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Original Article

Clinical Profile, Etiology and Role of Endotherapy in Chronic Calcific Pancreatitis: An Experience from North India

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Abstract

Background: In recent years, we have witnessed an evolving landscape in the management of chronic pancreatitis (CP). Endoscopy plays a pivotal role in CP management. Because the management of CP is problematic, we aimed to review and evaluate the role of endoscopy in the management of CP.

Methods: This study was carried out in patients with painful chronic calcific pancreatitis who were admitted to the Department of Gastroenterology at the Sher-I-Kashmir Institute of Medical Sciences (SKIMS), Srinagar. This was an observational prospective study. We included 67 patients with painful chronic calcific pancreatitis and pancreatic duct abnormalities (stones, strictures, or ductal variations) in our study. These patients had to access exocrine and endocrine status before any therapeutic measures. All the patients underwent endoscopic retrograde cholangiopancreatography (ERCP) as a therapeutic measure. After ERCP, the patients were followed up for 2 years to assess improvement in pain (visual analog scale score reduction), endocrine status (HBA1C reduction), or exocrine status (Fecal elastase reduction).

Results: 67 patients were included in the study. Among them males were 32 (47.8%), females were 35(52.5%) and the age distribution studied were as in the age group of 15-30 years, patients were 23 (34.3%), in 30-45 years, there was 20 (29.9%), in age group of 45-60 year, patients were 20 (29.9%), and in the age group of 60-75 years, the patients were 4 (6%). Etiology was sought in all patients; alcohol-related CP was seen in three patients (4.5%), genetic in 11 (16.4%), IgG4 in one (1.5%), pancreatic divisum in 6 (9.0%), hyperparathyroidism in on1e (1.5%), and idiopathic in 45 (67.2%). All patients underwent ERCP for their symptoms to reduce ductal pressure, which is postulated as one of the hypotheses for pain in CP. Pancreatic duct (PD) clearance was attempted in all patients (complete in 42 [62.7%], partial in 17 [25.4%], and failed in 8 [11.9%]). These patients were followed for a period of two years after endotherapy, and the important predictors for pain reduction were single PD stones, disease in the head and body, and non-stricturing disease.

Conclusion: Endotherapy offers a high rate of success in selected patients, clearance being better in distal disease and CP without PD strictures, suggesting early disease usually gets cleared very easily.

Keywords: Chronic pancreatitis, Pain, Stones, Strictures, ERCP

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Introduction

Chronic pancreatitis (CP) is an irreversible illness with an estimated prevalence between 4% and 5%.[1] The chronicity of this disease, with its peculiar features of frequent acute exacerbations, significantly affects the patients' quality of life. Initially, this disease starts with recurrent attacks of acute pancreatitis (AP), and over a few years, it leads to calcification of the pancreatic tissue, leading to dysfunction of the gland and is thus aptly termed as pancreatic cirrhosis.[2] This disease has a varied etiology; alcohol consumption is the most common contributing factor, causing around 70% of all cases,[3] and other etiologies of CP include genetic mutations, autoimmune pancreatitis, hypercalcemia, and idiopathic CP.[4] Most authors believe that AP, recurrent acute, and CP are distinct entities. A wealth of data supports that AP, recurrent AP (RAP), and CP are a continuum of a single disease.[5,6] Recent evidence supports the notion that more than one "etiology" is present in most patients. The TIGAR-O classification system is based on risk modifiers, not etiologies that may interact to produce pancreatic disease: toxic-metabolic, idiopathic, genetic, autoimmune, recurrent, and severe AP-associated CP, and obstructive etiologic factors.[7] The development of this classification system is based on the principle that an individual's risk of developing CP is determined by one or more risk factors.[8] The two-hit hypothesis model can be used to outline the pathogenesis of CP.[8] In the setting of pre-existing AP risk factors (genetic, metabolic, and environmental), an initial episode of AP (first hit) initiates or activates the immune system, followed by complete recovery or pathological progression to CP. Overall, approximately 20% of patients with AP experience recurrence, and 36% of RAP patients go on to develop CP.[4] This slow destruction of pancreatic tissue, irrespective of etiology, manifests as abdominal pain, which is the most common presenting symptom of CP.[6-9] Steatorrhea and diabetes are other presenting symptoms associated with the loss of exocrine and endocrine

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functions of the pancreas, respectively.[10] Endocrine and exocrine manifestations usually occur in the late course of the disease, with a mean duration of 10-20 years.[10] Diagnosis of CP is usually made by imaging preferably cross-sectional radiology; parenchymal abnormalities are best detected by endoscopic ultrasound,[11] while for ductal changes, contrast enhanced tomography abdomen (CECT) or magnetic resonance cholangiopancreatography (MRCP) is the gold standard.[12] Currently, the need for endoscopic retrograde cholangiopancreatography (ERCP) to establish the diagnosis of CP is obsolete, except for the diagnosis of pancreatic divisum-related CP.

Because of its diverse manifestations, the management of CP is also divided under the care of endoscopists, surgeons, radiologists, endocrinologists, and pain specialists. Medical management involves pain medications and pancreatic enzyme supplementation.[13-15] With the advent of new technologies such as ERCP, endoscopic shock wave lithotripsy, and endoscopic ultrasound, management of complications of CP such as pseudocyst drainage, stricture dilatation with stent placement, and other endoscopic interventions such as celiac plexus block or neurolysis for pain relief can be performed with fair success.[16] However, choosing among various therapeutic and palliative modalities while weighing their risks and benefits makes the management of CP challenging. Ideally, pancreatic endotherapy is indicated in patients with CP who have failed or are unlikely to respond to medical therapy and who have ductal disease in the form of strictures, stones, or any ductal anatomical variations and is usually aimed at relieving pain or managing any of the above-mentioned complications.

Aim of the study

1. To study the etiology of CP in our population.
2. To correlate ductal abnormalities on MRCP/ERCP with symptoms and symptom severity.
3. To follow-up of patients at 2 years to assess reduction of visual analog scale (VAS), fecal elastase, and HbA1c level reduction with treatment.

Materials and Methods

This study was carried out in patients with painful chronic calcific pancreatitis who were admitted to the Department of Gastroenterology from March 2018 to May 2020 at the Sher-I-Kashmir Institute of Medical Sciences (SKIMS), Srinagar. SKIMS is a 700-bedded, largest tertiary care teaching hospital in the Northern Indian State of Jammu & Kashmir.

This study was an observational study. Data were retrospectively and prospectively collected. After acquiring ethical clearance from the Institutional Ethical Committee, we included 67 patients of painful (Connoted by high VAS score > 5/10) chronic calcific pancreatitis with pancreatic duct abnormalities (stones, strictures, or ductal variations) in our study. The VAS is a commonly used tool to rate pain and includes a score of 0 to 10, where a score of 0 indicates no pain, a score of 5 indicates distressing pain, and a score of 10 indicates unbearable pain. All patients underwent a basic physical examination, baseline assessment of pain, and routine baseline investigations, including full biochemical investigations. These patients were subjected to baseline VAS scores and exocrine and endocrine status before any therapeutic measures, which included fecal elastase estimation and HbA1C levels. In addition, this profile was used to detect the etiology of CP, including SPINK/CFTR mutations, intact parathyroid hormone (iPTH) levels, serum IgG4 levels, and tumor markers. All the patients underwent ERCP as a therapeutic measure. After ERCP, the patients were followed up for a period of 2 years to assess improvement in pain (VAS score reduction maximum and minimum VAS score used were 0 and 10, respectively), endocrine status (HBA1C reduction), or exocrine status (Fecal elastase reduction).

Exclusion Criteria

1. Asymptomatic chronic calcific pancreatitis.
2. CP with no ductal abnormalities (PD stones, PD strictures. Pancreatic masses, and or pancreatic cysts.)
3. Patients who were lost to follow-up for 2 years.

How Was the diagnosis of Chronic Pancreatitis Established?

The first step in diagnosing CP in our patients was to seek a detailed history, duration, and severity of symptoms. A history was obtained to elucidate the various risks that might have led to CP. In addition, imaging studies were integral to the diagnosis of CP. In our patients, diagnosis of CP was made on the basis of imaging features by using MRCP: (Cambridge classification).

Table 1 shows Cambridge grading of CP based on findings on MRCP.[17] ERCP has remained only for therapeutic purposes in the management of ductal complications.

Statistics

Measures of central tendency, such as mean, standard deviation, sensitivity, specificity, and calculation of *P* values, were performed using simple statistics. We also applied logistic regression to calculate various parameters. Statistical analysis was performed using the SPSS Software.

Table 1. Cambridge grading of chronic pancreatitis based on findings on MRCP

Grade	Main pancreatic duct	Side branches
Normal	Normal with filling of duct to side branches	Normal
Equivocal	Normal	<3 Abnormal
Mild	Normal	>3 Abnormal
Moderate	Abnormal	>3 Abnormal
Severe	Abnormal with at least one of the following: Large cavity (>10 mm) Obstruction or stricture Filling defect (s) Severe dilatation or irregularity	>3 Abnormal

Results

This study was conducted in patients of painful chronic calcific pancreatitis admitted in the Department of Gastroenterology at SKIMS, Srinagar, and the results obtained were; Among the studied population, males were 47.8% and females were 52.5%. The various age groups were studied and the majority were in the age group of 15-30 years; etiology was sought in all patients; alcohol-related CP was seen in three patients (4.5%), genetic in 11 (16.4%), IgG4 in 1 (1.5%), pancreatic divisum in 6 (9.0%), hyperparathyroidism in 1 (1.5%), and idiopathic in 45 (67.2%). All patients underwent ERCP and various endotherapeutic strategies were assessed to reduce their symptoms. Pancreatic duct (PD) clearance was attempted in all patients (complete in 42 [62.7%], partial in 17 [25.4%], and failed in 8 [11.9%]). These patients were followed for a period of two years after endotherapy, and the important predictors for pain reduction were single PD stones, disease in the head and body, and non-stricturing disease. The detailed results and their statistical significances are outlined in below results.

Discussion

This study was carried out in the Department of Medical Gastroenterology, SKIMS, Soura Srinagar, in patients with painful CP over a period of 2 years. CP is an irreversible process that is usually a challenge for endoscopists. Endoscopy can be proposed in certain circumstances in CP, such as ductal calculi, pancreatic duct and common bile duct (CBD) strictures, drainage of pseudocysts, and pancreatic duct disruption. The main indication of endotherapy in patients with chronic calcific pancreatitis is the control of relentless pain, which is achieved by various drainage procedures. These drainage procedures include sphincterotomy stone extraction and balloon dilatation of the strictures, usually followed by stenting. The aim of this study was to assess the role of endotherapy in the treatment of painful chronic calcific pancreatitis. We included 67 patients who had undergone ERCP for pain relief. Among them, 35 (52.2%) were females, and the remaining 32 (47.8%) were males. The majority were aged 30–60 years (60%) (Table 2). The various etiologies for chronic calcific pancreatitis studied were alcoholism (4.5%), genetics (16.4%), pancreatic divisum (9%), IgG4 (1.5%), hyperparathyroidism (1.5%), and idiopathic (67.2%) (Figure 1).

Pancreatitis is a complex syndrome characterized by diverse causes, presentations, and outcomes. We tried to study various clinical and biochemical parameters in our study group and what we noticed that the mean age of presenting symptoms was 37.75 years and their first presentation was severe upper abdominal pain with pain severity as assessed by VAS was 5.96.

Regarding their endocrine and exocrine insufficiencies mean HbA1c and mean faecal Elastase were 6.22% and 134 µg/g respectively (Table 2).

On cholangiography, all patients had pancreatic duct calculi, and the distribution of PD Stones was as follows: 50 patients (74.6%) had stones in the head and body regions, while 17 patients (25.4%) had stones scattered diffusely in the pancreatic duct. The majority of our patients had multiple calculi (55.5%). Pancreatic duct strictures were found in 20 (29.9 %) patients, whereas CBD strictures related to CP were found in 15 (22.4 %) patients (Table 3).

Among the various endotherapy drainage procedures performed in our patients, endoscopic sphincteroplasty

Table 2. Clinical and lab parameters

Parameter	Min.	Max.	Mean	Standard deviation
Age (y)	15	75	37.75	13.8
Pain severity (VAS)	3	10	5.96	1.49
HbA1c (%)	4	12	6.22	1.95
Fecal elastase (µg/g)	10	456	134	117
Hb (g/dL)	8.1	21	11.1	1.9
ESR (mm/h)	12	48	22.28	7.5
Bilirubin (mg/dL)	0.20	1.90	0.79	0.37
ALP (IU/mL)	20	798	184.54	188.1

VAS, visual analog scale; Hb, hemoglobin; ALP, alkaline phosphatase; ESR, erythrocyte sedimentation rate.

Table 3. MRCP imaging findings

Parameter	Number	Percent
PD calculi		
Head and body	50	74.6
Diffuse	17	25.4
PD stricture		
Yes	20	29.9
No	47	70.1
PD stone No.		
Single	30	44.8
Multiple	37	55.2
CBD stricture		
Yes	15	22.4
No	52	77.6

MRCP, magnetic resonance cholangiopancreatography; PD, pancreatic duct; CBD, common bile duct.

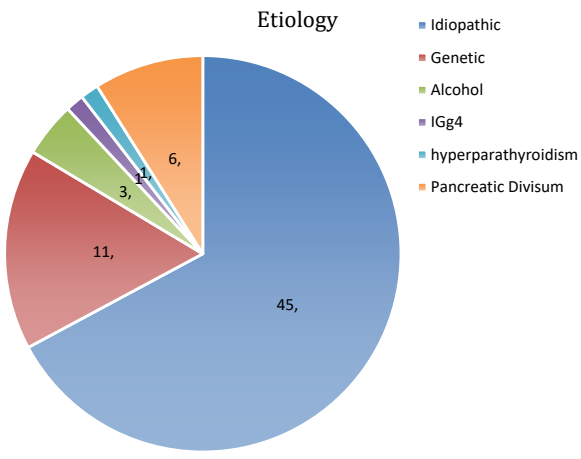

Figure 1. Etiology of chronic pancreatitis

(EST) was performed in all patients. Other procedures performed were EST combined with balloon dilation in 42 patients (68.6%), EST combined with balloon and hurricane dilatation in 20 (29%), and stenting in 43 (64%) patients, which included both biliary and pancreatic duct stenting (Table 4). The average number of ERCP sessions performed in each of our patients was two, and the response in terms of pain relief was observed in 52 (77.6%) patients once followed over 2 years. PD was cleared completely in 42 patients (62.5%), partially in 17 patients (25.4%), and failed in eight patients (11.9%) (Table 5). The complication rate for endotherapy in our study group was 7.85%, which was lower than that reported for surgical management. It has been reported that surgical intervention frequently has major complications associated with it, and these complications require further surgical intervention in up to 10.9% of patients and that there are minor complications in up to 28.3% of patients who undergo surgery.[18]

Table 4. Endotherapy

Parameter	Frequency	Percent
ERCP		
EST	67	100
EST + CRE	42	68
EST + hurricane dilatation	20	29
No. of sessions		
Single	12	17.9
Two	40	69.7
>Two sessions	14	21.4
PD stenting		
Single pancreatic stent	23	34.3
Biliary stent	16	23.9
SEMS	4	6.0

PD, pancreatic duct; ERCP, endoscopic retrograde cholangiopancreatography; CRE, controlled radial expansion; EST, endoscopic sphincteroplasty; SEMS, self expandable metallic stent.

Table 5. Endotherapy outcome

Parameter	Frequency	Percent
PD clearance		
Complete	42	62.7
Partial	17	25.4
Failed	8	11.9
Pain response		
Yes	52	77.6
No	15	22.4
Stricture dilatation		
Yes	8	40
No	12	60
Complication		
Panc reatitis	3	4.4
Bleed	1	1.45
Other	2	2.5

PD, pancreatic duct.

The cholangiographic changes were corroborated by patient symptoms, and it was found that diffuse PD calculi, PD stricture, and patients having multiple calculi had higher mean pain severity (calculated by VAS) as compared to single PD calculi, no PD stricture, and those patients where PD stones were primarily seen in the head region (Table 6). The ERCP clearance rate was also indirectly related to the PD diameter, as we observed a higher clearance rate in patients with minimally dilated PD. It was also observed that PD calculi in the head and body regions were cleared easily, and the same was observed in patients without PD strictures. (Table 7) Similarly, patients with a single PD stone, rather than multiple PD calcu li, showed good clearance with relative ease (Table 7).

These patients were followed for a period of two years and the primary outcome of ERCP was assessed on the basis of a reduction in pain score (calculated by VAS). The mean reduction in the VAS score calculated pre- and post-Endotherapy (ET) was approximately 2.48, and the main predictor of statistically significant pain relief was clearance of PD. We observed that patients who were completely cleared of PD stones had a mean VAS score of 3.05 as compared to 3.47 and 5.75 in patients with partial and failed PD clearance, respectively. It is pertinent to mention here that a VAS score below 3.5, which means no to less pain, was seen in 96% of patients studied over

Table 6. Various indices and their association with pain severity (calculated using VAS scale)

Parameter	N	Mean	Std. Deviation	Std. Error Mean
PD calculi				
Head & body	50	5.92	1.58	0.22
Diffuse	17	6.06	1.19	0.29
PD stricture				
Yes	20	5.95	1.05	0.23
No	47	5.96	1.64	0.24
PD stone				
Single	30	5.83	1.62	0.29
Multiple	37	6.05	1.39	0.22

PD, pancreatic duct.

Table 7. Indices & their effect on clearance on endotherapy

	PD clearance		
	Complete	Partial	Failed
PD stricture			
Yes	8(19%)	4 (23.5%)	8 (100%)
No	34 (81%)	13 (76%)	0 (0%)
PD calculi number			
Single	23 (54.8%)	7 (41.2%)	0 (0.0%)
Multiple	19 (45.2%)	10 (58.8%)	8 (100%)
PD calculi location			
Head & body	38 (90.5%)	10 (50%)	2 (25%)
Diffuse	4 (9.5%)	7 (41.2%)	6 (75%)

PD, pancreatic duct.

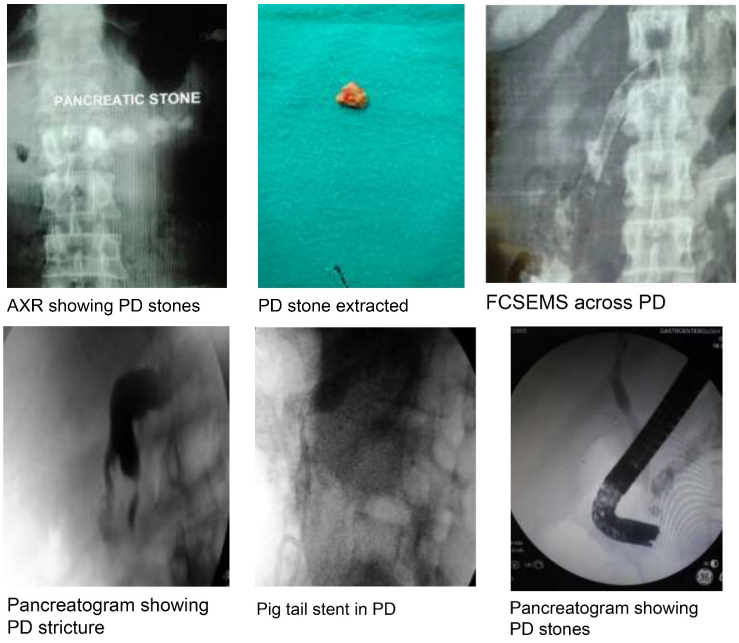

Figure 2. Various endotherapy related images in chronic calcific pancreatitis. AXR, abdominal X-ray

Table 8. Mean VAS after treatment

PD clearance	N	Mean	Std. Deviation	Std. Error	95% CI	
Complete	42	3.05	0.85	0.13	2.78	3.31
Partial	17	3.47	1.54	0.37	4.27	4.27
Failed	8	5.75	1.38	0.49	4.59	6.91

PD, pancreatic duct.

Table 9. Variables assessed before & after treatment (VAS, HBA1C, fecal elastase)

Parameter	Baseline	After 2 years	*P* value
VAS	5.96±1.49	4.09±1.22	0.005
HbA1C	6.22%±1.95	7.02%±2.01	0.242
Fecal elastase (µg/g)	134±117	148±134	0.132

a period of 2 years, and no pain (VAS score of around 3) was seen in 42 patients (approximately 76 %) (Table 8). However, there was no impact of PD clearance on exocrine and endocrine status (Table 9). A meta-analysis of 17 studies with 491 patients revealed a clearance rate between 37% and 100% and good pain relief.[19] Another review of 11 studies with over 1100 patients showed successful stone fragmentation in 89% of patients.[20]

Conclusion

The etiology of CP in our country is different from that in other parts of the world. Endotherapy offers a high rate of success in selected patients, better clearance in diseases involving the head and body, and without PD strictures (Figure 2). These factors suggest that early disease is usually cleared with relative ease. The response to treatment was assessed by reduction in the VAS (Pain score) and was better in patients with early CP.

Authors' Contribution

Data curation: Syed Mushfiq, Neeraj Dhar, Gulzar Ahmad Dar.
Formal analysis: G N Yattoo, Syed Mushfiq.
Funding acquistion: Nil.
Conceptualization: G N Yattoo.
Supervision: G N Yattoo.
Validation: G N Yattoo.
Visualization: Syed Mushfiq.
Writing orginal draft: Syed Mushfiq.
Writing reveiw and & editing: Saurabh Kaushik.

Competing Interests

The authors declare no conflict of interest related to this work.

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