

ORIGINAL ARTICLE

Factors affecting outcome after Frey procedure for chronic pancreatitis

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Abstract

Background. Debilitating abdominal pain remains the most common presentation of chronic pancreatitis and the treatment remains challenging. **Objective.** This prospective study analyzed the outcome of Frey's procedure in patients with inflammatory head mass. **Methods.** For the period between 2002 and 2007, 77 patients with chronic pancreatitis underwent Frey procedure for intractable abdominal pain. The mean follow-up was 14 months. For the purpose of analysis of the outcome, patients were grouped as poor pain control (19%) and good pain control groups (81%) based on the pain scores during follow-up. **Results.** There was no 30-day mortality. The logistic regression analysis showed that decreased volume percentage (48%) of head mass resected ($p=0.003$) and small diameter of the pancreatic duct ($p=0.05$) were associated with poor pain outcome. Subgroup analysis revealed that patients with small duct disease were associated with increased operative time ($p=0.001$), poor pain scores ($p=0.001$), and increased weight loss ($p=0.003$) during follow-up. **Conclusions.** Frey procedure can be performed with zero mortality and low morbidity in a high-volume center. It provides good pain relief in majority of the patients. Volume of the head mass cored affects pain outcome. Correlation between poor results in terms of pain relief and weight loss following Frey's procedure, and small duct disease supports the view that duct diameter is an important predictor of pain relief.

Key Words: *chronic pancreatitis, pain, head mass*

Introduction

Debilitating abdominal pain remains the most common presentation and indication for surgery in patients with chronic pancreatitis. The precise mechanism underlying the abdominal pain is uncertain. It may be related to ductal hypertension [1], increased parenchymal pressure, perineural inflammation [2] or as a complication of the disease. Therapeutic interventions developed to relieve the disabling pain include conservative [3,4] and surgical management [5]. Varied morphology of the gland has led to the evolution of diverse resection [6] and drainage [7] approaches.

About 18–50% of patients with chronic pancreatitis present with an inflammatory head mass [6] and its

resection was considered necessary to relieve the pain by extirpating the “pacemaker of pain” [8]. Although pancreaticoduodenectomy provided good pain control, increased long-term exocrine and endocrine dysfunction [9] led to a growing enthusiasm for duodenum preserving head resections [10]. In 1987, Frey et al. reported a new technique where patients with inflammatory head mass underwent local resection of the head of pancreas combined with longitudinal pancreatico-jejunostomy (LR-LPJ). Frey procedure avoids transection at the neck of pancreas and requires single anastomoses, as opposed to Beger's procedure which requires two anastomoses [11]. Frey procedure provided good pain control in 90% of the patients with low mortality and

morbidity [12]. This article aims to study outcome and short-term results of the Frey procedure in the treatment of chronic pancreatitis.

Patients and methods

This prospective study was done at Government Stanley Medical college Hospital, Chennai, India. Between 2002 and 2007, 77 patients with chronic pancreatitis underwent Frey procedure for intractable abdominal pain. All patients had a detailed history and clinical examination. The diagnostic workup includes ultrasonography (USG), computed tomographic scanning (CT), and magnetic resonance cholangiopancreatography (MRCP). The diagnosis of chronic pancreatitis was made on the basis of a history of typical abdominal pain and pancreatic calcification or dilatation of main pancreatic duct on imaging (US, CT scan, MRCP). The head of pancreas was considered enlarged when its maximum diameter was more than 35 mm [13]. Patients who have completed at least six months follow-up alone were included in the study. The main pancreatic duct was considered small or non-dilated if it measured 5 mm or less at neck [14]. The main pancreatic duct was considered dilated if it measured greater than 6–7 mm in its maximal diameter.

Pancreatic exocrine function was assessed by the presence of steatorrhea. Patients were requested to answer a questionnaire about number of stools per day, smell, appearance and color of the stools. Frequency of more than three stools per day, nauseating smell, greasy and pale stools was defined as steatorrhea [15]. Diabetes mellitus was defined as blood glucose level more than 200 mg/dL two hours after an oral glucose load of 75 grams. Pain was assessed using a scoring system consisting of a visual analogue scale, frequency of pain attacks, analgesic requirement, and time of disease-related inability to work [16].

Data collection

Data were obtained during hospital admission and during follow-up at outpatient department by face-to-face interview. The assessment interview recorded demographic data, severity of pain, analgesic requirement, etiology of the disease endocrine and exocrine insufficiency and co morbidities.

Surgery

Surgery was offered to those patients with intractable pain interfering with their daily activities and not responding to maximal medical treatment. The nature of surgery depended on morphology of the pancreas and its ductal system, and presence of other complications.

Surgical technique

The surgical procedure was performed as described by Frey and Smith [17]. Intraoperative ultrasonogram was used when there was difficulty in localization of MPD. The head and uncinata process of pancreas were cored out with diathermy. Antero posterior diameter of the head mass before and after coring was measured using calipers, and percentage of the total volume of the head mass was calculated. After perfect hemostasis, pancreaticojejunostomy was done with Roux limb of jejunum using a continuous 00 polyglactin. The cored pancreatic tissue was sent for histopathological examination. Unless major complications occurred, most patients were discharged by ninth postoperative day. Postoperative morbidity and mortality were considered “early” if they occurred within 30 days of surgery or in the same hospital admission and “late” if they appeared after 30 days of performance of surgery.

Follow-up

The patients were followed in the outpatient department every three months in the first year and every six months in second year and annually afterwards. The patients were asked to quantify their pain relief. Patients with pain score of 12 or less were considered to good pain control. Patients with pain score more than 12 and requiring readmissions for pain were considered to have poor pain control. Need for analgesics, weight gain or loss, stool frequency and need for antidiabetic drugs or insulin were recorded. Follow-up ranged from 6 to 42 months.

Statistical analysis

Data were reported as mean \pm SD. The patients were dichotomized into groups based on the presence of pain during follow-up, and univariate analysis was performed using the Pearson chi-square test for categorical variables and the student independent *t*-test for continuous variables. Backward stepwise logistic regression analysis was performed using parameters found to be significant on univariate analysis. The results were presented as odds ratio (OR) and 95% confidence interval (CI). The data were analyzed using a statistical software package (SPSS 11.5 version for Windows) A *P*-value of less than or equal to 0.05 was considered statistically significant.

Results

Seventy-seven patients were enrolled in the study. Preoperative details of patients are shown in Table I. The study includes 54 males (70%) and 23 females (30%) with a mean age of 34.09 ± 11.88 years (range 13–59). Tropical pancreatitis was the common etiology in 41 patients (53%), and chronic alcohol

Table I. Univariate analysis of demographic characteristics.

	Poor pain control (n = 15)	Good pain control (n = 62)	p-Value
Age, years (mean \pm SD)	32.27 \pm 7.13	34.53 \pm 12.77	NS
Sex			
Male, number (%)	12(80%)	42(68%)	NS
Female, number (%)	3(20%)	20(32%)	
Disease duration, years	2.77 \pm 1.59	4.05 \pm 2.67	NS
Etiology			
Alcoholic number (%)	6(40%)	30(48%)	NS
Tropical number (%)	9(60%)	32(52%)	
Diabetic, number (%)	5(33%)	17(27%)	NS
Steatorrhea, number (%)	9(60%)	9(14.5%)	NS

ingestion was implicated in the rest of 36 patients (47%). The mean age of tropical pancreatitis patients was 28.17 \pm 11.30 years compared with 40.83 \pm 8.72 years in alcoholic chronic pancreatitis. The mean interval between onset of symptoms and surgical intervention was 3.80 \pm 2.54 years. Twenty-two of 77 patients were diabetic and 18 patients had clinical steatorrhea. Six patients had both exocrine and endocrine insufficiency. Fourteen patients (18%) had small duct disease and 63 (82%) had large ductal system. All patients had an inflammatory head mass. The mean diameter of the head mass was 5.53 \pm 1.16 cm (range 3.6–7.8 cm). Head size in small duct disease (4.29 \pm 0.73 cm) was less compared to large duct disease (5.83 \pm 1.04 cm). The mean diameter of small and large duct was 4 \pm 0.67 mm and 8.46 \pm 2.63 mm, respectively. Histopathology of cored tissue revealed chronic pancreatitis in all patients. Additional procedures with Frey procedure included choledochoduodenostomy(2), splenectomy(1), cholecystectomy (3), and tube jejunostomy for feeding (1).

There was no 30-day mortality. In this series significant complications occurred in 14 patients (18%). It included pulmonary complications, wound infection, intraperitoneal abscess, intra-abdominal bleed, and pancreatic leak. All were managed conservatively except one patient who developed major intra-abdominal bleeding on seventh postoperative day and was managed by relaprotomy and ligation of bleeding pancreaticoduodenal artery.

The mean hospitalization stay for the entire group of patients was 11.2 \pm 3.78 days (range 9–24 days). The mean follow-up was 14 \pm 9.7 months (range,

6–42 months). Complete follow-up was obtained for all patients. Four patient's required hospitalization for recurrent pain. Two patients underwent celiac plexus blockade for pain relief. One patient died during follow-up due to hepatic failure.

For the purpose of analysis of the outcome, patients were grouped as poor pain control (15) and good pain control groups (62) based on the pain scores during follow-up. There was no significant difference between the two groups with regard to age, sex, disease duration, etiology, exocrine and endocrine insufficiency (Table I). There was no difference in morbidity, hospital stay and new onset exocrine and endocrine insufficiency between the two groups (Table II).

Among all the variables examined by univariate analysis (Table III), small pancreatic head, small duct diameter and decreased volume percentage of head mass cored were associated with poor pain control.

The final model of logistic regression analysis (Table IV) disclosed that decreased volume percentage of head mass cored ($p=0.003$) and small diameter of the pancreatic duct ($p=0.05$) were associated with poor pain outcome.

Subgroup analysis revealed that patients with small duct disease were associated with increased operative time ($p=0.001$), poor pain scores ($p=0.001$), and increased weight loss ($p=0.003$) during follow-up. Exocrine and endocrine function did not differ between the groups (Table V).

Two patients developed diabetes mellitus. Twelve Patients developed new exocrine insufficiency. Median increase in weight of 0.99 \pm 1.58 kg was found in

Table II. Analysis of outcome.

	Poor pain control (n = 15)	Good pain control (n = 62)	p-Value
Pain score, (mean \pm SD)	50.48 \pm 15.03	4.23 \pm 3.54	$p=0.001$
Morbidity, number (%)	4(27%)	10(16%)	NS
Hospital stay, days, (mean \pm SD)	11.67 \pm 5.57	11.10 \pm 3.22	NS
New onset diabetic, number (%)	1(7%)	1(2%)	NS
New onset steatorrhea, number (%)	3(20%)	9(15%)	NS

Table III. Univariate analysis of disease factors.

	Poor pain control (<i>n</i> = 15)	Good pain control (<i>n</i> = 62)	<i>p</i> -Value
Pancreatic head size, cm (mean ±SD)	4.39 ± 0.75	5.81 ± 1.08	<i>p</i> = 0.001
Pancreatic duct diameter, mm	4.47 ± 1.30	8.42 ± 2.72	<i>p</i> = 0.001
Volume percentage of head mass cored	48%	65%	<i>p</i> = 0.001
Pseudocyst, number (%)	5(6.5%)	12(15.5%)	NS
Associated procedures, number (%)	3(4%)	4(5%)	NS

32% of patients and weight loss of 2.70 ± 1.78 kg in 39%, and no change in weight in 29%. The mean hospital stay of the 77 patients was 11.2 ± 3.78 days (range 9–26).

Discussion

Surgical efforts to relieve pain associated with chronic pancreatitis should be tailored according to diameter of ductal system and presence or absence of inflammatory head mass. Traditionally, drainage procedures were reserved for dilated duct disease. Controversy exists in the presence of head mass, as the pancreatic duct dips deep in to the parenchyma and drainage procedures are ineffective [11]. Although resective procedures like pancreaticoduodenectomy were accepted as a safe procedure for head mass, Farkas and colleagues reported longer operating time, increased postoperative morbidity, longer hospital stay and lower quality of life scores following pancreaticoduodenectomy compared to organ preserving resections for head dominant disease [18]. Hence in recent years, there has been a shift from resectional procedures toward more organ preserving resections proposed by Beger [10] and Frey, which combine features of resection and drainage.

Unpredictable natural history and heterogeneity of patient population across the world have made comparison of different studies difficult. The study population in this series is different compared to that of western series in terms of etiology, age of presentation and morphology of pancreas and outcome of intervention.

Frey procedure is accepted as a “patient friendly” procedure with zero mortality and a low morbidity rates [19]. Our mortality and morbidity rates associated with the procedure is well within the acceptable range. Major postoperative complications in the current series include pancreatic leakage and delayed arterial bleeding. Arterial bleeding is a major life

threatening complication following head coring in the range of 2–3% [12,20,21]. Bleeding follows erosion of peripancreatic vessels by pancreatic fluid from an insufficient anastomosis or due to rupture of pseudoaneurysm [22]. One patient required relaparotomy and ligation of pancreaticoduodenal artery. Since the patient presented with severe intra-abdominal bleeding, angiography and embolization [22] was not considered in this patient.

The aim of surgical treatment of chronic pancreatitis is control of pain and preservation of exocrine and endocrine function. Following Frey procedure, 70–80% of the patients with varying follow-up had good pain control [11,12,23,24]. In the current series, 81% of the patients had complete pain relief and confirmed the observation made by others. The cause of poor pain outcome following surgery for chronic pancreatitis are multifactorial and include inadequate drainage of head, neuropathic changes and unrecognized cancer [25]. An incidence of 10–20% of persistent recurrent symptoms has been reported following Frey procedure [21].

Several risk factors for poor pain outcome have been described in the literature. Chronic narcotic use, pancreaticoduodenectomy in small ductal system, multiple abdominal surgeries before pancreatic intervention were associated with poor outcome [23]. In a recent report, preoperative exocrine insufficiency and postoperative surgical complications were found to be strongest predictors of poor pain outcome [26].

Frey and Amikura [23] advocate local resection of head for chronic pancreatitis with head mass irrespective of ductal diameter. The correlation between duct diameter and pain relief following surgery seem to be controversial. Some authors have suggested that duct diameter is crucial similar to our data [27], but there is disagreement on this point [23].

Ramesh and colleagues [28] reported 94% pain relief in small duct disease over a median follow-up of 39 months. Complete pain relief was obtained in 92%

Table IV. Logistic regression analysis of factors associated with poor pain outcome.

Variable	OR	95% confidence interval	<i>p</i> -Value
Pancreatic head size	0.25	0.04–1.68	<i>p</i> = 0.15
Volume percentage of head mass cored	0.82	0.72–0.92	<i>p</i> = 0.003
Pancreatic duct Diameter	0.54	0.29–1	<i>p</i> = 0.05

Table V. Analysis of small and large duct disease.

	Small duct (n = 14)	Large duct (n = 63)	p-Value
Operative time (min)	314 ± 77.27	246 ± 57	p = 0.001
Morbidity, number (%)	4 (29%)	10 (16%)	NS
Hospital stay, days, (mean ± SD)	11.57 ± 5.85	11.13 ± 3.17	NS
Pain score, (mean ± SD)	48.91 ± 19.8	5.31 ± 6.84	p = 0.001
New diabetic, number (%)	1 (7%)	1 (2%)	NS
New steatorrhoea, number (%)	2 (14%)	10 (16%)	NS
Weight gain in kg (mean ± SD)	0.57 ± 1.22	1.07 ± 1.64	NS
Weight loss in kg (mean ± SD)	2.28 ± 2.01	0.91 ± 1.59	p = 0.03

following longitudinal V shaped excision in small duct disease [29]. Our analysis shows pancreatic duct diameter to be an vital factor responsible for poor pain control. Among the 14 patients with small duct, 85% had poor pain outcome with mean pain scores of 56.79 ± 12.02 . Pain in small duct disease is due to multiple factors like inflamed nerves, pancreatic fibrosis and ischemia apart from increased ductal and parenchymal pressure. So a mere operative decompression rarely produces adequate pain relief.

Many techniques have been attempted to provide pain relief in small duct disease. Extended drainage by V-shaped excision of anterior aspect of pancreas by Izbicki et al. [29] provided complete pain relief. In order to maintain a patent small duct anastomosis, Cooperman advocated the technique of doubling the diameter of small ducts by reattaching the longitudinally incised duct to the surrounding parenchyma [30]. In the literature, reported outcome after surgery for small duct pancreatitis varies considerably between different centers, because an internationally accepted definition of small duct disease is not available. Hence a valid comparison of different study reports and operative techniques is not possible. The higher prevalence of poor pain outcome in small duct disease may be due to other potential factors like neuroimmune interactions operating in the pathogenesis of pain [31].

The mean volume percent of the head mass resected in the present series was 62%. Although Frey et al. [23] analyzed the relation between weight of the cored tissue and pain relief, the amount of the tissue cored depends on the size of the head, which is highly variable. Hence in the current series, volume percentage of the head mass cored was calculated and good pain relief was obtained when around 65% of total volume of head mass was cored. We also believe that extensive coring may lead to increased parenchymal loss leading to exocrine insufficiency. This fact is well observed in patients undergoing pancreaticoduodenectomies [32] and adverse effects on exocrine, endocrine function, nutrition, and quality of life are dependent on the amount of pancreas resected [33]. Hence an organ preserving adequate coring of the head to drain the ductal system will suffice.

We found no statistically significant correlation between head size and pain outcome. On the other hand, Keus et al. [24] reported that increased pancreatic head size was associated with good pain outcome following duodenum preserving resection.

A number of technical considerations should be discussed. The current data suggest that Frey procedure in small duct disease is associated with increased intraoperative time. We believe that difficulty in localization of small eccentric ducts contributes to the delay. Precise localization of pancreatic duct and ductal calculi with IOUS saves considerable operating time and avoids extensive dissection [34]. Although traditionally suture plication and cautery is used for coring the pancreatic head, it is associated with significant char artifact. The use of ultrasonic aspirator and dissector facilitates better visualized plane of dissection and avoids significant char artifact [35]. Head coring can be performed safely with reduced blood loss using ultrasonic coagulating shears (harmonic scalpel) [36].

The current report is subject to all limitations of a non randomized study. The chronic pancreatitis sample studied is from a large tertiary care center and therefore may reflect more severe disease than patients who are seen in a primary care setting. Also the sample size of small duct disease is small. Since it is a short-term study, quality of life analysis was not included in the current series.

Conclusions

In summary, Frey procedure can be performed with zero mortality and low morbidity in a high-volume center. It provides good pain relief in majority of the patients. Volume of the head mass cored affects pain outcome. Correlation between poor results in terms of pain relief, and weight loss following Frey's procedure, and small duct disease supports the view that duct diameter is an important predictor of pain relief.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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