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Chemical therapy for chronic pancreatitis: An assumption or an alternative?

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CURRENT MANAGEMENT OF CHRONIC PANCREATITIS

Chronic pancreatitis (CP) is a chronic disease characterized by progressive and irreversible changes to the pancreas.[1] The fundamental pathophysiological processes in CP involve chronic inflammation, pancreatic fibrosis, acinar atrophy, and blocked ducts. The destruction of acinar cells within the lobules by long-term fibrosis ultimately leads to the progressive destruction of pancreatic parenchyma and severe changes in the arrangement and composition of the islets, which eventually results in exocrine insufficiency (maldigestion and steatorrhea) and endocrine insufficiency (diabetes).[2] At the same time, fibrosis involving the pancreatic ducts leads to focal duct strictures, and the secondary stasis of secretions and calcification of protein plugs contributes to pancreatic calculi. These calculi obstruct the pancreatic ducts and increase pancreatic intraductal pressure, which leads to pain, exacerbates parenchymal loss, and worsens pancreatic function to varying degrees.[1]

The clinical hallmark feature of CP is abdominal pain, which affects up to 85% of patients.[3] The pain in CP is classically reported as epigastric with radiation to the back, but may present variably in severity, character, and duration.[4] The mechanism of pain in CP is poorly understood. Traditional theories have inferred that the origin of abdominal pain in CP is related to acinar cell injury, pancreatic duct obstruction, inflammation of peripancreatic nerves, and abnormal pain processing in the central nervous system.[5,6] Treatment of abdominal pain in patients with CP may consist of combinations of medical, endoscopic, and/or surgical approaches.[7] For patients without pancreatic duct obstruction, or those with a lower severity of pain, medical management with the use of antioxidants, pregabalin, acetaminophen, nonsteroidal anti-inflammatory drugs, or opioids is recommended.[8] However, medication cannot prevent the development of CP and once the medication is stopped, the pain will recur or be even more severe than before.

When pancreatic stones, increased intraductal pressure, or duct dilation is observed, efforts should be made to relieve the obstruction.[9] In small pancreatic calculi, endoscopic retrograde cholangiopancreatography (ERCP) followed by sphincterotomy and extraction is the treatment of choice. In the management of large pancreatic stones, extracorporeal shock wave lithotripsy (ESWL) can be offered as an adjunctive therapy to fragment large stones before endoscopic removal [10]. However, the high recurrence rate of calculi has been well documented in long-term follow-up, and rehospitalization is required for repeat interventions.[11] Surgical options include partial resection (*e.g.*, Whipple, distal pancreatectomy), drainage (*e.g.*, Puestow), and combined partial resection and drainage procedures (*e.g.*, Frey, Berne, and Beger).[12] For patients with established CP and disabling pain who have not improved with other therapeutic modalities or are at high risk of pancreatic cancer, total pancreatectomy with auto-islet transplantation can be subsequently

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performed.[13] However, as the duodenum and other surrounding organs are always removed in this operation, it can result in more trauma to the patient. Unfortunately, these approaches are often ineffective or have major consequences, so novel therapeutics are needed.

CHEMICAL PANCREATECTOMY

Based on the progressive fibrotic destruction of the pancreatic secretory parenchyma in patients with CP, Saleh *et al.*[14] reported a paradigm-shifting nonsurgical "chemical pancreatectomy" as a potential therapy for CP. It is generally acknowledged that the progression of CP begins with acinar cell dysfunction, followed by β-cell dysfunction and the inflammation of pancreatic nerves. Therefore, removal of the source of injury (inflamed exocrine tissue) may be beneficial for preventing the progression to β-cell dysfunction and minimizing the risk of future pancreatic ductal adenocarcinoma.

The study by Saleh *et al.*[14] introduced a new strategy to ablate the exocrine pancreas through pancreatic ductal infusion of acetic acid (AcA). Two days after AcA infusion, pancreatic histopathology showed acinar cell injury and necrosis with a marked decrease in amylase staining. Fat cells started to replace the exocrine pancreas at 4 weeks, a process that was complete by 8 weeks. One year after AcA infusion, the loss of exocrine pancreas was persistent with stable fatty replacement, indicating a lack of regeneration. Interestingly, chemical pancreatectomy preserved the integrity of the islets and, in turn, improved glucose tolerance and enhanced insulin secretion. Thus, it was demonstrated that AcA ablation did not adversely affect pancreatic endocrine function. Additionally, Saleh *et al.*[14] found that the number of neurons in the dorsal root ganglion was normal in AcA-treated mice, suggesting that AcA was not grossly cytotoxic to sensory neurons. Furthermore, the authors demonstrated that chemical pancreatectomy ameliorated pain-like behavior in caerulein-induced CP, which was likely due to resolution of the inflammation. Importantly, a high degree of similarity was found in the histological changes of normal mice, mice with caerulein-induced CP, and non-human primate (NHP) models after AcA treatment. These findings made it possible to transform chemical pancreatectomy into humans, which could potentially be a favorable approach in selected CP patients, such as those with disabling pain and who intend to have complete surgical removal of the pancreas.

However, the study by Saleh *et al.*[14] had some limitations. First, as the effect of the chemical pancreatectomy procedure has not been verified in patients with CP, further translational studies were required to make the therapy successful in humans. Second, there was no investigation of any further impacts of the treatment if the chemical ablation of the pancreas was insufficient. For example, since the remaining acinar cells may continue to develop CP, the treatment may increase the risk of pancreatic cancer. Third, there was no data evaluating the exocrine function, and it is possible that this method may aggravate exocrine damage and promote steatorrhea. Finally, pancreatic duct stones cannot be made in animal models of CP. Thus, it is difficult to evaluate the effect of pancreatic duct stones and duct stenosis on the infusion procedure of AcA.

In clinical practice, chemical resection methods such as ethanol or AcA injection are widely used in ablation of hepatocellular carcinoma (HCC), renal and bone tumors, and in other operations.[15] For example, in the use of chemical ablation for regional therapy of small HCC, much work has been done to establish the indications, the volume of ethanol or AcA injection, the infusion techniques, and the management of complications.[16] Eventually, a systematic chemical ablation process was established to improve the survival status of patients with HCC. There is still a long way to go to establish an accurate ACA ablation strategy for CP patients.

CHEMICAL DISSOLUTION OF PANCREATIC STONES

Solitary or multiple disseminated pancreatic stones are the most evident feature of chronic calcific pancreatitis (CCP) and can occur in about 50% of patients.[17] These pancreatic calculi obstruct the pancreatic ducts and produce upstream ductal hypertension and subsequent parenchymal hypertension, which leads to the typical pancreatic pain. Both endoscopic therapy and surgery aim to clear these calculi and reduce ductal hypertension. Pancreatic stones are composed mainly of calcium carbonate with an inner nidus of protein.[18] If calcium carbonate can be dissolved, the pancreatic stone can be removed.

A series of studies have been conducted to explore the effects of different solvents on pancreatic stone solubility. Lohse *et al.*[19] first demonstrated that pancreatic stones could be dissolved *in vitro* by a citrate solution. In animal models, the intraduodenal infusion of citrate increased the concentration and output of citrates in pancreatic juice.[20] In clinical practice, Güitrón administered a citrate solution into the duct via an endoscopically located nasopancreatic catheter for 72 h and 120 h in two patients with CCP.[21] Radiological studies showed that the calcifications became markedly less dense as citrate instillation continued and eventually disappeared completely. These results demonstrate the feasibility of citrate instillation into the pancreatic ducts to dissolve stones and relieve abdominal

pain. Furthermore, Sahel and Sarles have reported that oral citrate administration is effective for the dissolution of pancreatic stones and pain relief in patients with CCP.[22] Another weak organic acid, dimethadione (DMO)—a solvent for $CaCO_3$—has also been demonstrated to have efficacy in CCP.[23] Oral litholysis always uses the DMO precursor trimethadione (TMO), which is used as an antiepileptic agent and can be converted into DMO through metabolic demethylation *in vivo*. TMO was administered orally at a dose of 0.6–1.5 g/d, with the mean course for the litholytic therapy extended by about 78 months. As DMO concentrated in both plasma and pancreatic juice, it appeared to be high enough to dissolve calcium carbonate in patients with CCP: the pancreatic stones were significantly diminished in number and size and finally disappeared. Clinical studies demonstrated that the TMO treatment was effective in dissolving stones, with litholysis or partial litholysis in approximately 86% patients with CCP.[23,24] Additionally, the treatment was highly suggestive of a favorable effect of oral TMO on pancreatic endocrine function and exocrine function in patients whose pancreatic stones were dissolved.

However, oral litholytic therapy by the administration of TMO has some limitations. First, long-term administration of TMO will induce side effects such as photophobia, leukopenia, and hepatorenal disturbance. Second, if the patients discontinued TMO intake, the pancreatic stones recurred and gradually increased in size and number.[24] Furthermore, these studies have not been validated and there are no randomized or comparative trials with a large sample size to confirm the efficacy of the proposed treatment.

SUMMARY: CHEMICAL THERAPY FOR CP

In the management of pain control of CP, elimination of pancreatic stones and prevention of the progression of inflammation are two key components. ESWL, endoscopic therapy, and surgical drainage are the most common strategies for stone removal from large pancreatic ducts. Surgical pancreatectomy is effective in patients with poorly controlled pain or patients with suspicion of pancreatic cancer. However, these treatment modalities may fail for various reasons and cannot prevent the recurrence of stones. Will chemical therapy be a better alternative for CP therapy?

The studies described above provide an opportunity for the consideration of new chemical therapies for CP. Weak acids, such as DMO and citrate, provide new treatment approaches for the removal of pancreatic stones—not only from large pancreatic ducts, but also from small-branch pancreatic ducts. Pancreatic ductal infusion of AcA is a potential alternative of chemical pancreatectomy to surgical pancreatectomy. Liddle[25] imagined a picture that one day in the future, patients with CP would recover by "injecting AcA into the pancreatic duct". While we further hope that both pancreatic duct stones and chronic inflammation of the pancreatic parenchyma could be cured by chemical therapies, many more studies on chemical therapy for CP are warranted to realize this vision.

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Conflict of Interest

The authors declare no conflicts exist.

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