DEPARTMENT OF RESEARCH

Studying the Influence of Exposure to Maternal Voice on Oral Feeding Volumes in Preterm Infants

January 30, 2020

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DOES THIS PROJECT INVOLVE ANY NICU RESOURCES? ___ NO __X_ YES
(patients/families, clinical/non-clinical staff, medical records)

IF YES, HAS IT BEEN REVIEWED BY DR. MOORE OR HIS DESIGNEE? ___ NO __X_ YES

IF YES, SPECIFY REVIEWER: _____

DOES THIS PROJECT INVOLVE ANY URAP RESOURCES? __x_ NO ___ YES
(students used for recruitment, consenting, data collection)

IF YES, HAS IT BEEN REVIEWED BY DR. SMITH OR HER DESIGNEE? ___ NO ___ YES

IF YES, SPECIFY REVIEWER: _____

IS THIS A STUDENT OR TRAINEE PROJECT? ___ NO __x_ YES

IF YES, INDICATE LEVEL:
___ Medical/Dental Student
___ Resident
__X_ Fellow
___ Undergraduate
___ Other (specify _____)

IF YES, HAS FACULTY ADVISOR REVIEWED THE PROTOCOL? ___ NO _X_ YES

Note: Student researchers are required to attend the Scientific Review Committee

meeting when their protocol is discussed.

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Background/Introduction

Oral feeding is one of the primary functions of the neonatal brain. In preterm infant (PTI) population, competency at oral feeding is one of the major milestones in preparation for discharge. [1] Achievement of full oral feedings is directly associated with length of neonatal intensive care unit (NICU) stay. [2] Extremely low gestational age (GA) infants with dysfunctional oral feeding in early childhood have lower cognitive and language skills compared with those with normal oral feedings. Also, previous studies have shown a strong association between oral feeding and infant maturity and behavior state and positive feeding experience.[2]

Perinatal risk factors such as chronic lung disease, grades 3 to 4 intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), postnatal use of steroids, necrotizing enterocolitis (NEC) are associated with increased risk of adverse neurodevelopmental impairment.[3] However, in recent years, there is emerging evidence that non-medical developmental care interventions in the NICU such as kangaroo care, single family rooms, music and massage therapy may be beneficial for PTIs and improve their long term neurodevelopmental outcomes.[4 5] Beneficial effects of exposure to mother's voice and sounds on PTIs in the NICU are well documented.[6] Maturational progression of the auditory system begins in utero at approximately 24-26 weeks GA. Auditory input is critical for development of auditory cortex. PTIs exposed to mother's voice have bigger auditory cortex.[7] In addition, PTIs showed increased conversational turns (adult and infant vocalizations within 5 seconds) when parents were visiting the NICU compared to presence of nurses alone, suggesting that PTIs have preference for parent's voices.[8] In EEG studies, PTIs exposed to mother's voice showed increased simultaneous activation of multiple brain pathways.[9] Perhaps as a result of the net

stimulatory effect noted above, premature infants have been found to have increased cardiorespiratory stability after listening to mother's voices.[10,11]

Previous studies have examined the effect of mother's voice on oral feeding in PTIs[12,13]. Chrona et al used a pacifier activated music player with lullaby in mother's voice. The pacifier activated music player encouraged non-nutritive sucking and mother's voice was used as a positive reinforcement for non-nutritive sucking. Exposure to mother's voice for 5 consecutive days prior to feeds, was associated with increased oral intake and rate of feeding.[12] Blumenfeld et al, reported the use of mother's singing to PTIs only during oral feedings. This was a small study of 11 PTIs with GA between 31 and 34 weeks. They found no significant increase in volume of oral feedings or the rate of oral feeding during oral feeds with mother's voice exposure.[13] This study proposes to examine the association between exposure to mother's voice prior to and during oral feeding and oral feeding volume and rate in PTIs.

Research Question

To determine if it is possible to expose PTI in a systematic manner to mother's voices before their feeds and to determine if this exposure results in an increase in their oral intake? The results will be used to inform a randomized control trial if found feasible and an effect is noted.

Specific Aims

Primary aim 1: To compare oral feeding volumes in PTIs exposed to mother's voice with 2 historic matched controls without exposure to mother's voice.

Hypothesis: An intervention of exposure to mother's voice for at least 20 minutes just prior to and continuing during oral feeding will increase oral feeding volumes by 20% as compared to historic controls without the maternal voice exposure.

Primary aim 2: To compare Feeding Readiness Scale (FRS) scores and Quality of Nippling Scale (QNS) scores for infants exposed to mother's voice with 2 historic matched controls without exposure to mother's voice.

Hypothesis: Exposure to mother's voice will result in higher FRS and QNS scores by 1 point as compared to historic matched 2 controls without exposure to mother's voice.

Primary aim 3: To compare apnea and bradycardia episodes for infants exposed to mother's voice with 2 historic matched controls without exposure to mother's voice.

Hypothesis: Exposure to mother's voice will result in a 20% decrease in episodes of apnea and bradycardia as compared to historic matched 2 controls without exposure to mother's voice.

Secondary aim 1: To obtain feasibility data to inform randomized control trial

Tertiary aim 1: To compare oral feeding volumes in PTI when exposed to mother's voice with feeds immediately prior without exposure to maternal voice on the same day.

Hypothesis: Exposure to mother's voice will increase oral feeding volumes by 20% in PTI as compared to the feeds directly prior without exposure to maternal voice.

Tertiary aim 2: To compare FRS and QNS scores in PTI when exposed to mother's voice with feeds immediately prior without exposure to maternal voice on the same day.

Hypothesis: Exposure to mother's voice will result in higher FRS and QNS scores by 1 point as compared to the feeds directly prior without exposure to maternal voice.

Tertiary aim 3: To compare apnea, bradycardia and desaturation episodes after a feeding with exposure to maternal voice with feeding immediately prior to without exposure to maternal voice on the same day.

Hypothesis: Exposure to mother's voice will decrease the number of apnea, bradycardia and desaturation episodes after feeds by 20%.

Outcome Definitions/Data Points Collected

Primary outcomes:

Oral feeding volume after maternal voice exposure compared to 2 historic matched controls without voice exposure. The variable being measured will be the percentage of the total feeds taken orally.

FRS and QNS scores after maternal voice exposure compared to 2 historic matched controls without voice exposure. The variables are the FRS and QNS scores which are defined in Appendix 5.

Apnea, bradycardia or desaturation episodes after feeding with maternal voice exposure compared to 2 historic matched controls without voice exposure. The variables being measured will be either apnea, bradycardia or desaturation events noted by the nurses. Apnea is defined as a cessation of breathing for 20 seconds or more. Bradycardia is defined as a heart rate of

<100 beats per minute. Desaturation is defined as a drop in the saturation to <90% for ≥ 10 seconds.

Secondary outcomes:

Feasibility data including percentage of recordings or maternal voice exposure for at least 20 minutes prior to feeding of interest, percentage of maternal voice exposure missed, enrollment rate as a percentage, attrition rate as a percentage, and effect size as a percentage.

Tertiary outcomes:

Oral feeding volume after maternal voice exposure compared with control feeding immediately prior without voice exposure on the same day. See primary outcomes above for oral feeding variable and it's definition.

FRS and QNS scores after maternal voice exposure compared with control feeding immediately prior without exposure on the same day. See primary outcomes above for FRS and QNS variables being measured and their definition.

Apnea, bradycardia or desaturation episodes after feeding with maternal voice exposure compared with control feeding immediately prior without exposure on the same day. See primary outcomes above for the variables being measured and their definition.

Data Collection:

1. Infant demographics such as perinatal risk factors, neonatal morbidities, growth, nutrition and feeding information will be collected.
2. Infant feeding volume including oral and tube feeding with and without maternal voice exposure for each feed will be collected.

3. FRS and QNS scores will be collected for each feed.
4. Apnea, bradycardia and desaturation episodes will be collected for each feed.
5. Feasibility data including:
    a. Whether maternal voice exposure occurred on time
    b. Enrollment rate of PTI
    c. Attrition rate of PTI
    d. Number of maternal voice exposure missed
    e. Effect size
6. Retrospective data mentioned in points 1-4 for two matched controls without maternal voice exposure. See Sampling Method below for further details on matching criteria
7. The data will be stored in a secure computer, we will remove all personal identifiers from the study prior to publication.

Study Design

Design: Two center, controlled, pilot, prospective and retrospective interventional study.

Setting: NICU East at Connecticut Children's Medical Center (CCMC), Hartford, Connecticut and NICU West at CCMC, Farmington.

Target population:

PTIs admitted to NICU East at CCMC and NICU West at CCMC during time period between 3/1/2020 and 12/31/2020. The study will be initially started at the East campus, if however we are having trouble getting enough patients enrolled at the East campus, then we will also start enrolling patients at the West campus.

Inclusion/Exclusion Criteria

1) For prospective cases:

    a. Inclusion criteria:

    PTIs born between GA of 28 0/7 weeks and 34 6/7 weeks-

    1. Ready to start oral feeding attempts
    2. Taking a total daily oral intake < 50% of feeds on average in 2 days prior to starting intervention
    3. Mothers who are English speaking and over 18 years old

    b. Exclusion Criteria:

    1. Major congenital anomalies
    2. Non-English speaking
    3. Family history of suspected congenital hearing loss
    4. Failed hearing test in NICU
    5. Grade 3-4 IVH or PVL
    6. NEC requiring treatment
    7. Congenital infections such as cytomegalovirus which can lead to sensorineural hearing loss

2) For retrospective controls:

   a. Inclusion criteria:

   PTIs born between GA of 28 0/7 weeks and 34 6/7 weeks-

   1. Taking a total daily oral intake < 50% of feeds on average in first 2 days
   2. Mothers who are over 18 years old

   b. Exclusion Criteria:

   1. Major congenital anomalies
   2. Family history of suspected congenital hearing loss
   3. Failed hearing test in NICU
   4. Grade 3-4 IVH or PVL
   5. NEC requiring treatment
   6. Congenital infections such as cytomegalovirus which can lead to sensorineural hearing loss

Sampling Method/Recruitment Process

1. Parents will be approached when the PTI are at 30 weeks and 0/7 days GA or at the time of admission if born at GA greater than 30 weeks and 0/7 days.
2. Principal investigator will make sure potential subjects meet the inclusion/exclusion criteria.
3. The study will not be advertised.

4. We will sample retrospective controls by starting on 1/1/18 and proceed chronologically by the date of admissions till we can identify the first 2 admitted PTIs who meet the following match characteristics:
    a. GA
    b. Sex
    c. Post menstrual age of feeds
    d. Inclusion/exclusion criteria mentioned above
    e. NICU site (ie NICU East and NICU West)

Study Retention/Withdrawal

Subjects will be in the NICU, if the parents decide to withdraw from the study, that will be accounted for and their data will be deleted.

Study Procedures

Prospective cases

1. Informed consent will be obtained from mother after admission to the NICU and prior to initiation of oral feedings at 30 weeks and 0/7 days GA or later.
2. For infants enrolled in the study, mother's voice will be recorded on a study computer using Garage Band software (Apple Inc. Cupertino, CA) by Principal Investigator (PI).
3. For each infant, recordings of at least 30 minutes long in mother's voice of one or more of the following books:
    a. Where the Wild Things Are

b. Book of Lullabies

c. Goodnight Moon

d. Blueberries for Sal

e. Little Bear

f. True Story of 3 Little Pigs

Any other book of the parent's choice.

4. Readiness for oral feeding will be assessed on each infant using FRS.[14] Infant FRS are used as the basis of cue based feeding, which is standard of care. Cue based feeding combines non-nutritive sucking to promote awake behavior for feeding, observing and responding to the infant's behavior cues to regulate frequency, duration and volume of oral feedings.[14]
5. Mother's voice recording will be started 20-30 minutes prior to oral feeding by the nurse. This will coincide with routine nursing care performed prior to each feed. The recording will continue until infants feeding is completed and looped if necessary.
6. If the mother is there, she will be encouraged to read to the baby for 20-30 minutes instead of playing the recording.
7. PTI will be exposed to mother's voice recording for 2 feeds in 24 hour period, once per 12 hour shift. One period of voice exposure will be done during the day and one during the night.
8. NICU nurses, NICU nursing assistant or the mom will feed the baby and we will keep track of the person feeding. The nurses are currently documenting the volume of oral intake, FRS scores, QNS scores and apnea, bradycardia or desaturation events in the

medical records as part of their normal workflow. If the mom is breastfeeding, then milk weights will be used to estimate oral feeding volumes.

9. In order to control for exposure to maternal voice, we will ask the parents to not read to the PTI before and during the control feeding as part of the study consent. We will attempt to include the control feed before the parents come in for the day to visit the PTI, while trying to keep the person feeding the baby consistent between the control and intervention feed.
10. The recording will be played using WavHello SoundBub speakers (WavHello Inc., Los Angeles, CA), and the decibel level will be kept at <65 (using NIOSH Sound Level Meter App[15]) similar to the level used in previous studies.[16]
11. The feed prior to the one with exposure to mother's voice will serve as a control. We will continue the recordings until the PTI reaches full oral intake or 40 weeks postmenstrual age.

<u>Historical controls:</u>

1. Once we consent a patient for the study, we will identify 2 matched controls from infants admitted to our NICUs during 2018 and 2019 based on the sampling methodology detailed above.
2. Starting on day 3 of oral feeds, when the intervention will start, the percentage of intervention feed taken orally will be compared with the percentage of the same day feed as close as possible to the same time for the retrospective controls. For example, if the intervention happens at 9 am on day 3 of feeds, we will be comparing the

percentage of feed taken orally between this feed with the averages of the day 3 oral feedings at 9 am for our historic controls.

3. We will also compare the FRS, QNS scores between our intervention feeds and the average scores of out 2 retrospective controls.
4. We will also look at the documented apnea, bradycardia or desaturation episodes after our intervention feeds with the averages of our 2 retrospective controls.
5. Of note, there have been no major changes in the feeding protocols at the two NICU sites in the last 2 years.

Sample Size Justification

Prospective cases:

This is a pilot project. We expect to enroll 25 eligible infants during our study period. If on average it takes each patient 12 days to get proficient at oral feeding,[17] and we start collecting data on day 3 of oral feeding, that will give us a total of 10 days of data per infant, resulting in 20 data points per patient. As a result, 25 patients should give us approximately 500 data points, giving us an effect size d of 0.12. This sample size will be sufficient to get statistically significant information on the effects of exposure to mother's voice on oral feeding given a low effect rate with an alpha of 0.05 and a power of 80% for rejecting the null hypothesis.

Historical controls:

We expect to compare the data for each of the 25 enrolled eligible infants during our study period to averages of 2 historical controls. Therefore, if on average if takes each patient 12 days to get proficient at oral feeding, and we start collecting data of day 3 of oral feeding, that will

give us a total of 10 days of data per infant enrolled the same as above, giving us 20 data points in total per infant and 500 data points for the 25 case-controls giving up a low effect rate with an alpha of 0.05 and power of 80%, the same as above.

Feasibility, Accrual, and Expected Duration of Accrual

A convenient sample size of all eligible infants admitted to the CT Children's NICU East and CT Children's NICU West between 3/1/2020 and 12/31/2020 will be included. Every year about 180 PTI with GA between 28 0/7 weeks and 34 6/7 weeks are admitted in our NICU at CCMC East and about 110 patients at NICU West. Estimating that approximately 50% of PTI meet our inclusion and exclusion criteria, and an approximately 25-35% consent rate, we will attempt to enroll 25 eligible infants during our study period. We expect to start enrollment at NICU East followed by NICU West if needed.

In addition, we have spoken to multiple individual nurses at both NICU East and NICU West as well as presented the research at the NQRC and included their suggestions in the design of the study. Since the nurses will be doing the bedside data collection sheet, we will do an in-service for them prior to starting the study. In addition, we will create reference documents with the procedure, a bedside job aide and data collection sheet to help smooth the transition for the project (see documents attached)

Study Limitations

One limitation of the study is that the comparison of the feeds will be done with 2 matched retrospective controls as opposed to prospective controls. Another limitation will be the ambient noise in the NICU which the PTI's are exposed at any particular point in time.

Data Analysis

1. **Retrospective data**

    a. Analyzing oral volumes

        i. The enrolled infant will be matched with 2 retrospective controls from the same site as the enrolled infant. Starting on day 3 of oral feeds, when the intervention will start, the percentage of intervention feed taken orally will be compared with the percentage of the same day feed as close as possible to the same time for the retrospective controls using an independent 2 sample t test. For example, if the intervention happens at 9 am on day 3 of feeds, we will be comparing the percentage of feed taken orally between this feed with the averages of the day 3 oral feedings at 9 am for our historic controls.

    b. Analyzing FRS and QNS scores

        i. FRS and QNS scores will matched with 2 historic controls in the same was as mentioned above. Assuming a normal distribution, the results will be compared using an independent 2-sample t test. If they are not found to have a normal distribution using the Shapiro-Wilk test, then we will analyze the discrete variables using the Wilcoxon-Mann-Whitney test.

    c. Analyzing apnea, bradycardia or desaturation events

        i. Total number of apnea, bradycardia or desaturation events in the 3 hours after the intervention feed will be compared to the average of the 2 matched historic controls the same way as described above in point (a),

and being discrete variables, will be analyzed the same way as mentioned in point (b).

2. <u>Prospective data</u>

a. Analyzing oral volumes

i. Oral feeding volumes in percentage of feed taken orally after maternal voice exposure will be compared with oral feed volume immediately before the intervention feed on that day. This will control for learned behavior since any learning should affect both the intervention feed and oral feed in approximately the same way. Results will be analyzed using the single-sample, paired t-test for oral feeding volume. For example, if the intervention feed happens at 9 am on day 3 of feeds, it will be compared with the day 3 feeds at 6 am.

b. Analyzing FRS and QNS scores

i. FRS and QNS scores for the intervention feeds will be compared with the scores for the preceding feed without maternal voice exposure which will serve as the control. Results will be analyzed using the single-sample, paired t-test if the distribution of the discrete data is found to be normal using the Shapiro-Wilk test. If not, we will use the Wilcoxon signed-rank test.

c. Analyzing number of apnea, bradycardia or desaturation events

i. Total number of apnea, bradycardia or desaturation events for 3 hours after the intervention feed will be compared to the number of apnea, bradycardia or desaturation events for the 3 hours after control feed. Results will be analyzed the same way as mentioned above.

3. **Feasibility data**

   a. Analyzing recordings started on time, voice exposure missed, enrollment rate, attrition rate

      i. All of the above variables will be expressed as percentages.

   b. Analyzing effect size

      i. Effect size will be calculated as a percentage change from the control feeds for both the retrospective data and the prospective data as mentioned above. Example: (Intervention feed – control feed)/control feed x 100.

Administrative Organization/Roles and Responsibilities

Aditya Chhikara will be responsible for designing the study, data collection, data analysis and manuscript preparation.

Shabnam Lainwala will be responsible for designing the study, data analysis, and manuscript preparation.

David Sink will be responsible for the design of the study, data analysis, and manuscript preparation.

The PI will keep the data on an electronic Excel spreadsheet in secure password protected computers within a locked office area.

Use of Study Results

The study results will be used to obtain grant funding for the prospective randomized study and the results will be published in presentations and publications in perinatal journals such as Early Human Development or Journal of Perinatology.

Study Budget

The study will be paid from the fellowship funds of Aditya Chhikara.

Significance:

Maternal voices have been associated with increased cardio-respiratory stability and increased synchrony with the PTIs.[8,10,11] If exposure to maternal voices allows for increased feeding, then this would be a useful tool in helping premature infants along as they are learning to eat by mouth, potentially shortening the time it takes for them to learn how to eat. This might then result in shorter stays and concomitant cost savings for all parties involved. In addition, this might also encourage the habit of reading and to PTIs in the parents which might have significant positive long term language and neurodevelopment outcomes for them.[18,19]

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Appendices

Attached to email

Appendix 1: Data collection sheet

Appendix 2: Bedside data collection

Appendix 3: Bedside Job Aide

Appendix 4: Consent form

Appendix 5: Feeding cues and feeding scores

Appendix 6: Patient enrollment data

Appendix 7: Feasibility data

Appendix 8: Bedside consent form summary for nurses