Study Title: Nasal vs. Oral Intubation for Neonates Requiring Cardiac Surgery

University of Virginia IRB for Health Sciences Research Protocol #20789

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PROTOCOL

Background

1. Provide the scientific background, rationale and relevance of this project.

Neonates requiring cardiac surgery early in infancy frequently develop feeding difficulties including problems reaching full volume nutrition and transitioning to oral feeds. This is a particular challenge because adequate nutrition status is associated with improved outcomes for these patients. Feeding difficulties are multifactorial, and may arise due to prolonged post-operative intubation, surgical complications, or delay in initiating enteral nutrition. This results in longer hospitalizations, and need for invasive feeding interventions like nasogastric or gastrostomy tube feedings.

Kogon et al. (2007) conducted a retrospective review of 83 infants requiring cardiac surgery in their first 15 days of life. They found that 44.6% of these infants had difficulty transitioning from gavage to oral feeds. 9.6% of infants required invasive procedures (gastrostomy tube, Nissen fundoplication) to facilitate feeding. They identified increased risk adjusted congenital heart surgery (RACHS) score and prolonged intubation as risk factors for delayed transition and need for additional feeding procedures. Single ventricle physiology and presence of a shunt were additionally identified as risk factors for additional feeding procedures.

Piggott et all (2018) conducted a retrospective review of 79 neonates who required the Norwood procedure for congenital heart disease in their first 30 days of life. Of these patients, 59.5% required gastrostomy tube placement for feeding before discharge. They identified vocal cord dysfunction and longer duration of postoperative sedative/narcotic infusion as risk factors for gastrostomy tube placement. Patients who required gastrostomy feedings had a significantly longer hospital length of stay.

Skinner et al. (2005) conducted fiberoptic laryngoscopy in 33 neonates after Norwood single ventricle palliation compared with 18 infants after aortic arch reconstruction as part of biventricular repair. In the Norwood group, 48% of infants had some degree of swallowing dysfunction. 9% of Norwood infants were diagnosed with left vocal cord paralysis, 24% had aspiration on barium swallow, and 18% of infants required gastrostomy tube placement for feeding. In the aortic arch reconstruction group, 25% of infants were diagnosed with left vocal cord paralysis, 35% had aspiration on barium swallow, and 11% required gastrostomy tube placement for feeding. They concluded that vocal cord paralysis and aspiration occur in similar frequencies in neonates regardless of single or biventricular repair.

Both oral and nasal intubation routes are considered safe and acceptable in neonates. However, there have been only a few head-to-head trials to compare the two routes to each other in this population. Spitzer et al. (1982) conducted a trial of 86 neonates requiring intubation for mechanical ventilation. Infants were randomized to oral or nasal routes of intubation. The study found that nasally intubated infants had higher rates of post-extubation atelectasis. However, after accounting for weight, they found that the higher risk of post-extubation atelectasis was only present in infants < 1500 grams. Infants > 2500 grams (term size) were not at higher risk of post-extubation atelectasis. There was not a difference in the risk of local trauma (nasal erosions for nasal intubation, palatal groove formation for oral intubation) between groups. McMillan et al. (1986) conducted a trial of 91 neonates requiring intubation for mechanical ventilation. Infants were randomized to oral or nasal routes of intubation. In this study, nasal intubation was unsuccessful in 6 patients, who were subsequently successfully orally intubated without complications. They did not find increased risk of post-extubation atelectasis, endotracheal tube blockage, or accidental extubation in nasal compared to oral routes of intubation.

While both routes are safe and routinely used by cardiac anesthesiologists at UVA, there are several proposed advantages to nasal intubation in the neonatal cardiac population. Firstly, nasotracheal tubes are more comfortable to the patient as well as more easily secured. Because of this, thus patient requires less sedation to prevent accidental extubation. Secondly, without an oral endotracheal tube in place, the infant is able to practice non-nutritive sucking skills in preparation for oral feeding. A study by Pinelli et al. (2005) showed that non-nutritive sucking helped premature infants more quickly transition from gavage to oral feeding. With lower sedation and oral skills development, we believe that nasally intubated patients will more quickly learn to orally feed and avoid the need for gastrostomy.

Objectives/Hypothesis

Hypothesis: Nasotracheal intubation will allow for lighter sedation in the post-operative period as well as more rapid development of oral feeding skills for infants with congenital heart disease.

Primary outcome measures:
1) Time from surgery to full oral feeds.

Secondary outcome measures:
1) Dosage of sedating medications required post-operatively.
2) Hospital length of stay.
3) Need for tube feeds at discharge (NG or gastrostomy).

Study Design: Biomedical

1. Will controls be used?

No. Participants will be randomized to an intervention - either oral or nasal intubation. All infants will be intubated for surgery, so there is not a control group.

►IF YES, explain the kind of controls to be used.

Answer/Response:

2. What is the study design?

Randomized control study

3. Does the study involve a placebo?

No, participants will receive either oral or nasal intubation, both routes are considered safe and acceptable in neonates.

►IF YES, provide a justification for the use of a placebo

Answer/Response:

Human Participants

Ages: <2 weeks at the time of surgery
Sex: Male and female
Race: All

Subjects- see below

1. Provide target # of subjects (at all sites) needed to complete protocol.

A sample of 40 neonates in each group, for a total of 80 neonates, is required to have sufficient statistical power.

2. Describe expected rate of screen failure/ dropouts/withdrawals from all sites.

We anticipate that 10% of neonates will be unobserved on the primary outcome due to post-operative complications including need for ECMO or CPR >5 minutes.

3. How many subjects will be enrolled at all sites?

44 participants per group, for a total of 88

4. How many subjects will sign a consent form under this UVa protocol?

88 participants.

Inclusion/Exclusion Criteria

1. List the criteria for inclusion

- Patient is a neonate requiring cardiac surgery
- Patient is <2 weeks of age at the time of surgery
- Includes families who are educationally or economically disadvantaged
- Includes non-English speaking families

2. List the criteria for exclusion

- Patient has an estimated gestational age <37 weeks at the time of surgery
- Patient has known oro-facial or gastrointestinal anomalies
- Patient has known congenital or acquired devastating neurologic injury
- Patient was intubated for >5 days pre-operatively
- Patient required >5 minutes of CPR pre- or post-operatively
- Patient requires ECMO pre- or post-operatively
- Patient remains intubated two weeks post-operatively.
- Excludes infants >2 weeks of age at the time of surgery and other vulnerable populations including pregnant women, fetuses, prisoners, cognitively impaired

3. List any restrictions on use of other drugs or treatments.

None.

Statistical Considerations

1. Is stratification/randomization involved?

Yes.

►IF YES, describe the stratification/ randomization scheme.

Patients will be randomized to oral or nasal intubation using a block randomization scheme generated by a UVA statistician to generate equally sized oral and nasal groups. The concealment envelope with group assignment will be opened by the anesthesiologist, CRNA, or resident performing intubation at the time of surgery. After intubation, this intervention is impossible to blind. The research team and family will be able to see which group the patient is part of.

►**IF YES, who will generate the randomization scheme?**

_____ Sponsor
___x__ UVa Statistician. Insert name Mark Conaway
_____ UVa Investigational Drug Service (IDS)
_____ Other*:* Specify Answer/Response:

2. What are the statistical considerations for the protocol?

The null hypothesis to be tested is that the mean number of days to full oral feeding is the same with oral or nasal intubation. The alternative hypothesis is two-sided, and states that the mean number of days until full oral feeds differs between oral and nasal intubation.

3. Provide a justification for the sample size used in this protocol.

Preliminary data on 8 neonates yielded an average of 13.5 from surgery to NG tube removal, with a standard deviation of 11.7. With 40 participants per group, the two-sample t-test with unequal variances yields 80% power, with a 2-sided significance level of 5%, when the mean difference in time to oral feeding is 6 days. In this calculation, we assumed that the coefficient of variation is the same in the nasal and oral intubation groups, meaning that the within-group standard deviation is proportion to the mean. Allowing for 10% dropout/withdrawal yields a sample size of 44 per group, for a total of 88 participants.

4. What is your plan for primary variable analysis?

Initial analyses will use the two-sample t-test, and the associated confidence interval, to compare the groups. Secondary analyses of the primary outcome, the number of days until full oral feeding, will be based on negative binomial regression. In addition to providing an unadjusted comparison of the groups, the use of negative binomial regression will also allow us to estimate the difference between the groups adjusting for covariates, such as the RACHS score (estimates risk of cardiac surgery). While we anticipate that the randomization will balance the distribution of these covariates between the groups, the use of these covariates in a model can improve the precision in estimating the difference between the oral and nasal intubation groups.

5. What is your plan for secondary variable analysis?

A two-sample nonparametric test will be used to compare the average dosage of sedating medications required post-operatively. For hospital length of stay, analyses similar to those described above for days until full oral feeding will be used. The third secondary outcome is a binary variable, indicating the need for tube feeds at discharge. The chi-square tests will be used to compare the proportion of participants in each group requiring tube feeding at discharge.

6. Have you been working with a statistician in designing this protocol?

Yes

IF YES, what is their name?

Mark Conaway

7. Will data from multiple sites be combined during analysis?

No

INSTRUCTIONS: IF YES, answer the following questions

7(a). Does the study involve randomization?
Answer/Response:

IF YES, will randomization be done at each site or among sites?
Answer/Response:

7(b). Has the sample size calculation considered the variation among sites?
Answer/Response:

7(c). When combining the data from multiple sites to assess the study results, is the effect of the treatment to be tested (or the association to be tested) assumed to be the same across sites or vary among sites? What is the modelling strategy?
Answer/Response:

7(d). Is there a common protocol used in all sites?
Answer/Response:

IF NO, how will differences among sites, such as those related to the implementation, inclusion criteria, patient characteristics, or other sites characteristics, be considered to assess the study results?
Answer/Response:

Study Procedures-Biomedical Research

1. What will be done in this protocol?

Potential subjects will be identified in the weekly Pediatric Cardiothoracic surgical conference. Subjects' parents will be approached as part of routine pre-operative discussions regarding surgical timing and post-operative expectations. Parents will be introduced to the study, and consented at that time. This will typically take place in the week before surgery, barring emergent changes to the surgical schedule.

Neither oral nor nasal intubation are done purely for research purposes in this protocol. Intubation is a standard and necessary part of the planned cardiothoracic surgery. The cardiac anesthesiologists and CRNAs are experienced in both methods. Typically, the decision of which route is based on clinician decision after assessing the patient. Studies by Spitzer (1982), McMillan (1986), and Xue (2007) demonstrate that both routes are safe in children. Any neonatal intubation carries risk of local trauma, desaturation, and bradycardia. The additional risk of oral intubation is palatal grooving. The additional risks of nasal intubation include nasal ulcers and the possibility of post-extubation atelectasis in infants <1500 grams. Nasal intubation takes slightly more time than oral intubation.

After enrollment, the patient will be randomized with assignment in a sealed envelope. On the day of surgery, the envelope will accompany the patient to the operating room. The anesthesiology team will open the envelope and proceed with the assigned intubation method (oral or nasal). The CRNA or anesthesiologist will intubate using the UVA standard of care. If nasal intubation is complicated by unexpected anatomy (such as choanal atresia), or if the patient cannot tolerate the

longer time required for nasal intubation, then they will be orally intubated for patient's safety. These patients will remain in the study and will be analyzed in the oral intubation group. Intubation route does not affect the subsequent surgery.

The patient will arrive to PICU intubated. The electronic medical record will be used to collect data regarding surgical variables, post-operative sedation needs, and feeding outcomes. The treatment of these patients post-operatively will follow the standard of care PICU procedures, without differences based on study assignment. The post-operative protocols are described briefly here: Sedation needs are determined by standardized sedation scores and nursing protocols. Feeding advances are determined by standardized PICU protocol, with alterations based on RN and MD clinical assessment. The patient will be extubated when clinically appropriate, based on PICU MD assessment. After extubation, the patient is assessed by a Speech-Language Pathologist who determines the patient progress with oral feeding. Data will be collected through hospital discharge.

2. **If this protocol involves study treatment, explain how a subject will be transitioned from study treatment when they have completed their participation in the study.**
This protocol does not involve an experimental treatment. Both oral and nasal intubation are safe methods, and both are routinely used by the pediatric cardiac anesthesiologists at UVA. After intubation, the remainder of the infant's intra- and post-operative care will proceed by the standard of care. The subject will be extubated when clinically appropriate as determined by the PICU MD. If the patient requires emergent re-intubation while in the PICU, it will be performed orally. Patients who are re-intubated will remain part of the study as long as they do not meet other exclusion criteria (ex. Intubated >2 weeks, >5 min CPR, ECMO).

Subject Compliance with Study Procedures

1. **Explain how the study team will monitor the subject for compliance with the study procedures.**
The study anesthesiologists will perform the procedure. There is no need for the patient or family to comply.

2. **Describe criteria for when a subject is considered to be non-compliant with study procedures.**
There is no need for the patient or family to comply. All procedures are performed by the study team.

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