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Risk factors for pain after Frey's procedure in chronic pancreatitis

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Abstract

Pancreatic pain is the most frequent symptom of chronic pancreatitis (CP) and is difficult to treat. This retrospective study aimed to determine the risk factors for pain in CP.

From January 2009 and March 2014, 75 consecutive patients with CP who underwent Frey's procedure were reviewed for this study. According to Izbicki pain scores, these patients were divided into 2 groups: (1) pain (Izbicki pain score of >10 after a decrease of >50%) and (2) pain-free (Izbicki pain score of ≤10). Demographic data, medical history, postoperative variables, and follow-up evaluations of the patients were documented.

The postoperative pain score (11.8) was significantly lower than the preoperative score (51.8) after a median follow-up of 4.2 years. Alcoholism (odds ratio [OR] 7.767, $P = .002$) and preoperative analgesic medication use (OR 4.113, $P = .030$) were independent risk factors for pain.

Frey's procedure is an effective operation for pain relief in patients with CP. Alcoholism and preoperative analgesic medication use were 2 factors for failure to achieve complete pain relief.

Abbreviation: CP = chronic pancreatitis.

Keywords: alcoholism, analgesics, Frey's pancreaticojejunostomy, pain relief

1. Introduction

Chronic pancreatitis (CP) is a disease characterized by progressive inflammation, fibrosis, and tissue damage. It is well known that pancreatic pain is the most frequent symptom of CP and treatment of pain remains a serious challenge. Most patients require analgesics as the first step in pain management.[1] Initially, medical therapy works for many patients in managing pain, but eventually ineffective. Endoscopic therapy is considered when the main pancreatic duct is obstructed (strictures or stones). Despite the good outcome of medical and endoscopic therapy, studies have reported that about half of the patients with CP may undergo operative procedures in the course of the disease because of the ineffectiveness of medical or endoscopic therapy.[2] Hence, surgical therapy is recommended. Surgical intervention in CP has evolved from the classical Whipple resection to organ-preserving procedures (Beger's or Frey's procedure). All of these operative procedures, to some extent, mainly address pain relief and improve the quality of life. However, standard pancreaticoduodenectomy sacrifices the surrounding nondiseased organs with a loss of natural bowel continuity, which may contribute to high postoperative complication and pancreatic exocrine and/or endocrine insufficiency.[3] Recently, surgeons have favored organ-preserving operations (Beger's and Frey's procedure), which ensure sufficient pain relief and are effective in providing long-term improvement in the quality of life. In comparison with Beger's procedure, Frey's pancreaticojejunostomy is easier to perform and has low surgical risk.[4–6]

Although most patients have good postoperative pain control after Frey's pancreaticojejunostomy, some patients still suffer from abdominal pain. This study aimed to determine the risk factors for patients who failed to achieve complete pain relief in CP.

2. Materials and methods

This was a retrospective study conducted in the Department of Hepato-Biliary-Pancreatic Surgery, West China Hospital, Si chuan University, China, from January 2009 to March 2014.

Patients were evaluated by transabdominal ultrasound and computed tomography before surgery. Magnetic resonance imaging and magnetic resonance cholangiopancreatography techniques were used to detect early signs of disease and visualize the pancreatic main duct and pancreatic duct side branches. Endoscopic ultrasonography was considered if it was difficult to differentiate between CP and pancreatic cancer.

CP was diagnosed according to Marseilles criteria.[7] CP diagnosis was based on clinical history, physical examination, and imaging findings. Alcoholism was defined when alcohol intake exceeded 80 g/d for males and 60 g/d for females for at least 2 years in the absence of other causes.[8] According to the American Diabetes Association, diabetes is diagnosed if the fasting blood glucose concentration is >7 mmol/L.[9]

The Izbicki Pain Score System[10] was used to assess pain intensity. All of the selected patients questioned on 4 aspects:

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frequency of pain attacks, a visual analog scale of pain, analgesic medication used, and inability to work. According to pain relief at the end of follow-up, patients were classified into 2 groups: (1) pain (Izbicki pain score of >10 after a decrease of >50%) and (2) pain-free (Izbicki pain score of ≤10).[11] Data were collected by interviewer-administered questionnaires, telephone, letter, and e-mail inquiries before and after surgery.

Frey and Smith[12] described a hybrid procedure that combines partial resection of the head of the pancreas (resection) with lateral pancreaticojejunostomy (drainage). The main points of this procedure are extensive coring of the head of the pancreas and removal of all stones located in the main pancreatic duct and the side branch ducts.

The indications for surgical treatment were intractable pain, jaundice, pancreatic pseudocysts, and inflammatory mass of the pancreatic head. Exclusion criteria were as follows: small-duct disease, pseudocysts without duct pathology, histologically proven neoplasm in the pancreas, and coexisting malignancy of other organs.

3. Statistical analysis

SPSS software (version 17.0 SPSS) was used to analyze the outcome data. For categorical variables, χ^2 test or Fischer's exact test was used. Pain scores as well as laboratory tests were evaluated using Mann–Whitney *U* test. The logistic regression model was used to identify risk factors associated with only partial pain relief. A value of $P < .05$ was considered statistically significant.

4. Results

4.1. Demographics and disease-related data

Demographic characteristics are shown in Table 1. There were 64 males (85.3%) and 11 females (14.7%), with a mean age of 47 ± 11years (ranging from 12 to 71 years). The vast majority of the patients were males (85.3%), and the primary etiology of CP was chronic alcohol abuse in 45 patients (60%). In addition, 68% (51/75) of the patients smoked a median of 20 cigarettes per day. There were no cases of hereditary pancreatitis or autoimmune pancreatitis in our study. Furthermore, 16% (12/75) of the patients had previous endoscopic therapy with or without stent placement. The mean time between the first hospital visit and the surgical resection for CP was 42.7 months.

The pain group differed from the pain-free group in terms of pancreatic stone (24 vs 13, $P = .028$), alcoholism (28 vs 17, $P = .030$), diabetes (7 vs 17, $P = .025$), and preoperative analgesic medication use (30 vs 19, $P = .028$). No significant differences between these 2 groups were detected in terms of age at diagnosis of CP, male gender, body mass index (BMI), laboratory tests, smokers, time from diagnosis, steatorrhea, recurrent episodes of pancreatitis, pseudocysts, head mass, and endoscopic therapy with or without stent placement.

4.2. Pain assessment

After a median follow-up of 4.2 years, the mean Izbicki pain score (11.8) was significantly lower than the preoperative score (51.8). At the end of follow-up, 36 patients achieved complete pain relief. Before surgery, 70 (93.3%) of the patients with pain required analgesics, and 5 patients were opioid users. However, at follow up, only 16 patients required analgesics and no one was an opioid user.

4.3. Risk factors for poor pain relief

As shown in Table 1, 4 variables with $P \leq .05$ were selected as candidates for multivariate analysis by the logistic regression model. The results are presented in Table 2. Alcoholism (odds ratio [OR] = 7.767, $P = .002$) and preoperative analgesic medication use (OR = 4.113, $P = .030$) were independent risk factors for poor pain relief.

Preoperatively, 45 of 75 patients were diagnosed with alcoholic CP. Of the 45 cases, there were only 8 cases of

Table 1

Risk factors for pain relief Frey's procedure in univariate analysis.

	Overall	Pain group (n = 39)	Pain-free group (n = 36)	*P*
CP diagnosis, average age (SD), y	47 (11)	45 (11)	49 (10)	.161
Time from diagnosis (SD) (months)	42.7 (52.4)	51.4 (50.4)	33.2 (53.6)	.065
Male gender (%)	64 (85.3%)	33 (84.6%)	31 (86.1%)	.855
BMI, kg/m^2 (%)				.428
≥25	22 (29.3%)	13 (33.3%)	9 (25.0%)	
<25	53 (70.7%)	26 (66.7%)	27 (75%)	
Smoking history, n (%)	51 (68%)	25 (64.1%)	26 (72.2%)	.451
Alcohol consumption (%)				.030
No	30 (40.0%)	11 (28.2%)	19 (52.8%)	
≥80 g/d	45 (60.0%)	28 (71.8%)	17 (47.2%)	
Diabetes (%)	24 (32.0%)	17 (43.6%)	7 (25%)	.025
Steatorrhea (%)	6 (8.0%)	4 (10.3%)	2 (5.6%)	.746
Serum amylase (SD)	94.2 (85.1)	95.6 (97.1)	92.6 (71.3)	.714
Serum lipase (SD)	78.1 (69.3)	70.3 (55.1)	86.6 (82.0)	.787
Albumin (SD), g/L	41.5 (4.2)	41.6 (4.2)	41.3 (4.3)	.865
CA 19-9 (SD)	26.6 (42.1)	34.4 (53.3)	18.1 (22.7)	.270
Recurrent episodes of pancreatitis (%)	21 (28.0%)	15 (38.5%)	6 (16.7%)	.360
Pseudocysts (%)	27 (36.0%)	15 (38.5%)	12 (33.3%)	.644
Pancreatic stone (%)	37 (49.3%)	24 (61.5%)	13 (36.1%)	.028
Head mass (%)	11 (14.7%)	7 (17.9%)	4 (11.1%)	.403
Endoscopic therapy with or without stent placement (%)	12 (16.0%)	5 (13.5%)	7 (19.4%)	.494
Preoperative analgesic medication use (%)	49 (65.3%)	30 (76.9%)	19 (52.8%)	.028

BMI = body mass index, CA 19-9 = a tumor marker, CP = chronic pancreatitis, SD = standard deviation.

Table 2

Logistic regression analysis of factors for patients with unsatisfactory pain relief after Frey's procedure.

	Odds ratio	95% CI	P
Pancreatic stone	2.793	0.826–9.443	.098
Alcoholic	7.767	2.118–28.478	.002
Diabetes	2.519	0.740–8.582	.140
Preoperative analgesic medication use	4.113	1.149–14.719	.030

CI = confidence interval.

Table 3

Results of pain score for patients who did or did not continue alcohol consumption.

	Alcohol (n = 8)	Nonalcohol (n = 67)	P
Frequency of pain attacks, median (range)	62.5 (25–100)	25 (0–75)	.002
Visual analog scale, median (range)	22.5 (10–60)	10 (0–40)	.001
Analgetic medication, median (range)	0 (0–15)	0 (0–25)	.561
Inability to work, median (range)	25 (0–25)	0 (0–20)	.021
Pain score, median (range)	25.6 (11.3–43.8)	8.75 (0–32.8)	.001

continued alcohol consumption during follow-up. Of the 37 patients who stopped alcohol drinking, only 21 patients achieved complete pain relief. Results of the Izbicki pain scores of patients who did or did not continue alcohol consumption are presented in Table 3. The pain score was significantly lower among nondrinkers (8.75; ranging from 0 to 32.8 vs 25.6; ranging from 11.3 to 43.8) ($P < .001$).

Notably, operative effectiveness was closely related to the requirement of analgesics (Fig. 1). Patients who required analgesics before surgery scored higher than those who did not (mean score: 14.4 vs 6.9, $P = .005$).

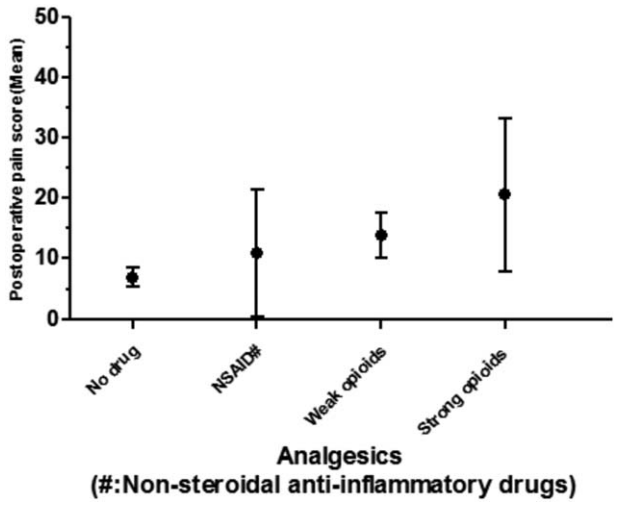

Figure 1. Patients who required analgesics before surgery scored higher than those who did not (mean score, 14.4 vs 6.9, $P = .005$).

Table 4

Results for 75 patients undergoing Frey's procedure.

	Pain group (n = 39)	Pain-free group (n = 36)
Enzyme use	6 (15.4%)	7 (19.4%)
Diabetes mellitus	24 (61.5%)	11 (30.6%)
New diabetes mellitus	7 (17.9%)	4 (11.1%)
Continued alcohol	8 (20.5%)	0 (0)
Continued smoking	9 (23.1%)	5 (13.9%)
Second surgery	2 (5.1%)	0 (0)

4.4. Postoperative data

The outcome of postoperative data is summarized in Table 4. Before surgery, 13 cases required diet control, 6 required oral drugs, and 5 required insulin therapy. After surgery, diabetes occurred in 24 (32.0%) of the patients, and 11 (14.7%) of the patients were newly diagnosed with diabetes mellitus. Moreover, steatorrhea increased from 6 patients before surgery to 15 patients after surgery. Thirteen patients required oral pancreatic enzyme supplementation and 2 patients needed a second surgery because of wound infection and intra-abdominal bleeding.

5. Discussion

Pancreatic pain is the most frequent symptom of CP, and persistent recurrent abdominal pain could lead to anxiety, depression, and even a low quality of life.[13,14] Pain in CP is complex and may have different forms in different etiologies of CP.[13] It may develop and vary over time. However, not all patients with CP suffer from severe abdominal pain. Pain seems to be constant and intense in some cases but not in others. Constant pain leads to higher rates of disability and hospitalization. In addition, the mechanism involved in pain remains complex and controversial.[15] In the past, several hypotheses were suggested to explain pancreatic pain such as the obstruction of structures (duodenum, bile duct, or pancreatic duct) that increased parenchymal pressure causing ischemia and the development of pseudocysts. However, these views were eventually found to be inaccurate. A more recent explanation for CP pain is nerves (changes in the neuroanatomy of pancreas, sensitization of visceral nerves, or central nervous system) that are abnormally large or injured.[16–19]

Although pain can be treated by conservative measures, the results are poor for a long-term follow-up period.[20] Surgical management is considered for nearly half of patients in the advanced stage of the disease.[2] Among the surgical procedures, Frey's procedure appears to be an effective technique for pain relief. For the 75 patients with CP, the postoperative pain score (11.8) was significantly lower than the preoperative score (51.8) after a median follow-up of 4.2 years. However, in the present study, we identified that 39 patients did not achieve complete pain relief and still suffered from chronic pain. In addition, we found 2 independent factors for failure of pain relief: preoperative analgesic medication use and alcoholism.

Patients who require analgesics had a higher risk for failure of pain. Most patients choose medical therapy as the first step in treating pain and nearly 50% patients with CP would be treated with opioids in the course of CP.[11] Interestingly, we also determined that patients who required analgesics before surgery scored higher than those who did not (mean score: 14.4 vs 6.9,

$P=.005$), indicating that patients who did not use analgesics before surgery may have an advantage. This founding was in agreement with Negi et al[21]; they found that patients who are more likely to use opiate medication before an operation may experience inferior pain control after surgery. Similarly, Alexandra et al[22] reported that only 57% of patients who used analgesics were judged pain-free after 5 years. Furthermore, an important goal of preoperative analgesic medication use is to reduce but not eliminate pain. And the long-term and high-dose analgesics prescribed to some patients may lead to negative effects such as narcotic addiction. Therefore, early surgical intervention should be performed before drug addiction becomes an issue.

Alcoholism was determined as one of the potential risk factors for pain. Alcohol consumption has long been recognized as a modifiable risk factor for pancreatitis. With reference to heavy alcohol drinking, the RRs from a meta-analysis were 1.37 (95% CI, 1.19–1.58).[23] Nearly 50% of pancreatitis cases are believed to be attributed to chronic heavy alcohol consumption.[24] Although epidemiological data associated with alcoholic CP are limited and its pathogenesis is poorly understood, clinical evidence indicates that cessation of alcohol can slow disease progression and have some beneficial effect on pain.[25] In our study,45 of 75 patients were diagnosed with alcoholic CP. Of the 45 cases, there were only 8 cases of continued alcohol abuse. The pain score was significantly higher among drinkers (25.6, ranging from 11.3 to 43.8) ($P<.001$). However, of the 37 patients who stopped alcohol drinking, only 21 patients achieved complete pain relief. The exact reason why abstinence helps in some cases but not in others remains unclear. Strate et al[26] demonstrated that alcohol abstinence has a close relationship with survival rather than pain relief. Unfortunately, we were unable to elucidate the relationship between alcoholism and pain symptoms. A possible explanation is that pancreatic fibrosis is an active, dynamic process. Patients with chronic inflammatory diseases tend to develop pancreatic fibrosis and even an inflammatory mass in the head of the pancreas, which may block the pancreatic duct, common bile duct, and duodenum, leading to obstruction, persistent jaundice, and severe pain. Although removal of part of the head of the pancreas can drastically reduce pain dramatically in most patients, some patients still did not experience better pain relief.

This study has several limitations. As this was a retrospective review, we used subjective measurements of pain, such as the visual analog scale. We also did not assess surgery complications because previous retrospective studies have reported lower surgical morbidity and mortality rates in Frey's procedure compared with Beger's procedure and pancreaticoduodenectomy.[27,28] Those studies concluded that Frey's procedure is an effective intervention for pain reduction and preventing the detrimental effects on quality of life. Furthermore, the sample size was small, and the time of our follow-up period was short. Hence, further studies concerning risk factors for pain are urgently needed.

In conclusion, Frey's procedure is an effective operation for pain relief of patients with CP. Patients had poor pain relief when preoperative analgesic medication use and alcoholism were involved. Alcohol abstinence may be significantly beneficial for pain relief. The findings of our study may contribute toward a better understanding the natural course of CP.

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