The Frey Procedure for Chronic Pancreatitis Secondary to Pancreas Divisum

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**IMPORTANCE** Pancreas divisum is an uncommon congenital anomaly that may result in chronic pancreatitis (chronic pancreatitis secondary to pancreas divisum [CPPD]) and intractable pain. We evaluated the role of the Frey procedure in the management of patients with pain related to CPPD as compared with patients with chronic pancreatitis secondary to alcohol (CPA) or idiopathic causes (ICP).

**OBJECTIVE** To review our experience with the Frey procedure for the management of chronic pancreatitis related to pancreas divisum.

**DESIGN** This was a 2-year institutional retrospective of patients undergoing the Frey procedure for chronic pancreatitis-related pain from April 2008 to June 2010.

**SETTING** Academic tertiary care referral center.

**PARTICIPANTS** A consecutive sample of 14 patients undergoing the Frey procedure for chronic pancreatitis and disease-related intractable pain. We sought to examine the utility of the Frey procedure in patients with CPPD as compared with CPA and ICP.

**INTERVENTION** The Frey procedure.

**MAIN OUTCOMES AND MEASURES** Perioperative outcomes and postoperative narcotic requirement were compared among patient groups.

**RESULTS** Fourteen patients underwent the Frey procedure. The etiology of the disease was pancreas divisum in 6 patients, alcohol in 5, and idiopathic in 3. The most common indication for surgery was intractable pain, and all patients had undergone endoscopic retrograde cholangiopancreatography for attempted relief in the past. There were no statistically significant differences in median operative time (263 minutes), intraoperative blood loss (425 mL), median length of stay (9.5 days), or rate of morbidity (21%) between the 3 etiologies. Two-thirds of patients required less or no opioid at follow-up, although follow-up was significantly longer for CPPD and ICP than CPA (median, 249, 259, and 42 days, respectively; *P* < .02).

**CONCLUSIONS AND RELEVANCE** In this series, outcomes for patients with CPPD treated with the Frey procedure were equivalent to those treated for CPA. Patients with pancreas divisum and a dilated pancreatic duct may be ideally suited for this surgical strategy. The potential advantage of this approach over minor duct sphincteroplasty and lateral pancreaticojejunostomy is the removal of the fibrotic tissue of the head of the pancreas, thought to be the epicenter of pain in this condition. The benefits over resection alone include a more extensive ductal drainage procedure.

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Chronic pancreatitis (CP) is a benign, progressive inflammatory disease affecting 3 to 10 per 100 000 people and characterized by chronic abdominal pain with exocrine and endocrine insufficiency.\textsuperscript{1,2} The exact etiology of the chronic pain is poorly understood but proposed mechanisms include main duct obstruction, increased parenchymal tissue pressure, and neural inflammation.\textsuperscript{3} Efforts to treat pancreatitis use a variety of medical, endoscopic, and surgical techniques directed toward symptom management and the prevention of pancreatitis-related complications.\textsuperscript{4}

Although alcohol abuse is the most common etiological factor of chronic pancreatitis, there are numerous other causes to consider. Pancreas divisum (PD) is the most common congenital anomaly that may lead to CP and is present in up to 14% of autopsy specimens. The surgical treatment of patients with PD remains controversial, in part because of the uncommon nature of symptomatic cases. Additionally, most series describe efficacy of surgical techniques and outcomes for patients with CP secondary to alcohol (CPA), with few detailing outcomes for patients with CP secondary to PD (CPPD).

Approximately 50% of all-cause patients with CP will eventually require surgical treatment\textsuperscript{5} and the decision regarding optimal surgical technique remains unclear. The objectives of surgery are to relieve pain and preserve pancreatic function. In general, the choice of procedure depends on the degree of duct dilation, glandular morphology, presence of a biliary or pancreatic duct stricture, and/or inability to exclude cancer. Surgical procedures can be categorized into 3 main groups: (1) duct-drainage procedures, (2) resectional procedures, or (3) combined drainage/resectional procedures such as the Frey procedure (local resection of the head of the pancreas combined with lateral pancreaticojejunostomy [LPJ]) or the Berger procedure (duodenum-preserving pancreatic head resection [DPPHR]).\textsuperscript{2-4,6}

The Frey procedure is favored by many surgeons as the surgical procedure of choice for the treatment of CP where alcohol is the etiology of the disease.\textsuperscript{7} To our knowledge, the efficacy of the Frey procedure in adults with CPPD has not previously been described. This study reviews a single institution’s experience using the Frey procedure for the treatment of CP over a 2-year period comparing outcomes in patients with CPA and those with CPPD.

### Methods

#### Data Collection

After institutional review board approval, a retrospective medical record review was performed on all patients who underwent the Frey procedure for CP from April 2008 to June 2010. Opioid analgesic, pancreatic enzyme, and diabetic medication use were noted preoperatively, at hospital discharge, and at follow-up. The diagnosis of CP was determined by a combination of clinical findings and imaging characteristics including computed tomography and/or magnetic resonance cholangiopancreatography and endoscopic retrograde cholangiopancreatography. Postoperative complications were graded using the Clavien complication system ranging from grade I (minor deviation from expected postoperative course) to grade V (patient death).\textsuperscript{7} Blood transfusion was a grade II complication. Serious complications were considered to be grades III to V.\textsuperscript{8} Pancreatic fistula was defined using the International Study Group on Pancreatic Fistula standardized definitions.\textsuperscript{9} Opioid use was quantified converting total daily opioid use to oxycodone equivalents per day.\textsuperscript{10}

#### Operative Technique

The Frey procedure was performed as previously described.\textsuperscript{11-13} A single surgeon was involved in all of the procedures as either the operating or assisting surgeon. In the setting of a prior LPJ, after partial resection of the pancreatic head, the jejunal limb was divided distal to the previous pancreaticojejunal anastomosis and a new LPJ anastomosis was created. Biliary bypass was performed if needed for relief of biliary stricture. Spleenectomy was performed in 1 case of splenic vein thrombosis with associated sinistral portal hypertension (Table 1).

### Results

The mean age of the cohort was 43.5 years (range, 27-60 years); there were 9 women and 5 men. All patients (n = 14) had clinical evidence of CP. The etiology of CP was PD (n = 6), alcohol (n = 5), or idiopathic (n = 3). The most common indication for surgery was intractable pain requiring narcotics (11 patients); 5 patients additionally had a documented pancreatic duct stricture causing recurrent attacks of pancreatitis and 3 had a concomitant common bile duct stricture. Two patients’ prior LPJ procedures had failed. All 14 patients had undergone endoscopic retrograde cholangiopancreatography with or without stenting in the past. Among the 11 patients who were taking opioid analgesics preoperatively, the median total preoperative opioid use was 115 mg of oxycodone equivalents per day (Table 2).

The median operative time was 263 minutes (range, 72-395 minutes) and median operative blood loss was 425 mL (range, 50-2200 mL). The patient with 2200 mL of blood loss had sinistral portal hypertension due to splenic vein thrombosis and ICP. Patients with CPA had a higher median operative blood loss than those with either CPPD or ICP (800 mL vs 400 mL vs 400 mL, respectively), although this difference was not significant. Four patients received blood transfusion perioperatively (3 with CPA, 1 with CPPD). Octreotide was used in the majority of patients postoperatively (12 of 14) and 2 patients were...
discharged taking octreotide for treatment of pancreatic fistulae. There was selective use of thoracic epidural analgesia (7 of 14) and opioid patient-controlled analgesia (9 of 14). The patient-controlled analgesia was stopped and oral opioid analgesics and clear liquids were initiated on median postoperative day 5. Three patients required postoperative intensive care unit admission (2 with CPA, the other with ICP). The mean length of stay in the intensive care unit was 2 days (range, 1-4 days). The median hospital length of stay was 9.5 days (range, 4-19 days) and was not significantly different between patients with CPPD (13 days), CPA (10 days), or ICP (8 days).

No mortality occurred in this patient cohort and the rate of major morbidity (Clavien grade III or higher) was 21%. Five patients did not have any complications, and the remaining 9 patients had 17 separate complications (Table 3). Of these, 5 had 1 complication, 2 had 2 complications each, and 2 patients had 4 complications. The majority of complications were grade I or II (14 of 17) and there were no grade IV or V complications.
The Frey Procedure for Chronic Pancreatitis

Grade I and II complications were evenly spread between patients with CPPD and those with CPA. Of the 3 grade III complications, 2 occurred in a single patient with CPPD who required a thoracentesis for a pleural effusion and reoperation for drainage of an International Study Group on Pancreatic Fistula grade C pancreatic fistula. The other grade III complication involved reoperation for bleeding from the pancreatic tail in a patient who had undergone a splenectomy for splenic vein thrombosis with sinistral portal hypertension complicating ICP. Two pancreatic fistulae developed, 1 grade B and 1 grade C (both in patients with CPPD).

Thirteen of the 14 patients attended at least 1 follow-up visit, with the average follow-up of 185 days (range, 36–442 days). Patients with CPA had significantly shorter follow-up periods than patients with either CPPD or ICP (42 days vs 249 days vs 259 days, respectively; P < .02). During follow-up, 3 patients had documented biochemical evidence of recurrent pancreatitis (1 patient with CPA, 2 with CPPD). At follow-up, 3 patients who were taking pancreatic enzymes preoperatively (2 CPPD, 1 CPA) were no longer taking them and 1 patient with CPA began taking enzymes during follow-up who had not required them preoperatively. Eleven of 14 patients were taking opioid analgesics to control their pain preoperatively and all patients were discharged taking opioid analgesics for immediate postoperative analgesia management. Seventy-eight percent (11 of 14) of patients had complete or partial relief of their pain symptoms during the follow-up period (Table 4). Five patients were no longer taking any opioids at their follow-up visit and 4 patients were taking a decreased amount compared with their preoperative use. The number of patients taking less or no opioid was equivalent across the pancreatitis subclasses (67% CPPD, 60% CPA, and 66% ICP taking less or no opioid). No cases of new-onset endocrine insufficiency were documented.

Discussion

The Frey procedure was first described in 1987 by Frey and Smith and combines LPJ with partial resection of the head of the pancreas. This procedure improves overall ductal drainage by decompressing the duct of Santorini and ducts to the uncinate process and also allowing for removal of any associated calculi. In addition, the partial head resection can be used to relieve symptoms related to benign pancreatic duct and common bile duct strictures. The Frey procedure was originally applied to patients with an enlarged, fibrotic pancreatic head and a dilated pancreatic duct. It has since been used in a variety of glandular morphologies and for complications of CP including patients who have had a prior LPJ procedure without relief of symptoms, those with chronic pancreatic pseudocysts, and those with pancreatic fistulae. The Frey procedure does not include transection of the pancreatic neck and therefore may reduce the risk of bleeding in patients with portal hypertension and may minimize operative time when compared with the DPPHR procedure. A randomized trial comparing the Frey procedure and DPPHR found that the Frey procedure was associated with a lower complication rate (9% vs 20%) and equivalent short- and long-term pain relief and quality of life. A nonrandomized trial including 92 patients by Keck et al also showed a trend toward better pain control after the Frey procedure as compared with DPPHR, with similar functional outcomes.

The published complication rate after the Frey procedure ranges from 7.5% to 42%. The most common complications include pancreatic fistula, intra-abdominal abscess, and bleeding. Complete or partial pain relief is obtained in 75% to 95% of patients and hospital admissions are significantly reduced. This single-institution series confirms the findings of prior studies that have demonstrated the safety and efficacy of the Frey procedure for the surgical treatment of CP predominantly in patients with CPA. The morbidity rate of 21% in our series was similar to other series, with the majority of the complications being minor. The majority of patients did not require an intensive care unit stay and the hospital length of stay was similar or shorter than other series. Most patients required fewer or no opioid analgesic medications at follow-up, demonstrating the clinically relevant pain relief afforded by the procedure. Importantly, this cohort demonstrates that the Frey procedure was equally efficacious and safe for patients with CPPD as it was in patients with CPA.

Pancreas divisum is the most common congenital anomaly of the pancreas, found in 4% to 14% of pancreata at autopsy but has been reported in up to 25% of patients with otherwise “idiopathic” acute pancreatitis. The majority of patients with PD remain asymptomatic; however, up to 5% can be expected to develop symptoms. This is likely the result of chronic ductal hypertension from inadequate flow through a functionally narrowed minor duct and/or papilla, which eventually results in CP. Pancreas divisum may also manifest as recurrent attacks of acute pancreatitis. All patients with PD in this cohort had evidence of minor duct dilation on their preoperative imaging studies, and all were felt to have CP. All had also undergone endoscopic retrograde cholangiopancreatography and had demonstrated transient relief of symptoms with pancreatic duct stenting. The Frey procedure was favored over

Table 4. Postoperative Pain Relief in Patients Undergoing the Frey Procedure

<table>
<thead>
<tr>
<th>Amount of Opioid Required</th>
<th>No. (%)</th>
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<tbody>
<tr>
<td>Postoperatively</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>3 (50)</td>
</tr>
<tr>
<td>&lt;Preoperatively</td>
<td>1 (17)</td>
</tr>
<tr>
<td>&gt;Preoperatively</td>
<td>1 (17)</td>
</tr>
<tr>
<td>Same as preoperatively</td>
<td>1 (17)</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>0</td>
</tr>
</tbody>
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Abbreviations: CPA, chronic pancreatitis secondary to alcohol; CPPD, chronic pancreatitis secondary to pancreas divisum; ICP, idiopathic chronic pancreatitis.
minor duct sphincteroplasty to remove the fibrotic focus of pancreatitis, thought to be the epicenter of pain in many patients, as well as adequately drain the pancreatic duct.

Surgical and endoscopic intervention is efficacious for patients with PD and symptoms of acute pancreatitis.26 Similar benefit has been more difficult to show for patients with CPPD. Schlosser et al27 have reported successful reduction or elimination of symptoms in 81% of 36 patients with PD treated with DPPHR in the setting of CP or recurrent acute pancreatitis. Their results demonstrated the safety and feasibility of this approach for patients with CPPD. Similarly, the benefit of a differentiated surgical approach allocating patients to either DPPHR or surgical reimplantation of the minor papilla and minor duct sphincteroplasty has been shown in 28 patients with symptomatic PD.28 This study divided patients with PD and pancreatitis into 2 distinct groups based on their degree of pancreatic fibrosis. Those patients with no evidence of chronic changes underwent surgical sphincteroplasty, whereas those with fibrotic features were offered either resectional procedures or DPPHR. Sphincteroplasty is an appropriate treatment for patients without chronic changes of pancreatitis, with success reported in 85% of patients with recurrent acute pancreatitis in a series of 100 patients with PD.29 The results of the tailored approach as described by Schneider et al28 also demonstrated a significant and durable reduction in pain in patients with symptomatic PD.

The addition of an LPJ to a resectional procedure in this context has not been considered previously but is well established as a treatment option for patients with CP and a dilated pancreatic duct secondary to etiologies other than PD and adequately addresses the critical issue of duct drainage, which is central to the disease process in PD. The combination approach afforded by the Frey procedure addresses the 2 major pathologies present in patients with PD; namely, it removes the fibrotic focus of CP present in the head while simultaneously decompressing the obstructed pancreatic duct.

Combining localized pancreatic head resection with duct drainage therefore would appear to be an attractive option for patients with CPPD and a dilated minor duct. The cohort reported herein supports that the Frey procedure for patients with CPPD can be expected to provide results at least equivalent to those seen for patients with CPA and provides evidence in support of this approach for patients with PD.

This study is limited by its retrospective nature and size. No standardized measures of pain, endocrine insufficiency, or exocrine insufficiency were used. Instead, opioid use, pancreatic enzyme supplement use, and diabetic agent use were used as surrogate markers for these conditions. In addition, the average follow-up was short and therefore we are unable to comment on long-term outcomes and the durability of the symptom relief. Similar studies have demonstrated durable pain relief after the Frey procedure for CPA with longer-term follow-up.17,20,21

In conclusion, we believe the Frey procedure is a safe and efficacious procedure for relief of the complications of recurrent acute pancreatitis and CP. It is not technically demanding and can be adopted by those trained to perform pancreatic surgery. It can be performed with little or no mortality, low morbidity, and low reoperation rates, supporting the safety of this approach. The extension of the indication for this operation to include patients with CPPD provides an important option to the challenges associated with CP.

REFERENCES
The Frey Procedure Is a Treatment for Chronic Pancreatitis, Not Pancreas Divisum

Bharath D. Nath, MD, PhD; Steven D. Freedman, MD, PhD; A. James Moser, MD

In this issue, Pappas et al1 report outcomes of duodenum-preserving pancreatic head resection and longitudinal pancreaticojejunostomy (Frey procedure) for painful chronic pancreatitis associated with pancreas divisum. In the context of a small case series, the outcomes of the Frey procedure appear similar to the comparison group of patients with Beger and Frey procedures.2

These data should not be extrapolated to patients with pancreas divisum who also have abdominal pain without severe chronic pancreatitis.3 Recent data reported by Bertin et al in 2012 indicate that “Pancreas Divisum Is Not a Cause of Pancreatitis by Itself but Acts as a Partner of Genetic Mutations.”4 These data indicate that patients with pancreas divisum are more likely to harbor genetic causes of chronic pancreatitis involving defects in CFTR, SPINK1, and PRSS1.4 The causes of the association between pancreas divisum and chronic pancreatitis remain unknown, but speculation exists that separated pancreatic ducts may actually improve the drainage of inspissated pancreatic secretions.5

Although the Frey procedure for the “separated” pancreas exhibiting features of severe chronic pancreatitis may produce results equivalent to previously published indications, these results are limited to the context of symptomatic chronic pancreatitis. The current data do not demonstrate that the Frey procedure is indicated for patients with recurring or chronic abdominal pain who also have pancreas divisum.

Current guidelines recommend that patients with pancreatic-type abdominal pain and pancreas divisum undergo gene mutation testing and smoking cessation before any consideration of endoscopic or surgical intervention. The majority of patients with pancreas divisum do not exhibit symptomatic chronic pancreatitis with resulting fibrosis and should not be considered candidates for the Frey procedure.

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Invited Commentary