Title: Continuous Positive Airway Pressure reduces Mechanical Ventilation in infants with Meconium Aspiration Syndrome: RCT

Subtitle: nCPAP reduces ventilation in MAS

Authors

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**Research Hypothesis**

In newborns with Meconium Aspiration Syndrome (MAS) [Population], nasal CPAP [Intervention] is more effective than standard care (hood oxygen 5 to 10 liter/min) [Control] in reducing the subsequent need for mechanical ventilation [Outcome] in the first 7 days of life [Time]

**Research Question**

Is nasal CPAP more effective than standard care (hood oxygen 5 to 10 liter/min) in reducing the subsequent need for mechanical ventilation in newborns with MAS

**Type of Study:** Stratified, Open label, Randomized Controlled Trial

**Place of Study:** Fernandez Hospital, Durushewar Hospital and Vijay Marie Hospitals.
Hyderabad, India

**Patients and methods**

**Inclusion Criteria**

- All infants with gestation >35 weeks and birth weight >2000grams and
- Admitted to the neonatal intensive care unit (NICU) in the first 24 hours of birth and
- Born through MSAF and had respiratory distress (defined as Downe score >4 and SpO₂<90% on room air) and
- Chest ray at admission was suggestive of MAS (hyper-inflated lung fields with diffuse non-homogenous opacity or reticulonodular pattern or low volume lungs with reticulogranularity and air-bronchograms).
Exclusion Criteria

- Intubation at admission
- Severe asphyxia (5-minute Apgar < 3 and cord pH < 7.00)
- Pneumothorax/air leak (visible on the admission chest radiograph), and
- Major malformations

Methods

All infants would be assessed for eligibility at admission to the NICU. Gestation would be assessed from the mother LMP or from the first trimester ultrasound scan. Signed informed consent would be obtained from the families of eligible infants within an hour of admission. Chest x-ray and arterial blood gas would be done in all infants pre-randomization. Eligible neonates would be randomized (stratified for center) to either bubble NCPAP or standard care, using a 1:1 ratio, in randomly permuted blocks of two or four. Random numbers would be generated by a web-based computer program (researchrandomizer.org). Individual group assignments would be placed in a serially numbered, opaque sealed envelope that would be opened only after obtaining consent from the parents. Patient recruitment would start after obtaining ethics approval from the institutional review board (IRB) and after registration with clinical trial registry, India.

Infants randomized to NCPAP group would be started on a bubble CPAP generator (Fisher and Paykel Healthcare, Inc.) using short bi-nasal prongs (Hudson Respiratory Care Inc, Temecula, California or Fisher and Paykel Healthcare). The starting NCPAP pressure will be 5 cm of water. NCPAP pressure and FiO2 would be adjusted to maintain
target saturations between 90 to 95%. The neonate would be weaned from NCPAP, when
the SpO2 is consistently > 90% on FiO2 less than 0.25 and respiratory distress is passive
(respiratory rate < 60/minute, no or mild retractions and no grunting). After weaning
from NCPAP, oxygen if needed will be administered either with a hood or with bi-nasal
oxygen prongs. NCPAP failure is defined as SpO2<90% on maximum NCPAP pressure
of 6cms of H2O and FiO2 of 1.0. All infants with NCPAP failure will be intubated and
placed on MV.

Infants randomized to the standard care group would be started on hood oxygen,
administered at 5 to 10 liters per min. Infants in whom saturations are below 90% for
more than 15 minutes on FiO2<1.0 would be rescued either with NCPAP or MV but at the
discretion of the treating team. Those rescued with NCPAP would qualify for mechanical
ventilated if SpO2< 90% consistently on a maximum NCPAP pressure of 6cms of H2O
and FiO2 of 1.0. Post extubation or after weaning from NCPAP, oxygen if needed will be
administered either with a hood or with bi-nasal oxygen prongs.

All enrolled infants will be actively assessed for any cardio respiratory dysfunction using
vital signs (heart rate, blood pressure, saturations and urine output), Downe score and
echocardiography. Management of co-morbid conditions such as pulmonary
hypertension, shock, seizures, renal dysfunction, fluid, electrolyte, acid and base
imbalances, use of high frequency oscillation (HFO) or sildenafil will be as per the
existing unit protocols. Surfactant will be given to infants requiring mechanical
ventilation (FiO2 0.50 or more for > 2hours) and in those with low volume lungs on the
chest x-ray (less than 7 posterior intercostal spaces). All the relevant perinatal data and
neonatal data till discharge or death would be collected prospectively in special forms designed for this trial.

Diagnosis of pulmonary hypertension (PPHN) will be based on clinical and echocardiographic criteria. Those diagnosed with PPHN will be managed with inotropes, respiratory support (NCPAP or MV) and or sildenafil. Inhaled nitric oxide will not be used. Shock will be defined as presence of clinical features and need for dopamine or dobutamine at a dose exceeding 10 microgram/kg/min.

**Primary Outcomes**

- Need for MV in the first 7 days of life

**Secondary Outcomes**

- Death
- Pneumothorax
- Need for surfactant
- Pulmonary hypertension
- Culture positive sepsis (onset of sepsis >72 hours of birth)
- Oxygen days and
- Duration of hospitalization.

**Ethical issues**

CPAP is already an established method of treatment modality for neonates with respiratory distress. Data Safety Monitoring (DSM) will also be formed before starting of the trial.
Sample size

Based on the available evidence, we assumed 30% incidence of mechanical ventilation in the standard care group and for an absolute reduction of 20% using NCPAP (based on a pilot study), the sample needed to recruit was 66 infants in each group with an alpha error of 0.5 and a power of 80%.

Statistics

Comparison between the study groups for discrete variables will be done with the Chi-square or Fisher’s exact test and continuous variables will be compared by Student’s t test or nonparametric tests as appropriate. p value <0.05 would be considered significant. Intention to treat analysis will be used and the statistician will be masked to the group allocation.


**Project title:** Randomized Control trial of Continuous positive airway pressure versus Standard care in neonates with moderate meconium aspiration syndrome in reducing the need for invasive ventilation

**Investigator:**

Dr Aakash pandita
Fernandez Hospital, Hyderabad

**i) Aims and methods of research:**

Meconium aspiration syndrome (MAS) is a problem related to aspiration of meconium into the lungs of the neonate before, during or immediately after birth. Babies with MAS have breathing difficulty and are traditionally treated with either oxygen and in severe cases with mechanical ventilation. Approximately 30 to 50% of infants diagnosed with MAS will require mechanical ventilation. The optimum modes of ventilation for MAS are not known. CPAP is a gentler and non invasive type of ventilation, not well tested in these infants. This modality of treatment is the first choice for other neonates with respiratory distress syndrome or congenital pneumonia. There is a strong physiological reason for this therapy to work in MAS. If it works it could decrease the need for oxygen days, need for ventilation and also duration of hospitalization. As there are no previous controlled trials of CPAP in this group of infants there is a need to test this modality in infants with MAS.

If you agree to participate in the study your baby will be randomized to receive the CPAP or hood Oxygen. And rest of the treatment will be according to the unit’s protocol.
ii) **Expected duration of the subject participation:**

Your baby will be enrolled in the study till the disease is under control and baby gets discharged.

iii) **The benefits that would be expected from the outcome of research to the subject or the others:**

The information from this study will help us to know the best mode of therapy for MAS. Your baby may not need ventilation if randomized in CPAP group or may not even require CPAP if randomized in Hood Oxygen group.

iv) **Any risks associated to the subject with the study:**

CPAP and Hood Oxygen both are accepted modality of treatment for MAS. Your baby will be monitored for the side effects and managed accordingly.

v) **Maintenance of confidentiality of records:**

All the information that you provide during the study will be kept confidential and utilized only for the study purpose.

vi) **Freedom of individual to participate and to withdraw from research at any time without penalty or loss of benefits to which the subject would otherwise be entitled:**

You are free not to participate in the study or to withdraw your baby from the study at any time. If you choose not to participate or withdraw your child from the study, your baby will receive the
usual care. You have the right to refuse the individual procedures. If you have any further questions, please contact one of the investigator or clinical team.

**Contacts:**

In the event that at any time during the course of the study you feel that you have not been adequately informed as to the risks, benefits, alternative procedures, or your rights as a parent of the study subject or feel under duress to continue against your wishes you can contact:

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Consent form

I parent/guardian of baby of __________________________ have been fully informed about the nature and purpose of the interventions involved with its possible benefits, risks and consequences. I hereby agree to allow my baby to participate in this intervention.

I furthermore recognize to fact that I am free to withdraw or discontinue his/her participation in this intervention at any time without prejudice to his/her Care.

Name

Signature: Date

OR verbal Consent given: Yes / no

Witness (or legal Representative):

Signature