Protocol #: 21-4214
Project Title:
Phase I clinical trial utilizing direct peritoneal resuscitation in liver transplant recipient population at increased risk of return to the operating room and early allograft dysfunction.
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Version Date: v11.01.21

I. Hypotheses and Specific Aims:
The central hypothesis is that direct peritoneal resuscitation is a safe therapy following liver transplantation and is associated with a reduced rate of return to the operating room.

AIM 1: Determine the safety profile of direct peritoneal resuscitation on liver transplant recipients at risk of return to the operating room and ICU admission. Hypothesis: Liver transplant recipients that receive DPR will have comparable complication rates to historic controls of liver transplant recipients with similar demographics.

AIM 2: Identify if direct peritoneal resuscitation demonstrates a trend towards a reduced rate of return to the operating room compared to historic controls. Hypothesis: DPR will demonstrate a trend of a reduce rate of return to the operating room of liver transplant patients after index operation compared to historic controls.

AIM 3: Identify if direct peritoneal resuscitation reduces the rate of early allograft dysfunction and other organ failure following liver transplantation with interval improvement in post-operative fibrinolysis activity. Hypothesis: DPR will reduce the rate of EAD of liver transplant patients compared to historic controls and is associated with increased fibrinolysis in the post-operative period.

II. Background and Significance:
The demand for a liver to treat end stage liver disease exceeds available organs, resulting in the preventable deaths of thousands of patients per year in the United States. Attempts to increase organ availability by liberalizing donor criteria with multiple comorbidities has resulted in a higher rate of organs with early allograft dysfunction (EAD). EAD is associated with a seven-fold increased risk of graft failure within the first five years of transplantation and 10-fold increase in mortality. EAD is common and there are no effective treatments. Due to slow function of the liver in EAD, bleeding following transplant is also prolonged and results in a higher rate of returning to the operating room after the initial operation for washout of old blood. Direct peritoneal resuscitation (DPR) is a technique used to reduce edema and improve the endothelium function through hypertonic dialysate infusion of the peritoneal cavity following hemorrhagic shock in trauma. DPR has also been described to have beneficial effects on the liver including increasing portal blood flow and reduced inflammation outside of liver transplantation. DPR may be an effective strategy to improve graft dysfunction following liver transplantation but has not been utilized in this context, and the mechanisms for improved liver function remain elusive. We believe DPR following liver transplant has three potential mechanisms to improve outcomes in liver transplantation. 1) Mechanical washout of retained blood in the abdomen to reduce the need for returning to the operating room 2) reduced edema of intra-

abdominal organs after transplant resulting in improved organ function. 3) Improve endothelium dysfunction of the liver resulting in a recovery of the coagulation system with improve clotting and resolution of fibrinolysis resistance. The last mechanism is particularly relevant to our work in liver transplantation, as we have recently appreciated that liver transplant recipients that sustain fibrinolysis resistance after surgery have an increased rate of EAD. DPR has the potential to be a therapeutic strategy to treat EAD, which occurs in 1 inf 3 liver transplant patients, which currently has no treatment. Conducting a phase I clinical trial on the safety of DPR in liver transplant recipients is an important first step in identification of a clinical strategy can reduce multiple operation in liver transplant surgery, attenuate EAD, and will provide important translation information if the mechanism of improved graft function is linked to regaining homeostasis of the fibrinolytic system.

III. Preliminary Studies/Progress Report:

Direct peritoneal resuscitation (DPR) is a strategy utilized in damage control trauma surgery to reduce visceral edema and improve organ perfusion[1]. We have used DPR as salvage therapy in four liver transplant patients with primary non function of the liver that had open abdomens due to visceral edema, to bridge them to successful re-transplantation. These four patients did not experience any complications related to the DPR treatment that we were aware of. All four patient when taken back to operating room for planned staged operation had significantly less blood in their abdomen than expected with resolution of bowel edema. The use of DPR in following liver transplantation has not previously been utilized to assess if this strategy can improve graft function following surgery. The University of Colorado completes over 100 liver transplants per year (100-130). The percent of potentially eligible patients for this study is estimated to be 10%. We anticipate completion of the study in 18 months after initiation.

IV. Research Methods

A. Outcome Measure(s):

- Primary outcome: Percent of patients that complete DPR infusion without reaching stopping criteria
- Secondary outcomes:
    - Rate of return to the operating room after index operation
        - Contrast to historic controls in existing research protocol (current n=21)
    - Abdominal compartment syndrome requiring reoperation
    - Percent of patients that complete DPR infusion
    - Percent of patients that are transferred to hospital ward
    - Rate of early allograft dysfunction
    - Blood product requirements during first 24 hours postoperatively
    - Need for renal replacement therapy (i.e. hemodialysis) during the first 7 days postoperatively
    - Hourly urine output for first 24 hours
    - Early infection (<7 days post-op)
        - Abscess
        - Peritonitis
        - Bacteremia
        - Pneumonia
    - Late infection (≥7 - 30 days post-op)

        - Abscess
        - Peritonitis
        - Bacteremia
        - Pneumonia
    - Mechanical bowel obstruction
    - Ileus/time to oral intake
    - Duration of insulin infusion post-operatively
    - Ventilator free days (up to 28 days post-op)
    - ICU free days (up to 28 days post-op)
    - Graft loss
    - Mortality
    - Need for chest tube during index hospitalization
    - Need for additional drainage during index hospitalization
    - Coagulation changes during peri-operative period
    - Hernia rate at 3 months following transplant

B. Description of Population to be Enrolled:

Liver transplant patients that meet inclusion/exclusion criteria will be asked if they would like to participate in this research study and will be consented prior to transplant. The rationale for using this patient population is that they historically have a high rate of ICU admission (>80%) after surgery, often require a second operation (>60%), and have renal dysfunction that would potentially benefit from peritoneal dialysis. Basic science data in animal models supports that DPR improves liver function after hemorrhagic shock[1], and could be beneficial to all liver transplant recipients, as these liver grafts undergo complete exsanguination in the donor prior to transplant. However, due to the placing of additional catheters and unproven benefit, this strategy cannot be justified in liberal use in this patient population.

Inclusion criteria:

- Adult liver transplant recipients ≥18 y/o
- Ability to consent
- Pre-operative Creatinine ≥1.1 (or on dialysis) and BMI ≥30

Exclusion criteria:

- Diaphragmatic injury
- Active spontaneous bacterial peritonitis (SBP) with initiation of antibiotic treatment within 72 hours of surgery

Stopping Criteria

- Drain output < DPR infusion for 2 consecutive hours
- RBC transfusion exceeds 10 units within first 24 hours of leaving OR
- Concern for abdominal compartment syndrome based on attending/fellow clinician judgment, or confirmatory assessment in sedated patients with anuria, increasing lactate, and bladder pressure > 15 mm hg

C. Study Design and Research Methods

We propose a phase I clinical trial to target a liver transplant recipient population at increased risk of return to the operating room and EAD, which will undergo close post-operative observation in the intensive care unit or post-anesthesia care unit undergoing extended stay.

Patients will be approached for consent if they meet eligibility criteria (BMI ≥ 30 and creatinine ≥ 1.1 or on dialysis) and are listed as a top 10 waitlist candidate based on blood group. The top ten patients are discussed at a weekly selection meeting and are closely followed by the transplant coordinators. If the patient is eligible for the study, a research team member will approach patient during routine pre-transplant clinic visits. Alternatively, due to numerous patients living in different states or long distances from UCHealth, a research team member may reach out and obtain phone consent with a witness. Patients that consent for enrollment in the study will be reminded at the time of hospital admission for their liver transplant that they consented to participate in the study. Patients that agree to proceed will have this documented in their electronic medical health record, with a chart review confirming BMI ≥ 30 and creatinine ≥ 1.1 or on dialysis. Patients that decide to decline study participation or don't meet criteria at hospital admission will have electronic medical record documentation that they will not participate in the study, and the attending surgeon will be notified from the research team that DPR will not be used in this patient in the setting of a clinical trial.

In consenting patients that confirmed they wanted to participate in the study at the time of hospital admission and meet enrollment criteria on admission weight and laboratory assessment, the attending surgeon will be notified of study enrollment. At the time of abdominal closure and determination that the patient will either go to extended stay or the intensive care unit, three drains will be placed per standard of care. Patients with planned admission to the hospital ward without extended stay would be excluded. An additional 19 French drain will be placed at the ligament of Treitz at the base of the mesentery. Following abdominal closure DPR will be initiated with commercially available 2.5% glucose-based peritoneal dialysis solution (Delflex; Fresenius USA) at a rate of 1.5 cc/kg/hr based on previously reported therapy in trauma[2]. Drains will be connected to continuous wall suction with Y tubing to one central canister for accurate output measures. This infusion will continue for the duration the patients stay in extended stay (8 hours) if they are deemed eligible for hospital ward admission, or for 24 hours if requiring ICU care. These patients will then be observed for their hospital course and monitored for outcomes listed above.

D. Description, Risks and Justification of Procedures and Data Collection Tools:

Direct peritoneal resuscitation (DPR) is a strategy utilized in damage control trauma surgery to reduce visceral edema and improve organ perfusion[1]. This resuscitation uses a hypertonic dialysate solution instilled into the abdomen to reduce endothelial swelling and increase capillary blood flow[3]. DPR has been demonstrated to improve hepatic perfusion and reduce inflammation[4] and is associated with transcriptional modification of liver, reducing the acute phase response to shock[5]. This strategy has also been utilized in brain dead organ donors with improve organ allocation and organ function[6]. We have recently used DPR in liver transplant patients with primary non function of the liver that had open abdomens due to visceral edema, to bridge them to successful re transplantation. The use of DPR in closed abdomens following liver transplantation has not previously been utilized to assess if this strategy can improve graft function following surgery. In our experience with open abdomens, DPR as a salvage therapy appeared to be safe with no unanticipated infections or bleeding complications. We therefore believe that this strategy can be safely implemented in liver transplant recipients.

A Data Safety Monitoring Board (DSMB) will be established to review data relating to safety and efficacy, to conduct and review interim analyses, and to ensure the continued scientific validity and merit of the study. The DSMB includes a group of physicians with a broad range of experience in using DPR or in management of peritoneal dialysis complications. This group includes:

Jason Smith MD PhD: Trauma surgeon at the University of Louisville. Lead investigator of numerous clinical trials using DPR in trauma, and world expert on technique.
Frederic Pieracci MD MPH: Trauma surgeon at Denver Health Medical Center. Decade of experience using DPR in trauma and other clinical settings.
Erik Peltz DO: Trauma surgeon in Kalispell, Montana: Prior trauma surgeon at the University of Colorado that implemented DPR in the surgical intensive care unit.
Peter Kennealey MD: Transplant surgeon at University of Colorado: Broad range of transplant practice including dialysis access. Has decades of experience placing peritoneal dialysis catheters and managing complications.
Esther Benamu MD: Transplant Infectious disease specialist at University of Colorado: Years of experience in managing post-operative complications in liver transplant and peritoneal dialysis catheter associated infections.
James Cooper MD: Transplant nephrologist at University of Colorado: Has decades of experience in managing patients on peritoneal dialysis.

The Steering Committee is a group of transplant surgery physicians that will review the DSMB report from the interval analyses and make a formal report to the IRB for continuation, modification, or cessation of the study. The PI will also be responsible for reporting any serious adverse or unexpected adverse events before interval analysis to the DSMB chair and IRB.

Hunter B Moore: Assistant Professor Surgery/ Study PI
James J Pomposelli: Professor of Surgery/ Surgical Director of Liver Transplant Surgery
Trevor L Nydam: Associate Professor Surgery/ Director of Research Transplant Surgery
Megan A Adams: Assistant Professor Surgery/ Associate Program Director

Risks

Direct peritoneal resuscitation involves the placement of an extra drain in the abdomen. This drain requires an additional small incision in the skin like the other drains placed (3 others as standard of care). There is a risk of a small scar from this incision. The risk of bleeding from this drain site is the same risk as other drains placed. This occurs under direct visualization and should have < 1% risk of causing additional bleeding. The risk of injuring other organs such as intestine is <1% from placement of the drain. The risk of the drain wrapping around bowel causing obstruction is estimated to be <1%.

The fluid injected into the abdomen is sterile dialysate solution. This solution contains sugar which could prolong the time the patient requires an insulin infusion following transplant. However, 100% of the target population based on our historic data were on an insulin infusion in the first 24 hours. We would anticipate that by the end of the DPR infusion the insulin requirements would decrease at the same rate as non DPR patients. There could be potential risk of requiring insulin beyond 24 hours, which is common in our patient population but unclear without conducting this research if DPR would increase this risk.

The risk of infection from peritoneal infusion is one of the most concerning potential risks. Peritoneal dialysis in liver transplant recipients has a ~40% rate of infection (PMID: 29162680). However, this is in the setting of the long-term placement of a catheter with patients changing themselves on and off their catheter in an outside hospital setting. These infections often occur months after catheter placement. The dialysis solution in this study will be administered within hospital sterile conditions and the duration will be 24 hours or less. We would anticipate that risk of early infection (<7 days) with DPR infusion is <5% and < 10% in the first 30 days. This outcome would be closely monitored by the

DSMB, any intra-abdominal infections diagnosed within 7 days of surgery would freeze the study until the case was reviewed by the DSMB.

With infusion of DPR in a closed abdomen there is a risk that the fluid in causes increased abdominal pressure resulting in organ failure. This occurs in the setting of occluded drains. Stopping criteria for DPR infusion occurs when drain output is not greater than DPR infusion volume for 2 sequential hours. We would anticipate a <1% risk of compartment syndrome requiring an urgent re operative intervention and a 10% risk of stopping DPR early to prevent development of compartment syndrome. If any patient develops acute abdominal compartment syndrome during DPR that required a reoperation, this will stop the study until the case was reviewed by the DSMB.

The rate of return to the operating room in the historically matched cohort from this study is 60% (compared to 20% in non-obese, lower creatinine recipients). We would anticipate a lower rate of returning to the operating room if DPR is successful as it is anticipated to wash out hematoma. The risk of causing increased bleeding from washing away too much clot is a theoretical risk as well. We included >10 units of red blood cells in the first 24 hours as stopping criteria as this represented >95th percentile in this targeted patient population and anticipate this to occur in <5% of patients in our study.

There is also a risk of developing a hernia with peritoneal dialysis. However, with the short duration of infusion in this study we do not anticipate a higher risk with DPR. Hernia rates in liver transplant are estimated to be 20% and will be monitored as an additional outcome in this study. The risk of an acute breakdown of abdominal closure (fascial dehisce) from DPR is a theoretical risk, that we estimate to be <1% and if occurred would be immediately reviewed by the DSMB and would stop the study until review approved continuation.

There is also a risk of loss of personal health information. All study data will be collected via medical chart review. Data from the electronic medical record will be analyzed post-operatively. Screening data will be reviewed to determine subject eligibility. Subjects who meet all inclusion criteria and none of the exclusion criteria will be entered into the study.

In order to minimize the risk of loss of confidentiality, the demographic data shared with the coordinating center will only include non-identifiable variables, such as gender, age, and diagnosis, but will exclude the 18 HIPAA identifiers such as name, telephone numbers, medical record number, etc. These will be grouped under a unique study identification number instead of a patient's name. Only the research team from the University of Colorado will have access to the master list linking a patient's name with his/her study code.

All data collected for this study will be stored short-term on an encrypted computer that is also backed up to a secure server with limited access at the University of Colorado. Long-term study data will be stored in a validated REDcap database.

E. Potential Scientific Problems:

Due to the inherent characteristics of the target population, this study will potentially face limitations in patient enrollment, confounding risk factors, and high risk of complications.

As described in Section III: Preliminary Studies, only around 10% of our transplant population will meet inclusion criteria. Despite the large clinical volume of our Transplant group, when considering limited consent windows, subject refusal to participate in this

study, and normal variations in organ availability, enrolling a large number of participants will require a significant amount of time. In this Phase I Trial, we expect to enroll up to 15 patients in two years, but actual enrolment will help us obtain a better sense of what enrolment periods may look like for future phase II or III study.

In addition, by targeting higher risk patients as defined by their elevated BMI and baseline creatinine (see inclusion criteria above), we are inherently introducing a series of additional risk factors that may affect study outcomes. Furthermore, these risk factors may inevitably result in an elevated number of complications that may warrant early termination of this study. To mitigate this, we have recruited a multidisciplinary DSMB with professionals from General Surgery, Trauma Surgery, Acute Care Surgery, Transplant Surgery, Infectious Diseases, and Nephrology. With regular meetings and scheduled interim analyses, the DSMB will have the necessary knowledge to make informed decisions on what complications and outcomes would be consistent with the standard-of-care and which ones could be attributed to study interventions.

Finally, implementing our proposed DPR protocol in new areas and with personnel not accustomed with its use may present a challenge in the early stages of study implementation. As proposed, we intend to enroll patients that will go to both our Surgical Trauma Intensive Care Unit (STICU) as well as the Post Anesthesia Care Unit (PACU). While DPR has been successfully used in our STICU, it has not been tried in the PACU before. To facilitate its implementation in a non-ICU setting, we have worked with a multidisciplinary team to develop a simplified DPR protocol that minimizes complexity and reduces human resources needs. Our proposed system will use Y connectors to funnel output from all three drains into a single reservoir. Output from this collector will be recorded on an hourly basis, which is already the standard practice of both the PACU and STICU. This multidisciplinary team, composed of MDs, Advance Practice Providers, and RNs familiar with the use of DPR, will be responsible for personnel training, preparation of supplies, feedback capture, and ongoing review of study implementation in both the PACU and STICU.

F. Data Analysis Plan:

We would target enrollment of 15 total patients for this phase I clinical study for the safety of DPR in liver transplantation with interval analysis of safety outcomes at 5 and 10 patients. The primary outcome of this study would be the rate of success DPR implementation in liver transplantation with a closed abdomen. Secondary outcomes would be descriptive analysis of all complications and clinical outcomes in the DPR cohort to provide data for a follow up Phase II clinical trial. We would also include an adaptive arm to expand to 25 patients if there is a high rate of successful completion of DPR, no early safety concerns (7 day outcomes) are identified by the DSMB, and we complete our second interval analysis of patients 10 within 12 months of initiating the study. Criteria for expansion will be completion of DPR (24 hours for ICU patients, 8 hours extended stay) in > 70% of patients. Safety concerns addressed by the DSMB will be based on descriptive analysis of the secondary outcomes of enrolled patients. Descriptive data on 24 historic controls (BMI ≥ 30 and creatinine ≥1.1) in our current observational coagulation data registry will be available to the DSMB for comparison, but a formal statistical comparison between the groups will not occur. Severity of liver disease [model for end stage liver disease (MELD)], pre-operative location of the recipient (home, hospital, ICU) and patient demographics (age, sex, type of liver disease) will also be available to DMSB to compare DPR enrolled patients to historic controls. Upon request of the DSMB, specific comparison of the DPR cohorts can be contrasted to historic controls of a specific demographic pattern (i.e.: age < 45, patient came from home). The University of Colorado performs > 100 transplants per year and we anticipate that we could complete the initial 15 patients in 18 months. If the enrollment is less than 5 patients at 6 months, we would discuss

liberalization of criteria to BMI≥30 with DSMB as enrollment criteria, which has a return to the operating room rate of 34% but is present in 28% of the population.

G. Summarize Knowledge to be Gained:

We anticipate DPR will show a safe profile in the immediate post-operative setting of liver transplantation and demonstrate a clinical strategy to reduce the return rate to the operating room, improve fibrinolysis and attenuate EAD. These data will provide the essential background data for a phase II R01 funded clinical trial to follow the PIs current R00 evaluating the mechanisms of fibrinolysis resistance and graft dysfunction in liver transplantation.

H. References:

1. Weaver JL, Smith JW. Direct Peritoneal Resuscitation: A review. *Int J Surg* 2016; 33(Pt B):237-241.
2. Smith JW, Garrison RN, Matheson PJ, et al. Direct peritoneal resuscitation accelerates primary abdominal wall closure after damage control surgery. *J Am Coll Surg* 2010; 210(5):658-64, 664-7.
3. Zakaria el R, Garrison RN, Kawabe T, et al. Direct peritoneal resuscitation from hemorrhagic shock: effect of time delay in therapy initiation. *J Trauma* 2005; 58(3):499-506; discussion 506-8.
4. Smith JW, Ghazi CA, Cain BC, et al. Direct peritoneal resuscitation improves inflammation, liver blood flow, and pulmonary edema in a rat model of acute brain death. *J Am Coll Surg* 2014; 219(1):79-87.
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6. Smith JW, Matheson PJ, Morgan G, et al. Addition of direct peritoneal lavage to human cadaver organ donor resuscitation improves organ procurement. *J Am Coll Surg* 2015; 220(4):539-47.