PCH IRB# 17-136

Title: A Multi-Center Randomized Trial of Transanastomotic Tube for Proximal Esophageal Atresia with Distal Tracheoesophageal Fistula Repair

PROTOCOL

Short Title: RCT TT TEF

NCT03730454

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Study PI: Justin Lee, MD

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Background/Purpose

Esophageal atresia a congenital condition requiring surgical intervention. The most common configuration is Gross type C, proximal EA with distal TEF (EA/TEF). The operation for type C includes tracheoesophageal fistula closure and esophageal anastomosis creation. Overall survival has improved dramatically in the past 50 years, 85%-95% in recent reviews as compared to 40% in the 1950s. [1-9] Although mortality has markedly decreased since the operation was first described, overall complication rate remains at 62%, with the most common complication being esophageal anastomotic stricture, 43%. [10]

During the creation of esophageal anastomosis, two common practices are either to use or not to use a transanastomtic tube (TT) across the anastomosis. The utility and benefits of TT have not been validated, however. In fact, there is a growing body of literature proving safety of omitting routine transanastomotic tubes and trends away from routine transanastomotic tubes placement. Patel et al. reported a retrospective review of 40 cases over a 12-year period where they found 17 cases managed without TT and early introduction of oral feeds were tolerated without an increased complication rate. [15] Albbad et al. reviewed 20 type C cases (9 with TT and 11 without TT) and found no difference in anastomotic strictures between those with or without TT. There was also no difference in time to first enteral feed, TPN duration, time to full enteral feeds, or total length of stay between those with or without TT. [16] A 15-year single center review of 110 esophageal atresia repairs found that TT does not protect against anastomotic leak but increase stricture rate. [18] An animal model study compared rabbits undergoing esophageal anastomosis with TT or without TT. Rabbits with TT had decreased diameter of the esophageal lumen, bursting pressure, and tissue hydroxproline in comparison to rabbits without TT. [17]. The Midwestern Pediatric Surgical Research Consortium published the largest multi-institutional retrospective review of 292 type C esophageal atresia repairs.[10] On univariate analysis, only utilization of a TT was significantly associated with strictures ($p=0.013$). On multivariate analysis after adjusting for both preoperative and perioperative variables, TT use remained significant with an odd ratio (OR) of 1.91 ($p=0.04$).
Despite the lack of rigorous data elucidating clinical benefits and efficacy, transanastomotic tubes are widely utilized in North America and Europe, with utilization rate of nearly 80% in recent reviews. [11-14]

Given the inherent limitations and biases of single center or retrospective analysis, there is a critical need for a prospective randomized multi-institutional study to validate the role of TT. The Western Pediatric Surgical Research Consortium (WPSRC) consists of 10 children's hospitals, including Phoenix Children's, Doernbecher Children's Hospital, Primary Children's Hospital, Lucille Packard Children's Hospital, Seattle Children's Hospital, Colorado Children's Hospital, Children's Hospital of Los Angeles, Rady Children's Hospital, Benioff Children's Hospital, and University of Texas Southwestern Medical Center (Children's Medical Center of Dallas). The WPSRC will conduct a prospective randomized control trial comparing the effects of TT use. Target enrollment is 150 type C esophageal atresia repair patients. Subjects will be randomized to surgical repair either with or without transanstomotic tube (TT). Primary outcome will be symptomatic anastomotic stricture development requiring dilation within 12 months.

National Clinical Trial number:

The NCT number for this study is NCT03730454

Hypothesis

We hypothesize that the use of TT during esophageal anastomosis creation will result in increased anastomotic stricture rate.

Specific Aims

- To compare anastomotic stricture rate (primary outcome) between the two groups of esophageal atresia repair with or without transanastomotic tubes.
- To evaluate associated risk factors for development of anastomotic strictures, including gap length, anastomotic leak, and postoperative acid suppression.
- To document treatment strategies (preoperative, intraoperative, and postoperative) and associated primary and secondary outcomes.

Method

Study Design

This is a prospective, multicenter, randomized control study conducted at nine hospitals: Phoenix Children's, Doernbecher Children's Hospital, Intermountain Primary Children's Hospital, Lucile Packard Children's Hospital, Seattle Children's Hospital, Children's Hospital Colorado, Children's Hospital Los Angeles, Rady Children's Hospital, Benioff Children's Hospital, and University of Texas Southwestern Medical Center (Children's Medical Center of Dallas).

- Group A will undergo standard repair of esophageal atresia and tracheoesophageal fistula closure. On completion of the esophageal anastomosis, a 5 FR transanastomotic tube ***will be*** left in place across the esophageal anastomosis for 5 days.
- Group B will undergo standard repair of esophageal atresia and tracheoesophageal fistula closure. On completion of the esophageal anastomosis, a transanastomotic tube ***will NOT*** be left in place across the esophageal anastomosis for 5 days

After the 5-day period, the surgeon may choose to keep the tube in place for postoperative feeding or place a tube in for postoperative feeding. If the transanastomotic tube is unintentionally removed before 5 days, the decision to replace the tube will be at the treating physician's discretion. The subject will remain in the study with early removal noted. Preoperative workup, intraoperative, and postoperative management at each participating institution will be documented and further analyzed.

Randomization Process

We created 15 blocks of 10 per block randomized within block either Group A or Group B. We anticipate each site to contribute minimum 10 cases and maximum 50 cases.

Study Population

Infants diagnosed with proximal esophageal atresia and distal tracheoesophageal fistula who are surgically repaired with primary esophageal anastomosis will be selected for the study. We anticipate each site to contribute minimum 10 cases and maximum 50 cases. Once each hospital receives Institutional Review Board approval, research staff will screen (to determine study eligibility) and collect data according to following criteria:

Inclusion Criteria

- Infants diagnosed with type C esophageal atresia: proximal esophageal atresia and distal tracheoesophageal fistula
- Primary repair of the esophageal atresia within the first six months of life
- Minimum follow up of 1 year (12 months)

Exclusion Criteria

- Other types of esophageal atresia without esophageal anastomosis creation
- Major anomaly that influences likelihood of developing primary outcome or affects surgical treatment considerations

When the parent/legally authorized representative (LAR) is not physically available for the consenting process, remote consenting will be attempted using Docusign or a Docusign equivalent (see Appendix 2 for Docusign consent guidance). If the parent/LAR does not have access to remote consenting, telephone consent is permissible given: 1) the time-sensitive nature of the procedure, and 2) that these cases are usually transferred to tertiary referral centers, and thus the parent/LAR and infant are often not in the same building. If telephone consenting is used, the study team will attempt to fax a copy of the consent form to the parent/LAR for review. However, as soon as possible, the LAR must be provided with a written copy of the informed consent to complete and sign, along with the consenting individual and/or study investigator (see Appendix 1 for telephone consent guidance).

Study Duration Enrollment of the study is anticipated to continue for approximately 24 months after initiation of the study.

Follow Up

All patients enrolled in the study will be followed up to 12 months. Follow-up will be the equivalent of standard of care at each institution, which, for example, is often 2-week post-operative appointments and annual visits. Given that the primary outcome will be symptomatic anastomotic stricture development requiring dilation within 12 months, a phone call or follow-up visit is required to ensure that no data is missed at 12 months post-operation.

- Assess for signs/symptoms of anastomotic stricture
- Based on symptoms determine the need for imaging studies and endoscopic dilation

- Determine durability and effectiveness of endoscopic dilation
- Assess for secondary outcomes of the study including reflux symptoms, tracheomalacia, oral aversion, and all cause readmission rate.

Data Collection

A standardized dataset will be collected from all enrolled patients at all participating sites within the WPSRC. Patient data capture will begin from available prenatal data to deliver and continue throughout preoperative, intraoperative and postoperative course. A minimum of 12-month follow up will be obtained in order to characterize long-term outcomes. Research staff from each site will be in charge of documenting each patient's prenatal course, in-hospital course, and follow- up visits. For a detailed list of all data variables to be collected, please refer to the attached data collection forms and REDCap data dictionary codebook. For data form completion, please refer to the study Manual of Operation. All data will be collected and managed using REDCap (Research Electronic data capture) software hosted at Phoenix Children's. All study data will be validated both centrally and at each individual institution for completeness of data entry and accuracy. Missing data will be reobtained to the degree possible, and outliers will be reconfirmed to be accurate.

Data Management/Storage

Data will be collected and entered remotely from each site into a REDCap based application. The pooled data will be stored, maintained, and protected at the Phoenix Children's Research Institute Data. Research Electronic Data Capture (REDCap) is a secure web-based application which provides an intuitive interface for collection of research data. This system offers access via secure authentication (user ID and password) by clinical site users through the Internet, has audit trails for data manipulation and user activity, and can easily export data into formats for use in major statistical packages. Phoenix Children's is a REDCap consortium institutional partner. Data will be stored on a MySQL database server that is housed in a HIPAA-compliant server room and protected by a firewall.

The coordinating center will be responsible for creating, designing, and customizing the project in REDCap. Since the study qualifies as human subjects' research, all sites must have IRB approval prior to gaining access to the REDCap data platform for this study. Each collaborating site will manage its own patient data and protection of PHI and privacy. All data entered into the database will be visible to approved research staff from the coordinating site. Upon study completion and if requested from a participating investigator; a completely de-identified dataset(s) will be provided by the coordinating site.

Statistical Plan

Phoenix Children's will be responsible for data analysis. Statistical support will be provided by the University of Arizona College of Medicine. Services will include ongoing consultation, sample size and power calculations, statistical analyses, and result reporting. Statistical analysis will be performed using statistical software and will include but not limited to descriptive

statistics, regression analysis to assess associations, univariate and multivariate associations, and binary outcomes and rates. The data analysis will be set up to determine risk factors for primary and secondary outcomes of this study.

The overall stricture rate, with or without the tube, is estimated to be 43% [10]. The sample size was calculated by referencing the most recent retrospective multivariate analysis where they found 48% stricture rate in the tube group and 25% stricture rate in the no tube group. Based on this retrospective study we calculated 68 in each group to reject the null hypothesis that the stricture rate is equal with probability (power) 0.8. The type I error probability associated with this test of this null hypothesis is 0.05. We will use an uncorrected chi-squared statistic to evaluate this null hypothesis. Statistical analysis and calculations have been reviewed by Paul Kang (paulk@email.arizona.edu) statistician from the University Of Arizona College Of Public Health, Division of Epidemiology and Biostatistics,

Outcomes

Primary

Primary Outcome Measures:

1. Symptomatic anastomotic stricture requiring dilation (time frame: up to 12 months)

Secondary Outcome Measures: (see Manual of Operation for a complete list of secondary outcomes)

1. Anastomotic leak: (time frame: up to 12 months)
2. Recurrent fistula: (time frame: up to 12 months)
3. Vocal cord injury: (time frame: up to 12 months)
4. Unplanned return to OR: (time frame: up to 12 months)
5. Duration of parenteral nutrition: (time frame: up to 12 months)
6. Length of stay: (time frame: up to 12 months)

Potential Pitfalls and Strengths

As has been previously mentioned, the use of a transanastomotic tube (TT) during the esophageal anastomosis creation has been debated in the literature with no clear answer. Proponents of TTs believe that TTs can allow earlier initiation of enteral feeds and potentially prevent anastomotic leak and stent the anastomosis. The largest available retrospective data would refute the benefits of TTs with no difference in the median number of postoperative days until initiation of enteral feeds in repairs with TT versus without TT (8.0 days versus 9.4 days, p=0.24). [10] All the available studies in the literature are retrospective studies that allow only for associations and not causation between variables and outcomes. The surgical practice has not changed based on the retrospective findings, proven by the fact that nearly 80% of the repairs are performed with TTs.[10] The decision to use a TT could also represent a selection bias since we do not know reasons for using the TT such as long gap, comorbidities, or intraoperative findings.

In addition, the literature does not have a consistent definition of long gap or what constitutes anastomosis under tension.

The strength of this study will be its prospective, randomized, and multicenter design. Prospective design will validate a causation between TT and stricture development. Randomization process will incorporate all other known and presumed risk factors for anastomotic stricture. All known risk factors will be analyzed for confounding effects: including but not limited to distance between proximal and distal gap, tension at the anastomosis, anastomotic leak, and postoperative acid suppression use. Multicenter design will allow for accruement of larger sample size alleviating the small sample size limitations of the existing studies in the literature. The critical data collection will be the anastomotic tension and distance. We have created multiple different metrics of distance and anastomotic tension.

1) Preoperative chest x-ray: Number of vertebral bodies between the proximal esophageal pouch and carina (with proximal tube pushing down on the proximal pouch)
2) Intraoperative measurement of the distance between the anastomosis and tracheoesophageal fistula closure site.
3) Need for any intraoperative lengthening procedures such as mobilization, myotomy, or flap lengthening maneuvers.
4) Surgeon subjective assessment of the anastomotic tension: (none, mild, moderate, and severe)

Potential Risks/Benefits

Infant participation and all other preoperative, intraoperative, and postoperative management will not deviate from current clinical practices and involves no more than minimal risks. Since there are no experimental procedures, no medications, and no additional labs ordered for this study, the study poses no potential medical risks to patients. The data collecting research staff will abstract the required data elements from the hospital, registry, and clinic notes but will not participate in patient care. The primary risk of this study is confined to maintaining patient confidentiality. To minimize the risk of confidentiality loss, the research staff will adhere to the following: All hard copies of research records from individual subjects containing identifiable and private information will be secured (locked), stored, and accessible only to research staff. All electronic research records meeting the above criteria will be computer password protected and securely stored in the REDCap database. Any transfer of de-identified data will be done in an encrypted manner. Code numbers will be used to identify the patient in the data collections forms and in REDCap. Patient identifiers will be destroyed as early as possible. Presentations or publications based on the results of this study will not contain identifiers or linkage to individual patients.

The most common complication remains anastomotic stricture and the morbidity of anastomotic stricture includes series of endoscopic dilations and increased resource utilization. Although the use of transanastomotic tube remains historically favored and currently the most common practice pattern, there appears to be little rationale to continue to routinely use transanasotmtoic tube. A retrospective multi-institutional analysis by the Midwest Pediatric Surgical Consortium identified the use of transanastomotic tube as the most statistically significant predictor of

developing anastomotic stricture. However, skepticism about this finding remains and a real change in the surgical practice remains to be seen for various reasons. First, esophageal atresia is a rare disease, occurring with an incidence of 1 in 3500 live births. [19] As for many other rare diseases, most available studies on esophageal atresia are small retrospective series from tertiary centers, and the quality of the data remains limited due to the low statistical power and selection bias. Second, practice pattern variations in the operative approach and postoperative management is immense. [20] Third, the volume of EAs repaired per year per surgeon remains small, 1-3 cases in 67% of the practicing pediatric surgeons. [20]. There is a critical need for multi-institutional prospective studies with large patient numbers to achieve the data that can lead to best practices and reduction in health care costs. The impact of a multi-institutional prospective randomized control trial is likely to strongly influence the surgical behavior and change the management of esophageal atresia repair. We believe that this study will significantly contribute to determining the ideal intraoperative and postoperative management of the type C esophageal atresia and tracheoesophageal fistula.

Data Safety Monitoring Board

An independent data safety monitoring board (DSMB) will review and analyze safety data on a regular basis for the conduct of this study. The coordinating site has developed a data monitoring plan to ensure the accuracy and integrity of the study data utilizing guidance provided by the National Institutes of Health and University of California Irvine (see below outline)[21-25]. In summary, this is a multi-institutional investigation within the Western Pediatric Surgical Research Consortium. This group holds monthly teleconferences to discuss study activities. During this call, participating sites can connect and address operational, enrollment, and data collection issues, report study progress, and offer feedback and insight to "Frequently Asked Questions" which will be created and accumulated. Each site will perform an internal audit(s) for data source verification, data completeness, and data accuracy. REDCap data reports will be generated at intervals to assess for data completeness. In addition, research coordinators and investigators from each site may be asked to prepare monthly or quarterly reports documenting compliance and enrollment numbers. During the duration of the study, statistical services and epidemiological consultation will be available to the coordinating site.

I. Roles and Responsibilities

The primary responsibilities of the Data and Safety Monitoring Board (DSMB) are to

1) Periodically review and evaluate the accumulated study data for participant safety, study conduct, progress, and quality of completed study data

2) Make recommendations to the consortium concerning the continuation, modification, or termination of the trial.

II. Membership

The membership of the DSMB will reflect the disciplines and medical specialties necessary to interpret the data from the clinical trial and to fully evaluate participant safety.

Three members selected are

Dr. Deborah Tom, Medical Staff Section Chief, NICU Medical Director, Phoenix Children's

Dr. Luis Goncalves, Director of Fetal Imaging, Phoenix Children's

Dr. Michelle Kim, Pediatric Anesthesiologist, Phoenix Children's

The membership will reflect:

- Expert(s) in the clinical aspects of the disease/patient population being studied;
- Investigators with expertise in current clinical trials conduct and methodology.

Ad hoc specialists may be invited to participate at any time if additional expertise is desired.

Conflict of Interest

No member of the DSMB should have financial, proprietary, professional, or other interests that may affect impartial, independent decision-making by the DSMB.

III. Meetings

The DSMB will meet when 50% of the data has been collected and at the conclusion of data collection. At the initial meeting, the DSMB should discuss the overall background, study design, protocol, manual of operation, and data collection list. Statistical guidelines will be discussed to address stopping the study for safety concerns and, where relevant, for efficacy based on plans specified in the protocol. The DSMB will convene to examine the accumulated safety and enrollment data, review study progress, and discuss other factors (internal or external to the study) that might impact continuation of the study as designed. Meetings may be held by conference calls or videoconferences or as face-to-face meetings.

DSMB Meeting Format

Open Session: Issues relating to the general conduct and progress of the study are discussed including adverse events, enrollment, demographic characteristics, comparability of groups with respect to baseline factors, protocol compliance, site performance, quality control, and timeliness and completeness of follow-up. Outcomes and efficacy data are reviewed with the study statistician available for consultation at this session. The lead investigator and the study biostatistician should be in attendance in order to present results and respond to questions. This session is open to study investigators, and research coordinating staff.

IV. Study Reports for DSMB Meetings

Reports are prepared by the principal investigator and study statistician. Reports for meetings of the DSMB consist of two separate parts:

Part I: Data Quality Report

Upon completion of Data User Agreement, if required by participating sites, the lead principal investigator will generate a report of data completeness, timeliness, and accuracy of data collection from REDCap. All collected cases will be reviewed by the participating sites and the lead principal investigator and shared with the DSMB.

Party II: Study Safety Report

This report will include study-related adverse events, adherence to the protocol performance of participating centers, and confidentiality of the study data (such as protocol violations, unmasking, etc.). Factors external to the study such as scientific or therapeutic developments that may impact participant safety or the ethics of the study will be addressed if applicable.

VI. Reports from the DSMB

The DSMB should conclude each review with their recommendations to the consortium as to whether the study should continue without change, be modified, or be terminated.

1) Continuation without change
2) Modification(s) necessary based upon the review of the safety data
3) Early termination of the study due to concerns about subjects' safety, inadequate performance, rate of enrollment, or statistical guidelines.

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Appendix 1: Telephone Consent Process

(Version 2, 03.2020, drafted by Jodie Greenberg, based on model from Carrie Rau at Primary Children's)

- When the parent/legally authorized representative (LAR) is not physically available for the consenting process, telephone consent is permissible given: 1) the time-sensitive nature of the procedure, and 2) that these cases are usually transferred to tertiary referral centers, and thus the parent/LAR and infant are often not in the same building.
- As soon as possible, the LAR at the treating hospital must be provided with a copy of the consent form.
- At that point, the remainder of the consenting process must be followed:
    - Clarification of any study details and procedures.
    - If there are any further questions to be answered.
    - Obtain appropriate signatures and dates from all parties involved, including the LAR, consenting individual, and investigator (all dates should be entered on the day the form was signed and not the date of the phone call).
    - Review for completeness and accuracy.
    - Provide a copy of the form(s) to the LAR.

Telephone Discussion and Consent Form Signatures

- Ensure that all aspects of the consenting documents are reviewed and that participant's questions have been answered.
- Ask the LAR if they would like to participate.
- Discuss any additional sections on the consenting documents that need to be answered/signed.

If remote subject has received copy of the consenting documents or when LAR receives the consent form in person:

- Confirm that the LAR has read the consenting documents in their entirety.
- Guide the LAR where to sign.
- Remind the LAR to leave the "person obtaining consent" and "investigator" lines blank.
- Explain in detail to LAR to bring the consenting documents back to the hospital where the baby is being treated (or how to otherwise send back to study team).

Document all details of the remote consent process:

- Create a note documenting each stage of the consenting process that has taken place.
    - Please utilize local regulations for this process (e.g,, At Phoenix Children's a consent documentation checklist is mandated).
- Document when the consent was presented to the patient's legally authorized representative.
- Document when the phone call took place, the details of what was discussed, and what questions were asked

If applicable:

- When the partially signed consent was received and when it was signed by the study team
- Any errors and how they are/will be corrected.
- When a copy of the fully signed consenting documents were given to the subject.

Appendix 2: Docusign Consent Process

1. If LAR is not present in-person, call them telephonically to discuss the study.

2. If LAR has access to Docusign (requires email and access to inbox), send over TEF Consent Form and have the investigator review with the LAR over the phone.

3. If LAR agrees to participate, they will print name, sign, and date in the designated fields. If the LAR decides not to participate, void the document in Docusign stating that the LAR chose not to participate in the study.

4. Once LAR has completed their section consenting to participate, the investigator and person obtaining consent will be notified and prompted to complete their section of the consent form via email.

5. Once the form is completed, send a copy to the LAR for their records.