

**WATCHFUL WAITING: DEFERRED LADD PROCEDURE IN PATIENTS WITH CONGENITAL HEART
DISEASE, HETEROTAXY SYNDROME, AND KNOWN INTESTINAL MALROTATION**

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Abstract

Purpose: Infants born with Heterotaxy Syndrome (HS) often have intestinal malrotation in addition to severe congenital heart disease (CHD). Given the catastrophic risk of midgut volvulus, where the vascular supply to the gut is cut off causing necrotic bowel and possible future short-gut syndrome following surgery, an elective Ladd procedure is recommended at the first diagnosis of malrotation. In patients with severe CHD, however, the risk of complications from prophylactic surgery is high, especially in infancy prior to stable cardiac palliation. This study sought to determine whether deferring a Ladd procedure during the first six months of life in infants with CHD is safe by focusing on the incidence of volvulus in the HS population, morbidity of volvulus and morbidity of an elective Ladd procedure.

Methods: Medical records of patients with HS and intestinal malrotation at Phoenix Children's Hospital from 2006-2011 were reviewed. Stage of heart surgery, severity of heart disease, diagnosis of intestinal malrotation, and timing of Ladd procedure if applicable were recorded.

Results: 31 patients with HS and intestinal malrotation were identified. Of the 31, 9 had a Ladd procedure prior to six months of age, 2 for volvulus and the other 7 either electively or for less severe GI symptoms that were not suggestive of volvulus. The other 22 did not have a Ladd procedure prior to six months of age. There was one death (1/22) from a non-gastrointestinal cause in a patient who had not undergone a Ladd procedure. There were no deaths in the 9 patients who underwent a Ladd procedure (0/9).

Conclusions: Given the low overall incidence of volvulus in HS, and with continued vigilance for obstructive symptoms, this study suggests that delaying the Ladd procedure in asymptomatic patients with HS and CHD and intestinal malrotation is safe. Watchful waiting may reduce the incidence of cardiac complications during the Ladd procedure by allowing for stabilizing cardiac surgical palliation prior to elective abdominal surgery.

Table of contents

Introduction/Significance	Page 1
Research Materials and Methods	Page 4
Results	Page 5
Discussion	Page 6
Future Directions	Page 13
Conclusions	Page 14

List of Figures and Tables

Table 1 - Results	Page 7
Table 2 – Demographics	Page 8
Table 3 - Cardiac Diagnoses	Page 9
Table 4 - Statistics	Page 10

Introduction/Significance

Heterotaxy Syndrome (HS) is a disorder characterized by abnormal positioning of organs in the body. The positioning of the organs along the body's axis happens during the first 1-3 months of fetal development, but the cause of HS is still unknown.¹ There is variable cardiac, intestinal and splenic anatomy among patients with HS. Up to 90% of children with HS have intestinal malrotation,² which is abnormal arrangement of the bowels. Normal arrangement of the organs of the thoracic and abdominal cavity are on a left-right axis and this is called "situs solitus." A complete reversal of this is called "situs inversus." HS is neither of these but rather a lack of sidedness that manifests itself clinically in complicated cardiac disease and malrotation of the bowels. It is sometimes referred to as "situs ambiguous."¹ It has been estimated that the prevalence of "situs ambiguous" is about 1 in 10,000 live births.³

Prior to advances in cardiac surgery the mortality rate for those with HS was high secondary to their cardiac disease. With advances in cardiac surgery, however, the mortality rate today is much lower in these infants. Now, controversy surrounds the prophylactic use of Ladd procedure in this population group as although those with HS are surviving longer, they still have complex physiology and the surgery and anesthesia is not without its risks and risks are increased in this population.^{1,4,5,6,7} One study demonstrated that patients with HS undergoing cardiac surgeries had increased "mean length of postoperative hospital stay (17 vs 11 days)" increased need for mechanical ventilation (11 vs 4 days)" along with "elevated were rates of tracheostomies (6.9% vs 1.6%; odds ratio, 4.6), extracorporeal membrane oxygenation support (12.6% vs 4.9%: odds ratio, 2.8), prolonged ventilatory courses (23% vs 12.3%; odds ratio, 2.1) and postsurgical deaths (16.1% vs 4.7%; odds ratio, 3.9)" when compared to control groups with cardiac disease but not HS.⁵ Another study that specifically looked at the Ladd procedure revealed "a complication rate of 57% after a prophylactic Ladd procedure compared with a complication rate of 9% in the symptomatic non-HS population."²

Peritoneal bands known as “Bands of Ladd” are often present in patients with intestinal malrotation and HS. These “Bands of Ladd” attach the cecum to the abdominal wall inappropriately in the right upper quadrant. “Bands of Ladd” and intestinal malrotation are worrisome because they create a substrate for intestinal volvulus. Intestinal volvulus is the twisting of a loop of intestine upon its mesenteric vascular supply, which can lead to life threatening bowel ischemia and necrosis. In addition to death secondary to volvulus, a lifetime of short gut syndrome can happen after the dead bowel is removed. Because of the devastating risk of intestinal volvulus and the known safety and efficacy of the Ladd procedure in other patient populations⁸ the current standard of care is to perform prophylactic Ladd procedure for anyone with known intestinal malrotation at or near the time of initial diagnosis.

The Ladd procedure is a surgical operation in which a surgeon divides the bands of Ladd, repositions the cecum and colon into a more orthotopic position, and usually performs an elective appendectomy. The Ladd procedure eliminates the majority of the risk for intestinal volvulus.

The rationale behind this study was that just 10-20 years ago patients with severe cardiac abnormalities from heterotaxy syndrome had mortality rates that were so high from their cardiac abnormalities the secondary problems of possible volvulus were not addressed as death occurred before incidence (Chang). Through medical and surgical innovation this population group is living past the neonatal period and the prophylactic indication and timeframe for Ladd procedure may be different than that of other population groups.⁹

Aims of the study:

- Determine the incidence of volvulus in the HS population.
- Determine the risk of death or emergent surgery in the HS no-Ladd procedure population.

Our hypothesis was that the Ladd procedure for asymptomatic patients with severe cardiac abnormalities from heterotaxy syndrome is not indicated in infancy prior to corrective heart surgery because the risk of the treatment likely exceeds the risk of ongoing observation in this group of asymptomatic infants with high-risk cardiac anatomy.

Research Materials and Methods

Institutional Review Board (IRB) approval was obtained from Phoenix Children's Hospital with IRB deferral approval from the University of Arizona College of Medicine - Phoenix. A retrospective chart review of charts from Phoenix Children's Hospital from 2006-2011 was completed. Patients were identified by International Classification of Diseases - Volume 9 (ICD-9) codes, as well as the Current Procedural Terminology (CPT) Code for the Ladd procedure. The codes used are listed as follows:

- ICD-9 Intestinal malrotation - 751.4, 751.8, 751.9
- ICD-9 Cardiac malpositions/dextrocardia/heterotaxy - 746.87
- ICD-9 Ladd Procedure - 54.95
- CPT Ladd Procedure – 44055

Using the list generated from searching those codes in the electronic health record from 2006-2011, patients were then manually screened and separated into cohorts. Cohorts are as follows below:

Cohort 1: Heterotaxy Syndrome Elective Ladd Group (HSEL): Patients with Heterotaxy Syndrome (HS) who underwent an prophylactic Ladd's procedure in their first 6 months of life at Phoenix Children's Hospital during the time period of 2006-2011.

Cohort 2: Heterotaxy Syndrome No Ladd Group (HSNL): Patients with Heterotaxy Syndrome (HS) who did not undergo an prophylactic Ladd's procedure in their first 6 months of life at Phoenix Children's Hospital during the time period of 2006-2011.

Cohort 3: Non-Heterotaxy Syndrome + Ladd Group (NHSL): Patients without Heterotaxy Syndrome or other structural heart disease that underwent a prophylactic Ladd's procedure during their first 6 months of life at Phoenix Children's Hospital during time period of 2006-2011.

Results

Cohorts 1 & 2: Heterotaxy Syndrome Elective Ladd Group (HSEL) & Heterotaxy Syndrome No Ladd Group (HSNL):

A total of 31 patients with HS and intestinal malrotation were identified. Of the 31, 9 had a Ladd procedure prior to six months of age, 2 for volvulus and the other 7 either electively or for less severe GI symptoms that were not suggestive of volvulus. Non-volvulus was confirmed by intra-operative records.

The other 22 children with HS did not have a Ladd procedure prior to six months of age. There was one death (1/22) after 6 months of age (at age 18 months) from a non-gastrointestinal cause in a patient who had not undergone a Ladd procedure. The cause of death was cardiac arrest during an elective catheterization. It was confirmed this patient's death was unrelated to malrotation and lack of receiving a Ladd procedure.

There were no deaths in the 9 patients who underwent a Ladd procedure (0/9) in their first 6 months of life.

Cohort 3: Non-Heterotaxy Syndrome + Ladd Group (NHSL):

A total of 109 children with malrotation without HS were identified from records. They were identified using the malrotation and/or Ladd procedure code. Of the 109, 34 children without HS were identified as having an elective Ladd before 6 months of age. Also from the 109, 18 were identified as having a volvulus and requiring an emergent Ladd procedure before 6 months of age. The rest, 57, were identified by having a Ladd procedure after 6 months of age.

There was one presumed death in the group that had a Ladd procedure prior to 6 months of age, but it was unrelated to the procedure. Records show patient being sent home to hospice secondary to complications from a chromosomal anomaly, but no death record was available for further specifics.

In comparing incidence of volvulus before 6 months of age, patients without HS seem to have a higher incidence: 24.0% (18/75) in NHS group vs. 8.3% (2/24) in HS group. This gives the NHS group an odds ratio of 0.317. The HS group odds ratio for volvulus was 0.091. The relative risk (RR) of volvulus NHS vs HS is 3.47 showing increased risk for NHS patients (p-value = 0.089 using Barnard's test). Numbers for patient groups are shown in Table 1 and statistics are shown in Table 4.

Table 1**Results**

	HS n = 31	NHS n = 109
Ladd procedure before 6 months, no volvulus	7	34
Ladd procedure before 6 months, with volvulus	2	18
Did not have Ladd procedure before 6 months	22	57
Total	31	109

HS = Heterotaxy Syndrome; NHS = Non-Heterotaxy Syndrome

Table 1: Results from data collection

Table 2**Demographics**

Characteristic	HS received elective Ladd procedure prior to six months	HS did not receive Ladd procedure prior to 6 months	NHS received elective Ladd procedure prior to six months	p-value
% Male	57% (4 males, 3 females)	27% (6 males, 16 females)	56% (19 males, 15 females)	
Mean Birth weight (kilograms)	3.284	3.150	2.498	P=NS between HS groups; Significant between HSNL and NSH at p=0.041559 and between HSEL and NHS p=0.029203.
Mean Weight last visit before six months (kilograms)	4.984	6.151	4.953	P=NS between HS groups; Significant between HSNL and NSH at p=0.015739; between HSEL and NHS p=NS.
Mean Age at last visit before six months (months)	4.250	4	4	P=NS for all groups
Mean O2 sat at last visit before six months	87%	85%	98%	P=NS between HS groups; Significant between HSNL and NHS and between HSEL and NHS at p = < 0.00001

Table 2: Demographics and comparison of patients studied

Table 3**Cardiac Diagnoses of patients with Heterotaxy Syndrome who received an elective Ladd Procedure**

Patient no.	Cardiac Diagnoses
1	SV, bilateral superior vena cava, unbalanced AV septal defect, PA, TAPVR, discontinuous pulmonary arteries
2	DILV, left AV valve atresia
3	DORV, AV canal defect, D-TGA, PS, mesocardia
4	SV, Mild PS, D-TGA, interrupted IVC, DIV, common AV valve, double outlet chamber with d-transposition
5	2 ventricles, interrupted aortic arch, hypoplastic aortic arch, multiple VSDs
6	Complete AV canal, COA with interrupted IVC
7	Unbalanced AV septal defect, D-TGA, severe pulmonary stenosis

SV single ventricle, *PA* pulmonary atresia, *TAPVR* total anomalous pulmonary venous return, *DILV* double inlet left ventricle, *AV* atrioventricular, *DORV* double outlet right ventricle, *PS* pulmonic stenosis, *D-TGA* d-transposition of great arteries, *DIV* double inlet ventricle, *VSD* ventricular septal defect

Table 3: Anatomy of heart of the patients with HS who received an elective Ladd procedure

Table 4**Statistics**

		p-value (Barnard)
Incidence of volvulus in HS Cohort that did not have an elective Ladd Procedure	8.3% (2/24)	
Incidence of volvulus in NHS Cohort that did not have an elective Ladd Procedure	24.0% (18/75)	
Relative Risk of volvulus NHS vs HS	3.47 (risk increased in NHS)	0.089
Odds Ratio of volvulus for HS	0.091	
Odds Ratio of volvulus for NHS	0.317	

Table 4: Statistical analysis of results

Discussion

The main finding of this study is that the risk of volvulus in HS appears low. It was interesting to find in this study that there were only 2 deaths and they were unrelated to malrotation or the Ladd procedure. It was hypothesized that the mortality from the Ladd procedure in those with HS would be high and would give that conclusion that “watchful waiting” in asymptomatic patients with HS is best. The findings of only 2 deaths unrelated to the Ladd procedure would not suggest watchful waiting, but, what does suggest watchful waiting from this study is that patients without HS seem to have a higher incidence of volvulus: 24.0% (18/75) in NHS group vs. 8.3% (2/24) in HS group along with the fact that no catastrophic events happened from watchful waiting. Due to their cardiac disease patients it is very likely these patients with HS are at or near an inpatient tertiary center where prompt surgical evaluation and operation can take place quickly if necessary. Although the numbers regarding relative risk in this study were not statistically significant (p-value = 0.089), the Papillion paper suggests the same finding. Papillion goes on to explain it may be related to type of malrotation in patients with HS that is protective against volvulus.⁴

Additionally, the true incidence of midgut volvulus in patients with heterotaxy syndrome and malrotation is not known. Prospective studies involving these high-risk patients will help determine the risk of volvulus in this patient population compared to patients without congenital heart disease who have what is called typical malrotation. Currently, it is thought that patients with heterotaxy syndrome are at lower risk for volvulus and the reasons are only theoretical. Patients with heterotaxy syndrome and atypical malrotation may have malposition of the duodenum and inversion of the superior mesenteric artery and vein on radiological studies but when the anatomy is evaluated with laparoscopy, they often have a wide mesentery of the small intestine and minimal Ladd’s bands. They have some other anatomical challenges that may require intervention, such as proximal obstruction of the duodenum or jejunum from bands to the porta hepatis and centrally located gallbladder. Some of these patients also have gastric anatomy that makes them prone to outlet obstruction with the pylorus located retrogastric in the right upper quadrant. So some patients who may not need

intervention to prevent the possibility of midgut volvulus may need intervention for feeding intolerance. That intervention carries the risk of postoperative bowel obstruction and the benefits of the surgery must be balanced with the risk in these fragile cardiac patients.

Adding weight to this theory that those with HS have less risk of volvulus is a study by Hill et al out of Emory University and Children's Healthcare of Atlanta that suggests that the direction of atrial isomerization in patients with HS may help predict true malrotation. The current data suggests anywhere from 40% to 90% of patients with HS have malrotation.² The study by Hill shows that HS patients with left atrial isomerization (LAI) have less of an incidence of true malrotation when malrotation is investigated. Their conclusion was expectant management should be considered in the asymptomatic patient with HS with LAI. This also helps to point to a reason why those with HS in this study have less incidence of volvulus; those with HS, at least those with LAI, have less malrotation than was once believed.¹⁰

Due to the small number of HS patients undergoing elective Ladd, we were unable to demonstrate any increase or decrease in mortality for those receiving an elective Ladd procedure.

It is worth discussing the papers of those that advocate for a prophylactic Ladd procedure. Yu et al suggested that elective Ladd procedure was well tolerated by HS patients and should therefore be offered to every patient with HS. Their thought process was that the patients have the same complication rate as the general population. While our study was underpowered to address this, this may suggest that the decreased incidence of volvulus in the HS population is notable. Mortality of HS patients was great in the Yu study vs NHS patients.⁷

A paper by Tashjian et al also makes the argument for a prophylactic Ladd procedure showing a 14% risk of postoperative bowel obstruction after an elective Ladd procedure. Their argument was the same as Yu's in that the "small but significant incidence of midgut volvulus in patients with malrotation" is reason enough to perform an elective Ladd procedure being that it has "an acceptably low morbidity."⁶

Future Directions

Being a retrospective chart review, this study lends itself to the beginning of a prospective trial regarding the management of patients with HS and malrotation. Given the low numbers of patients with HS a randomized controlled trial at one center may not be feasible. That being said, we would recommend, based on the results of this study and supported by the work of others, watchful waiting on patients with HS during their first month of life. Our suggestion regarding the management of patients with HS would be watchful waiting. One recommendation to ensure that patients with HS receive prompt surgical evaluation if presenting with signs of volvulus, would be to create a registry of patients with heterotaxy so that when they enter an emergency room with any sort of GI symptom the general surgery staff are immediately notified to investigate if potentially the child has volvulus. For this record of safety to continue a high level of suspicion and sufficient parent education for symptoms of volvulus would be recommended for any child with heterotaxy who has not undergone a Ladd procedure.

Another consideration for future studies is the radiographic diagnosis vs. the intra-operative diagnosis of malrotation. The Papillion study suggests radiographic evidence of malrotation on upper gastrointestinal fluoroscopy (UGI) does not translate into true malrotation when operative records are reviewed. The Papillion study came to the same conclusion as this study: "While rotation abnormalities are common in heterotaxy, risk of volvulus is low. Following operation, the risk of bowel obstruction and of need for reoperation is higher. We advocate avoiding operation in the asymptomatic patient."⁴ Similar studies are needed to properly assess the pre-operative radiographic findings in HS to best make decisions for each individual patient.

Conclusions

Given the low overall incidence of volvulus in HS, and with continued vigilance for obstructive symptoms, this study suggests that delaying the Ladd procedure in asymptomatic patients with HS and CHD and intestinal malrotation is safe. Watchful waiting may reduce the incidence of cardiac complications during the Ladd procedure by allowing for stabilizing cardiac surgical palliation prior to elective abdominal surgery.

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