Title: Prone Versus Supine Positioning and the Impact on Bronchopulmonary Dysplasia in Very Low Birth Weight Infants

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Title: Standardized prone positioning compared to usual positioning of very low birth weight infants receiving respiratory support and the effect on bronchopulmonary dysplasia (bpd).

Hypothesis: Standardized prone positioning in ventilated, very low birth weight, preterm infants will lead to a reduction in moderate (Grade 2) to severe (Grade 3) BPD as assessed at 36 weeks post conceptional age (PCA).

Background: Bronchopulmonary Dysplasia (BPD) occurs most often in those infants born less than 32 weeks gestation and in those weighing less than 1500 grams at birth. While its definition is somewhat variable, the diagnosis usually rests on the duration of need for oxygen and use of positive pressure ventilation. That is, oxygen use for ≥28 days, before 36 weeks PCA or discharge, whichever is earlier, coupled with use of positive pressure ventilation including invasive (via endotracheal tube or tracheostomy tube) as well as non-invasive modalities such as nasal continuous positive airway pressure (NCPAP), non-invasive positive pressure ventilation (NIPPV), nasal cannula (NC) or high flow nasal cannula (HFNC).(1) With three clinical classifications of severity, mild, moderate and severe, we find that 16% of infants in large cohort studies with a weight less than 1000 grams at birth will have severe BPD.(2) However depending on the definition of â€œsevere BPDâ€□ used, it could encompass up to one third of all premature infants(1). For 2019, The Childrenâ€™s Hospital at Montefiore-Weiler Division Neonatal Intensive Care Unit had 34 of 107 (31.7%) very low birth weight infants (VLBW), i.e those born less than 1500 grams, who were diagnosed with moderate to severe BPD. BPD was defined as utilization of a ventilator or continuous positive airway pressure (CPAP), use of HFNC or regular flow NC >2L at 36 weeks PCA. Of the 107 VLBW infants identified, 9 died.

There is considerable practice variation in the respiratory management of BPD patients.

Significant practitioner and institutional variation exists in the â€œpreferredâ€□ mode of ventilation for these patients. Volume and pressure targeted ventilation, or the hybrid pressure regulated volume limited strategy, as well as neurally adjusted ventilatory assist (NAVA) ventilation are options for ventilator management that may be utilized in the care of BPD patents. Additionally, supportive therapies such as gastroesophageal reflux (GER) prevention and/or treatment, use of other respiratory medications (bronchodilators, inhaled steroids and caffeine) and routine use of sedatives are among other strategies that some have employed. Other management options may include preferential prone positioning of the infant to facilitate gas exchange.

There is evidence in adults that prone positioning may augment oxygenation during treatment of acute respiratory distress syndrome (ARDS).(3) A systematic review showed that it may confer a decreased risk of death as well in adults with severe ARDS.(4) Prone positioning of infants and children has been suggested to also result in improvement in arterial oxygen content when compared to supine position for respiratory distress.(5) In a Cochrane review by Gillies and colleagues, prone positioning was superior to supine positioning with small but significant increases in PaO2 and SaO2. Decreased episodes of hypoxia and decreased respiratory rates were observed. The benefit seemed to be predominantly in preterm ventilated neonates.(5) Cochrane systematic reviews done in 2016 by Rivas-Fernandez and colleagues; Balaguer and colleagues in 2013 noted similar results.(6,7)

In most NICUs, positioning of an infant is not standardized; hence a mechanically ventilated infant may rest in lateral, supine or prone position at any given time and alternated per the individual nursing routine or perception of patient preference. There is a specific anatomical distribution of airflow such that in spontaneously breathing premature infantsâ€™ posterior

portions of the lung fill first. Additionally, it was noted that the right lung fills first in this same patient population, likely due to its more vertical anatomic position.(8) Gravity had little effect on regional ventilation distribution. In 2015 Vendettuoli and colleagues evaluated positional effects on lung mechanics in preterm infants with acute as well as chronic lung disease. Eighteen infants were assessed, 9 in both the acute and chronic lung disease groups respectively.

There was no statistical improvements noted for acute respiratory distress, however a decrease in respiratory system resistance was noted for infants with BPD during prone positioning.(9) In 2018 Zhong and colleagues randomized 79 preterm mechanically ventilated infants to supine vs prone positioning. Fraction of inspired oxygen (FiO2), peak inspiratory pressure, mean inspiratory pressure, and duration of ventilation were significantly lower in the prone group than in the supine group ($P < 0.05$).(10)

There were no reports of adverse events in pediatric patients in the aforementioned studies. However in adult patients adverse effects such as pressure sores and tracheal obstruction were reported.

While the prior studies have shown temporal benefit for preterm, ventilated infants who undergo prone positioning, many are short term studies and none have assessed its impact on severity of BPD.

Objective: We aim to evaluate in this pilot study whether standardized prone positioning compared to usual positioning improves moderate to severe BPD rates as assessed at 36 weeks post conceptional age in VLBW preterm infants with BPD.

Material and methods

Study plan:

We aim to enroll and randomize infants born at less than 1500 grams at birth, who remain

on positive pressure support for at least 7 days after birth AND/OR on any other respiratory device such as nasal cannula with flow rates greater than 2LPM receiving supplemental oxygen of greater than 21% for at least 7 days after birth. Positive pressure for the purposes of this study is defined a nasal cannula delivering a flow of 2 LPM or higher, continuous positive airway pressure (CPAP), non-invasive positive pressure ventilation or non-invasive mechanical ventilation (NIPPV/NIMV), as well infants who are intubated or have a tracheostomy for oxygenation and ventilation related to their lung disease, irrespective of the mode of ventilation. We will exclude infants who were previously on room air without a respiratory device who were intubated for the purposes of surgery and were not receiving respiratory support as defined above prior, those intubated for other airway issues such as tracheal stenosis, broncheo- or tracheomalacia, etc and not for the management of BPD. Additional patients to be excluded include those with suspected or proven genetic or other major congenital anomalies that may impact cardiac and lung function including cardiac and lung anomalies, as well as those at the time of enrollment who require surgeries that will impact their ability to be placed in prone positioning (eg gastroschisis, omphalocele, etc).

Patients meeting the aforementioned criteria will be assigned to 1. usual care in which positioning and duration in each position is random per usual nursing routine OR 2. Receive standardized scheduled daily prone positioning starting on day of life 7.

As part of normal developmental care, most infants are evaluated and have care rendered (touch-time), if stable, and repositioned at set three-hour intervals to permit uninterrupted sleep and/or rest. The hands-off interval will be maintained throughout the study interval. Infants randomized to the standardized scheduled daily prone positioning will be placed in prone body position for a total of 6 hours daily, that is prone position for 3 hours, followed

by supine positioning for 3 hrs, then placed in prone position for another 3-hour interval. Standardized daily positioning will occur for randomized patients until 36 weeks or discharge whichever is first. If needed, position aids, which are part of the normal care routine in our ICU, may be used to facilitate maintenance of prone or supine positioning.

Identification: Each day, NICU admissions will be reviewed via the electronic medical record and infants who are born with a birthweight of less than 1500 grams will be identified. On day of life (DOL) 5-7, of those infants identified, those parents of infants who are still maintained on positive pressure ventilation and or >21% FiO2, will be approached and consented for inclusion in the study.

Consent: Families will be approached in person in the Neonatal Intensive Care Unit or Post-Partum Unit between DOL 5-7 and consent obtained for participation in the study by Dr. Thompson-Branch or Dr. Havranek. One parental signature will be required. Written study material and copies of consent forms will be provided for families to keep. There will be no cost to the patient and no remuneration offered. Families may withdraw consent at any point of the study. See separate consent form, appendix 1.

Procedures: Consent will be obtained between DOL 5-7. Subjects will undergo block randomization. Once randomized, those patients who are assigned to standardized, scheduled prone positioning, will be placed in prone position, with the head turned either right or left per nursing or patient desire, for a total of 6 hours daily, during daytime hours, if clinically stable. They will be placed in prone position for 3 hours, followed by supine positioning for 3 hours, then placed in prone position for another 3-hour interval. If needed, position aids, which are part of the normal care routine in our ICU may be used to facilitate maintenance of prone or supine positioning. If an infant is felt to be too unstable, or significantly

intolerant of prone positioning, they may be positioned per nursing or patient comfort. If infant was already in the prone position per nursing routine prior to the start of prone positioning per study protocol, we will await change to a different position before initiating study protocol for infants assigned to scheduled prone positioning. This is to avoid infants being placed in prone position for > 3 consecutive hours at a time). Alternating between supine and position allows us to detect any short term immediate changes in oxygenation and vital signs attributable to a change in positioning between prone and supine.the two positions.

Both infants randomized to standardized prone positioning and usual positioning will have a bedside card card identifying that the infant is a study participant and will serve as a way to document the number of times any infant enrolled in the study is placed in prone positioning even if not randomized to standardized prone positioning. The bedside card also facilitates the infantâ€™s nurse being aware of the time of day for prone into supine position change for those who are randomized to prone positioning. On the weekly anniversary of the infantâ€™s first placement in prone position for the study, physiologic and clinical data will be retrieved.

Risk/Benefit: anticipated medical, social, psychological, and/or legal risks are minimal; however uncommon risks to be being placed prone may include movement or dislodgement of a breathing tube or of an intravenous (IV) catheter. These uncommon risks will be minimized by staff paying strict attention to the positions of these devices during movement from prone to supine position and vice versa. Additionally, documentation of the positions of these devices is routine and will permit tracking of change in position of the devices. Potential benefits include a decrease in the severity and occurrence of moderate to severe BPD, a common condition of the lung related to premature birth.

Data storage and maintenance of confidentiality: Data will be reviewed and retrieved from the electronic medical record into a computerized study data form kept on a password protected computer in a locked office. Only the 2 study personnel, Dr. Thompson-Branch and Dr. Havranek will access study files to check or edit data. Consent forms will also be kept in a locked office. The study database will be permanently deleted and paper data collection tools will be shredded. Subjects will not be video or audiotaped during this study.

Personnel: Neonatologists Dr. Alecia Thompson-Branch and Dr. Tomas Havranek will be responsible for consenting families and determining randomization assignment. Bedside nurses along with respiratory therapists will be responsible for position changes and documentation of physiologic metrics and vital signs as part of the normal ICU care practice. Dr. Thompson-Branch will collect study data for analysis. Nurse practitioner Nefertiti Cano, RN, BSN, DNP, will be responsible for assigning the primary outcome of moderate or severe BPD, at or after 36 weeks post conceptional age. She will be provided a list of study participants identified only study number at 36 weeks post conceptional age, their respiratory support parameters and will assign the primary outcome of moderate (Grade 2) or severe (Grade 3) BPD.

Randomization: Block randomization with variable block sizes will be performed in order to ensure equal sample sizes over time. The treatment (standardized prone positioning) ratio to control (usual positioning) ratio will be 1:1. The randomization list will be generated by the study statistician and will be maintained under locked conditions. Blinding of staff is inherently not feasible as scheduled prone position changes are obvious to caretakers.

Evaluations and measures: Incidence and severity of BPD will be assessed at 36 weeks post conceptional age. As part of usual NICU care, infants, especially those on respiratory support have vital signs and other physiologic parameters recorded routinely every 3 hours,

but this may occur as frequently as every hour in the sickest infants. Enrolled infants will have physiologic data and vital signs evaluated and recorded at start of hands-on time, at the 1 hour mark after scheduled position change to prone, at the time of switch to supine, 1 hour after 2nd switch to prone position, and at the time of conclusion of study positional changes. For infants randomized to usual care, we will record similar data from a period of 3 hands-on intervals (total of 9 hours).

We aim to record and collect the following data once weekly on the weekly anniversary of the infantâ€™s first study prone positioning and the date of randomization onto the study for those study participants who were randomized to usual care: transcutaneous CO2 (TCO2) if available or PCO2 from any blood gas, SaO2 from cardiopulmonary monitors, PaO2 from arterial blood gases within 1 hour of positional change (if available), ventilator or other respiratory support modality settings and direction of changes within 1 hour of positional change. Specifically, percent change in inspired oxygen, change in ventilator rate (breaths per minute), tidal volume (milliliters), peak inspiratory pressure (cm H2O), positive end expiratory pressure (cm H2O) and the number of episodes of oxygen desaturations will be collected. Current comorbidities, most recent chest x-ray findings within a 7day interval will also be documented once weekly.

Other data: duration of time on any respiratory support (days), duration of use of endotracheal tube, non-invasive positive pressure ventilation (NIPPV) and continuous positive airway pressure (CPAP), time to FiO2 of 21% (irrespective of type of respiratory interface), type of medications to treat BPD (use of oral, inhaled or intravenous postnatal steroids for mitigation of BPD, caffeine, diuretics daily or intermittent), presence of pulmonary hypertension as documented by echocardiogram, use of sedatives and analgesics, pharmacologic treatment of

GERD, use of inhaled nitric oxide on DOL 7 or later. Additionally, the mode of ventilation at 7 days after birth, DOL when maximal feeds achieved (total fluids of 160 milliliters per kilogram per day), DOL at which feeding by mouth was initiated and DOL at which feeds were administered by mouth only, diagnosis of plagiocephaly, and the duration of NICU stay. Demographic data of interest include gestational age at birth (weeks), maternal comorbidities, infant comorbidities, growth status (small, appropriate or large for gestational age), weight at birth (kilograms) and use of antenatal steroids.

Weekly physiologic and ventilatory data will be collected until the infant reaches 36 weeks postconceptional age or discharge from the NICU, or is on 21% FiO2, i.e â€œroom air,â€□ without any respiratory interface, whichever is earlier. For the purposes of our study, the primary outcome of moderate (Grade 2) to severe (Grade 3) BPD will be clinically defined and assigned at 36 weeks PCA based on the 2019 study by the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network which assessed the definition of BPD that best predicted early childhood morbidity.(11) The definitions are as follows:

Severe (Grade 3) BPD: If an infant requires invasive positive pressure ventilation via an endotracheal or tracheostomy irrespective of the amount of FiO2.

Moderate (Grade 2) BPD: If an infant requires nCPAP, NIPPV, HFNC, or NC > 2 liters per minute flow and receiving ≥ 21% FiO2.

Infants receiving NC 2 liters per minute or lower flow rates, irrespective of the FiO2 received, will be considered as having mild (Grade 1) BPD and will not be assigned the primary outcome.

Statistical Considerations: Demographic and clinical variables assessed at baseline will initially be summarized by intervention arm using standard descriptive statistics to confirm

that patient characteristics are distributed similarly across groups. The difference between the intervention and control arms in the rate of BPD at 36 weeks post-conceptional age and other outcomes will be estimated, along with corresponding 95% confidence intervals. In exploratory analyses, the chi-square test will also be applied to assess whether the rates of BPD and other binary outcomes are significantly different between groups, and the two-sample t-test will be used compare the mean values of continuous variables measured at a specific visit. Logistic and linear regression models will also be fit to the data to adjust for any baseline characteristics that are not balanced across groups despite randomization. Weekly physiologic, ventilator and other clinical data will be obtained and analyzed using generalized linear mixed models, with the logit link for binary outcomes and the identity link for continuous outcomes, to account for the correlation in repeated measures from the same infant. Missing data will be handled by analyzing the available data as well as by multiple imputation using chained equations. All analyses will be based on the intent-to-treat approach, and results will be viewed as exploratory and hypothesis generating.

We plan to randomize a total of 60 patients 1:1 to intervention and control (N=30 per arm). Since this is a pilot trial, the goal is to obtain preliminary data on effect sizes. Therefore, formal power calculations were not performed. With 30 patients per arm, the precision, as measured by the width of the 95%CI, with which the true intervention effect (i.e., difference between groups) can be estimated is +/- 25% or better. For example, to gauge the magnitude of the primary outcome of BPD incidence and the potential benefit of standardized prone positioning, we evaluated 2019 BPD rates in our NICU. There were 107 patients described as VLBW at birth. Of those, 34 infants developed moderate to severe BPD, a rate of 31%. If the observed BPD rate is reduced to 21% in the intervention arm for a between group difference of

10%, then the corresponding width of the 95% CI for the true difference will be +/- 22%. We anticipate performing this pilot study over 2-3 years to account for yearly variations in the admission of VLBW patients.

Data Safety Monitoring: While no major safety events were reported in the studies in the pediatric population, the safety of our neonates and infants are of utmost concern. Safety concerns will be monitored real time by bedside nurses and respiratory therapists and addressed by the attendings and medical personnel on clinical service in debrief sessions as is customary, should an event occur. During the daily NICU morning huddle, study patients will specifically be discussed to ascertain if any safety events occurred in the prior twenty-four hours. This data will be documented in the study data collection form. Specific attention will be paid to indwelling devices such as central venous catheters, cutdown venous catheters, percutaneously inserted central catheters, incidental extubation, skin integrity, and need for sedation above and beyond the norm for the individual patient.

"Back to sleep" messaging promoting reduction of sudden Infant Death Syndrome (SIDS) by placing infants, who are close to discharge home, on their backs to sleep, will be reinforced with families and staff per our usual unit initiative. A bedside procedure document will be provided to standardize the technique for altering between prone and supine positions. We will establish a data safety monitoring board comprised of a separate group of two uninvolved neonatologists and an uninvolved statistician to review the safety data after every 15th patient enrolled in the study. The statistician will be responsible for evaluating if there is a statistically significant increase in safety events; the neonatologists will assess the severity and clinical impact of the safety events. Should the data safety monitoring board indicate a concern of increased safety events in the prone position group compared to the usual positioning group, at their discretion

they may make suggestions for discontinuing the study or suggest modifications to the current protocol to permit continuation of the study.

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