Study Protocol

Official Title: Initiation of Acid Suppression Therapy Prospective Outcomes for Laryngomalacia

ClinicalTrials.gov ID (NCT number): NCT04614974

Protocol Date: 05/14/2021

Scientific Background

Laryngomalacia (LM) is the most common cause of stridor in infants. Symptoms of gastroesophageal reflux (GER) are often seen in the setting of LM; therefore, acid suppression therapy (AST) has been empirically used in the management of this disorder. Our team recently performed a retrospective chart review assessing improvement of airway and dysphagia symptoms, weight gain, and need for surgery with AST. We have found that there was a similar improvement between LM severity groups and the majority of patients received AST. It is unclear if these improvements are due to AST or natural resolution of the disease. With heightened concerns of side effects related to AST in infants, particularly among those born prematurely, judicious use of these medications is needed. We are now performing a prospective study looking at the outcome differences in patients with laryngomalacia who are evaluated by speech language therapy (SLP) alone versus those with SLP evaluation and AST. There is no gold standard in treating mild and moderate LM patients and therefore this study would help establish these guidelines.

Study Objectives

Purpose: To determine the outcome differences in patients 6 months and younger with laryngomalacia and dysphagia who are evaluated by speech language therapy (SLP) alone versus those with both SLP evaluation and acid suppression therapy (AST)

Hypothesis: We hypothesize that there will be no differences in outcomes between those that had SLP alone versus those that had both SLP and AST.

Study Design & Methods

Design: Prospective clinical trial with survey

Methods:

All Department of Pediatric Otolaryngology Airway clinic patients with a referral diagnosis of laryngomalacia will have their medical records screened for eligibility. All eligible families with infants that qualify for the study will be approached the day of clinic by their licensed physician to discuss the study. They will be given the Pittsburgh Airway Symptom Score (PASS) questionnaire and the Infant Gastroesophageal Reflux Questionnaire (I-GERQ-R) at the beginning of the appointment. The physician will then perform the standard procedures at the clinic appointment. The Flexible Laryngoscopy Findings sheet will be filled out in conjunction with the clinic procedures for objective data. The surveys will then be scored to determine true GERD (score >=16) and severe laryngomalacia (LM) (RED questions on the PASS), which would further exclude these patients. There are 12 total questions on the I-GERQ-R. On the PASS, questions 1 & 2 are in the GREEN category and signifies mild LM, YELLOW signifies moderate LM, and RED is severe LM. On the PASS questionnaire, "Yes" to either #1 or #2 and

nothing else is mild LM, "yes" to at least one #3-5 and none of #6-10 is moderate LM, and "yes" to any of the #6-10" indicates severe LM. There are 10 total questions on the PASS.
Mild and moderate LM patients will be block randomized the day before the appointment to receive speech language therapy alone or speech language therapy with famotidine (Pepcid). Both treatments are standard of care in these patients as well as watchful observation. Speech language therapy is part of the normal clinic visit for LM patients. There is no gold standard of care for LM, therefore this trial is important to establish this. Patients will be randomized in both mild and moderate LM blocks before the appointment, as providers are unaware of the severity until the time of the appointment. After the appointment, if the family does not want to participate, the name will be taken off the randomization sheet completely or off the unused block.

These patients will then be re-evaluated at their follow up appointment in 1 to 4 months. The families will take the PASS and I-GERQ-R surveys again to determine LM severity. If Pepcid is discontinued due to intolerance of side effects, they will be kept in the study in the same arm. If the family opts out of the follow-up appointment or they do not need to follow-up in-person, families will take the post surveys via REDCap or by mail. A REDCap link will be sent along with a letter to the caregivers to the caregivers' email address on file. If the families do not fill out the surveys within 2 weeks, paper copies of the surveys along with a letter to the caregivers will be sent to the caregivers' home address on file. If the families do not return the paper copy or the electronic copy of the surveys, researchers will call the participants for a reminder and will ask if the family wants another paper copy or survey link. The family may also answer the survey questions over the phone.

Eligibility Criteria

Inclusion:

- Pediatric patients ages 0 to 6 months who do need meet the criteria at the initial appointment for supraglottoplasty
- Seen in UPMC CHP Otolaryngology Department
- Laryngomalacia without prolonged (>20 seconds) cyanosis, apnea, nor failure to thrive.

Exclusion:

- Children over the age of 6 months old will be excluded from participation.
- Premature infants (<37 weeks gestation)
- Patients with lung disease.
- Laryngomalacia with cyanosis, apnea, and failure to thrive
- Sleep induced laryngomalacia
- Patients with craniofacial abnormalities
- Patients with a syndrome
- Patients with additional airway abnormalities, seen before or at consult
- Patients with symptoms that necessitate surgery
- Patients with prior cardiac surgery
- Patients with AST prescribed prior to the initial ENT consult.

Statistical Analysis Plan

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Study Outcomes

Primary Outcome

- Airway Symptom Score Change From Consult (Baseline) to 3 Month Follow-up Appointment.
    - This will be parent-reported and measured using the Pittsburgh Airway Symptom Score (PASS) questionnaire. The PASS is a scale from 0-10 with a higher score indicating a worse outcome. This outcome will be assessed at the consult and the 3 month follow-up appointment.
- Infant Gastroesophageal Reflux Questionnaire (I-GERQ-R) Score Change From Consult (Baseline) to 3 Month Follow-up Appointment.
    - This will be parent-reported. There are 12 questions on the surveys on a scale of 0-42. A higher score indicates a worse outcome. Those with a score of >=16 on this survey at the initial consult are excluded from the study, indicating true gastroesophageal reflux disease (GERD). This outcome will be assessed at the consult and the 3 month follow-up appointment.
- Change in Incidence of Airway Symptoms From Consult up to 1 Year Assessed Via Electronic Medical Chart Review.
    - Change in incidence of airway symptoms from consult up to 1 year assessed via electronic medical chart review. Notes from the Department of Otolaryngology will be reviewed which include reported symptoms from caregivers and symptoms seen upon exam. Airway symptoms included periods of apnea, chest wall retractions, cyanosis, stridor, noisy breathing, and increased respiratory rate.
- Change in Incidence of Dysphagia Symptoms From Consult up to 1 Year Assessed Via Electronic Medical Chart.
    - Change in incidence of dysphagia symptoms from consult up to 1 year assessed via electronic medical chart review. Notes from the Department of Otolaryngology will be reviewed which include reported symptoms from caregivers and symptoms seen upon exam. Dysphagia symptoms included choking, coughing, gagging with feeds and/or emesis after feeds.

Secondary Outcomes

- Weight (kg) From Consult up to 1 Year.
    - Weight change in kilograms assessed from medical chart review from consult up to 1 year
- Number of Participants With the Need for Supraglottoplasty Surgery (Escalation of Treatment) up to 1 Year.
    - The need for escalation of treatment with supraglottoplasty surgery will be assessed through medical chart review up to 1 year.

- Number of Participants With the Need for Acid Suppression Therapy Medication (Famotidine) From Speech Language Therapy Alone Group From the Day After the Consult up to the 3 Month Follow up Appointment.
    - The speech language therapy alone group will be assessed for the need for a prescription for acid suppression therapy (famotidine) from the day after the consult up to 1 year.
- Number of Participants With Each Type of Laryngomalacia (Types 1-3) Found on the Flexible Laryngoscopy Procedure at the Consult.
    - All patients will be scoped with a flexible laryngoscopy at the initial consult and the type of laryngomalacia (Types 1-3) will be noted.
- Number of Participants With the Need for a Different Acid Suppression Therapy Medication (Other Than Famotidine) From the Day After the Consult up to the 3 Month Follow up Appointment.
    - Both groups will be assessed for the need for a different acid suppression therapy medication (other than famotidine) from the day after the consult up to the 3 month follow up appointment.

Sample Size Calculation

Based on data from Dang et al [1], 62 participants per group will be needed to address the hypothesis that there is no difference in airway symptom improvement between AST and no-AST groups with alpha=.05 and power=.80 (two-tailed Fisher's exact test, G*Power 3.1). Target enrollment will be 160 participants (80 in the AST group and 80 in the no-AST group, with 40 with mild laryngomalacia and 40 with moderate laryngomalacia in each group) to account for attrition.

[1] Dang S, McCoy JL, Shaffer AD, Tobey ABJ, Dohar JE, Simons JP, Maguire RC, Padia R. Initiation of acid suppression therapy for laryngomalacia. Am J Otolaryngol. 2022;43(3):103434. doi:10.1016/j.amjoto.2022.103434

Analyses

Stata/SE 16.1 will be used for all statistical analysis.
P value < .05 will be used for statistical significance.

Baseline characteristics will be compared between AST and no-AST groups using Chi-squared or Fisher's exact test for categorical data and t-test (normally distributed) or Wilcoxon rank-sum (not normally distributed) for continuous data. Primary outcome measures will be change in LASS and I-GERQ-R scores from initial visit to follow-up and change in airway and dysphagia symptoms assessed by chart review during the 1 year following the initial visit. The LASS and I-GERQ-R scores will be compared between initial and follow-up surveys using Wilcoxon signed-rank tests. Change scores (post-pre) will be calculated for LASS and I-GERQ-R, and differences in the improvement in scores based on laryngomalacia severity or randomization group will be evaluated using Wilcoxon rank-sum tests. Associations between LASS or I-GERQ-R and time between initial and follow-up surveys will be evaluated using Spearman rank correlation. Symptoms and weight at initial and follow-up visits will be compared using McNemar's and Wilcoxon signed-rank tests, respectively. Change in weight percentile based on laryngomalacia severity or randomization group will be evaluated using Wilcoxon rank-sum tests.

Cross-Over
Intent-to-treat analysis will be performed.

Analysis Inclusion
Only those who meet eligibility criteria will be included in the final analysis. Specific outcome measures will be ascertained only in patients who complete follow-up questionnaires, as indicated.

Missing Data
Data imputation will not be used for missing data.

Harms

Serious adverse events and non-serious adverse events resulting in emergency department visits will be collected up until 1 year following the initial consult appointment.