TITLE

A randomized controlled prospective study to compare the incidence of biliary complications after liver transplantation

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Aim
To prospectively compare the incidence of biliary complications after liver transplantation in patients who are randomized to undergo biliary reconstruction with and without biliary stents.

Secondary Aim
To retrospectively evaluate the incidence of biliary complications after liver transplantation in non-randomized patients who undergo biliary reconstruction with or without biliary stents in the same time period.

Background
Despite tremendous advances in other areas of orthotopic liver transplantation, biliary reconstruction remains a major hurdle. Morbidity related to biliary complications has been estimated to be as high as 30%.[1] The risk of biliary complications can be related to the type of transplant performed and the technique used for reconstruction of the bile duct. One of the main techniques of performing biliary reconstruction is a choledochocholedochostomy which can be performed over an anastomotic stent. Although placement of biliary stents is routine practice in many liver transplant centers around the country, there is no evidence to support their use. As of now both the placement and non-placement of a stent are essentially "standard of care. What has been extensively studied in the literature is the use T-tubes. In the early years of liver transplant, T-tubes were touted as a great mechanism to prevent anastomotic biliary strictures.[2] However, their unanimous use is no longer supported as several retrospective and prospective studies have shown that their routine use led to more biliary complications including bile leaks, cholangitis, displacement of the tube, and bile duct obstruction.[3-5] Although, biliary stricture formation may been have prevented, the rate of biliary complications did not offset this benefit. This was largely due to the fact that a T-tube created an additional defect in the bile duct wall. Given these findings, in the 1990s, many transplant centers started performing biliary reconstruction without the use of T-tubes.[6]

In our center, many of our transplant surgeons now perform the biliary anastomosis over a pediatric feeding tube which is used as a stent. The hope is that use of these internal stents will help prevent post-operative biliary strictures without the added risk of biliary complications seen with T-tubes. It is expected that the stent will migrate out on its own in the early days/weeks after a transplant. However, the practice of using stents in biliary anastomosis is not uniform and there are no established guidelines to support their indiscriminate application. We have designed a prospective randomized trial to evaluate the effect of stent placement on biliary complications and its effect on morbidity.

Study Design
A randomized prospective study will be conducted of patients at Vanderbilt University Medical Center (VUMC) who undergo liver transplantation from March 1st, 2014 until approximately 120 patients are randomized. We will simultaneously perform a review of patients at VUMC who undergo liver transplantation but cannot be randomized for logistical reasons (i.e. hepatic encephalopathy, timing of the transplant procedure, or

language barriers). Data from the two groups will be evaluated independently and comparatively. The inclusion of both groups of data is critical to avoid bias in the findings due to inadvertent selection of patients who may not have the same risk for biliary complications. All data will be de-identified and stored using a secure database, REDCap.

Inclusion Criteria

- 18years and older
- Have receive a decreased full size liver graft
- Need for hepaticojejunostomies or reduced size grafts

Recruitment

Informed consent will be sought from new patients undergoing evaluation from liver transplant during their clinic visit with the transplant surgeon. For those patients currently on the waitlist for transplant, who have already undergone evaluation, consent will be sought during their subsequent upcoming clinic visits before transplant. We will also seek out patients who are currently hospitalized and are on the liver transplant waitlist. Lastly, for those patients with no clinic visits in the near future but for whom transplant is imminent, we will reach out to them at their preferred contact number to discuss the proposed project and seek informed consent.

Due to timing of the liver transplant procedure or the ability of the patient to understand the informed consent document, some patients may not be able to provide informed consent and will not qualify for randomization. Use of a stent in these patients will be determined at the discretion of the surgeon. A retrospective review of the data for these patients will be conducted.

Randomization

Patients will be prospectively randomized to 2 groups.

- Group 1 will undergo biliary reconstruction with stent placement at the anastomosis site.
- Group 2 will undergo biliary reconstruction without stent placement.

Randomization will be performed with sealed envelopes before liver transplantation. The envelope will be opened during the operation and the randomization arm will be revealed to the surgeon immediately prior to the start of the biliary anastomoses.

Surgical Procedure

The surgical procedures are standardized. The operation will be performed exclusively by

5 hepatobiliary surgery attendings, each with individual experience of over 100 liver transplantations.

Follow-up Procedure

The patient will be followed up per standard of care for their liver transplant.

If they were randomized to receive a stent placement, they will undergo an abdominal x-ray about 3 months after transplant. This x-ray is to see if the stent has been retained in the bile duct or if it needs to be extracted by an endoscopic procedure. This abdominal x-ray is standard of care.

Outcome

Our primary outcome of interest is biliary complications. We will compare the incidence of biliary strictures, biliary leaks, cholangitis, and stones between the group that receives biliary stents and the group that does not. We will determine the time interval between transplantation to the occurrence of a complication. We will collect data on reoperations, conversion to hepaticojejunostomies, performance of an endoscopic retrograde cholangiopancreatography (ERCP) and additional hospital days incurred as a result of the biliary complication.

Statistical Analysis

The probability of being free of a biliary complication and the probability of liver graft survival will be estimated by the Kaplan Meier method. Continuous variables will be analyzed using Student's t test, or Wilcoxon's rank sum test. Categorical variables will be analyzed using Chi-square test or Fisher's exact test. Multivariable proportional hazards regression will be performed to adjust potential confounders. A P value of <0.05 will be considered statistically significant.

Limitations

Potential confounders include the etiology of liver disease, the patient's age at the time of transplant, the donor age, gender, body mass index, MELD score, the total operation time, cold ischemia time and warm ischemia time.

References:

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2. Shaked A. Use of T-tube in liver transplantation. Liver Transpl Surg 1997; 3 (5 suppl 1):22–23.
3. Stratta RJ, Wood RP, Langnas AN. Diagnosis and treatment of biliary tract complications after orthotopic liver transplantation. Surgery 1989; 106: 675–684

4. Vallera RA, Cotton PB, Clavien PA. Biliary reconstruction for liver transplantation and management of biliary complications: overview and survey of current practices in the United States. Liver Transpl Surg 1995; 1 (3): 143–152.
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Appendix 1

Data Sheet

Patient age at time of transplant
Gender
BMI
Etiology of cirrhosis
Listed MELD score
Calculated MELD score based on the MELD-Na formula
Total operation time
Cold ischemia time
Warm ischemia time
Stent placed at time of biliary reconstruction
Biliary complication
Type of biliary complication
- Leak
- Stricture
- Cholangitis
- Biliary stones
- Retained stent
  - Additional procedure for stent extraction
  - Cost of procedure
  - Complications from this additional procedure

Management of biliary complication
- ERCP
- Sphicterotomy

Time to first biliary complication from time of transplant
Length of hospital stay for biliary complication
Readmissions
- Time to first readmission
- Indication for readmission