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Original Research Article

Long-term symptom resolution following the surgical management of chronic pancreatitis

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A B S T R A C T

Background: Pervasive symptoms from chronic pancreatitis despite noninvasive management is an indication for surgical intervention. Frey and Whipple procedures are appropriate options for proximal pancreas disease; however, data are limited on symptomatic outcomes.
Methods: We conducted a retrospective analysis of patients who underwent surgical intervention for chronic pancreatitis of the proximal pancreas from 2005 to 2019. Preoperative patient characteristics and postoperative outcomes were evaluated.
Results: One hundred forty patients underwent surgical intervention for chronic pancreatitis, 91 Whipple and 49 Frey procedures. Mean age was 53 years (SD 12), and mean BMI 24 (SD 5.6). At post-operative follow-up, 74 % were asymptomatic, and 84 % at average follow-up of 2 years. Groove pancreatitis, lack of post-operative delayed gastric emptying, and decreased length of stay were predictive of symptom resolution.
Conclusions: Whipple and Frey procedures are appropriate surgical options for chronic pancreatitis affecting the proximal pancreas. Both lead to sustained symptom resolution for most patients.

1. Introduction

Chronic pancreatitis is characterized by recurrent inflammation and fibrosis, resulting in pervasive symptoms of abdominal pain, early satiety, nausea, malnutrition, and pancreatic insufficiency.[1,2] Though there are limited data on the true prevalence of chronic pancreatitis, an estimated 5 to 14 per 100,000 patients are diagnosed annually in the US.[3] While the overall incidence and prevalence of chronic pancreatitis remain relatively low, it contributes a significant morbidity and financial burden, with an annual healthcare cost exceeding $3 billion, largely due to increased utilization and symptom palliating efforts.[3–5] Furthermore, disability secondary to chronic pancreatitis symptoms creates a substantial personal burden, with increased work absenteeism and reduced quality of life.[6–8] Treatment efforts initially focus on symptom management and reversal of instigating factors, consisting primarily of medical and endoscopic techniques; however, up to 50 % of all cases of chronic pancreatitis eventually require surgical intervention due to persistent symptoms, most commonly debilitating abdominal pain.[9,10] Additionally, current data suggest that surgery is superior to endoscopy in maintaining symptom resolution and preserving pancreatic function.[11–14]

The operative approach for chronic pancreatitis depends on the degree of ductal dilatation and the anatomic area of prominent disease. For disease primarily in the pancreatic head, pancreaticoduodenectomy (Whipple) or local pancreatic head resection with longitudinal pancreaticojejunostomy (Frey) are the preferred strategies.[15,16] Several cohort studies have shown symptom resolution with Frey and Whipple procedures for chronic pancreatitis, with 75–80 % symptomatic relief in the early post-operative period.[10,17–20] While evidence exists to support the surgical management of chronic pancreatitis, the current literature is limited to small sample sizes, short duration follow-up, or single procedure inclusion criteria.[10,17–19]

Given the relative lack of data on the long-term outcomes of surgical management for chronic pancreatitis isolated to the pancreatic head and proximal pancreas, we sought to evaluate both Whipple and Frey procedures for symptom management in patients with chronic pancreatitis, with a focus on long-term symptom resolution.

2. Methods

Data for patients undergoing Frey or Whipple procedures for chronic pancreatitis between January 2005 and December 2019 at Emory

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University Hospital in Atlanta, GA were reviewed retrospectively. The procedure performed was decided based on the following algorithm: patients with groove pancreatitis underwent Whipple procedure; patients with an inflammatory mass in the head of the pancreas underwent Whipple procedure; patients with inflammatory changes in the head of the pancreas (with or without calcifications) and dilated pancreatic duct underwent Frey procedure. If it was technically not possible to perform a Whipple procedure, a Frey procedure was completed. Chronic pancreatitis with distal pancreatic duct strictures were managed by distal pancreatectomy and are not included here.

Surgical pathology was reviewed, and patients whose final pathology was inconsistent with chronic pancreatitis were excluded from analyses. Electronic medical records were reviewed for demographics, comorbidities, etiology of pancreatitis, preoperative imaging findings, operative details, histopathology results, postoperative course, postoperative complications, postoperative symptom resolution, and long-term symptom resolution. Postoperative complications were defined as those occurring within 30 days of surgery and graded according to the Clavien-Dindo (CD) classification. Postoperative and long-term symptom resolution were derived from reported symptoms at the first postoperative visit and the most recent follow-up visit, respectively. Patients were divided into two groups based on symptom resolution at the first postoperative visit, which was defined as resolution of their initial presenting or reported symptom. In sensitivity analyses, symptomatic was defined as narcotic use at time of follow-up or pancreatic enzyme supplementation at time of follow-up.

Data analysis was performed using Statistical Package for Social Sciences (SPSS, Version 28.0.1, IBM Corporation). Univariate analyses were used to analyze demographic data, comorbidities, operative details, postoperative course, postoperative complications, and long-term symptom resolution. Chi-square or Fisher's exact test was used to compare proportions between groups. Continuous data were analyzed using Student's t-test and Mann-Whitey *U* test where appropriate. Univariable and multivariable logistic regression models were created to evaluate factors affecting symptom resolution. Significance is reported as a p-value less than 0.05 ($p < 0.05$). All statistical tests were two sided and homogeneity of samples was confirmed. Categorical data are presented as totals and frequencies; continuous data are presented as means and standard deviations, unless otherwise noted.

3. Results

One hundred forty patients underwent surgical intervention for chronic pancreatitis during the defined study period, 91 Whipple and 49 Frey procedures; 9 patients did not have any post-operative follow-up data available and were excluded from symptom analysis. Table 1 shows the demographic characteristics of the study population. The average age was 53 years (SD 12.4), and 61% of the cohort was male. Nearly half of the study population used tobacco within the 12 months preceding surgery, and 33% cited a history of significant alcohol use. Eighty-five patients (64.9%) reported taking narcotics preoperatively (67.0% asymptomatic versus 57.1% symptomatic, $p = 0.086$). Thirty-one percent developed chronic pancreatitis secondary to alcohol use, 9% idiopathic, and 5% secondary to gallstone disease. Over 30% of patients had at least one intervention prior to surgery, and 24 patients (17%) required supplemental nutrition via total parenteral nutrition (TPN) or tube feedings due to malnutrition. Pancreatic enzyme supplementation was required in 24% of the cohort preoperatively. Of 140 patients undergoing operative intervention for chronic pancreatitis, 103 (74%) were asymptomatic at postoperative follow-up, and 117 (84%) were asymptomatic at an average follow-up of 2 years. There were no significant differences in demographics between those who had symptom resolution at the first postoperative visit and those who remained symptomatic.

In the overall cohort, 22 patients (15.7%) had evidence of groove pancreatitis on preoperative imaging, 21 within the symptom resolution cohort and 1 within the persistently symptomatic cohort ($p = 0.035$). Sixty-seven (48%) had an inflammatory mass, and 75% had pancreatic ductal dilatation on preoperative imaging, which did not significantly

Table 1
Cohort demographics.

	Total (n = 131)		Asymptomatic (n = 103)		Symptomatic (n = 28)		p-value
Age (mean, SD)	53.01	12.39	53.35	12.55	52.94	12.66	0.881
Male	85	60.7%	64	62.1%	17	60.7%	0.891
White	99	70.7%	75	72.8%	18	64.3%	0.378
BMI[a]	24.18	5.585	24.05	5.36	24.53	5.57	0.706
Etiology							0.437
Alcohol use	43	30.7%	32	31.1%	10	35.7%	0.640
Idiopathic	19	13.6%	13.6	10.4%	2	7.7%	0.679
Gallstone	7	5.0%	7	6.8%	0	0.0%	0.156
Other	9	6.4%	8	7.8%	1	3.6%	0.436
Prior Intervention	49	35.0%	38	80.9%	9	19.1%	0.642
Nutritional Supplements	24	17.1%	17	16.8%	7	25.0%	0.326
Pancreatic Enzyme Supplementation	31	23.7%	24	23.3%	7	25.0%	0.752
Procedure							0.124
Whipple	91	65.0%	65	63.1 %	22	78.6%	
Frey	49	35.0%	38	36.9%	6	21.4%	
Comorbidities							
Hypertension	60	42.9%	44	47.3%	13	61.9%	0.227
Diabetes Mellitus	43	30.7%	31	30.1%	9	32.1%	0.835
COP[b]	10	7.1%	8	7.8%	2	7.1%	0.902
Alcohol Use	46	32.9%	38	36.9%	7	25.0%	0.240
Tobacco Use	67	47.9%	51	50.0%	12	42.9%	0.503
Preop Imaging							
Groove Pancreatitis	**28**	**20.0%**	**24**	**24.0%**	**1**	**3.7%**	**0.019**
Inflammatory Mass	69	49.3%	51	51.0%	14	51.9%	0.937
PD[c] *Dilation*	108	77.1%	83	83.0%	19	70.4%	0.143

Nutrition supplements include preoperative total parenteral nutrition or tube feeds.
Symptomatic refers to symptomatic at post-operative visit.
[a] BMI, body mass index (kg/m^2).
[b] COPD, chronic obstructive pulmonary disease.
[c] PD, pancreatic duct.

differ between those with symptom resolution and symptom persistence (Table 1).

Postoperative complications and long-term symptomatology are presented in Table 2. New pancreatic enzyme supplementation was required in 15 (11.7%) of the operative cohort. There were significantly fewer patients in the asymptomatic cohort requiring post-operative narcotics at the first postoperative follow-up compared to the symptomatic cohort (37% versus 64%, respectively, p = 0.037) and at long-term follow-up (9.7% versus 32.1%, respectively, p = 0.015). Twenty-seven patients (19.3%) presented to the ED within 30 days of discharge, which did not significantly differ between asymptomatic and symptomatic at follow-up visit. Roughly 50% of the entire cohort experienced a complication, 13.6% of which were graded Clavien-Dindo III or IV. There were 5 clinically significant pancreatic fistulas (Grade B or C), which were evenly distributed between symptomatic and asymptomatic at postoperative follow-up. Seven patients required reoperation for postoperative complications. There was a significantly higher proportion of patients experiencing delayed gastric emptying or ileus during the postoperative period in the persistently symptomatic cohort than the asymptomatic cohort (25% versus 10% respectively, p = 0.035).

On univariate analyses, postoperative DGE (OR for symptom resolution 0.326, CI 0.111–0.956, p = 0.035) and increased LOS (OR for symptom resolution 0.911, CI 0.852–0.974, p = 0.006) were found to be significant in predicting symptom persistence at first postoperative visit, with groove pancreatitis being a significant predictor in symptom resolution at first postoperative visit (OR 8.211, CI 1.058–63.737, p = 0.019), these remained significant predictors on multivariate analyses (Table 3). Repeat univariate and multivariate analyses were completed to evaluate factors associated with long-term symptomatology. DGE (OR 0.311, CI 0.102–0.945, p = 0.032), ED visit within the first 30 postoperative days (OR 0.208, 0.078–0.557, p = 0.003), and clinically significant pancreatic leak (OR 0.257, 0.06–0.996, p = 0.049) were predictive of lack of long-term symptom resolution on univariate analyses. ED visit within the first 30 postoperative days remained significant in predicting long-term symptom persistence on multivariate analyses.

In sensitivity analyses, defining symptomatic based on narcotic use or use of pancreatic enzyme supplementation at postoperative follow-up, there were no differences in predictors of persistence symptoms compared to the previously described results.

4. Discussion

Our analyses demonstrate that Whipple and Frey procedures are appropriate options for surgical intervention for chronic pancreatitis isolated to the pancreatic head or proximal pancreas. Over 70% of patients experience symptom resolution within the first 30 postoperative days, which increases to 84% at a mean follow-up of 2 years, suggesting improved and sustained long-term symptomatic relief. We found that groove pancreatitis, postoperative DGE, and length of hospitalization were significant predictors in symptom persistence or resolution.

These findings support and expand on the current data surrounding surgical intervention for chronic pancreatitis. Kempeneers and colleagues evaluated long-term pain relief after Frey or extended lateral pancreaticojejunostomy in chronic pancreatitis patients with a dilated main pancreatic duct of 5 mm or larger. They report 60% complete or near-complete symptom resolution; however, they included only patients without pancreatic surgical history and required opioid use for pain management preoperatively. Additionally, a Whipple was not offered at their institution for those with groove pancreatitis or significant inflammatory mass in the pancreatic head. Another study with reported a reduction in objective pain score of 36 points in patients undergoing Frey procedure for chronic pancreatitis, with use of preoperative narcotics and postoperative complications being significant predictors of failure to achieve symptom resolution; however, they do not differentiate between type of complication and only include patients undergoing Frey procedure. We similarly found that postoperative complications, namely delayed gastric emptying, and increased length of stay were predictors of symptom persistence at post-operative follow-up and long-term follow-up among those undergoing Whipple or Frey procedures.[10,17–19]

These data highlight the success of operative intervention for those with chronic pancreatitis isolated to the proximal pancreas or pancreatic head; however, medical management remains a frequently utilized treatment modality for this patient population. In the presented data, all patients had previously failed maximal medical therapy at the time of surgical intervention. Current practice guidelines support medical management as the first-line treatment for chronic pancreatitis and referral for endoscopic or operative interventions for those with persistent symptoms despite maximal non-invasive therapies.[21] However, the ESCAPE clinical trial supports early operative intervention in those with

Table 2
Operative and post-operative outcomes.

	Total (n = 131)		Asymptomatic (n = 103)		Symptomatic (n = 28)		p value
Operative minutes	202.25	98.85	198.09	97.52	217.72	104.22	0.380
EBL[a] (cc)	203.92	200	231.59	189.20	288.50	256.32	0.265
Patients Requiring OR Transfusions (n, %)	4	2.9%	3	2.9%	1	3.6%	0.830
Patients Requiring Postop Transfusions (n, %)	3	2.1%	3	2.9%	0	0.0%	0.418
New Pancreatic Enzyme Supplementation	15	11.5%	5	17.9%	10	9.7%	0.386
Length of stay, days	**9.49**	**7.67**	**8.25**	**4.32**	**14.04**	**13.61**	**<0.001**
ED[b] Visit	27	19.3%	20	19.6%	6	21.4%	0.831
Readmission	23	16.4%	17	16.7%	6	21.4%	0.559
Any Complication	64	45.7%	50	48.5%	14	51.9%	0.760
Clavien III or IV Complication	19	13.6%	12	13.0%	4	16.0%	0.703
Pancreatic Leak	10	7.1%	5	4.9%	4	14.3%	0.080
Clinically significant leak	5	3.6%	2	2.9%	2	7.1%	0.143
VTE[c]	1	0.7%	1	1.0%	0	0.0%	0.601
DGE[d]/Ileus	**18**	**12.9%**	**10**	**9.8%**	**7**	**25.0%**	**0.035**
Reoperation	7	5%	3	3.2%	3	12.0%	0.074
MI[e]	1	0.7%	1	1.1%	0	0.0%	0.603
CVA[f]	1	0.7%	1	1.1%	0	0.0%	0.603

Symptomatic refers to symptomatic at post-operative visit.
[a] EBL, estimated blood loss.
[b] ED, emergency department.
[c] VTE, venous thromboembolism.
[d] DGE, delayed gastric emptying.
[e] MI, myocardial infarction.
[f] CVA, cerebrovascular accident.

Table 3
Risk factor analysis for post-operative symptom resolution.

Variable	Univariate			Multivariate		
	OR	95 % CI	p-value	OR	95 % CI	p-value
Age	1.003	0.970–1.037	0.880			
Gender	0.942	0.400–2.218	0.891			
Body Mass Index	0.984	0.904–1.070	0.703			
Race	1.488	0.613–3.611	0.378			
Etiology: Alcohol	0.811	0.337–1.953	0.640			
Etiology: Idiopathic	1.533	0.413–5.685	0.521			
Etiology: Gallstone	1.073	1.018–1.130	0.156			
Pancreatic Duct Dilation	2.056	0.774–5.461	0.143			
Groove Pancreatitis	**8.211**	**1.058–63.737**	**0.019**	**7.616**	**1.000–61.669**	**0.050**
Inflammatory Mass	0.966	0.413–2.263	0.937			
Nutrition Supplements	0.607	0.223–1.653	0.326			
Prior Intervention	1.234	0.508–3.001	0.642			
Alcohol Use	1.754	0.682–4.510	0.240			
Tobacco Use	1.333	0.574–3.098	0.503			
Hypertension	0.533	0.209–1.458	0.227			
Diabetes Mellitus	0.909	0.370–2.231	0.835			
Operative Minutes	0.998	0.994–1.002	0.380			
Length of Stay	**0.911**	**0.852–0.974**	**0.006**	**0.906**	**0.840–0.978**	**0.011**
Any Complication	0.876	0.375–2.046	0.760			
Presence of DGE	**0.326**	**0.111–0.956**	**0.035**	**0.301**	**0.091–1.000**	**0.050**
Pancreatic Leak	0.306	0.076–1.227	0.080			
Infection	1.529	0.520–4.500	0.438			
Emergency Room Visit	0.894	0.320–2.496	0.831			
Readmission	0.733	0.259–2.079	0.559			

Variables included in multivariate analysis include: age, gender, etiology, groove pancreatitis, alcohol use, tobacco use, diabetes mellitus, length of stay, complications.

chronic pancreatitis given significantly lower patient-reported pain scores for those who underwent early surgery compared to those receiving medical-endoscopic therapy first.[12] Of 44 patients in the endoscopy-first group, comprised of maximal medical therapy followed by endoscopic intervention as indicated, only 2 patients (5% of the cohort) experienced success on medical therapies. Furthermore, endoscopy failed to ameliorate symptoms in over 60% of those undergoing endoscopic intervention, with over half of those requiring surgery. These findings suggest that medical and endoscopic therapies are inadequate in sufficiently managing chronic pancreatitis; although, more data are needed to supplement this single randomized control trial and support early surgical intervention.

The resolution of symptoms from chronic pancreatitis is crucial not only for patient quality of life but also for healthcare expenditures and overall survival. A study evaluating long-term survival following surgical management of chronic pancreatitis found that nearly 25% of patients have persistent narcotic requirements following surgical intervention, and persistent narcotic dependence was the only factor associated with worsened overall survival.[22] Though the most common cause of mortality was infections and cardiac events, both occurring at several years postoperatively, psychosocial causes including substance abuse and suicide contributed significantly to overall mortality and occurred earlier in the postoperative course. In conjunction with our data, which suggest that over 80% of patients experience symptom resolution in the long-term, highlight the importance of surgical referral for patients with chronic pancreatitis, to mitigate symptomatology and potentially improve overall survival in this population.

We found a higher proportion of patients with groove pancreatitis within the post-operative and long-term symptom resolution cohorts than those with persistent symptoms. Additionally, in univariate analyses, groove pancreatitis was a significant predictor of symptom resolution at post-operative and long-term time points. Of the 22 patients with imaging findings of groove pancreatitis, 82% underwent pancreaticoduodenectomy to resect the paraduodenal groove and the area of pathologic concern. Because groove pancreatitis is more strongly associated with alcohol consumption or tobacco use as the etiology of inflammation, compared to chronic obstruction or exocrine dysfunction in classic chronic pancreatitis, it may be considered an independent pathology; however, because the management is similar to that of "classic" chronic pancreatitis, we do continue to include groove pancreatitis as a subset of those with broader chronic pancreatitis. Additionally, there are few studies on the outcomes of surgical intervention for persistent symptoms secondary to groove pancreatitis. Short-term cohort studies have shown symptom resolution with small sample sizes and maximum follow-up 6 months; however, there are limited data on the long-term symptomatology in this population.[23–25] We show sustained significant symptom improvement in this subset of patients.

Our results should be viewed within the restrictions of certain limitations. This is a retrospective single-center review, potentially limiting the generalizability of our results. However, our findings of long-term symptomatic relief in patients undergoing Whipple and Frey procedures for chronic pancreatitis are in line with currently published literature. Symptomatology, including pain, was not defined using an objective measure; the presence of persistent symptoms was abstracted from subjective reports of symptoms congruent with pancreatitis at follow-up visits. Several patients (30 patients) did not have follow-up after the initial post-operative visit, limiting our ability to define their long-term symptomatic relief. It is also important to note that our cohort had a prevalence of diabetes of nearly 31 %, whereas the national estimated prevalence of diabetes in the United States is 8–10%,[26] which could limit the generalizability of these results. However, the complication rates presented here are in line or lower than those presented in the current literature for Whipple procedures and Frey procedures performed for all indications.[27–29] Furthermore, the population presented here is representative of patients with chronic pancreatitis, which has been associated with diabetes prevalence upwards of 30%–40%.[30]

5. Conclusions

In conclusion, operative intervention via Whipple or Frey for pervasive symptoms due to chronic pancreatitis limited to the pancreatic head or proximal pancreas provides durable symptomatic relief and should be considered in appropriate surgical candidates. Given the significant financial burden of healthcare utilization and multiple procedures aimed at symptom palliation, the sustained symptomatic relief from surgical intervention has the potential to decrease healthcare expenditures related to chronic pancreatitis.

CRediT authorship contribution statement

Savannah R. Smith: Writing – review & editing, Writing – original draft, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Mohammad Raheel Jajja:** Writing – review & editing, Supervision, Investigation, Formal analysis, Data curation, Conceptualization. **Juan M. Sarmiento:** Writing – review & editing, Supervision, Project administration, Investigation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

This work is not under consideration for publication elsewhere and has been approved for submission and publication by all authors.

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