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Randomized Control Trial Comparing Somatostatin Analogues with Perioperative Antibiotics versus Prolonged Antibiotics

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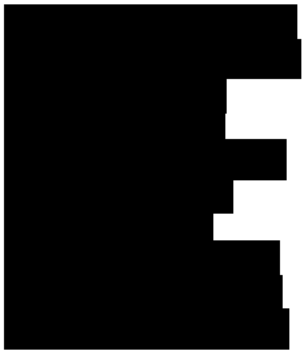


A.SYNOPSIS AND SIGNIFICANCE OF THIS RESEARCH

Pancreatic fistula is a major complication following pancreatic resection[1]. It is one of the most significant and severe events following gastrointestinal surgery accounting for patient dissatisfaction, delay to chemotherapy as well as increased length of hospitalization associated with increased costs with negative economic impacts[2].

Somatostatin analogues have been used for reduction of pancreatic fistula. Numerous reports in the literature exist about the reduction of pancreatic fistula rate with usage of somatostatin analogues. More recently there has been suggestion that prolonged postoperative antibiotics may also reduce incidence and/or severity of pancreatic fistula. This led to development of a risk based, post-pancreatectomy treatment protocol which included both somatostatin analogues and prolonged antibiotics after pancreatic resection. A prospective assessment of this protocol compared to historical controls demonstrated significant advantages and reduced cost of care [2,3]. An important question is the value of prolonged antibiotics in this bundled protocol or could similar results be seen with somatostatin analogues alone

This study aims to determine the individual treatment effect of somatostatin and whether duration of antibiotic therapy coupled with octreotide provides improved outcomes after pancreaticoduodenectomy. The comparison will be between short course/perioperative antibiotics (3 doses) versus our current protocol of extended duration of antibiotics (5 days postoperatively).

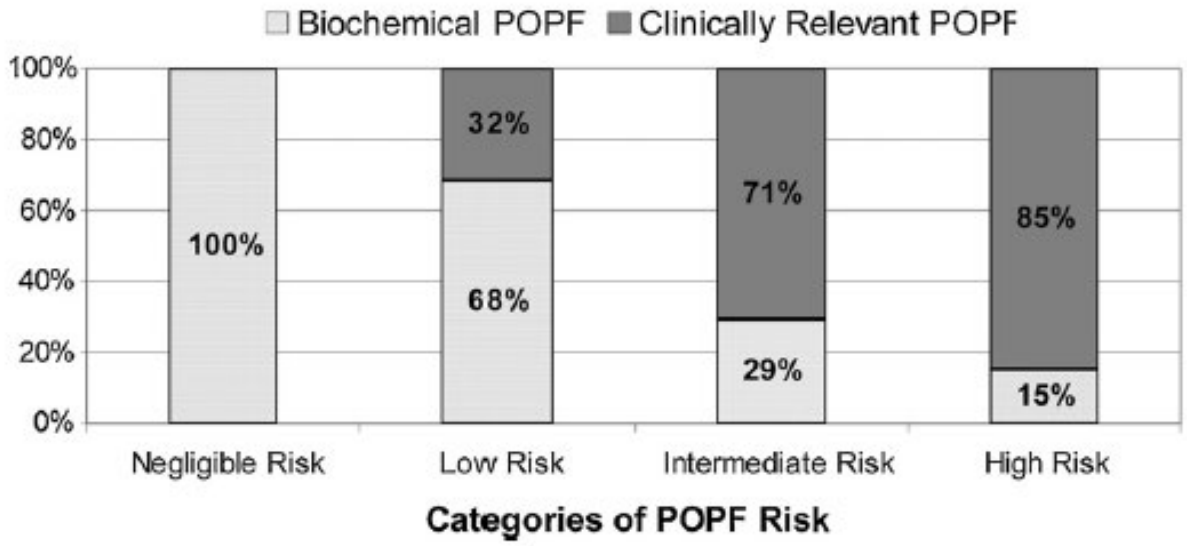


Figure 2. Character of pancreatic fistula according to the Fistula Risk Score among patients with pancreatic fistula (n = 93) after all pancreatoduodenectomies performed between January 2002 and May 2011 (n = 445). POPF, postoperative pancreatic fistula.

B. BACKGROUND

In 2017, Shubert et al[3] published our institutional results on comparison of historic controls with results following implementation of a prospective, surgeon-driven, risk based pathway following pancreaticoduodenectomy. The results of the study showed that after implementation of this pathway there were significant differences observed in ICU length of stay as well as hospital length of stay. Among patients who developed postoperative pancreatic fistula, the pathway implementation was associated with decreased odds of having a higher grade of POPF.

This table highlights the bundled approach involved in the pathway:

Risk-based pathway for pancreatoduodenectomy.

		Negligible risk	Low risk	Intermediate risk	High risk
Infectious disease/ microbiology	Intraoperative bile culture	–	–	+	+
	Prophylactic treatment of bacteriobilia × 5 days	–	–	+	+
	5 additional days for positive bile culture	–	–	+	+
Function	Octreotide 150 μg SQ every 8 hours for 7 days	–	–	+	+
Drainage	Additional drain	–	–	–	+
Nutrition	Prophylactic feeding jejunostomy tube placement	–	–	–	+

SQ, subcutaneously.

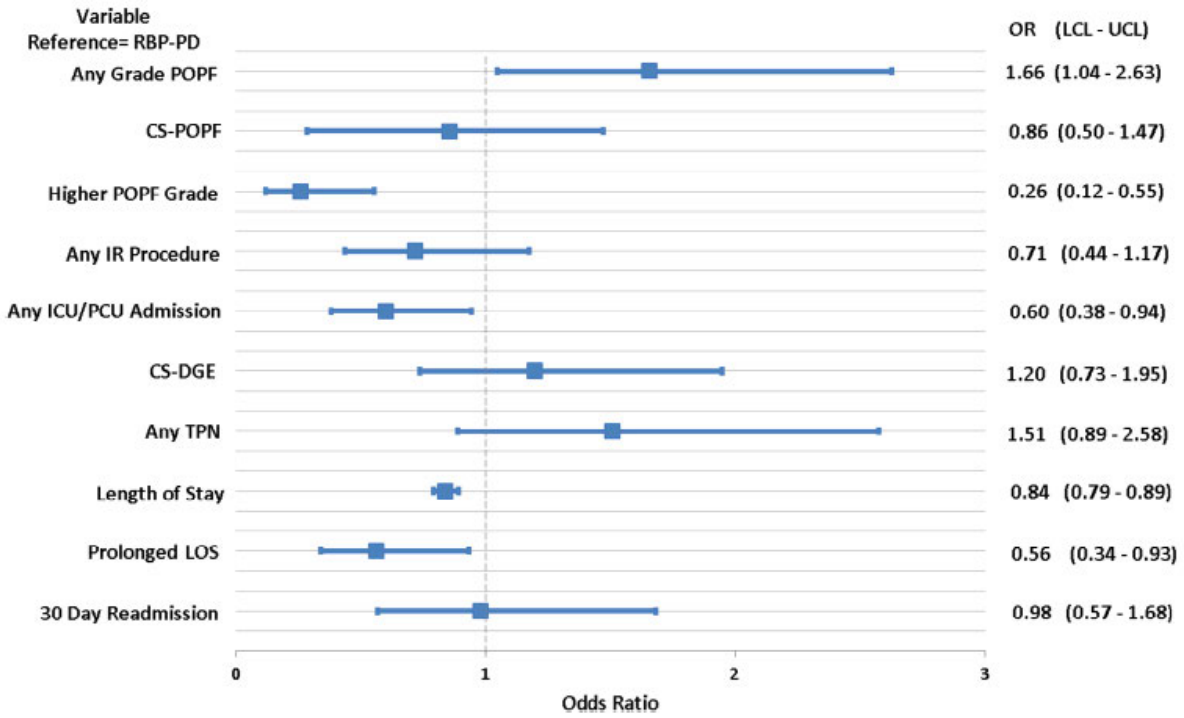
To date, there has been an abundance of literature on the impact of somatostatin analogues on the incidence, morbidity and mortality associated with pancreatic fistula, leak and abscesses. Meta analyses and Cochrane reviews have suggested that these analogues although, reduce perioperative complications; they do not reduce perioperative mortality [4,7,8].

There is no data in the literature highlighting which components within the bundle independently contribute to outcomes such as differences in ICU length of stay, hospital stay as well as decreased severity of pancreatic fistula when they do occur. There is minimal data in the literature on the impact of perioperative antibiotics on incidence of pancreatic fistula and/or if the severity of pancreatic fistula is reduced with the use of antibiotics.

Therefore, we propose the first randomized, controlled trial in which there is a comparison of octreotide with routine prophylactic antibiotics **(intraoperative dose plus 24 hours of postoperative antibiotics)** compared to octreotide with prolonged antibiotics (5days) in patients who are intermediate to high risk for fistula based on our pancreatic fistula score calculator.

C. PRELIMINARY OBSERVATIONS:

Preliminary observations based on the implementation of the surgeon driven pathway as mentioned above demonstrated statistically and clinically relevant improvement in outcomes, decreased costs and decrease in overall resource utilization on multivariate analyses.



Between 2014 and 2017 multiple institutional studies have been conducted attempting to show that somatostatin analogues lead to a reduction in pancreatic fistulae. Some authors have shown that this reduction may not exist but that they may have a role in reduction of postoperative complications such as bleeding.

Given the incidence of pancreatic fistulae and its associated morbidity when it does occur, it is crucial to have a prospective randomized, controlled trial comparing these analogues with the use of antibiotics to understand which agent, if any, contributes to the reduction of this grave complication.

It is imperative to identify the impact of the individual components of this pathway to help delineate the agents that contribute to the differences in outcomes and measures. Therefore, we propose this

randomized trial to assess the impact of standard dosing of perioperative antibiotics with extended duration of antibiotics as described in the bundled pathway approach.

D. METHODS AND DESIGN

We propose to begin this prospective, randomized study to assess the benefit of standard perioperative antibiotics (3 doses) versus our current protocol of prolonged antibiotics (minimum 5 days). Both groups will receive somatostatin analogues per the existing risk-based pathway.

Patients with planned pancreatoduodenectomy will be eligible for inclusion. Per our current standard practice, a pancreatic risk score will be assessed using established factors of gland texture, pathology, pancreatic duct diameter (mm) and intraoperative blood loss (ml). This data will be entered into the patient's record
As part of our current practice, intermediate or high risk patients receive the following treatment intervention:

IV Antibiotic	**# of Postop Doses for 24 hour duration (Group 1)**	**# of Postop Doses for 5 day duration (Group 2)**
Ceftriaxone	1	5
Metronidazole	2	15
Piperacillin/Tazobactam (Zosyn)	3	20
Levofloxacin	1	5

PATIENTS AND METHODS

Study treatment:

After intraoperative fistula risk score determination, patients will be randomly assigned to one of two treatment groups:

Group 1 (200 people): therapy with octreotide (150mcg subcutaneous q8h for 7day) and routine perioperative dosing of **antibiotics (intraoperative dose plus 24 hours of antibiotics postoperatively)**

Group 2 (200 people): therapy with octreotide (150mcg subcutaneous q8h for 7day) with one intraoperative dose of antibiotics plus extended duration (5 days).
If surgery is on Friday study coordinator will call OR to collect risk score and randomize patient.

After randomization via Redcap, an email will be sent out to Pharmacist, surgical team, and staff.

Inclusion:

1. Patients undergoing a Whipple procedure for various diagnoses (neuroendocrine tumors, adenocarcinoma, benign cystic neoplasms, duodenal and ampullary malignancies, etc) who are deemed intermediate-high risk as per our institutional protocol as shown above.

2. Patients > 18 years of age with the above mentioned diagnoses

Exclusion:

1. Negligible and low risk patients
2. All patients undergoing arterial resection.
3. Age <18 years
4. Currently pregnant

Outcomes:

The primary outcome will be length of hospital stay

The secondary outcome will be the incidence of pancreatic fistula after pancreatic surgery (defined as postoperative drain output of fluid with amylase content more than 3 times the maximum normal serum value and exceeding 10 mL/24 h for more than 3 d). This will be diagnosed based on clinical and biochemical parameters. When clinical suspicion exist, cross sectional imaging in the form of CT abdomen/pelvis with intravenous contrast (when applicable) will be utilized to demonstrate the presence or absence of a drainable collection.

The incidence of pancreatic fistula will be compared amongst the two groups to identify the impact of antibiotics on incidence of pancreatic fistula. By comparing these two groups, we will be able to identify whether an extended course of antibiotics contribute to reduction in pancreatic fistula in intermediate and high risk patients undergoing pancreatic surgery. Further, this can serve as a basis for future studies with respect to testing other analogues and their contribution to reduction of pancreatic fistula.

SAMPLE SIZE and POWER:

This study has been powered for the primary outcome; comparison of the length of hospital stay between the study arms of octreotide plus standard of care antibiotics versus octreotide plus prolonged antibiotics. The sample size assumes a two sample test comparison of independent groups, a two-sided test at α=0.05. Using preliminary estimates reported in a paper by Shubert, mean=12.0 days with a standard deviation of 10.0. With 200 patients in each of the two study arms there will be 80% power to detect a difference in LOS of greater than or equal to 2.8 days, and effect size of 0.28. We will increase the sample size by 10% to allow for dropouts, bring the total enrollment to the study to 440 patients.

#patients/arm	Total #patients	Rate in "other" arm	Rate reduction

50	100	9.5%	22.5%
100	200	15.3%	16.7%
150	300	18.0%	14.0%
200	400	19.8%	12.2%

We are accounting for patients who may refuse to participate after randomization, patients who undergo laparoscopy and are found to have metastatic disease or those who are found to be inoperable at the time of laparotomy. Therefore, to be included in the study, patients must be randomized, deemed fit to tolerate a somatostatin analogue, as well as undergo pancreatic resection, thereby having the appropriate risk factors should they develop a pancreatic fistula.

RANDOMIZATION:

Patient randomization will be conveyed using REDCAP system. The randomization will be stratified on age (dichotomized as <60 versus ≥60), risk category (High versus Intermediate), and surgeon The randomization will be done using permuted blocks of size two and four.

E. DATA ANALYSIS:

The primary outcome of this study is length of stay (LOS). This outcome will be compared between treatment arms using a two-sample Test. Linear regression in multiple variable models to assess the association of treatment arm with length of stay including relevant covariates in the model such as gender, age, Open versus minimally invasive approach, etc. The secondary outcome of interest is the fistula rate within 90 days. Assuming all patients have complete follow-up, univariate and multiple variable logistic regression will be used to assess the association of duration of antibiotic therapy and the odds of fistula. We assume that the number of fistulas identified will be approximately 60 in the enrolled patients. With this number of events a multiple variable model may include up to six variables. If there is censoring of follow-up in patients, death or lost to follow-up the survival methods will be used in analysis, Kaplan Meier estimates at 30 days and Cox models. An alpha-level of 0.05 will be considered for statistical significance.

F. DSMB approval

The trial will require DSMB approval due to the large study population as well as randomized nature of the study.

Given the duration of antibiotic use will be less in Group A compared to Group B this may account for increased incidence of pancreatic fistula and infection due to the shorter course .

The Mayo Clinic Department of Surgery Data Safety and Monitoring Board (DSMB) will evaluate and adjudicate Serious Adverse Events and Specified Adverse Events as reported by the Investigators for relatedness to device and procedure. The DSMB will also be given the listings of all other adverse events (not Serious and not Specified) for review and to determine if additional adjudication is required. The DSMB will be given any information requested to adjudicate adverse events. The DSMB will meet yearly, or more or less often as needed.

All adverse events grade III or higher will be recorded and monitored. Serious adverse events reported to DSMB will include: 90-day postoperative mortality, any grade III (requiring surgical, endoscopic, or radiological intervention) or grade IV morbidity (life-threatening complications requiring ICU

management of organ dysfunction), antibiotic-related complications (severe allergy, C. Difficile), pancreatic fistula, sepsis.

The stopping rules specified below are based on the knowledge available at the study development. We note that the adverse event stopping rule may be adjusted at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatments under investigation. The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the pre-specified rules below

Accrual will be temporarily suspended to this study if at any time we observe events considered at least possibly related to study treatment (i.e. an adverse event with attribution specified as "possible", "probable" or "definite") that satisfy one of the following:

- **If >10% experience a 90 day mortality**
- **If >45% of all patients experience a Clavien Dindo grade 3 or higher adverse event**

We note that we will re-review all grade 4 and 5 adverse events deemed "unrelated" or unlikely to be related" to verify their contribution and monitor for previously unrecognized treatment-related adverse events.

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H. BUDGET JUSTIFICATION

This study will be supported by the Department of Surgery Executive committee. $10350.00 will be provided for statistical support. Study coordinator support will be provided by the DOS Clinical Research Office.