

BMJ Open Protocol: randomised trial to compare nasoduodenal tube and nasogastric tube feeding in infants with bronchiolitis on high-flow nasal cannula; Bronchiolitis and High-flow nasal cannula with Enteral Tube feeding Randomised (BHETR) trial

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To cite: Parlar-Chun R, Lafferty-Prather M, Gonzalez V, *et al*. Protocol: randomised trial to compare nasoduodenal tube and nasogastric tube feeding in infants with bronchiolitis on high-flow nasal cannula; Bronchiolitis and High-flow nasal cannula with Enteral Tube feeding Randomised (BHETR) trial. *BMJ Open* 2019;**9**:e025405. doi:10.1136/bmjopen-2018-025405

► Prepublication history and additional material for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2018-025405>).

Received 23 July 2018
Revised 25 March 2019
Accepted 26 March 2019



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ABSTRACT

Introduction High-flow nasal cannula (HFNC) is a non-invasive form of respiratory support used increasingly in bronchiolitis. HFNC provides a variable amount of positive pressure similar to continuous positive airway pressure (CPAP). The positive pressure in CPAP can distend and loosen oesophageal sphincter pressure leading to increased reflux. It is unclear if HFNC causes a similar action. Feeding tubes are used to provide nutrition and hydration to patients that are unable to safely take oral feedings. If there is increased reflux from HFNC, this would increase the risk of aspiration. Our institution places nasoduodenal tubes (NDT) to eliminate this risk. The purpose of the study is to infer if there is a difference between NDT and nasogastric tube (NGT) feeding with regard to length of respiratory support, number of emesis, number of chest X-rays and readmission/emergency room revisit rates.

Methods and analysis Patients with bronchiolitis, on high-flow nasal cannula, and whose primary physicians have decided on feeding tube for nutrition/hydration will be approached for consent and enrolment. Patients will be randomised to NGT or NDT in variable block sizes and stratified into low- and high-risk groups. Outcomes will be analysed by both a frequentist and Bayesian statistical approach.

Ethics and dissemination The trial was approved by local institutional review board. Every attempt will be made to reduce to an absolute minimum the interval between completion of data collection and release of study results through appropriate dissemination mediums including abstracts, poster presentations and journal publications.

Trial registration number NCT03346850; Pre-results.

INTRODUCTION

Bronchiolitis is a viral lower respiratory tract infection that can cause respiratory distress

Strengths and limitations of this study

- There has been no prior randomised control trial regarding the type of feeding tube in infants with bronchiolitis on high-flow nasal cannula.
- Trial is block randomised with allocation concealment.
- There are a few exclusion criteria resulting in increased generalisability.
- Both frequentist statistical analysis and Bayesian analysis will be used to estimate the probability of benefit.
- Clinicians could not be blinded.

and failure secondary to inflammation of bronchial tissue and subsequent airway obstruction due to airway secretions and oedema. This disease typically affects children less than 2 years old and is most severe in those under 3 months of age. Infants are at high risk of severe illness if they are born premature, or have chronic lung/heart disease, immunodeficiency, abnormal airway anatomy or neuromuscular disease. Clinical features of bronchiolitis may include nasal congestion, respiratory distress, wheezes and/or crackles and atelectasis. Bronchiolitis hospitalisation is overall declining, but remains the most common reason for hospitalisation in infants in the USA; annual hospital-related charges amount to a few billion dollars in the USA.¹

The route of nutrition and hydration in bronchiolitis remains an area of interest. For tachypnoeic infants, oral feeding may pose a risk for pulmonary aspiration.² Recently,

however, a study suggested the incidence of aspiration-related respiratory failure in otherwise healthy, term children with bronchiolitis on high-flow nasal cannula (HFNC) receiving oral nutrition was low.³ Nevertheless, there are instances in which children with bronchiolitis on HFNC will not take adequate oral feeds to meet daily nutritional demands, or it cannot be done safely, and feeding tube placement is necessary. Numerous paediatric societies such as the American Academy of Paediatrics (AAP) strongly recommend nasogastric (NG) or intravenous fluids for hydration.⁴ Intravenous fluids with nil per os status is advantageous for the infant in imminent respiratory failure, but the choice of various tonicity of fluids and risk of iatrogenic hyponatraemia is a concern.⁵ Additionally, nutrition will suffer if prolonged intravenous fluids are given without any supplemental nutrition. The timing of introduction of enteral nutrition is also vital as recent guidelines from the American Society for Parenteral and Enteral Nutrition suggest introduction of enteral nutrition for critically ill children within the first 24 to 48 hours of an intensive care unit admission, as well as achieving 66% of goal feeds in the beginning improves clinical outcome.⁶

This question of how best to provide nutrition to patients with bronchiolitis is compounded when the patient is being supported with HFNC. HFNC is increasingly used in a variety of medical settings as non-invasive ventilation in infants with bronchiolitis. HFNC provides humidified air at flows that provide a variable amount of positive pressure. This positive pressure may complicate feeding in bronchiolitis. There are studies in adults on continuous positive airway pressure (CPAP) that show increased positive pressure can create a decreased oesophageal sphincter tone and increased incidences of gastro-oesophageal reflux.^{7,8} It is unclear if there is a similar effect in infants on HFNC therapy. Physiological studies do record changes in oesophageal pressure.⁹ A decrease in oesophageal sphincter tone and increased reflux could lead to subsequent aspiration of gastric contents during nasogastric feeds.

Rationale for study

At our institution, infants with bronchiolitis who are on HFNC receive nasoduodenal (ND) tube feeds. As compared with NG tube feeds, ND tube feeds are thought to minimise gastric reflux and potential airway aspiration. However, ND tubes are technically more difficult to place and provide continuous feeds which are less physiological than bolus gastric feeding. For those infants who are not ready for oral feeds, but would benefit from enteral nutrition, an NG tube, in general, is easier to place. To date, no randomised trial compares two modalities (NG vs ND) of tube feeds in infants with bronchiolitis on HFNC.

Choice of comparators

Our current standard of practice is placement of an ND tube in patients with bronchiolitis on HFNC. Given NG tube feeding has been studied in infants with bronchiolitis

and is supported by the AAP and other various organisations, this modality will be compared with our institution's standard of care.

Objectives

Research hypothesis

As NG tube feeding appears to be well-tolerated in infants with bronchiolitis on HFNC, we hypothesise there will be no difference in duration of respiratory support, the number of emeses and peak respiratory support between patients receiving NG tube feeds compared with ND tube feeds. We also hypothesise there will be no difference in these outcomes in the subgroup of the high-risk population (as defined in 'Interventions').

Primary objective

To compare the duration of respiratory support between the NG and ND tube feeding groups.

Key secondary objectives

To determine if differences exist between the NG and ND feeding groups with regards to:

- ▶ Number of emesis as recorded by bedside nursing.
- ▶ Peak flow rates on HFNC.
- ▶ Duration of HFNC.
- ▶ Instances of failure of HFNC – defined as escalation of respiratory support to CPAP, bilevel positive airway pressure (BiPAP) or intubation with mechanical ventilation.
- ▶ Occurrences of aspiration pneumonia – defined as an outcome determined by the patient's primary physician with subsequent antibiotic treatment.
- ▶ Number of X-rays for tube placement.
- ▶ The overall length of hospital stay.
- ▶ Emergency and hospital readmissions within 7 and 30 days post discharge.

Other secondary objectives

To determine if high-risk infants (criteria listed below in 'Interventions') have differences between the NG and ND tube feeding groups in regards to the objectives above.

Trial design

The BHETR trial is designed as a single centre, randomised, non-blinded, equivalence trial with two parallel groups and a primary outcome of the length of time requiring respiratory support. Randomisation will be in blinded blocks and stratified by low- and high-risk groups with an allocation ratio of 1:1.

Study setting

The 'BHETR trial' will be conducted at a single tertiary-care, academic children's hospital. We will recruit patients who are inpatients in the paediatric intermediate medical unit of Children's Memorial Hermann Hospital affiliated with UTHealth McGovern Medical School at Houston. This randomised trial will recruit subjects from January 2018 until May 2019.

Eligibility criteria

Inclusion criteria

- ▶ All infants up to 12 months of age admitted for bronchiolitis requiring HFNC for whom the treating physician has decided to place a feeding tube.

Exclusion criteria

- ▶ Infants with craniofacial anomalies that prevent tube placement.
- ▶ Infants who had surgery compromising oesophageal sphincter tones such as Nissen fundoplication or congenital hiatal hernia.
- ▶ Infants initially requiring CPAP or mechanical ventilation.
- ▶ Infants transferred from the paediatric intensive care unit (PICU).
- ▶ Infants transferred from a non-Hermann facility who are already on HFNC.

Interventions

For all eligible patients on HFNC ready for tube feeding, a review of their past medical history will determine which category to classify the intervention group – low-risk or high-risk. High-risk patients are those born prematurely (<37 weeks gestation), and/or a previous diagnosis of neuromuscular disorders, seizures, cerebral palsy, eosinophilic oesophagitis, upper airway disorders (ie, laryngomalacia), hemodynamically unstable congenital heart disease or medically managed gastro-oesophageal reflux as determined by consensus among paediatric gastrointestinal and pulmonary specialists. Low-risk patients, on the other hand, are that born term (≥ 37 weeks gestation) without any of the previously listed comorbidities. Once the caregiver consents to the study and the patient are enrolled, the university-affiliated ‘REDCap’ software will be used to assist with stratified block randomisation for NG tube or ND tube placement.

Once the patient is randomised, the study investigators will notify a member of the medical team caring for the patient about the patient’s assignment of feeding tube type. The feeding tube is subsequently placed, and an X-ray is obtained for placement confirmation (X-ray confirmation is standard of practice at our hospital for both NG and ND tubes). Feeds are given continuously through an ND tube and as a bolus over 30 min every 3 hours through an NG tube. The total kcal/kg/day given is standardised for the patient’s age and weight. The patient is provided with the same caloric density formula (or expressed breast milk) that they are given at home. Because of practicality, neither the study investigators, medical team nor the caregivers could be blinded to the feeding modality chosen through randomisation.

Modifications

Patients typically continue to be fed via the route determined by randomisation until HFNC is discontinued. We expect patients to be managed via standard bronchiolitis protocol at our institution. There is no specific

flow weaning protocol off HFNC, and will be driven at the discretion of the primary physician. Respiratory viral panels will also be obtained at the discretion of the primary physician. The caregivers can withdraw from the study at any point. Should the patient experience any adverse events, such as vomiting or aspiration, it is at the discretion of the primary physician caring for the patient to change the feeding route, hold or discontinue feeds.

Outcomes

The total duration of respiratory support was selected as the primary outcome measure. This outcome measure serves as a surrogate measure for clinically relevant aspiration. There is no standard definition for aspiration, and there is no gold standard to determine if aspiration has occurred. By choosing length of respiratory support, the study uses a clinically relevant outcome with the presumption that increased aspiration events would lead to longer duration of support. While aspiration is multifactorial, randomisation will help nullify the confounders and isolate the role of the type of tube feeding. Secondary outcome measures include the number of documented emesis, maximum respiratory support received, total duration of HFNC therapy, number of X-rays obtained to confirm tube placement, number of attempts for tube placement by the nursing staff, adverse events during placement or while the tube is in place (ie, nosebleeds, tube dislodgement), instances of aspiration-related respiratory events, instances of HFNC failure (need for BiPAP, CPAP or mechanical ventilation with intubation), hospital length of stay and emergency room visits and hospital readmissions within 7 and 30 days after discharge.

Participant timeline

Once a patient has been enrolled in the study, the patient remains enrolled throughout the acute care hospitalisation until discharged. A telephone follow-up interview occurs 30 days after discharge.

Sample size

The sample size was based on retrospective data analysis of bronchiolitis admissions at our institution over the past 3 years. Low-risk infants had an average duration of respiratory support of 86.8 hours (SD=26), while high-risk infants had an average duration of respiratory support of 97.6 hours (SD=39.6). Assuming $\beta=0.8$ and $\alpha=0.05$, $n=36$ and $n=86$ were calculated to be able to detect a difference at 24 hours in the duration of respiratory support in the low- and high-risk groups, respectively.

Recruitment

Patients are recruited continuously throughout the year; however, peak enrolment is expected to occur during ‘respiratory season’, which is typically between October and March. When patients with bronchiolitis are admitted on HFNC from the emergency room, or started on HFNC after admission to the inpatient ward and deemed ready for enteral tube feeding, the patient is

eligible for enrolment and the study investigators will ask the caregivers to consent to the study.

Allocation

After a patient has been identified as meeting inclusion criteria and consent is obtained, baseline data is entered into 'REDCap' in which randomisation occurs. Participants will be randomly assigned to either the NG or ND tube feeding group with a 1:1 allocation and will be stratified by risk level as previously defined. Investigators will be blinded to the block size and the block size will vary.

Allocation concealment will be ensured as the assigned group will not be revealed by 'REDCap' until after the patient has been recruited into the trial and the baseline data has been entered into 'REDCap'.

Blinding

Trial participants, caregivers, medical personnel and investigators will not be blinded to the study group assignment due to the obvious differences in the interventions. Study group assignment will be blinded to the statistician as de-identified data will be used for analysis.

Data collection methods

After informed consent has been obtained, the investigator obtaining consent will gather the baseline parameters from the hospital electronic medical record (EMR) and from the parents. This data will be entered into UTHHealth REDCap. The bedside nurse will be informed of the patient's enrolment and will be given a data collection form for tube placement to document the number of attempts needed to place the tube as well as any adverse events associated with the initial tube placement as well as any future tube placement needed if the tube becomes dislodged. An investigator will retrieve this form prior to the patient's discharge from the hospital. An investigator will assess for any subsequent emergency department visits or hospital admissions via hospital EMR and a phone call to the parent 30 days after discharge from the hospital. Three attempts will be made to contact the parent. If after three attempts, the investigator is unable to contact the parent, the patient will be considered lost to follow-up.

After the patient is discharged from the hospital, the clinical parameters data collection form will be completed in REDCap using information obtained from the nursing form, hospital EMR and the 30 day follow-up phone call using the variable definitions agreed on by the investigators. A second investigator will independently enter the baseline parameters as well as the clinical parameters into REDCap. The principal investigator will then compare the duplicate sets of data and address any discrepancies to ensure validity.

Retention

All randomised patients will be included in an intention-to-treat analysis. The primary treating physicians may choose to change the method of feeding at any point if they are concerned about adverse events. Similarly, if the

patient requires subsequent admission to PICU, the study will not dictate feeding methods at that time.

To maximise retention to the 30 day post-discharge follow-up phone call, investigators will obtain a working phone number and/or email address from the parents at the time of consent and enrolment into the study. Parents will be told to expect a phone call and/or email 30 days after discharge.

Data management

Paper baseline parameters and nursing forms will be kept in a file cabinet in a secure office. All data will be entered electronically and stored on a UTShare account and on UTHHealth REDCap, both of which are private health information protected and require two-factor authentication. As described above, each set of data will be entered twice with each duplicate data set compared by the primary investigator, and discrepancies addressed to ensure data validity.

Within the data collection forms in REDCap, calculators have been programmed to calculate the length of time on respiratory support as well as other outcome measures from entered date/time data entries to minimise human calculation error.

Statistical methods

Outcomes

All analyses will be intent-to-treat. Differences in total length of respiratory support 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 logistical models, and a total number of secondary outcomes will be assessed with negative binomial models.

Additional analyses

In this small pilot study, some treatment effects that could 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, for example, for binary outcomes, the prior relative risk will be centred at 1.0 with 95% prior interval of 0.5 to 2.0. Depending on the results of the pilot, the need for a larger trial will be assessed.

Data monitoring

Formal committee

Not applicable - a data monitoring committee is not needed as risks are expected to be minimal.

Interim analysis

An interim analysis will be performed when 50% of patients have been randomised and will be performed by an independent statistician who is blinded to the treatment allocation. A standard normal deviate test will be

calculated to determine if the rate of adverse events are significantly different between the two groups ($p < 0.05$).

Harms

Adverse events related to tube placement is recorded by nurse responsible for placing the tube. The route of feeding may be changed at the discretion of the primary physician if the particular tube placed is believed to be causing harm to the patient, such as worsening respiratory distress or aspiration pneumonia.

Auditing

Independent, periodic audits will not be performed. The investigators will perform self-assessments to ensure the data collected were for patients admitted for bronchiolitis and the other inclusion criteria. Data for each patient is collected by two separate investigators and then verified by the principal investigator to ensure good data quality. 'REDCap' is able to compare two entries for irregularities.

Research ethics approval

The protocol and the template informed consent forms contained in appendix were approved by UTHealth's Committee For the Protection of Human Subjects (our institution's institutional review board [IRB]) with respect to scientific content and compliance with applicable research and human subjects regulations.

Protocol amendments

Any modifications to the protocol which may impact the conduct of the study, the safety of the patient or any changes to the objectives, design, population, sample sizes, procedures or significant administrative aspects will have a formal amendment to the protocol and approved by the IRB prior to implementation.

Protocol Version available in online supplementary materials appendix 1.

Patient and public involvement

Patients were not involved in the development of the research question, study design or recruitment into the study.

Consent

Members of the study team, all who are familiar with the trial and study design, will obtain written consent from patients' caregivers. All consent and information sheets are available in English and Spanish. See online supplementary materials appendix 2.

Confidentiality

All study-related information will be stored securely at the study site. All participant information will be stored in locked file cabinets in a secured office. Electronic data

will be stored on the university cloud storage that requires two-factor authentication and private health information security.

DISSEMINATION POLICY

Every attempt will be made to reduce to an absolute minimum the interval between completion of data collection and release of study results through appropriate dissemination mediums including abstracts, poster presentations and journal publications.

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Contributors RP-C conceived of the study. RP-C, AG, ML-P and VG initiated the study design and implementation. CP is conducting the primary statistical analysis. All authors contributed to refinement of the study protocol and approved the final manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Parental/guardian consent obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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REFERENCES

1. Meissner HC. Viral bronchiolitis in children. *N Engl J Med* 2016;374:62–72.
2. Khoshoo V, Edell D. Previously healthy infants may have increased risk of aspiration during respiratory syncytial viral bronchiolitis. *Pediatrics* 1999;104:1389–90.
3. Sochet AA, McGee JA, October TW. Oral nutrition in children with bronchiolitis on high-flow nasal cannula is well tolerated. *Hosp Pediatr* 2017;7:hpeds.2016-0131–55.
4. Ralston SL, Lieberthal AS, Meissner HC, *et al*. Clinical practice guideline: the diagnosis, management, and prevention of bronchiolitis. *Pediatrics* 2014;134:e1474–e1502.
5. Wang J, Xu E, Xiao Y. Isotonic versus hypotonic maintenance IV fluids in hospitalized children: a meta-analysis. *Pediatrics* 2014;133:105–13.
6. Mehta NM, Skillman HE, Irving SY, *et al*. Guidelines for the provision and assessment of nutrition support therapy in the pediatric critically ill patient. *JPEN* 2017;41:706–42.
7. Shepherd K, Hillman D, Eastwood P. CPAP-induced aerophagia may precipitate gastroesophageal reflux. *J Clin Sleep Med* 2013;9:633–4.
8. Ozcelik H, Kayar Y, Danalioglu A, *et al*. Does CPAP treatment lead to gastroesophageal reflux in patients with moderate and severe OSA? *Eur Arch Otorhinolaryngol* 2017;274:1223–9.
9. Milési C, Baleine J, Matecki S, *et al*. Is treatment with a high flow nasal cannula effective in acute viral bronchiolitis? A physiologic study. *Intensive Care Med* 2013;39.