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A multicenter study of total pancreatectomy with islet autotransplantation (TPIAT): POST (Prospective Observational Study of TPIAT)

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ABSTRACT

Background/objectives: Total pancreatectomy with islet autotransplantation (TPIAT) is considered for managing chronic pancreatitis in selected patients when medical and endoscopic interventions have not provided adequate relief from debilitating pain. Although more centers are performing TPIAT, we lack large, multi-center studies to guide decisions about selecting candidates for and timing of TPIAT.

Methods: Multiple centers across the United States (9 to date) performing TPIAT are prospectively enrolling patients undergoing TPIAT for chronic pancreatitis into the Prospective Observational Study of TPIAT (POST), a NIDDK funded study with a goal of accruing 450 TPIAT recipients. Baseline data include participant phenotype, pancreatitis history, and medical/psychological comorbidities from medical records, participant interview, and participant self-report (Medical Outcomes Survey Short Form-12, EQ-5D, andPROMIS inventories for pain interference, depression, and anxiety). Outcome measures are collected to at least 1 year after TPIAT, including the same participant questionnaires, visual analog pain scale, pain interference scores, opioid requirements, insulin requirements, islet graft function, and hemoglobin A1c. Health resource utilization data are collected for a cost-effectiveness analysis. Biorepository specimens including urine, serum/plasma, genetic material (saliva and blood), and pancreas tissue are collected for future study.

Conclusions: This ongoing multicenter research study will enroll and follow TPIAT recipients, aiming to evaluate patient selection and timing for TPIAT to optimize pain relief, quality of life, and diabetes outcomes, and to measure the procedure's cost-effectiveness. A biorepository is also established for future ancillary studies.

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Introduction

Chronic pancreatitis (CP) and recurrent acute pancreatitis (RAP) represent a spectrum of disease in which patients suffer from episodic and progressive inflammation and fibrotic replacement of the exocrine and endocrine pancreas [1]. Affected patients often suffer from abdominal pain which can be severe and difficult to treat, ultimately resulting in impaired quality of life, inability to attend work or school, and increased health care utilization with repeated emergency department visits or hospitalizations [2–8]. First-line therapies for CP and RAP include low-fat diet, pancreatic enzyme therapies to reduce pancreatic stimulation, comprehensive pain management, and endoscopic retrograde cholangiopancreatography (ERCP) for endoscopic sphincterotomy and stent placement [9–12]. When medical and endoscopic therapies fail in patients with debilitating pain and consequent life disruption, surgical therapy is considered including ductal drainage or parenchymal resection procedures, depending on pancreatic duct and tissue morphology. In some patients, particularly those with diffuse small duct disease or with genetic pancreatitis or those who have failed lesser surgeries, total pancreatectomy with islet autotransplantation (TPIAT) may be considered [13].

In TPIAT, the goal of pancreatectomy is to relieve pain and restore quality of life, while islet autotransplantation is intended to reduce the burden of post-surgical diabetes [14]. Centers performing TPIAT have individually reported improvements in health-related quality of life, reduction in pain symptoms, and reduction in opioid use [13,15–17]. Despite pain symptom improvement, however, about half of patients may require opioid analgesics 1 year after surgery, and about 25% 5 years after TPIAT [13,15]. In one single-center analysis, about 15% of patients reported pain burden at 1–3 years after TPIAT similar to what they experienced before TPIAT [13]. Preliminary data suggest that poor outcomes might be associated with specific risk factors such as past alcohol abuse disorder or prolonged opioid use, while children may have greater chance of pain relief and insulin independence [18–20]. Diabetes outcomes vary greatly, ranging from full insulin independence soon after TPIAT in 30–50% of patients, to complete failure of the islet graft either due to low islet mass available for isolation or poor survival of the transplanted islets [13,19,21–23].

With increasing utilization of TPIAT as a therapy for CP and RAP, larger collaborative studies of carefully phenotyped and followed TPIAT recipients are critical to identify patient, disease, and surgical characteristics that may guide selection of candidates likely to benefit from TPIAT, avoid TPIAT surgery for those unlikely to benefit, and to determine the optimal timing of TPIAT. The variability in approach to TPIAT from different centers represents an obstacle to performing high quality comparative effectiveness studies that can guide management and ensure optimal patient outcomes. This was identified as a key research gap by experts convening at the National Institutes of Diabetes and Digestive and Kidney Diseases (NIDDK)-sponsored workshop to define research priorities in TPIAT in July 2014 [24,25]. To address these critical research gaps, a multicenter research consortium was formed under a 5-year grant from the NIH (grant R01DK109124, PI M. Bellin) to prospectively collect data about pain, quality of life, glycemic control, and cost-effectiveness in patients undergoing total pancreatectomy or completion pancreatectomy with islet autotransplant (TPIAT), under a study protocol entitled: Advancing Treatment for Pancreatitis: a Prospective Observational Study of TPIAT (**POST**). The specific aims of the POST study are to determine patient and disease characteristics and timing of intervention associated with optimal pain and quality of life outcomes (SA 1), to determine patient and disease characteristics and timing of intervention associated with optimal diabetes outcomes (SA 2), and to assess the cost-effectiveness of TPIAT (SA 3).

Methods

Participating centers

The current POST consortium members include the University of Minnesota, Baylor Medical Center, Medical University of South Carolina, Cincinnati Children's Hospital, John Hopkins Medical Institutions, Dartmouth-Hitchcock Medical Center, University of Chicago, University of Pittsburgh Medical Center, and The Ohio State University Wexner Medical Center, with additional membership anticipated. Member sites and contact information are listed on the study website at www.tpiat.study, and the study is registered on ClinicalTrials.gov (NCT03260387).

All sites submit data to a data and coordinating center (DCC) at the University of Minnesota Division of Biostatistics that includes a biostatistician, study manager, and database manager. The DCC maintains a secure, regulatory-compliant web site that is used to enter study data, to post reports for use by enrollment site coordinators and investigators, and to download paper case report forms (CRFs) and other study documents (e.g., the manual of procedures). Data is double entered from CRFs into the electronic data-capture system by participating sites.

Study aims and participant eligibility

The study's aims are to identify characteristics associated with favorable pain, quality of life, and diabetes outcomes and to measure the cost-effectiveness of TPIAT (Table 1). To address these aims, 450 participants of any age, who are undergoing TPIAT to manage CP or RAP, are eligible for enrollment. Patients who undergo TPIAT for a diagnosis other than CP or RAP (i.e. tumor or trauma) are excluded, as are patients having a primary partial pancreatectomy (distal or Whipple/pancreatic head resection) with IAT, due to potential impact of the residual pancreas on pain and diabetes outcomes. By design, the study does not define CP or RAP, except that participants must meet the clinical criteria to undergo TPIAT as established by the participating center. The rationale for this approach is that the study is intended to encompass the current full spectrum of patients undergoing this procedure in the U.S., to determine which patients are likely to benefit from surgery. Baseline CRFs capture the symptoms and procedures that lead to the diagnosis of CP or RAP, as well as prior clinical course and treatments performed.

Study assessments

Participants are assessed before surgery (within 3 months) and postoperatively at 6 months, 1 year, and then yearly until the end of the study (up to 4 years). Recruitment is planned such that each participant will have $\geq$1 year of follow-up by the end of the grant period. To optimize retention of participants, many of whom live far from the treating center, follow-up visits are performed face-to-face or remotely by telephone interview, with lab measurements obtained at a local clinic when follow up occurs remotely. Key baseline characteristics collected from participant interview and medical records include demographics; etiology of pancreatitis; disease duration; prior medical, endoscopic, and surgical

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