 ± 61.9</td>
<td>437.6 ± 38.4</td>
</tr>
<tr>
<td>Inhaled Dose %</td>
<td>20.3 ± 2.5</td>
<td>17.5 ± 1.5</td>
</tr>
</tbody>
</table>
The Effect of Aerosol Mask Type on Aerosol Drug Delivery

Delivery of albuterol was greater with the standard oronasal mask using both mesh and jet nebulizers (20.3 ± 2.5% and 7.7 ± 0.6%, respectively) compared with the oronasal mask with nose cushion (17.5 ± 1.5% and 5.4 ± 1.1%, respectively). The nasal mask (2.0 ± 1.1% and 0.8 ± 0.2%, respectively) had the lowest deposition. Both oronasal masks were more efficient than the nasal mask by 15–20 fold, with either type of nebulizer.

The Effect of Nebulizer Type on Aerosol Drug Delivery

The vibrating mesh nebulizer resulted 2–3 fold larger dose than the jet nebulizer in the mean inhaled percent of the dose delivered with all types of aerosol masks. The mesh nebulizer delivered significantly more drug deposition than the jet nebulizer with the standard oronasal mask (p=0.0001), the oronasal mask with nose cushion (p=0.0001), and the nasal mask (p=0.047).

Figure 6. Comparison of jet nebulizer (dark bar) and mesh nebulizer (gray bar) inhaled mass percent (Mean – SD) for the standard oronasal mask, the oronasal mask with cushion and the nasal mask.
CHAPTER V

DISCUSSION

Pediatric patients on noninvasive ventilation could require aerosol therapy and in a relatively short period of time. Therefore, timely and efficient delivery of aerosol drugs should provide an essential medical role in decreasing airway obstruction, ventilator impairment, and respiratory distress. A study conducted by Nava et al. (2001), demonstrated superior aerosol drug delivery through noninvasive ventilation than without positive pressure. Fauroux et al. (2000), analysed pediatric patients with cystic fibrosis demonstrated 30% increase in aerosol drug delivery with the use of nebulization delivered with noninvasive ventilation than without noninvasive ventilation. Therefore, the use of aerosol delivery on noninvasive ventilation could increase aerosol drug delivery, and decrease work of breathing.

Dai. (2014), Michotte. (2014), Claver. (2006), Abdharh. (2010), Chatmongkolchart. (2002), 7 clinical studies Brandão. (2009), França. (2005), Mukhopadhyay. (2009), Nava. (2001), Pollack. (1995), Galindo-Filho. (2015), and Reychler. (2007), assessed aerosol drug delivery in adult noninvasive ventilation. Although there are numerous adult studies in this field, there are only two pediatric noninvasive ventilation studies. One in vitro study, White et al. (2013), was designed to assess the influence of different positions/exhalation leak valves on the ventilator circuit on aerosol deposition in pediatric patients receiving noninvasive ventilation, and one in vitro/in vivo study, Fauroux et al. (2000), was planned to assess differences in aerosol delivery with and without noninvasive ventilation. Nonetheless, there is insufficient objective
information to the guide physician while choosing the best device for aerosol drug delivery in children who receive noninvasive ventilation. It would be difficult to extrapolate from the results of adult noninvasive ventilation aerosol studies and to utilize in the pediatric patient. Children have smaller tidal volumes, higher respiratory rate, lower inspiratory/expiratory ratios, and smaller airways than adults. Earlier studies have recommended that these elements in infants and small children give to lower inhaled drug delivery than in adults (Schüepp KG, Straub D, Möller A, Wildhaber JH, 2004).

The major discovery of the recent study was that the type of nebulizers and masks had an impact on aerosol drug delivery to this simulated passive pediatric lung model receiving noninvasive ventilation.

**Impact of Nebulizer Type**

The vibrating-mesh nebulizer delivered more aerosol drug than the jet nebulizer, in all conditions examined. This study found that VMN is 2-3 fold more efficient than JN. This result agrees with the findings of Galindo-Filho et al. (2015), who evaluated mesh and jet nebulizers during noninvasive ventilation by using radio-aerosol pulmonary index and radio-aerosol mass in pulmonary compartments settings in vivo study. They assess radio-aerosol by using the gamma camera. They found that drug delivery with VMN was more than 2-fold greater than JN in healthy subjects. However, the inhaled mass percent of the JN and the VMN in their research was higher than this study. This variance is predictable due to the population examined in this study (pediatrics population) compared to the adult population in their study. Ari, A., de Andrade, A. D., Sheard, M., AlHamad, B., & Fink, J. B. (2015) reported that the aerosol collection with adult lung model was larger than a pediatric model, regardless of the nebulizer.
device type (JN and MN) (p<0.05). Additionally, aerosol deposition was significantly larger in an adult lung model than the infant lung model used with JN (p=0.001 and p=0.002, respectively) and MN (p=0.001 and p=0.005, respectively).

Impact of Interface Type

The mouthpiece, nasal pillows, nasal mask, oronasal mask, total facemask, and helmet are often utilized with noninvasive ventilation. Although the choice of masks is depended on the pediatric patient tolerance and facial skin breakdown, it is essential to notice that certain interfaces (the total facemask and helmet mask) are not suitable for aerosol drug therapy through noninvasive ventilation because of patient contact to aerosol drug and flow from the noninvasive ventilation (Hess DR, 2005). While aerosolized medications are produced to patients getting noninvasive ventilation, therapist must consider leaks of the aerosol drug into the eyes of the patient (Kelly JT, Asgharian B, Kimbell JS, and Wong B, 2004).

There are limited studies that examine the clinical efficiency of the interfaces on pediatric receiving NIV. In this study, we exam the standard oronasal mask, the oronasal mask with nose cushion, and the nasal mask. These interfaces are used with pediatric patients who receive NIV. Regardless of the nebulizer device type, both oronasal masks were more efficient than the nasal mask by 15–20 fold. The results were expected and depended on the expected nasal deposition of aerosol droplets 2 to 7 µm in size, 40 to 99% of the aerosol inhaled during noninvasive ventilation is similarly to deposit in the nose. (Chen YS, 2003 and Kelly JT, Asgharian B, Kimbell JS, and Wong B, 2004). Aerosol deposition in nasal passages significantly reduces drug delivery to the lung, and could reduce bronchodilator efficacy compared to inhalation with an oronasal.
When the standard oronasal mask is compared to the oronasal mask with nose cushion, this study found that the standard oronasal mask was more efficient than the oronasal mask with nose cushion with either type of nebulizer. Differences in the amount between the standard oronasal mask and the oronasal mask with nose cushion could be the characteristics of the interface. The presence of the nose cushion will disturb the way the aerosol may effect and disturb the deposition of inhaled aerosols drugs in the filter.

**Impact of Delivery Technique**

The delivery of aerosolized medication is affected by the type of aerosol device and masks used during noninvasive ventilation, the place of the leak port, and the location of the aerosol device in the circuit (Chatmongkolchart S, Schettino G, Dillman C, Kacmarek R, and Hess D. 2002, Branconnier M, and Hess D. 2005). Bi-level ventilators consume either a mask or a single limb circuit with a leak port that works similar a passive exhalation port from the patient. The position of the leak port is essential for aerosol therapy during noninvasive ventilation, as it promotes the loss of aerosol to the environment; therefore, regardless of the type of aerosol device used during NIV, putting the interfaces before the leak port increases aerosol delivery during noninvasive ventilation (Michotte and colleagues (2014), Abdelrahim (2010), Branconnier et al (2005), and Dai et al (2014)). Previous studies reported that aerosol deposition during NIV will be influenced by the NIV settings. The aerosol delivery will be decreased when increasing the expiratory pressure, while an increase in aerosol deposition in patients receiving NIV was seen when increasing the inspiratory pressure. Therefore, an aerosol device located between the leak port and facemask could produce up to 25% of the nominal dose to the patient.
operating on high inspiratory and low expiratory pressure settings during NIV (Chatmongkolchart at el. 2002).

Limitations

The results of this study must not be widespread to the varied range of respiratory parameters representing different age ranges of pediatrics because this study used one set of respiratory patterns. While it is well recognized that pediatric patients mostly have highly unpredictable respiratory patterns when awake, which influences deposition, and this is more worsened by their intolerance of the interface. Simulating such variations in respiratory parameter or the failure to tolerate a carefully fitting interface was outside the possibility of this study. Since the study model delivers a very regular flow, volume, and frequency during aerosol treatment, the results of this study could overvalue aerosol drug delivery in vivo. Also, results of aerosol medication using these models has limited success because of less aerosol to airway due to effect of oral cavity.

Clinical Implications

Physicians frequently request the efficiency of nebulizers that are utilized with various masks. In this study, we compared the use of jet nebulizer and mesh nebulizer with three types of masks in pediatrics receiving NIV. The statistics showed that mesh nebulizer was superior to jet nebulizer in positions of aerosol drug delivery, and aerosol deposition taken with the standard oronasal mask was greatest, regardless of the aerosol device examined in this study.
Suggestions for Future Research

Further studies are required in medical situations to control the clinical efficiency of aerosol treatments with higher doses and their effect on a patient’s care, consequences, and source operation. Different breathing patterns must be tested to control how aerosol deposition would be influenced by different diseases and patient situations. In future research, the use of the V-60 NIV is suggested due to the prevalence of the device in acute health care.

Conclusion

Delivery efficiency in a simulated pediatric lung model receiving NIV was influenced by the style of aerosol device and masks used for aerosol therapy. Aerosol drug delivery was greatest with the standard oronasal mask with both jet and mesh nebulizers, while the nasal mask was least effective in these simulated pediatric lung model receiving NIV. Delivery effectiveness of jet nebulizer was less than mesh nebulizer in all conditions examined in this study.
References


Branconnier M, and Hess D: Albuterol delivery during noninvasive ventilation. Respir Care. 2005 ;50:1649–16


Hess DR: Aerosol therapy during noninvasive ventilation or high-flow nasal cannula. Respir Care. 2015;60:880–893.

Iosson N: Images in clinical medicine. Nebulizer-associated


