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Cold milk as a novel therapy for dysphagia in preterm infants

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Title	**Cold milk as a novel therapy for dysphagia in preterm infants**
Short Title	**Cold milk for dysphagia in preterm infants**

Brief Summary	It is estimated that 30-70% of very low birth weight (VLBW) preterm infants will be diagnosed with swallowing dysfunction (dysphagia), which often leads to airway compromise in the form of laryngeal penetration and/or tracheal aspiration during oral feeding attempts. Chronic airway compromise results in a persistent inflammatory state, with disease progression that can be devastating for already fragile and developmentally immature lungs in preterm infants. At this time, there are limited therapeutic options for dysphagia in VLBW infants during oral feeding. In a recent publication, our research group was the first to demonstrate that short-duration of oral feeding with cold liquid reduces dysphagia occurrence from 71% to 26%. However, these data must be further validated for the effectiveness and safety of a full duration feeding before being recommended for routine clinical practice. The objective is to identify preliminary evidence for the efficacy and safety of feeding full oral cold milk for dysphagia management in preterm infants. We hypothesize that oral feeding of cold milk in preterm infants with dysphagia will improve suck/swallow/breathe coordination and decrease penetration/ aspiration to the airway. We further hypothesize that cold milk intervention will have no adverse effects on intestinal blood flow, as assessed by Doppler Ultrasound. This is significant because there is a critical need to identify effective and safe evidence-based treatment options for dysphagia management in preterm infants. This prospective study will seek to enroll Subjects who meet the following inclusion criteria: 1) preterm infants less than 34 weeks gestation), 2) admitted to NYU- Langone Long Island Hospital NICU, 3) Post-menstrual age (PMA) > 35 weeks at the time of the study, 4) receiving no or minimum respiratory support ($\leq$2 lit/min low-flow nasal cannula), 5) tolerating at least 50% of their enteral feeding orally, 6) having symptoms of swallowing dysfunction during oral feeding (clinical dysphagia) and 7) referred by the medical team for video fluoroscopic swallow study (VFSS) and/or fiberoptic endoscopic evaluation of swallowing (FEES). To assess the efficacy of cold milk in treating dysphagia, study subjects will first have an oral motor feeding assessment using an FDA approved device called the nFant® Feeding Solution (510k cleared, # K143507), used routinely in many NICUs as well as VFSS and/or FEES. To assess the safety of using cold milk, subjects will receive a doppler ultrasound before and after the ingestion of cold liquid feeding to assess the mesenteric blood flow.
Objectives	Evaluate the effectiveness of cold milk to improve penetration/aspiration in preterm infants with dysphagia, as well as to evaluate the safety of oral feeding of cold milk in preterm infants
Methodology	Prospective Study

Endpoint	1. Evaluate the effectiveness of cold milk to improve penetration/aspiration in preterm infants. The primary outcome will be the percentage of swallows with aspiration and/or penetration for cold milk compared with room temp milk (a total of 15 swallows will be assessed by VFSS and FEES). Based on our preliminary results, we expect to find a significant decrease in penetration and aspiration during the initial cold swallows (5 swallows). We expect this improvement to be sustained on the subsequent cold swallows (10 swallows) following the 15-minute cold liquid feeding. A decrease of 30% in penetration and/or aspiration with cold milk will be considered significant. Similarly, a 30% improvement of feeding coordination as assessed by nFant device will be considered significant. 2. Evaluate the safety of feeding cold milk in preterm infants. We will evaluate whether cold milk will cause hypothermia (assessed by measuring Axillary temperatures), change in vital signs (respiratory rate, heart rate, and oxygen saturation) as well as change in mesenteric blood flow indices (assessed by abdominal ultrasound). . These changes with cold milk feeding will be expressed as % change compared to base line (room temp milk).
Study Duration	2 years
Participant Duration	The subjects will participate in the study for approximately 48 hours during their NICU hospital stay
Population	Preterm Infants less than 34 weeks gestation admitted to NYU- Langone Long Island Hospital NICU. (n=42)
Study Sites	NYU- Langone Long Island Hospital
Number of participants	42

1. Introduction, Background Information and Scientific Rationale

Approximately half a million preterm infants are born every year in the USA.[1,2] It is estimated that 30-70% of very low birth weight (VLBW) preterm infants will be diagnosed with swallowing dysfunction (dysphagia), with an inverse relationship between the severity of dysphagia and gestational age (GA).[3-6] Although the pathophysiology of dysphagia is multifactorial,[4,7-9] the discoordination between swallowing and breathing is the most prevalent cause of dysphagia in preterm infants,[10] which often leads to airway compromise in the form of laryngeal penetration and/or tracheal aspiration into the lungs.[7,11] Chronic airway compromise results in a persistent inflammatory state, with disease progression to chronic lung injury and *bronchopulmonary dysplasia (BPD)* that can be devastating for already fragile and developmentally immature lungs in preterm infants.[4,7]

A challenge facing clinicians is the limited therapeutic options for dysphagia in VLBW infants during oral feeding. Currently, the most widely used option for this population is the thickening of feedings to alter the bolus flow and maneuverability in the oropharynx to improve airway protection.[12-15] However, such an option has limited efficacy, especially if feeding breast milk, since human milk enzymes can interfere with the desired milk consistency.[16] One alternate technique in adults is to use cold foods to stimulate a safer swallow.[17] The theoretical basis for this technique is to provide increased sensory information to the sensory receptors within the pharynx, to trigger more efficient swallowing movements.[14,15,18-21] Cold temperature stimulates the sensory thermo-receptors in the pharyngeal area via cation channels expressed in the visceral afferents of the cranial nerves. Animal studies have demonstrated that these channels are activated by cold stimulus leading to thermoregulatory responses and protective reflexes.[22] the use of cold stimulation has proven to reduce airway compromise in adults with dysphagia.[17,23,24] However, for preterm infants, the use of cold feeds has not been well investigated, leaving

clinicians with very limited therapeutic options. The significant lack of dysphagia research in preterm infants hinders any evidence-based approach to this frequent problem.

In a recent publication, our research group was the first to demonstrate that short-duration of oral feedings with cold liquid (5 swallows) reduces dysphagia occurrence from 71% to 26% as assessed by VFSS.[25] Our preliminary data further confirms that oral cold milk feeding significantly improves suck/swallow/breathe coordination as evident by bedside oral feeding scoring scales. However, these data must be further validated for the effectiveness and safety of a full duration feeding before being recommended for routine clinical practice.

The objective of this application is to identify evidence for the efficacy and safety of feeding full oral cold milk for dysphagia management in preterm infants. We hypothesize that oral feeding of cold milk in preterm infants with dysphagia will improve suck/swallow/breathe coordination and decrease penetration/aspiration to the airway. We further hypothesize that cold milk intervention will have no adverse effects.

2. Potential Risks & Benefits

For the study purpose, the FEES will be used to assess swallowing coordination with cold milk for a total of 15 swallows only.

Risks associated with FEES- FEES is a routine procedure done in the NICU and is ordered by the medical team. It is also possible that FEES will cause epistaxis, or respiratory distress during the FEES. Although it is unlikely given the previous reports in using it in preterm babies, as well as in adults and pediatrics. The diameter of the FEES scope is similar in size to the nasal gastric tube that most preterm infants have already, which is commonly well tolerated in preterm infants, even during oral feedings. Several studies demonstrated its safety in children. However the procedures will only be conducted in the presence of an attending Neonatologist to ensure airway safety in case of any adverse events. The FEES will be ordered by the medical team as clinically indicated (the clinician can do the FEES for the entire feeding or portion of the feeding).

Development of cold stress in response to cold liquids- It is possible that infants feeding cold liquids will develop cold stress. Several studies have assessed the effects of cold feeds in healthy term and healthy preterm infants but not in the context of dysphagia. These studies revealed no significant adverse effects including no difference in sleep pattern, vocalizations, motility, intake, feeding behavior, weight gain, temperature or regurgitation.[26] Blumenthal and colleagues[27] reported that cold feeds were well tolerated and produced no obvious clinical effects. Other studies found no significant differences in gastric residuals in preterm infants (28-30 weeks gestation age) fed cold (0-4°C) versus room temperature (25°C) milk,[28] as well as no effect regarding gastric emptying time.[27,29] Based on the current literature in preterm infants, the 15-minute exposure to cold liquid is expected to result in little risk.[30]

Cold Stress Prevention - As part of our study design, we are employing frequent axillary and gastric content temperature checks to ensure participant safety. Furthermore, infants' vital signs (blood pressure, respiratory rate, heart rate, and oxygen saturation), and evidence of any respiratory compromise, will be monitored and recorded.

Radiation Exposure - For this study, we aim to visualize 15 swallows, which will take approximately 18 seconds. Compared to the typical range of radiation time of 90-180 seconds in routine VFSS. The radiation exposure related to this research equals 10-20% of what an infant would be exposed to during a typical routine VFSS.

Radiation Exposure Prevention – Our study design will include various radiation sparing techniques: 1) Commination, which restricts the x-rays to a smaller area on the subject; 2) Pulsed fluoroscopy, which takes 30 frames/second, instead of the continuous fluoroscopy of 60 frames/second; 3) The radiologist will utilize intermittent fluoroscopy to turn the radiation on only at the time of swallowing; 4) A lead shield will be placed on the subjects' lap to protect reproductive organs from radiation scatter.

Known Potential Benefits

The subjects may or may not personally benefit from being in this study. The results of this research (the safety and effectiveness of cold milk for each subject) will be disclosed to the medical team for further consideration. If the

results confirm safety and efficacy for that infant, the medical team can consider using cold milk to treat the infant's dysphagia which can be a significant benefit to the subject.

3. Objectives

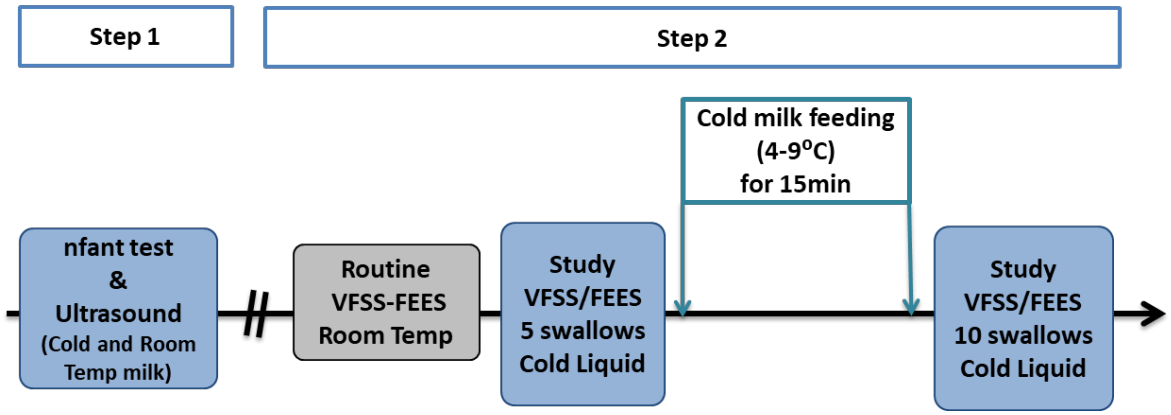
The first objective is to identify preliminary evidence for the efficacy of feeding full oral cold milk for dysphagia management in preterm infants. We hypothesize that oral feeding of cold milk in preterm infants with dysphagia will improve suck/swallow/breathe coordination and decrease penetration/aspiration to the airway. Our second objective is to confirm the safety of this practice. We hypothesize that cold milk intervention will have no adverse effects on intestinal blood flow as assessed by Doppler Ultrasound. These objectives are significant because there is a critical need to identify effective and safe evidence-based treatment options for dysphagia management in preterm infants.

4. Study Design

This will be a prospective study, with each infant serving as their own control. All study subjects will meet the inclusion/exclusion criteria listed in Section 5 of this proposal and informed consent will be obtained. The subject will be considered for the study if the medical team diagnosed the infant with clinical dysphagia and decided to obtain Video Fluoroscopic Swallow Study (VFSS), or Fiberoptic Endoscopic Evaluation of Swallowing [FEES] or both to help manage the dysphagia (such as delay oral feeding till the child is more mature or use feeds thickeners). The VFSS and FEES are not a requirement for step 1 however abnormal VFSS and FEES are requirement for step 2.

The following study procedures will be done before the routine VFSS/FEES testing ordered by the medical team:

Study Protocol Timeline



- Step 1 (bedside procedures):

  - We will evaluate the infant's sucking, swallowing, and breathing patterns using a non-invasive FDA approved equipment (nFant® Feeding Solution). This device is in clinical use for several years and routinely used in several NICUs. The nFant has a wireless sensor within the nipple to assess sucking and swallowing coordination during feeding. This machine is not routinely used in NYU- Langone Long Island Hospital NICU because of costs but will be available only for infants enrolled in this research study. The nfant assessments will be performed by the research team under two separate feeding conditions, standard room temperature (RTS) and cold temperature (CS, at 4-9°C) of milk/formula for an entire feeding (15-20 minutes). The two feedings will be done on the same day but may not necessarily be two consecutive feedings (depending on the baby's eagerness to feed orally). The order of each condition will be randomized to control for fatigue. Inter- and intra-rater reliability measures will be calculated. The nfant assessments will include the following measurements:
    - peak amplitude - the displacement of the nipple during compression phase normalized from a calibrated 0% to 100%;
    - duration - how long or drawn out sucking events are from onset to end in seconds;

- frequency - the rate at which consecutive suck events are occurring in Hertz;
- suck bursts - number of sucks per burst, duration and number of bursts, and active time spent sucking;
- suck smoothness - the number of velocity changes in a nipple amplitude trace during a suck.

- The axillary temperature will be measured immediately prior to and after each feeding condition. It will also be measured at 10, and 30 minutes after the CS feed, at the same time the gastric content temperatures are taken. Infants' vital signs will be recorded (blood pressure, respiratory rate, heart rate, and oxygen saturation), as well as evidence of bronchospasm, lethargy, respiratory distress, apnea, tachypnea, cyanosis, bradycardia, or tachycardia.

- Doppler ultrasound (Sonosite Edge Ultrasound system, Sonosite, Inc, WA) will be used to measure intestinal blood flow indices including the superior mesenteric artery flow (SMA), peak systolic velocity, SMA mean velocity, SMA end-diastolic velocity, resistive index, pulsatility index, portal vein volumetric blood flow, as well as heart rate and mean arterial blood pressure. Intestinal blood flow monitoring via Doppler ultrasound will be performed 6 times for each participant, performed one hour before and at 30 and 60 minutes after both bedside feeding conditions (RTS and CS). Measurements will be taken at the bedside in the supine position.

- Step 2 (done 24-48 hours after step 1):
  - Infants will be transported to the radiology suite and undergo VFSS and or FEES, as ordered by the treating medical team (Figure1: the blue boxes indicate procedures done for research purpose only. None of the research procedures are experimental and are approved tests for neonates including VFSS, FEES, nfant test and abdominal ultrasound).
  - Routine procedure for VFSS or FEES will be followed as ordered by the medical team. This procedure is part of the routine clinical care and not considered part of the research study.

  - If no dysfunction is noted, the procedure will end, and the child will no longer be eligible for further participation in this research study. If dysfunction (penetration/aspiration) either on the VFSS or FEES study is noted, the child will be eligible to participate in the next phase of the study.

  - Immediately following the initial VFSS-FEES assessment, the infants will remain in the same seated position with the FEES scope in place. While keeping all variables from the standard VFSS-FEES the same, the infant will be fed cold barium (4-9°C) using the same nipple. A total of 5 swallows will be visualized using VFSS and FEES, labeled "Cold Swallows-1 (CS1)." These 5 swallows assessment are done for the research purpose only.

  - If the dysphagia didn't improve, the study would end, and the child will no longer be eligible for participation further in this research study.

  - If the dysphagia improves with cold liquid, VFSS will then be turned off and the infants will then be fed their regular feeds (formula or expressed breast milk as indicated by the medical team) chilled to an approximate temperature of 4-9°C for a total of 15 minutes, or until the infant shows signs of feeding completion. The cold feeding will be replaced every 5 minutes to make sure that the temperature is maintained at 4-9°C to minimize habituation effect.[30]

  - After the 15 minute period, the infant will be re-assessed by VFSS-FEES using cold barium from the same bottle (10 swallows, labeled "Cold Swallows-2" [CS2]). This design evaluates whether a full feeding of cold liquid will result in decreased penetration or aspiration compared to RTS condition. These 10 swallows assessment are done for the research purpose only).

  - The axillary temperature will be monitored every 10 minutes. Infants' vital signs (blood pressure, respiratory rate, heart rate, and oxygen saturation), as well as evidence of any respiratory compromise, will be recorded. A neonatologist will be next to the baby at all times. The baby will return to the NICU after the study accompanied by the NICU team, including the neonatologist.

Depending on the scheduling of the VFSS/FEES testing by the infant's medical team, the research team might need to do Step 2 before Step 1, as described above. There will be at least 24 hours period between the two steps.

The results of the testing with cold milk will be disclosed to the medical team. The research team is ethically obliged to disclose the results of efficacy and safety of cold milk use in each child to their treating team. The medical team can decide if that will be an option for dysphagia treatment. The research team will not interfere with that decision. Of note, the results of this research requires enrollment of 42 infants to test the hypothesis that cold milk is effective and safe for dysphagia in preterm infants. If efficacy and safety are demonstrated, clinicians can use cold milk without the need to do all the safety and efficacy measures detailed in this study for each child in the future. However, for the participants in this study, if efficacy and safety is demonstrated for that particular child, it will be safe to use cold milk for that specific child if the medical team desires. However again, the medical team will decide to use this information or not to treat dysphagia. We also changed the protocol so the results of this research can be disclosed to the family by the clinical team only.

Data collection sheets will be immediately labeled with a unique identifier with no identifying or protected information. Consent forms and data collection sheets will be kept in a secure location for up to six years in accordance with institutional policies. Digital images obtained from VFSS and FEES procedures will be saved onto a writable DVD and immediately labeled with a unique identifier with no link to identifying or protected information. In order to minimize loss of patient confidentiality, all participant data forms will be coded with a subject ID number and will not contain the name, medical record number, date of birth, or other identifiable information. A master spreadsheet that links the study number to the medical record number will reside on REDCap.

Chart Review – For this study patient data will be collected including date of birth, gestational age at birth, birth weight, gender, and ethnicity. Furthermore, patient charts will be reviewed to track infants' clinical courses and diagnoses (such as respiratory distress, BPD, NEC, incidence of infections, retinopathy of prematurity, and intraventricular hemorrhage, etc.). All patient records will be assigned unique numerical codes and study records will be kept in a secure database. Coded sheets linking a subject's name to a subject's identification number will be stored separately in a password protected document only accessible to research personnel.

Data Sources and Case Ascertainment:
Cases will be obtained through a search for inclusion criteria using EPIC.

Statistical Considerations-

Statistical Analysis and Estimated Sample Size: To evaluate whether cold liquid will improve aspiration and penetration, event rates during CS compared to RTS, as well as corresponding 95% confidence intervals, will be computed. Aspiration and Penetration variables will be assessed for normality using histograms and the Kolmogorov-Smirnov (K-S) test. Wilcoxon Signed-Rank test will be used to evaluate the specific aim 1, i.e., compare changes in aspiration and penetration between RTS and CS. Aspiration and penetration will be evaluated using different methods (FEES and VFSS). ***Power and Sample Size:*** Our preliminary data showed a mean change of 44 and 36% in aspiration and penetration, respectively. For power computation, we conservatively assumed an average change of 30% and a common standard deviation of 25 in both aspiration and penetration. We simulated data using a two-sided Wilcoxon Signed-Rank Test (the non-parametric equivalent of the paired t-test) with alpha=0.05 significance level and a pre-post correlation of 0.20, which revealed that a sample size of N=25 subjects would provide us more than 95% power to detect a large effect size both in aspiration and penetration. These simulation results are based on 10000 Monte Carlo samples. Assuming a conservative estimate that 60% of infants with clinical dysphagia will have a positive VFSS or FEES test, we expect that we will need to enroll 42 subjects to have 30 subjects with a positive dysphagia test. NYU- Langone Long Island Hospital *Hospital NICU is a Regional Perinatal Center (one of 17 NICUs in the state of New York designated to provide the highest level of care to neonates in NY State). The average number of VLBW infants admitted is 90-100/year and at least 40-45 infants/year will have clinical dysphagia referred for VFSS-FEES testing (3-4 patients/month). Therefore, we are confident that we will have sufficient sample size over the 2-year grant period to conduct the proposed aims.*

2: Evaluate the safety of feeding cold milk in preterm infants.

Axillary temperatures, as well as mesenteric blood flow indices, will be compared between the CS and RTS feeds. A Two One-Sided Test (TOST) will be used to evaluate whether the body temperature and blood flow indices are equivalent before and after the cold liquid swallow. Equivalence will be determined if the 90% confidence interval of pre-post change is contained within the predefined margin of ±0.5. ***Power and sample size:*** The study subjects are the same subjects enrolled in Aim 1 (n=42). We have simulated data assuming a margin of equivalence from -0.5° C to 0.5° C, significance level 0.05, TOST and 10000 Monte Carlo samples. With the planned sample size for aim 1 (N=42), we will have sufficient power (>80%) to detect equivalence when the margin of equivalence is from -0.5° C to 0.5° C and the actual mean difference is zero.

5. Study Enrollment

Inclusion Criteria

1) Viable preterm infants less than 34 weeks gestation), 2) admitted to NYU- Langone Long Island Hospital NICU, 3) PMA > 35 weeks at the time of the study, 4) receiving no or minimum respiratory support (≤2 lit/min low-flow nasal cannula), 5) tolerating at least 50% of their enteral feeding orally and 6) having symptoms of swallowing dysfunction during oral feeding (clinical dysphagia). 7) referred by the medical team for VFSS and/or FEES assessments.

Exclusion Criteria

Exclusion criteria include children with other comorbidities, such as IUGR, upper airway anomalies, brain injury, neuromuscular disease, or life-threatening congenital disease.

Total Number of Participants and Sites

We will need 42 subjects over a 2 years period.

Vulnerable Subjects

Our population will include children by nature of the study objectives.

The study has potentially greater than minimal risk, but there is possible direct benefit to the individual subject. Although previous studies as well as our preliminary study didn't show any evidence of cold stress in response to cold milk feeding, it is a potential risk. In addition there will be minor increase in radiation exposure as described previously. Currently there is no effective treatment for dysphagia in preterm infants. The results of this research (the safety and effectiveness of cold milk for each subject) will be disclosed to the medical team. If the results confirm safety and efficacy for that infant, the medical team can consider using cold milk to treat the infant's dysphagia which can be a significant benefit to the subject.

Subjects Identification, Recruitment and Consent Process

- Patients would already be admitted to NYU- Langone Long Island Hospital NICU due to premature birth. Physicians will refer patients for a feeding/swallowing consult with the clinical SLP when identified as having symptoms of swallowing dysfunction during oral feeding (clinical dysphagia). The research team will identify possible subject's eligibility through EPIC query.

- Our recruitment plan: All subjects will be infants admitted to the NYU- Langone Long Island Hospital neonatal intensive care unit. Subjects will be identified based on referral for feeding/swallowing consult, followed by confirmation of meeting all inclusion/exclusion criteria by the research team using EPIC query. There will be no restrictions regarding sex, race, or ethnic origin. After the consent is obtained, all study participants will be deemed medically stable to tolerate the study protocol by their attending neonatologist.

- This study will use a NYU Data Core generated list of patients meeting the inclusion criteria who have agreed to be approached for clinical research.

- Once potential subjects have been identified, the study team will notify the subject's treating physician (TP) that they have patients eligible to participate using the following method: The treating physician will be contacted by secure messaging through EPIC, by phone, or in person and asked to permit study team to directly contact potential subjects. The treating physician may also contact study team for direct patient referrals. Once contact is made, patients will be told the reason they are being contacted and will be asked if they are interested in participating in this specific study. Should the potential subjects agree, the study team will provide the subjects with information regarding the next steps for participation.

- The research team will approach the parents to discuss this research project during their visit to their infant in the NICU. Alternatively, the research team will call the parents on the phone to set a meeting time during their next visit to the NICU. The parents will be asked to meet in a private room in the NICU to explain all the details regarding the research and consent process and answer all their questions. The parents will be provided a copy of the consent form and will be given a chance to read the consent form privately (for at least a couple of hours or till next day if they wish). The research team will meet with the parents again in a private room to further answer any questions before signing the consent form if they agreed to participate in the study.
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- Information contained within the consent will be written at an eighth-grade level to help ensure universal comprehension. All members of this research team have been trained in human subject research and will review the consent form in detail with the potential subject's representatives. The subject's representatives will be provided the opportunity to have all questions answered. Comprehension will be judged by the research team through the patient verbalizing understanding and asking appropriate questions. If English is not a primary language, a translator will be provided via telephone (Cyracom) to obtain consent in the subject's representative's primary language. The translator's identification number will be recorded. A copy of the consent will be given to the patient, with the original maintained in a locked file cabinet. Coercion to obtain consent within this timeframe will not occur. Please see further details regarding informed consent process, in the section below titled: "*Ethics/Protection of Human Subjects".*

6. Sample Size Determination

Our preliminary data (REF) showed a mean change of 44 and 36% in aspiration and penetration, respectively. For power computation, we conservatively assumed an average change of 30% and a common standard deviation of 25 in both aspiration and penetration. We simulated data using a two-sided Wilcoxon Signed-Rank Test (the non-parametric equivalent of the paired t-test) with alpha=0.05 significance level and a pre-post correlation of 0.20, which revealed that a sample size of N=25 subjects would provide us more than 95% power to detect a large effect size both in aspiration and penetration. These simulation results are based on 10000 Monte Carlo samples. Assuming a conservative estimate that 60% of infants with clinical dysphagia will have a positive VFSS or FEES test, we expect that we will need to enroll 42 subjects to have 30 subjects with a positive dysphagia test.

<u>Informed Consent Process</u>

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the infants' parents. Consent forms will be IRB-approved and the parents (defined as either the mom or dad if they are legally married) will be asked to read and review the document. The study investigators will explain the research study to the parents and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Parents will have the opportunity to carefully review the written consent form and ask questions prior to signing. The parents should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The parents will sign the informed consent document prior to any procedures being done specifically for the study. The parents may withdraw consent at any time throughout the course of the study. A copy of the signed informed consent document will be given to the parents for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

A copy of the signed informed consent document will be stored in the subject's research record. The consent process, including the name of the individual obtaining consent, will be thoroughly documented in the subject's research record. Any alteration to the standard consent process (e.g. use of a translator, consent from a legally authorized representative, consent document presented orally, etc.) and the justification for such alteration will likewise be documented.

Participant and Data Confidentiality

Data collected will be de-identified and stored into REDCap electronic data capture, according to NYU Langone Health policy on data storage. This database will be accessed through computers and network managed by NYU-Langone Long Island Hospital. All investigators and sub-investigators listed in this proposal will have access to the study data. Identifiable information will not be recorded; instead, each subject would have his or her own sequential identification number. Any paper record will be stored in a locked cabinet at NYU- Langone Long Island Hospital. Data will be stored for up to 5 years. Any paper records will be disposed through a confidential shredder.

Participant confidentiality is strictly held in trust by the participating investigators and their staff. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party. Representatives of the IRB may inspect all documents and records required to be maintained by the investigator. The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the NYU- Langone Long Island Hospital Hospital. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems by research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at NYU-Langone Long Island Hospital Hospital.

Safety Monitoring Plan

As requested by NIH, Safety Monitoring Plan is established as detailed below:

This Safety Monitoring Plan is intended to describe processes in place for tracking and reporting Serious Adverse Events (SAE) and Adverse Events (AE), in compliance with NYU Institutional Review Board (IRB) and NICHD policy as well as ensuring the validity and integrity of the data obtained from this study.

This trial will be submitted for approval to the NYU IRB. The research will not occur without NYU IRB prior approval. The PI will submit regular IRB updates as required by local IRB rules, including immediate IRB notifications of serious adverse events, protocol deviation/violations and annual continuing review. This trial will be registered at clinicaltrials.gov.

All participant information will be secured in a database with password protection. The research nurse will receive only coded information that is entered into the database under those identification numbers. Electronic communication with outside collaborators will involve only unidentifiable information.

Roles and Responsibilities

Principal Investigator Responsibilities

The Principal Investigator (PI) is responsible for study oversight, including ensuring human subjects' research protections (HSP), by designating appropriately qualified, trained research staff, and medical clinicians to assess, report, and monitor Adverse Events (AEs). The PI, Sub-investigators, and study team members, will have current HSP certification and participate in research educational sessions, based on the current NIH and IRB guidelines.

Drs. Hanna (PI), Dumpa and Kamity (Sub-Investigators) will have primary responsibility for monitoring participants' well-being and ensuring that the information collected in this study remains confidential. Participants will be deemed

medically stable to be transported to the radiology suite and tolerate the study protocol by their attending neonatologist. The procedures (VFSS, FEES, nfant and IDFS) will be conducted in the presence of Dr. Hanna and/or Dr. Kamity and/or Dr. Dumpa (all staff neonatologists in addition to being study investigators) to ensure airway safety in case of any adverse events.

Data Safety Monitoring Board (DSMB) Responsibilities

- A Data Safety and Monitoring Committee (DSMB) will be created in accordance with established NIH policies. The members will be experts in neonatology (Teofilita Isaacson, MD, chair of the DSMB), pediatric pulmonary medicine (Melodi Pirzada, MD), pediatric nephrology (Manju Chandra, MD), pediatric gastroenterology and clinical trial design and ethics (Tuvia Marciano, DO) and biostatistics (Meredith Akerman, MS), who are not investigators in the trial.

- The DSMB will meet regularly to review the protocols with respect to maintaining human subject protection, ethical and safety standards, monitor the safety of ongoing clinical trials, and advise the research team on this conduct. It will report to the PI and make recommendations if necessary. All data and deliberations of the DSMB will be strictly confidential. Decisions to alter or halt studies are the responsibility of the DSMB chair. The DSMB may recommend protocol modifications based on concerns for patient welfare or scientific integrity. The committee will be privy to statistical data and case report forms that it may require for its deliberations. It will review interim reports of patient accrual and outcome measures provided by the PI. Each report analyses will include treatment group and present all patients exits, mortality, and other major clinical events. After reviewing each such report, the DSMB will assess the need to perform further in-depth evaluation of the benefits and risks of continuing the study. If it is determined that the study objectives have not been satisfied based on data accrued to date, if patient safety would be compromised by continuation of the study, or if there are severe unanticipated problems with study conduct, the DSMB may recommend to the NICHD that the trial be terminated.

- The DSMfB will meet quarterly as well as after each enrollment of 10 patients (a*n Interim Analysis of the results as well as all AEs will be presented).* Emergency meetings will be scheduled immediately (maximum within 48 hours) following any reported SAEs. Any death will requires expedited reporting by the DSMB chair (within 24 hours of study's knowledge of death).

- DSMB report will be submitted to NIH within one week after each quarterly scheduled meeting. However, any action by the DSMB resulting in a temporary or permanent suspension of the clinical study will be reported to the NIH Program Official responsible for the grant within 48 hours. Any death will requires expedited reporting to NIH program officer within 24 hours of study's knowledge of death.

Reportable Adverse Events, including Serious Events

Definitions

Adverse Event (AE), also referred to as an adverse experience, is any untoward medical occurrence in humans, whether or not considered intervention related, which occurs during the conduct of a clinical trial. Any change in clinical status, routine labs, x-rays, physical examinations, etc., that is considered clinically significant by the study investigator is considered an AE. Adverse events will include: hypothermia (defined as temp less than 35.5 degree C) , abnormal changes in vital signs including respiratory rate (apnic episodes or respiratory rate more than 70/min) , heart rate (less than 70/min or more than 220/min) , and oxygen saturation (less than 85%), . The staff nurses normally records any abnormal vital signs findings as part of their routine NICU care for all babies. These data will continuously be recorded during the cold feeding (usually around 15 minutes). Changes in vital signs can be a routine and frequent occurrences in preterm babies as part of their pathophysiology, The following AEs if occurred during the cold feeding will result in study termination for that baby and notification of the DSMB committee:

1- Any incidence of hypothermia
2- More than 2 episodes of apnea
3- Tachypnea defined as increase respiratory rate more than 70/min for more than 2 minutes
4- More than 2 episodes of bradycardia (defined as HR less than 70 for more than 10 seconds).
5- Tachycardia (defined as HR more than 220) for more than one minute

6- More than 2 episodes of desaturation (defined as O2 saturation less than 85%) for more than 30 seconds

Serious Adverse Events (SAEs), as determined by the PI, are any event that results in any of the following outcomes:

1. Death
2. Life-threatening SAE (life-threatening means that the study participant was, in the opinion of the investigator, at immediate risk of death from the reaction as it occurred)
3. Inpatient hospitalization or prolongation of existing hospitalization
4. Persistent or significant incapacity or substantial disruption of the ability to conduct normal life function.
5. Important medical event that may not result in one of the above outcomes, but may jeopardize the health of the study participant or require medical or surgical intervention to prevent one of the outcomes listed in the above definition of SAE.

Participants in these studies will likely have pre-existing medical conditions, those pre-existing conditions will not be reported as adverse events. New events or the worsening through frequency or intensity of pre-existing conditions will be reported as adverse events within the context of the study.

Elicitation of Adverse Events and Serious Adverse Events

AEs and SAEs may be discovered through any of these methods:

- Observing the participant by the research team
- Observing the participant by the NICU team caring for the baby (which will be done in an objective manner)
- Questioning the participant's parent or legal guardian (which will be done in an objective manner)
- Receiving an unsolicited complaint from the NICU medical team and/or participant's parent or legal guardian
- Reviewing of medical records/source documents

The PI and study staff will review all data collection forms on an ongoing basis for data completeness and accuracy as well as protocol compliance. It is anticipated that data verification will be performed by someone other than the individual originally collecting the data, or by double-data entry. A statement reflecting the results of the ongoing data review will be incorporated into the Annual Report for the Independent Monitor

Reportable AEs and SAEs will be documented on the Adverse Event Form first and will be recorded within the participant's records. Source documents, including copies of electronic medical records may be attached to the record when requested. Only the participant's study ID will be provided on source documentation, all other protected health information (PHI) must be redacted prior to report submission.

Assessment of Severity:

The PI will review all adverse events for seriousness (AE or SAE), severity (e.g. Grade 1-3) and causality during review of medical records, and will consult with other research personnel as needed. The investigator will document (signature/date) an assignment of severity (e.g., Grade 1-3) and make the initial determination of the causality of the event to the study intervention/procedures. The investigator may not delegate someone other than a clinician licensed to make diagnoses to this responsibility. The results will be submitted to the DSMB for review, verification and taking appropriate action as needed.

Guidelines for Assessing Severity of an Adverse Event

The PI/DSMBwill use the following definitions when assessing severity of an Adverse Event:

- Grade-1/ MILD: Participant has minor findings, but tolerates them well and no or minimal intervention is required
- Grade-2 / MODERATE: Participant experiences enough symptoms or findings to require intervention
- Grade-3 / SEVERE: Participant experiences symptoms or findings that require significant intervention

Guidelines for Determining Causality of an Adverse Event

The PI/DSMB will use the following question when assessing causality of an adverse event to the study product/intervention: Is there a reasonable possibility that the study product/intervention caused the event? "Reasonable possibility" means that there is evidence to suggest a causal relationship between the study intervention/procedures and the adverse event. An affirmative answer designates the event as a suspected adverse reaction.

SAE Reporting and Management Procedures

- Study staff will be trained to extract, evaluate, and report adverse events according to the protocol requirements and under the direct supervision of the PI. Unexpected, serious, and intervention-related serious adverse events (SAEs) will be reported to the DSMB, NYU IRB, and NIH immediately. Any adverse events, breaks of confidentiality, or any other data or safety issues that arise will be immediately brought to the attention of the NYU- IRB. All events will be reported within 24 hours of having received notice of the event. Dr. Kamity and Dr. Dumpa will be responsible for completing an Adverse Events Form should an event occur.

- The following information will be reported for each event and must be reviewed by the investigator or designee: 1) description of the event, 2) start date, 3) stop date, 4) severity of the event, 5) causal relationship to study product/intervention, 6) seriousness, 7) outcome of the event, and 8) if action with study product/intervention was required.

- Drs. Hanna, Dumpa and Kamity will collaboratively gather any information needed to investigate the event and to determine subsequent action. Any subsequent action will be documented and reported to the NYU IRB and the Program Officer at NICHD. Adverse event reports will be reported in the annual continuing review report to the NYU IRB to ensure participant safety. Procedures to protect patient confidentiality and systems to ensure secure file transfer of sensitive data will be in place.

Study Halting/Termination:

The study will stop immediately if any of the following is to occur:

1- Any Serious Adverse Events (SAEs), as detailed in the Data and Safety Monitoring Plan, will result in the immediate stopping of the study. The SAE will be reported immediately (within 48 hours) to the Data Safety Monitoring Board (DSMB) and the NIH program officer responsible for the study. Any death will requires expedited reporting (within 24 hours of study's knowledge of death). No further enrollment will be allowed until the DSMB determines that this event was unrelated to the study procedures.
2- Frequent AEs as a result of cold milk feeding that deemed to be excessive by the PI or the DSMB will trigger study halting. No further enrollment will be allowed until the DSMB determines that these events were unrelated to the study procedures.
3- The decision by the DSMB to halt the study at any time point at their discretion. Any action resulting in a temporary or permanent suspension of the clinical study will be reported to the NIH Program Official responsible for the grant. During the funding of this study, any action by the FDA (if applicable), NYU IRB or one of the study investigators that results in a temporary or permanent suspension of the study will be reported to the NIH Program Official immediately.

Research Use of Stored Human Samples, Specimens, or Data

Intended Use:
Data collected under this protocol may be used to study efficacy and safety of cold liquid feedings. Human samples and/or specimens will not be obtained.

Storage:
Data will be stored using codes assigned by the investigators. Data will be kept in REDCap.. Only investigators will have access to the data.

Data Handling and Record Keeping

Once the data is collected on the data collection sheet, they will be immediately assigned a unique identifier. No link between this identifier and patient information will be made. No protected information or patient identifiers will be collected either. The data collected will be entered into RedCap within 2 days of collection. The original copies of the consent will be kept in a locked file cabinet. Consent forms will be kept in a secure location for up to six years in accordance with institutional policies.

Future Use of Stored Specimens

There will be no collected biospecimens to be stored.

Study Finances

Funding Source

NIH R21 Grant

Costs to the Participant

None

Participant Reimbursements or Payments

None

DISSEMINATION PLAN FOR CLINICAL TRIAL:

This clinical trial does not meet the criteria for an “applicable clinical trial” since this study does not involve the use of any drug, biological or device products. The Principal investigator (PI) will assume the role of the responsible party and will ensure compliance to the NIH policy on dissemination of NIH-funded clinical trial information.

Registering at ClinicalTrials.gov:

This trial will be submitted for approval to the NYU- Langone Long Island Hospital University Hospital Institutional Review Board and no patient enrollment will occur without IRB prior approval. In accordance with the NIH policy on dissemination of NIH-funded research, this clinical trial will be registered at ClinicalTrials.gov not more than 21 days of enrollment of the first study participant.

Submitting results to ClinicalTrials.gov:

The PI will be the responsible party to report the clinical trial information. Registration information including descriptive information, recruitment information, location and contact information of the study PI and administrative data will be submitted.

The date of the last participant receiving an intervention will be reported as the primary completion date. In the event that the study enrollment is terminated prematurely, the study findings as well as reasons for early termination of the study will be made available on clinicaltrials.gov. All the results are submitted to clinicaltrials.gov within 12 months of primary completion date.

	Action	Timeline
1.	Register on ClinicalTrials.gov	Within 21 days of first patient enrollment
2.	Results information entered on ClinicalTrials.gov	Within 12 months of primary completion date

Making results publicly discoverable:

The results of the study will be submitted to ClinicalTrials.gov for public posting, including inconclusive results that do not amount to a publication, thus ensuring that the research findings are publicly available. The results information reported will include participant baseline characteristics, outcomes and statistical analyses, the protocol and statistical analysis plan, and administrative information. Adverse events pertaining to the study interventions and protocol deviations will also be submitted to ClinicalTrials.gov. In addition, all manuscripts published will be made publicly available on Pubmed Central.

Informed consent:

We will include a specific statement in the informed consent documents about posting of the clinical trial information at Clinical Trials.gov. This information will be discussed with the study participants prior to obtaining consent for study enrollment.

Monitor and manage data quality:
We will conduct internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. The study staff will participate in a start-up meeting during which time the protocol will be reviewed and discussed and formal training will occur with regard to the assessments, rating scales being used, procedures for data entry and management.

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