

Current Surgical Treatment for Chronic Pancreatitis

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Abstract

Chronic pancreatitis (CP) is a painful, yet benign inflammatory process of the pancreas. Surgical management should be individualized because the pain is multifactorial and its mechanisms vary from patient to patient. Two main pathogenetic theories for the mechanisms of pain in CP have been proposed: the neurogenic theory and the theory of increased intraductal/intraparenchymal pressures. The latter theory is strongly supported by the good results of drainage procedures in the surgical management of CP. Other possible contributing factors include pancreatic ischemia; a centrally sensitized pain state; and the development of complications, such as pseudocysts and stenosis of the duodenum or common bile duct. Common indications for surgery include intractable pain, suspicion of neoplasm, and complications that cannot be resolved with radiological or endoscopic treatments. Operative procedures have been historically classified into 4 categories: decompression procedures for diseased and obstructed pancreatic ducts; resection procedures for the proximal, distal, or total pancreas; denervation procedures of the pancreas; and hybrid procedures. Pancreaticoduodenectomy and pylorus-preserving pancreaticoduodenectomy, once the standard operations for patients with CP, have been replaced by hybrid procedures, such as duodenum-preserving pancreatic head resection, the Frey procedure, and their variants. These procedures are safe and effective in providing long-term pain relief and in treating CP-related complications. Hybrid procedures should be the operations of choice for patients with CP. (J Nippon Med Sch 2011; 78: 352–359)

Key words: chronic pancreatitis, mechanism of pain, surgical treatment, surgical indication, hybrid procedures

Introduction

Chronic pancreatitis (CP) is a progressive inflammatory disorder in which pancreatic secretory parenchyma is destroyed and replaced by fibrous tissue¹. The disease is characterized by recurrent episodes of intractable pain and other symptoms,

such as diarrhea, steatorrhea, and diabetes mellitus, due to pancreatic exocrine and endocrine insufficiency¹. In particular, attacks of severe pain lead to repeated hospitalization and lower quality of life². The medical treatment for CP-associated pain often fails because of narcotic dependency³. Therefore, intractable pain is the most common indication for surgical treatment in patients with

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CP^{1,2}.

Surgical approaches to the management of CP have made great progress over the past several decades because of a better understanding of the pathophysiology of CP, the development of diagnostic methods, and improved outcomes of major pancreatic surgery³. The objectives of surgery are to relieve pain and to preserve pancreatic function¹. Recently, surgical procedures have provided long-term pain relief and good postoperative quality of life along with lower rates of mortality and morbidity than with nonsurgical treatments³. Additionally, novel hybrid procedures, such as the Beger and Frey procedures have been introduced¹. These procedures provide good pain relief and improve quality of life in patients with CP^{1,2}. Therefore, this article provides an updated perspective on surgery for CP.

Mechanism of Pain in Patients with CP

The cause of pain in CP is complicated and unclear. The neurophysiologic pain pathways involve the transmission of visceral afferent nociceptive information through the splanchnic nerves, sympathetic nervous system, spinal cord, and, ultimately, to the brain.

Demir et al.⁴ have summarized the recent findings about 3 possible mechanisms of pain in CP: peripheral nociception, peripheral pancreatic neuropathy and neuroplasticity, and central neuropathy and neuroplasticity. They concluded that pain in CP should be considered as neither solely peripheral nociceptive nor only peripheral pancreatic neuropathic, but rather as a mixed type of pain.

The following theories have been proposed to explain pain in CP.

Neurogenic Theory

The neurogenic theory focuses on the peripheral pancreatic and central neuropathy and neuroplasticity described by Demir et al.⁴. Several recent studies have revealed neural alterations: eosinophilic infiltration of intrapancreatic nerves in patients with painful CP^{5,6}. Ultrastructural analysis of intrapancreatic nerves in CP have shown severe

neural damage, such as disrupted perineurium, edematous neural contents, and penetration of inflammatory cells into the interior of nerves^{5,6}. The damage to intrapancreatic nerves leads to numerous peripheral neuroplastic changes, such as hypertrophy and sprouting of intrapancreatic nerves^{5,6}. Recent studies have demonstrated a key correlation between the extent of neural damage and the intensity and frequency of pain in patients with CP^{5,6}. Repeated visceral afferent stimulation may result in a “centrally sensitized” pain state. This is a result of repeated stimulation of pain receptors as a consequence of tissue injury and visceral inflammation^{5,6}. These peripheral nerve endings have increased sensitivity, a lower threshold to stimulation, and prolonged and enhanced responses to stimulation^{5,6}.

Interstitial and Intraductal Hypertension

According to Demir et al.⁴, ductal hypertension due to constriction or calculi and increased intraparenchymal pressure as a result of fibrosis could activate the intrapancreatic nociceptors. Thus, increased pancreatic interstitial and ductal pressures cause a compartment syndrome that may cause pain in CP. Pancreatic ductal hypertension is thought to be caused by continuing exocrine secretion against a proximal obstruction due to single or multiple strictures or calculi or both^{5,6}. Surgical treatment frequently relieves pain and decreases the pressure of a dilated pancreatic duct, although some studies have reported no significant relationship between pressure and pain or between pressure reduction and pain relief⁷.

Inflammatory Mass

Pain in CP is frequently present in patients with an inflammatory mass in the pancreatic head and can be effectively relieved by resection of the pancreatic head. The inflammatory mass may involve pancreatic and peripancreatic nerves and cause stenosis of the common bile duct or duodenum, all of which lead to pain⁶. The “pacemaker” of the pain of CP is generally believed to lie in the head of the pancreas⁶.

Pseudocyst

Acute exacerbations of CP may lead to pancreatic pseudocyst formation, which can cause intense pain by compressing adjacent organs⁶. Although a majority of pseudocysts disappear spontaneously, persistence or enlargement of pseudocysts may lead to persistent pain in patients with CP⁶.

Indications for and Timing of Surgical Treatment

Surgical Indications

Surgical treatment can be considered when conservative therapy or endoscopic intervention has failed. The common indications for surgery are intractable pain, suspicion of neoplasm, and unresolved stenosis of the duodenum or common bile duct^{2,3,8,9}. Other indications are complications that cannot be resolved with radiological or endoscopic treatment^{2,3,8,9}. Currently, the acceptable indications for surgery are as follows.

1. Intractable pain
2. Suspicion of malignant neoplasm
3. Uncontrollable complications
 - a. Unresolved common bile duct stenosis
 - b. Pseudoaneurysms or vascular erosions not controlled with radiological intervention
 - c. Large pseudocysts not controlled with endoscopic treatment

Timing of Surgical Interventions

The aims of surgical treatment in patients with CP are to relieve intractable pain and to preserve pancreatic exocrine and endocrine functions as much as possible. Therefore, the timing of surgery in patients with CP should take these aims into account^{8,9}.

Nealon et al.¹⁰ compared the outcomes of conservative treatment and surgery and concluded that early operative drainage should be performed before irreversible functional or morphologic damage of the pancreas has occurred. Ihse et al.¹¹ have also recommended that surgical treatment should be performed for patients with obstructive chronic pancreatitis or biliary pancreatitis before pancreatic insufficiency develops. Complications of adjacent organs should be treated surgically as soon

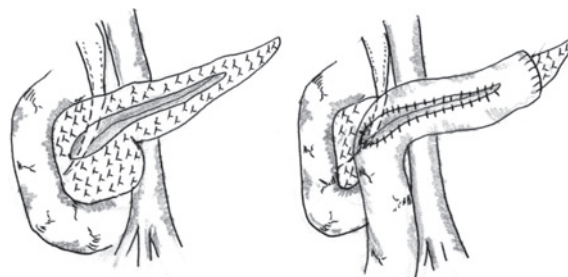


Fig. 1 Schematic illustration of the modified Puestow procedure

as they are diagnosed⁸.

Selection of Surgical Procedures

Operative procedures have historically been classified into 4 categories.

1. Decompression procedures of diseased and obstructed pancreatic ducts
2. Resection procedures of the proximal, distal, or total pancreas
3. Denervation procedures of the pancreas
4. Hybrid procedures

Surgical denervation, however, has been reported to be ineffective as a first-line treatment^{3,4}. On the other hand, hybrid procedures combining resection of the pancreatic head with decompression have been introduced and have been proven to be as safe and effective as decompression or resection alone^{3,8,9}.

Decompression Procedures

For patients with ductal dilation without a inflammatory mass in the pancreatic head, laterolateral pancreaticojejunostomy is an effective drainage operation.

In 1958, Puestow and Gillesby¹² reported longitudinal decompression of the body and tail of the pancreas into a Roux limb of the jejunum. In 1960, Partington and Rochell¹³ described side-to-side longitudinal pancreaticojejunostomy without resection of the pancreatic tail, known as the modified Puestow procedure (**Fig. 1**). This procedure achieved short-term pain relief with low rates of morbidity and mortality in 61% to 91% of patients¹⁴⁻¹⁶. However, pain recurred within 3 to 5 years in up to 30% of patients¹⁴⁻¹⁶. The principal cause of failure of

the Puestow operation is the lack of adequate decompression of the proximal ducts in the head of the pancreas¹⁷.

Resection Procedures

Proximal pancreatectomy

Pancreaticoduodenectomy (PD) has been considered an efficient means of relieving intractable pain and treating complications in patients with an inflammatory mass in the head of the pancreas. Recent studies of PD for the treatment of CP have found that short-term pain relief was achieved in 71% to 89% of patients¹⁸. The morbidity rate, however, remains at about 40%, and the mortality rate has been reduced to less than 5% at high-volume surgical centers¹⁹.

Pylorus-preserving PD (PPPD)²⁰ has been performed in an attempt to improve postoperative nutritional status. However, some studies have shown no significant nutritional differences between PPPD and PD^{21,22}. A retrospective study by Jimenez et al.¹⁹ of 72 patients undergoing PD or PPPD for CP found comparable rates of long-term pain relief, diabetes mellitus, and enzyme supplementation. In addition, an increased rates of delayed gastric emptying and marginal ulceration after PPPD have been reported²³.

The most severe disadvantages of these procedures are the resection of the duodenum and the significant loss of pancreatic endocrine and exocrine function.

Total pancreatectomy

Total pancreatectomy (TP) should not be chosen as a first-line procedure. The indications for TP may be limited to failure of previous resection or severe, intractable pain with complete pancreatic insufficiency. In general, this procedure is thought to offer no better pain relief than does PD or PPPD for patients with CP.

Recently, TP for CP has been increasingly performed with islet cell autotransplantation. The most severe morbidity after TP is brittle, insulin-dependent diabetes, and lethal episodes of hypoglycemia often occur in patients with apancreatic diabetes^{3,24}. However, islet cell autotransplantation is contraindicated for 25% to

30% of patients with CP because their islet cell function is already impaired because of severe diabetes, and, as a result, successful engraftment is difficult³. Further studies are needed before clinical application because several problems, such as islet unresponsiveness and apoptosis after isolation and engraftment, must first be solved³.

Distal pancreatectomy

Distal pancreatectomy (DP) has been used to treat patients with CP who have focal inflammatory changes, isolated duct stricture, or pseudocyst, localized to the body and tail.

The procedure is associated with a significant risk of symptomatic recurrence. Long-term pain relief is achieved in only 60% of patients, and completion pancreatectomy is required for pain relief in 13% of patients²⁵. In addition, pancreatic endocrine and exocrine insufficiency develops in half of patients who undergo DP³.

Hybrid Procedures

Duodenum-preserving pancreatic head resection (Fig. 2a)

In 1980, duodenum-preserving pancreatic head resection (DPPHR) was first described by Beger et al.²⁶, who reviewed the results of 380 DPPHR operations in 1997²⁷. The neck of the pancreas is divided above the portal and superior mesenteric veins, and pancreatic tissue is excavated along the inner aspect of the duodenum. The common bile duct can be decompressed, if necessary. The reconstruction is performed by means of 2 pancreatojejunostomies with the Roux limb of the jejunum to drain the distal pancreas and to cover the remaining pancreatic head tissue and the decompressed bile duct. Longitudinal pancreaticojejunostomy can be added if the main duct in the body and tail of the pancreas is obstructed.

According to Beger et al. 50% of patients required decompression of the common bile duct, and longitudinal pancreaticojejunostomy was performed in 10% to 15% of cases²⁸. In more than 80% of patients, pain relief was achieved, and endocrine and exocrine functions were also preserved²⁸. The incidence of new diabetes ranges from 8% to 21%,

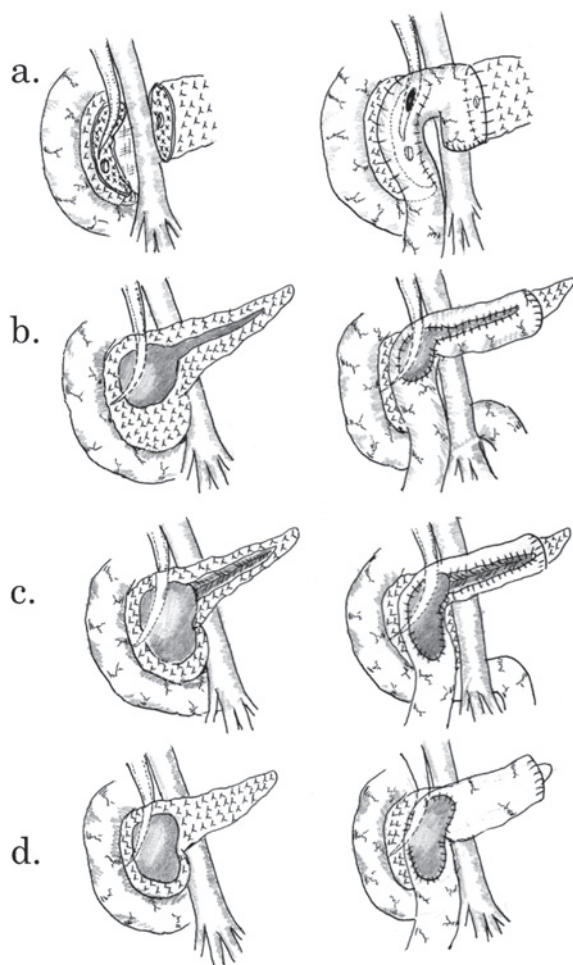


Fig. 2 Schematic illustrations of the hybrid procedures

- a: Duodenal-preserving pancreatic head resection (DPPHR)
 b: Frey procedure
 c: Hamburg modification
 d: Berne modification

and some patients show an improvement in glucose metabolism²⁹. The DPPHR procedure is now widely accepted throughout the world.

Frey procedure (Fig. 2b)

The Frey procedure was described by Frey and Smith in 1987³⁰. This operation is a modification of Beger procedure and the Partington-Rochelle procedure. The pancreatic neck above the portal and super mesenteric veins is preserved, which decreases the intraoperative bleeding. The excised head of the pancreas is linked to the longitudinally opened duct in the body and tail of the pancreas. To avoid penetrating the posterior capsule of the head, Frey and Amikura¹⁷ recommended that the posterior limit of resection should be the back wall of the

opened duct of Wirsung. The locally excised head of the pancreas is covered with the opened Roux-en-Y limb of jejunum. This procedure is contraindicated for patients with a large inflammatory mass in the pancreatic head without stenosis of the left-sided pancreatic duct.

Hamburg modification (Fig. 2c)

Izbicki et al.³¹ introduced the Hamburg modification procedure, a modification of the Frey procedure. The procedure is the combination of the wider excavation of the pancreatic head and longitudinal V-shaped excision of the ventral aspect of the pancreas.

Small duct disease is the indication for this procedure. Yekebas et al.³² have reported that mortality and morbidity rate were 0% and 19.6%, respectively, and that 89% of patients were free of pain at follow-up.

Berne modification (Fig. 2d)

Farkas et al.³³ have reported organ-preserving pancreatic head resection, a coring out of the pancreatic head without lateral pancreaticojejunostomy. This approach was also described by Gloor et al.³⁴ as the "Berne modification," combining the advantages of the Beger and Frey procedures. However, if the duct is large or the mucosa of the duct is obviously inflamed, a long longitudinal pancreaticojejunostomy is appropriate for preventing recurrent stricture.

Comparison of the Hybrid Procedures and Resection Procedures

Several large studies comparing hybrid procedures and resection procedures are shown in **Table 1**.

PD or PPPD versus DPPHR

Two randomized prospective studies comparing DPPHR and PPPD or PD have clearly shown the benefits of DPPHR in terms of pain control and postoperative pancreatic function. Klempa et al.²¹ demonstrated in a study of 43 patients with a follow-up period of 3 to 5 years that those receiving DPPHR had better pain relief, a shorter hospital stay, and less postoperative pancreatic dysfunction than did those who underwent PD. Buchler et al.³⁵ have found that after 6 months patients undergoing

Table 1 Several studies comparing different procedures

Author (ref. No.)	Year	Study design (patient number)	Morbidity	Mortality	Pain relief	New onset DM	QOL score	Follow-up
Klempa 21	1995	RCT PD vs DPPHR (21 vs 22)	NC	0% vs 5%	60% vs 70%	38% vs 12%	NA	5 Y
Buchler 35	1995	RCT PPPD vs DPPHR (20 vs 20)	NC	0% vs 0%	40% vs 75%	NA	NA	6 M
Aspelund 36	2005	A single-cohort PD vs DPPHR & Frey (7 vs 24)	40% vs 25% & 16%	6% vs 0%	NA	25% vs 8%	NA	3 Y
Izbicki 37	1998	RCT PPPD vs Frey (30 vs 31)	53% vs 19%	0% vs 3%	NS	NS	NA	2 Y
Strate 38	2008	RCT PPPD vs Frey (30 vs 31)	NS	NA	NS	65% vs 61%	NA	7 Y
Farkas 39	2006	RCT PPPD vs Bern (20 vs 20)	40% vs 0%	0% vs 0%	90% vs 85%	NA	NA	3 Y
Izbicki 41	1997	RCT DPPHR vs Frey (38 vs 36)	32% vs 22%	0% vs 0%	89% vs 92%	8% vs 6%	NC	8.5 Y
Riediger 42	2007	Nonrandomized PPPD vs DPPHR or Frey (90 vs 42 vs 50)	NS	NA	NS	NS	NA	5 Y
Koninger 43	2008	RCT Berne vs DPPHR (33 vs 32)	21% vs 20%	0% vs 0%	NA	NA	71 vs 66	2 Y

NS: not significant, NA: not available

DPPHR have better pain relief and better postoperative pancreatic function than do patients undergoing PPPD and have a similar morbidity rate. A retrospective study by Aspelund et al.³⁶ has shown that the rate of major complications is 25% after DPPHR and 40% after PD.

Frey procedure versus PPPD

Izbicki et al.³⁷ performed a prospective randomized study of 61 patients to compare the Frey procedure and PPPD and found over a follow-up period of 2 years that patients who underwent the Frey procedure had a lower morbidity rate (19%) and better quality of life scores (71%) than did those who underwent PPPD (53% and 43%, respectively) and had a similar degree of pain relief. Strate et al.³⁸ have recently found in a randomized trial of the Frey procedure and PPPD that rates of pain relief, pancreatic function, and survival were similar for both procedures after an average follow-up period of 7 years. However, the rates of new diabetes were 61% (Frey procedure) and 65% (PPPD), both of which were twice as high as those before surgery.

Berne modification versus PPPD

Farkas et al.³⁹ examined 40 patients randomly

assigned to undergo PPPD or the Berne modification and found that the Berne modification produced pain relief equal to that of PPPD but was also associated with shorter operating time, less intraoperative blood loss, a lower rate of postoperative morbidity, a shorter hospital stay, and a better quality of life than was PPPD. Anderson et al.⁴⁰ has also shown that the Berne modification produced good pain relief and no significant complications.

DPPHR versus the Frey procedure

Izbicki et al.⁴¹ examined 74 patients randomly assigned to DPPHR or the Frey procedure with an average follow-up period of 8.5 years. This study showed no significant differences between the procedures in terms of pain intensity, mortality rate, exocrine or endocrine insufficiency, and global quality of life. Aspelund et al.³⁶ have found a lower incidence of new diabetes (8%) for both DPPHR and the Frey procedure compared with PD (25%). However, there were no significant differences in pain relief or complications between DPPHR and the Frey procedure.

On the other hand, long-term pancreatic insufficiency is closely associated with the

progression of the underlying disease, because the late incidence of diabetes seems to be similar for DPPHR, the Frey procedure, and PPPD. Riediger et al.⁴² have reported long-term outcomes in a nonrandomized series of 224 patients followed up for a median of 5 years after PPPD, DPPHR, or the Frey procedure. There was no significant difference in the rate of endocrine or exocrine dysfunction between the operations.

Berne modification versus DPPHR

Koninger et al.⁴³ have performed a randomized, controlled trial comparing the Berne method and DPPHR. They found that long-term pain relief and quality-of-life score did not differ significantly between the procedures.

Conclusions

The surgical technique must be adjusted for the pathomorphological changes of the pancreas. Both PD and PPPD, once the standard operations for patients with CP, have been replaced by hybrid procedures, such as DPPHR, the Frey procedure, and their variants. These procedures are safe and effective in providing long-term pain relief and in treating CP-related complications. The hybrid procedures should be the operations of choice for patients with CP. Although surgical treatment provides effective long-term pain-relief and improves quality of life, it does not stop decreases in either endocrine or exocrine function. Therefore, strategies to improve or maintain pancreatic endocrine and exocrine functions remain an important field of research.

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