



LONG-TERM OUTCOMES FOLLOWING FREY'S PROCEDURE FOR CHRONIC PANCREATITIS – A TEN-YEARS OF SINGLE-CENTER EXPERIENCE FROM A TERTIARY CARE CENTER IN SOUTH INDIA

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ABSTRACT

Background/Aim: Chronic pancreatitis (CP) is surgically treated in selected patient populations. Frey's procedure (FP) is the most commonly described procedure for CP with head mass. This study is being conducted to determine the long-term outcome and efficacy of FP in patients with CP in South India of various etiologies. **Methods:** This is a retrospective study of patients who underwent FP at our institution. Clinical features, perioperative findings, and follow-up results were evaluated. A subgroup analysis of pain relief was performed between alcoholics and non-alcoholic groups and between patients receiving FP alone and FP with additional procedures. **Results:** Of the 181 patients, alcohol was the causative factor in 99 (54.69%), gallstones in 20 (11.04%), and idiopathic in 62 (34.25%). With a median follow-up of 43.49 months (range 12-72 months), 78 (43.09%) patients experienced complete pain relief. Due to persistent pain and the presence of preoperative diabetes mellitus (DM), pain relief in patients with postoperative complications was incomplete. New DM and exocrine dysfunction were reported in 25 years (13.81%) and 15 (8.28%) patients. Patients with a history of alcohol abuse, smoking, weight loss, and postoperative complications are associated with newly developed diabetes. **Conclusion:** FP is a safe surgical option for CP with acceptable perioperative complications and appropriate short-term and long-term pain management in properly selected patients. Continuous pain and preoperative DM were independent predictors of incomplete pain relief after FP. Symptoms associated with alcohol abuse, smoking, and weight loss were associated with the development of post-FP DM in the study population.

KEYWORDS : Frey's procedure, Chronic pancreatitis

INTRODUCTION

Chronic pancreatitis (CP) is a progressive inflammatory disease that leads to irreversible destruction of the pancreatic parenchyma. Patients suffer from chronic pain, dyspepsia, or diabetes (DM) due to permanent loss of pancreatic exocrine and endocrine function^[1-3]. The normal pancreatic fibrous replacement may be associated with persistent abdominal pain, the development of exocrine dysfunction, and ultimately diabetes mellitus. Chronic pancreatitis is easily clinically recognizable at an advanced stage. It is usually associated with the narrowing and dilation of pancreatic ducts, stones, diffuse parenchymal calcifications, and the digestive and metabolic effects of organ failure. In addition, enlargement of the pancreatic head causes local complications such as bile duct stenosis and duodenal compression.

However, identifying patients with early and mild illnesses remains a challenge. The lack of a clinically appropriate classification system for chronic pancreatitis contributes to contradictions in disease management. Treatment decisions, ideally taken after appropriate multidisciplinary input from surgical, endoscopic, and radiologic experts, are better made in the context of individual circumstances such as patient symptoms and anatomic findings rather than classification systems based on etiology or morphologic severity. Significant personal and socio-economic implications include poor quality of life, disability, and shortened life expectancy^[4].

The main indications for surgical intervention in the case of CP are intractable pain, local complications, suspected malignancies, and other methods of failure such as medical and endoscopic treatment^[5]. Pain is the main symptom of CP, so the main goal of treatment is to relieve the pain. In patients with advanced illness, medical and endoscopic treatment is often associated with inadequate symptom relief. Up to 50% of patients may undergo surgery during the disease course^[6]. Current evidence suggests that surgery is more effective than endoscopic treatment in terms of faster, more effective, and longer-lasting pain relief^[7].

Approximately 18-50% of patients with chronic pancreatitis present with an inflammatory mass on the head^[8], and its resection is necessary to relieve pain by removing the "pacemaker of pain". The choice of surgery is generally determined by the degree of dilation of the pancreatic duct, glandular morphology, local complications, and the surgeon's experience and preferences. The modified Puestow procedure was the standard procedure in the past. The main reason this procedure fails is that it does not address the inflammatory mass of the pancreatic head, the so-called CP "pain pacemaker"^[10]. Frey et al.^[11] described a new hybrid surgery that combines local excision of the pancreatic head with longitudinal pancreaticojejunostomy. Various pancreatic resections have been proposed to address this issue, including pancreaticoduodenectomy (PD) and Beger. Both PD

and Frey's methods (FP) have similar long-term results. However, short-term results support organ preservation procedures^[12,13].

Of these methods, FP is technically simple. The long-term results of the Frey and Beger procedures are similar, but FP has shorter surgery times and lower morbidity than the Beger procedure. Regular FP is performed for patients with head mass CP. Most patients after FP have proper postoperative pain management, but some still experience abdominal pain. The purpose of this study is to report the experience of FP for CP in terms of efficacy and long-term outcomes from tertiary care centers in South India.

Patients And Methods

The present study is a retrospective observational study of the database that was prospectively maintained at our institute between January 2010 and December 2020. Records of all patients who underwent Frey's surgery during this period were reviewed. Patients who underwent surgery other than FP were excluded. Surgery was provided to patients with intractable pain who interfered with their daily lives and did not respond to maximum treatment. FP was performed when the pancreatic head was enlarged (> 3.5 cm) with a pancreatic duct diameter of 5 mm or more by contrast-enhanced CT abdomen (pancreatic protocol). CP was diagnosed based on clinical features and imaging discrimination of pancreatic duct and parenchymal changes (calcification, atrophy, duct dilation). Three-phase computed tomography (CT) of the abdomen was the imaging technique of choice for assessing the severity of the disease. Magnetic resonance cholangiopancreatography (MRCP) and endoscopic retrograde cholangiopancreatography (ERCP) were performed to assess and treat associated biliary obstruction. Diagnosis of CP was confirmed histopathologically after surgery. Upper gastrointestinal endoscopy was performed to rule out associated gastric ulcers and varicose veins. CA 19-9 was measured when a malignant tumor was suspected. Demographic data, test results, perioperative results, and follow-up results were recorded for all patients. Evaluation of results included postoperative complications, long-term pain management, and exocrine and endocrine dysfunction.

Factors associated with incomplete pain management and newly developed diabetes were analyzed. The results after adding other procedures were also analyzed. Patients with biliary stricture and intractable pain were subjected to upfront surgery without endotherapy. An ERCP stent is placed before surgery in patients with cholangitis.

Surgical Procedure

Surgery was performed as described by Frey and Smith^[11]. Complete exposure and Kocherization of the pancreas were followed by palpation to access the pancreatic duct with aspiration using a 22G needle. The Wirsung duct was then opened by electrocautery over its entire length. Before enucleation of the pancreatic head, a series of 3-0 polypropylene hemostatic sutures was placed on the pancreatic head approximately 0.5 cm from the duodenum along the overall length of the C-loop. These sutures allow traction and hemostasis during excision of the pancreatic head.

Electrocautery was used to enucleate the head and uncinate process of the pancreas. Bleeding during coring can be controlled by cauterization or 5-0 polypropylene suture. The surgeon's left hand was placed behind the head of the pancreas and the thickness of the head of the pancreas was palpated to assess the depth of the incision during head coring. The posterior limit of resection was the back wall of the opened duct of Wirsung and the duct to the uncinate. The intervention of the pancreatic head, including the Santorini

duct, and all tissue above it were resected to give rise to 5 mm thick pancreatic tissue in the C-loop of the duodenum. If the bile duct was accidentally opened during this dissection, the bile duct was drained into the same roux limb for drainage. A pancreaticojejunostomy (PJ) was performed with a single layer of continuous 3-0 polypropylene sutures. In the presence of pseudocysts, surgical drainage was performed by side-to-side cysto-jejunostomy on the same Roux-en-Y limb used for PJ. Surgery was completed by jeuno-jejunal anastomosis about 40 cm distal to the pancreatic anastomosis. All mesenteric and mesocolic rents were closed. An abdominal drain was placed along the PJ up to the splenic hilum. All removed pancreatic tissue was sent for histopathological examination.

Antibiotics and venous thrombosis prophylaxis were administered to all patients according to institutional protocols. Epidural analgesia has been routinely used for perioperative pain management. The epidural catheter is removed 4 days after surgery and the patient initiated oral analgesics in a stepwise approach, preferably non-narcotic analgesics.

Postoperative mortality includes all deaths that occur during current hospitalization or within 90 days of surgery. Postoperative complications were assessed using the Clavien-Dindo classification^[14]. Pancreatic fistula, post-pancreatic bleeding, and delayed gastric emptying are classified according to the guidelines of the International Research Group on Pancreatic Surgery (ISGPS)^[15-17].

Diabetes (DM) was defined as fasting blood glucose above 126 mg/dl and serum glycosylated hemoglobin (HbA1c) above 6.5%. Exocrine pancreatic insufficiency (EPI) is considered in patients with a frequency of stools of 3 times or more per day with a foul odor, and greasy, light-colored stools^[18]. Our facility for measuring fecal elastase was not available, making it impossible to routinely perform biochemical tests to assess pancreatic exocrine function.

Pain patterns are classified as "continuous" in patients with chronic relentless pain and "relapsed" in patients with recurrent acute exacerbations with or without chronic relentless pain.^[19] Izbicki Pain Score assessed pain intensity^[20]. Pain scores were assessed before and at each visit after surgery (3 months after surgery if incisional pain was not an issue). Here, we compare the preoperative pain score with the final follow-up. Pain relief during follow-up was categorized as complete (Izbicki pain score less than 10) or incomplete (Izbicki pain score greater than 10 after a 50% or greater reduction)^[21].

All patients were followed up every 3 months for the first 2 years of surgery, every 6 months for 2 to 5 years, and once a year after 5 years. During follow-up, parameters of weight, pain management, a requirement of analgesics, enzyme supplementations and hospitalization, blood glucose levels (both fasting and postprandial), and complications associated with chronic pancreatitis are recorded. Follow-ups ranged from 12 to 72 months. Follow-up intervals were not uniform, as many patients came from distant rural areas and were intended to follow up according to possible circumstances. Postoperative status is available by phone.

RESULTS

A total of 238 patients received FP for CP during the study period. Among them, 57 patients were excluded from the study due to a lack of follow-up. Therefore, 181 patients who underwent FP were included. Preoperative clinical parameters are summarized in **Table 1**.

Table 1: Preoperative patient demographics (n = 181)

Variables	N (%)
Age (years)	36.34 (13 – 65)
Male: Female	127/54 (2.35:1.0)
The interval between symptoms of CP and surgery (months)	43.82
History of alcohol abuse	99(54.69%)
History of smoking	40(22.09%)
Association with Gallstones	20(11.04%)
Idiopathic	62(34.25%)
Peripancreatic local complications	
Bile duct stenosis	19(10.49%)
Pancreatic pseudocyst	11(6.07%)
Arterial pseudoaneurysm	03(1.65%)
Left-sided portal hypertension	07(3.86%)
Pancreatic ascites	03(1.65%)
Clinical presentation	
Abdominal pain	181(100%)
Recurrent	128(70.71%)
Constant	53(29.28%)
Weight loss	100(55.24%)
Diabetes mellitus	60(33.14%)
Insulin-dependent	12(6.62%)
Oral hypoglycemics	48(26.51%)
Exocrine insufficiency	20(11.04%)

CP – Chronic Pancreatitis

There were 127 men (70.16%) and women (29.83%) with an average age of 36.34 years (range 20-58 years). Alcohol abuse was identified in 99 (54.69%) patients, gallstones in 20 (11.04%), and the rest were idiopathic CP 62 (34.25%). Forty patients (22.09%) were smokers. The median interval between the onset of pancreatitis symptoms and surgery was 43.81 months. All patients suffered from severe chronic abdominal pain with the previous hospitalization for the same. The indication for surgery was persistent pain. The most commonly used opioids before surgery were tramadol hydrochloride and acetaminophen. Local complications around the pancreas were found in 43 patients. Biliary atresia was the most common local complication, followed by pseudocysts. Preoperatively, DM was apparent in 60 (33.14%) patients and EPI was found in 20 (11.04%) patients. Only FP was performed in 117 patients. Forty-nine additional procedures were performed on 40 patients. The most common additional procedure was cholecystectomy, followed by choledochoduodenostomy (Table 2).

Table 2: Operative procedures done

Frey's procedure alone	117
Additional procedures	59
Cholecystectomy	26
Choledocho-duodenostomy	13
Choledocho-jejunostomy	06
Distal pancreatectomy with Splenectomy	10
Cysto-jejunostomy	05

The median intraoperative blood loss was 182.59 ml. Twenty-eight patients received blood transfusions during hospitalization. The main pancreatic duct diameter was 10.11 mm (range 7-12 mm). The median length of hospital stay after surgery was 9.48 days (range 7-25). Forty-five patients had 49 postoperative complications observed (Table 3).

Table 3: Postoperative complications (n-49)

Complication grade	Complications (n- 49)	Details of complications
I	35	Mild wound infections, managed in the ward (n-29) Grade A pancreatic fistula (n-6)

II	07	Uncontrolled hyperglycemia (n-2) Psychiatric illness requiring medications (n-5)
IIIa	06	Severe wound infection requiring secondary suturing (n-06)
IIIb	01	Postoperative haemorrhage requiring re-exploration (n-1)
IVa, IVb, V	0	

Pancreatic leaks (grade A) were observed in 6 patients. Postoperative bleeding occurred in one patient who was subjected to relaparotomy (bleeding from the branch of the gastroduodenal artery was controlled). There were no deaths for 90 days. Nineteen patients required readmission due to abdominal pain during the follow-up period, which was conservatively managed. Histopathology confirmed chronic pancreatitis in all patients.

Long-term results

The median follow-up was 43.49 months (range 12-72 months). A total of 6 patients died during follow-up due to uncontrolled DM and chronic renal failure. Complete pain relief was achieved in 78 (43.09%) patients. The remaining patients had partial pain relief (Table 4).

Table 4: Risk factors for long-term incomplete pain relief

Variable	Complete pain relief (n-78)	Incomplete pain relief (n – 103)	p-value
Male	51(65.38%)	76(73.78%)	0.221
Alcohol	38(48.71%)	60(58.25%)	0.203
Smoker	13(16.66%)	27(26.21%)	0.125
Duration of pain >3yrs	57(73.07%)	82(79.61%)	0.302
Pre-op continuous pain	54(69.23%)	55(53.39%)	0.031
Preop pain score	44.91	46.11	0.100
Analgesic intake	15.19	15.48	0.138
Preop DM	19(24.35%)	41(39.80%)	0.028
Preop EPI	7(8.97%)	13(12.62%)	0.438
Weight loss	48(61.53%)	52(50.48%)	0.138
Local complications	12(15.38%)	20(19.41%)	0.481
Preop biliary stricture	5(6.41%)	14(13.59%)	0.119
PD diameter(mm)	10.27	9.91	0.166
Post-op complications	14(17.94%)	35(33.98%)	0.016
Continued alcohol consumption	22(28.20%)	41(39.80%)	0.105
Duration of follow-up (months)	41.53	44.97	0.102

DM – Diabetes Mellitus, EPI – Exocrine Pancreatic Insufficiency, PD – Pancreatic Duct

One patient had persistent pain and was treated with a percutaneous Celiac plexus block, 2 months after surgery. Fifty patients had to take painkillers (usually paracetamol or tramadol) from time to time.

Thirty-two patients had mild pain but were not accustomed to taking painkillers regularly. Nineteen patients had to be re-admitted due to acute exacerbations of CP after FP.

Table 5 shows the pain scores before and after surgery. Persistent pain and preoperative DM were significantly associated with a reduced likelihood of achieving persistent pain relief.

Prior to surgery, 99 of the 181 patients were alcohol abusers. 63 (63.63%) continued drinking after FP during follow-up. However, this does not reflect the incomplete pain relief seen in our study.

Table 5: Comparison of pain scores before and after surgery

Variable	Pre-op (mean +/- SD)	Follow-up (mean +/- SD)	Paired t-test P-value
Frequency of pain attacks	52.76	19.88	<0.001
Visual analog pain scale	63.78	22.09	<0.001
Pain medications	15.35	2.29	<0.001
Incapacity to work	51.24	15.33	<0.001
Pain score	45.77	14.86	<0.001

Table 6: Risk factors for new-onset of DM

Variable	Yes (n-25)	No (n - 96)	p-value
Male	18	63	0.546
Alcohol	18	40	0.007
Smoker	09	11	0.003
Duration of pain >3yrs	19	61	0.241
Preop EPI	02	03	0.275
Weight loss	11	59	0.037
Local complications	07	21	0.518
Preop biliary stricture	04	05	0.066
Post-op complications	10	17	0.017
Duration of follow-up (months)	47.52	42.87	0.106

EPI – Exocrine Pancreatic Insufficiency; DM – Diabetes Mellitus

New DM occurred in 25 (13.81%) patients. Predictors of New onset DM (Table 6) are those who develop alcohol abuse, smoking, a history of weight loss at onset, and postoperative complications. The newly developed EPI was developed in 15(8.28%) Patients. In the final follow-up, 85 (46.96%) patients had endocrine dysfunction and 25 (13.81%) patients had exocrine dysfunction. All patients with exocrine dysfunction were treated with pancreatic enzyme supplementation.

Table 7: Comparison of outcomes Alcoholic vs. Non-alcoholic causes

Variables	Alcoholic (n - 99)	Non-alcoholic (n - 82)	p-value
Short term results			
Operative blood loss(ml)	185.41	179.88	0.731
Blood transfusions	12	15	0.246
Postop complications	31	18	0.158
Postop length of hospital stay(days)	9.707	9.207	0.339
Long-term results			
Complete pain relief	38	40	0.159
Pain score at follow up	16.39	13.01	0.026
New-onset DM	18	7	0.061
New-onset exocrine insufficiency	10	5	0.331

DM – Diabetes Mellitus

Table 7 shows the results for alcoholic and non-alcoholic patients who received FP. There were no significant differences in short-term results such as surgical blood loss, blood transfusions, postoperative complications, and postoperative hospital stays. For long-term results, follow-up pain scores were significantly higher in the alcoholic group (p-0.026). Other variables such as complete pain relief, new-onset DM, and new-onset PPI were comparable between the two groups.

In a subgroup analysis of patients who received only FP and

those who received additional procedures, postoperative complications were significantly higher in patients who received FP and additional procedures. All other variables were equivalent between the two groups (Table 8).

Table 8: Comparison of outcomes FP alone vs. Additional procedures

Variables	FP alone (n - 132)	Additional procedure (n - 49)	P-value
Male	86(65.15%)	41(83.67%)	0.016
Alcohol	68(51.51%)	31(63.26%)	0.158
Smoker	27(20.45%)	13(26.53%)	0.381
Duration of pain >3yrs	90(68.18%)	38(77.55%)	0.218
Preop pain score	46.37	45.54	0.308
Analgesic intake	15.40	15.34	0.757
Preop DM	45(34.09%)	15(30.61%)	0.658
Preop EPI	14(10.60%)	06(12.24%)	0.754
Weight loss	76(57.57%)	24(48.97%)	0.301
Local complications	14(10.60%)	27(55.10%)	<0.001
Preop biliary stricture	0(0%)	19(38.77%)	<0.001
PD diameter(mm)	10.15	9.95	0.608
Post-op complications	28(21.21%)	21(42.85%)	0.003
New-onset DM	15(11.36%)	10(20.40%)	0.117
New-onset EPI	10(7.57%)	05(10.20%)	0.568
Continued alcohol consumption	41(31.06%)	20(40.81%)	0.217
Duration of follow-up (months)	43.09	44.57	0.591

FP – Frey’s Procedure; EPI – Exocrine pancreatic insufficiency; DM – Diabetes Mellitus

DISCUSSION

Surgical treatment of chronic pancreatitis is primarily aimed at relieving severe pain and addressing local complications of pancreatitis. Frey’s procedure has become the standard surgery for painful CP associated with an enlarged pancreatic head. This procedure provides significant and persistent pain relief in most patients with acceptably low perioperative complications. The study achieved long-term pain management in 43.09% of patients over an average follow-up of 43.49 months. However, 56.90% of patients had incomplete pain relief. Persistent pain and the high levels of preoperative pain suggested by preoperative DM are detrimental to long-term pain relief.

There is also evidence that early surgical duct decompression may delay the development of pancreatic exocrine and endocrine deficiencies in patients with dilated ducts and relatively conserved glandular function^{[22],[23]}. The patient cohort presented to the tertiary care center at a later stage of disease than the primary care center excludes options for early surgical intervention.

FP is associated with low surgical mortality (range 0-3%) and morbidity (range 17-42%)^{[1],[10],[24]-[26]}. Therefore, it is considered a safe procedure for CP. In this study, consistent with other reported series, 24.86% of patients had postoperative complications and no operative mortality. The most common complication in our study was mild postoperative wound infection, and most patients with wound infection received regular dressing in the ward. In particular, in the case of CP the incidence of pancreatic fistula after surgery is low^{[1],[10],[24]-[26]}.

The hard texture of the pancreatic parenchyma may explain this because it holds the sutures better and reduces the ability of the CP to secrete the pancreas. Nevertheless, the risk of fistulas can be explained by the length of the anastomosis.

The incidence of relaparotomy after FP varies between 2% and 9%, and bleeding is the most common reason^{[11],[24],[26]}. Similarly, however, in this study, one patient needed repeated laparotomy to control bleeding from the branched gastroduodenal artery.

An unfortunate aspect of surgical treatment of CP is poor pain management or pain recurrence. Several factors have been described as predictors of the inability to achieve sustained complete pain relief after surgery. These include chronic pain lasting more than 3 years, continuous pain patterns, preoperative drug addiction, 5 or more preoperative endoscopy, inadequate tube decompression, postoperative complications, and continued alcohol use after surgery^{[24],[29]}.

In our study, very few patients 10 (5.52%), underwent endoscopic therapy before surgery. 56.09% of patients had incomplete pain management during the follow-up period. Continuous preoperative pain and preoperative DM were associated with incomplete pain relief in this study. Other established factors were not associated with incomplete pain relief in our study. This discrepancy can be explained by the fact that the number of endoscopic surgeries is low, opioid use is low (tramadol hydrochloride), and patients are less dependent on preoperative opioids.

Nutrition and endocrine and exocrine functions are essential in assessing the success of surgery to relieve pain and treat complications of chronic pancreatitis. Endocrine and exocrine dysfunction of the pancreas is common in long-term follow-up of CP patients. It depends on the type of intervention and the progression of the underlying disease process. According to a recent review, organ-conserving surgery such as Frey and Beger is preferred over PD because it has beneficial effects on the endocrine and exocrine function when some type of head resection is indicated for CP^[12]. The incidence of new-onset DM and new onset EPI varied in the range of 10-36% and 7-83%, respectively, depending on the length of follow-up and identification methods^{[11],[10],[11],[24],[26]}. In this study, as in the other reported series, 13.81% of patients experienced newly developed DM. In our study, duration of illness, alcohol abuse, smoking, symptoms associated with weight loss, and postoperative complications were associated with the development of newly developed diabetes. This can be explained by the fact that CP is a progressive disease and that reduced exocrine and endocrine function is not the result of an intervention, but the natural consequence of the disease. The longer the follow-up and duration of the disease, the higher the incidence of new DMs. In this study, 8.28% of patients developed new EPI. This is less than the reported series^{[11],[11]}. This discrepancy may be due to a different definition of exocrine pancreatic insufficiency and a decrease in fat intake in the patient population. In one study, Balakrishnan et al. showed that overt steatorrhea was found in 20% of their patients. The low incidence of steatorrhea is due to a low-fat diet. 76% of patients developed steatorrhea when fat intake was increased experimentally from an average intake of 27 g/day to 100 g/day^[30].

The strength of our research is that it is one of the largest FP cohorts with acceptable follow-up and satisfactory results.

Limitations

Our study is a retrospective cohort study and includes only patients who have undergone surgery. Exocrine pancreatic insufficiency was diagnosed based on the clinical manifestations of steatorrhea. Very few patients received endoscopic treatment before surgery 10 (5.52%). Follow-up is available to all patients, but most are from remote locations, so constant follow-up intervals are not possible in patient populations.

In summary, a long-term follow-up of this study showed that

Frey's procedure is a safe and effective option for patients with chronic pancreatitis. Properly selected patients have acceptable short-term and long-term results with acceptable perioperative morbidity and mortality. Continuous pain and preoperative DM were independent predictors of incomplete pain relief after FP. Symptoms associated with alcohol abuse, smoking, and weight loss were associated with the development of post-FP DM in the study population.

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