taVNS And N-Acetylcysteine For Oromotor Rehabilitation In Infants Of Diabetic Mothers

NAC + taVNS in IDM Who Are Poor Oral Feeders

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PROTOCOL TITLE:

taVNS and N-Acetylcysteine for Oromotor Rehabilitation in Infants of Diabetic Mothers

PRINCIPAL INVESTIGATOR:

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Study Endpoints (if applicable)

- **Primary outcome variables:** Daily po feeding volumes, comparing volumes before taVNS, to volumes during treatment within group, and comparing slopes of change in feeding volume during treatment between cohorts. We will also compare categorical number of infants who achieve full oral feeds and avoid a G-tube in this group compared to our prior IDM cohort who only received taVNS and were largely non-responders (8/9).
- **Secondary outcomes:** Increase in [GSH] in BG by MRS before and after 3-4 days of NAC; Change in MRS metabolites and DKI metrics in EC, CC, IFOF, PTR, before and after NAC+taVNS treatment.
- **Safety Outcomes:** Gastric intolerance/emesis; bradycardia with taVNS (HR <80bpm for 5 seconds)

Inclusion and Exclusion Criteria/ Study Population

Inclusion Criteria: Infants of diabetic mothers who are failing oral feeding, >39weeks gestation at enrollment, who are clinically stable, on minimal respiratory support (nasal cannula or room air), and clinical team has determined are G-tube candidates. We will include any IDM infant failing oral feeds, without a designated HgbA1c, as glucose control during pregnancy may be unknown in some infants transferred into tertiary care centers. *Thus, we are using the same entry criteria we will employ in a phase II clinical trial.*

Exclusion Criteria:

1) Unstable infants or those requiring respiratory support involving positive pressure.
2) Infants <39 weeks gestation at enrollment.
3) Major unrepaired congenital anomalies or anomalies that limit feeding volumes
4) Infants with cardiomyopathy
5) Repeated episodes of autonomic instability (apnea or bradycardia) which are not self resolving *
6) Inability or unwillingness of subject or legal guardian/representative to give informed consent

*Preterm infants commonly have short periods of shallow or absent breathing or lower heart rate termed apnea and bradycardia, respectively, and most are being treated for these physiologic manifestations of prematurity with caffeine, an effective central stimulant. Infants are on cardiorespiratory monitors through the nursery stay with recording devices to capture events and play them back. However, nearly all of these events are self-resolving, meaning the infant resolves the breathing pause or bradycardia on their own. Infants who require repeated episodes of stimulation to come out of these events are defined as *unstable*. Similarly, infants on significant respiratory support with continuous positive airway pressure (CPAP) device or other form of high respiratory support are not stable enough for oral feeding, and receive only oral stimulation.

Congenital syndromes may be included if the infants do not have major, unrepaired anomalies or anomalies that limit feeding volumes.

We will enroll all IDMs who qualify and whose parents consent to the study including all racial and ethnic groups. We will only enroll neonates and infants of diabetic mothers as this is the group under study and are trying to avoid a G-tube.

Number of Subjects

We will enroll 10 infants of diabetic mothers who are failing oral feeding and have been determined likely to need a G-tube.

Prospective participants will be identified by the PI (Dr. Jenkins) at the Shawn Jenkins Children's Hospital (SJCH) neonatal intensive care units and checked for potential inclusion.

Data Management

Statistical analysis and power analysis: The purpose of this pilot is to determine the effect size, if any, of adding NAC to taVNS, in order to inform our planned R01 clinical trial application. Our proposed sample of 10 IDM infants would allow us to detect moderate effects on the following outcomes due to adding NAC.

1. **Increase in daily po feeding volumes:** Our existing IDM cohort (n=9) had increase of 1.3±1.7 ml/kg/d over 10 days before taVNS, vs 7.0ml/kg/d during taVNS in responders (including the 1 IDM responder). Even with this small sample, 4 IDM responders would allow us to detect a significant difference between prior to and during NAC+taVNS (power 80%, a =0.05, paired t-test).
2. **Number of IDM achieving full oral feeds**: If 6 out of 10 IDMs achieve full oral feeds with NAC+taVNS, we will determine a significant difference in response rate vs taVNS alone (1/9 responders) by X^2 analysis.

Detailed Management Protocol

1. After obtaining consent, a **baseline MRS** will be obtained prior to starting NAC, along with a **baseline (0.5ml) heelstick blood sample in EDTA tubes**.
2. NAC will be started at **75 or 100 mg/kg/dose n.g. q 6h**, **administered 1h before a feed,** for a **total of 14 days**. *All infants have existing n.g. tubes for administering the remaining volume of the feed not taken by mouth. We will monitor for emesis with n.g. NAC administration.*
3. We will follow the clinical practice, based on USP 795 standards for non-sterile preparations (i.e., a 14 day beyond-use date). IDS will dispense a 24-hour supply in 4 unit dose syringes and the patient's **bedside nurse will dilute the dose with sterile water 1:3 prior to NG administration**. **A sterile water flush of 1ml will be given before and after the NAC dose to clear the n.g. tube.**
4. If frequent emesis accompanies NAC ng administration, we will dilute in a greater volume of saline (1:4) and hold a dose to make sure emesis is not due to NAC, but due to some underlying condition such as gastroesophageal reflux
5. After 3-4 days of NAC administration, a **second MRS** will be **obtained within 2hours after a NAC dose**. MRS will be performed without sedation, after a feed with MedVac® swaddling to induce sleep, as per our usual clinical protocol.
6. Blood samples (0.5ml) will be obtained by heelstick before, 1h, 2h and 4h after the NAC dose by heelstick for pharmacokinetic studies, timed around the NAC dose immediately before the MRS scan. Specimens will be stored in the locked Shawn Jenkins Children's Hospital research lab on 2nd floor. Dr. Jenkins will collect patient samples and separate plasma into coded tubes without other identifiers and place in -80 freezer. Dr. Garner will analyze these coded specimens in her lab with Dr Wiest, discarding when samples are spent in the assay or at end of study, when all samples have been analyzed.
7. We will monitor for emesis with NAC administration, though we expect none with n.g. administration. All infants who have not achieved oral feeds have n.g. tubes through which the remainder of the feeds are given.
8. **On day 4 of NAC administration, we will begin twice daily taVNS-paired with bottle feedings**, 30 min each feed, stimulation on while infant is sucking, and off with rest or burping, **for a total of 14 days**.
9. The taVNS protocol will be the same employed for the existing IDM cohort: We will start at 0.2 and increase by 0.1mA until we observe a facial response to taVNS (the perceptual threshold, PT). We will then stimulate at 0.1mA<PT, on with sucking, off with rest. If the infant is crying and not easily consoled during taVNS feed, we will decrease microcurrent to ensure this is not due to change in perception of the stimulation.
10. We will monitor for skin redness on the left ear after taVNS treatment and monitor for transient heart rate decrease upon determining the perceptual threshold, and the rebound in 60 seconds. We will also monitor for heart rate <80bpm for 5 seconds (bradycardia) during taVNS feeding, though we did not observe this in our prior study.
11. We may extend taVNS-paired feedings, if the baby is making substantial progress in feeding volumes, and the parent and clinical team agree. We will not extend NAC dosing.
12. We will perform the **third MRS** after the 14 days of taVNS-paired feeding treatment.

13. MRIs will not be read by hospital neuroradiology, but will be read by Drs. Bhatia and Turner, and if concerns arise, the images will be referred to the clinical team and neuroradiology.

Specimen Collection

1. A baseline (0.5ml) heelstick blood sample in EDTA tubes will be obtained prior to starting NAC.
2. Blood samples (0.5ml) will be obtained before, 1h, 2h and 4h after the NAC dose by heelstick for pharmacokinetic studies, timed around the NAC dose immediately before the MRS scan.
3. Dr Jenkins will collect the blood samples and will labeled them according to participant ID and sample time, without other identifiers.
4. The blood samples will be centrifuged and plasma separated and frozen at -80^{0}C in the Pediatric Clinical Trials room on 2nd floor of SJCH, until samples can be processed for HPLC analysis by Dr. Garner in her and Dr. Wiest's lab in the quadrangle.

Withdrawal of Subjects

- If parents wish to withdraw the infant from the study they may do so at any time, but they may not withdraw from the study procedures and still receive treatment as our outcomes depend on these tests in this very small sample size. We also have limited funds for NAC and cannot afford to continue to pay for the drug and treat without collecting our outcome variables. We may still collect outcome data, but the infant will not continue to receive treatment if the parent wishes to withdraw.

Statistical analysis and power analysis:

3. **Increase in daily po feeding volumes:** Our existing IDM cohort (n=9) had increase of 1.3$\pm$1.7 ml/kg/d over 10 days before taVNS, vs 7.0ml/kg/d during taVNS in responders (including the 1 IDM responder). Even with this small sample, 4 IDM responders would allow us to detect a significant difference between prior to and during NAC+taVNS (power 80%, a =0.05, paired t-test).
4. **Number of IDM achieving full oral feeds**: If 6 out of 10 IDMs achieve full oral feeds with NAC+taVNS, we will determine a significant difference in response rate vs taVNS alone (1/9 responders) by X^2 analysis.
5. **Secondary dMRI outcomes**, using our existing IDM cohort, we expect FA change/week in left PTR (0.031±0.003) in NAC+taVNS responders vs our IDM taVNS (0.016±0.003) requiring 3 in each group, or 8 IDMs for FA change/wk in CC (0.028±0.004 NAC+taVNS vs 0.02±0.006 taVNS alone) with a=0.05, 80% power, t-test (G*Power 3.1).