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Long-term pain relief with optimized medical treatment including antioxidants and step-up interventional therapy in patients with chronic pancreatitis

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Abstract

Background and aim: Abdominal pain is difficult to treat in patients with chronic pancreatitis (CP). Medical therapy including antioxidants has been shown to relieve pain of CP in the short-term. Our aim was to study the long-term results of optimized medical and interventional therapy for pain relief in patients with CP with a step-up approach.
Methods: All consecutive patients with CP were included prospectively in the study. They were treated medically with a well-balanced diet, pancreatic enzymes, and antioxidants (9000 IU beta-carotene, 0.54 g vitamin C, 270 IU vitamin E, 600 µg organic selenium, and 2 g methionine). Endoscopic therapy and/or surgery were offered if medical therapy failed. Pain relief was the primary outcome measure.
Results: A total of 313 patients (mean age 26.16 ± 12.17; 244 males) with CP were included; 288 (92%) patients had abdominal pain. The etiology of CP was idiopathic in 224 (71.6%) and alcohol in 82 (26.2%). At 1-year follow-up, significant pain relief was achieved in 84.7% of patients: 52.1% with medical therapy, 16.7% with endoscopic therapy, 7.6% with surgery, and 8.3% spontaneously. The mean pain score decreased from 6.36 ± 1.92 to 1.62 ± 2.10 ($P < 0.001$). Of the 288 patients, 261, 218, 112, and 51 patients were followed up for 3, 5, 10, and 15 years, respectively; 54.0%, 57.3%, 60.7%, and 68.8% of them became pain free at those follow-up periods.
Conclusion: Significant pain relief is achieved in the majority of patients with optimized medical and interventional treatment.

Introduction

Chronic pancreatitis (CP) is a chronic progressive inflammatory disease of the pancreas.[1] The prevalence of CP varies from 10–125/100 000 population in different countries being much higher in some countries, for example, India.[2–5] It is a major health problem worldwide and is associated with considerable morbidity and even mortality. The predominant causes of CP are alcohol abuse, genetic mutations, and idiopathic.[4,6] The natural history of CP is characterized by recurrent acute exacerbations of pancreatitis in the early stage. In the late stage, there is impairment of the functional capacity due to progressive pancreatic damage leading to diabetes and steatorrhea.[7] Pain is the most prominent and troublesome clinical feature of CP.[8–10] Unfortunately, the exact pathophysiology of pain in CP remains poorly understood. Multiple factors have been suspected, which include recurrent and chronic inflammation, ductal obstruction, neuropathy, parenchymal ischemia, and complications of CP such as pseudocyst.[11–16] Oxidative stress has been shown to be important in the pathophysiology of CP. It has been shown that patients with CP have increased oxidative stress because of generation of free radicals and inadequate antioxidant defense.[17] We have previously shown in a randomized controlled trial (RCT) that antioxidant supplementation resulted in significant pain relief in patients with CP at least on a short-term basis.[18] Whether the response is durable in the long-term is not known. [19,20] The long-term response to optimized medical therapy has not been addressed systematically in patients with painful CP. Endoscopic and surgical therapy including resectional procedures are advocated in advanced CP. A recent RCT showed that surgical drainage resulted in better long-term pain relief than endoscopic therapy.[21] Medical therapy is generally not considered effective for patients with dilated pancreatic duct and calculi although a study did show that the long-term results of medical and surgical therapy might be similar.[22] Thus, it is important to study the long-term response to medical therapy in consecutive patients with CP including those with dilated pancreatic duct and calculi. The objective of the present prospective study was to examine the long-term pain response to optimized medical therapy including antioxidants and interventional therapy in a step-up approach in patients with CP.

Methods

Study design. Prospective observational study.

Setting. A tertiary care academic center.

Patients. All patients with CP attending the Pancreas Clinic in our hospital, during the period from January 2008 to August 2011 were included in the study. One hundred fifty-four patients, who were part of a previous study[23] and being followed up prospectively, were also included in the present study.

Diagnosis of chronic pancreatitis. The diagnosis of CP was made in the appropriate clinical setting if there was evidence of pancreatic duct dilatation and irregularity and/or pancreatic calcification on imaging studies that included ultrasonography, endoscopic retrograde cholangiopancreatography, contrast enhanced computed tomography scan, and/or magnetic resonance cholangiopancreatography.[1] Patients with preserved pancreatic functions and no atrophy of pancreatic parenchyma on imaging were labeled as having less advanced CP.

Etiology of chronic pancreatitis. The etiology of CP was determined as follows:[23] (i) Alcoholic CP: If a patient was drinking >60 g (females) or >80 g (males) of alcohol per day for >5 years; (ii) Hereditary CP: If >2 first-degree relatives were suffering from CP with an autosomal dominant pattern of inheritance, and those without autosomal dominant inheritance were labeled as familial chronic pancreatitis; (iii) Metabolic: If there was evidence of hyperparathyroidism or hypertriglyceridemia; (iv) Traumatic: If there was a history of definite abdominal trauma with imaging evidence of pancreatic injury and subsequent ductal dilatation; and (v) Idiopathic: If no definite cause of CP was identified.

Assessment of pain and its response to therapy. All the patients underwent a detailed questionnaire-based evaluation. Data regarding age at onset, age at diagnosis, presenting symptoms, type of pain, duration of disease, and family history were recorded. The type of pain was defined as recurrent episodes of pain (type A) or continuous chronic pain (type B). A detailed history of pain: frequency of attacks, number of painful days, severity, and treatment required for pain, that is, oral analgesics, parenteral analgesics, or hospitalization was noted. These parameters were used to calculate pain score at different time intervals as reported earlier.[24] The pain score was derived by adding the score of frequency of pain and score of treatment required depending on the severity of pain with a maximum score of 12 (Supporting Information S1).

Assessment of pain was not carried out on a visual analog scale because of subjective bias and individual patient tolerance. Patients were contacted telephonically and by mail and were advised to come for follow-up for personal interview.

Assessment of complications. Diabetes mellitus was diagnosed as per World Health Organization guidelines.[25] Steatorrhea was diagnosed if the stool fat was >7 g per 24 h as measured by Van de Kamer method.[26] Stool fat was measured only in those with clinical symptoms suggestive of steatorrhea. Complications of CP such as pseudocyst, biliary stricture, pseudoaneurysm, and carcinoma during the course of the disease were noted.

Management of chronic pancreatitis. Optimized medical treatment comprised of dietary advice, pancreatic enzymes, antioxidants, and analgesics. The dietary advice included eating small frequent meals, avoiding calorie-rich meals (e.g. fried food), and home-made balanced nutrition diet with appropriate distribution of calories (carbohydrates ~60%, proteins 10–15%, and fat 25–30% of total energy intake) as reported previously by us in a RCT.[24] No major dietary restrictions were advised. Regular counseling for de-addiction for smoking and alcohol was carried out periodically. Analgesics—starting with non-steroidal anti-inflammatory drugs first and later opioids (Tramodol)—either oral or parenteral were prescribed on demand depending upon the previous response and degree of pain. Pancreatic enzyme replacement therapy was prescribed in the dose of 3–4 capsules with each major meal, each containing 8000 units of lipase and ~30 000 USP of proteases (Digestomen-P, Menarini Raunaq Pharma, New Delhi, India). Antioxidants consisting of 9000 IU beta-carotene, 0.54 g vitamin C, 270 IU vitamin E, 600 µg organic selenium, and 2 g methionine (Betamore-G, Osper Pharmanautics, New Delhi, India) were given in three divided doses. Subsequent to our previously reported RCT,[18] antioxidants are prescribed to all patients as a part of medical therapy. The duration of treatment was initially 3 to 6 months depending on the response. In patients with initial response, the antioxidants were given for another 3–6 months if the pain recurred after withdrawal. Patients were asked to come for follow-up initially at 1 month, then at 3 and 6 months. In addition, they were asked to report any time if they had acute exacerbation of pancreatitis. We collected survival data till the last follow-up or by telephonic interview with the patient and family. It was not taken from a registry.

Interventional step-up therapy. The step-up therapy meant scaling up the treatment from medical to interventional. Endoscopic and/or surgical treatment was offered if medical treatment failed. Endoscopic therapy consisted of pancreatic sphincterotomy, removal of calculi and/or pancreatic duct stenting. Extra-corporeal shock wave lithotripsy was used to fragment large calculi. Surgery comprised of lateral pancreaticojejunostomy and the pancreatic head was cored out if the pancreatic head was bulky with head predominant disease (Frey's procedure).

Primary outcome measure. Pain relief in response to specific therapy was the primary outcome measure. The criteria for response were as follows:

Pain relief. It was assessed in those patients who had a prospective follow-up of >6 months. More than 50% reduction in pain score after intervention was taken as significant pain relief.

Pain-free patients. Patients who had no pain for >1 year were considered as being pain-free.

Burnt-out CP. In patients with no pain for >1 year along with features of an atrophic pancreas and dilated pancreatic duct; the disease was considered as having burnt-out.

Ethical clearance. Institutional Ethics Committee clearance was obtained and patients were included after an informed written consent.

Statistical analysis. Data are expressed as mean and SD. Student's paired or unpaired *t*-tests for comparing quantitative data, and Chi square test for qualitative data were used as appropriate. Kaplan–Meier survival analysis was carried out for probability of long term survival. A *P*-value of <0.05 was considered significant. *P*-values were two tailed. SPSS (version 15.0, SPSS Inc., Chicago, IL, USA) program was used for statistical analysis.

Results

A total of 313 CP patients were included; 244 (78%) were men. Their mean age at onset of disease was 26.2 ± 12.2 years. In patients with idiopathic CP, the mean age at onset of disease was 21 ± 10.5 years whereas the mean age at onset in alcoholic CP was 37.4 ± 8.3 years. The mean duration of disease was 8.9 ± 6.2 years at inclusion. The etiology of CP was idiopathic in 224 (71.6%), alcohol in 82 (26.2%), hereditary in six (1.9%), and hyperparathyroidism in one patient.

Clinical profile. Of 313 patients with CP, pain was the presenting symptom in 288 (92%) and the remaining 25 (8%) patients had painless disease (Table 1). Most patients (87.7%) presented with recurrent episodes of pain while 12.3% had continuous chronic pain. A comparison of patients with idiopathic and alcoholic CP is given in Table 2.

Table 1 Clinical features of patients with chronic pancreatitis ($n = 313$)

Age at onset (years)	26.16 ± 12.17
Duration of disease (years)	8.87 ± 6.24
Number of patients with pain	288 (92%)
Type of disease	
Large duct	267 (85.3%)
Small duct	46 (14.7%)
Pancreatic calcification	240 (76.3%)
Atrophic pancreas	219 (70%)
Smokers	89 (28.4%)
Number of patients with complications of CP	
Diabetes	109 (34.8%)
On presentation	20 (18.3%)
During follow-up	89 (81.7%)
Pseudocyst	76 (24.3%)
On presentation	19 (25%)
During follow-up	57 (75%)
Biliary obstruction	37 (11.8%)
Steatorrhea	31 (10.5%)
Portal vein thrombosis	14 (4.5%)
Gastrointestinal bleeding	11 (3.5%)
On presentation	2 (18.2%)
During follow-up	9 (81.8%)
Pancreatic cancer	6 (1.9%)
On presentation	3 (50%)
During follow-up	3 (50%)
Mortality	18 (5.7%)

Pancreatic functions. Diabetes was present in 109 (34.8%) patients; 89 developed diabetes after the diagnosis of CP and 20 prior to the diagnosis of CP. The mean age at onset of diabetes was 34.0 ± 9.2 years. Clinical steatorrhea was present in 31 (10%) patients.

Complications of CP. Pseudocyst developed in 76 (24.3%), biliary stricture in 37 (11.8%), gastrointestinal (GI) bleeding in 11 (3.5%), and pancreatic carcinoma in 6 (1.9%) patients. The causes of GI bleeding were esophageal varices in five, and gastric fundal varices and pseudoaneurysm and duodenal ulcer in two patients each.

Management and response to treatment. The response to therapy in terms of pain relief was analyzed in 288 patients with painful CP. Their disease duration was 9.2 ± 6.3 years. They had a prospective follow-up of 3.8 ± 3.5 years. Of the 288 patients, 244 (84.7%) had significant pain relief including 24 (8.3%) who had spontaneous remission of pain. The mean pain score decreased significantly from 6.36 ± 1.92 to 1.62 ± 2.10 ($P < 0.001$) before and after treatment (Table 3). The response to treatment was similar in patients with idiopathic and alcohol related CP (Table 4). Excluding 154 patients, who were part of an earlier study,[23] from the analysis did not affect the results. Optimized medical therapy including antioxidants was given to 243 patients, 24 were given pancreatic enzymes and analgesics, and no specific medical therapy was required in 21 patients, except oral analgesic on demand as they had mild infrequent pain. The mean duration of antioxidant therapy was 9.4 ± 3.3 months. Of the 288 patients, 150 (52.1%) responded to medical therapy.

Requirement for interventional step-up therapy. Endoscopic therapy was required in 67 patients for pain relief; 17 of them required extra-corporeal shock wave lithotripsy. Of these 67 patients, 48 responded to endoscopic treatment. Twenty-six patients required surgery, 23 for pain relief, and 3 for carcinoma. Of the 26 patients, six had undergone prior endoscopic therapy. lateral pancreaticojejunostomy was carried out in 22 patients, Whipple's operation in three and Frey's procedure in one patient. Of the 26 patients, 22 responded to surgery. Thus, 70/288 (24.3%) patients responded to interventional therapy.

Additional endoscopic therapy. In 29 patients, endoscopic retrograde cholangiopancreatography was carried out for biliary diseases (stricture, choledocholithiasis) or pseudocyst. Pseudocyst was managed conservatively in 54 (71.1%) of the 76 patients, 19 underwent cystogastrostomy—14 endoscopic and 5 surgical, 3 underwent percutaneous drainage, and 11 required endoscopic transpapillary stenting. The response to either medical or interventional therapy in patients with additional cause of pain such as pseudocyst or cancer, has been included in the overall response presented.

Long-term pain response. Of the 288 patients with pain, 150 (52.1%) became pain free. The mean pain-free period was 4.4 ± 3.81 years. With increasing duration of disease and follow-up, the number of pain-free patients increased. As the duration of disease increased from ≥3 years, ≥5 years, ≥10 and ≥15 years

Table 2 Comparison of patients with ICP and ACP

Variable	ICP ($n = 224$)	ACP ($n = 82$)	*P*-value
Age of onset (years)	21.69 ± 10.55	37.36 ± 8.27	0.001
Sex (male)	156 (69.6%)	82 (100%)	<0.001
Duration of illness (years)	9.43 ± 6.58	7.51 ± 4.77	0.001
Smoking (*n*)	26 (11.6%)	61 (74.3%)	<0.001
Type of disease (%)			0.58
Large duct disease	192 (85.7%)	68 (82.9%)	
Small duct disease	32 (14.3%)	14 (17.1%)	
Pancreatic calcification (%)	173 (77.2%)	61 (74.4%)	0.64
Atrophic pancreas (%)	156 (69.6%)	58 (70.7%)	0.29
BMI (kg/m^2)	20.64 ± 4.08	20.37 ± 3.26	0.56
Complications (%)			
Diabetes	74 (33%)	31 (37.8%)	0.49
Age at onset of diabetes	31.1 ± 8.81	39.69 ± 7.65	0.001
Steatorrhea	20 (8.9%)	14 (17.0%)	0.06
Pseudocyst	32 (14.2%)	42 (51.2%)	0.001
Biliary obstruction	20 (8.9%)	17 (20.7%)	0.009

ICP, idiopathic chronic pancreatitis; ACP, alcoholic chronic pancreatitis

Table 3 Reduction in pain score with different modalities of treatment

	Pain score at inclusion*	Pain score after therapy	Reduction in pain score	*P*-value
Medical ($n = 150$)	6.14 ± 1.79	1.60 ± 1.92	4.54 ± 2.39	<0.001
Endotherapy ($n = 48$)	6.74 ± 1.85	2.17 ± 2.36	4.56 ± 2.84	<0.001
Surgery ($n = 22$)	7.52 ± 2.67	1.89 ± 2.88	5.63 ± 4.89	<0.001
No. response to treatment ($n = 44$)	6.97 ± 2.13	6.34 ± 2.08	0.63 ± 2.32	N.S.

*Pain score at inclusion means pain score before the start of a particular therapy, that is, medical or endoscopic or surgery

Table 4 Comparison of response to treatment in patients with ICP and ACP

Response to various therapies	ICP ($n = 224$)	ACP ($n = 82$)	*P*-value
Overall response	176/201 (87.5%)	63/80 (78.7%)	0.06
Medical treatment	104	43	
Endotherapy	40	8	
Surgery	15	6	
Spontaneous response	17	6	
No response	25	17	

ICP, idiopathic chronic pancreatitis; ACP, alcoholic chronic pancreatitis

of disease, the percentage of pain-free patients increased to 54% (141/261), 57.3% (125/218), 60.7% (68/112), and 68.8% (35/51), respectively. The pain score (median) reduced with increasing duration of disease and follow-up as shown in Figure 1. The mean pain score at 1 year of disease was 6.2 (range 0–12) and it decreased to 0 by 26 years. Figure 2 shows the probability of patients being pain free over a period of time. On univariate analysis, type of therapy, active smoking and active consumption of alcohol were significantly different in patients with response as compared with those without response. However, on multivariate analysis, none of these factors was significant predictor of response.

Burnt-out disease. The disease burnt out in about one-fifth, that is, 62 (19.8%) patients at last follow-up. Of these, 14 patients had burnt-out disease at baseline. With increasing duration of disease, additional 19/228 (8.3%), 15/115 (13.0%), and 8/51 (15.6%) had burnt out their disease at 5, 10, and 15 years, respectively. The remaining six patients developed burnt-out disease after 15 years of follow-up. The mean time to burn out was 7.79 ± 5.86 years. The mean follow-up since burn-out was 4.93 ± 3.63 years.

Non-response to pain. Forty-four (15.3%) of the 288 patients had no response and continued to have pain. Young age and less advanced chronic pancreatitis with adequate pancreatic reserve were the likely causes of non-response in about one-half of non-responder patients. Other causes of non-response were continuing alcohol abuse and smoking, pseudocyst, and pancreatic stent *in situ* for a prolonged period (Table 5).

Late recurrence of pain. Of the 288 patients with pain as the presenting feature, 16 patients had an interval recurrence of pain, that is, pain reoccurred after a long pain-free period. The median pain-free interval was 9.13 ± 4.34 years (range 3–20) in them. Three out of these 16 patients had developed pancreatic cancer, which was the cause of recurrence of pain. The interval recurrence of pain led to a secondary peak of pain score of 3 at 30 years, but the mean pain score decreased again to 0 after 31 years of disease (Fig. 1).

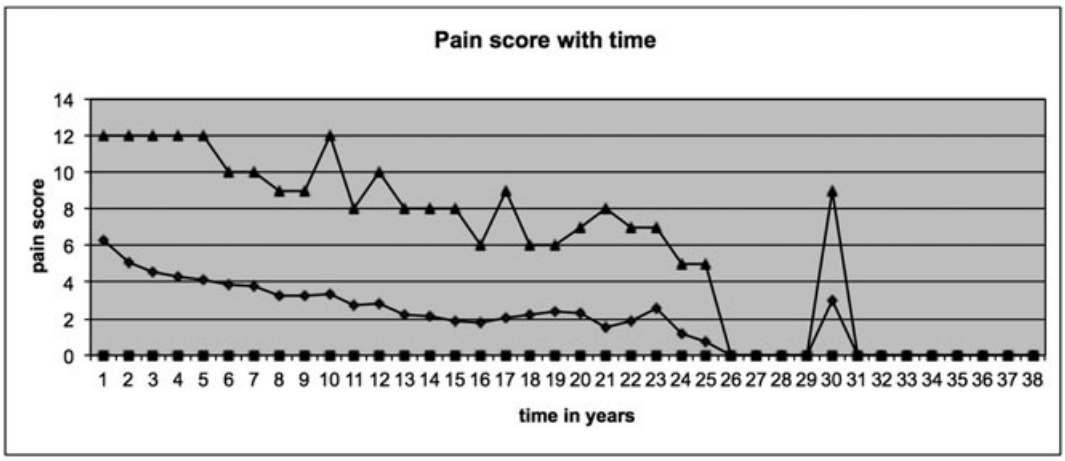

Figure 1 Pain score (median and inter-quartile range) with increasing duration of disease in patients with chronic pancreatitis.

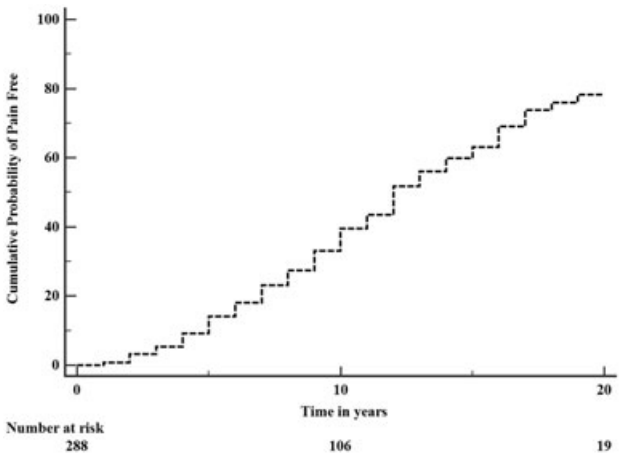

Figure 2 Kaplan–Meier curve showing the probability of patients being pain free over a period of time.

Table 5 Possible causes of no response to therapy ($n = 44$)

Causes	*N*
Young age and less advanced chronic pancreatitis	24
Continuing alcohol	5
Continuing to smoke (no alcohol)	4
Consuming alcohol and smoking	1
Pseudocyst	3
Inflammatory mass	3
Stent induced	2
Neurogenic pain	1
Inadequate endotherapy	1

Survival. Eighteen (5.7%) patients died during follow-up. The common causes of death were diabetic complications, pancreatic cancer, GI bleeding, and cirrhosis of the liver. The mean age of patients at the time of death was 49.64 ± 10.71 years, and the mean duration of disease at the time of death was 10.33 ± 4.3 years. The Kaplan–Meier survival estimate is shown in Figure 3. The probability of surviving after 10 years of onset of disease was 92% and after 38 years was 83%. The causes of death are summarized in Table 6.

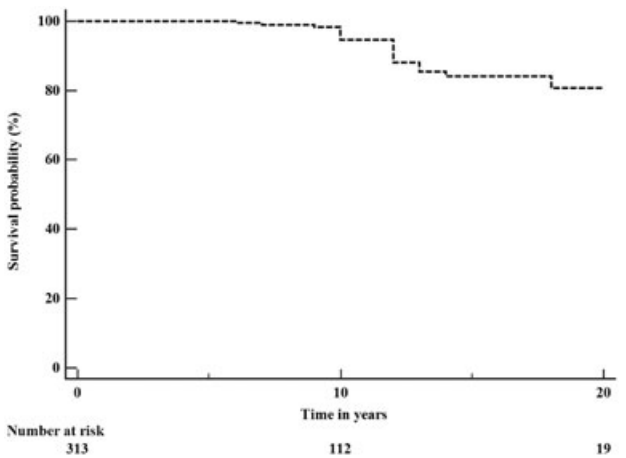

Figure 3 Kaplan–Meier curve showing the probability of survival of patients after the onset of chronic pancreatitis.

Table 6 Causes of death in patients with chronic pancreatitis ($n = 18$)

Diabetic complications	4
Pancreatic cancer	3
Gastrointestinal bleeding	3
Cirrhosis	2
Tuberculosis	1
Cavernous sinus thrombosis	1
Myocardial infarction	1
Road traffic accident	1
Acquired Immunodeficiency syndrome (AIDS)	1
Not known	1

Discussion

Pain is the most prominent and difficult to treat symptom in patients with CP. One of the major reasons for ineffective therapy is that the mechanism of pain in CP is not well understood. In the present study, we assessed the effect of optimized medical and interventional therapy for pain relief. The present study has shown that significant pain relief was seen in over half of patients with medical therapy. The proportion of patients becoming pain-free increased to about 68% with increasing follow-up at 15 years. Optimized medical therapy consisted of a combination of analgesics, pancreatic enzymes, adequate nutrition, antioxidants, and regular advice to quit smoking and alcohol wherever applicable. One of the active components of medical therapy was antioxidants. Among the proposed mechanisms of pain, oxidative stress is one of the widely accepted hypotheses.[17,27–29] We and others have shown that antioxidant supplementation reduces the oxidative stress and relieves pain significantly in patients with CP.[18,30,31] A recent RCT had shown that antioxidants were ineffective in patients with predominantly alcohol induced CP.[32] However, several shortcomings of the study such as improper patient selection, continued alcohol intake and smoking, opiate dependence, failed endoscopic/surgical therapy etc. limited the generalizability of the study.[33,34] Recent meta-analyses have shown beneficial effect of antioxidants in patients with CP.[35–37]

Antioxidants may be associated with some side effects. A meta-analysis had shown higher mortality with long-term use of antioxidants given for a mean of 2.7 years as preventing therapy for diseases such as cancers, coronary artery disease, and infections.[38] Adverse events were also reported with intravenous antioxidants in patients with acute pancreatitis.[39] However, none of the previous studies on the short-term use of oral antioxidants in patients with CP reported significant adverse effects. A deficient antioxidant status in such patients could be the reason for good tolerance.

The response to medical therapy cannot probably be ascribed exclusively to antioxidants. Because the medical therapy comprises of dietary advice, enzymes, and counseling for cessation of alcohol and smoking, these measures might have had an effect in their own right. Indeed, evidence exists for each of these active measures in relieving pain. Nordback *et al*[40] showed in a RCT that 30-min counseling for stopping alcohol consumption resulted in fewer patients developing recurrent pancreatitis compared with the control group. We have shown in a RCT that a dietary advice for a well-balanced diet benefit patients with CP.[24] A well-balanced diet not only improves the malnutrition but also helps in adequate intake of vitamins and minerals—natural sources of antioxidants. Although pancreatic enzymes probably do not reduce pain in the majority of patients with CP, this remains one of the most commonly prescribed therapies and might be beneficial at least in some patients.[41]

However, not all patients responded to medical therapy in the present study. The response to therapy might also depend on the stage of the disease. The commonest cause of inadequate response was young age of the patient with less advanced chronic pancreatitis in the present study. Such patients have adequate functional parenchymal reserve and thus are likely to have recurrent exacerbation of pancreatitis something just the opposite of those with a burnt-out disease.[9] In such patients there is a need to develop medical therapy, which can work at the level of acinar cells to target the basic pathophysiological perturbations. On the other hand, some patients with advanced CP did not respond to medical therapy and required endoscopic therapy and/or surgery after failure of medical therapy in the present study. Endoscopic therapy or surgery is usually required in patients with advanced disease with an obstructed pancreatic duct with calculi and/or stricture after failure of medical therapy.[1]

One of the issues is that the response to therapy may vary with different etiologies of chronic pancreatitis. In the present study, the majority of patients had idiopathic CP and only about one quarter had alcohol related CP. The response to therapy, however, was similar in idiopathic and alcohol-related CP. Idiopathic CP as described from India was also known as tropical chronic pancreatitis. However, we have shown that the so-called tropical pancreatitis is hardly seen in India and the phenotype of the disease has changed.[23,42] Genetic mutations in the *SPINK1* and *CFTR* genes are quite common in them as have been reported in idiopathic CP from other parts of the world.[23,43,44] Furthermore, an important study showed that histological features and inflammatory cell reaction were similar in patients with different etiologies of CP including idiopathic CP from west, alcoholic CP, and tropical CP.[45] Idiopathic CP described from other countries may be somewhat different from idiopathic CP in India as our patients are younger and have different genetic background. In particular, N34S *SPINK1* mutation is seen in about 40% of patients with idiopathic CP compared with 15–20% in western patients with idiopathic CP.[46] Recently, we have shown that polymorphisms in *CLDN2* and *MORC4* genes are also associated with CP in India as has been reported in Caucasian patients with CP.[47,48] In view of the differences in the etiology of CP between our patient population and western patients with predominantly alcohol-related CP, the results of our study should be validated in other patient populations before their generalizability is accepted.

Pain relief in patients with CP could also be due to natural course of the disease and may be due to a burnt-out phenomenon.[9,49] Ammann and Muellhaupt[22] had shown that most patients with CP achieved pain relief over a mean of 17 years either with or without surgical therapy attesting to a burnt-out phenomenon. That about 2/3 of patients had long-term pain relief, and 20% patients had a burnt-out disease in the present study attest to this phenomenon. During the process when recurrent inflammation causes pain, appropriate treatment help relieve symptoms before continuous/recurrent acinar cell injury, inflammation, healing, and fibrosis lead to pancreatic atrophy and functional impairment. However, about 30% of patients continued to have pain even after 15 years suggesting continued pancreatic inflammation and need for treatment in them.

One of the important observations in the present study was a late recurrence of pain in 16 patients after a mean of 9 years, which was unusual after a prolonged pain-free interval; three of these patients had developed pancreatic cancer. Thus, one should suspect development of pancreatic cancer in patients with new onset of pain after a long pain-free period.

The prognosis of patients with CP seems to be quite good because about 80% of patients had relief from pain and the probability of survival was 92% after 10 years and 83% after 38 years of onset of CP. The possible reasons for a good prognosis are improved understanding of the disease, better therapy, and greater health care access and delivery.

One of the limitations of the present study was lack of a comparator group. It might be difficult to ascertain if the response was due to therapy or spontaneous. Significant relief from pain in >80% of patients, which was temporally related to therapy, however, suggests response to treatment.

Thus, we conclude that about half of patients with CP had pain relief while receiving optimized medical therapy including antioxidants and additional 30% patients achieved pain relief after endoscopic and/or surgical therapy. Long-term pain relief up to 15 years suggested a burnt out phenomenon.

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