Comparison Between Gastric and Post Pyloric Tube Feedings in Bronchiolitis Patients Requiring High Flow Nasal Cannula

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Protocol Title:	Comparison Between Gastric and Post Pyloric Tube Feedings in Bronchiolitis Patients Requiring High Flow Nasal Cannula
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Population:	All children less than 12 months old admitted to Children's Memorial Hermann Hospital TMC for bronchiolitis requiring high flow nasal cannula therapy
Number of Sites:	Single site – Children's Memorial Hermann TMC
Study Duration:	Continuous enrollment until sample size reached
Subject Duration:	Duration of acute hospitalization

General Information

- There are no clear guidelines on appropriate route for nutrition in infants with bronchiolitis, especially during the use of high flow nasal cannula (HFNC). Enteral feed nutrition is achieved by nasogastric (NGT) and nasoduodenal tube (NDT) in general or intravenous hydration (IVF) until the infant's respiratory status improves. This practice varies between hospitals and evidences are anecdotal. We will compare gastric versus post pyloric tube feedings in children less than 12 months old admitted for bronchiolitis requiring high flow nasal cannula therapy

Background Information

- Bronchiolitis is the most common cause of hospitalization among infants during the first 12 months of life. HFNC is becoming increasingly common in supportive care for these patients. No randomized control trials currently exist regarding the safety of tube nutrition in patients receiving HFNC.
- The purpose of NDT feeds is to prevent gastric reflux and subsequent airway aspiration. However, NDT feedings are more difficult to place and less physiologic than gastric feedings. High flow nasal cannula provides humidified air at flows that provide a variable amount of positive pressure. There are cohort studies in adults with Continuous Positive Airway Pressure (CPAP) that show that increased positive pressure can create a decreased esophageal sphincter tone and increased incidences of gastroesophageal reflux. It is unclear if a similar mechanism exists for HFNC therapy.
- Our hypothesis is that NGT is well tolerated during HFNC without serious adverse events. We hypothesize that there will be no difference in length of HFNC therapy, number of emesis, peak respiratory support between patients receiving NGT compared to NDT. We also hypothesize that there will be no difference in these outcomes in the subgroup of high risk population: premature infants, neurological disorders, gastroesophageal reflux patients.

Objectives

- The primary objective is to compare length of respiratory support, number of emesis documented by nursing, peak respiratory support (flow of HFNC, or y/n on CPAP/MV), and ER revisit/hospitalization rates between the gastric feeding group and the post pyloric feeding group

- The secondary objective is to perform an analysis of the highest risk population: premature (born < 37 weeks gestation), neuromuscular disorders, seizures, cerebral palsy, EOE, upper airway disorders – laryngo/tracheomalacia, hemodynamically unstable heart disease, medically managed GERD; and compare the same outcomes between NGT and NDT feedings in this group compared to the low risk group (>37 weeks gestation with none of the above comorbidities).

Study Design

- Design will be a randomized controlled trial.
- Stratified Block Randomization will be done for both high risk population and low risk population through REDCap.
- Duration of study will be until calculated sample size is reached. Subjects will be followed during their acute hospitalization and then followed up by phone interview 7 days and 30 days after discharge
- The primary outcome is total length respiratory support. If HFNC causes increased rates of reflux and subsequent aspiration, we expect length of therapy to be increased in NGT group compared to the NDT group.
- Our secondary outcomes include number of emesis, peak respiratory support, number of x-rays obtained, length of stay, and ER revisit and hospital readmission rates.
- Safety assessments by clinicians will be done daily by primary physician based off of standardized criteria of number of emesis in conjunction with need for increased respiratory support to determine if feeds should be held or not. Patients that transferred to the PICU will be an outcome we track however this study will not dictate ICU feeding management.
- No blinding for study authors involved as they are attending physicians caring for the infants
- Data will be blinded for the statistician and the investigator making follow up phone calls

Study Population

- Inclusion criteria: All admitted patients less than 12 months old for bronchiolitis requiring high flow nasal cannula therapy at Children's Memorial Hermann.
- Exclusion criteria: Patients with craniofacial abnormalities that prevent tube placement. Patients with prior surgery compromising esophageal sphincter tone such as Nissen fundoplication or congenital hiatal hernia surgery are excluded. Patients requiring CPAP and mechanical ventilation are also excluded from the study.
- Recruitment strategy: When patients are either started on HFNC on the inpatient floor or transferred from the emergency room on HFNC without enteral nutrition, caretakers will be asked to consent to the study by the study investigators when the primary physicians have made the clinical decision to start tube feedings.

Study Procedures

- Once consented, patients will be randomized into a NGT or NDT group – via stratified block randomization module on UTH REDCap
- Chest X-ray will be obtained to confirm placement of tube before feeding is initiated
- Feeds will be initiated in a standardized rate and volume
- Patients will be continued to be fed according to randomization until HFNC is discontinued.
- Caretakers can withdraw patients from study at any point
- Primary physicians can withdraw patient from study at any point if they are concerned about adverse events

- Bronchiolitis and HFNC will be managed per standard bronchiolitis protocol
- Continued admission and subsequent discharge will be determined by primary physician
- Information to be gathered includes demographic information (age, sex, race, weight), historical information (birth history, past medical, family history), and information about the course of the admission (length of stay, number of emesis, number of x rays performed, antibiotics used, peak respiratory support, number of revisits to ER and rehospitalizations)
- Data will be collected through chart review in EMR as well as phone follow up interview 7 days and 30 days after discharge by blinded investigators

Data and Safety Monitoring

- Adverse events including reflux and subsequent aspiration are theoretically possible and the purpose of this study. There have been several studies involving nutrition in bronchiolitis that have shown NGT feedings to be safe (3,4,5). If the clinician believes that aspiration/reflux is the cause of worsening respiratory distress and respiratory support, the mode of feeding can be changed if deemed necessary by treating physician.
- A review will be conducted by the safety coordinator of the research team at the 50% enrollment mark. Because this is a randomized control trial with equal groups, a standardized normal deviate test as described in https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1471979/ will be calculated at this time. The cumulative results of adverse events will be used with $p < 0.05$ as the level of significance. If it is shown that there is increased aspiration and this arm is not safe, the trial and study will end.

Statistics

- Statistical analysis will be performed by UT Houston statistician or through CCTS
- Based on retrospective data of bronchiolitis admissions over the past 3 years, the average length of HFNC for low risk infants were 83.3 hours with a standard deviation of 29.5. The average length of HFNC for high risk infants were 87.75 with a standard deviation of 40.06. Assuming B of 0.8 and alpha of 0.05, an N of 48 and 88 were calculated to detect a difference of 24 hours in the duration of HFNC in the low and high risk group respectively.
- $p < 0.05$ to be used for level of significance
- All randomized subjects will be included in the analysis. Subsequent subgroup analysis will be performed on gestational age at birth, weight at study entry, birth weight, mode of delivery PMH by organ system, viral organism, and level of respiratory support.
- In the case that the calculated sample size is not reached by the end of the second respiratory season, enrollment will continue until Bayesian analysis performed annually for up to 2 years identifies 90% or greater probability that there is a difference of respiratory support duration between the two groups or until planned sample size is met.

Statistical Analysis Plan

All analyses will be intent-to-treat. Differences in length of HFNC therapy between treatment groups will be assessed with a regression model including treatment and risk group (stratifying variable) as covariates. Rates of secondary outcomes will be assessed using log binomial or logistic models, and total number of secondary outcomes will be assessed with negative binomial models. In this small pilot study, some treatment effects that would be considered important by family members and clinicians (reduced hospital days) may not be statistically significant. As a result, Bayesian analyses will also be performed to estimate the probability of benefit. Neutral, weakly informative priors will

be used for the treatment effect, e.g. for binary outcomes, the prior relative risk will be centered at 1.0 with 95% prior interval of 0.5-2.0.

Ethics

- IRB approval will be sought from CPHS
- Consent will be obtained prior to any enrollment into the trial.
- A consent form will be printed and handed to each patient describing the purpose of the trial and the risks involved

Data handling and record keeping

- Data will be stored on UTShare account and requiring 2 step authentication and PHI protected as well as the UT Houston REDCap.
- There will be no paper records
- Data will be kept until ten years after completion of study

Quality control and assurance

- Self assessments will be made to check that data collected were for patients admitted for bronchiolitis and the other inclusion criteria

Publication Plan

- Dissemination of knowledge from this study by resident education, nursing education, abstract and poster presentation leading to medical journal publication

CITATIONS

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