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Review

Management of chronic pancreatitis: recent advances and future prospects

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***Abstract*:** As a progressive fibroinflammatory disease, chronic pancreatitis (CP) often manifests as recurrent bouts of abdominal pain with or without complications, causing a heavy burden of health care. In recent years, some meaningful insights into the management of CP have been obtained from randomized controlled trials, systematic reviews, and meta-analyses, which were of great importance. Based on this research, it is shown that there are various treatments for CP. Therefore, it is of great importance to choose a suitable strategy for patients with CP individually. Relevant evidence on the management of CP was summarized in this review, including nutrition supplements, medication, endoscopy, surgery, exploration of novel therapies as well as evaluation and prediction of treatment response.

Keywords: chronic pancreatitis, endoscopy, evidence-based practice, pain, practical management, surgery

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Background

Chronic pancreatitis (CP) is a progressive fibro-inflammatory disease with an annual incidence of 5–8 per 100,000 and a prevalence of 42–73 per 100,000 in the United States.[1] In 2018, more than 37,000 CP patients required emergency department visits (over 12 visits per 100,000 persons). The readmission rate of CP was 27%, ranking second among digestive diseases, with costs of over 27,000 dollars per readmission.[2] CP is commonly associated with risk factors such as tobacco, alcohol, or genetic factors, and often manifests as recurrent bouts of abdominal pain with or without complications including pancreatic pseudocysts, biliary strictures, pancreatic exocrine/endocrine insufficiency, and bone loss.[3] Previous studies have indicated that patients with CP suffered a higher risk of pancreatic cancer compared with the normal population.[4,5] In addition, low quality of life among patients with CP also exerts a negative effect on psychiatric conditions such as anxiety and depression.[6] Nowadays, management of CP mostly focuses on pain, nutrition, pancreatic stones, and complications due to little evidence on exact etiology.[7]

Over the last decades, the management of CP has gradually developed from surgical resection toward multidisciplinary approaches including medication, endoscopy, and surgery, which were mainly based on high-quality clinical evidence. A large number of randomized controlled trials (RCTs) have resolved a wide variety of clinical problems and have been adopted in numerous clinical guidelines. However, previous technical restrictions are overcome with the rapid development of science and technology, and new RCTs are required to provide new evidence through evaluation and comparison. This review aims to provide an overview of current clinical practice concerning the management of CP, especially focusing on RCTs (both completed and uncompleted), systematic reviews, and meta-analysis, as well as some retrospective studies with meaningful results.

Nutritional support

Previous studies have shown that almost half of CP patients suffer from malnutrition according to the Global Leadership Initiative on Malnutrition criteria.[8] In spite of its high prevalence of

malnutrition, there is still a lack of gold standard in screening and evaluating the nutritional status of CP patients. In previous studies, only body weight and biochemical blood parameters were used to evaluate CP patients' nutritional status. To date, nutrition management is still focusing on pancreatic enzymes and micronutrient supplements.

Pancreatic enzyme replacement therapy

In the first decade of the 21st century, pancreatic enzyme replacement therapy (PERT) was the standard therapy to prevent maldigestion, malnutrition, and excessive weight loss in patients with CP. Since 2010, several RCTs have focused on evaluating the efficacy of pancreatin in the form of delayed-release capsules and enteric-coated mini-microspheres.[9–13] In 2020, a phase I, open-label, randomized, crossover trial focusing on the bioavailability of a pancreatic enzyme product revealed a significant increase of lipase, chymotrypsin, and amylase released into the duodenum after the uptake of pancreatin product with meals compared with the ingestion of meals alone.[14] A *post hoc* analysis of 15 trials showed that PERT could significantly improve fat absorption and mal-digestive symptoms with long-term administration.[15] Besides, two meta-analyses in 2016 and 2017 revealed that PERT could improve the nutritional status of CP patients, but these two studies came to the opposite conclusion in terms of the pain-relieving effect of PERT.[16,17] As for the application status of PERT, a cross-sectional observational study involving 1006 patients with CP from Europe showed that only 64% of the patients were correctly treated with PERT.[18] And a mixed-methods study in East China revealed that the rate of good adherence to PERT was only 12.8%.[19] These studies indicated that the application status of standardized treatment with PERT is not yet satisfactory.

To date, most pancreatic enzyme products are oral delayed-released and recommended to be taken with meals. However, there is a lack of unified criteria for screening, surveillance, and evaluation of malnutrition during PERT. Recently, some clinical issues have still further investigated, such as the dosage of pancreatic enzymes and its effect on pain. A prospective, observational clinical trial in the United States is recruiting participants to evaluate the effect of an oral capsule with pancrelipases on symptoms related to pancreatic exocrine insufficiency (PEI; NCT04949828). Although there is no evidence of pain relief through PERT, the relationship between PERT and pain relief is highly concerned by researchers. In India, Talukdar *et al.* hypothesize that negative feedback of cholecystokinin by non-enteric coated pancreatic enzymes may exert the function of pain relief and are conducting a double-blinded RCT focusing on the effect of non-enteric coated enzymes substitution on pain in CP patients (NE-PERT trial, NCT05042284).

Micronutrient supplements

Due to impaired absorption, deficiency of micronutrients is common in CP patients with PEI. Previous studies have revealed an obvious association in CP patients between bone diseases and PEI due to maldigestion of fat-soluble vitamins including vitamin D, which has a significant role in the process of bone formation.[20,21] It was reported that the prevalence of osteopathy (e.g. osteopenia, osteoporosis) in patients with CP ranged from 36.5% to 57.0%.[22–27] The observational study '*Prospective Evaluation of Chronic Pancreatitis for Epidemiologic and Translational Studies (PROCEED Study)*' was completed in 2022. A cross-sectional analysis from the PROCEED study involving 282 patients with CP showed that the prevalence of osteopathy on dual-energy X-ray absorptiometry scan was 56.0%, and higher prevalences of traumatic and spontaneous fracture were observed in the cohort of CP patients with osteopathy.[26]

Although the prevalence of osteopathy in CP patients is relatively high, clinicians and patients have not paid enough attention to it and the relevant treatment is inadequate. This situation may be attributed to little evidence of pathological mechanisms and the natural course of osteopathy in patients with CP. Presently, an interventional RCT from Finland is ongoing to investigate whether vitamin D substitution (10 μg or 100 μg daily) could prevent the development of CP after the first attack of acute pancreatitis (NCT02965898). This trial will be primarily completed in 2024 and may help in understanding osteopathy in the background of CP.

Dietary management

There is little evidence of dietary recommendations for patients with CP. However, both patients

and nutritionists need to pay attention to dietary management due to the presence of PEI and malabsorption in the process of CP. Except for PERT, an adequate and appropriate diet is also critical for patients with CP. Generally, the European Society for Parenteral and Enteral Nutrition recommends that patients with CP should adhere to a well-balanced diet; fat restriction is not recommended to prevent weight loss and nutrient insufficiency in CP patients.[28]

In 2017, a prospective, double-blinded RCT from Brazil showed that symbiotics could improve the clinical and laboratory profiles of patients with CP and might be a cost-effective therapeutic option for better clinical outcomes.[29] In addition, a study aiming at assessing the tolerability and feasibility of administering soy bread in patients with CP found that the compliance was excellent, and at least one proinflammatory cytokine was reduced with a short-term intervention using soy bread.[30] However, this study had significant limitations as it only included 10 participants.

In 2020, Wiese *et al.*[31] from Germany analyzed the results of 11 RCTs (6 for antioxidant treatment, 3 for vitamin D supplement, 1 for oral nutritional supplements, and 1 for symbiotics supplementation) and found that a well-balanced diet was the cornerstone recommendation for preventing malnutrition in patients with CP, but there was still lack of well-designed large-scale RCTs.[31] Then, they conducted a cross-sectional observational cohort and the results showed that 63% of CP patients had moderate or severe malnutrition (NCT04474743).[32] At the same time, they also attempted to evaluate the effect of intensified nutritional therapy on the nutritional status of malnourished patients with CP (NCT04476056). This clinical trial may be conducive to understand the feasibility and effectiveness of dietary management in CP.

Medication

Medication therapy in patients with CP is commonly aimed at pain relief. Nowadays, medication therapy of most CP patients follows the WHO analgesic ladder including non-steroidal anti-inflammatory drugs (NSAIDs) and opiates.[33] Besides, researchers are attempting to investigate whether other medicine therapies, such as antioxidants and pregabalin, have analgesic effects on pain in patients with CP.

NSAIDs and opiates

Severe and constant abdominal pain is a major factor for poor psychological and physical health in CP patients.[34] Although the WHO's three-step analgesic ladder has been recommended to be administrated to CP patients for more than 10 years, relevant clinical evidence is still scarce.

Han *et al.*[35] are conducting the PAIR trial to investigate the effect of administration with indomethacin (50 mg) twice a day on the progression of CP (NCT04207060). There will be 32 patients with CP enrolled in this trial, and the changes in prostaglandin E2 concentration, pain, and quality of life will be measured and recorded. Besides, rectal indomethacin is also used for preventing pancreatitis in patients with CP who receive endoscopic treatment, which will be discussed later in '*Extraction of pancreatic stones*'.

Owing to the problems of drug addiction and abuse, opiates are strictly prescribed for chronic non-cancer pain. According to a cross-sectional study on the long-term use of opioids, CP was the leading diagnosis, accounting for 30.0% (44/210).[36] Other studies focusing on the application situation of opioids revealed that opioid use disorder was high in patients with CP and significantly related to readmission.[37,38] Although the dose of opiates is often used as one of the indicators of effectiveness in most clinical trials, there is no relevant study of opiates' effect on pain due to CP.

Antioxidants

The effect of antioxidants on CP has been investigated for a long period of time. Studies from the United Kingdom[39,40] and India[41] indicated various benefits of antioxidant therapy, including an increase in antioxidative biomarkers and a decrease in fibrotic markers in the blood. However, their conclusions were opposite in terms of pain relief and quality of life. Therefore, researchers conducted some meta-analyses focusing on these controversial issues. Two meta-analyses including 9 RCTs (390 CP patients) in 2013 and 8 RCTs (573 CP patients) in 2015 found that antioxidant therapy might be associated with pain relief.[42,43] Besides, a systematic review published by the Cochrane Library involving 12 RCTs (585 CP patients) suggested that antioxidants could alleviate pain to a certain extent, but the clinical relevance was uncertain.[44] Aiming to

explore the efficacy of antioxidants and magnesium, the EUROPAC-2 study (NCT00142233, first posted in 2005) was officially completed in 2020 without results published. In the same year, a double-blinded RCT conducted by Singh in India including 107 CP patients revealed that antioxidant therapy had no effect on markers of fibrosis, endocrine and exocrine functions, oxidative stress, inflammation, nutritional status, pain, and quality of life.[45]

Although antioxidants are still considered to be beneficial to pain relief and regarded as a complementary therapy in the clinical management of CP, whether antioxidants have analgesic effects is still unclear, and more high-quality and large-scale RCTs are still needed in the future.

Pregabalin

As an analog of γ-aminobutyric acid, pregabalin has been investigated whether it has an analgesic effect on CP patients. In 2011, a double-blind RCT conducted by Olesen *et al.* in a cohort of 64 CP patients found that more effective pain relief was observed after 3 weeks of pregabalin (150–300 mg, twice daily) treatment compared with placebo treatment.[46] Further studies revealed that pregabalin could inhibit central sensitization manifested as spreading hyperalgesia, which might be mediated through subcortical mechanisms.[47,48] Besides, it was also confirmed by a population pharmacokinetic model that pregabalin had a well-absorption profile in patients with CP.[49] However, a systematic review published in 2016 by Cochrane Library which only included the study of Olesen *et al.* in 2011 suggested that the relevant evidence of pregabalin administration in CP patients was of low-to-moderate quality because of the short-term period of the trial and more adverse events compared with placebo group.[50]

Except for monotherapy with pregabalin, some RCTs were conducted to evaluate the effect of antioxidants combined with pregabalin. In 2016, Talukdar *et al.* conducted a double-blinded RCT involving 87 patients to evaluate the effect of antioxidants combined with pregabalin for 2 months. It was shown that antioxidant plus pregabalin could significantly relieve pain in CP patients after ductal clearance.[51] Moreover, a prospective, double-blinded RCT from India in 2020 including a total of 90 patients with CP revealed that the combination of antioxidants and pregabalin could significantly reduce pain, requirement of non-opioid analgesics, and the number of hospital admissions, improving the overall satisfaction among patients.[52] However, more high-quality evidence is needed in the future as the efficacy and safety of pregabalin administration to CP patients in the short and long term are still unclear.

S-ketamine

In 2011, Bouwense *et al.* from the Netherlands conducted a blinded crossover RCT involving 10 patients with CP who received S-ketamine (2 μg/kg min) or a placebo for 3 h. It was confirmed that S-ketamine was effective in increasing pain threshold, though this effect did not outlast the infusion.[53] Based on this result, the RESET trial involving 40 CP patients was conducted. In this single-center trial, patients were randomized to receive 8 h of intravenous S-ketamine followed by oral S-ketamine, or a matching placebo for 4 weeks (1 mg of midazolam was added to active and placebo treatment). After an 8-week follow-up, researchers would investigate the long-term effect, measure experimental pain, and collect neurophysiological imaging to evaluate pain processing in CP.[54] However, this trial has been terminated prematurely in 2021 (EudraCT 2013-003357-17). Despite the termination of the RESET trial, other researchers were still interested in the effect of ketamine. In 2023, a case series including 14 patients with CP reported by Ertem *et al.* showed that ketamine infusion during hospitalization achieved significant pain relief, which suggested that ketamine infusion might be safely administrated in CP patients hospitalized with pain.[55] By and large, the effect of ketamine on abdominal pain in patients with CP is still unclear and needs further investigation.

Other drugs

Recently, the TACTIC trial (NCT02693093) involving 260 CP patients is initiated to evaluate the effect of NI-03 (camostat mesylate, one of the serine protease inhibitors) on patients with CP. In this trial, patients will be administered a single dose of NI-03 (100, 200, or 300 mg) three times a day for 28 days, and the efficacy and safety will be evaluated by pain score and quality of life.[56] This trial will be of great importance for exploring new ideas in medication treatment for CP.

Except for these drugs used in clinical practice, there are also other drugs being tested for efficacy in animal experiments, including catechin hydrate,[57] nintedanib,[58] aspirin,[59] and pirfenidone.[60] But these preliminary studies are only pilot explorations for the possibility of other drugs without sufficient significance in clinical management.

Endoscopic treatment

In the treatment of CP, minimally invasive endoscopic treatment mainly includes endoscopic retrograde cholangiopancreatography (ERCP) and other endoscopic interventional approaches, aiming to decrease the pressure of the pancreatic duct in CP patients.[7] At present, a lot of RCTs have been performed to investigate the clinical effect of endoscopic treatment on CP, and most of them focus on pancreatic stones, biliary strictures, endoscopic ultrasound (EUS), and post-ERCP pancreatitis (PEP).

Extraction of pancreatic stones

As a common and characteristic feature in the process of CP, pancreatic stones can hinder the drainage of pancreatic juice, which increases the pressure of the pancreatic duct, leading to abdominal pain. Therefore, to reduce the pressure of the pancreatic duct, pancreatic stone extraction with endoscopic intervention is the main strategy in the treatment of CP.[61] Presently, most RCTs on endoscopic extraction of pancreatic stones focus on the timing, methods, and accessories in the process of endoscopic intervention. In 2019, an RCT from Japan involving 20 patients with mild symptomatic pancreatic stones was conducted to explore the efficacy of early endoscopic intervention in mild symptomatic pancreatic stones in comparison with the wait-and-see policy. Although it was prematurely terminated because of poor patient enrollment, the existing results showed that early endoscopic intervention might be beneficial for symptomatic CP patients in terms of reducing the frequency of acute attacks and improving atrophy of the pancreas.[62]

Extracorporeal shock wave lithotripsy (ESWL) is a highly effective treatment method for pancreatic stone fragmentation, especially for stones larger than 5 mm.[63,64] Previous retrospective cohort studies have shown that ESWL is safe and effective for CP patients, even for those who are geriatric,[65] pediatric,[66] postoperative,[67] or with pancreatic pseudocysts.[68] However, the evidence from RCT on the safety and efficacy of ESWL on pancreatic stones is still of scarcity. In 2020, to evaluate the efficacy of ESWL on radiolucent pancreatic stones, an RCT in China on a prospective cohort including 52 patients with radiolucent pancreatic stones was completed (NCT04628273). In 2022, another RCT in Belgium and Italy involving 50 patients with CP was completed, aiming to compare the rate of pain relief and stone clearance between ESWL alone and ESWL combined with endoscopic drainage (NCT00133835). In addition to these two completed but not published RCTs, two RCTs are in progress. One of them is the SCHOKE trial in Denmark enrolling 106 participants aiming to evaluate the effect of ESWL combined with endoscopic treatment for pain in CP patients compared with sham procedures (NCT03966781).[69] Another one is a trial from India involving 80 participants aiming to investigate predictors of pain relief in patients who undergo ESWL (NCT04490083). The results from these completed and ongoing RCTs will be of great significance for further evaluation of the safety and efficacy of ESWL on pancreatic stones.

Pancreatoscopy-directed lithotripsy (electrohydraulic or laser) is considered another effective therapy for the extraction of pancreatic stones when ERCP and ESWL are not available or effective.[64] A prospective multicenter RCT from Germany was completed to evaluate the efficacy of digital single-operator pancreatoscopy (DSOP) in patients with CP and symptomatic pancreatic stones. The cohort of this study enrolled a total of 40 symptomatic CP patients with three or more stones (>5 mm) located in the pancreatic head or body. The results showed that complete stone clearance was achieved in 90% (36/40) of the participants, which indicated that the DSOP-guided strategy was safe and effective in treating symptomatic pancreatic stones in these highly selected CP patients.[70] Besides, another RCT from France is ongoing, aiming to recruit 44 patients with CP to assess the efficacy of DSOP in detecting residual pancreatic stones after endoscopic treatment (NCT04672642). Furthermore, three more RCTs are ongoing to compare the efficacy of ESWL and pancreatoscopy-directed lithotripsy in treating pancreatic stones. Among them, two trials come from the United States (NCT04158297, NCT04115826[71]) and one trial comes from

China (NCT05326542). The results of these RCTs will provide new evidence of the value of ESWL and pancreatoscopy-directed lithotripsy for the treatment of pancreatic stones. Nevertheless, pancreatoscopy-directed lithotripsy is a challenging procedure and must be performed by experienced endoscopists. When it comes to some special situations (e.g. pancreatic stones coexisted with pancreatic duct stricture), pancreatoscopy-directed lithotripsy may not be effective in addressing the stricture below the stones because of spatial limitation, which restricts the application of pancreatoscopy-directed lithotripsy.

During ERCP operation, baskets and balloons are commonly applied in the extraction of pancreatic stones. A single-blind RCT from China aiming to recruit 104 patients with CP is ongoing to compare the efficacy of basket and balloon in the removal of pancreatic duct stones in ERCP procedures by evaluating the rate, time, and times of successful stone clearance and the complications related to ERCP operations (NCT05289362). The results of this trial will help clarify whether a basket or a balloon should be used in the process of ERCP, and the optimal application order when both of them are needed.

Management of main pancreatic duct (MPD) stricture

As a major cause of pancreatic duct obstruction, MPD stricture was another highlight in CP research. According to the guidelines of the European Society of Gastrointestinal Endoscopy, one single plastic stent is recommended as an initial approach in patients with CP concurrent with dominant MPD stricture, and multiple side-by-side plastic stents or self-expandable metallic stents (SEMSs) may be a more acceptable and non-invasive strategy for patients who have a refractory stricture.[72] However, this was a weak recommendation with low-quality evidence.

In 2022, Alberto *et al.* conducted a systematic review and meta-analysis, with 19 studies and 300 patients included. The results indicated that stricture and pain resolution of covered SEMS were, respectively, achieved in 91% and 92% of CP patients with MPD stricture.[73] However, they failed to carry out stratified analyses on specific stent characteristics, such as length, anti-migration properties, metal type, and covering material. Recently, a multicenter RCT including 67 CP patients treated with soft fully covered SEMS, a novel option for MPD stricture in CP, showed that 47.7% of the patients presented stent migration and 50.7% of the patients had plastic stent placement within 90 days after the placement of soft fully covered SEMS, which indicated this novel type of SEMS did not achieve the expected effect.[74] In addition, another study from South Korea including 35 patients with CP and refractory MPD stricture revealed that fully covered SEMS was effective for relieving pancreatic stricture with a clinical success rate of 82.9%, but the rate of stent-induced *de novo* stricture was also high (48.6%).[75] So far, the evidence is still of scarcity. In the future, as material science and medical engineering develop rapidly, well-designed studies are still needed with regard to the short- and long-term benefits of covered SEMS for the treatment of MPD stricture in patients with CP.

Management of benign biliary stricture (BBS)

As another complication of CP which may cause severe abdominal pain and jaundice, the incidence of BBS ranges from 3% to 46% in patients with CP.[76] It often needs to be distinguished from malignant diseases such as cholangiocarcinoma and pancreatic cancer. In the last century, BBS caused by CP was mainly treated by surgical operations. Recently, it has been confirmed by numerous cohort studies that endoscopic intervention is a safe and effective strategy for the treatment of BBS,[77,78] and it is recommended in many clinical guidelines.[7,72,79]

RCTs on the management of BBS mostly focus on the comparison of clinical outcomes between plastic stents and metallic stents. In 2015, a multicenter RCT in Finland enrolled 60 CP patients with BBS and followed up with these patients for up to 2 years to evaluate the safety and feasibility of multiple plastic stents (MPS) *versus* covered SEMS. It was revealed that both types of stents were highly effective in long-term relief of BBS caused by CP.[80] In 2016, a multicenter, open-label RCT in the United States showed that covered metallic stents were not inferior to MPS in terms of biliary stricture resolution. However, this trial had limited reference value because CP patients only accounted for 31.3% (35/112), and no subgroup analysis was conducted.[81] In 2021, another multicenter RCT involving 160 CP

patients with BBS was completed. In this trial, patients were treated with MPS or fully covered SEMS for 12 months and then followed up for 12 months. It was confirmed that both MPS and fully covered SEMS were safe and effective in biliary stricture resolution, while fully covered SEMS required fewer endoscopic interventions than MPS in 2 years.[82]

Furthermore, an RCT in Finland involving 30 CP patients with BBS will be completed in 2023 to figure out the optimal duration of stenting and the diameter (10 or 12 mm) of the covered SEMS (NCT01929538). The results of this trial will be of great importance for optimizing endoscopic strategy in the treatment of BBS caused by CP.

Application of EUS

Except for ERCP, EUS is another effective approach that plays a complementary role in the diagnosis and treatment of CP. To date, most RCTs on EUS focus on the diagnostic performance and pain relief effect of therapeutic EUS intervention.

In 2017, the protocol of an open-label trial in the United Kingdom on the application of elastography in EUS was first posted on *ClinicalTrials.gov*. In this trial, 104 patients (patients with suspected CP and patients with abdominal pain but without risk factors or any other tests suggesting CP) will be recruited, and their elastography strain ratio will be measured during EUS procedures based on conventional EUS Rosemont criteria (NCT03173118). The results from this trial will be beneficial for the differentiation and detection of abnormal changes at an early stage, reducing the incidence of complications related to CP.

In addition, some RCTs about therapeutic EUS are ongoing. Previous RCTs have confirmed that EUS-guided interventions are effective in reducing cancer pain.[83] In 2012, a single-center, single-blinded RCT including 40 adult patients with CP who received EUS-guided celiac plexus block (EUS-CPB) indicated that triamcinolone plus bupivacaine was not superior to bupivacaine alone with regard to pain relief or lengthening effects of EUS-CPB.[84] Besides, an RCT in the United States was completed in 2020 to compare the effect of EUS-CPB *versus* EUS-guided celiac ganglia block (EUS-CGB) on pain in CP patients (NCT03070210). Furthermore, another RCT in the United States aiming to recruit 35 CP patients is ongoing to determine the clinical impact of EUS-guided celiac plexus neurolysis (EUS-CPN) on abdominal pain resulting from CP (NCT04403074). In 2021, the protocol of the Prospective Registry Of Therapeutic EndoscopiC ulTrasound (PROTECT) trial was first posted on *ClinicalTrials.gov*. The PROTECT trial aimed to investigate the long-term outcomes of therapeutic EUS procedures. A total of 510 participants including CP patients will be enrolled, and it is estimated to end in 2023 (NCT04813055). In the next few years, the results of these trials will provide new evidence of therapeutic EUS on CP.

Complications related to endoscopic treatment of CP

Compared with surgery, endoscopic treatment is less invasive and more easily accepted by most patients with CP. However, there are still some complications related to endoscopic treatment, such as bleeding, perforation, infection, and pancreatitis. In recent years, research on PEP and post-ESWL pancreatitis are study highlights of complications related to endoscopic treatment.

In 2017, an observational study involving 2028 ERCP procedures from Changhai Hospital in China showed that the incidence of PEP in patients with CP was similar to that in patients with biliary diseases, while the severity of PEP in patients with CP was lower.[85] Afterward, another observational study from the same team was conducted to identify the risk factors of PEP and post-ESWL pancreatitis. Among the 714 patients with CP involved in this study, 11.2% (80/714) and 4.6% (33/714) of the patients developed post-ESWL pancreatitis and PEP, respectively. It was confirmed that steatorrhea, multiple pancreatic stones, and stones located at the head combined with the body or tail of the pancreas were independent protective factors for post-ESWL pancreatitis, while the history of acute exacerbations, post-ESWL pancreatitis, and stricture dilation during ERCP were identified as risk factors for PEP.[86]

Routine pre-procedural administration of rectal indometacin has been confirmed to be a protective factor of PEP and recommended by many clinical guidelines to prevent PEP.[87,88] However, it remains unknown whether routine administration of rectal indometacin is similarly

effective in preventing post-ESWL pancreatitis. In 2022, a total of 1370 patients with CP were enrolled in an RCT (RIPEP trial) from Changhai Hospital in China and randomly divided into two groups receiving 100 mg of rectal indometacin or glycerin (placebo) suppositories 30 min before ESWL. It was shown that 9% (60/685) and 12% (84/685) of the patients developed post-ESWL pancreatitis in the rectal indometacin group and the placebo group, respectively (relative risk: 0.71, 95% CI: 0.52–0.98; $p = 0.042$).[89] It is worth noting that the pathogenesis of PEP and post-ESWL pancreatitis still needs to be further investigated.

Other RCTs on endoscopic treatment of CP

There are several other RCTs ongoing focusing on the indications, timing, and equipment of endoscopic intervention. In the United States, a single-center pilot RCT is ongoing to comprehensively investigate the value of endoscopic therapy to CP, including endoscopic sphincterotomy, stricture dilation, pancreatic stone extraction with or without mechanical or electrohydraulic lithotripsy, ESWL, and stent placement. The clinical outcomes of 30 CP patients will be evaluated by measuring pain scores and quality of life (NCT04232670). However, considering the small number of participants and the large number of variables, this trial has limited clinical value and may not provide valuable evidence for clinical practice.

Abdominal pain is the common reason for patients with CP to seek medical support such as medication and endoscopic treatment. However, for patients with CP who never or seldom suffer pain, it is usually unknown whether endoscopic intervention is necessary and effective. Therefore, an RCT (EACH trial) from Changhai Hospital in China involving 60 patients with painless CP is conducted to explore whether these patients can benefit from endoscopic interventions (e.g. ERCP, ESWL) by evaluating pancreatic endocrine and exocrine function, quality of life, and other aspects compared with conventional strategy such as nutrition supplement and medication (NCT05261997). Besides, the timing of endoscopic intervention is a critical factor that affects the clinical outcomes of patients with CP. In 2022, the protocol of the TEST trial from Changhai Hospital in China was first posted on *ClinicalTrials.gov* to explore the optimal time interval between ESWL and ERCP during the treatment process of CP. A total of 225 CP patients will be recruited in this trial and randomly divided into three groups of various time intervals (12 h, 12–36 h, and >36 h). The optimal time interval will be determined by measuring the success rate of pancreatic duct cannulation, the success rate of pancreatic stone clearance, and the rate of complications (NCT05270434).

Surgical strategy

Except for medication and endoscopy, surgical resection is another effective strategy for intractable pain and suspicion of malignancy in patients with CP.[90,91] The surgical strategies commonly used in clinical practice include pancreatic ductal drainage, pancreatic resection, and a combination of drainage and resection procedures.[3] The commonly used surgical procedures include the Whipple procedure, Puestow procedure, Frey procedure, Beger procedure, Berne modification, total pancreatectomy, islet autotransplantation (TPIAT), etc.[92] To date, most research on surgical strategies has focused on the comparison of clinical outcomes between different surgical procedures.

Pylorus-preserving pancreaticoduodenectomy versus *duodenum-preserving pancreatic head resection (including Frey procedure, Berge procedure, and Berne procedure)*

As a vital digestive lumen, the duodenum is of great importance in preserving digestive function and post-operation rehabilitation. Therefore, a great many studies focused on the comparison between duodenum-preserving and duodenum-resecting procedures. To date, the Frey procedure (longitudinal pancreaticojejunostomy combined with local pancreatic head excision), the Berge procedure (duodenum-preserving resection of the head of the pancreas), and the Berne procedure are the most commonly used in pancreatic surgery.

A series of research from Germany compared the clinical outcomes between pylorus-preserving pancreaticoduodenectomy (PPPD) and the Frey procedure for CP with the pancreatic head lesion. In the first study of a 2-year follow-up, the rate of pain relief was comparable between the PPPD group and the Frey procedure group. The rate of in-hospital complication and the improvement of

quality of life in the PPPD group were 53.3% and 43%, respectively, while those in the Frey procedure group were 19.4% and 71%, respectively. This result indicated that both PPPD and Frey procedures were effective in terms of pain relief, while the Frey procedure could reduce in-hospital complications and achieve a better quality of life.[93] However, the subsequent study of 7-year follow-up indicated that no difference was observed in these two groups regarding quality of life, pain control, and pancreatic exocrine/endocrine function.[94] Furthermore, the 15-year follow-up study showed that the Frey procedure could provide a higher quality of life and longer median survival time.[95] In a word, these short-term and long-term follow-up studies suggested that the Frey procedure was more favorable than the classical resection procedure.

Except for the Frey procedure, the Berge procedure was also commonly used, especially for patients with large pancreatic head mass, biliary obstruction, and duodenal obstruction. In 2012, a prospective RCT involving 85 CP patients on evaluation of short-term and long-term results of duodenum-preserving and duodenum-resecting strategies (including both Frey procedure and Berge procedure) showed that these two strategies were equally effective in pain relief, quality of life, and exocrine/endocrine pancreatic functions.[96] In addition, the ChroPac trial from 18 hospitals across Europe with a cohort of 250 CP patients followed up for 24 months after surgery showed no difference in quality of life, incidence, and severity of serious adverse events between partial pancreatoduodenectomy group (PPPD or classic pancreatoduodenectomy with distal gastrectomy) and duodenum-preserving pancreatic head resection (DPPHR) group.[97]

In 2016, a review from Cochrane Library including five RCTs (292 CP patients) indicated that the evidence on shorter hospital stays of DPPHR than PPPD was low quality, and no evidence was shown on the differences in mortality, adverse events, and quality of life between these two procedures.[98] However, another systematic review involving 385 CP patients suggested that DPPHR was more favorable than PPPD in terms of operative time, blood transfusion, hospital stay, quality of life, weight gain, and occupational rehabilitation.[99] Besides, Guo *et al.* conducted a meta-analysis involving 44 studies (30 studies investigated CP) to compare the efficacy of DPPHR and PPPD. It suggested that both two procedures had equal effects on improving quality of life and pain relief, while more severe symptoms and more complications resulted from PPPD procedure in comparison with DPPHR.[100] Nowadays, organ-sparing procedures are gradually being widely accepted. Of note, it is required for surgical decision-making to combine patients' conditions with doctors' expertise in clinical practice.

Total pancreatectomy and islet autotransplantation

Except for resection and drainage, TPIAT is the last resort for severe pain and disability resulting from CP, which provides a rare opportunity for pathology and pathogenesis research in CP. The survival of islet autograft is the key and difficult point of TPIAT. Although researchers have made many attempts to improve the survival of islet autograft after TPIAT, such as autologous mesenchymal stem cell and islet co-transplantation,[101] etanercept,[102] carbon monoxide-saturated mediums (NCT02567240), α-1 antitrypsin (NCT02947087), hydroxychloroquine (NCT03283566), and reparixin (NCT01967888), there is currently no practical way to improve the survival of islet autograft.

Although the portal vein remains the most frequently used site for islet implantation, researchers are still attempting to explore other alternative sites for islet implantation, including the spleen, kidney capsule, peritoneum, and omental pouch.[103] However, most of these attempts were based on animal experiments. Presently, in the United States, Mulier *et al.* are conducting the iSite trial enrolling 45 patients with CP and diabetes mellitus to compare the outcomes of intra-portal alone and combination of intra-portal and omental pouch (NCT03779139). The iSite trial is estimated to be completed by the end of 2023.

In addition, the pancreatic endocrine function and long-term prognosis of patients are also research highlights for TPIAT. Khazaaleh *et al.* conducted a meta-analysis involving 21 studies and 1011 patients (60.1% of patients were idiopathic or alcohol-induced CP). It showed that 31.8% of adult patients and 47.7 children patients were insulin-independent after TPIAP.[104] As for the quality of life, Takaki *et al.* from Japan evaluated the efficacy of TPIAP among five patients with CP followed-up for 12 months and found a

significant improvement in quality of life among these patients.[105]

At present, in the United States, the POST (A Prospective Observational Study of TPIAT) trial involving 450 participants (NCT03260387) and the TOPPER trial involving 100 participants (NCT05287737) are ongoing to determine the clinical outcomes of patients with CP undergoing TPIAT. Observation indicators include pain score, quality of life, cost-effectiveness, and endocrine/exocrine pancreatic functions. The POST trial will be completed in 2023 after a 4-year follow-up, while the TOPPER trial is estimated to end in 2047 after a 15-year follow-up. The results of these trials will contribute to clarifying the therapeutic value of TPIAT in CP.

Other RCTs with regard to surgical strategy for CP

The administration of medication and technical aspects of surgical procedures may also affect the prognosis of patients with CP. In 2015, a single-blinded RCT including 75 CP patients undergoing the Frey procedure indicated that the administration of synbiotic composition (*Streptococcus faecalis, Clostridium butyricum, Bacillus mesentericus, Lactobacillus sporogenes*, and *Fructooligosaccharides*) could significantly reduce septic complications, hospital stay, and postoperative antibiotic requirement.[106] Besides, an RCT in Lithuania with a cohort of 103 patients (including a portion of CP patients) was conducted to compare the applications of single-layer continuous suture and two-layer interrupted suture in constructing pancreatojejunostomy after Frey modification. It was shown that a single-layer continuous suture was safer, faster, and less complex than a two-layer interrupted suture.[107] In addition, the NUTRIWHI trial in the United States aiming to recruit 128 participants (including CP patients) is ongoing to assess the impact of enteral and oral nutrition on the clinical outcomes of patients who undergo Whipple surgery (NCT05042882).[108]

With the development of robotic and laparoscopic surgical techniques, robotic and laparoscopic pancreaticoduodenectomy is gradually becoming a reality. Jin *et al.* from China are working on a multicenter phase III non-inferiority RCT (PORTAL trial) aiming to assess the feasibility and safety of robotic pancreaticoduodenectomy for benign and malignant lesions of the head of the pancreas (including CP) compared with open pancreatoduodenectomy.[109] In terms of laparoscopic pancreaticoduodenectomy, other trials of pancreatic or periampullary tumors (PLOT trial,[110] PADULAP trial,[111] and a multicenter RCT in China[112]) showed that shorter hospital stay and a more favorable postoperative course in laparoscopic pancreatoduodenectomy than open pancreatoduodenectomy. However, the LEOPARD-2 trial in the Netherlands showed that laparoscopic pancreatoduodenectomy might cause more complication-related deaths than open pancreatoduodenectomy, and no difference in time to functional recovery between these two groups.[113] These results from pancreatic or periampullary tumor surgery also have certain reference significance for the surgical treatment of CP.

Endoscopy *versus* surgery

It was known to all that both endoscopy and surgery are effective in the treatment of CP. However, the choice of endoscopy or surgery is crucial for both patients and doctors as the subsequent treatment process varies widely, which could even affect the rest of the patient's life. Therefore, the comparison of outcomes between endoscopy and surgery has been a research highlight over a long period of time. The data from the Scandinavian Baltic Pancreatic Club database showed that only 7% of the patients with CP underwent pancreatic surgery; pain (54%) was the most common indication, and most patients underwent endoscopic procedures before surgery.[114] To date, the widely accepted concept is that surgery is more effective, while endoscopy is minimally invasive and considered as the first-line treatment.

Before the year of 2010, there were two famous RCTs focusing on the comparison of endoscopy and surgery. In 2003, a report from Czech included 72 CP patients who were randomly assigned to endoscopy (sphincterotomy, stenting, and stone removal) or surgery (resection and drainage). Although the initial success rates of these two groups were similar, complete pain relief and weight gain were more frequent in the surgery group, which indicated that surgery was superior to endoscopy with regard to long-term outcomes.[115] Likewise, another report in 2007 from the Netherlands including 39 CP patients

with a follow-up of 2 years showed that surgery was more effective than endoscopy for patients with obstruction of the MPD due to CP.[116] In 2011, the 5-year follow-up of the same cohort as that in the report in 2007 (39 CP patients) showed that more pain relief and fewer procedures were achieved in patients who chose surgery rather than endoscopy as the initial treatment method. Moreover, it is worth noting that 47% of the patients in the endoscopy group eventually underwent surgery.[117] Based on these two cohorts, two systematic reviews from the Cochrane Library in 2012 and 2015 suggested that surgery was superior to endoscopy in terms of pain relief for patients with obstructive CP, while no difference was observed regarding morbidity and mortality between these two strategies.[118,119]

Recently, great progress has been made in ESWL and laser lithotripsy, further expanding the applications of endoscopy in the treatment of CP. The ESCAPE trial provided new evidence for the initial treatment of CP. In this trial, 88 patients with CP were randomized into the early surgery or endoscopy-first group and followed up for over 18 months. The results showed that lower pain scores and fewer times of intervention were achieved in the early surgery group compared with the endoscopy-first group. However, no significant difference was observed regarding complications, mortality, hospital admissions, pancreatic function, and quality of life between these two groups.[120,121]

Explorations in novel therapies

Neuromodulation

In 2013, it was confirmed by Bouwense *et al.* that patients with CP showed signs of altered central processing of nociception, which indicated that neuromodulation on altered central processing of pain might be of great significance in pain relief.[122] In 2019, the protocol of a double-blinded sham-controlled RCT from Denmark was published to determine the effect of 2-week cervical transcutaneous vagal nerve stimulation on abdominal pain due to CP.[123] Although cervical nerve stimulation could reduce the functional connectivity of limbic structures, no significant pain relief was observed in patients with CP compared with the sham treatment group.[124,125] Nevertheless, neuromodulation opens up a new horizon for the treatment of CP.

Cognitive-behavior therapy

Furthermore, researchers and psychologists are also attempting to find a way of pain intervention based on the Internet to improve self-management of pain in patients with CP. A total of 30 patients with definite or suspected CP were randomized into the Internet cognitive-behavior therapy (CBT) group or the control group. Patients in the Internet CBT group received courses on pain in pancreatitis for 8 weeks, while patients in the control group continued their usual care. The results showed that the patients in the Internet CBT group made greater progress in pain self-management than those in the control group.[126] This was the first trial to demonstrate pain self-management through CBT in patients with CP, suggesting that Internet CBT might be a novel approach for pain relief in the process of CP.

Energy therapy (Pranic Healing)

Compared with other treatment methods, energy therapy (Pranic Healing) has the advantages of being non-invasive, non-contact, non-pharmacological, and natural. An interventional clinical trial (ET&CP trial) in the United Kingdom enrolling 100 participants is ongoing to investigate the efficacy of energy therapy in pediatric patients with chronic pain caused by CP or inflammatory bowel disease (NCT05394272). In this trial, patients will accept 8 weeks of weekly energy therapy sessions. Pain scores and biological samples will be analyzed to evaluate the effect of energy therapy.

Evaluation and prediction of treatment response

Pancreatic quantitative sensory testing

It is difficult to quantitively assess pain symptoms in CP research. Recently, a series of standardized stimulations have been used in quantitative sensory testing (QST) to map the pain system, which is a novel tool to investigate and evaluate chronic pain. At present, there are two trials ongoing to distinguish phenotypes characterized by segmental sensitization of the pancreatic viscerotome and systemic sensitization with pathological central pain processing (NCT03434392), to evaluate the ability of pancreatic QST (P-QST) to predict response to invasive therapies for CP with pain symptoms, and to develop a predictive model for

individualized prediction of treatment response (NCT04996628).

Other studies for evaluation and prediction

Evaluation and prediction of efficacy are critical for the management of CP. The QOLAPI trial (NCT03632616) and EQuiPP trial (NCT05012150) are recruiting participants to evaluate the effect of endoscopic therapy on quality of life, pain, and pancreatic function of patients with CP. With regard to social factors, the PEPCP (Personalized Education and Pain Response in Chronic Pancreatitis) trial is recruiting participants to evaluate the impact of personalized education on pain response in patients with CP (NCT04654377). With the application of an evidence-based integrated management algorithm, the Dutch Pancreatitis Study Group is running the COMBO trial, the first stepped-wedge cluster-RCT involving 26 centers, to investigate the effect of an evidence-based integrated therapeutic approach on CP patients' quality of life and pain severity compared with conventional therapeutic approaches (ISRCTN13042622).[127] Among the 1165 patients with CP included, it was shown that nutritional status, pancreatic exocrine function, employment status, and patients' coping strategy were the influential and important factors in improving the quality of life.[128]

Besides, the Chronic Pancreatitis Prognosis Score, a dynamic multi-variate scoring system similar to the Child-Pugh Score for liver cirrhosis, has been developed and validated for the evaluation of hospitalization and readmission risk of CP patients.[129,130] The results of this research will be of great importance to predict which patients with CP will benefit from different kinds of therapies.

Conclusion

CP is a complex and heterogeneous disease and the choice of treatment needs to be individualized. Abdominal pain is the most common complaint that disturbs and annoys patients with CP. Nowadays, surgery and endoscopy are still first-line approaches for CP, and studies focusing on these two therapies are getting more detailed, including complications, evaluation, and prediction. Medication is considered an adjuvant and supplementary treatment for CP, and the indications of drugs are gradually expanding with the development and application of new drugs. In addition, other novel therapies such as CBT and energy therapy have been introduced based on multidisciplinary concepts, which will bring new hopes for the treatment of CP.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

All authors had approved the submitted version and agreed personally accountable for their contributions.

Author contributions

Chao Han: Conceptualization; Data curation; Formal analysis; Investigation; Writing – original draft; Writing – review & editing.

Yan-Wei Lv: Data curation; Formal analysis; Writing – original draft; Writing – review & editing.

Liang-Hao Hu: Conceptualization; Formal analysis; Funding acquisition; Investigation; Supervision.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

All data are available online.

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