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Title: Using CO2 Detector with Mask Positive Pressure Ventilation in the Delivery Room: A Randomized Trial

A. Study Purpose and Rationale:

Purpose: To determine whether using a CO2 detector (Pedi-Cap) with positive pressure ventilation during initial neonatal resuscitation provides more efficient ventilatory support and helps achieve outcome of increasing heart rate faster than PPV without a CO2 detector.

Assuring proper ventilation is a crucial aspect of ensuring a successful transition from fetal to neonatal life. Preterm infants are at highest risk of requiring interventions to assist ventilation and highest risk of being injured by such interventions. Animal studies have shown that even brief periods of ventilation after birth can be injurious to the premature lung[1, 2]. Kaufman et al showed that tidal volumes during PPV breaths are significantly higher than tidal volumes during spontaneous CPAP supported breaths or during spontaneous breathing breaths[3]. Assisting ventilation in the least injurious way is the goal of neonatal resuscitation, but the details of how to best achieve this goal are still not all clear. The current neonatal resuscitation guidelines recommend initiation of positive pressure ventilation (PPV) when the infant's heart rate (HR) is less than 100 beats per minute or the infant has inadequate spontaneous respirations or apnea. Many places, including our institution most commonly start with bag-mask ventilation and approximately 10% of all births require bag-mask ventilation[4]. PPV is critical to resuscitation, but evaluating effectiveness of PPV in the moment is difficult.

Providers typically watch for chest rise to determine effectiveness of PPV, but it has been shown that it is hard to judge quality of PPV by chest rise alone. Tracy et al used chest rise to guide ventilating pressure and found that 26% of infants had admission pCO2 values <30mmHg [5]. Brugada et al found intraobserver and interobserver assessment of chest rise has high variability during simulated resuscitation[6]. Poulton et al demonstrated that providers' assessements of chest rise correlated poorly with measured expiratory tidal volume[7]. Another issue with providing high quality PPV is obstructed breaths, which were idenitfied via respiratory function monitoring by Schmolzer et al and shown to be a frequent occurance that is difficult to detect without CO2 detectors[8].

In the NICU, end tidal CO2 monitoring has increased and improved provider's ability to provide more precise – adequate, but gentle – ventilation to neonates. However the use of CO2 confirmation and monitoring in the delivery room is less studied. A simulation study showed that CO2 detectors improved PPV during the first minute and improved time to administration of first appropriate breaths[9]. Studies in live neonates have been inconclusive regarding benefit of CO2 feedback during bag-mask resuscitation. Leone et al and Finer et al described recognition of airway obstruction via Pedicap during PPV[10,11]. Kong et al failed to show improvement in admission pCO2 values for babies who had received PPV with CO2 monitoring, but Kang et al showed that the difference in expired CO2 levels may only be detectable during the first 10 minutes and have equalized by 10 minutes[12,13]. Schmolzer et al showed that using a respiratory function monitor during PPV was associated with significantly less mask leak, more mask adjustments, a lower rate of excessive tidal volumes, and more neonates on CPAP vs intubated on admission[8]. No study to date has shown improvement in efficacy of PPV when CO2 detector is used using outcomes such as HR stabilization, intubation, or other pulmonary complications.

Our unit primarily uses bag-mask ventilation strategies to provide PPV during neonatal resuscitation and does not routinely use CO2 monitoring while providing PPV. We have a large volume of preterm deliveries and have recently installed the BedMaster data collection system in our transitional nursery, which continuously streams physiologic data such as heart rate, oxygen saturation, and respiratory rate into a database. This combined with an in person observer will allow accurate recording of PPV administration and it's effect on vital signs, including HR. We hypothesize that using PPV with CO2 monitoring will reduce the time from initiation of PPV to time when heart rate is greater than 100 and support the use of CO2 detectors to improve PPV.

B. Study Design and Statistical Analysis:

The study is a prospective randomized controlled study to assess whether using a CO2 detector with PPV during neonatal resuscitation improves outcomes. The study will combine live, timed observations during the first 30 minutes of life, BedMaster data, and the medical record to determine outcomes (See Study Procedure).

Randomization: Just prior to birth, researcher will open opaque envelope that will reveal randomization to use of Pedi-cap CO2 detector or standard of care without CO2 detector. The bag and mask setup for the study will include CO2 detector (Pedi-cap) in both arms to control for any effect of the presence of the device, but in the control group, the output will be concealed.

Primary outcome is time from initiation of PPV to time HR greater than 100. Secondary outcomes will include time to HR over 120, respiratory support on admission to NICU (CPAP, none, intubation), need for intubation and mechanical ventilation, time on ventilator, time to SpO2 greater than 90%, and need for supplemental oxygen at 36 weeks gestational age.

Power analysis and statistics:

Based on a prior study by Yam et al of preterm infants receiving PPV, where median time to HR over 100 was 73s and interquartile range was 24-165 seconds[14], this study will require 100 subjects (50 in each arm) to detect a reduction of approximately 20% with significance value (α) of 0.05 and power (β) of 0.8. We plan to enroll this number of babies in the study.
Statistical analysis will consist of T-test on group means for continuous variables including primary outcome. Chi square test of proportions will be run for categorical variables. Additionally, baseline and demographic data (See below) will be recorded for each infant and logistic regression will be performed to evaluate for confounding.

C. Study Procedures:

Basic procedures: 1. Eligible subject identified in Eclipsys 2. Mother approached by member of research team for explanation of study and informed consent (after primary provider has obtained patient's permission to speak with researcher). 3. Randomization to CO2 detector or control. 4. Patient is born and resuscitated as per hospital standards while data is collected.

Babies will be placed on resuscitation bed and treated as per hospital standards. No additional interventions or pain are anticipated.
Data that will be extracted from Medical Record include:

-Resuscitation interventions provided including: chest compressions, epinephrine, intubation.

-Other interventions during the first 3 days of life: use of CPAP, use of mechanical ventilation and settings, surfactant use.

-Outcomes: pneumothorax and IVH.

-Demographic and background data: birth weight, gestational age (best obstetric estimate) sex, multiple gestation, maternal anesthesia, reason for delivery, delivery method, exposure to antenatal steroids, exposure to antenatal magnesium sulfate, APGAR scores.

-Data from BedMaster include:
The following items will be evaluated over the first 30 minutes of life:

- Heart Rate: duration <100 bpm, time HR over 100 bpm, and time stable above 120bpm.
- SpO2: time to value 90%
- RR: incidence of apnea (>10 seconds), longest duration of apnea

- PPV time started, duration, starting PIP, highest PIP, average PIP, average PEEP (these parameters are not currently recorded by Bed Master but may soon be added).

-*Data to be recorded/measured by dedicated observer*: time of birth, time of cord clamping, time reaching resuscitation bed, time CPAP started, time PPV started, duration of PPV, PPV device used, time HR is available by ECG, time HR is available by SpO2, time HR is above 100, use and time of intubation.

Duration of data collection for study is estimated to take about 1.5 years to enroll sufficient number of subjects. Each subject's participation will last until corrected gestational age of 36 weeks (1-4 months).

D. Study Drugs: N/A

E. Medical Devices: Pedi-cap (CO2 detector) will be used in this trial. The device is already a standard part of practice for intubation and mechanical ventilation and is commercially available. It's use for detecting obstructed breaths with mask PPV have been published in the past[5,6]. This study aims to determine the usefulness of the device for mask PPV in the delivery room.

F. Study Questionnaires: None

G. Study Subjects:
Inclusion criteria: Born at 23- 32 weeks gestational age at a time when dedicated observer is available. Patient must be resuscitated in the TN and must require PPV during resuscitation.

Exclusion criteria: Congenital diaphragmatic hernia, known anatomical lung abnormality, congenital heart disease, does not receive PPV during resuscitation.

H. Recruitment of Subjects:
Antenatal consent will be obtained from mothers admitted to the Labor and Delivery Unit who are at $\leq$ 32 weeks gestation as identified in Eclipsys. A member of the study team will approach mothers on admission to obtain informed consent after mother's primary physician or neonatologist providing perinatal consult has verified mother is willing to discuss a study.

I. Confidentiality of Study Data:
Data will be collected and stored using a REDCap database that will be created for the study. Only authorized members of the study team will have access to the password protected database. Data will be coded for any export out of the REDCap database and the code will be kept in REDCap.

J. Privacy Protections:
Subject privacy will be protected and data will be kept private as above.

K. Potential Risks:
There is a potential risk of loss of confidentiality.

L. Data and Safety Monitoring:
Will monitor data monthly to ensure no significant differences are occurring between the groups that could suggest CO2 detectors are significantly helpful or harmful.

M. Potential Benefits:
There may or may not be direct benefit to study participants, but that benefit is likely small. There may be future societal benefits of a better method for providing PPV and improvement in care to help decrease lung injury.

N. Alternatives:
Parents may choose not to allow their infants' to be included in the study. Their infants will be treated with standard of care bag and mask without Pedi-Cap (CO2 detector).

O. Compensation to Subjects: none

P. Research at External Sites:
-Not applicable. All data will be collected at MSCHONY.

References:

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