

Predictors of Post-Operative Pain Relief in Patients with Chronic Pancreatitis Undergoing the Frey or Whipple Procedure

Amitasha Sinha¹ · Yuval A. Patel¹ · Michael Cruise² · Karen Matsukuma² ·
Atif Zaheer^{3,7} · Elham Afghani¹ · Dhiraj Yadav⁴ · Martin A. Makary^{5,7} ·
Kenzo Hirose^{5,7} · Dana K. Andersen⁶ · Vikesh K. Singh^{1,7}

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Abstract

Background Post-operative pain relief in chronic pancreatitis (CP) is variable. Our objective was to determine clinical imaging or histopathologic predictor(s) of post-operative pain relief in CP patients undergoing the Whipple or Frey procedure.

Methods All patients who underwent a Whipple ($n=30$) or Frey procedure ($n=30$) for painful CP between January 2003 and September 2013 were evaluated. A toxic etiology was defined as a history of alcohol use and/or smoking. The pre-operative abdominal CT was evaluated for calcification(s) and main pancreatic duct (MPD) dilation (≥ 5 mm). The post-operative histopathology was evaluated for severe fibrosis. Clinical imaging and histopathologic features were evaluated as predictors of post-operative pain relief using univariable and multivariable regression analysis.

Results A total of 60 patients (age 51.6 years, 53 % males) were included in our study, of whom 42 (70 %) reported post-operative pain relief over a mean follow-up of 1.1 years. There were 37 (62 %) patients with toxic etiology, 36 (60 %) each with calcification(s) and MPD dilation. A toxic etiology, calcifications, and severe fibrosis were associated with post-operative pain

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✉ Vikesh K. Singh
vsingh1@jhmi.edu

Amitasha Sinha
amitashasinha@gmail.com

Yuval A. Patel
yuval.patel@duke.edu

Michael Cruise
mwcruiase@gmail.com

Karen Matsukuma
kmatsuku@gmail.com

Atif Zaheer
azaheer1@jhmi.edu

Elham Afghani
ellie.afghani@gmail.com

Dhiraj Yadav
yadavd@upmc.edu

Martin A. Makary
mmakary1@jhmi.edu

Kenzo Hirose
khirose1@jhmi.edu

Dana K. Andersen
andersendk@mail.nih.gov

- ¹ Division of Gastroenterology, Johns Hopkins Medical Institutions, Baltimore, MD, USA
- ² Department of Pathology, Johns Hopkins Medical Institutions, Baltimore, MD, USA
- ³ Department of Radiology and Radiological Science, Johns Hopkins Medical Institutions, Baltimore, MD, USA
- ⁴ Division of Gastroenterology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA
- ⁵ Department of Surgery, Johns Hopkins Medical Institutions, Baltimore, MD, USA
- ⁶ National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD, USA
- ⁷ Pancreatitis Center, Johns Hopkins Medical Institutions, Baltimore, MD, USA

relief on univariable analysis (all $p < 0.01$). However, only a toxic etiology was an independent predictor of post-operative pain relief (OR 5.7, 95 % CI 1.3, 24.5, $p = 0.02$).

Conclusion Only a toxic etiology, and not imaging or histopathologic findings, independently predicts post-operative pain relief in CP patients undergoing the Whipple or Frey procedure.

Keywords Chronic pancreatitis · Post-operative pain relief · Alcohol · Smoking

Introduction

Pancreatic surgery is often utilized to treat pain in patients with chronic pancreatitis (CP) that do not respond to medical and/or endoscopic therapy.¹ However, rates of post-operative pain relief in CP patients undergoing surgery are variable, ranging from 62 to 85 %.^{2–7} Prior studies have tried to determine the pre-operative features that can predict post-operative pain relief. These studies have shown that alcoholic CP patients with main pancreatic duct (MPD) dilation undergoing pancreatic resection/drainage procedures demonstrate higher rates of pain relief.^{2–4,8} The presence of calcifications on pre-operative imaging has also been associated with post-operative pain relief in nearly 75 % of patients.^{3,5,6,9} A recent study, evaluating post-operative pain relief and pancreatic fibrosis in large duct CP patients undergoing the Frey procedure found that patients with severe fibrosis had a greater resolution of pain than those with mild fibrosis.⁷ However, the primary limitation of these prior studies is the focus on only one factor and the lack of multivariable analysis that adjusts for the presence of other clinical, histopathologic, or morphological features that might impact post-operative pain relief in patients with CP.

The objective of our study is to investigate several potential predictors of post-operative pain relief in patients undergoing the Whipple or Frey procedure for painful CP.

Methods

Patient Population

This study was approved by our Institutional Review Board with a waiver of informed consent and Health Insurance Portability and Accountability Act authorization. The demographic, clinical, and procedural data was collected for all adult (age ≥ 18 years) patients, who underwent either a Frey procedure (local resection of pancreatic head with lateral pancreaticojejunostomy) or Whipple procedure (classic or pylorus-preserving pancreaticoduodenectomy), for painful CP between January 1, 2003, and September 30, 2013, through a review of the paper and electronic medical records. Patients who underwent the Puestow procedure or distal pancreatectomy were not included, as we would be unable to

retrieve histopathology of the head of pancreas, which can possibly interfere with the homogeneity of the assessment of fibrosis on histopathology.¹⁰ The decision for the type of operation was based on the discretion of the surgeon. Patients who underwent Whipple procedure were earlier in the decade; however, all patients underwent surgery for pain. Patients without an adequate surgical histopathology specimen or those who had autoimmune pancreatitis on histopathology were excluded. We also excluded patients who did not have a pre-operative abdominal computed tomography (CT) scan or those without a follow-up visit.

A toxic etiology was defined as either a history of alcohol abuse and/or smoking.¹¹ History of heavy alcohol use was defined patients who were reported continuous and/or binge drinking documented on CAGE questionnaire.¹² Patients with rare social drinking were not a part of this cohort. Patients who were defined as smokers were active smokers with use of $\geq 1/2$ packs per day. An idiopathic etiology was defined by the absence of any known toxic, metabolic, or genetic risk factors for CP. Genetic mutation analysis was not commonly performed at our institution during the period of this study.

The pre-operative abdominal CTs of all patients were evaluated for calcifications and MPD dilation by a radiologist. Dilation of MPD was defined as ≥ 5 mm diameter of MPD in the head of pancreas.¹³

The hematoxylin and eosin (H&E)-stained serial sections from the surgically resected formalin-fixed pancreatic tissue were analyzed for fibrosis at $\times 20$ magnification. Fibrosis was scored on a scale of 1–6, as previously described by Kloppel and Maillet.¹⁴ A fibrosis score of 5 (40–79 % and diffuse fibrosis) or 6 (80–100 % and diffuse fibrosis) was defined as severe fibrosis.¹⁵ Two pathologists independently reviewed and graded the slides for fibrosis, and any discrepancy was resolved through consensus.

Post-operative pain relief was retrospectively assessed on the basis of the last recorded follow-up visit. Pain relief was defined as resolution of pre-operative abdominal pain and no ongoing narcotic analgesic requirement. All patients in our cohort underwent similar pre-operative and post-operative pain management, independent of the etiology of CP.

Statistical Analysis

Demographic and clinical characteristics were reported using descriptive statistics; continuous variables were expressed as mean \pm SD; and dichotomous variables were expressed as a percentage. Univariable analysis was performed using

Student's *t* test for continuous variables and Fisher's exact test for categorical variables. Multivariable analysis for post-operative pain relief was performed using multiple logistic regression and expressed as an odds ratio (OR) with 95 % confidence interval (CI). A *p* value of <0.05 was deemed statistically significant. All statistical analysis was conducted using Stata version 12 (StataCorp LP, College Station, TX).

Results

The demographic, clinical, and procedural data was collected for 80 consecutive adult patients who underwent a Frey or Whipple procedure for painful CP between January 1, 2003, and September 30, 2013. We excluded five patients who did not have an adequate surgical histopathology specimen and nine patients who had evidence of autoimmune pancreatitis. We also excluded three patients who did not have a pre-procedural abdominal CT and three patients without a follow-up visit. A total of 60 patients were included in the final analysis.

Table 1 describes the demographic, clinical, morphologic, and histopathology characteristics of the study cohort. The majority of our patients were white (68 %) and male (53 %). There were 37 (62 %) patients with a toxic etiology and 31 (48 %) patients with a history of documented acute recurrent pancreatitis. MPD dilation and calcification(s) were the most common morphologic features, both found in 60 % of our cohort. There were equal number of patients treated with the Whipple and the Frey procedure. A total of 70 % patients reported post-operative pain relief over a mean follow-up period of 1.1 years. There were no statistically significant differences in the patient characteristics or morphologic features between the 2 subsets of patients (data not shown).

Table 2 compares the demographic, clinical, morphologic, and histopathologic characteristics of patients with and without post-operative pain relief. The mean follow-up between the two groups was equivalent. A toxic etiology, presence of calcification(s), and severe fibrosis were all significantly associated with post-operative pain relief on univariable analysis. While the pre-operative mean MPD diameter was greater in the patients who reported post-operative pain relief versus patients who continued to have pain, this was not statistically significant. There was no difference in the post-operative pain relief rates between patients who underwent the Frey versus Whipple procedure.

Table 3 describes the multivariable analysis of factors associated with post-operative pain relief. Only a toxic etiology independently predicted post-operative pain relief (OR 5.7, 95 % CI 1.3, 24.5, *p*=0.02).

Table 4 demonstrates the clinical, demographic, morphologic, and histopathologic characteristics stratified by etiology in CP. The patients in the toxic CP group were significantly more likely to be black males. There was no difference in the type(s) of pancreatic surgery between the toxic and idiopathic

Table 1 Demographic and clinical characteristics of the study cohort

	N=60
Demographics	
Age, mean ± SD (years)	51.6 ± 12.5
Male	32 (53.3)
White	41 (68.3)
Etiology of chronic pancreatitis	
Toxic	37 (61.7)
Alcohol only	7 (11.7)
Smoking only	13 (21.7)
Alcohol and smoking	17 (28.3)
Idiopathic	23 (38.3)
Surgical procedure	
Whipple	30 (50)
Frey	30 (50)
Clinical	
History of acute recurrent pancreatitis	31 (51.7)
Number of acute pancreatitis episodes, mean ± SD	4.2 ± 2.8
Insulin dependent diabetes mellitus	13 (21.7)
Duration of pain, mean ± SD (years)	5.4 ± 5.5
Morphology	
MPD diameter, mean ± SD (mm)	5.7 ± 3.1
MPD dilation	36 (60)
Calcification	36 (60)
Parenchymal calcifications	34 (56.7)
MPD stone(s)	32 (53.3)
Calcification and MPD dilation	30 (50)
Histopathology	
Severe fibrosis	36 (60)
Duration of follow up, mean ± SD (years)	1.1 ± 1.1
Post-operative pain relief	42 (70)

Values are expressed in numbers (%) unless specified otherwise
SD standard deviation, MPD main pancreatic duct

group. Patients with toxic CP had an increased prevalence of calcification(s) and severe fibrosis on histopathology compared to idiopathic CP (all *p*<0.001). While the mean MPD diameter was greater in the toxic CP group, the overall percentage of patients with MPD dilation was equivalent. Patients with toxic CP had significantly higher rates of post-operative pain relief as compared to idiopathic CP (89 vs. 39.1 %, *p*<0.001).

Discussion

While many prior studies have evaluated a single factor associated with pain relief after surgical procedures for CP, the present study is the first to evaluate multiple clinical, morphologic, and histopathologic features as possible predictor(s) of

Table 2 A comparison of demographic, clinical, morphologic, and histopathologic characteristics in patients with post-operative pain relief versus no post-operative pain relief

	Post-operative pain relief (n = 42)	No post-operative pain relief (n = 18)	p value
Age, mean ± SD (years)	51.7 ± 12.5	51.3 ± 12.9	0.92
Toxic etiology	33 (78.6)	4 (22.2)	<0.001
Type of procedure			
Whipple	22 (52.4)	8 (44.4)	0.78
Frey	20 (48.6)	10 (55.6)	0.78
History of acute recurrent pancreatitis	23 (54.7)	8 (44.4)	0.57
Insulin dependent diabetes mellitus	8 (19.1)	5 (27.8)	0.50
Duration of pain, mean ± SD (years)	4.9 ± 4.4	6.6 ± 7.4	0.28
Duration of follow up, mean ± SD (years)	1.1 ± 1.1	1.1 ± 1.1	0.82
Calcification	31 (73.8)	5 (27.8)	0.001
MPD diameter, mean ± SD (mm)	6.0 ± 3.9	4.9 ± 2.3	0.22
MPD dilation	27 (64.3)	9 (50)	0.39
Severe fibrosis	31 (73.8)	5 (27.8)	0.001

Values are expressed in numbers (%) unless specified otherwise
SD standard deviation, MPD main pancreatic duct

post-operative pain relief in CP. Our study found that a toxic etiology is the only independent predictor of post-operative pain relief.

Prior studies evaluating post-operative pain relief among CP patients undergoing a drainage and/or resection procedure have reported a greater improvement of symptoms in patients with extensive calcifications^{2,3,8} and ductal changes.^{2,8} However, nearly 90 % of the patient population in these studies were alcoholics^{2,4,9} who typically demonstrate more morphological changes when compared to patients with idiopathic CP. It is possible that the pain relief attributed to the presence of calcifications and/or ductal dilation in prior studies was related to a toxic etiology, as majority of the patients were alcoholics with unknown smoking status. Cooper et al. reported that severe fibrosis was associated with a greater resolution of pain among CP patients undergoing the Frey procedure,⁷ which is limited to those CP patients with a dilated duct.

Table 3 Multivariable analysis of factors associated with pain relief after the Frey or Whipple procedure

	OR	95 % CI	p value
Toxic etiology	5.7	1.3, 24.5	0.02
Calcification(s)	1.0	0.2, 5.5	0.99
Severe fibrosis	2.9	0.6, 12.5	0.17

Values are expressed in numbers (%)

Table 4 Comparative analysis of toxic versus idiopathic CP

	Toxic CP (n = 37)	Idiopathic CP (n = 23)	p value
Age, mean ± SD (years)	51.1 ± 11.7	52.3 ± 13.9	0.73
Male	25 (67.6)	7 (30.4)	0.007
Race			
White	21 (56.8)	20 (86.9)	0.02
Surgical procedure			
Whipple	18 (48.7)	12 (52.2)	1.0
Frey	19 (51.3)	11 (47.8)	1.0
Clinical			
History of acute recurrent pancreatitis	18 (48.7)	13 (56.5)	0.6
Insulin-dependent diabetes mellitus	11 (29.7)	2 (8.7)	0.11
Duration of pain, mean ± SD (years)	5.5 ± 4.7	5.4 ± 6.7	0.96
Morphological			
MPD diameter, mean ± SD (mm)	6.3 ± 3.7	4.7 ± 2.5	0.06
Dilated MPD	25 (67.6)	11 (47.8)	0.18
Calcifications	31 (83.8)	5 (21.7)	<0.001
Histopathology			
Severe fibrosis	28 (75.8)	8 (34.8)	0.003
Outcome			
Post-operative pain relief	33 (89.2)	9 (39.1)	<0.001

Values are expressed in numbers (%) unless specified otherwise
SD standard deviation, MPD main pancreatic duct

However, this study did not stratify post-operative pain relief rates based on the etiology of CP. While our and prior studies have all demonstrated an association between toxic etiology, calcifications, and severe fibrosis with post-operative pain relief, we have shown that a toxic etiology is the only independent predictor of post-operative pain relief.

The association between MPD dilation and post-operative pain relief is unclear. While some studies have reported pain improvement in patients with large duct CP after the modified Puestow² and Frey¹⁶ procedures, there have been several studies which have demonstrated that post-operative pain relief is independent of MPD diameter.^{8,17,18} Our study failed to demonstrate any association between MPD dilation and post-operative pain relief. There are several potential explanations for this finding. The first is that prior studies focused on alcoholic large duct CP, whereas our study also had many patients with idiopathic large duct CP. The second is the growing recognition that pain in CP is not due to ductal hypertension but to neuropathic changes that occur due to ongoing inflammation and fibrosis that eventually results in peripheral and central sensitization.^{19,20} Therefore, any intervention that simply addresses ductal hypertension may not result in pain relief. The third is that several factors, including delayed timing of

intervention from the onset of symptoms (>3 years), pre-operative opioid use, and higher number (>5) of endoscopic procedures, adversely impact pain relief.²¹ However, in the present study, there were no statistically differences in the post-operative pain relief rates between patients with a toxic or idiopathic etiology that received opiates and/or endoscopic therapy before surgery (data not shown).

Nearly 60 % of idiopathic CP patients in our patient cohort continued to have post-operative pain after a mean of 1-year follow-up. There might be several possible reasons for this. First, idiopathic CP is most likely due to undiscovered genetic mutation(s), which can result in a developmental “field defect,” which is present in all the cells of the pancreas and a partial resection would not eliminate the risk of developing CP in the remnant pancreas.²² Second, the morphological changes of CP occur over a long period of time and presence of less fibrosis in the remnant pancreas can result in further inflammatory insults and ongoing pain.

Our study has several important implications for the management of patients with CP patients. First, toxic CP are good candidates for the Whipple and Frey procedures as evidenced by the results from our study as well as prior studies that report robust rates of post-operative pain relief among alcoholic CP patients undergoing pancreatic drainage and/or resection procedures. In addition, a prior study reported a significantly lower quality of life and islet yield in alcoholic CP versus nonalcoholic patients undergoing total pancreatectomy and islet auto transplantation (TP/IAT).²³ The poor pain outcomes after TP/IAT in alcoholic CP may be partly attributable to selection bias of patients with more severe CP and delayed surgery.^{24,25} Results from our study suggest that Whipple and Frey procedures provide adequate pain relief in patients with a toxic etiology and preclude the need for a radical surgical procedure like TP/IAT. Second, idiopathic CP patients may be better candidates for TP/IAT. As there is less fibrosis in idiopathic CP, these patients are at risk of ongoing inflammatory insults to the remnant pancreas that can result in chronic pain after undergoing a partial pancreatectomy. In addition, these patients can also expect a greater islet yield due to the presence of less fibrosis. Of the 409 TP/IAT procedures performed over 34 years at the University of Minnesota, 21 % of the patients had a prior pancreatic surgery but only 7 % of the total patient cohort had toxic CP.²⁶ This suggests that many failed resection and/or drainage procedures occurred in idiopathic CP, who then subsequently underwent TP/IAT for management of ongoing pain. This approach is far from optimal for three reasons. The first is the inconvenience, cost, and risks posed to the patient of a reoperation. The second is that since prior surgical drainage procedures result in reduced quantities of islets, there is a substantially increased risk of post-operative insulin-dependent diabetes. The third is that pancreatic re-operation also essentially precludes the ability to perform the procedure laparoscopically, which is likely to

become more common with the increasing focus on and proliferation of minimally invasive surgical techniques.

There are limitations to our study. First, post-operative pain relief was evaluated as a dichotomous outcome instead of using a validated pain assessment tool. However, pain relief at follow-up was based on patient report and ongoing narcotic analgesic use. Second, post-operative pain relief was only evaluated over a short-term period. A possible explanation is that being a tertiary care center, a significant number of patients were referred for surgery, and also that patients who experienced resolution of pain were less likely to follow-up. Repeat analysis of patients after excluding patients with only 1-month follow-up revealed an increase in strength of association between pain relief and toxic etiology (data not shown). In addition, our rates of post-operative pain relief are similar to prior studies. One study reported an improvement in the pain scores of >90 % patients undergoing Frey or Whipple procedure for painful CP,²⁷ and a follow-up study evaluating the same cohort of patients revealed that the pain response only improved over a follow-up period of nearly 15 years.^{28,29} It is also important to note that most of the patients in our study cohort had a toxic etiology (61 % with a history of alcohol abuse and 78 % with a history of smoking). Another recent study evaluating pain relief after Frey procedure in painful CP reported post-operative pain relief in 91 % of the patients undergoing operative procedure at a mean follow up of 6 years,³⁰ and >90 % of the patients had alcoholic CP. Further evaluation using a larger cohort of patients would be beneficial to confirm the findings of our study. Third, the duration and dose of alcohol and smoking for patients in the toxic CP was not quantified. However, qualitative use of alcohol and smoking was readily identified during the retrospective review of the medical records. In addition, all of the patients in our cohort had clear morphologic changes of CP and no other identifiable etiology of CP. Fourth, no patients in our cohort underwent genetic mutation analysis. Therefore, our subjects classified as “idiopathic” likely included some patients with undiagnosed genetic mutations. However, genetic mutation analysis is not routinely obtained in CP patients due to inconsistent coverage by insurance plans and a lack of a clear subsequent intervention based on the results. In addition, there are several genetic mutations which can predispose a patient to develop CP; therefore, a negative result based on testing for the four commercially available gene mutations (*PRSS1*, *SPINK1*, *CFTR*, *CTRC*) does not necessarily exclude the presence of a genetic mutation, such as more recently discovered mutations in carboxypeptidase³¹ and the calcium sensing receptor³² cannot be assayed at the present time. A recent study reported an increased prevalence of genetic mutations in patients labeled as “idiopathic” CP.³³ Our results suggest that idiopathic CP patients should be evaluated for known genetic mutations as this can potentially assist the clinician in determining which type of operative procedure, i.e.,

drainage/partial resection versus TP/IAT, is most suitable for their patients. Fifth, surgical histology was obtained from the head of the pancreas, which may not be representative of the histopathology of the entire gland, particularly since CP can be a focal and patchy disease. However, all patients underwent an operative procedure in our cohort for pain, which enriches for severe CP. Even in patients undergoing TP/IAT, only a few core biopsies are usually obtained from the head and body/tail region to preserve as many islets as possible for isolation and autotransplantation.

In summary, toxic CP patients are more likely to experience higher post-operative pain relief rates than idiopathic CP patients after the Whipple or Frey procedure. Contrary to prior published data, neither radiologic features like MPD dilation and presence of calcification(s) nor fibrosis on histopathology were associated with post-operative pain relief. This should be considered when deciding the appropriate surgical treatment for patients with CP.

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