A DISSERTATION ON

TO EVALUATE THE EFFICACY OF DIAGNOSTIC MODALITIES USED IN CHRONIC PANCREATITIS - PROSPECTIVE HOSPITAL BASED OBSERVATIONAL STUDY

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CERTIFICATE

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I hereby declare that this dissertation entitled **"TO EVALUATE THE EFFICACY OF DIAGNOSTIC MODALITIES USED IN CHRONIC PANCREATITIS"** was prepared by me under the direct guidance and supervision of **Prof. DR. T. S. BALASHANMUGAM**, PSG Hospitals, Coimbatore.

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ABBREVIATIONS

CP	Chronic Pancreatitis
TCP	Tropical Calcific Pancreatitis
CT	Computer Tomography
MRCP	Magnetic Resonance Cholangiopancreatography
EUS	Endoscopic Ultrasonography
ERCP	Endoscopic Retrograde Cholangiopancreatography
PERT	Pancreatic Enzyme Replacement Therapy
MPD	Main Pancreatic Duct
CBD	Common Bile Duct
PDS	Pancreatic Duct Stones
EPS	Endoscopic Pancreatic Sphincterotomy

INTRODUCTION

Chronic pancreatitis is a continuous or recurrent inflammatory disease of the pancreas characterized by progressive and irreversible morphological changes.It typically causes pain and permanent impairment of pancreatic function. Late in the course of the disease a progressive loss of endocrine and exocrine functions occur.

AIM:

To study the efficacy of imaging modalities like USG,CT, MRCP, and EUS in a case of chronic pancreatitis.

REVIEW OF LITERATURE

Definition:

Chronic Pancreatitis is defined as a progressive inflammation of the pancreas characterized by irreversible morphologic changes that typically causes pain and or permanent loss of exocrine and or endocrine function. Pain is the predominant feature and is associated with pancreatic calcification, diabetes and steatorrhoea. Chronic pancreatitis can lead to malignancy after many years.(1,2)

The newer imaging techniques like endoscopic ultrasonography (EUS), endoscopic retrograde pancreatography (ERCP), Magnetic resonance imaging changes are useful in detecting early changes in ducts and parenchyma. The identifications of genetic mutation associated with chronic pancreatitis like SPINK 1, CFTR, PRSS, have provided opportunities for identifying patients at risk for idiopathic pancreatitis. This review of literature will focus on epidemiology, classification of chronic pancreatitis, etiopathogenesis and genetic developments in chronic pancreatitis.

Incidence

In chronic pancreatitis incidence found to be around 3 – 10 patients in 100000 population. The prevalence is now estimated to be around 13 per 100000 people(3). Idiopathic chronic pancreatitis is prevalent both in Western countries and India. Recent study shows that chronic pancreatitis previously classified as tropical pancreatitis represents idiopathic chronic pancreatitis in India. The true incidence and prevalence of chronic pancreatitis in India are not known(4).This is because studies related to idiopathic pancreatitis have been difficult to do because of insidious onset, difficulty in diagnosis, and the fact that the disease presents often as acute or recurrent pancreatitis without any definite evidence of chronic pancreatitis(5).

Etiology:

The exact etiology is partially known. Ethanol is considered as the commonest cause accounting for more than 50% of case along with other factors like hereditary, environmental anatomical variation, metabolic, genetics. Many classification systems have been proposed for chronic pancreatitis. These classification include,

i. The Marseille classification (1963) and revised Marseille classification in 1984(6).

ii. The Marseille-Rome classification of 1988(7).

iii. The Cambridge classification of 1984(8).

iv. The Japan Pancreas Society classification for CP (9).

v. TIGAR -O classification(10).

TIGAR – 0 classification systems was proposed by Etemad and Whitcomb in 2001 and is based on primarily on the etiology of chronic pancreatitis and takes into account of newer developments such as genetic mutations.

TIGAR -O Classification System for Chronic Pancreatitis

Toxic Metabolic

- Alcoholic
- Tobacco Smoking
- Hypercalcemia
- Hyperlipemia
- Chronic Renal Failure

Idiopathic

- Early onset
- Late onset
- Tropical

Genetic

- Autosomal dominant: cationic trypsinogen gene mutation
- Autosomal recessive / modifiers genes: CFTR mutations, SPINK1 Mutations

Autoimmune

- Isolated autoimmune CP
- Associated with other autoimmune diseases (Sjogren syndrome - associated CP)

Recurrent and severe acute pancreatitis

- Post - necrotic (severe acute pancreatitis)
- Recurrent acute pancreatitis
- Vascular disease / ischemic
- Radiation injury

Obstructive

- Pancreas divisum
- Sphincter of Oddi disorder (controversial)
- Duct obstruction (e.g) tumour
- Periampullary duodenal wall cysts
- Post –traumic

Genetic :

Until more recently few data existed on the genetic basis of chronic pancreatitis. The only known hereditary form of chronic pancreatic insufficiency that was well studied was cystic fibrosis.

Research has focused on the SPINK1-N34S gene mutation, which also is associated closely with tropical (50%), alcoholic (6%), or idiopathic (20%) c chronic pancreatitis.

One of the major discoveries in chronic pancreatitis was the description of the point mutation in patients with autosomal dominant hereditary pancreatitis. Several variants of the mutation of the cationic trypsinogen gene all lead to a malfunction of trypsinogen. Hereditary pancreatitis presents typically in a bimodal pattern of childhood and adulthood. Trypsinogen gene mutation found in hereditary pancreatitis which is an autosomal dominant disease carries 80% penetrance.

Despite great advances in the knowledge of genetics in pancreatitis, currently it is advised to evaluate for mutations only in patients with hereditary pancreatitis.

Autoimmune :

Autoimmune chronic pancreatitis (AIP) is a rare but distinct form of chronic pancreatitis that is associated with autoimmune features. AIP is characterized by specific histopathologic and immunologic features. The morphologic hall marks are periductal infiltration by lymphocytes and plasma cells and granulocytic epithelial lesions with consequent destruction of the duct epithelium and venulitis.

The pathogenesis of AIP values a cellular CD4+ and CD8+ T cells) and humoral immune mediated attack of the ductal cells and pancreatic ducts resulting in cytokine mediated inflammation and periductular fibrosis, which leads to obstruction of the pancreatic ducts.

AIP shows mild abdominal pain and diffuse enlargement of the pancreas without calcifications or pseudocysts.

On laboratory examination, these patients have hypergammaglobulinemia and autoantibodies, such as antinuclear and anti-smooth muscle antibodies.

Obstructive :

Chronic pancreatitis results in block of the main pancreatic duct. The most common etiologies include scars of the pancreatic duct, tumors of the ampulla of Vater and head of the pancreas, and trauma.

Stone and duct obstruction theory explains the stagnation of pancreatic juice and stone formation or acute recurrent pancreatitis and periductular fibrosis (necrosis fibrosis theory). Histopathologic characteristics of chronic pancreatitis resulting from obstruction include uniform distribution of interlobular and intralobular fibrosis and marked destruction of the exocrine parenchyma in the territory of obstruction, without significant protein plugs and calcifications.

Chronic pancreatitis results from plugging of the pancreatic duct. The origin of chronic pancreatitis was within the lumen of the pancreatic ductules in contrast to the origins of acute pancreatitis which tends to be inside the acinar cell. Increased lithogenicity of pancreatic fluid leads to the formation of eosinophilic proteinaceous aggregates, which precipitate and obstruct the pancreatic ductules.

Alcohol decreases the formation and the secretion of pancreatic juice, making it more viscous ; low in bicarbonate ; rich in protein, enzymes and calclium crystals ; and deficient in lithostatin.

Alcohol also has been shown to mediate the release of gastrointestinal hormones by increasing cholecystokinin releasing factor, which affects pancreatic juice formation and flow. The pancreatic stones and plugs are believed to produce ulceration of the ductal epithelial cells resulting in inflammation, obstruction, stasis, fibrosis which leads to formation of stones.

Mechanism of chronic pancreatitis was a dysregulation and increased activity of the hepatic mixed function oxidases leading to oxidative stress. This theory places the acinar cell at the major area of injury by oxidative stress, usually as a result of steady exposure of xenoiotics that induce the cytochrome P-450 enzymatic system, while depleting glutathione.

Pancreatitis is triggered through interference of the methionine to glutathione transsulfuration pathway, resulting in diversion of free radicals in to the pancreatic tissue, with consequent activation of inflammation and fibrosis of the ductules with low flow of pancreatic juice, inhibition of lithostatin, and precipitation of proteins and calcium (Braganza 1998 ; Wilson et al, 1990). Alcohol also may contribute to increase the oxidative stress resulting from

depletion of scavengers, such as selenium, vitamin E and C and riboflavin, and help to induce or propagate the damage.

Alcohol and its toxic metabolites cause accumulation of intracellular lipids and fatty acid ethyl esters, which produce damage to the acinar cell. The alterations of intracellular lipid metabolism lead to fatty degeneration, apoptosis and scarring of the pancreatic parenchyma with impairment of the pancreatic microcirculation.

It was shown that these fat cells exists in the human pancreas, can migrate into the periacinar spaces, and are activated by alcohol and acetyl aldehyde, transforming into scar producing cells. The necrosis fibrosis hypothesis views the development and course of chronic pancreatitis as a consequence of severe pancreatitis, emphasizing that fibrosis is a late development resulting from repeated attacks of acute (alcoholic) pancreatitis, which initially lead to inflammation and necrosis.

The necrosis fibrosis hypothesis has significant supporting evidence from epidemiologic and large follow up studies, which showed recurrent attacks of acute pancreatitis leads to chronic pancreatitis.

The recurrent attacks of acute pancreatitis in hereditary pancreatitis also support the necrosis fibrosis hypothesis. One important aspect that partially negates this hypothesis is the fact that the type of fibrosis that follows acute attacks of pancreatitis involves short lived collagen type III and procollagen type IV and not the long lasting collagen types I and IV (Casini et al 2000).

The primary pathogenic factor leading to chronic pancreatitis is an outflow obstruction likely resulting from duct inflammation, destruction and fibrosis which likely are the result of an immunologic attack on a specific genetic, structural or acquired antigen of the periductular epithelium. The target of this attack may be some specific genetic or acquired antigen on the duct epithelium.

Chronic pancreatitis seems to be an autoimmune or duct destroying disease, analogous to primary sclerosing cholangitis. The assumption is supported by several observations, such as the radiologic and histologic similarity of chronic pancreatitis and primary sclerosing cholangitis, the activation of cytotoxic T.lymphocytes in the periductular areas of the pancreas in patients with alcoholic chronic pancreatitis, and the occasional association of chronic pancreatitis and primary sclerosing cholangitis.

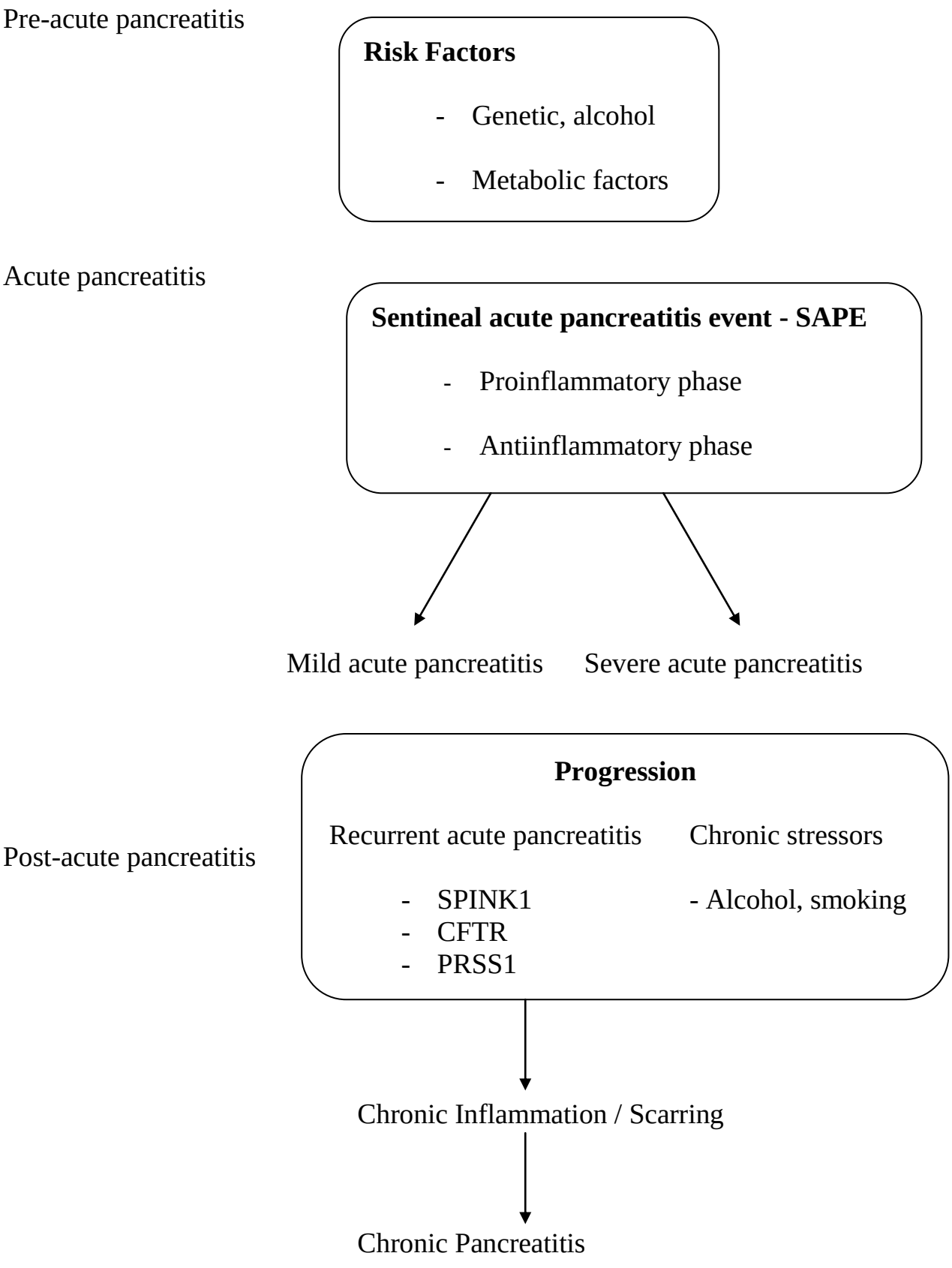
The SAPE hypothesis tries to provide a “final common pathway” for the many etiologies for pancreatitis. The basic aspect is that there needs to be susceptibility (genetic or through ongoing insult, such as alcohol toxicity). The critical sentinel event appears and triggers the process causing acute and chronic pancreatitis. Further activation of the immunologic system and the stellate cells propagates chronic pancreatitis, and the end result is fibrosis and calcifications.

PATHOGENESIS

Current theories for pathogenesis of chronic pancreatitis can be broadly divided into two types

1. Duct obstruction theory-Alterations in the physical and chemical properties of pancreatic secretions which leads to duct obstruction as the main cause of pancreatic damage.
2. Toxic metabolic theory- continuous injury to pancreatic acinar cells produces inflammation, necrosis, and fibrosis with duct obstruction .

Progression from pre-acute pancreatitis to chronic pancreatitis (11).



RECENT CONCEPTS

Two important concepts have emerged as being important in the pathogenesis of CP including the so-called TCP. These include oxidative stress and genetic mutations.

Oxidative Stress

Oxidative stress (OS) has been implicated recently in the pathophysiology of CP(12-13). Xenobiotics are detoxified in the body through phase I and phase II pathways chiefly in the liver(14). Increased exposure to alcohol, nicotine, petrochemical fumes may overwhelm the capacity of phase I and phase II detoxification pathways and result in oxidative stress. OS will damage these cell either directly by cell membrane destruction, depleting the cells of antioxidants or free radical mediated injury(15-16).

Genetic Mutation:

The role of genetic mutations in CP has been studied for more than 30 years. Initial studies were directed toward the association of HLA genes with pancreatitis. In 1950s, Comfort et al(17) described Heridatary Pancreatitis as a highly penetrant, autosomal dominant condition. In 1998, studies showed

an increased incidence of CFTR gene mutations in patients who had idiopathic CP(18-19). In a landmark study, Whitcomb et.all50. reported arginine to histidine substitution at residue 117 (subsequently renamed as R122h) in the cationic trypsinogen gene on the long arm of chromosome 7 (7q35) in hereditary pancreatitis. Witt and colleagues said that mutations in the SPINK 1 gene were associated with CP(20). The discovery of heterozygotes individuals with mutations in multiple genes and the resultant additive effect on disease underscores the complex nature of genotype and phenotype expression in CP

Idiopathic chronic pancreatitis (21)

Idiopathic chronic pancreatitis includes in whom no risk factors can be found. The discovery of new genetic factors, environmental factors and metabolic factors will reclassify - and reduce the numbers of patients in this category. Idiopathic chronic pancreatitis has long been shrouded in mystery as far as its etiopathogenesis is concerned. Many different theories have been proposed like immune-mediated injury and environmental toxins however newer studies have discarded above hypothesis. Idiopathic CP that is common in India is also known by some authors as tropical calcific pancreatitis (22).

Early and late onset

The age of onset in idiopathic pancreatitis is bimodal as observed by Layer et al. In early onset calcification and exocrine and endocrine deficiency develops slowly than late onset. In late onset pain was absent in nearly 50% of patients. Pbtizone (23) identified SPINK 1 mutation in about 25% of patients with idiopathic chronic pancreatitis. Patients with SPINK1 mutation developed pancreatitis before age of 20 in many studies.

Tropical Chronic Pancreatitis

Tropical chronic pancreatitis is known as a type of idiopathic CP occurring in tropical countries. They can be sub-grouped as Tropical calcific pancreatitis. TCP Characterised by frequent episodes of pain abdomen in childhood, extensive pancreatic calcification and pancreatic dysfunction but no diabetes at time of diagnosis. The other group is called as fibrocalculous pancreatitis diabetes (FCPP) in which diabetes mellitus is the first major complaint(24). The etiology of tropical calcific pancreatitis is poorly understood. Many theories such as environmental factors, malnutrition, dietary Toxin like cyanogenic glycosides and micronutrient deficiency have been proposed. Recent reports from genetics studies have shown significant association between (SPINK1 and cationic trypsinogen mutation).

CLINICAL FEATURES

Recurrent acute Pancreatitis(25)

All patients have recurrent attacks of upper abdominal pain at the onset. The pain is accompanied by nausea and vomiting in around 90% of patients. Patients can also present with severe pancreatitis which is associated with organ failure.

Chronic Pancreatitis

Abdominal pain is the common presenting symptom localized to the epigastric region. The natural history of pain is highly variable and can present as intermittent or chronic pain. The other symptoms include diarrhea, weight loss, endocrine insufficiency (diabetes), jaundice or complications of acute episodes. The physical examination does not help to establish diagnosis however fullness, tenderness can be elicited. Patients with advanced disease show signs of malnutrition

Approach to Determine etiology of recurrent Pancreatitis:

Evaluation of a patient after the first attack of pancreatitis includes a careful history, lab studies (lipid profile, serum calcium, Anti nuclear anti body, Liver function tests) and USG abdomen(26,27). Half of the patients with acute pancreatitis will have a recurrence. EUS / MRCP should be done to identify gall bladder sludge, small CBD stones, pancreas divisum, pancreatic tumors and early chronic pancreatitis. In clinical practice, ERCP is seldom done. For patients with idiopathic acute pancreatitis, selective use of genetic testing may be appropriate. For the patient with RAP, especially in the setting of an appropriate family history, genetic testing for cationic trypsinogen gene (PRSS1), SPINK 1 gene can be done. The role of genetic testing for these mutations is less clear and controversial.

Chronic Pancreatitis:

The diagnostic approach to chronic pancreatitis has evolved considerably in recent years. The investigations used can be summarized as below:

- Imaging of pancreas and pancreatic ducts.
- Tests for pancreatic exocrine insufficiency: to assess the degree of exocrine dysfunction (e.g., fecal chymotrypsin) and sometimes to monitor replacement therapy (e.g., fecal fat estimation).
- Tests for pancreatic endocrine deficiency.

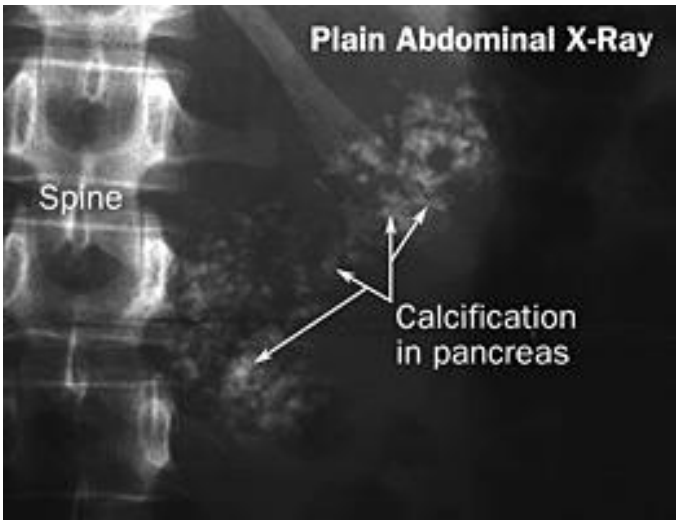
Biochemical Blood Tests

Serum trypsin exists mainly as the cationic form of its precursor trypsinogen. In states of pancreatic insufficiency, the precursor gets converted to active trypsin. The active trypsin is mostly bound by protein inhibitors and become undetectable by catalytic assays (28). The study by pezzilli (29) et all has found it to be 28% sensitive but 100% specific in identifying chronic pancreatitis. However, other studies have shown it to be only 50-60% sensitive in detecting chronic pancreatitis. Serum lipase and amylase levels are elevated during acute pancreatitis but are of limited value to diagnose chronic pancreatitis.

IMAGING METHODS:

Plain X ray :

A plain x ray abdomen ,though not by itself diagnostic of chronic pancreatitis,can detect calcification in the pancreatic area.Pancreatic calcification is more commonly associated with alcoholic and tropical pancreatitis.X ray abdomen is of limited value as a diagnostic measure because CT scan can demonstrate calcium deposition as well as other finding associated with chronic pancreatitis.



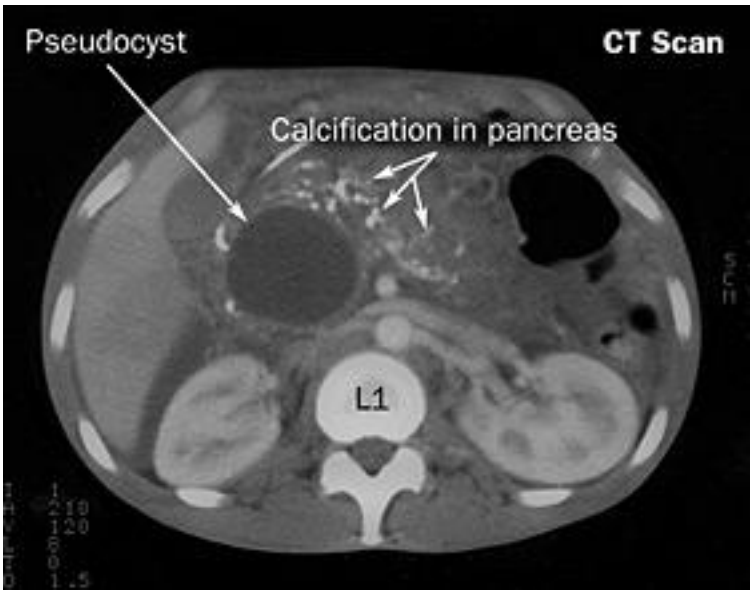
Transabdominal Ultrasonography

Transabdominal ultrasonography can be used to visualize alterations of the pancreatic duct, pancreatic calcification or stones and pancreatic cysts or pseudocysts. Pancreatic stones are visible as intra-pancreatic hyper-reflective echoes with acoustic shadows.Dilatation of the pancreatic duct can be seen more clearly in the head and body of pancreas rather than in the tail region.Abdominal ultrasound is highly sensitive in detecting severe chronic pancreatitis but the sensitive is much less in milder forms of the disease(30).

Computed Tomography (CT) Scan(31)

Computed tomography scan is one of the important diagnostic modalities in detection of chronic pancreatitis. In chronic pancreatitis, a non-contrast-enhanced CT scan shows chronic pancreatitis. The contrast-enhanced pancreatic imaging produced by thin-multidetector row scanners can detect any abnormality in the morphology of the gland, any parenchymal attenuation, any dilation or stones in the pancreatic duct and pancreatic pseudocysts.It can also identify vascular complications such as pseudoaneurysms, and venous thrombosis of the splenic or pancreaticoduodenal artery(32).

CT scan is as specific as ultrasound but more sensitive. CT scan cannot detect early parenchymal changes and effects on small pancreatic ducts, but advanced stages and complications of the disease can be evaluated with high reliability. CT is most sensitive to detect calculi. CT is excellent method to detect advanced stage but not for early stage of chronic pancreatitis.



CT GRADING

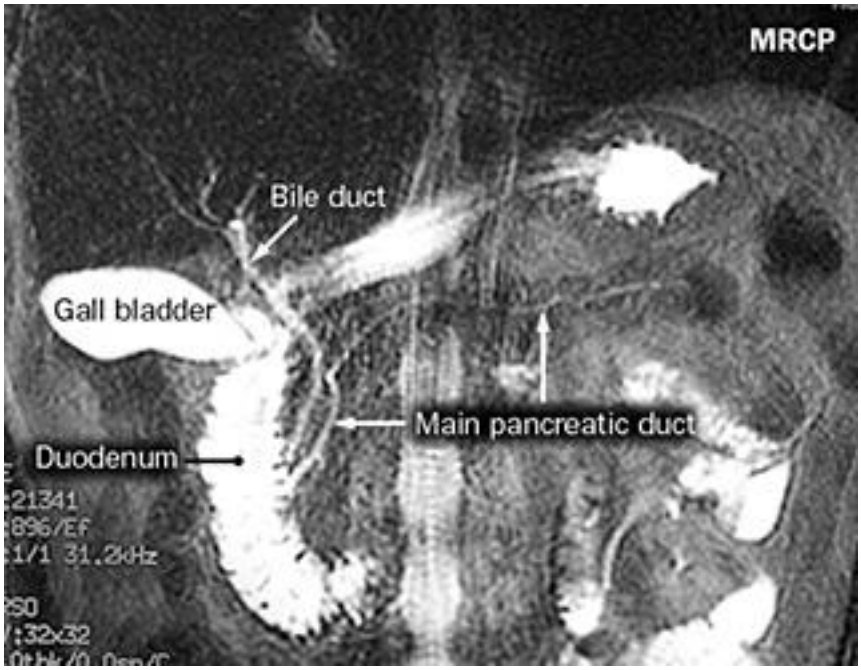
GRADE	CT FINDING
Normal	No abnormal findings
equivocal	one of the following mild dilatation of pancreatic duct(2-4mm) gland enlargement<2-fold normal
mild-moderate	pancreatic duct dilatation(>4mm) focal necrosis or parenchyma cavity<10mm increased echogenicity of duct wall
severe	cavity>10mm intraductal filling defect calculi/pancreatic calcification ductal obstruction(stricture) severe duct dilatation or irregularity

Magnetic Resonance Imaging (MRI)(33)

Magnetic resonance imaging cannot detect extraductal pancreatic calcification as well as CT scan can. Both T1and T2 weighed images may be used to detect severe forms of chronic pancreatitis, though the findings are less specific in the elderly patients.

MRCP can provide a 3- dimensional image of main pancreatic duct which provides valuable information about strictures, dilatations and filling defects. It is superior to ERCP in demonstrating the upstream of pancreatic duct distal to an obstructing lesion.

Secretin -enhanced MRCP can also assess the exocrine function of pancreas.



Endoscopic Retrograde Cholangiopancreatography(ERCP)

ERCP can be used as a diagnostic as well as therapeutic tool in patients with chronic pancreatitis. It can detect dilatation and stenosis of pancreatic ducts, pancreatic stones or cysts.

However, as ERCP can be associated with iatrogenic acute pancreatitis, it is not preferred as a diagnostic modality. ERCP may be useful in distinguishing chronic pancreatitis from pancreatic cancer.

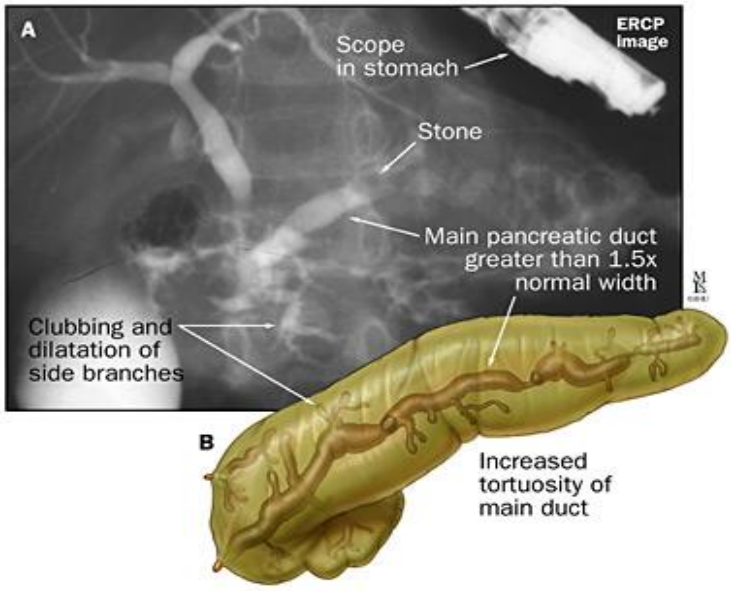
ERCP used to treat calcific obstruction of distal, main pancreatic duct and drain symptomatic pancreatic pseudocysts. Also used to remove pancreatic calculi, dilate strictures and insert stents.

ERCP is less sensitive than other modality to detect small duct disease.

Cambridge classification

Grade	Main pancreatic duct	Side branches
Normal	Normal	Normal
Equivocal	Normal	<3 abnormal
Mild	Normal	>=3 abnormal
Moderate	Abnormal	>=3 abnormal
Severe	Abnormal with at least one of the following large cavity(>10mm) obstruction filling defect severe dilatation or irregularity	>=3 abnormal

ERCP demonstrating severe chronic pancreatitis.

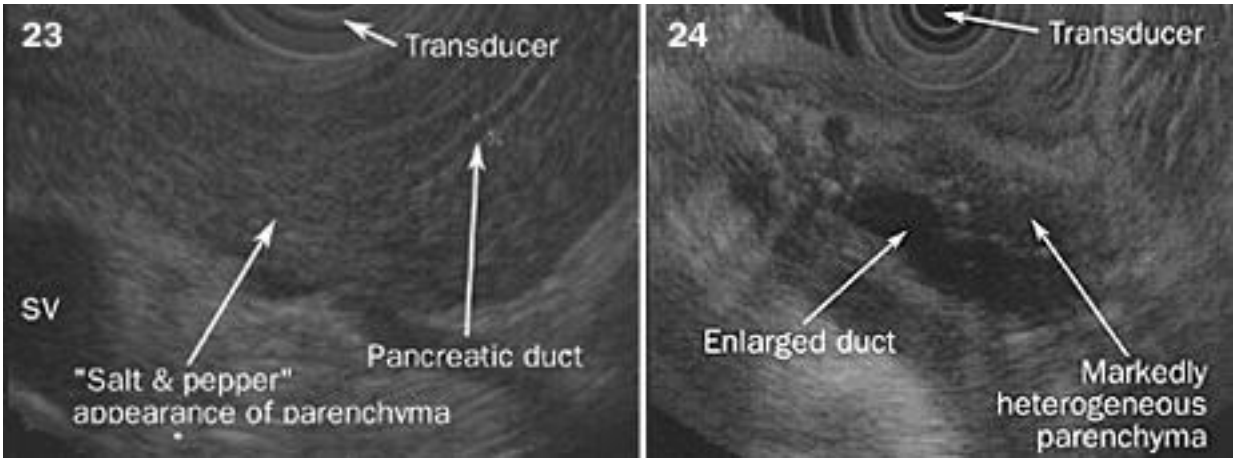


Endoscopic Ultrasonography (EUS)(34)

Endoscopic ultrasound is the diagnostic modality of choice to evaluate patients with early or mild chronic pancreatitis. EUS helps enables the clinician to assess the pancreatic parenchyma as well as the pancreatic duct. Parenchyma features include atrophy, hyperechoic foci, stranding, cysts and lobularity. The ducts are studied for narrowing, dilation, irregularity, calculi, side-branch dilation and hyperechoic walls.

EUS is considered superior to ERCP or MRCP for detection of early or mild changes of chronic pancreatitis as well as small duct involvement. EUS can also be used as a guide to fine needle aspiration of focal pancreatic lesions to differentiate inflammatory and malignant mass lesion. (35)

Parenchymal abnormalities	Hyperechoic foci Hyperechoic strands Lobularity of contour Cyst
Ductal abnormalities	Main duct dilatation Main duct irregularity Hyperechoic ductal walls Visible side branches Calcification



Sensitivity and specificity of Radiological and Endoscopic Investigation in Chronic Pancreatitis

Test	Sensitivity	Specificity
Plain x ray abdomen	-	-
ultrasound abdomen	-	-
CT abdomen	75-90	85
ERCP	75-90	90
MRCP	85	100

TREATMENT

The treatment of chronic pancreatitis is complex and often an interdisciplinary approach is indicated with the possibility of conservative medical, endoscopic and Surgical therapy.

Management options for chronic pancreatitis include medical, endoscopic and surgical treatments. Patients with chronic pancreatitis seek medical attention because they suffer from abdominal pain, weight loss or diabetes.

Treatment of Pain(36,37)

The pathophysiology of pain in chronic pancreatitis is incompletely understood. The proposed theories are ductal and mechanical mechanism, neuropathic, oxidative stress and central mechanism of pain. The management of pain in chronic pancreatitis is frustrating both for patients and clinicians. The following tables summarize the management of chronic pancreatitis.

Mechanisms of Pain in Chronic Pancreatitis and Management Options(38)

Proposed mechanism of pain	Management options
Duodenal Obstruction	Surgical bypass or endoscopic stent
Bile duct obstruction	Endoscopic stent or surgery
Pseudocyst	Endoscopic, surgical or percutaneous drainage
Pancreatic duct obstruction (stone or stricture)	Endoscopic or surgical ductal decompression
Tissue hypertension and ischemia	Antioxidants, endoscopic and surgical ductal decompression
Intra-pancreatic nerve injury	Celiac plexus block or neurolysis
Visceral nerve sensitization	Tricyclic antidepressants, SSRI, combined serotonin and norepinephrine re-uptake inhibitors
Central nerve sensitization	Tricyclic antidepressants, SSRI, combined serotonin and norepinephrine re-uptake inhibitors
Elevations in cholecystokinin	Non-enteric coated pancreatic enzymes

Options for Medical Management of Pain in Chronic Pancreatitis(36, 37)

Agent	Dose
Propoxyphene with acetaminophen	1 - 2 p.o. q.8h.
Tramadol (50 mg)	1 - 2 p.o. q.8h.
Antioxidants	A combination of 500 – 1000 mg of Vit C, 250-300 IU of Vit E, 500 – 800 ug of selenium, 2 g of methionine, 9000 – 10,000 IU of beta carotene per day in divided doses
Tricyclic antidepressants	Amitriptyline (start at 25 mg q.h.s.)
Pancreatic enzymes	Non enteric coated, protease content 25,000 – 50,000 USP with each meal Co- treatment with H2 blockers and PPI if needed to prevent degradation by gastric acid

Pancreatic exocrine enzyme supplemention :

When weight loss or steatorrhea (15g/day) or both develop supplementation is indicated. Enzyme supplementation is given so that good amounts of lipase reach duodenum along with the food. With the currently available pancreatic enzymes supplement preparation azotorrhea can be abolished, whereas steatorrhea can be reduced but not totally corrected. Side effects are rare except soreness of mouth, perianal irritation, abdominal pain, diarrhea, constipation, allergic reaction and fibrosing colonopathy in cystic firbrosis patiet. Dose of lipase: 2500 u lipase / kg body weight per meal.

Antioxidant therapy:(39)

There is significant pain relief with antioxidants in patients with alcoholic pancreatitis, and it leads to a significant decrease in oxidative stress in these patients supporting oxidative stress hypothesis. Antioxidant used was a combination of organic selenium, ascorbic acid, beta-carotene, tocopherol, methionine per day in divided doses. Antioxidants have emerged as effective therapy for CP.

Supportive measures in managing patients with chronic pancreatitis include diet and pain medications. The diet should be moderate fat (30%), high protein (24%) and low carbohydrate (40%) content. Patients with partial obstruction could benefit from addition of promotility agents.

Pancreatic Enzyme Replacement Therapy (PERT):

Pancreatic enzyme replacement therapy in chronic calcific pancreatitis is offered to all patients with symptoms. The dose is adjusted according to response .Starting with high dose 100,000 -150000 IU/day in divided dose taken along with food and stepped down to least possible dose to alleviate the symptoms . Proton -pump inhibitors should be given to every patient who is on PERT. The possibility of pancreatic decompression either endoscopically or surgically should be done in patients with intractable pain.

Endoscopic Treatment :

The aim is to relieve the pain and treat the complications associated with the disease. The advantage of endotherapy - high success rate and low morbidity. The various options according to the various scenario are described below

Endoscopic Pancreatic Sphincterotomy (EPS):

This is the only documented mode of therapy in patients with CP who have mild to moderate pancreatic duct changes even in the absence of ductal obstruction. There are two types pull type and needle knife sphincterotomy. These are done over a stent.Restenosis is less common following long incision of pull type sphincterotomy (40). Complications include pancreatitis, bleeding and perforation.(41)

Endoscopic Management of Pancreatic Duct Stricture

Stricture of the MPD and resultant upstream hypertension is one of the common cause for pain.Stricture could be due to inflammation or fibrosis.

MPD stricture is defined as high grade narrowing with one of the following

1) MPD dilatation >6mm beyond the stricture
2) Failure of contrast to flow alongside a 6 Fr nasopancreatic catheter
3) Presence of pain during continuous perfusion of the catheter with normal saline for 12- 24 hours.

Dilatation of tight stricture is carried out with teflon bougies or balloon dilator following a large bore stent .There is no definite protocol for stent diameter, duration or number of stent to be placed.

Endoscopic Treatment of Pancreatic Duct Stones

PDS are the end result of CP in up to 50% patients. Stones <5mm can be generally extracted with Dormia basket or balloon following EPS. Stones larger than >5mm are often impacted and difficult to extract, these stones need to be fragmented using ESWL before extraction. The aim of fragmentation is to break the calculi to fragments of 3mm or less. In select group of patients with large calculi, ESWL is a useful tool for fragmentation and this is followed by endotherapy helps in PD clearance and pain relief of pain.

Endoscopic Management of CBD Stricture Secondary to CP

Biliary drainage is indicated when the patient has jaundice, cholangitis. Biliary drainage is advised as it can lead to secondary biliary cirrhosis. The different types of stents used are plastic stents, self-expanding metal stents (SEMS)-uncovered, covered and partially covered.

Endoscopic Management of Pancreatic Duct Leaks

PD leaks occur as a result of blow out of the duct following obstruction by a stone or stricture. It could be partial or complete and leaks lead to fluid collection, pseudocyst, ascites or an external or internal fistula. Trans ampullary stent placement offers the best treatment as it converts the high pressure ductal system into a low pressure one with preferential flow across the stent.

Endoscopic Management of Pseudocyst

Treatment is reserved for symptomatic pseudocyst or those increasing in size. Smaller cyst can be followed up.Pseudocyst can be approached transmural or the transpapillary route. Complications include bleeding ,infection or leak with mortality around 0.5%. Endoscopic drainage of pseudocyst is the preferred first line of treatment with a good success rate.

Major limitations of endoscopic intervention are stent clogging, migration and cholangitis.

SURGERY :

The principle of surgery in CP is to achieve long lasting pain relief, treat local complications, preserve pancreatic function with improvement in quality of life. Several patients undergoing surgery may have more than one indication for surgery and the procedure must be tailored accordingly.

Indications for surgical intervention

1. Intractable pain.
2. Suspicion of malignant neoplasm.
3. Persistent bile duct and duodenal obstruction.
4. Vascular complications not controlled by radiology.
5. Left sided portal hypertension not controlled by endotherapy.
6. Pseudocyst not ammenable to endotherapy.

Two types of surgical intervention are available : drainage and resection procedure. “Hybrid operations” such as Freys, Izbicki operation and modification of Beger operation in an attempt to combine resection and drainage procedure.

Two less commonly performed operation are denervation and pancreatic autotransplantation.

Drainage procedure :

Rationale for drainage procedures

1. Decompressing the dilated, hypertensive ductal system
2. Reducing the intrapancreatic parenchymal pressure
3. Restoring pancreatic blood flow

Puestows drainage procedure reported good results with longitudinal decompression of body and tail by a Roux limb ensuring wider drainage .However these are all partial drainage procedures. Partington and Rochelle described a refined technique of Puestow procedure. It consists of a side to side long pancreaticojejunostomy, at least 10 cm without resection of the pancreatic tail.

Patient with a dominant mass in the head of the pancreas and a dilated pancreatic duct do not profit from a drainage procedure only. In addition to the drainage approach Beger and Izbicki proposed excavation of the head of the pancreas or the V shaped exacavation of the body along the main pancreatic duct followed by a pancreaticojejunostomy.

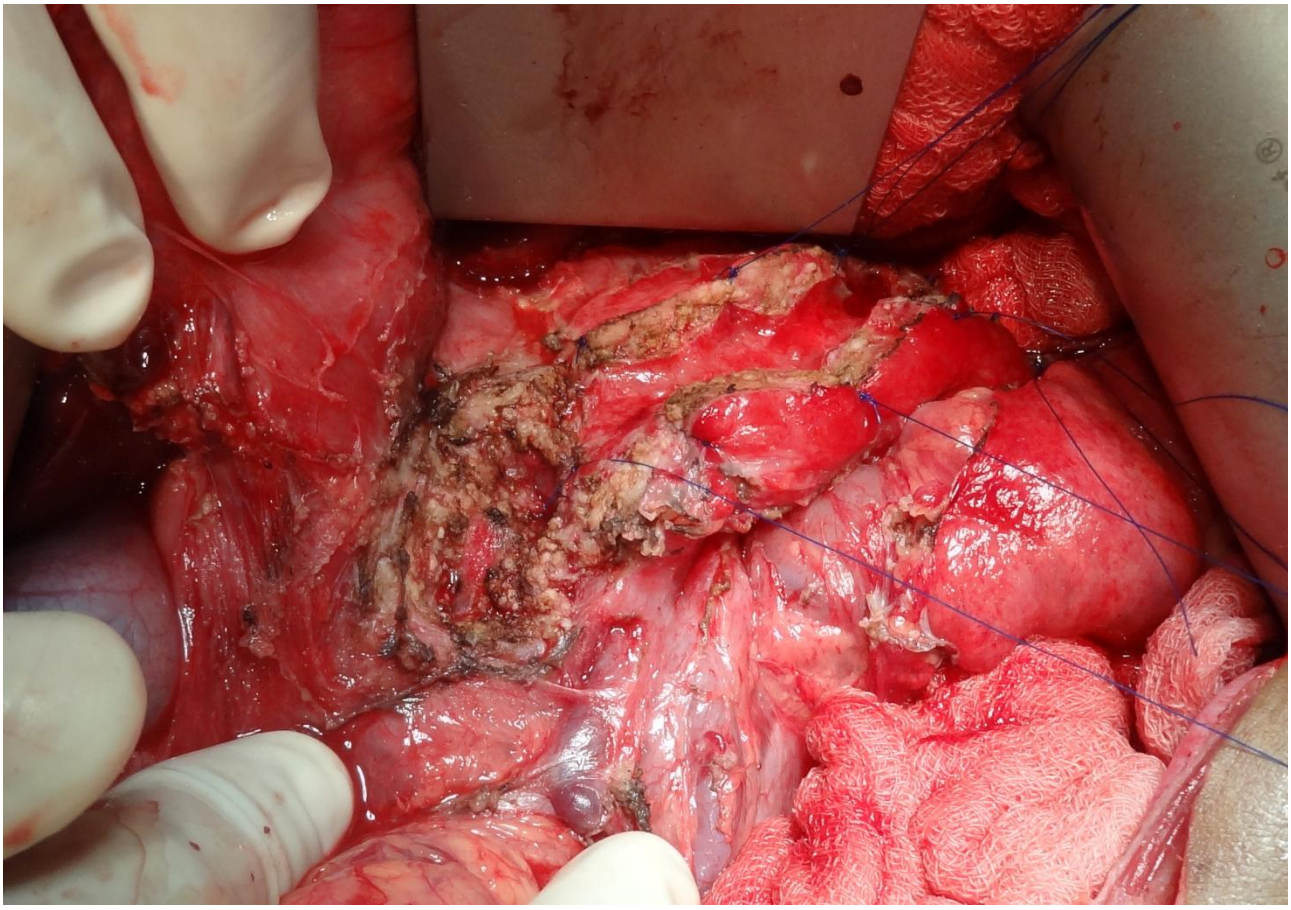
Resection procedures :

Whipple's procedure, Pylorus preserving pancreatico duodenectomy, Beger procedure, Berne modification of the Beger procedure (DPPHR) are the various resection procedure with merits and demerits. 30-50% patient of CP have pancreatic head enlargement. The head is considered the pace maker in CP and procedures which addressed the problem in the head have shown superior pain relief compared to duct drainage alone.

Beger's procedure (DPPHR) preserved the duodenum when compared to the whipples procedure, which was the standard procedure in patient with chronic pancreatitis for a long time. Patient who underwent Beger Procedure had greater weight gain, better glucose tolerance and high insulin secretion capacity. Improved pain status, lower frequency of acute episodes of chronic pancreatitis, rate need for further hospitilization, low early and late mortality rates and restoration of quality of life, DPPHR seems to be able to delay the natural course of the chronic pancreatitis.

Frey procedure which involve local pancreatic head excision. combined with longitudinal pancreaticojejunostomy can be considered as a standard procedure in chronic pancreatitis and has under gone evaluation in multiple trails, confirming its effectiveness as a surgical procedure for chronic pancreatitis.

Frey's Procedure



MATERIALS AND METHODS

Study Design

Prospective and observational analysis of patients with chronic pancreatitis admitted in PSG Hospital, Coimbatore, during the period Jan 2011 - June 2012.

Study Population

Study will be conducted in 30 patients with chronic pancreatitis admitted in PSG Hospital in general surgery and medical gastroenterology departments.

Ethical approval:

The study protocol was approved by the Institute Human Ethics Committee (IHEC) prior to the start of the study.

Inclusion Criteria

All chronic pancreatitis patient admitted in our hospital will be included in the study.

Exclusion Criteria:

1. Patient's with previous history of surgery for chronic pancreatitis.
2. Chronic pancreatitis in children.
3. Malignancy.
4. Patient who do not consent.

Diagnosis of chronic pancreatitis:

The diagnosis of chronic pancreatitis was made based on clinical setting and evidence of pancreatic duct dilatation, irregularity and/ or pancreatic calcification on imaging studies.

Work up

All patients underwent complete blood counts, biochemical investigations including liver function test, renal function, fasting blood sugar, serum calcium, lipid profile, serum amylase and lipase. The following imaging studies were done relevant to the individual patients

1. Transabdominal ultrasonography.
2. Contrast enhanced CT abdomen.
3. MRCP / EUS if indicated.

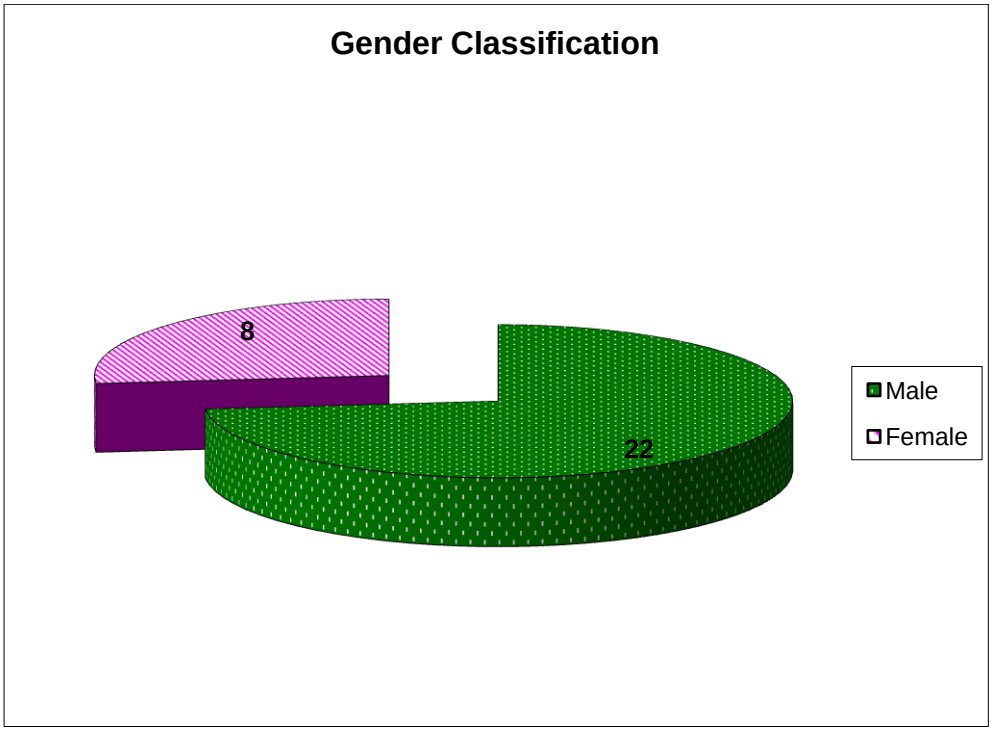
Complications of Chronic Pancreatitis like diabetes mellitus, steatorrhoea, bile duct obstruction, pseudocyst were diagnosed as per standard criteria either biochemically or imaging.

RESULTS

Males are affected more than female patients.

Gender Classification

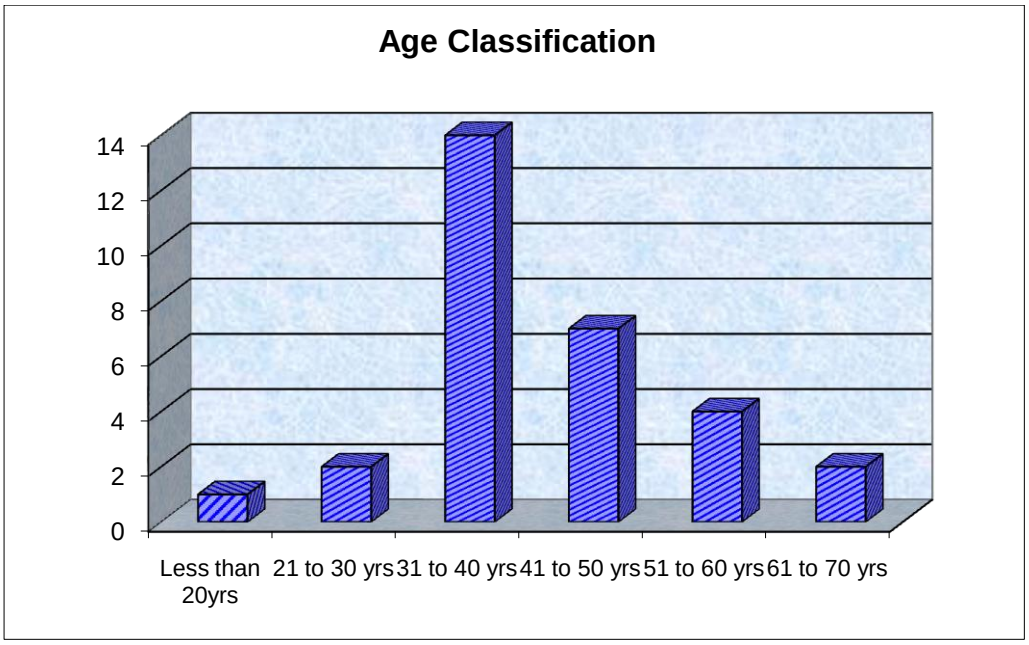
Gender	Frequency	Percent
Male	22	73.3
Female	8	26.7
Total	30	100.0



Age Classification

There were 30 patients included with the youngest being 18 years and oldest being 62 years male .Most patients presented in their 3rd decade of life.

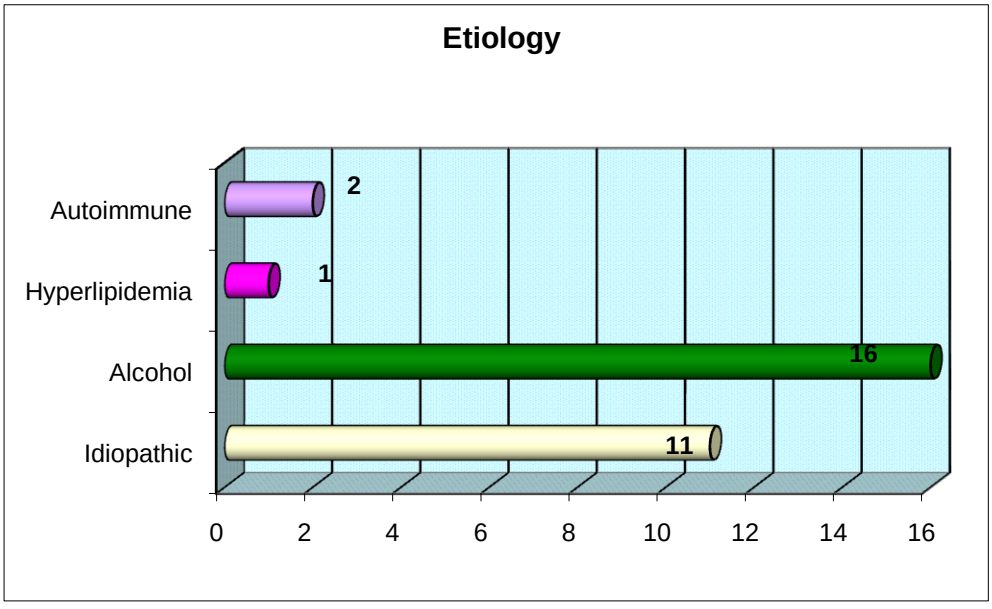
Age	Frequency	Percent
Less than 20yrs	1	3.3
21 to 30 yrs	2	6.7
31 to 40 yrs	14	46.7
41 to 50 yrs	7	23.3
51 to 60 yrs	4	13.3
61 to 70 yrs	2	6.7
Total	30	100.0



Etiology

The common etiological factor was alcohol followed by idiopathic pancreatitis.

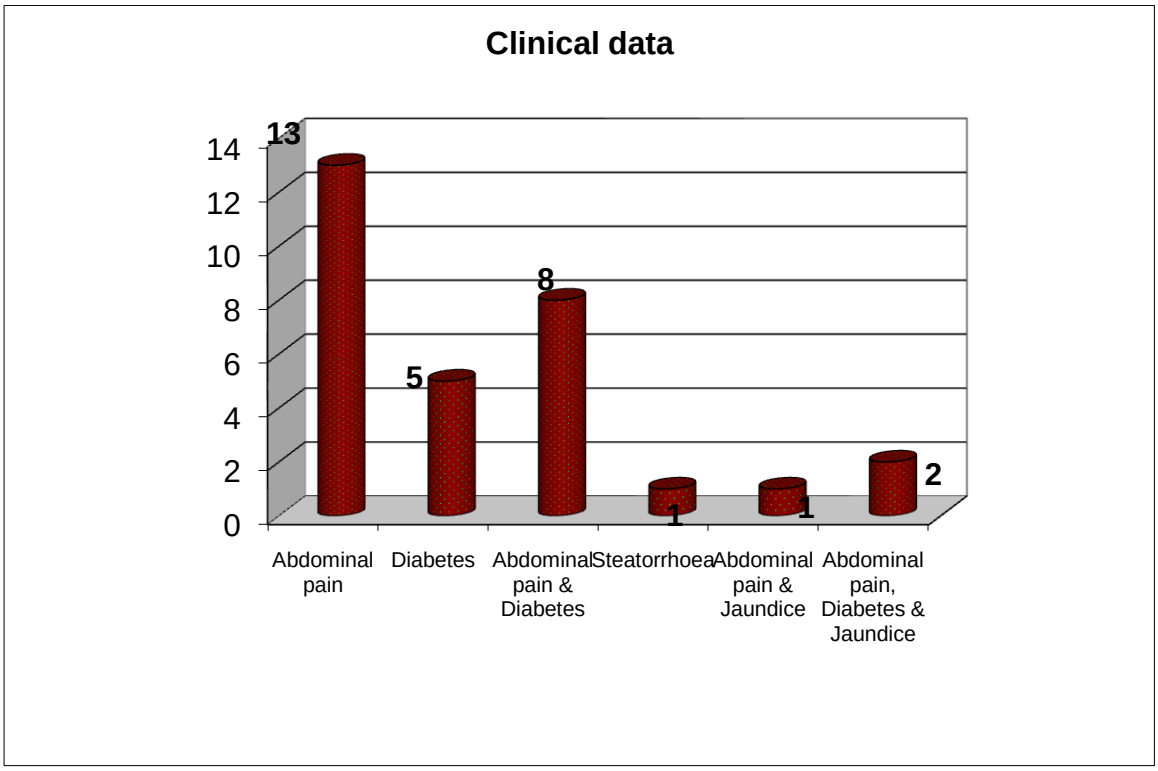
Etiology	Frequency	Percent
Idiopathic	11	36.7
Alcohol	16	53.3
Hyperlipidemia	1	3.3
Autoimmune	2	6.7
Total	30	100.0



Clinical Data

Nearly 24 /30 patients had pain as their clinical symptoms

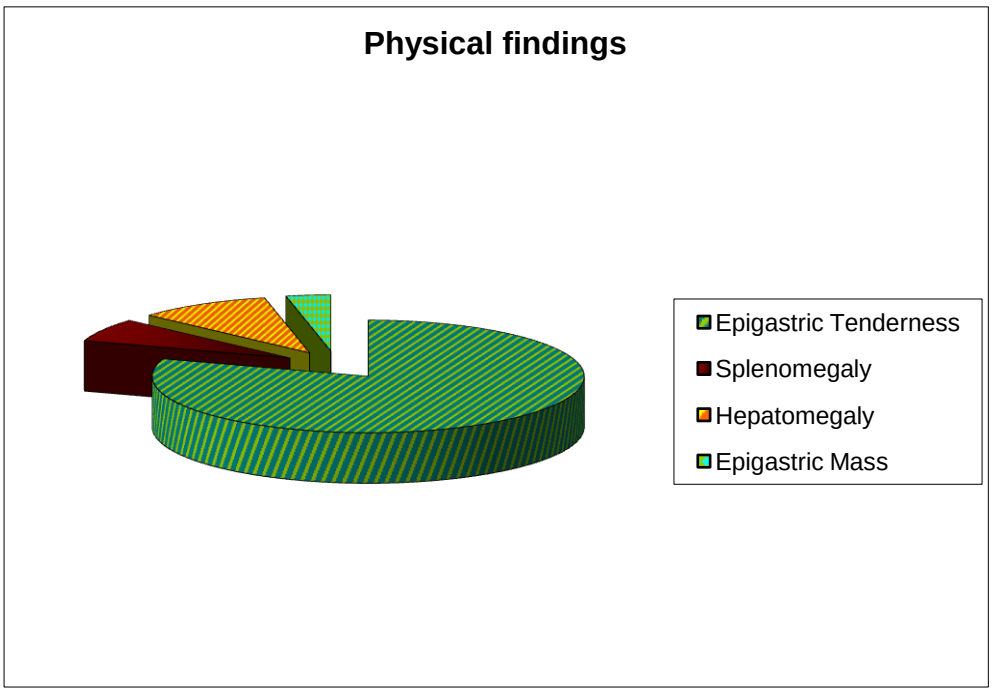
Clinical Data	Frequency	Percent
Abdominal pain	13	43.3
Diabetes	5	16.7
Abdominal pain & Diabetes	8	26.7
Steatorrhoea	1	3.3
Abdominal pain & Jaundice	1	3.3
Abdominal pain, Diabetes & Jaundice	2	6.7
Total	30	100.0



Physical findings

Most of the patient presented with epigastric tenderness 80%.

Physical findings	Frequency	Percent
Epigastric Tenderness	24	80.0
Splenomegaly	2	6.7
Hepatomegaly	3	10.0
Epigastric Mass	1	3.3
Total	30	100.0

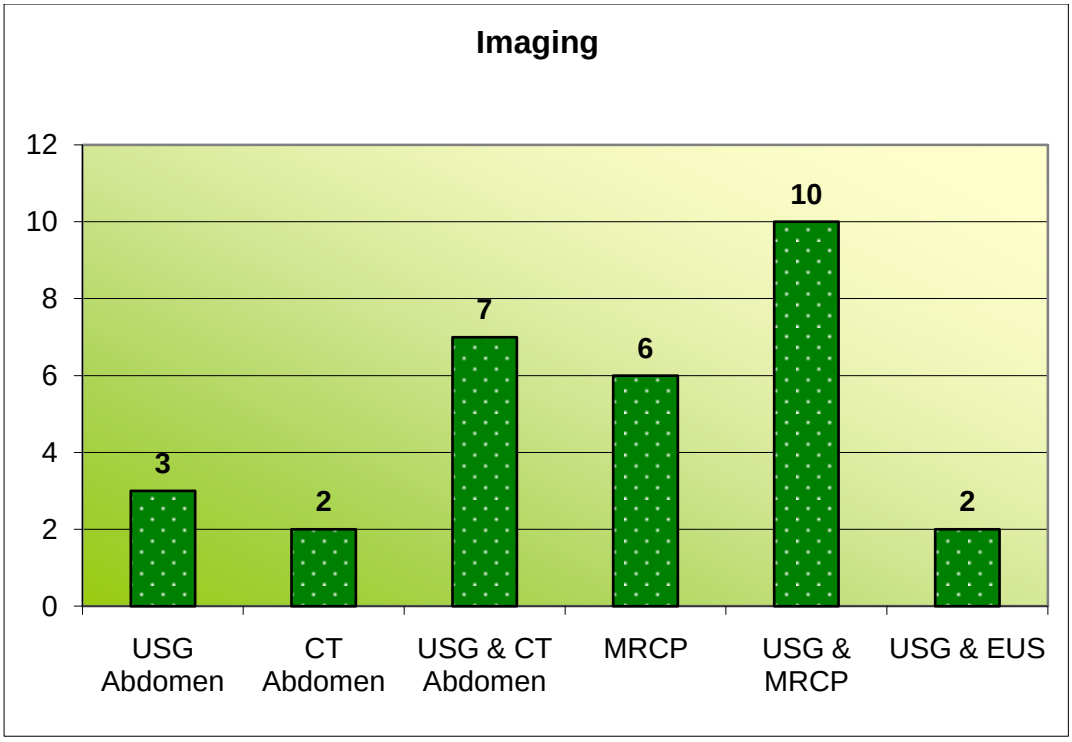


Imaging

Ultrasound and MRCP was the commonly done imaging.

Imaging	Frequency	Percent
USG Abdomen	3	10.0
CT Abdomen	2	6.7
USG & CT Abdomen	7	23.3
MRCP	6	20.0
USG & MRCP	10	33.3
USG & EUS	2	6.7
Total	30	100.0

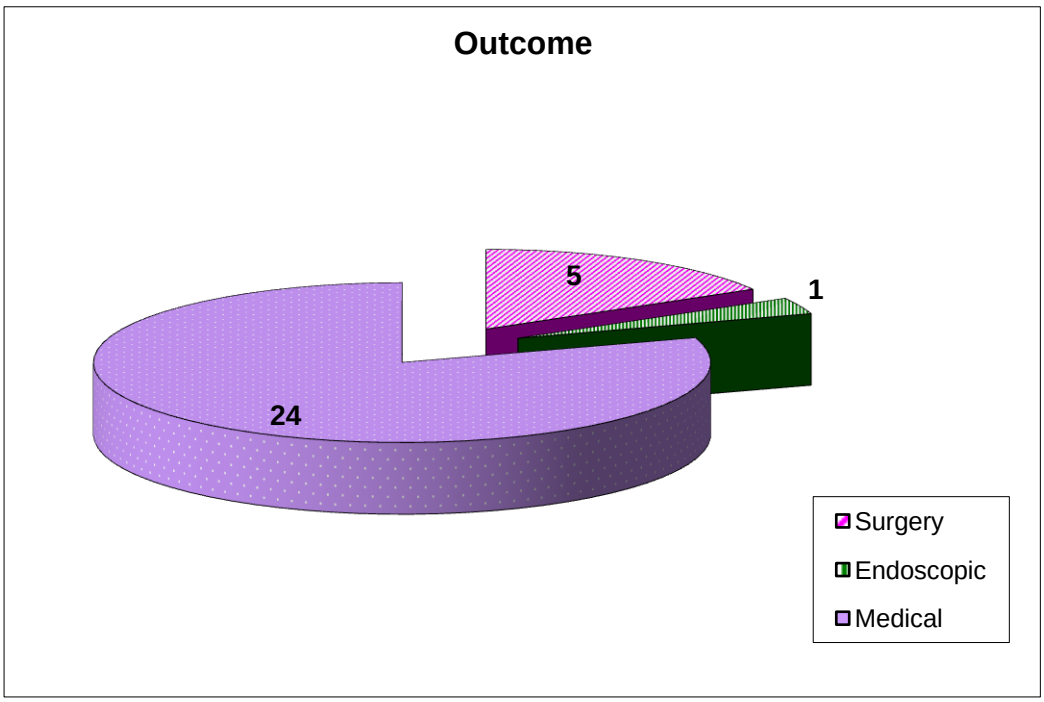
Imaging	Frequency	Percent
USG Abdomen	22	73.3%
CT Abdomen	9	30%
MRCP	16	53.3%
EUS	2	6.7%


Imaging
12
10
8
6
4
2
0
3
2
7
6
10
2
USG Abdomen
CT Abdomen
USG & CT Abdomen
MRCP
USG & MRCP
USG & EUS

Outcome

Medical management is the first line of treatment.

Outcome	Frequency	Percent
Surgery	5	16.7
Endoscopic	1	3.3
Medical	24	80.0
Total	30	100.0



DISCUSSION

The current study is a prospective analysis of 30 patients diagnosed to have chronic pancreatitis.

The mean age of CP in our study was 38.5 years,the youngest being 18 and oldest being 62 yrs.A study by Balakrishnan (42)et al showed mean age of patient was 32 years.

Majority of patients with idiopathic chronic pancreatitis (ICP) were young with mean age of 33.0 ± 13.0 years whereas patients with alcohol related chronic pancreatitis were significantly older than patients with ICP with the mean age of patients with alcohol induced chronic pancreatitis being 41.5 ± 9.9 years .

Majority of the patients in our study were male (73.3%).Data from prospective nationwide study from India showed male prepordance. Study by Balakrishnan(42)et al showed male to female ratio of 2:7:1. A study from Delhi and Lucknow showed majority of their patients with tropical pancreatitis were males.

In our study alcohol(53.3%) is the most common etiology followed by idiopathic(36.7%).Study in brazil observed 797 consecutive cases of chronic pancreatitis from 1963 to 1987 in the cities of Belo Horizonte and São Paulo. Alcoholism was the main etiological agent, responsible for 714 cases (89.6%). (43)

Pain was the common presentation in our study which was similar to other studies by Layer et al(44). Balakrishnan et al(42). Shallu midha et al(45) reported 97 % presented with pain which was almost similar to our data.

Diabetes was seen in 48% patient in our study which is different from study conducted by Geeverghese(46) and Tandon et al who in their study showed upto 90% of patients having diabetes. The study by Balakrishnan(42) et al showed higher incidents of diabetes upto 70%. The study from Lucknow reported diabetes in 26% of patients with idiopathic chronic pancreatitis. Midha et al(45) also reported 27% patients having diabetes in chronic idiopathic pancreatitis.

In our study 80% of patients presented with epigastric tenderness which is the same in a study done by Midha S et al (45) which has reported more than 90% present with epigastric tenderness.

Ultrasound was done in 22 patients in our study of which only 50-60% are diagnostic. Parenchymal calcifications are missed only the ductal calcification and the dilatation are picked up as well the complications .The ultrasound has a lower sensitivity in detecting pancreatic calcifications than computed tomography. Study from all India institute of medical science showed usefulness of ultrasonographic evaluation of calcific pancreatitis.

Ultrasound is first line imaging modality used in CP. It is simple, noninvasive, easy to perform. In routine clinical situation, USG is the easiest method to detect the complication of chronic pancreatitis and to follow patients with chronic pancreatitis. Use of ultrasound for diagnosing chronic pancreatitis is limited to advanced stage.

In our study CT was done in 9 patients (29%) with specificity of 80%.In our study 87.87% had parenchymal calcification 75% had ductal dilation and only 21% had ductal calculi.

CT is more sensitive in identifying ductal dilatation and calcification .CT is more sensitive when compared to USG abdomen. CT scan cannot detect early parenchymal changes and effects on small pancreatic ducts, but advanced stages and complications of the disease can be evaluated with high reliability. CT is most sensitive to detect calculi.

CT remains the best screening tool for detection of chronic pancreatitis and exclusion of other intra abdominal disorders that may cause symptoms indistinguishable from chronic pancreatitis on clinical grounds alone.

Charnley et al(47) have found that CT cannot detect early changes of chronic pancreatitis or define the degree of ductal abnormality, whereas MRCP is more specific for ductal abnormality .

MRCP was done in 16 patients (53%) with specificity of 100% in our study. In our study 6 patients had ductal calculi and the remaining had ductal dilatation and atrophy of the pancreas.

The advantage of this modality is noninvasiveness. MRCP is replacing ERCP as a non-invasive diagnostic modality with main pancreatic duct involvement. Calvo et al (48)have found it to be more than 85% sensitive and 100% specific in detecting abnormalities of the main pancreatic duct.

The incidence of Pancreatic Duct Stones (PDS) is less than 1% in normal population, while it is about 30% in CP patients(49). PDS can lead to the damages of pancreatic tissues and corresponding clinical symptoms(50-51). It was reported that 12%-22.2% of PDS patients finally develop pancreatic adenocarcinoma (52-53). Therefore, early diagnosis of PDS is of very important clinical significance.

Compared with other imaging techniques, MRCP is easy to perform and has no contraindication. It could provide detailed information about pancreatic duct and common bile duct. Therefore, MRCP is widely applied in the diagnosis of PDS.

MRCP was considered less sensitive in detection of side branch abnormality, which is a frequent finding in CP. It has also limited application in detection of milder forms of the disease. Secretin enhanced MRCP is more sensitive and specific to MRCP alone in detection of early CP. In conclusion, secretin injection-MRCP might allow an earlier diagnosis of chronic pancreatitis and reduce the rate of false-negative cases detected with MRCP.

ERCP is considered as a gold standard to diagnose early chronic pancreatitis. ERCP is, at present, the most sensitive diagnostic method for evaluation of early changes in the main pancreatic duct and its side branches. ERCP is considered invasive diagnostic modality and the risk for iatrogenic pancreatitis is more. MRCP may probably become a valid, noninvasive alternative to diagnostic ERCP in patients with mild pancreatic disease. ERCP is reserved for therapeutic purpose only.

ERCP is done in 1 patient as a therapeutic procedure for removal of small duct stones and placement of stent in Main Pancreatic Duct (MPD).

As the 5 patient who underwent surgery had large ductal calculi . In our setup as ESWL is not available, surgery is done for these patients.

Stones <5mm can generally be extracted with Dormia basket or balloon following Endoscopic Pancreatic Sphincterotomy(EPS).However , stones >5mm are often impacted and difficult to extract by these technique.

Tandan M, Reddy V,et al (54) showed patients with large pancreatic duct calculi in the head and body region with pain are subjected to fragmentation prior to expulsion using ESWL .Significant relief in pain score and decrease in analgesic requirement were seen in 84% of patients on short term follow up.

The outcome in our study, out of 30 patients 24 (80%)underwent medical management and only 5 (16%)underwent surgery.

Modified Puestow's is the most commonly performed surgical drainage procedure and has good results in pain relief post operatively.

In our study 4 patients underwent modified Puestow's as the patient had dilated pancreatic duct and stones, and one patient underwent head coring procedure (Frey's Procedure) as the patient had pancreatic head mass. Post operatively no patient had pancreatic leak and none developed endocrine insufficiency. Post-operative pain relief is 65%.

Frey et al (55) developed a modification of duodenum preserving pancreatic head resection which represents a hybrid technique between the Beger and Partington Rochelle procedure. In Frey's procedure rim of pancreatic tissue of entire head is preserved and is used to sew to the opened jejunum. Due to the safety and relative simplicity of the procedure compared to Beger's, Frey's procedure is widely accepted in India.

Management of CP is a multidisciplinary task .Medical management is the first line of treatment. If patient does not respond to medical treatment, patient is subjected to endoscopic / surgical treatment. Surgery is the last resort if patient does not respond both to medical and endotherapy.

CONCLUSION

In this prospective observational study conducted in 30 patients with chronic pancreatitis at PSG Hospital, Coimbatore, the following conclusions were made.

- Most of the patients in their 3rd decade of life.
- Male preponderance was observed in the ratio 2.7:1
- Most common etiological factor was alcohol followed by idiopathic .
- Pain abdomen and epigastric tenderness is the common presentation in our study.
- In our study MRCP was the commonly done imaging modality in diagnosing Chronic Pancreatitis as the morphologic changes in the glandular tissue, ductal anatomy, degree and level of pancreatic duct obstruction are well made out in comparison to CT. In our small study group it has been seen that MRCP scores over CT in diagnosis of CP having specificity of 100%.
- Though CT is less specific than MRCP in diagnosing CP, still it is a valuable radiological tool in diagnosing CP in centers where MRCP is not available.
- Efficacy of EUS can not be concluded in our study as it was done in only two patients.

- Medical management is the first line treatment in CP.
- Out of 30 patients, 5(16.7%)underwent surgery. Four out of five patients underwent modified Puestow's as this is the commonly performed surgery for chronic pancreatitis, one underwent head coring (Frey's Procedure).
- Post operatively pain relief was 65% in our study.
- None of the patient had pancreatic leak.

PROFORMA

1. Name :
2. Age :
3. Sex :
4. Clinical Data :
    - Abdominal pain
    - Diabetes
    - Steatorrhea
    - Loss of weight
    - Jaundice
5. Physical findings
    - Epigastric tenderness
    - Epigastric Mass
    - Hepatomegaly
    - Ascites
6. Investigations :
    - Blood – Sugar, Urea, Creatinine
    - Serum Amylase, lipase
    - Oral glucose tolerance test
    - Haemogram
    - Liver function test

7. Imaging
    - Plain X ray – abdomen
    - Ultra sound – abdomen
    - CT Scan – abdomen
    - MPCP
    - EUS
8. Treatment
    - Medical management
    - Endotherapy
    - Surgery

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