Prospective Randomized Trial Evaluating the Effect of Closed Suction Drainage versus Closed Straight Drainage after Distal Pancreatectomy

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Johns Hopkins Medicine - eForm A

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1. Abstract

a. Provide no more than a one page research abstract briefly stating the problem, the research hypothesis, and the importance of the research.

Distal pancreatectomy (DP) is an operation performed for benign, premalignant and malignant disease of the pancreas. With recent advances in the operative and perioperative care of patients undergoing PD, the operative mortality of the procedure has been reduced to less than 1% in highvolume centers. However, post-operative complications still occur in approximately 30-50% of patients. The most common complication after distal pancreatectomy is leakage from the remnant gland or a pancreatic fistulae (PF). In order to identify and treat PF earlier, most surgeons routinely drain the abdominal cavity after DP. However the optimal drain for routine drainage is unknown.

We hypothesize that closed suctioning drains may contribute to the development and/or prolongation of PF because of high negative pressures. Therefore, we propose a project comparing closed suctioning drains versus closed non-suctioning. The primary aim of this study is to test the hypothesis that non-suctioning drains will lead to fewer clinically significant PF and infectious complications after DP.

2. Objectives (include all primary and secondary objectives)

The primary endpoints of the study will be the development of POPF, as recently defined and graded by the International Study Group of Pancreatic Surgery (ISGPS).

Secondary endpoints will include length of hospital stay, need for enteral or parenteral nutrition, need for radiologic or surgical intervention, septic complications, and perioperative mortality.

3. Background (briefly describe pre-clinical and clinical data, current experience with procedures, drug or device, and any other relevant information to justify the research)

Prophylactic drainage of the abdominal cavity is frequently utilized by surgeons to prevent intra-peritoneal collections of blood, bile, chyle, pancreatic, biliary and gastrointestinal juices. The collections, particularly bile and pancreatic fluid can become infected and are potentially caustic to adjacent tissue and structures. Additionally, many surgeons believe that prophylactic drains are useful in detecting complications early, and early intervention can prevent the development of higher degrees of complications.

To date, all studies evaluating drainage following pancreatic resection have focused primarily on pancreaticoduodenectomy and have compared closed suction drains to no drainage. Pancreatic fistula develop in approximately 30% of patients undergoing distal pancreatectomy and 20% will be clinically significant. Although the only RCT to date from MSKCC comparing closed suction drainage to no drainage following pancreatic resection was a negative trial, only 40 of these patients had a distal pancreatectomy, all had closed suction drains placed and it was inadequately powered to detect a difference. Importantly, another study from MSKCC demonstrated very high pressure gradients generated by 3 different types of closed suction systems which vary based on the fullness of the system and when "stripped" reach levels as high as - 225mmHg. We theorize that high negative pressure could contribute to the development or prolongation of complications and leakage from the pancreatic remnant.

Despite evidence-based data questioning the utility of routine drainage in pancreatic surgery, most surgeons around the world and at Johns Hopkins still routinely drain the pancreatic transection margin following distal pancreatectomy with closed suction drains. However, some surgeons have abandoned closed suction drains for closed non-suctioning drains which function by draining to gravity pressure. These drains still prevent fluid collections and allow for early detection of complications but do not generate the same high negative pressures. Clearly the optimal drain to drain the peritoneal cavity following distal pancreatectomy is still unclear for the majority of pancreatic surgeons.

4. Study Procedures

a. Study design, including the sequence and timing of study procedures (distinguish research procedures from those that are part of routine care).

Head-to-head Prospective Randomized Trial: At operation, consented patients will be randomized after removal of the DP specimen to either drain with a single closed suctioning Jackson Pratt versus a closed non-suctioning straight drain. Patients will be stratified based on the surgeon's assessment of the gland texture, as hard versus soft. All drains will be positioned near the pancreatic transection margin. Recorded variables at the time of surgery will include pancreatic gland texture, pancreatic duct diameter, blood loss, and intraoperative time.

Since both types of drains are currently used by surgeons at JHH, we believe that there is no significant change to what is considered routine care of these patients. Surgeon preference currently dictates the drain choice at the time of operation.

b. Study duration and number of study visits required of research participants.

Our plan is to randomize 134 pts per arm (268 total). Approximately 115 DPs are performed annually at JHH. Based on a patient recruitment rate of 90%, the estimated period to complete this trial will be 31 months.

The endpoints of the study are events noted in the 90-day postoperative period, therefore no additional study visits will be required for the study participants, other that their postoperative hospital stay and routine postoperative visits. A case report form (Appendices Section) will be used to facilitate routine collection of standardized information from every subject in order to reliably detect and grade POPF and other complications. This form will be completed by the study coordinator on the day of discharge +/- one day, on the day of re-discharge (in case of readmission) +/- one day, on the day of any postoperative outpatient visit +/- one day, and at 90 days from surgery +/- two weeks. This information will be collected either over the telephone.or in person (eg, in the hospital inpatietn setting or at ordinary, outpatient, patient-care clinic visits).

c. Blinding, including justification for blinding or not blinding the trial, if applicable.

This will not be a blinded trial.

d. Justification of why participants will not receive routine care or will have current therapy stopped.

Participants in both groups will receive standard surgical and post-surgical care.

e. Justification for inclusion of a placebo or non-treatment group.

Both study groups will receive standard treatment (DP) for their pancreatic pathology.

f. Definition of treatment failure or participant removal criteria.

Treatment failure is defined as the development of any condition that poses identifiable risk to participant safety, or the incidence of POPF at significantly higher rate that the control group.

g. Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.

Patients will continue to receive standard post-operative care if their participation in the study ends prematurely, or after the study ends.

5. Inclusion/Exclusion Criteria

All patients undergoing DP at Johns Hopkins Hospital (except children < 18 years old, pregnant women, adults lacking capacity to consent, non-english-speakers, and prisoners),

irrespective of diagnosis, comorbidities, or administration of neoadjuvant therapy are eligible for this study.

6. Drugs/ Substances/ Devices

a. The rationale for choosing the drug and dose or for choosing the device to be used.
b. Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed.
c. Justification and safety information if non-FDA approved drugs without an IND will be administered.

This trial does not involve the use of a specific drug or device.

Study Statistics

a. Primary outcome variable.

The primary endpoints of the study will be the development of POPF, as recently defined and graded by the International Study Group of Pancreatic Surgery.

b. Secondary outcome variables.

Secondary endpoints will include length of hospital stay, need for enteral or parenteral nutrition, need for radiologic or surgical intervention, septic complications, and perioperative mortality.

c. Statistical plan including sample size justification and interim data analysis.

The incidence of either POPF after DP is approximately 30%, based on retrospective studies validating the ISGPS definition. A clinically significant reduction of the event rate to 15% in the treatment group would require enrollment of 134 patients per arm (268 total), assuming a 2-tailed test with α of 0.05 and power of 0.80. We therefore plan to consent and enroll 300, accrue 270 (roughly 90% of 300).

Interim analysis will be performed after recruitment and analysis of 150 patients.

d. Early stopping rules.

The trial will be terminated prematurely, if statistically significant differences between the groups or potential safety risks are identified.

7. Risks

a. Medical risks, listing all procedures, their major and minor risks and expected frequency.

This research adds no additional risk to a patient undergoing a DP. Patients will be randomized to one of two widely accepted drainage techniques. If in the opinion of the surgeon at the time of surgery, one technique has a perceived advantage over the other, that patient will undergo the technique felt to be indicated.

Therefore, medical risks are those of DP: bleeding, infection, anesthesia risks, fistula formation, pain, stroke, death, myocardial infarction, non-healing wound, diabetes mellitus, need for reoperation.

b. Steps taken to minimize the risks.

Preoperative anesthesia evaluation, cardiology clearance when necessary, optimization of the management of patient's comorbities, perioperative antibiotic prophylaxis, perioperative and postoperative pain control, nutritional support.

c. Plan for reporting unanticipated problems or study deviations.

The principal investigator will monitor patient safety and care. Adverse events or unanticipated problems will be reported in the Department of Surgery monthly research meeting. Necessary changes to the study protocol will be made on an as needed basis.

This is a Level I study under the SKCCC Data and Safety Monitoring Plan. The SKCCC Clinical Research Office Quality Assurance Group will perform periodic audits on this study. All trial monitoring and reporting will be reviewed annually by the SKCCC Safety Monitoring Committee.

d. Legal risks such as the risks that would be associated with breach of confidentiality.

Participants will be required to sign an informed consent in order to enroll in this study. The privacy and confidentiality of the patients in this study will be preserved in the standards of HIPAA and privacy policy of the Johns Hopkins Hospital. All de-identified protected health information will be saved in password-protected hospital computer drives. Access to data collected in this study will be limited to the research team members. If a patient's confidentiality is accidentally breeched, the patient will be notified by the principal investigator and measures will be taken to rectify such events.

e. Financial risks to the participants.

Monetary risks are similar to those for any patient undergoing DP. This includes the cost of surgery and rehabilitation, time off from employment, and adjuvant therapy if indicated.

8. Benefits

a. Description of the probable benefits for the participant and for society.

This study aims to assess whether one drainage technique is associated with decreased postoperative morbidity. If one technique is found to be superior to the other, both the individual study participants as well as the entire society will benefit, by minimizing the somatic, psychological, and financial costs associated with DP complications. All participants will receive the superb surgical and medical care provided by the Johns Hopkins Hospital.

9. Payment and Remuneration

a. Detail compensation for participants including possible total compensation, proposed bonus, and any proposed reductions or penalties for not completing the protocol.

Patients will not be monetarily compensated for participating in this study.

10. Costs

a. Detail costs of study procedure(s) or drug (s) or substance(s) to participants and identify who will pay for them.

The costs of this study are mainly administrative. These include salary support for the study coordinator and conference-related expenses for the investigators. No additional staff will be acquired for this project. We will attempt to obtain intramural funding to cover these expenses. The cost of perioperative care of patients undergoing DP at the Johns Hopkins Hospital are not expected to differ between the treatment and control groups. Some surgeons use suctioning drains and other use non-suctioning drains; therefore on average this trial is expected to result in no additional cost.