# **Research Protocol**

##### Research Project Title (Full)

A randomized controlled non-inferiority trial comparing early outcomes following duct to duct biliary anastomosis either with or without stent placement in adult patients undergoing whole liver transplantation.

##### Research Project Title (Short)

The utility of bile duct stent placement in liver transplantation

##### Investigators

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##### BACKGROUND

The decision to use trans-anastomotic biliary stents in liver transplant is predominantly at the discretion of the surgeon and influenced by previous practice rather than scientific evidence. The preferred technique for biliary reconstitution during liver transplant is a choledochocholedochostomy (duct to duct anastomosis). This technique is associated with a lower rate of biliary complications compared to hepaticojejunostomy, it also has the added advantage of easy access to the biliary system via endoscopic retrograde cholangiography (ERCP) to manage complications when they do occur.

The estimated incidence of biliary complications following liver transplantation ranges between 10 and 25%. These complications can cause significant morbidity, retransplantation and mortality. The biliary complication rate is higher in split liver grafts or grafts that have been donated after cardiac death (DCD). Presently, there is conflicting research as to whether bile duct stenting is advantageous, detrimental or no different to the absence of a stent. Retrospective observational data from the Princess Alexandra Hospital (PAH) published by Ong and colleagues did not identify a difference in biliary complications but did show that stented patients were more likely to require further intervention (Ong M, 2018). Due to the limitations in observational data, a randomized controlled trial was proposed to validate these findings.

The perceived advantages of a biliary stent include reduction in biliary complications especially when the bile duct diameter is small. Disadvantages include stent blockage and the requirement for post-operative endoscopic intervention in the event of a retained stent.

##### *OBJECTIVES*

The purpose of this study is to quantitatively compare early outcomes following duct to duct anastomosis during whole liver transplantation with or without a biliary stent. Randomised comparative data showing non-inferiority in the stent-free group could result in fewer post-operative biliary/endoscopic interventions, and change our current, non-standardised practice.

##### *HYPOTHESIS*

Biliary stent placement during duct to duct anastomosis in whole liver transplantation confers no benefit with respect to biliary anastomotic complications when compared to a stent-free anastomosis but does result in a greater number of post-operative interventions to remove retained stents.

##### MEthods

*TRIAL DESIGN*

A single-blinded randomised controlled trial with parallel treatment arms will be conducted. Patients in the control arm will receive a biliary stent (stent group). Patients in the treatment arm will not receive a biliary stent (no-stent group). Allocation ratio will be 1:1 across the two arms.

*PARTICIPANTS*

Eligibility Criteria

Participants in the trial will be adult patients on the liver transplant waiting list who are planned to receive a whole liver allograft with a duct to duct biliary anastomosis from brain dead donors. Surgeons in the liver transplant team who have agreed to participate in this trial will have the allocation arm disclosed to them after complete graft reperfusion including completion of the arterial anastomosis. The allocation to stent or no-stent must be adhered to, to reduce selection bias. Contingency planning for a surgeon who is not comfortable with the allocation will be to have an alternative surgeon available to perform the anastomosis.

Exclusion Criteria

Patients will be excluded from the project if they are planned to receive any graft other than a whole liver from a brain dead donor. Given the higher biliary complication rate in split liver and DCD grafts these have been excluded. Patients who have a biliary reconstruction involving a hepaticoenterostomy will also be excluded. On occasion it is necessary to defer biliary reconstruction because of bleeding or because of recipient haemodynamic instability. This event occurs uncommonly, but has the potential to skew results because biliary complications are likely to be higher, and allocation may be asymmetrical across arms.

Setting

Princess Alexandra Hospital, Brisbane, Australia is the location of this single centre study. Participants will be approached during established transplant suitability work-up, in both outpatient and inpatient scenarios. Randomization will occur prior to allocation of the first participant. Allocation disclosure to the surgeon will take place following completion of all vascular anastomoses, prior to the biliary anastomosis. This avoids any subconscious procedural bias up to the point of the biliary anastomosis. *Monitoring and a*ssessment of outcomes will occur in a combination of inpatient and outpatient settings.

Enrolment Process

Participants meeting inclusion criteria will be approached in the outpatient and inpatient setting. The medical staff on the transplant team will initiate discussion with the aid of an information brochure. Other members of the transplant team include clinical nurse coordinators. Culturally appropriate support persons and interpreters will be available where required. The participant will be given the opportunity for questions and time to deliberate on the decision to be involved. Informed consent will be required and documented prior to participation in the trial.

When a participant presents for admission for liver transplantation further opportunity for questions will be offered and consent will be confirmed. The participant will be advised that they can decide to opt out of the project at any time up until they commence anaesthesia. Only patients consenting to enrolment will be included in statistical analysis. Opting out prior to anaesthesia will not impact on the allocation sequence, or results, because disclosure of the treatment arm will occur after this point i.e. intraoperatively. Outcome measures will be recorded on patients who initially consent but subsequently drop out prior to intervention to allow for post-hoc analysis if concerns arise regarding unrecognized influences creating selection bias e.g. surgeon influence on patient participation prior to allocation.

Data Collection

Data will be prospectively collected at specific time points. At enrollment into the trial the participant details are added to a power trials chart accessible by the three investigators on the hospital hard drive. The signed consent forms will also be uploaded to this interface. Once the participant has been allocated, data input into an excel spreadsheet will occur perioperatively (during admission), upon discharge and at routine 6 month follow up appointment. Additional entries will occur if there are admissions for complications.

Information will be gathered from patient electronic medical records for a period of 6 months post-transplant to assess for biliary complications and secondary outcome measures.

Data Management

Data will be stored on the PAH hard drive accessible only to the investigators in this study. Disclosure of information will be for the purposes of presentation or publication and the data will be de-identified and presented in statistical format. Upon completion of the project the folder will be deleted to maintain patient confidentiality.

Patient withdrawal

A participant can withdraw at any time from the study up until they are taken into the operating theatre and anaesthesia is commenced. There will be no implications to withdrawal and liver transplantation will proceed as planned. If a patient does initially consent and then decide to withdraw consent this will be recorded for post-hoc analysis.

*INTERVENTIONS*

The intervention required in the control arm or stent group is the placement of a trans-anastomotic stent during the duct to duct anastomosis of a liver transplant. The stent is an infant feeding catheter composed of polyvinyl chloride cut to a length that allows it to be positioned across the anastomosis and through the Sphincter of Oddi. The length is approximately 150mm with the proximal end positioned in the common hepatic duct and the distal end in the duodenum. The diameter of the catheter used is at the surgeon discretion and is either 05 or 06 CH, corresponding to outer diameters of 1.67mm and 2.00mm respectively.

No intervention is required in the treatment arm (no-stent group) as the biliary anastomosis is performed without a stent.

*OUTCOME MEASURES*

Pre-intervention baseline characteristics of the donor liver allograft and recipient will be accounted for by randomisation. Donor age and cold and warm ischaemic times will be measured. Recipient age, aetiology and indication for liver transplant as well as Model for End-Stage Liver Disease (MELD) score will be collated. Differences across study arms will be assessed for statistical significance. Intraoperative documentation of the transit time flow measurement across the vascular anastomoses and documented complexity or difficulty associated with the vascular anastomoses will also be recorded (e.g. utilization of vascular grafts or performing the arterial anastomosis more than once). Post-intervention events including early and late complications will be documented.

Primary outcomes will be biliary complications including bile leak and stricture formation for a period of 6 months post transplant. Bile leak is defined as a clinically significant leak resulting in delayed removal of postoperative drains or requiring intervention (percutaneous, endoscopic or operative). Bile duct stricture is defined as a clinically significant stenosis requiring radiological or surgical intervention.

Secondary outcomes include requirement for further intervention including re-operation, ERCP or percutaneous transhepatic cholangiography (PTC) and mortality. Complications related to stent placement (including blockage) and its extraction by endoscopy will also be assessed.

*SAMPLE SIZE*

A sample size of 80 patients was calculated to provide a statistically significant result with 95% confidence and 80% power using an online power calculator (http://powerandsamplesize.com). The retrospective observational data generated from Ong et al showed a biliary complication rate of 29.9% and 7.9% in the control (stent group n=88) and treatment arms (no stent group n= 37) respectively. A 10% non-inferiority margin was deemed clinically acceptable.

*RANDOMISATION TECHNIQUE*

Randomisation will be achieved by a computer-generated table using the online website (<https://www.sealedenvelope.com)>. Allocation to study arms will be in a 1:1 ratio, in blocks of 20 to minimise asymmetrical allocation on completion of patient accrual. Each allocation (stent, or no stent) will be printed and placed in order (1-100) in an opaque sealed (with glue and staple) envelope by three investigators and stored within a secure combination-lock safe. Only the three investigators and the clinical nurse coordinator (CNC) for liver transplant in operating theatres will know the four-digit code to minimise any potential observer/investigator interference. One of these four persons will be available at the allocation time to access the safe.

*BLINDING*

Randomisation will occur prior to commencement of the study and will be blinded to all participants except the three investigators. Allocation will be revealed to the operating surgeon after the vascular anastomoses are completed during liver transplant. One of the three investigators or the CNC will access the safe and inform the surgeon of the allocation result. The patients will be blinded to the allocation until they are informed that an abdominal x-ray is required to assess stent position 4 weeks post liver transplant. Assessors will be independent of the randomization and allocation process.

*STATISTICAL TECHNIQUE*

**Detail of statistical methods and subgroup analyses**

##### results

*PARTICIPANT FLOW*

Consort flow diagram will be utilised as the proforma for participant flow through the trial



*RECRUITMENT*

Participant recruitment will begin 1st March 2019 for two years. Outcomes will be measured up to 6 months post transplant.

##### other information

*REGISTRATION OF TRIAL*

**The trial will be registered on the Australia and New Zealand Clinical Trials Registry (ANZCTR)**

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##### *Resources*

No additional resources or funding are required for this project. The use of biliary stents is currently an option during liver transplantation. The stent is an infant feeding catheter readily available in theatre stores.

Device

Approved name: Infant feeding catheter

Composition: Polyvinyl chloride

Supplier: Queensland Health

Approved indication: Nasogastric feeding

Believed mode of action: Decompression of bile duct

Known adverse events: Blockage

Known contra-indications or warnings: Nil known

##### references

Ong M, Slater K, Hodgkinson P, Dunn N, Fawcett J. To stent or not to stent: the use of transanastomotic biliary stents in liver transplantation and patient outcomes. ANZ J Surg. 2017; 88 :603-606.

Consort checklist: https://jamanetwork.com/journals/jama/fullarticle/1487502