A Pilot Study in Endoscopic Therapy on Quality of Life and Pain in Chronic Pancreatitis: The EQuiPP Study

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I. Objectives

The purpose of this study is to examine the effect of pancreatic endotherapy (**PET**) on patient-centered outcomes in patient with chronic pancreatitis. Specifically, the aims of this study include:

1) To examine the effect of PET on quality of life in patients with chronic pancreatitis with the hypothesis being that PET improves quality of life.

2) To examine the effect of PET on pain in patients with chronic pancreatitis while also identifying which pain profiles will respond to specific PET modalities with the hypothesis being that PET improves pain in patients with certain pain profiles.

3) To qualitatively assess the impact of PET on patients with chronic pancreatitis in regards to patient preferences and experiences.

II. Background and Rationale

Chronic pancreatitis often leads to intractable pain which places significant burden on patients and our healthcare system. In the US, an estimated 39,413 annual visits were attributed primarily to chronic pancreatitis, representing a 12% increase in the span of a decade.[1] Furthermore, there were 12,770 annual admissions, with a 12.9% readmission rate, costing an estimated $133,586,970 a year nationally.[1] As one would expect, pain can significantly worsen the quality of life of patients with chronic pancreatitis as seen in the North American Pancreatitis Study-2 (NAPS2), which involved the largest cohort of patients with chronic pancreatitis. Constant pain, in particular, was independently associated with poor quality of life, greater pain medication use and higher rates of disability and hospitalizations.[2] The poor understanding of the exact mechanism of pain in chronic pancreatitis makes disease treatment particularly challenging with leading theories including mechanical causes such as ductal and parenchymal hypertension as well as neuropathic causes secondary to chronic activation, hypertrophy, and inflammation of intrapancreatic nerves and abnormal pain processing in the central nervous system.[3]

Unfortunately, pain management with opiates represents a mainstay of treatment, carrying the risk of addiction along with significant morbidity and mortality.[4] From this standpoint, PET offers a potential treatment method for patients with complications of chronic pancreatitis such as pancreatic duct stones and strictures, biliary strictures, and pancreatic fluid collections.[5, 6] Despite the status of PET as a 1st-line therapy for these complications, our understanding of the effectiveness remains limited in that most of the studies examining PET have largely evaluated technical outcomes such as stricture resolution or stone clearance as opposed to patient-centered outcomes. In the landmark trials comparing endoscopic drainage with surgical drainage of patients with chronic pancreatitis and ductal obstruction, the Izbicki pain score was used, which while validated, consists of only 4 items: a visual analog scale and questions addressing pain frequency, pain medication and inability to work which fail to measure the holistic impact of

pain.[7-9] Within this context, patient-centered outcomes such as quality of life remain inadequately studied in the field of PET, limiting our understanding of how PET affects patients. Furthermore, patients and physicians often have different preferences for treatment modalities and value treatment risk/benefit trade-offs on varying levels.[10] Thus, there exists a critical need to understand and integrate patient values and preferences regarding various PET to better inform both patients and physicians in choosing the best treatment for each individual patient.

III. Procedures

A. Research Design

This is a prospective single-center study that will assess the effect of PET on quality of life and pain in patients with chronic pancreatitis. The study involves the administration of questionnaires and performing quantitative sensory testing prior to, during, and after PET completion.

B. Sample

For the power calculation, the primary outcome will be change in quality of life from pre- to 6 months post-PET as defined by a change of at least 15.8 points on the PANcreatitis Quality of Life Instrument (PANQOLI) score, which in the validation study of the instrument was found to represent a clinically meaningful outcome.[11, 12] A sample size calculation was performed using a linear mixed effects model with 80% power and significance (α) of 0.05. This demonstrated the need for 13 patients per PET modality. Assuming a drop-out rate of 20%, we would therefore require 16 patients for each PET modality, and as we are examining 5 modalities, this would require a total of 80 patients.

Inclusion Criteria: Adults ($\geq$ 18 years old) with painful chronic pancreatitis being referred for PET. PET modalities will include pancreatic duct stenting for stricture therapy, pancreatic duct lithotripsy for stone clearance, celiac plexus block for pain relief, biliary stenting for CP-related biliary strictures, and transmural drainage of symptomatic pancreatic fluid collections.

Exclusion Criteria: Subjects who have previously undergone PET or pancreatic surgery, pregnant females, subjects unable to consent, and imprisoned individuals.

All patients will be recruited from our Pancreas Clinic where patients are seen prior to performance of any PET. Screening will be performed during this clinic visit and all follow-up will be performed either in-person at our clinic or electronically in a virtual format.

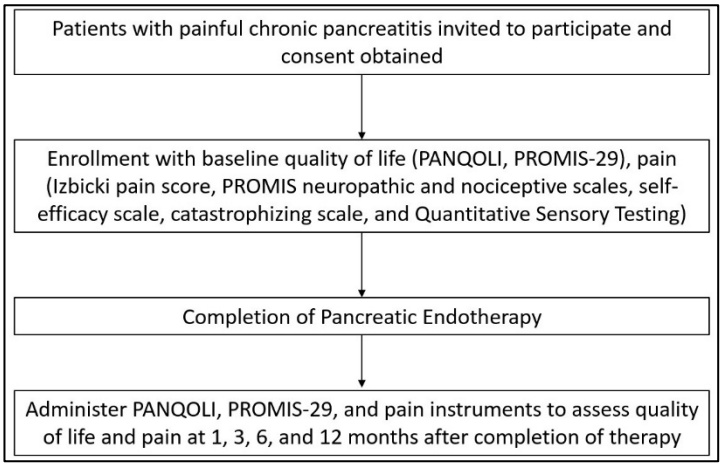
C. Measurement / Instrumentation

The *primary outcome* will be change in quality of life from before PET to 12 months after completion of PET using the PANQOLI[12] score. *Secondary outcomes* will include change in scores on the PROMIS-29[13], Izbicki[9] pain scores, PROMIS neuropathic and nociceptive pain scales, University of Washington self-efficacy pain scale and pain catastrophizing scale, technical success, adverse events, and pain medication dosage. Additionally, quantitative sensory testing measurements will be taken at the beginning of the study.

The PANQOLI is the only chronic pancreatitis-specific quality of life instrument and has been validated in a multicenter study.[12] The PROMIS-29 is a global quality of life instrument that is endorsed by the NIH and is currently utilized by the Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer. The PROMIS pain scales and the University of Washington pain scales represent additional methods of measuring the different aspects of pain.

D. Study Procedures

In the single-arm clinical trial, enrolled subjects will present for an initial baseline evaluation followed by 4 follow-up visits at 1, 3, 6, and 12 months post-PET completion (**See Figure**).



During the baseline visit, subjects will fill out the PANQOLI[12] and the PROMIS-29[13] in addition to a demographics questionnaire. Demographic information will include disease-specific information detailing current and prior treatments, etiology, and Charlson comorbidity index. For the second aim, participants will complete the PROMIS neuropathic and nociceptive pain scales, and University of Washington self-efficacy pain scale and pain catastrophizing scale, in addition to reporting their current pain medication use (in daily morphine equivalents). Prior to receiving PET, all subjects will receive quantitative sensory testing measurements.

All data collection will be performed on REDCap. Only study personnel will have access to the REDCap database. All personal information will be deleted once the study is completed.

E. Internal Validity

Potential threats to the validity of the proposed study includes the inherent subjectivity of instruments that is also subject to recall and recency bias. The selected instruments however are validated and were chosen to reflect the nature of chronic pancreatitis. Another threat includes the inherent variability in PET procedural success. While a 100% technical success rate is unrealistic, our prior studies have demonstrated technical success rates near 90%.[14, 15] An inherent limitation will be the variable number of procedures needed to achieve technical success, which we will include as a continuous variable in the logistic regression model and also address in our qualitative analysis. Using an intention-to-treat approach, we will also follow patients regardless of technical success. Additionally, the lack of control group limits the validity of this study. The study group will not be compared with a control group in the pilot study, limiting our understanding of the effect of PET in relation to not performing endotherapy. This will need to be addressed in a future randomized sham-controlled trial.

F. Data Analysis

Comparison of PANQOLI scores before and after PET will be analyzed using a linear mixed effects model. Comparison of PROMIS-29 and pain scales will be performed using a linear mixed effects model as well. All comparisons will be done for each follow-up time interval. Multivariable logistic regression using a forward selection model will be performed to attempt to identify predictors for improved quality of life. A p value < 0.05 will be considered statistically significant.

Descriptive statistics will be used to depict QST thresholds for conditioned pain modulation, pressure pain, pressure tolerance and cold pressor endurance times prior to PET. To identify whether certain QST pain patterns or pain scale scores are associated with an improvement in PANQOLI score, chi-square tests and t-tests will be used.

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