

Research Protocol

The research protocol is the detailed written plan of the study. Writing the protocol forces the investigator to organize, clarify, and refine all the elements of the study. Therefore, a protocol is necessary for all research studies, including those that are unfunded, or are as simple as a chart review. The protocol describes the background, research question, hypothesis, design, methodology, procedures, statistical considerations, and organization of a research study. The important sections of a research protocol are described below.

1. Study Team

Andrea Lampland MD: principal investigator, recruitment of patients, oversight of study execution, data analysis, presentation of data, manuscript composition

Mark Mammel MD: co-investigator, recruitment of patients, oversight of study execution, data analysis, presentation of data, manuscript composition

Brenda Plumm RCP: study coordinator, identification of eligible patients, study execution, data compilation

Pat Meyers RCP: research assistant, identification of eligible patients, study execution

Cathy Worwa RCP: research assistant, identification of eligible patients, study execution

2. Project Title

Observational crossover study comparing oxygenation and ventilation using SiPAP versus CPAP to treat respiratory distress in low birth weight infants.

3. Introduction

Background/Significance

In the face of exogenous surfactant and use of antenatal steroids, respiratory distress syndrome (RDS) remains a leading cause of morbidity and mortality in premature infants (1). RDS is the result of a series of complex, interrelated events, including atelectasis, ventilation-perfusion mismatching, and lung inflammation/injury (2). The cascade of events which typifies RDS and its long-term counterpart, chronic lung disease (CLD), is rooted in the intrinsic deficits of the premature lung as well as exacerbated by mechanical ventilation, a mainstay of therapy. For this reason, scientists and clinicians alike continue to search for treatment modalities that will not only treat RDS but also decrease the incidence of chronic lung disease. The use of non-invasive ventilatory strategies, such as nasal continuous positive airway pressure (NCPAP), in the treatment of RDS are thought to provide constant positive distending pressure while minimizing lung inflammation and injury associated with mechanical ventilation (3). Avoidance of intubation and increased use of NCPAP to treat respiratory distress syndrome has been shown to decrease the incidence of chronic lung disease (4,5). In those babies that require intubation and mechanical ventilation, use of NCPAP at the time of extubation has been shown to decrease extubation failure (6).

Investigation is ongoing into the various forms of non-invasive ventilation available to treat respiratory distress in premature infants. Recently, studies have documented that the use of non-invasive nasal intermittent mechanical ventilation (NIPPV), with short inspiratory times and

adequate ventilation rates, can adequately treat hypoventilation, apnea of prematurity, and decrease extubation failure when compared to the use of CPAP (7). This being said, only a select few ventilators can provide synchronized NIPPV and our current ventilators used in the Children's Hospitals and Clinics – Minnesota NICU do not provide this mode of non-invasive ventilation. Our respiratory therapy department, however, has recently acquired the Viasys CPAP delivery system that can provide both conventional nasal CPAP, at a constant pressure delivery, as well as SiPAP, a newer bi-level pressure delivery system. Unlike the constant airway pressure delivered by CPAP, SiPAP systems cycle the positive airway pressure between two levels and allow patients to breathe throughout the respiratory cycle, with the potential to improve both oxygenation and ventilation during this cycling of pressures.

There has been only one study to date looking at the ability of SiPAP to improve ventilation and oxygenation in the premature infant as compared to the standard use of nasal CPAP (8). Standard nasal CPAP delivers a constant distending pressure to promote oxygenation and recruitment of the lung. With this, it has little effect on ventilation, as there are no mechanical changes in pressure delivery to promote movement of a tidal volume of air. SiPAP has the potential to improve both ventilation and oxygenation, as it changes the mean airway pressure delivery over time to promote tidal volume movement (ventilation) as well as recruitment of atelectatic lung tissue (oxygenation).

This study will provide new findings regarding the oxygenation and ventilatory capacity of SiPAP in the low birth weight population. The ability to use SiPAP as a noninvasive ventilatory tool in the LBW population would have significant clinical impact because this population is highly prone to requiring intubation and invasive mechanical ventilation if failing conventional nasal CPAP due to suboptimal ventilation and persistent hypercarbia. Similarly, it has the potential to extend information already demonstrated in the NIPPV literature showing that a noninvasive ventilatory strategy can often times keep these low birth weight infants from experiencing the deleterious effects of intubation and mechanical ventilation.

The results of this study will be synthesized into a manuscript and submitted for publication at a prominent pediatric journal, with possibilities including the Journal of Pediatrics or Critical Care Medicine. The results will also be submitted for presentation at the Western Society for Pediatric Research and the Pediatric Academic Society/Society for Pediatric Research conferences. Lastly, the results of our study have the potential for impacting our respiratory care strategies in the NICU as currently, without the ability to provide NIPPV, we have no noninvasive ventilatory strategy to avoid intubation and mechanical ventilation in the LBW infants that are failing conventional CPAP due to inadequate ventilation.

Research Question

In low birth weight infants with respiratory distress, what are the effects on oxygenation and ventilation when using SiPAP versus CPAP?

4. Study Design and Methodology

Hypothesis

LBW infants will achieve the same levels of oxygenation and improved ventilation when treated with SiPAP versus CPAP

Overview/Scope

Study Design

Non-blinded, randomized crossover study.

****Crossover study design was chosen as using the patient as his/her own control has the potential to amplify differences while using a smaller sample and has the potential to minimize intra-patient variability that cannot be adequately controlled for within the study design.**

Time Frame/Duration

After parental consent is obtained, the patients will be randomized by sealed-envelope shuffle to a starting mode of CPAP or SiPAP. The patients will then enter the 4-hour study consisting of one-hour blocks alternating between CPAP and SiPAP.

Analysis

Sample Size

As this is an observational crossover study, sample size has been chosen from review of our NICU data, current literature relevant to the topic as well as review of similarly structured crossover trials. Justification of sample size: We would like to see a change in pCO₂ of >5 torr between the two intervention groups. Estimates SD of the means is 10. Using this information, 20 pairs would show a difference of 6.44 torr at 80% power. Therefore a sample size of 20 has been chosen.

Analytic Approach

Physiologic data (HR, RR, BP, transcutaneous CO₂, O₂ saturation, FiO₂ requirement, apneic/bradycardic events) as well as 3-channel pneumogram results of central apnea will be analyzed using an unpaired t-test adjusted for carry-over effects in crossover studies. These statistical analyses have previously been used and validated in published manuscripts of crossover type studies (9). P-values of <0.05 will be considered statistically significant.

5. Subjects

Subjects

20 low birth weight infants who are inpatient in the NICU at Children's Hospitals and Clinics – St. Paul and being treated with CPAP.

Recruitment

Patients will be recruited from the Children's Hospitals and Clinics – St. Paul NICU daily census.

Enrollment

Eligibility will initially be determined by birth weight noted on the NICU census. If a patient's birth weight is <2500 grams, then further review of the medical chart will ensue to see if all inclusion criteria are met/exclusion criteria are not met. Once the patient is deemed a potential study candidate, an investigator will approach the parent(s) regarding study enrollment and will obtain informed consent.

Inclusion Criteria

1. LBW infant (birth weight <2500 grams)
2. Currently on nasal CPAP
3. Use of nasal CPAP for >24 hours prior to study initiation
4. If history of intubation with mechanical ventilation, patient will be extubated >24 hours prior to study initiation
5. FiO₂ requirement of 25-50%

Exclusion Criteria

1. FiO₂ requirement >0.5
2. Congenital defects/deformities of the head, pulmonary or cardiovascular systems
3. Chromosomal abnormalities/genetic syndromes
4. Active medical treatment for symptomatic PDA
5. Active medical treatment for culture proven sepsis
6. Within 24 hours of invasive surgical procedure

6. Study Procedures

Data Requirements

After parental consent is obtained, the patients will be randomized by sealed-envelope shuffle to a starting mode of CPAP or SiPAP. The infant hospital chart will be reviewed for prenatal history and current medical history at the time of enrollment. The patients will then enter the 4-hour study consisting of one-hour blocks alternating between CPAP and SiPAP.

Baseline vital signs will be obtained prior to starting the study. A transcutaneous CO₂ monitor as well as pneumogram impedance band will be placed on the trunk for continuous respiratory data acquisition. Physiologic data will be obtained from continuous bedside cardiorespiratory and pulse oximetry monitors used routinely on all patients in the NICU. A 3-channel pneumogram (heart rate, oximetry, thoracic impedance) will be performed throughout the study to quantify central apneic events. Supplemental oxygen will be provided to attain a goal oxygen saturation of 88-90%, within the standard NICU guidelines.

Visit Schedule

N/A

Drug/Device, Handling, Storage (If Applicable)

N/A

Follow-Up

The study will conclude after the 4-hour study block. No long-term follow-up will be necessary after the study is completed.

Patient Withdrawal, Completion, Death

If a patient withdraws or dies prior to study completion, the patient's data will be confidentially destroyed and not be included in the final data analysis.

7. Risks/Benefits

Potential Risks

Transcutaneous CO₂ monitoring is non-invasive, however, as it does come in contact with the skin and therefore can cause local irritation to the skin where it is applied. Medical record data will be collected and presents the risk of breach of confidentiality.

Methods to Minimize Risks

Data collected will be maintained in a password-protected database. All paper copies will be stored in a locked file cabinet in the Infant Diagnostic & Research Center, Children's Hospitals and Clinics – St. Paul. All patients will be coded at the time of study entry and data will be collected under that code and separated from client name.

Due to the short duration of the study, it is unlikely that the transcutaneous CO₂ monitor will cause any skin irritation, however, if any is noted, the monitor will be removed and replaced immediately. The study will cause minimal disruption of routine care as the patients will already be on CPAP prior to study entry and the changes from CPAP to SiPAP during the study only require changing the settings on the CPAP machine (no changing of equipment on the infant). All other routine NICU care as prescribed by the NICU team will continue during the study period. A member of our research team will be present during the entire study; therefore, it will not require any work by the physicians, nurses or respiratory therapy personnel.

Potential Benefits

There is clearly documented benefit to patients enrolled in clinical studies as compared to non-study patients, however, besides this general benefit, there are no specific benefits to the patients in this study. The results of the study have the potential for benefiting the science of neonatal respiratory therapies as currently, without the ability to provide NIPPV, we have no noninvasive ventilatory strategy to avoid intubation and mechanical ventilation in the LBW infants that are failing conventional CPAP due to inadequate oxygenation or ventilation.

Adverse Events for which study will be terminated

1. Increase in baseline supplemental oxygen requirement of >0.30.
2. New onset of severe (needing vigorous stimulation) or multiple prolonged (>5/hour) apneic and bradycardic episodes.
3. NICU care team's assessment of clinical deterioration prompting early termination of study.

8. Administrative Procedures

Patient Confidentiality

All patients will be assigned a randomly generated code at the time of study entry and all data will be collected under that code and separated continuously from client name.

Data Management

Data collected will be maintained in a password-protected database on a Children's IDRC computer. All paper copies will be stored in a locked file cabinet in the IDRC, Children's Hospitals and Clinics – St. Paul. The results of this study will be synthesized into a manuscript and submitted for publication at a prominent pediatric journal, with possibilities including the Journal of Pediatrics, Pediatrics, or Critical Care Medicine. The results will also be submitted for oral presentations at the Western Society for Pediatric Research and the Pediatric Academic Society/Society for Pediatric Research conferences. Data will be maintained for one year in a locked file cabinet in the IRDC, after which time, the data will be destroyed.

9. References

1. Stevens, T. P., M. Blennow, and R. F. Soll. Early surfactant administration with brief ventilation vs. selective surfactant and continued mechanical ventilation for preterm infants with or at risk for respiratory distress syndrome. Cochrane Database Syst Rev (3) 2004; CD003063.
2. A. Fanaroff and J. Martin. Neonatal-Perinatal Medicine, 7th ed. 2001. Mosby-Year Book, Inc. St. Louis, MO. Ch. 42, pg.1003.
3. Jobe AH, Kramer BW, Moss TJ, et al. Decreased indicators of lung injury with continuous positive expiratory pressure in preterm lambs. Pediatric Res 2002; 52:387-392.

4. Linder W, Vossbeck S, Hummler H, Pohlandt F. Delivery room management of extremely low birth weight infants: spontaneous breathing or intubation? *Pediatrics* 1999; 103:961-967.
5. Gittermann GK, Fusch C, Gittermann AR, et al. Early nasal continuous positive airway pressure treatment reduces the need for intubation in very low birth weight infants. *Eur J Pediatr* 1997; 156:384-388.
6. Davis PG, Henderson-Smart DJ. Nasal continuous positive airway pressure immediately after extubation for preventing morbidity in preterm infants. *Cochrane Database Syst Rev* 2003; 2:CD000143.
7. Davis PG, Lemyre B, de Paoli AG. Nasal intermittent positive pressure ventilation (NIPPV) versus nasal continuous positive airway pressure (NCPAP) for preterm neonates after extubation. *Cochrane Database Syst Rev* 2001;3:CD003212.
8. Migliori C, Motta M, Angeli A, et al. Nasal bilevel vs. continuous positive airway pressure in preterm infants. *Pediatr Pulmonol* 2005; 40:426-430.
9. Lampland AL, Plumm B, Meyers P, Worwa C, and Mammel MC. Observational study of humidified high-flow nasal cannula compared with nasal continuous positive airway pressure. *Journal of Pediatrics* 2009; 154(2): 177-182.

10. Appendix

Include all additional, relative materials in the Appendix. This might include the following: Data Collection Forms (DCFs), including abstract sheets, questionnaires, interview questions, phone screenings, solicitation letters, surveys, etc. If you are using an existing instrument, you need to document the validity of that instrument.

Table 1. Study Flow Sheet

Table 2. Data collection sheet

Table 1. Study Flow Sheet of randomized, observational crossover study of CPAP versus SiPAP in LBW infants

Entry Criteria:

LBW infant (birth weight <2500 grams)

Currently on nasal CPAP

Use of nasal CPAP for >24 hours prior to study initiation

If history of intubation with mechanical ventilation, patient will be extubated >24 hours prior to study initiation

FiO₂ requirement of 25-50%

Exclusion criteria:

FiO₂ requirement >0.5

Congenital defects/deformities of the pulmonary or cardiovascular systems

Active treatment for symptomatic PDA

Active treatment for culture proven sepsis

Within 24 hours of invasive surgical procedure

Study Flow:

1. Informed consent of parents
2. Chart review with pre-study data obtained
3. Pneumogram set-up and started
4. Transcutaneous CO₂ monitor placed on patient
5. Baseline physiologic data obtained
6. CPAP at 6cmH₂O x 1hr
7. TcCO₂ and physiologic data obtained at 10min intervals through 60min block
8. SiPAP at Rate=20, I_{time}=1sec, PIP and PEEP adjusted to target MAP delivered on CPAP 6cm H₂O (with minimum PEEP of 4 cm H₂O) x 1hr
9. TcCO₂ and physiologic data obtained at 10min intervals through 60min block
10. CPAP at 6cmH₂O x 1hr
11. TcCO₂ and physiologic data obtained at 10min intervals through 60min block
12. SiPAP at Rate=20, I_{time}=1sec, PIP and PEEP adjusted to target MAP delivered on CPAP 6cm H₂O (with minimum PEEP of 4 cm H₂O) x 1hr
13. TcCO₂ and physiologic data obtained at 10min intervals through 60min block
14. Study concluded, TcCO₂ monitor removed, pneumogram band removed, patient placed on pre-study CPAP settings per care team orders

Table 2. Demographics Data Collection