

**Study Protocol and**  
**Statistical Analysis Plan**

A Prospective Open Randomized Clinical Trial of Non-invasive Ventilation Versus Standard Therapy for Children Hospitalized With an Acute Exacerbation of Asthma

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**A prospective open randomized clinical trial of non-invasive ventilation versus standard therapy for children hospitalized with an acute exacerbation of asthma.**

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## RESEARCH PROTOCOL

### **Hypothesis and aims.**

Acute asthma produces greatly increased work of breathing and increased oxygen requirement secondary to bronchial narrowing and airway obstruction by inflammatory secretions. There is growing evidence that non-invasive ventilation can reverse these processes more efficiently than conventional asthma therapy. Surprisingly, there have not yet been any large scale prospective controlled studies to investigate this hypothesis, (either in adults or children). Consequently, the aim of this study is to determine if the use of non-invasive positive airway pressure, for children admitted to hospital with an acute exacerbation of asthma, reduces their work of breathing, need for adjunctive medications, and shortens the length of hospital stay, compared to current standard therapy.

### **Study background.**

Asthma is a common, chronic disorder of reversible airway obstruction caused by a triad of airway inflammation, bronchial smooth muscle contraction and increased airway secretions [1]. While there have been huge advances in the control of chronic childhood asthma, acute exacerbations remain common, particularly during the viral season. Acute asthma has a low mortality rate but the condition is so common that it imposes a very high health care burden. Studies by our own group [2] and others [3] have shown that asthma exacerbations remain a major cause of emergency room visits and a leading cause of hospitalization in children. The patient burden at Children's Hospital in Vancouver, is similar to published studies showing that asthma accounts for 3% to 7% of all pediatric ED visits with a mortality rate of 2 to 3 per million children in North America [3]. Any therapy that could improve the outcome in acute asthma would have significant medical and economic benefits.

There are two types of non invasive ventilation (NIV).[4] The first is continuous positive airway pressure (CPAP) where the patient breathes against a constant pressure delivered by face mask. The second is BiPAP – here the patient's breathing is assisted by cycling between high and low pressures at a pre-set rate. It is analogous to traditional ventilation but without the need for intubation. After its introduction around 1990, NIV rapidly gained acceptance in the treatment of a wide range of respiratory conditions[5]. Machines are relatively cheap and the non-invasive pressure delivery minimizes side effects compared to traditional ventilators. NIV is now the commonest form of ventilatory support used in intensive care units.

The standard therapy for acute asthma is based on oral or intravenous corticosteroids to control the acute inflammation plus a range of bronchodilators to reverse airway narrowing – the commonest of these is the beta agonist salbutamol. Most children admitted to hospital with acute asthma will improve with this well-established clinical framework [6]. A few children do not respond

However, a minority will not respond adequately to such management and require adjunctive medications, usually requiring admission to the ward, and sometimes to the ICU. Medical treatments commonly used in addition to beta agonists, include intravenous magnesium sulfate, inhaled anticholinergics and aminophylline. The evidence base for the efficacy of such treatments is limited and inconsistent, and adverse side effects are common [7].

There is growing evidence that positive airway pressure delivered by a non-invasive face mask, can reduce airway obstruction and also improve ventilation-perfusion mismatch. The resulting decrease in respiratory work and reduced need for added oxygen, shortens hospital stay and minimizes exposure to multiple medications [8]. In recent years the use of non-invasive positive pressure ventilation for management of a range of acute respiratory pathologies has become increasingly common. Results from studies in this area are encouraging, however most studies to date have been small and retrospective [9]. There is very little prospective controlled research to guide clinical practice concerning non-invasive ventilation in asthma. In view of the limited information available in the published literature, we believe that a prospective controlled trial of the value of BiPAP in acute asthma would provide a valuable evidence base to guide the management of this common clinical problem.

### **Literature Review:**

Although non-invasive ventilation is increasingly used for treatment of asthma in emergency medicine[10], there is surprisingly little relevant research literature. Recent literature reviews [9,11], including a Cochrane review based on only 5 studies[12], all conclude that the therapy is promising but that there is an urgent need for large controlled studies. Meduri, in adults[13] and Williams in children[14] published retrospective reviews of their clinical experience with non-invasive ventilation in acute asthma. Both claimed that non-invasive ventilation (NIV) was at least safe, and likely effective but neither included controls.

From a physiological point of view, there is good theoretical support for the use of NIV in acute asthma. The administration of positive pressure ventilation leads to bronchial distention and enables maintenance of small airway patency. This decreases airway resistance, recruits areas of atelectasis and facilitates clearance of secretions[15].

As noted, there have been very few prospective studies of NIV in the management of acute asthma. The addition of NIV to conventional therapy, in a small prospective adult study, showed significantly shorter ICU and hospital stays in the treatment arm[15]. A prospective randomized crossover study of 20 children with lower airway obstruction[16], reported a significant improvement in respiratory rate and clinical asthma score when receiving non-invasive ventilation, which worsened on conversion to standard medical treatment. A recent prospective randomized controlled pilot study [17] compared NIV to standard management in 20 patients with status asthmaticus. The study identified

significant improvements in respiratory rate and clinical asthma scores in the NIV treatment arm.

## **Research Methods:**

### *Overview of study design:*

The aim of the study is to determine if the use of NIV, for children admitted to hospital with an acute exacerbation of asthma, reduces their work of breathing, need for adjunctive medication, length of hospital stay, and need for intubation and mechanical ventilation. Study design will be prospective, randomized and controlled. The tightly fitting face mask necessary for NIV makes it impossible to make this a blinded study.

The principal enrollment criteria will be children over 2 years of age presenting to the ER with acute asthma. After diagnosis, all children are treated with standard therapy (systemic steroids plus 3 doses of inhaled salbutamol and 1 dose of inhaled ipratropium over a 1 hour period then hourly salbutamol). The principal decision between discharge track and admission track will be made at 2 hours after first steroid dose. Admission criteria are based on sequential PRAM scores.

After initial asthma treatment and observation in the emergency room, to determine which patients can be discharged home, those who need admission will be asked to join the study, then consented and randomized. There will be three treatment groups:

- BiPAP: standard steroid dose, hourly salbutamol and BiPAP at 15/5 cm H<sub>2</sub>O by face mask with rate 10 to 15/min, oxygen as needed.
- CPAP: standard steroid dose, hourly salbutamol and 8 to 10 cm H<sub>2</sub>O constant pressure by face mask, oxygen as needed.
- Conventional therapy: standard steroid dose plus hourly nebulized salbutamol, nebulized ipratropium q 6 hrly, magnesium sulphate 50 mg/kg IV (4 doses q 6 hrly), loading dose of aminophylline 6 mg/kg IV if no progress, oxygen as needed.

All children will be admitted to a small 3 bed respiratory unit. They will be closely monitored and objectively scored every 4 hours using the PRAM asthma clinical severity score (Pediatric Respiratory Assessment Measure)[18]. End points will be: time to reach room air, time to reach PRAM score <3, numbers requiring intubation and mechanical ventilation and medication use. Those children older than 5 or 6 yrs, will also perform lung function tests twice daily. Projected patient enrollment will be at least 30 in each arm. Estimated study duration is 6 months.

### *Inclusion criteria:*

In order to avoid confusion with viral bronchiolitis, the study is open to all children over 24 months old who present to the emergency department diagnosed with an acute asthmatic attack severe enough to require hospital admission.

*Diagnostic criteria:*

The biggest challenge in asthma research is determining an unambiguous clinical definition that allows one coughing/wheezing child to be distinguished from another. Our group has recently published a large study of the best diagnostic indicators in tachypneic children[20]. Based on that work, our diagnosis of asthma will depend on respiratory rate greater than WHO's age-dependent criteria, a history of similar previous episodes and wheezing heard on auscultation by an experienced physician. These criteria provide a diagnostic sensitivity and specificity of 85%[20].

*Exclusion criteria:*

- Clinical suspicion of bacterial pneumonia: focal crackles or bronchial breathing, and/or major chest x-ray findings.
- Impending respiratory failure at presentation requiring direct PICU admission
- Any contraindication to BiPAP use including altered mental status, recent bowel surgery, intractable vomiting, inability to protect airway, pneumothorax.
- Receiving maintenance dose of oral steroid at time of hospital admission
- History of serious unrelated illness such as congenital heart disease or bronchopulmonary dysplasia.

*Measured Outcomes:*

- Length of time to reach a PRAM score of  $\leq 3$
- Time to room air.
- Total medication use per 12 hr period.
- Numbers failing treatment and transferred to ICU.
- Numbers in each group requiring hospital readmission within 48 hours of discharge
- Time to reach FEV1 >80% predicted in those children able to perform PFTs.

*Study summary:*

- Identify patients aged  $\geq 2$  years attending the Emergency Department with a significant acute asthma exacerbation (using criteria above).
- Begin steroids and initial protocolised standard bronchodilator therapy. Observe in ER and score PRAM hourly.
- Research coordinator is informed and provides parents and child with study information to read during the child's period of observation in the ED.
- A decision about study inclusion should be made 2 hours post-steroid administration in children with PRAM of 8 or more.
- Once admission decision has been made, child is eligible for the study. Obtain consent from the parents and assent from child where possible. If the child is too unstable, assent will be explained and collected when the child is capable.

- After consent, participants will be randomized to one of the three treatment arms in blocks of six, using consecutively numbered opaque envelopes stored in the ED.

#### *Management of treatment groups:*

Participants will be randomized into one of three treatment arms – BiPAP, CPAP, conventional therapy. In addition to standard therapy, the three treatments will consist of:

- BiPAP group (Trilogy device) to be started in the ER after randomization, pressures 16/5 cm H<sub>2</sub>O, with rate of 10 to 15 / minute plus hourly salbutamol.
- CPAP group (Trilogy device) to be started in ER after randomization. Starting pressure 8 cm H<sub>2</sub>O, increased to 10 cm H<sub>2</sub>O if no clinical response and hourly salbutamol.
- Conventional therapy, hourly nebulized salbutamol, nebulized ipratropium q 6 hrly, magnesium sulphate 50 mg/kg IV (4 doses q 6 hrly), loading dose of aminophylline 6 mg/kg IV if no progress.

#### General care for all three groups:

All three treatment arms will receive the following standard care:

- Oxygen to keep saturations  $\geq 92\%$  for all three groups.
- Standard course of oral steroid: dexamethasone 0.3mg/kg/dose once daily for 4 consecutive days,
- On-call research coordinator to assess the patients and record data.
- If a patient in any of the treatment groups deteriorates, they will be managed in the usual way with medical review and admission to ICU as required.

#### Criteria for study termination:

- Failure to tolerate BiPAP (persistent agitation and tachycardia, refusal to wear mask) resulting in the need for its discontinuation despite appropriate administration of sedation.
- Signs of impending respiratory failure in either study arm should immediately prompt discussion with the ICU team and discontinuation of study participation

#### Study enrolment:

Parents will be approached while their child is receiving initial asthma therapy in the Emergency Room of the Post Graduate Institute of Paediatric Medical Research in Chandigarh, India. Parents will be approached by one of the two local study coordinators (both are qualified paediatricians), during the child's 2 hour observation period in the Emergency Department. At that time parents will be given the invitation letter, written in local language (Hindi) and the research coordinator will answer any questions they have. If they cannot read, the information will be read to them in a private room. If the child fails to improve and requires hospital admission, consent for study participation will be sought once the decision to admit has been made. This will not delay treatment in any way. Children will only be eligible to enroll in the study whilst they are in the Emergency

department. Previously admitted ward patients are not eligible. All study information and consent documents are attached in section 9.

#### Randomization:

Once consent has been obtained, treatment selection will be decided using consecutively numbered envelopes randomized in groups of six. These envelopes will be stored in a box in the Emergency Department. Once consent has been obtained, an envelope will be selected in numerical sequence to determine the child's allocated treatment group. The envelope will then be stapled to the consent form to enable the investigator to know each patient's subject study number.

#### Safety Monitoring:

Although there are decades of experience confirming the safety of NIV in children, this study represents a significant change to well-established conventional therapy so extra levels of observation of the treatment groups have been included in the study design:

- The study hospital has agreed to set aside a 3 bed ward dedicated to the duration of the study. It will be staffed by 4 nurses and 2 qualified pediatricians who will provide continuous 24 hr a day coverage for the study participants. Staff salaries for the study will be covered by study funds.
- Since this is an open study, we plan to perform an interim review of adverse events after 10 patients have been enrolled in each treatment arm. The clinical reviewer will be Dr Skippen and the statistical reviewer will be Boris Kuzeljevic - both from Children's Hospital, Vancouver.
- The head of ER at PGIMER, Chandigarh, has agreed to be the local external monitor. The research coordinators will be the most likely people to pick up adverse events. All RCs will be trained in the study protocol, including the reporting process in the event of an adverse event. Nursing staff are also aware of the need for extra monitoring and the need to report potential problems.

#### Sample size calculation.

In order to have an impact on common practice, we would define a significant treatment effect as a 25% reduction in time to PRAM of 3. In order to demonstrate this effect with a power of 80% and a 5% chance of a type 1 error, we need an estimate of mean time to PRAM of 3 plus standard deviation from previous published work. Unfortunately, there is very little published information to act as a guide. The only published pediatric study that provides relevant data is a pilot study by Basnet et al.[17] Using only 10 patients in each arm, they showed BiPAP reduced time in ICU (48+/- 16 hrs vs. 36+/-14 hrs). They used a clinical score to guide management but it was different to the PRAM. If we take the higher of these standard deviations as a rough guide to the average ICU admission time and combine it with a power of 80% and type 1 error risk of 5%, we will need 26 patients in each arm to detect a 25% reduction in time to PRAM of 3. It must be emphasized that the shortage of relevant literature makes this only a rough estimate.



Statistical analysis.

Outcomes in the two treatment arms of the study (BiPAP and CPAP), will be compared to those in the control group (conventional acute paediatric asthma treatment). The principal end points will be analysed in the following ways:

1. Changes in asthma score over time.

The PRAM respiratory distress score is based on objective and subjective observations so the final values are non-parametric. Multiple comparisons over time, between treatment group and control, will be made with the Kruskal-Wallis test with Dunn's post-hoc test.

2. Time to reach asthma score <3.

The value will be measured in hours after starting treatment so the values will be parametric. Comparison between treatment and control values will be made using t test.

3. Total number of pharmacological treatments per day.

The total number of drug treatments will be calculated for each 12 hour period. These are parametric values. Comparisons between control and treated group of repeat measures over time, will be made by analysis of variance with Tukey's post-hoc test.

4. Lung function tests.

Standard spirometry and flow-volume loops will be performed with portable equipment in children old enough to cooperate. The main measured end point for analysis will be the change in Forced Expiratory Volume in 1 second (FEV1) over time. These values are parametric. Multiple comparisons between control and treated groups will be made by analysis of variance with Tukey's post-hoc test.

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## Appendix.

PRAM score (Ducharme, 2008)

Signs	0	1	2	3
<b>Suprasternal retractions</b>	Absent	Absent	Present	Present
<b>Scalene contractions</b>	Absent	Absent	Present	Present
<b>Air entry</b>	Absent	Decreased at bases	Widespread decrease	Widespread decrease
<b>Wheezing</b>	Absent	Expiratory only	Inspiratory and expiratory	Audible
<b>O2 saturation in room air</b>	>95	92-94%	90-92%	<92

Severity categories:

Mild: 0 – 3

Moderate 4 – 7

Severe: ≥ 8