DISSERTATION

"A CLINICAL STUDY OF THE EFFICACY OF ULINASTATIN IN TREATMENT OF ACUTE PANCREATITIS"

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CERTIFICATE

This is to certify that, the dissertation entitled

"A CLINICAL STUDY OF THE EFFICACY OF ULINASTATIN IN TREATMENT OF ACUTE PANCREATITIS"

is the bonafide work done by **DR.K.SURENDAR**, during his **M.S. (General Surgery)** course **2017-2020**, done under my supervision and is submitted in partial fulfilment of the requirement for the M.S.(BRANCH-I)- General Surgery of The Tamilnadu Dr.MGR Medical University, May 2020 examination.

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DECLARATION

I, certainly declare that this dissertation titled **"A CLINICAL STUDY OF THE EFFICACY OF ULINASTATIN IN TREATMENT OF ACUTE PANCREATITIS"** represents a genuine work of mine. The contributions of any supervisors to the research are consistent with normal supervisory practice, and are acknowledged.

I also affirm that this bonafide work or part of this work was not submitted by me or any others for any award, degree or diploma to any other University board, either in India or abroad. This is submitted to The TamilNadu Dr. M.G.R Medical University, Chennai in partial fulfilment of the rules and regulations for the award of Master of Surgery Degree Branch I (General Surgery).

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As I walk down the memory lane I realize with a deep sense of humility that what I have done now would not have materialized, but for certain luminaries, who have enlightened my path to wisdom.

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LIST OF ABBREVATIONS

AP Acute Pancreatitis
UTI Ulinastatin
APFC Acute peripancreatic fluid collection
ANC Acute Necrotic collection
WON Walled off necrosis
DIP Drug induced pancreatitis
IAP Idiopathic acute pancreatitis
UTI Ulinastatin
ACS Abdominal compartment syndrome
CRP C-Reactive protein
PRL Procalcitonin
PSA Patient specific Analgesia
DIP Drug induced pancreatitis

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INTRODUCTION

- Acute pancreatitis is one of the most common condition seen in our emergency setup
- Inspite of maximum intensive care , the mortality rate and morbidity of Acute moderate and severe pancreatitis is high.
- Hence there is an urgent need for effective management of the condition requiring newer drugs like Ulinastatin in reducing morbidity and mortality of Acute Pancreatitis

AIMS AND OBJECTIVES

To compare the efficacy of ulinastatin in addition to standard treatment versus only standard treatment in subjects with moderately severe or severe acute pancreatitis

REVIEW OF LITERATURE

HISTORICAL ASPECT:

Pancreatitis is defined as an inflammation of glandular parenchyma leading to injury possibly irreversible destruction of pancreatic acini. The pathologic process results in self-limited disease with no sequelae or in catastrophic autodigestion with dangerous systemic cytotoxic effects and fatal life threatening complications in the acute severe form.

The definition & classification of pancreatitis into acute and chronic inflammation is defined by different pathologic, clinical, and etiogenetic factors.

MARSEILLE CONSENSUS MEETING(1963):

The effort to classify and define pancreatitis by experts led to the Marseille Consensus Meeting in 1963. The panel of pancreatologists agreed that acute and chronic pancreatitis were different form of diseases because of different morphologic features. Relapsing pancreatitis was defined by the presence of multiple episodes in a morphologic pattern of acute or chronic disease.

The characteristic features of the two diseases were the pathologic benign course of acute inflammation, with biological restitution in the acute condition & the progressively worsening parenchymal lesions in the chronic

condition .The histology-based classification cannot provide clinically useful definitions. From the clinical point of view, both acute & chronic pancreatitis had a similar pattern, in the early phases of the disease process.

MARSEILLE CALSSIFICATION OF PANCREATITIS:

Feature	Acute Pancreatitis/Acute Relapsing Pancreatitis
Clinical characteristics	Single/multiple episodes
Morphologic characteristics	Not defined
Course	Clinical and biologic restitution if the cause is removed

ATLANTA MEETING (1992)

In 1992, panel of pancreatologists in Atlanta proposed the classification system of acute pancreatitis , included both clinical and morphologic features of pancreatitis. It resulted in a classification system better able to characterise the individual patient and predict disease severity with its systemic responses.

ATLANTA CLASSIFICATION (1992)

Terminology	Definition	Clinical Manifestation	Pathology
Acute pancreatitis	Acute inflammatory process with involvement of other organs	Mild with minimal organ involvement; severe disease characterized by organ failure	Interstitial edema, intrapancreatic or extrapancreatic necrosis
Acute fluid collections	Occur early, lack a wall	30% to 50% in severe pancreatitis	Absence of well-defined wall
Pancreatic necrosis	Devitalized pancreatic parenchyma	Multiorgan failure	Extensive vessel, acinar cell, islet cell, and pancreatic duct damage
Postacute pseudocysts	Nonepithelialized collection of pancreatic juice	Main symptom pain; rarely palpable	Well-defined wall with clear, often sterile contents
Pancreatic abscess	Circumscribed intraabdominal collection of pus	If present, infection	Pus confined within a wall of granulation tissue

DEFINITION AND CLASSIFICATION OF PANCREATITIS IN THE MODERN ERA:

The classifications of pancreatitis in the last 30 years had provided crucial advances in the definition of the inflammatory processes of pancreatitis and formulating clinical strategies. But still there is need for definite clinical assessment of severity and more objective terms to describe the local complications. In 2012, two major contributions were published to address the remaining clinical questions. First, Atlanta Classification of 1992 was updated through an international consensus. In this revised Atlanta Classification, a new severity classification is proposed together with definition for diagnosing acute pancreatitis. Both interstitial and necrotizing pancreatitis are defined, as well as the individual local complications are included. Revised Atlanta Classification outlines the early and late phases of the disease, with the late phase typically limited to moderate or severe pancreatitis. Severe acute pancreatitis is defined solely by the presence of persistent organ failure, the main determinant of mortality.

In the same year of publication of the Revised Atlanta Classification, the determinant-based classification of acute pancreatitis severity was published by a multidisciplinary panel of experts. This classification used persistent organ failure & infectious peripancreatic necrosis

as determinants of mortality in acute pancreatitis, to classify patients into four categories. The rationale for this classification is that either event may occur at any stage of disease and hence two specific phases (early and late) are not defined.

REVISED ATLANTA CLASSIFICATION:

Mild acute pancreatitis	No organ failure No local or systemic complications
Moderately severe acute pancreatitis	Organ failure that resolves within 48 hr Local or systemic complications without persistent organ failure
Severe acute pancreatitis	Persistent organ failure >48 hr

DETERMINANT BASED CLASSIFICATION:

	Mild AP	Moderate AP	Severe AP	Critical AP
(Peri)pancreatic necrosis	No	Sterile	Infected	Infected
	And	And/or	Or	And
Organ Failure	No	Transient	Persistent	Peristent

ACUTE PANCREATITIS :

Acute pancreatitis (AP) is an acute inflammation of the pancreas causing injury or destruction of acinar components of pancreas. It is clinically characterized by severe abdominal pain especially in epigastric region and elevated blood levels of pancreatic enzymes mainly amylase and lipase. AP can vary from milder form to severe diease with potentially fatal complications. In Revised Atlanta classification, AP is classified into two main types: interstitial edematous pancreatitis & necrotizing pancreatitis. AP with its associated local or systemic complications is a major cause of morbidity and mortality world-wide, mortality ranges from approximately 1% to 20% in mild to severe cases.

ETIOLOGY AND PATHOGENESIS OF ACUTE PANCREATITIS:

Gallstones and alcohol abuse accounts for 60% to 80% of all AP cases. The frequency of each of these etiologies relies largely on the population being studied. In both the East and West, biliary pancreatitis is more common in women and alcoholic pancreatitis is more common in middle-aged men. About 10% of cases are caused by diverse causes, such as malignancy, hyperlipidemia, hypercalcemia, viral infection, drugs, and iatrogenic causes. 30% of AP cases are idiopathic.

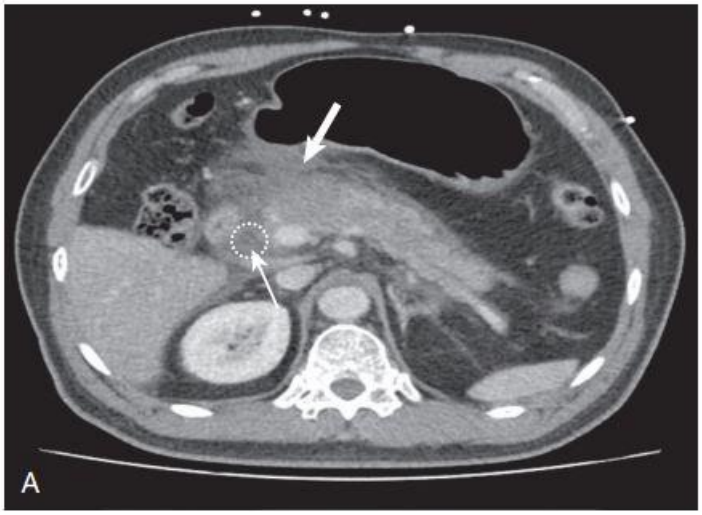
Acute Biliary Pancreatitis:

Migratory gallstones causes biliary pancreatitis in 4-8% of the cholelithiasis patients. The incidence of acute biliary pancreatitis is higher in female compared to male (69% vs 31%) increasing with age. The clinical presentation is similar to alcoholic pancreatitis, but endocrine and exocrine deficiencies are less likely in biliary pancreatits than in alcoholic patients, the pancreas appears histologically normal after complete clinical recovery.

Opie had observed that impacted gallstone at the papilla of Vater in two patients with severe pancreatitis in 1901. From there on, pathogenesis of biliary pancreatitis is extensively investigated which includes ampullary obstruction, bilio-pancreatic reflux, gallstone-related factors, and genetics. Ampullary obstruction by gallstones initiates, sustains and aggravates biliary pancreatitis. Acosta and Ledesma (1974) found gallstones in the stool of 94% of patients with biliary pancreatitis, compared with 8% of control subjects with gallstones without pancreatitis, prooving that the crucial event is probably not the impaction of a stone in the common bile duct (CBD), but the passage of a gallstone through the ampulla of Vater. Local edema or spasm of the ampulla might also lead to obstruction of the pancreatic duct. Transient obstruction will lead to increased pressures in the pancreatic duct, causing extravasation of pancreatic juice into interstitium and injury of the gland. Hypersecretion of pancreatic enzymes after a meal will increase the

pressure in an already obstructed duct from the migrating gallstone and intensifying the injury. Endoscopic sphincterotomy prevents the recurrent attacks of biliary pancreatitis correlating the causative role of transient obstruction by gallstones in pancreatitis. Factors contributing to the pathogenesis of biliary pancreatitis are that facilitate the passage of gallstones from the gallbladder into CBD and then through the ampulla. Small gallstone diameter (<5 mm), wide cystic duct (>5 mm) and high stone load (>20 gallstones) are risk factors for biliary pancreatitis. Other gallstone-associated features that increase the risk for development of biliary pancreatitis include mulberry shape and irregular surfaces.

The variations or mutations in the genes that encode pancreatic enzymes or their inhibitors have been suggested as potential risk factors for development of AP. SPINK1 encodes a potent inhibitor of trypsin activity within the pancreas, and mutations in SPINK1 are significantly higher in patients with AP. A mutation in ABCB4 gene, which encodes a multidrug resistance protein involved in the transport of phosphatidylcholine across the canalicular membrane of hepatocytes is also implicated in AP.



A, Cross-sectional (CT) image of acute biliary pancreatitis. Thin arrow, Small gallstones within common bile duct (circle); thick arrow, edematous head and neck of pancreas with peripancreatic fluid

Acute Alcoholic Pancreatitis

Alcoholic pancreatitis is more common in men, from tendency for males to drink more rather than a gender-based difference in susceptibility.The peak age for presentation of alcoholic pancreatitis : 40 to 60 years. Daily alcohol consumption on average in alcoholic pancreatitis : 100 to 150g/day.

The risk for pancreatitis tends to increase with greater doses of alcohol. But clinically evident pancreatitis develops in only a minority of heavy drinkers . These observations indicate that alcohol alone may not

cause pancreatitis unless accompanied by additional genetic and environmental factors. Alcohol sensitizes the pancreas, these additional genetic and environmental factors then initiate pancreatitis.

Alcohol tends to increases secretion of two nondigestive proteins, lithostathine and glycoprotein GP2 in the pancreas. They precipitate out within the ducts to form aggregates that enlarge and calcify to form intraductal calculi. These protein plugs and ductal calculi have the potential to facilitate disease progression. Typsinogen can be activated by cathepsin B within acinar cells, leading to a cascade of autodigestion characteristic of pancreatitis. The pancreas metabolizes alcohol via both oxidative and nonoxidative pathways, producing the toxic metabolites acetaldehyde and fatty acid ethyl esters (FAEEs). Oxidative alcohol metabolism generates reactive oxygen species (ROS) and depletes ROS scavenger glutathione. The products of alcohol oxidation (acetaldehyde and ROS) and nonoxidative metabolism of alcohol (FAEEs) causes acinar cell injury. Oxidant stress from the metabolism of alcohol causes destabilization of zymogen granules and lysosomes, resulting in pancreatic injury. FAEEs from nonoxidative metabolism of alcohol causes destabilization of lysosomes in acinar cells, thus increasing the potential for contact between lysosomal and digestive enzymes, leading to their intracellular activation and autodigestion of the gland. Environmental or genetic factors provide a second

hit for triggering clinical pancreatitis. Smoking is the most important environmental factor involved in triggering the pancreatitis. Bacterial endotoxemia - Lipopolysaccharide , an endotoxin found in the cell wall of gram-negative bacteria has a role in the initiation and progression of alcoholic pancreatitis.

Nonbiliary and Nonalcoholic Acute Pancreatitis:

In one quarter of cases, less frequently a myriad of etiological factors are implicated in causing non-biliary and non-alcoholic AP. Improved understanding of AP, with advances in genetics, molecular biology, and pathology, AP is often the result of complex interaction between host and environmental factors.

Metabolic Causes:

HYPERTRIGLYCERIDEMIA:

Hypertriglyceridemia accounts for 1% to 10 % of all AP cases. AP secondary to hypertriglyceridemia occurs in triglyceride levels >10 mmol/L fasting. This is confounded by the presence of other coexisting factors, such as poorly controlled diabetes mellitus, obesity, alcohol abuse, pregnancy, and hypothyroidism. It is associated with types I, IV, and V hyperlipidemia. Excess triglycerides are hydrolyzed by pancreatic lipase and released in the pancreatic microvasculature, results in high

concentrations of free fatty acids (FFAs), which overwhelms the binding capacity of albumin and self-aggregate to micellar structures with detergent properties. This in turn causes acinar cell and pancreatic capillary injury, resulting in ischemia and forms an acidic milieu that starts the vicious circle of triggering more FFA toxicity. Ischemia is exacerbated by the increased viscosity of blood from the elevated levels of chylomicrons. The injury to the acinar cells and microvasculature causes amplification of inflammatory mediators and free radicals, leading to necrosis, edema, and inflammation of the pancreas. Mild to moderate hypertriglyceridemia (< 5 mmol/L)seen in nearly half of patients in the early phase of AP. This is an epiphenomenon rather than a true precipitant because of the high prevalence of hypertriglyceridemia in the general population. Genetic predisposition to hypertriglyceridemic AP is also seen such as Lipoprotein lipase deficiency, mutations in cationic trypsinogen (PRSS1), serine protease inhibitor Kazal type 1 (SPINK1), cystic fibrosis transmembrane conductance regulator (CFTR), and tumor necrosis factor superfamily member 2 (TNF2) genes ,polymorphisms in CFTR and TNF genes.

HYPERCALCEMIA:

Hypercalcaemia is rare cause of AP with prevalence of 1% to 4%. Elevated parathyroid hormone and hypercalcemia cause calcium deposition in the pancreatic duct. Hypercalcemia-induced cellular injury

occurs by activation of pancreatic enzymes by a trypsin-mediated mechanism, causing acinar cell damage, pancreatic autodigestion, and pancreatitis. Another mechanism is the formation of pancreatic calculi by modifying pancreatic secretion lead to protein plug formation resulting in ductal obstruction. Acute hypercalcemia also increases the permeability of the pancreatic ductal membrane, allowing enzymes to leak and injure the pancreatic parenchyma. Hypercalcemia results from calcium infusion during total parenteral nutrition and occurs in patients with myeloma, leukemia, vitamin D poisoning, disseminated cancer, or severe hyperthyroidism have been associated with pancreatitis. Reciprocally, treatment of the hypercalcemia regardless of the cause resolve the AP.

INBORN ERRORS OF METABOLISM:

Acute pancreatitis is seen in a variety of inborn errors of metabolism which are rare but more common in neonatal and pediatric patients. These include familial disorders like hyperlipidemias,disorders of branched-chain amino acid degradation, homocystinuria, hemolytic disorders, acute intermittent porphyria, and several amino acid transporter defects, type I glycogen storage disease (von Gierke). The common physiobiochemical processes are hyperlipidemia, lactic acidosis, hypoglycemia, and hyperuricemia which could initiate pancreatitis.

Chronic Renal Failure and Dialysis-Related Causes:

Acute pancreatitis is seen in end-stage renal disease, including chronic renal failure and dialysis-related complications. The incidence of pancreatitis is higher in patients undergoing peritoneal dialysis (PD) than those receiving hemodialysis (HD). Toxic substances in PD dialysate, alterations in serum calcium and PTH levels, coexisting bacterial and viral infections can initiate AP.

Drug-Induced and Toxin-Induced Pancreatitis:

Drug-induced pancreatitis (DIP) - incidence of 0.1% to 2% of AP cases. Prompt withdrawal of the offending agent and supportive care is necessary. Accumulation of a toxic metabolite/intermediary and hypersensitivity reactions cause immune-mediated injuries and pancreatic duct constriction, localized angioedema effect in the pancreas, and arteriolar thrombosis. Angiotensin-converting enzyme (ACE) inhibitors, antidiabetic agents, statins, 5-ASA and derivatives, antibiotics and valproic acid are the common offending drugs.

Toxins can also cause AP. The toxins include scorpion's venom, organophosphate anticholinesterase insecticides, organic solvents, pentachlorophenol and diethylglycol.

Infectious Causes:

BACTERIAL CAUSES:

Pancreatitis can be caused by bacteria through hematogenous, lymphatic seeding or ascending infection of the pancreatic duct from the biliary tree or the gastrointestinal tract. Mycoplasma pneumoniae has been implicated as a cause of pancreatitis from antibody detection.Other pathogenic bacteria, such as Leptospira interrogans, Campylobacter jejuni, Salmonella typhi, Brucella, Yersinia enterocolitica, Y. pseudotuberculosis, Legionella, Nocardia, Mycobacterium tuberculosis, and M. avium as causes of sporadic cases of pancreatitis.

VIRAL CAUSES:

Viruses is the first and largest group of infectious agents associated with AP. Diagnosis is based on detection of antiviral antibodies coupled with the clinical diagnosis of pancreatitis after exclusion of the common causes. Mumps (single-stranded DNA paramyxovirus) was implicated as a cause of AP in 1905, by Lemoine and Lapasset . AP is a complication in the course of fulminant liver failures. Hepatitis B is the hepatitis virus most implicated in AP. In HIV patients, coexisting conditions such as alcohol use, biliary disease, and malignancies associated with acquired immunodeficiency syndrome (AIDS) (e.g.,Kaposi sarcoma, lymphoma) in HIV/AIDS patients; the use of

antiretroviral and other medications in their treatment (e.g., corticosteroids, ketoconazole, sulfonamides, pentamidine, metronidazole, isoniazid) and opportunistic infections (e.g., mycobacteria, cytomegalovirus, herpes simplex, cryptosporidiosis) all can contribute to the pathogenesis of AP. Other viruses to cause AP include coxsackievirus type B, cytomegalovirus, varicella-zoster, and herpes simplex.

FUNGAL AND PARASITIC CAUSES:

Fungal and parasitic infestation - rare cause of AP. The fungus Aspergillus , parasite - Ascaris lumbricoides (nematode) . It is common in in developing countries and endemic in tropical countries (20%-82% of the population) .AP is triggered by the obstruction of the pancreatic duct, in pediatric patients, in whom the duct is much narrower relative to the parasite.

Iatrogenic or Traumatic Pancreatitis:

Post–endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP) is the most feared and common iatrogenic cause of AP, occurring in approximately 1% to 3% of patients undergoing diagnostic ERCP, 2% to 5% receiving therapeutic ERCP. PEP is defined as new or increased abdominal pain that is clinically consistent with AP and associated pancreatic enzyme elevation, at least three times the upper normal limit within

24 hours after the procedure and resulting hospitalization of 2 nights or more.

Traumatic pancreatitis:

Patients with pancreatic trauma are seen usually with a triad of abdominal pain, leukocytosis, and elevated serum amylase levels. Both blunt and penetrating trauma can injure the pancreas. It occurs in less than 2% of blunt trauma cases but in 12% to 30% of penetrating trauma caused by gunshot or stab wounds. The damage can be mild to very severe, from a contusion to a severe crush injury or transection of the gland, particularly where the pancreas crosses over the spine, resulting in pancreatic ascites and acute duct rupture. Healing of pancreatic ductal injuries can lead to scarring and stricture of the main pancreatic duct, with resultant obstructive pancreatitis proximally.

Autoimmune Pancreatitis:

Autoimmune pancreatitis (AIP) is a rare but distinct disorder that has a dramatic response to corticosteroid treatment . Radiologically, AIP is characterized by segmental, diffuse, or irregular narrowing of the main pancreatic duct and diffuse enlargement of the pancreas, elevated levels of serum immunoglobulin G (>twice the upper limit of IgG, particularly of the IgG4 subtype), the presence of autoantibodies, and histopathologically by

lymphoplasmacytic infiltration and fibrosis. AIP is subdivided into type 1 (lymphoplasmacytic sclerosing pancreatitis, LPSP) and type 2 (idiopathic duct-centric pancreatitis, IDCP). Cardinal features includes imaging of pancreatic parenchyma and duct, serology, extra -pancreatic involvement, histology, and an optional criterion of response to corticosteroid therapy.

Anatomic or Congenital Causes:

Anatomic variants or congenital anomalies can lead to AP. Pancreas divisum (PD) is the most common congenital variation of pancreatic ductal anatomy, occurring in as many as 7% to 12% of individuals. The failure of the derived ventral and dorsal pancreas to fuse embryologically results in separate ductal systems. Partial fusion results in the incomplete PD, and the dorsal duct drains through the major papillae via the ventral duct. This communication is generally narrow and may be inadequate for drainage. The inability of minor papillae to accommodate the flow when the pancreas is stimulated or over time leads to relative obstruction and ductal hypertension, causing injury leading to pancreatitis. Annular pancreas is another rare anatomic condition resulting in the entrapment of both the CBD and duodenum by the annular growth of the pancreas. or the PD. The sphincter of Oddi (SO) is a complex of smooth muscle surrounding the terminal CBD, main pancreatic duct, and common channel. Sphincter of Oddi dysfunction (SOD) refers to the abnormality of SO contractility that can

manifest clinically as pain, pancreatitis, or deranged liver function tests. Anomalous pancreaticobiliary duct junction (APBJ) results in pancreatic reflux in the biliary tree. Reflux of bile into the pancreas seldom occurs because of the higher pressure in the pancreatic duct compared to the bile duct.

Tumors:

Pancreatitis can be the first presentation of pancreaticobiliary and periampullary tumors. This should be considered in patients with the index pancreatitis episode who are older than 40 years, with constitutional symptoms such as loss of weight and appetite or new onset of diabetes. The most common pathology associated with pancreatitis are IPMN , mucinous cystic neoplasms, ampullary tumors, islet cell tumors, and pancreatic adenocarcinoma.

Genetic Causes:

There is culminating evidence for a genetic basis for pancreatitis. This was led by the discovery that gain-of-function mutations in trypsinogen lead to hereditary pancreatitis. These include SPINK1 , CFTR, PRSS1, anionic trypsinogen (PRSS2), MCP-1-2518 G allele, calcium-sensing receptor (CASR) and chymotrypsinogen C (CTRC) . Patients with these mutations are at increased risk of pancreatitis caused by hypercalcemia and hyperlipidemia.

Idiopathic Acute Pancreatitis:

The cause for AP is unidentifiable in 30% of patients, conventionally classified as having idiopathic acute pancreatitis (IAP) . Idiopathic acute recurrent pancreatitis (IARP) is defined when patients have more than one episode of IAP. Evaluation of IAP/IARP is prudent because most untreated patients with IARP experience recurrent episodes that result in chronic pancreatitis . Many of these IAP/IARP cases are caused by genetic mutations or drugs/toxins.

ASSESSMENT OF ACUTE PANCREATITIS

Diagnostic Assessment

The diagnosis of AP is based on the clinical presentation of the patient supported by serum levels of amylase and lipase. History should focus on common causes, such as gallstones and heavy alcohol intake. AP is characterized by acute and constant pain localized in the epigastrium or right upper quadrant that radiates to the back . The pain typically lasts for several days and associated with nausea and vomiting. However, in metabolic causes or alcohol abuse, pain may be poorly localized and less acute. Physical signs depend on the severity of pancreatitis. In mild pancreatitis, abdominal examination usually reveals upper abdominal tenderness without features of peritonitis. In severe cases, pancreatitis may mimic other causes of acute

abdominal emergencies. Severe pancreatitis with necrosis may result in exudates tracking along the falciform ligament and retroperitoneum, resulting in Cullen and Grey Turner signs. Serum levels of amylase and lipase are obtained for the diagnosis of AP. An elevation exceeding three times the normal upper limit of serum amylase or lipase supports the diagnosis of pancreatitis. Serum amylase concentrations generally rise within a few hours after symptom onset and return to normal within approximately 5 days. It is important to note that amylase levels may not be elevated in as many as 19% of AP patients on admission. Furthermore, amylase levels may also be elevated in the absence of pancreatitis in patients with renal impairment, salivary gland diseases, and other extrapancreatic abdominal conditions (e.g., acute appendicitis, perforated viscus, intestinal obstruction, mesenteric ischemia). Serum lipase levels have the added advantage of remaining elevated during a longer period and have a higher specificity versus amylase. Other laboratory tests, such as trypsinogen activation peptide and trypsinogen-2 levels, have been shown to be more specific. Occasionally, diagnosis of AP based on the clinical presentation and biochemical investigations alone may be difficult. In these patients, cross-sectional imaging scans such as ultrasound, contrast-enhanced computed tomography (CT), or magnetic resonance imaging (MRI) should be performed on admission to confirm the diagnosis and exclude other abdominal conditions . **CT scan has sensitivity of 87% to 90% and specificity of 90% to 92% for detecting pancreatitis**. Imaging

may also identify the cause of pancreatitis and its associated complications.

Definition and Classification of Severity of Acute Pancreatitis

Most episodes of AP have a mild and self-limiting course . However, approximately 20% of cases may progress to severe pancreatitis, resulting in major local and systemic complications with a significant risk of mortality. In the clinical setting, early identification of patients on admission allows for aggressive treatment. Targeted therapy such as enteral feeding, endoscopic sphincterotomy, or antibiotics may be initiated at the appropriate time in select patients .

The first classification system for pancreatitis was established in Marseille in 1965. Since then, the standard tool for defining severe pancreatitis has been the Atlanta classification(1992). This was based on clinical, radiologic, pathologic findings and categorized pancreatitis into mild interstitial and severe necrotizing pancreatitis. The main drawback is that no distinction was made between predicted (based on Ranson and APACHE II criteria) and actual (based on organ failure) severity for severe AP. The initial Atlanta classification also failed to recognize that the number of organs failing and the duration of organ failure which were important prognosticators for AP. As a result of the better understanding of the pathophysiology and outcomes of necrotizing pancreatitis and organ failure, the

Atlanta classification was revised in 2012 based on an international Internet-based consensus .The updated classification defined three degrees of severity for AP instead of two and recognized that pancreatitis is an evolving, dynamic condition and that disease severity may change during the course of disease. Another important revision included the definitions for pancreatic and peripancreatic collections and the distinction between collections composed of fluid versus those arising from necrosis, containing solid components. Parallel to the development of the revised Atlanta classification, the determinant-based classification (DBC) was developed based on a large international survey (2012). In this system, pancreatitis was stratified into four degrees of severity: mild, moderate, severe, and critical . The DBC was based on two main principles to overcome the limitations of the original Atlanta criteria. First, it was based on actual factors of severity, such as necrosis and organ failure, rather than predictive factors of severity, such as the APACHE II and Ranson criteria. Second, the factors of severity used in this system had a direct causal association with severity. Patients classified as mild, moderate, severe, and critical had mortality rates of 0%, 3.6%, 33.8%, and 87.5%, respectively.

Clinical Assessment:

Prediction of the likely course and outcome of AP is of utmost importance when the patient with pancreatitis is admitted to the hospital. However, this

can be challenging, even for experienced clinicians. In the vast majority (75%-80%) of patients, AP is a mild disease with a benign course and without associated mortality. However, the main challenge is to identify patients who are most likely to progress to severe pancreatitis and experience major complications. These patients could potentially benefit from early intensive care monitoring and treatment. In addition to the initial clinical assessment, several prognostic criteria have been developed to aid the clinician in predicting the clinical course of pancreatitis. These prognostic criteria include severity scoring systems based on clinical parameters and laboratory results (e.g., Ranson criteria), radiology-based criteria (e.g., Balthazar score), and single biomarkers (e.g., CRP). Mortality from AP follows a biphasic distribution. Early death is usually from the development of severe and irreversible multiorgan dysfunction, whereas late death occurs in the latter phase of the illness, with organ failure the end result of sepsis and its sequelae. Persistent or deteriorating multiorgan dysfunction in the first 7 days after admission is the most significant predictor of death.

Scoring Systems for Assessing Severity of Pancreatitis:

Since the 1970s, several scoring systems have been devised to predict the clinical course of AP. Early prediction of severe disease is important to identify patients who are at greater risk of subsequent severe morbidity and mortality. The first, most widely used scoring system was the Ranson criteria.

The Ranson criteria were formulated based on the identification of 11 significant prognostic factors from 43 clinical and laboratory variables assessed in 100 acute episodes of pancreatitis. The main limitations associated with the Ranson criteria were that prognostication was only complete after 48 hours and that it only functioned accurately at the extremes of the scale (less than three criteria predicted survival, and more than three predicted death) and less well at intermediate scores.. In Japan the Japanese Severity Score (JSS) is used to predict severity and mortality from AP.

Currently, the Acute Physiology and Chronic Health Evaluation (APACHE II) system together with the Ranson criteria remain two of the most commonly used systems for the risk assessment of AP. It is a complex, physiologically based classification system based on the most abnormal values of 34 variables, taking into account the patient's baseline health status. The APACHE system was simplified to the APACHE II scoring system, based on 12 physiologic variables, age, and five organ-based chronic health points. The APACHE II system has determination of disease severity on admission,recalculation and assessment of disease progression. A new scoring system termed the Bedside Index for Severity in Acute Pancreatitis (BISAP) was proposed as simple and accurate method for the early (<24 hours of admission) identification of patients at risk of mortality. Regular clinical review and timely intervention remains the mainstay of treatment

in AP. It is interesting to note that only the 2015 Japanese guidelines recommend the use of scoring systems in the assessment of pancreatitis (JSS).

Scoring Systems	Year	Parameters*
Ranson	1974	At admission: age (>55 yr), WBC (>16,000/mL), glucose (>200 mg/dL), LDH (>350 IU/mL), AST (>250 IU/mL) At 48 hours: hematocrit (decrease >10%), BUN (increase >5 mg/dL), calcium (>8 mg/dL), Pa_{O_2} (>60 mm Hg), base deficit (>4 mEq/L), fluid sequestration (>6 L)
Glasgow	1984	Age (>55 yr), WBC (>15,000/mL), glucose (>180 mg/dL), BUN (>45 mg/dL), Pa_{O_2} (<60 mm Hg), calcium (<8 g/dL), albumin (<3.2 g/dL), LDH (>600 IU/L)
APACHE II Acute Physiology and Chronic Health Evaluation	1989	Temperature, MAP, heart rate, respiratory rate, Pa_{O_2}, arterial pH, bicarbonate, sodium, potassium, creatinine, hematocrit, WBC, GCS score, age, chronic health points
SOFA Sepsis-related Organ Failure Assessment	1996	MAP, Pa_{O_2}/Fi_{O_2}, creatinine, GCS, platelet count, bilirubin Score: 1-5, based on severity of each parameter
SIRS Systemic inflammatory response syndrome	2006	Temperature (<36° C or >38° C), heart rate (>90/min), respiratory rate (>20/min) or Pa_{CO_2} (<32 mm Hg), WBC (<4000/mm^3, >12,000/mm^3, or >10% bands)
POP Pancreatitis Outcome Prediction score	2007	Age, MAP, Pa_{O_2}/Fi_{O_2}, arterial pH, BUN, calcium (these scores use normal ranges)
PANC 3	2007	Hematocrit (>44 mg/dL), body masss index (>30 kg/m^2), pleural effusion
BISAP Bedside Index for Severity in Acute Pancreatitis	2008	BUN (>25 mg/dL), impaired mental status (GCS score <15), SIRS (>2), age (>60 yr), pleural effusion
Haps Harmless Acute Pancreatitis Score	2009	Abdominal tenderness, hematocrit (>43 mg/dL for men or >39.6 mg/dL for women), creatinine (>2 mg/dL)
JSS Japanese Severity Score	2009	Base excess (≤3 mEq/L), Pa_{O_2} (≤60 mm Hg or respiratory failure), BUN (≥40 mg/dL) or creatinine (≥2 mg/dL), LDH (≥2× upper limit of normal), platelet (≤100,000/mm^3), calcium (≤7.5 mg/dL), C-reactive protein (≥15mg/dL), SIRS (≥3), age (≥70 yr)

Laboratory Assessment:

Single-Parameter Biochemical Markers:

C-REACTIVE PROTEIN:

C-reactive protein (CRP) is an acute-phase protein predominantly synthesized in the liver in response to various infective and noninfectious stimuli, resulting in elevated serum levels . Because of its easy availability in clinical

practice, CRP has been used widely to distinguish mild from severe AP and, at a cutoff level of 150 mg/L, has been shown to have a diagnostic accuracy of 70% to 80% when measured within the first 48 hours of disease onset. Presently, CRP is frequently considered the "gold standard" single biochemical marker for the risk stratification of AP and is used as the comparison when assessing new potential biomarkers . A major limitation of CRP is the relatively long delay in achieving peak systematic values at 72 to 96 hours after onset of disease, making very early assessment of severity impossible.

HEMATOCRIT:

The hematocrit value has been shown to be a prognostic marker for the severity of AP. Its prognostic significance emphasizes the pathophysiologic role of fluid loss in the severity of pancreatitis and the role of vigorous fluid replacement in the course of disease. A hematocrit of more than 44% on admission or the absence of a fall in hematocrit during the first 24 hours after admission was found to be a clear risk factor for pancreatic necrosis, organ failure, or pancreatic infection. Hematocrit greater than 50% has also been shown to predict severe pancreatitis.

PROCALCITONIN:

Procalcitonin (PCT) has been widely used as a biomarker of bacterial infection or sepsis. At a cutoff level of 1.8 ng/mL, PCT was able

to predict the development of infected necrosis in patients with pancreatitis with sensitivity and specificity of more than 90%. PCT was able to predict serious complications such as pancreatic infections and death with a sensitivity of 79% and specificity of 93% at a cutoff level greater than 3.8 ng/mL within 48 to 96 hours from symptom onset . Sensitivity and specificity of PCT for thedevelopment of severe AP was 72% and 86%, respectively. The sensitivity and specificity of PCT for prediction of infected pancreatic necrosis were 80% and 91%.

Imaging Assessment:

Computed Tomography:

The two main indications of cross-sectional imaging in AP: Confirmation of the diagnosis in cases of diagnostic uncertainty , prognostication and detection of complications in AP. Dynamic contrast-enhanced CT scan is the imaging modality of choice for staging AP and for detecting complications. CT can detect pancreatic necrosis with a sensitivity of 87% . Interstitial edema and fluid collections can be recognized in early-phase inflammation on CT. Pseudocysts, acute necrotic collections, and walled-off pancreatic necrosis may develop when the disease progresses. The morphologic changes in AP form the basis for current radiologic scoring systems. CT scoring systems can be stratified into two groups. Unenhanced CT scoring systems - Balthazar grade and pancreatic size index (PSI) evaluate the extent of

pancreatic and peripancreatic inflammatory changes whereas “mesenteric edema and peritoneal fluid” (MOP) score, extrapancreatic score (EP), and extrapancreatic inflammation on CT (EPIC) score evaluate peripancreatic inflammatory changes and extrapancreatic complications. Contrast-enhanced CT scores evaluate the presence and extent of necrosis, including the CT severity index (CTSI) and the modified CT severity index (MCTSI). Based on the CTSI, the severity of AP is classified into five grades (0-4) on unenhanced CT, whereas the degree of necrosis is measured and given a score of 0 to 6. The sum of these two scores is used to calculate the CTSI, and a score of 7 or greater has been shown to be predictive of high morbidity and mortality . CTSI of 3 or less correlated with a mortality of 3%, versus 92% with CTSI greater than 7. Modified CTSI was subsequently proposed, which took into account extrapancreatic complications such as pleural effusion and vascular complications. In 2007, De Waele and colleagues proposed a CT score based on factors in extra -pancreatic inflammation, such as ascites, pleural effusion, retroperitoneal inflammation, or mesenteric inflammation, termed “extrapancreatic inflammation on CT score” (EPIC). The authors demonstrated that with a score of 4 or greater within the first 24 hours, EPIC could predict severe AP and mortality with 100% sensitivity and 71% specificity . This system also has the added advantage of not requiring the use of contrast-enhanced CT, unlike previous CT-based systems.

MODIFIED CT SEVERITY INDEX:

Points, Grade	Criteria
Evaluation of Pancreatic Morphology	
0, A	Normal pancreas consistent with mild pancreatitis
2, B/C	Focal or diffuse enlargement of the gland, including contour irregularities and inhomogeneous attenuation with or without peripancreatic inflammation
4, D/E	Pancreatic or peripancreatic fluid collection or peripancreatic fat necrosis
Additional 2 points	Extrapancreatic complications, one or moreof the following: pleural effusion, ascites, vascular complications, parenchymal complications, or gastrointestinal tract involvement
Scoring Pancreatic Necrosis	
0	No pancreatic necrosis
2	≤30% pancreatic necrosis
4	>30% pancreatic necrosis

Predicting Morbidity and Mortality With the CT Severity Index Combining Scores

Index	Morbidity	Mortality
0-3	8%	3%
4-6	35%	6%
7-10	92%	17%

Magnetic Resonance Imaging:

MRI in pancreatitis is useful alternative to CT scan in significant renal impairments and contrast allergies.

PRESENTATION, DIAGNOSIS, AND INITIAL MANAGEMENT:

The initial diagnosis of AP is based on fulfilling at least two of the following three criteria: **clinical presentation (upper abdominal pain), laboratory assay (serum amylase or lipase >3 times the upper limit of normal), and/or imaging criteria (computed tomography [CT], magnetic resonance, ultra-sonography) (Working Group IAP/APA, 2013)**.

Assessment of Severity:

The main factor determining the clinical outcome is the degree of systemic organ disturbance during the early hours and days after admission to hospital. More than half of all deaths in AP occur within the first 2 weeks of illness as a consequence of multiple organ failure. Hypoxemia and renal impairment have long been recognized as early indicators of severe AP. The persistence or worsening of these systemic manifestations of AP will determine the outcome. Deteriorating organ dysfunction is associated with the great majority of fatality in AP. The presence of systemic inflammatory response syndrome (SIRS) helps in identifying the risk of developing systemic organ dysfunction.

Close monitoring in a critical care environment is warrented. Early management of AP is dependent on understanding of the natural history of the illness, the potential for clinical deterioration, and repeated clinical assessment. **The revised Atlanta Classification (Banks et al, 2013) recognizes three grades of severity of pancreatitis**:

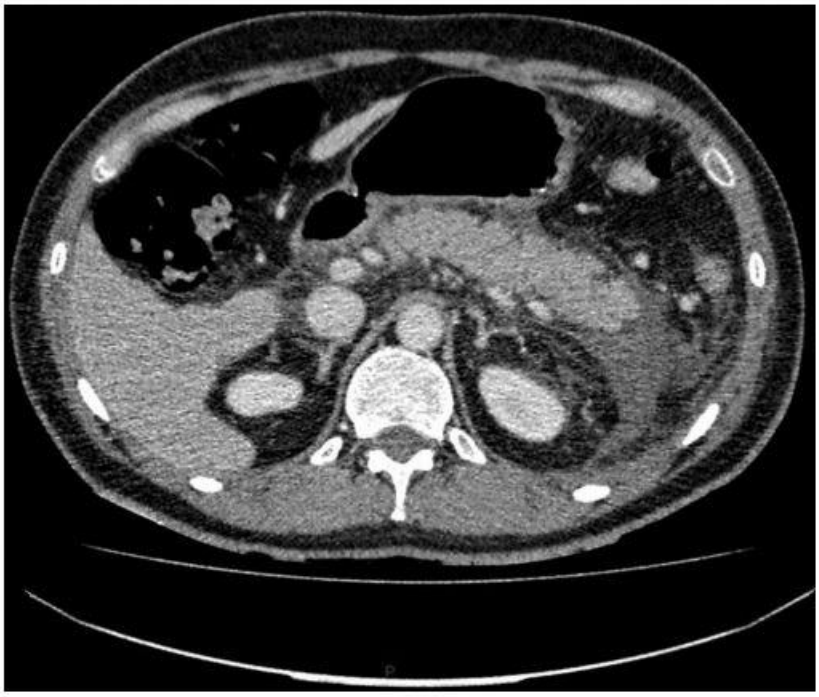
Mild AP—defined by the absence of organ failure or local complications

Moderately severe AP—defined by the presence of transient organ failure (resolving within 48 hours) or local complications developing in the absence of organ failure

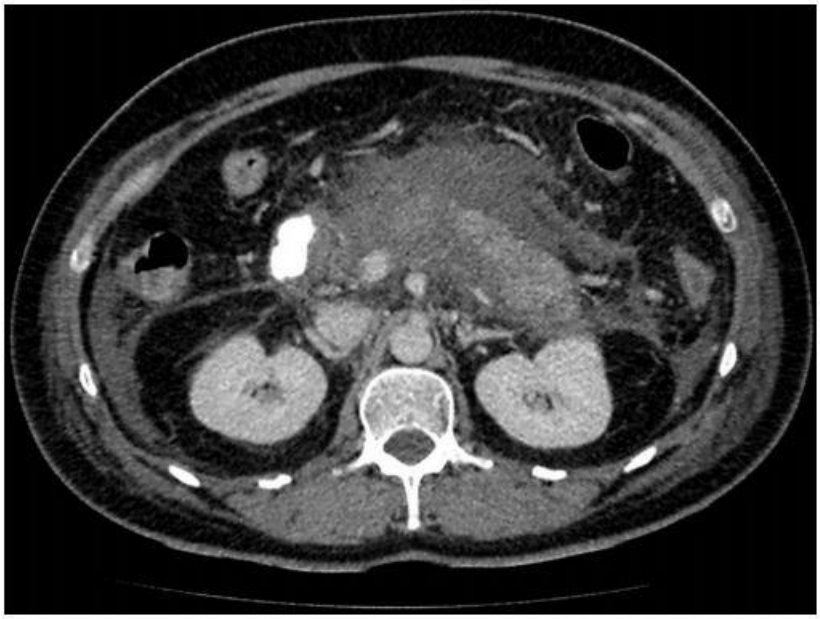
Severe AP—defined by the presence of persistent organ failure (>48 hours) with or without local complications

Clinical definition of severity and the pathologic or radiologic discrimination between interstitial edematous pancreatitis and necrotizing pancreatitis must be distinguished. Most cases of interstitial edematous pancreatitis will have a mild clinical course. But necrotizing pancreatitis is associated with increased risk of systemic and local complications. Hence the severity of pancreatitis is defined by the clinical course rather than the presence or absence of pancreatic necrosis

INTERSTITIAL EDEMATOUS PANCREATITIS



NECROTISING PANCREATITIS:



Initial Management:

International Association of Pancreatology (IAP)/American Pancreatic Association (APA) guidelines of 2013 (Working Group IAP/APA, 2013) recommends important guidelines in managing AP.

Pain Control:

Pain is a prominent feature of AP. Most patients during initial hours following hospital admission will require parenteral opiate analgesics. The duration and severity of pain in AP can be variable. Opiods reduces the need for supplementary analgesia and hence opioid analgesia remains the treatment of choice. In patients with protracted and severe pain, administration of opiates by a patient-controlled analgesia (PCA) pump may occasionally be required. There has been interest in the potential role of epidural analgesia, particularly in patients with severe AP, because of the known effects of thoracic epidural on splanchnic perfusion and tissue oxygenation in experimental models, as well as potential improvements in respiratory complications and shock. There are no clinical trials of thoracic epidural analgesia in patients with AP, and the effects of thoracic epidural analgesics on human splanchnic circulation are less clear (Harper & McNaught, 2014). In addition, there remain practical concerns over logistics,

patient selection, dura -tion of treatment, and the additional complexity of monitoring of circulatory response that limit the potential usefulness of this approach in patients.

Fluid Therapy and Resuscitation:

Early and appropriate fluid therapy within the first 24 hours of admission is strongly recommended by Current guidelines for managing AP. This helps to reduce the incidence of SIRS and subsequent organ failure(Working Group IAP/APA, 2013). The intervention most likely to improve outcome is rapid and effective restoration of circulating volume. Volume resuscitation is the Holy Grail of critical care. The Crystalloids are preferred and current guidelines specifically recommend Ringer's lactate in AP. Various studies shows decreased incidence of SIRS with Ringer's lactate compared to normal saline. Normal saline has proinflammatory effect and can cause hyperchloremic metabolic acidosis when resuscitated with large volumes of saline. Volume and rate of fluid resuscitation that is be required in the first 24 hours : rate of 5 to 10 mL/kg/hr .Adequate fluid resuscitation has decreased requirement for mechanical ventilation and decreased risk of abdominal compartment syndrome (ACS), sepsis and associated mortality. The hematocrit of > 35% within 48 hours had decreased rates of sepsis and mortality when compared with patients having a target hematocrit of < 35% within 48 hours.

Resuscitation of the patient with AP must be guided by restoration of physiologic homeostasis such as urine output, lactate, mixed venous oxygen saturation, base deficit, pressure and flow parameters. A urinary catheter, arterial line, and central venous line helps in monitoring these parameters. Oxygen delivery equation helps in goal-directed therapy:

$$DO_2 = [1.39 \times Hb \times SaO_2 + (0.003 \times PaO_2)] \times \text{cardiac output}$$

(DO_2 = oxygen delivery; Hb = hemoglobin; PaO_2 = partial pressure of oxygen in arterial blood; SaO_2 = oxygen saturation of arterial blood)

Oxygen delivery can be increased by:

1. Avoiding anemia: rare in the hemoconcentrated patient with pancreatitis but apparent as the resuscitation progresses

2. Administer supplemental oxygen via face mask, mechanical ventilation

3. Increase cardiac output by increasing preload (fluid therapy), increasing afterload (vasoconstrictor therapy), improving contractility (inotropic support)

Organ Failure:

Respiratory, cardiovascular, renal, and intestinal dysfunction are the most common systemic complications seen in AP. Respiratory failure is managed in ICU by maximizing noninvasive support or by mechanical ventilation. Cardiovascular collapse is managed by early volume resuscitation and

vasoactive agents. Renal failure commonly occurs in severe AP due to decreased renal perfusion pressure. It is treated by restoring circulating volume and dialysis. Recovering renal function is a helpful indicator of global physiologic improvement in AP. Gastrointestinal failure also occurs due to reduced intestinal perfusion and is worsened by splanchnic vasoconstriction. The clinical features include as nausea, vomiting, and abdominal distension. The Failure to tolerate enteral nutrition and the breakdown of the intestinal barrier function are the two clinically important consequences of Gastrointestinal failure which leads to bacterial translocation, bacteremia, and infected pancreatic necrosis.

Intraabdominal Hypertension /Abdominal compartment syndrome (ACS):

ACS is defined as sustained intra-abdominal pressure > 20 mm Hg (with or without abdominal arterial perfusion pressure <60 mmHg) which is associated with new-onset organ failure. ACS is seen in the context of severe AP. The association between intra -abdominal hypertension (IAH) and disease severity, organ failure, and mortality is demonstrated by various studies. Raised intraabdominal pressure may be a surrogate marker of an impending negative outcome. Invasive treatment for ACS in AP should only be considered in patients with a sustained intraabdominal pressure greater than 25 mm Hg and new-onset organ failure refractory to medical therapy and nasogastric/rectal tube decompression. Invasive treatment

options are percutaneous catheter drainage of ascites, laparostomy, or subcutaneous linea alba fasciotomy

Nutrition:

Patients having clinically mild AP do not usually require additional nutritional support. Patient directed nutrition has to be encouraged and dietry restriction must be avoided. Early nutritional support is essential in Sever AP because of its catabolic state. The enteral route must be preferred over parenteral nutrition for several reasons including:

1. Enteral feeding will contribute to preserving gut barrier function , reduction of bacterial translocation , reduction in the incidence of infected pancreatic necrosis & organ failure.

2. Enteral support reduces gastric colonisation by pathogenic bacteria hence reducing the risk of sepsis

3. Parenteral route has more complications for itself like sepsis

4. Enteral nutrition is cheaper

ULINASTATIN(UTI):

Ulinastatin is a protease inhibitor which reduces hyperamylasemia and post-ERCP pancreatitis (Japanese randomized, double-blind, placebo-controlled trial)[4]. Prophylactic use of Ulinastatin decreases the levels of serum and drain amylase as well as the incidence of postoperative pancreatitis following pancreaticoduodenectomy[5]. Ulinastatin proven to be effective agent fin immune modulation to prevent organ dysfunction and promote homeostasis.[3-5]UTI acts as a protease inhibitor which inhibits inflammatory markers such as trypsin, pancreatic elastase activity, polymorphonuclear leukocyte elastase activity and the endotoxin-stimulated production of TNF alpha and interleukin 1, 8 and 6 [6-7]. It also provides anti-shock effect similar to steroid hormones[8]. It seems to inhibit coagulation and fibrinolysis in an abdominal surgery study[9]. Hence, UTI acts as an effective agent for immune modulation to prevent organ dysfunction and promote homeostasis[10]. The drug widely used in Japan, China and Korea for the treatment of all stages of acute pancreatitis especially moderately severe and severe pancreatitis.

The study (BSV-UTI-AP-0110)[13] which was conducted by BSV evaluated Ulinastatin for the treatment of mild and severe acute pancreatitis. A prospective, multicentric, double-blind, placebo-controlled, randomized, phase III clinical study done to assess the efficacy and safety of intravenous (IV) Ulinastatin versus placebo along with standard supportive care in subjects with

acute pancreatitis. The study included adults, aged 18 to 70 years (both inclusive), both gender, with acute pancreatitis of any severity (mild or severe). The subjects had been randomized with at least 120 evaluable subjects and randomized in a 1:1 ratio such that, the first subject number had equal probability of being assigned to Ulinastatin + standard supportive care (Study Group) OR standard supportive care(control group).

An informed consent was obtained from subjects before recruitment. A randomization block scheme was used to ensure that balance between treatments was maintained. All the Study Group subjects received Ulinastatin at a dose of 2,00,000 IU dissolved in 100 mL normal saline as IV infusion over one hour twice a day (12 ±2 hours apart) for 5 days in both mild and severe acute pancreatitis. All Control Group subjects received placebo dissolved in 100 mL normal saline as IV infusion over one hour twice a day (12 ±2 hours apart)) for 5 days in both mild and severe acute pancreatitis.

The study was planned to have at least 120 evaluable subjects. A total of 154 subjects were screened of which 135 subjects were randomized. Of the 135 randomized subjects, 129 completed the study.Men or non-pregnant, non-lactating women between 18 and 70 years of age (both inclusive) who had elevated serum C-reactive protein (CRP) level and any 2 of the following criteria: 1) abdominal pain characteristic of acute pancreatitis; 2) serum amylase and/or lipase ≥ 3 times the upper limit of normal (ULN); 3) characteristic

findings of acute pancreatitis on ultrasonography, contrast-enhanced computed tomography (CT) or magnetic resonance imaging.A total of 135 subjects were randomized and treated (ITT population). These subjects were first classified and grouped based on the severity of their acute pancreatitis condition. The classification was based on APACHE II scores. Of the 135 subjects, 65 subjects were classified under the mild pancreatitis group and 70 subjects in the severe pancreatitis group. Of the 65 subjects with mild pancreatitis, 32 were randomized in the Study Group (received Ulinastatin) and 33 in the Control Group (received placebo). Similarly, of the 70 subjects with severe pancreatitis, 38 subjects were randomized in the Study Group and 32 in the Control Group. A total of 129 subjects received the study drugs as per the protocol-specified duration (minimum of 6 doses should have been administered to the subject to be eligible for efficacy analysis) and had at least 1 efficacy assessment at the end of the study treatment (mITT population).Of the 135 randomized subjects, 129 completed the study. Three subjects discontinued study participation due to withdrawal of consent (2 subjects) and ‘discharged against medical advice’ (1 subject). One subject with severe pancreatitis randomized in the Study Group died within 2 days after receiving the study drug. This subject received only 1 dose of the study drug and hence was excluded from efficacy analyses. Two subjects in the Study Group were identified as ‘Screening Error’ since they were later diagnosed as having multiple organ failure with no pancreatitis.

In this study, there was reduction in serum CRP values from baseline on Day 7 in all the groups. The reduction was numerically higher in the Ulinastatin group of mild pancreatitis subjects as compared to placebo; however reduction did not reach statistical significance. In severe pancreatitis subjects, the mortality was lower in Ulinastatin group as compared to Placebo, which was significant (p=0.048). Though the hospitalization duration was shorter in Ulinastatin group (mild and severe pancreatitis subjects), but the difference was not significant. New-onset organ dysfunction was lower in the Ulinastatin group as compared to placebo in the severe pancreatitis, the difference observed was significant (p=0.0026). Ulinastatin was well tolerated and the safety results demonstrated a favorable safety profile of Ulinastatin. There was only one instance of infusion-related toxicity (transient rash). Apart from deaths due to underlying disease, there were no other SAEs or other significant AEs. The incidences of AEs were less in the Ulinastatin group as compared to the placebo group. Ulinastatin was safe and well tolerated in Indian subjects with mild or severe pancreatitis. The study yielded favourable results with Ulinastatin in severe pancreatitis subjects demonstrating reduction in mortality and new-onset organ dysfunction.

Name and Description of Investigational Product:

Ulinastatin (Urinary trypsin inhibitor) is a glycoprotein purified from human urine and belongs to the superfamily of Kunitz-type serine protease inhibitor that reduces the pro-inflammatory response as a result of sepsis, acute pancreatitis, trauma or surgery. inhibitors. U-Tryp™ (Ulinastatin for Injection is a sterile formulation of 50000 I.U/100000 I.U. Ulinastatin, available inas a clear colourless liquid.

COMPOSITION:

Each U-Tryp™ vial contains:

Active ingredient:

Ulinastatin J.P. - 50,000 I.U. / 1,00,000 I.U.

Excipients:

m-cresol B.P. (0.03% w/v), Sucrose I.P., Disodium hydrogen phosphate dihydrate B.P., Tween 80 I.P., Phosphoric acid I.P.

Table 1: Formulation of Ulinastatin

Ingredient	Amount
Active Ingredient	
Ulinastatin (UTI)	100000 I.U.
Other Ingredients	
Disodium hydrogen phosphate dehydrate	4.256 mg
Sodium Chloride	18 mg
Mannitol	80 mg
Sucrose	20 mg

Indications:

- **Severe Sepsis:**

Sepsis is defined as the presence (suspected or proven) of infection together with systemic inflammatory response syndrome (SIRS) in the presence of, or as a result of, suspected or proven infection. 'Severe sepsis' is defined as sepsis associated with one evidence of the following features: cardiovascular organ dysfunction, acute respiratory distress

syndrome (ARDS)tissue hypoperfusion or hypotension. The pathological mechanism involves the release of pro-inflammatory cytokines like TNF α, Interleukins (IL) 1, 6, 8 and chemokines. These cytokines can act directly to affect organ function or dysfunction of two or more organs. Indian incidence is estimated to be about 750,000 cases per year. The most common causes for sepsis are trauma, burns, abdominal sepsis and pneumonia. Septic shock is the most common they may act indirectly through secondary mediators. These can also cause of mortality in the intensive care unit.Despite aggressive treatment, mortality ranges from 15% in patients with sepsis to 40-60% In patients with septic shock. The release of tissue-factor by endothelial cells leading to fibrin deposition and disseminated intravascular coagulation (DIC). There is a continuum of clinical manifestations from SIRS to sepsis to severe sepsis to septic shock to Multiple Organ Dysfunction Syndrome (MODS).

Common predisposing factors for sepsis are diabetes mellitus, concurrent anticancer drugs and corticosteroids and immunocompromised status. The best two prognostic factors are APACHE II score and number of organ dysfunctions. In a large Indian hospital based study of 5,478 ICU admissions, SIRS with organ dysfunction was present in 25%, sepsis in 52.77%, severe sepsis in 16.45% with median APACHE II score =13 (IQR 13 to 14). The overall mortality in ICU patients was 12.08% but in patients with sepsis it was 59.26%.

The most common cause for severe sepsis is bacterial infection; the most commonly affected sites being the respiratory tract, abdomen and urinary tract. Severe sepsis can also be caused by viruses (e.g. influenza, dengue), parasites (e.g. falciparum malaria) and fungi (e.g. Candida). Additionally, noninfectious conditions, such as burns and trauma can also lead to severe sepsis. In this part of this paragraph, we are relying on the agreed international definition of Sepsis which says that Sepsis is "the clinical syndrome defined by the presence of both infection and a systemic inflammatory response." (Refer to page 3 of the annexure to this note.) These infections can be caused by bacteria, fungi, parasites or viruses. (Please refer to page 10 of the annexure to this note.) In is part of this paragraph, we have given examples of the types of infection that can lead to sepsis and severe sepsis. [2-4] Common predisposing factors are very young or old age, diabetes mellitus, cirrhosis, weakened immune systems due to HIV, cancer or treatment with cytotoxic drugs/radiation, immunosuppressive drugs (e.g. corticosteroids) and invasive devices. The documented incidence of sepsis worldwide is 1.8 million cases annually with an estimated 20,000 deaths per day. [5] Severe sepsis is reported to account for around 15% of ICU admissions at tertiary hospitals in India; and despite treatment, mortality is reported in more than 50% of the patients. [6] Ulinastatin acts by reducing the pro-inflammatory process and promotes homeostasis, resulting in reduction in mortality and new

organ dysfunctions. This part of the updates the pack insert with recent publications.

- **Mild and Severe Acute Pancreatitis:**

Acute pancreatitis: is an acute inflammatory process of the pancreas initiated by theIntrapancreatic activation of proteases like trypsin and subsequent auto-digestion of the pancreas. The trypsin may activate other pathways, such as complement, coagulation or fibrinolysis, extending the process outside the gland. Occasionally SIRS may develop, mediated by cytokines and pancreatic enzymes released in to general circulation that may affect distant organs, giving rise to organ failure, shock or metabolic alterations which may further progress to MODS. Biliary stones and alcohol abuse are responsible for 70% to 75% of cases. The disease is classified as mild when there is localized edema and inflammation, whereas the severe disease is associated with pancreatic and peripancreatic complications like necrosis, abscess or pseudocyst and/or remote organ failure. The diagnosis of mild and severe acute pancreatitis requires 2two of the following 3three features: 1) upper abdominal pain of acute onset often radiating through to the back, 2) serum amylase or lipase activity greater than 3 times normal, and 3) findings on crosssectional abdominal imaging consistent with acute pancreatitis. [11] In the early phase, which lasts only a week or so, the

systemic manifestations are related to the host response to the cytokine cascade, which manifests as SIRS and/or the compensatory[8] Acute pancreatitis carries an overall mortality rate of 10%-15%; the severe disease exists in around 20% with mortality approaching 30%-40%. Ulinastatin, by inhibiting the activity of proteases, exerts localized as well as generalized anti-inflammatory syndrome (CARS) that can predispose to infection. When SIRS or CARS persist, organ failure sets in. The late phase of acute pancreatitis, which can persist for weeks to months, is characterized by systemic signs of ongoing inflammation, local and systemic complications, and/or by transient or persistent organ failure. Acute pancreatitis is severe effect, resulting in around 20% patients, and is associated with high morbidity and mortality. Mortality is approximately 32%reduction in the initial few days, mainly from organ failure, and later, if necrotic tissue becomes infected, 19% in the third week and 37% in the fourth.

Dosage and Administration:

For both severe sepsis and acute pancreatitis:

Ulinastatin 200,000 IU administered IV over 1 hour twice daily (12 ± 2 hours apart) for 5 days.

Standard treatment therapy for moderately severe or severe acute pancreatitis will be provided based on the International Association of Pancreatology (IAP) treatment guidelines. This will be administered to subjects in both treatment arms as per the institute's practice. Ulinastatin should be administered with caution if patient has a history of allergy.

1. Ulinastatin should be avoided in pregnant & lactating women.
2. Ulinastatin cannot replace and should only be used as an adjuvant to standard treatment (antimicrobials, fluids, vasoactive agents, ventilation etc.) for severe sepsis
3. The safe dosage for children is not determined yet.

Contraindications:

Hypersensitivity to the drug.

Description of the Study Population:

The study population will consist of patients hospitalized with an episode of severe acute pancreatitis. The patients will be randomized in a 1:1 ratio to receive ulinastatin in addition to standard therapy treatment or only standard treatment.

METHODOLOGY

STUDY OBJECTIVES AND PURPOSE

Primary objective:

To compare the efficacy of ulinastatin in addition to standard treatment versus only standard treatment in subjects with moderately severe or severe acute pancreatitis

Purpose

Ulinastatin is a protease inhibitor that reduces the levels of pro-inflammatory cytokines to promote homeostasis and improves microcirculation. Since there is no specific treatment available for acute pancreatitis, we would like to study efficacy of this drug in acute pancreatitis.

STUDY DESIGN

Efficacy Evaluation

Mortality due to any cause will be reported. Subjects who are discharged before Day 28 or Day 90 will be advised to come for follow up on Day 28 and Day 90 for morbidity reporting. If subjects does not return for the scheduled follow-up visit (Day 28 and Day 90) post discharge from hospital, data on morbidity and mortality will be collected by telephonic contact with subject or subject's relatives/ friends or subject's medical records.

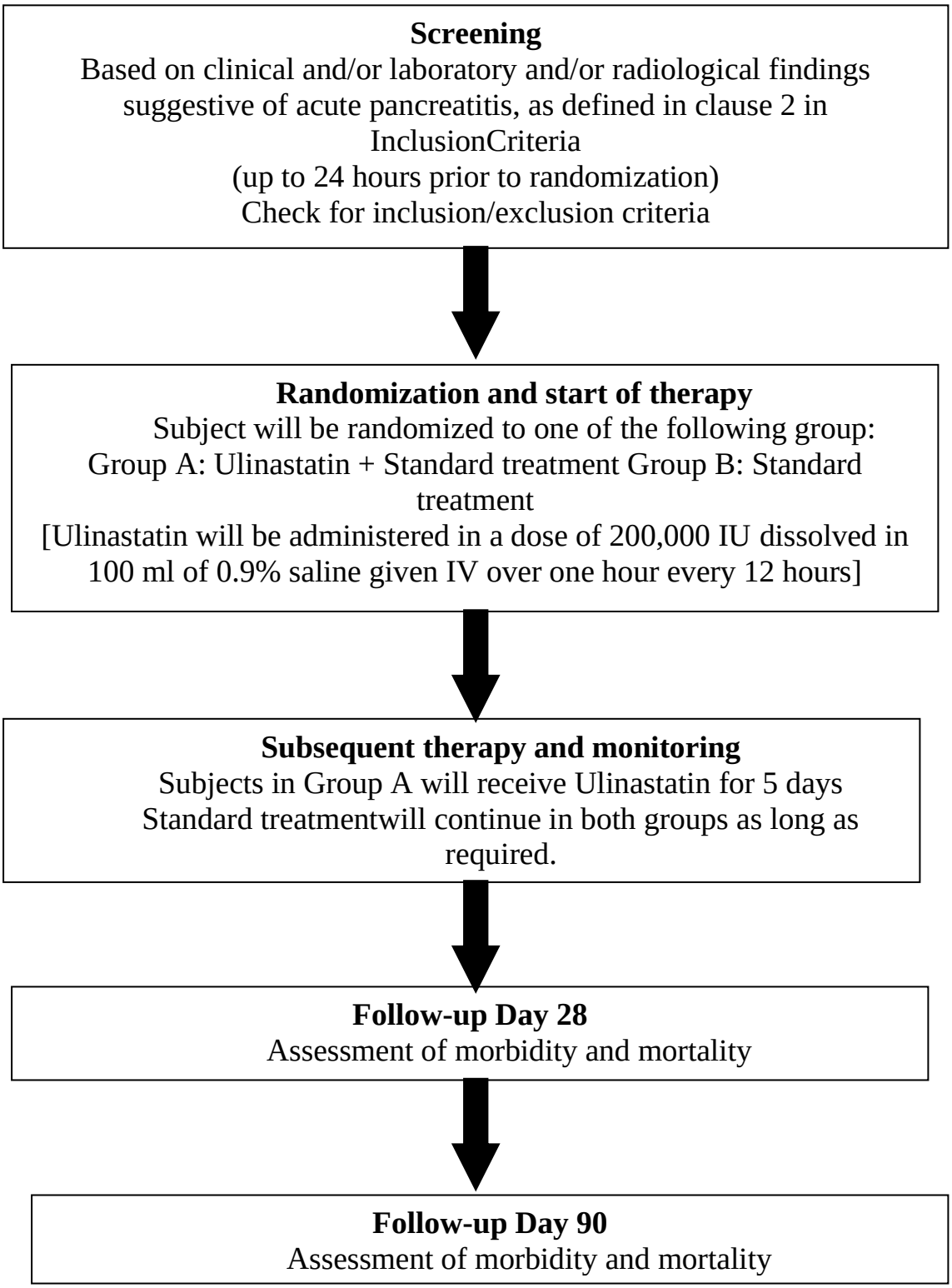
Description of Type and Design of Study:

This is a prospective, randomized, parallel-group, clinical study to assess the efficacy of intravenous (IV) ulinastatin in addition to standard treatment versus only standard treatment in subjects with moderately severe or severe acute pancreatitis. The subjects will be randomized into two groups

- Group A: Subjects in this group will receive Ulinastatin + standard treatment. Subjects in Group A will receive ulinastatin administered by IV infusion in a dose of 200,000 IU administered over 1 hour twice daily (12 ± 2 hours apart) for 5 days (Days 1 to Day 5). A minimum of 6 doses should have been administered to the subject to be eligible for efficacy analysis.
- Group B: Subjects in this group will receive only standard treatment.

A block randomization scheme will be used to ensure that balance between the groups is maintained at each center. Subjects will be randomized in a 2:1 ratio such that, at each

FLOWCHART


Screening
Based on clinical and/or laboratory and/or radiological findings suggestive of acute pancreatitis, as defined in clause 2 in InclusionCriteria
(up to 24 hours prior to randomization)
Check for inclusion/exclusion criteria
Randomization and start of therapy
Subject will be randomized to one of the following group:
Group A: Ulinastatin + Standard treatment Group B: Standard treatment
[Ulinastatin will be administered in a dose of 200,000 IU dissolved in 100 ml of 0.9% saline given IV over one hour every 12 hours]
Subsequent therapy and monitoring
Subjects in Group A will receive Ulinastatin for 5 days
Standard treatmentwill continue in both groups as long as required.
Follow-up Day 28
Assessment of morbidity and mortality
Follow-up Day 90
Assessment of morbidity and mortality

Study Medication, Dose, Dosage Regimen, Dosage Form:

Ulinastatin (Urinary trypsin inhibitor) is a glycoprotein purified from human urine and belongs to the superfamily of Kunitz-type serine protease inhibitor that reduces the pro-inflammatory response as a result of sepsis, acute pancreatitis, trauma or surgery.

U-Tryp^{TM}(Ulinastatin for Injection is a sterile formulation of 50000 I.U/100000 I.U. Ulinastatin, available inas a clear colourless liquid.

COMPOSITION:

Each U-Tryp^{TM} vial contains:

Active ingredient:

Ulinastatin J.P. …….. 50,000 I.U. / 100,000 I.U.

Excipients:

m-cresol B.P. (0.03% w/v), Sucrose I.P., Disodium hydrogen phosphate dihydrate B.P., Tween 80 I.P., Phosphoric acid I.P.

Dosage and Administration:

Ulinastatin 200,000 IU administered IV over 1 hour twice daily (12 ± 2 hours apart) for 5 days.

Standard treatment therapy for moderately severe or severe acute pancreatitis will be provided based on the International Association of Pancreatology (IAP) treatment guidelines. This will be administered to subjects in both treatment arms as per the institute's practice.

Description of the Sequence and Duration of Events during Study:

Sufficient number of subjects hospitalized with an episode of severe acute pancreatitis will be screened for inclusion in the study. The screening will include demography, medical, personal, general examination, vital signs measurement, physical examination, and with a clinical diagnosis of severe acute pancreatitis

Screening Visit (Day 0)

- Subject Information/Written Informed Consent
- Subject number allocation
- Demographic details (Age, date of birth, gender)
- Medical history
- Inclusion / Exclusion criteria (including assessments for inclusion/exclusion criteria)
- Height, body weight
- Physical examination

- Vital signs (heart rate, blood pressure, body temperature and respiratory rate)
- Clinical laboratory assessment: as per Investigator's discretion
- Modified Marshall Score assessment
- Previous and concomitant medication

Randomization and Investigational Product administration (Day 1):

After all eligibility criteria are fulfilled; the subject will be allocated to either

Group A:

Ulinastatin + standard treatment or group B: standard treatment.

Ulinastatinadministration will be started as follows:

Ulinastatin 200,000 IU administered IV over 1 hour twice daily (12 ± 2 hours apart) for 5 days.

Standard treatment therapy for moderately severe or severe acute pancreatitis will be provided based on the International Association of Pancreatology (IAP) treatment guidelines. This will be administered to subjects in both treatment arms as per the institute's practice.

- Vital signs (heart rate, blood pressure, body temperature and respiratory rate)
- Physical examination
- Investigation or interventions
- Ulinastatin and/or standard treatment (as per treatment group – Group A or Group B)
- Documentation of Concomitant medication (after administration of the study medication)
- Modified Marshall Score assessment will be done daily for first 2 weeks, and then weekly.

Modified Marshall score details:

Organ system	Score				
	0	**1**	**2**	**3**	**4**
Respiratory (PaO_2/FiO_2)	>400	301–400	201–300	101–200	≤101
Renal* (serum creatinine, mg/dl)	<1.4	1.4–1.8	1.9–3.6	3.6–4.9	>4.9
Cardiovascular (systolic blood pressure, mm Hg)†	>90	<90, fluid responsive	<90, not fluid responsive	<90, pH<7.3	<90, pH<7.2

A score of 2 or more in any system defines the presence of organ failure.

*A score for patients with pre-existing chronic renal failure depends on the extent of further deterioration of baseline renal function. No formal correction exists for a baseline serum creatinine ≥134 μmol/l or ≥1.4 mg/dl.

†Off inotropic support.

IP administration for five days

- Vital signs
- Physical examination
- Ulinastatin and/or standard treatment (as per treatment group – Group A or Group B)

- Documentation of Concomitant medication (after administration of the study medication)
- Documentation of Adverse Events
- Documentation of infusion related toxicity
- Documentation of interventions (tracheostomy, ventilator support,vasopressor use, renal replacement etc.)
- Modified Marshall score assessment
- Clinical laboratory assessment: at Investigator's discretion

Day 6 till Discharge

- Vital signs
- Physical examination
- Documentation of Concomitant medication (after administration of the study medication)
- Documentation of Adverse Events
- Documentation of interventions (tracheostomy, ventilator support, vasopressor use, renal replacement etc.)
- Modified Marshall score assessment daily for first 2 weeks then weekly
- Clinical laboratory assessment at Day 6 and other as done at Investigator's discretion

Follow-up Day 28 and Day 90:

Subjects who are discharged before Day 28 or Day 90 will be advised to come for follow up on Day 28 and Day 90 for morbidity reporting. If subjects do not return for the scheduled follow-up visit (Day 28 and Day 90) post discharge from hospital, data on morbidity and mortality will be collected by telephonic contact with subject or subject's relatives/ friends or subject's medical records.

SELECTION AND WITHDRAWAL OF SUBJECTS:

Inclusion Criteria:

Subjects may be included in the study if they meet all of the following criteria:

1. Males and females, aged 18 years to 75 years, inclusive
2. Any 2 of the following 3 must be present
    a. Upper abdominal pain characteristic of acute pancreatitis (acute onset of persistent, severe, epigastric pain often radiating to the back)
    b. Serum amylase and/or lipase ?3 times the upper limit of normal
    c. Characteristic findings of acute pancreatitis on contrast-enhanced CT or MRI or ultrasonography
3. Diagnosis of moderately severe or severe acute pancreatitis, based on the revised Atlanta classification for acute pancreatitis

Exclusion Criteria:

Subjects will be excluded from the study if any of the following exclusion criteria apply prior to enrollment:

4. Mild pancreatitis (absence of organ failure, local or systemic complications)
5. History of or radiological evidence of chronic pancreatitis (pancreatic atrophy or calcification, ductal irregularity or dilatation)
6. Post-ERCP (endoscopic retrograde cholangiopancreatography) pancreatitis
7. Significant co-morbidities at screening, as judged by the Principal Investigator
8. Anticipated need for intervention, surgical or endoscopic within 7 days of screening
9. Moribund state in which death is perceived to be imminent within 48 hours
10. Known hypersensitivity to any component of the investigational product
11. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test (>5 mIU/mL)
12. Participation in any other clinical study within 30 days prior to study enrollment

Subject Withdrawal Criteria:

The subject will receive oral and written information about the study, which includes information about the right to withdraw from the study at any time without prejudice to future treatment. In addition, the subject may be withdrawn at the Investigator's discretion at any time if regarded in the subject's best interest.

TREATMENT OF SUBJECTS:

Study Medication(s) including Name(s), Dose(s), Dosing Schedule(s), Route(s), Treatment Period(s), Follow-up Period(s)

Ulinastatin

Active compound	ulinastation
Strength	50,000 IU and 100,000 IU
Route of administration	Intravenous infusion
Manufacturer	Bharat Serums and Vaccines Ltd.

Dosage and administration:

Ulinastatin 200,000 IU administered IV over 1 hour twice daily (12 ± 2 hours apart) for 5 days.

Standard treatment therapy for moderately severe or severe acute pancreatitis will be provided based on the International Association of Pancreatology (IAP) treatment guidelines. This will be administered to subjects in both treatment arms as per the institute's practice.

Subjects who are discharged before Day 28 or Day 90 will be advised to come for follow up on Day 28 and Day 90 for morbidity reporting. If subjects do not return for the scheduled follow-up visit (Day 28 and Day 90) post discharge from hospital, data on morbidity and mortality will be collected by telephonic contact with subject or subject's relatives/ friends or subject's medical records.

Assesment of Efficacy parameters:

Description of Efficacy Variables:

Mortality due to any cause will be reported. Subjects who are discharged before Day 28 or Day 90 will be advised to come for follow up on Day 28 and Day 90 for morbidity reporting. If subjects do not return for the scheduled follow-up visit (Day 28 and Day 90) post discharge from hospital, data on morbidity and mortality will be collected by telephonic contact with subject or subject's relatives/ friends or subject's medical records.

Primary efficacy variable:

- Proportion of subjects with all-cause mortality at Day 28 from initiation of treatment

Secondary efficacy variable:

- Proportion of subjects with all-cause mortality from Day 29 to Day 90 from initiation of treatment
- Proportion of subjects with new-onset organ failure, according to the modified Marshall scoring system, up to Day 90 from initiation of treatment
- Incidence of individual organ failures according to the modified Marshall scoring system (lung, cardiovascular system, hematologic system, kidney)
- Proportion of subjects requiring an intervention for organ failure (e.g. mechanical ventilation, renal replacement therapy, vasopressors/inotropes.)
- Length of ICU stay
- Length of hospital stay

- Incidence of local complications (e.g., acute peripancreatic fluid collection, pancreatic pseudocyst, acute necrotic collection and walled-off necrosis)

STATISTICS:

Sample size justification:

Published studies have reported mortality rate of 10%-20% in subjects with severe acute pancreatitis [Campos, 2008; Fu, 2007; Johnson CD, 2004, Banks, 2006, Johnson CD, 2001]. Reduction in mortality in the Ulinastatin group, in various controlled clinical studies, ranged from 30% to 50%, versus control groups receiving placebo. A reduction in the complication rates by 40% has been considered for sample size estimation in a study of lexipafant in acute pancreatitis [Johnson CD, 2001].In the previous study conducted in severe acute pancreatitis by BSV (Abraham, 2013), the mortality was 6% in the Ulinastatin group and 18% in the placebo group.Based on the literature data for Ulinastatin, study conducted by BSV in subjects with acute pancreatitis, and literature data on mortality for presently available therapies, it was assumed for sample size calculation that the mortality rate will be 5% in the Ulinastatin group and 14% in the Placebo group. Sample size estimation is performed considering the hypothesis mentioned below with superiority margin (∂) of 5%

H0:P1 – P2 $\leq \partial$ vs H1: P1 – P2 > ∂ Where, ∂ is superiority margin

Statistical Method:

Biostatistician will perform the statistical evaluation using appropriate statistical tests. More details on statistical analysis will be stated in statistical analysis plan (SAP).Qualitative data (e.g., pathology, clinical findings, etc.) will be presented in the form of frequency and percentage and compared between the two groups by Pearson's chi-square test with continuity correction where necessary. Normally distributed quantitative data will be represented in the form of mean (SD) as per the distribution of the variable. Comparison of quantitative variables between the two groups will be done using unpaired t test for normally distributed variables and by Mann – Whitney test for data not normally distributed. Categorical variables will be described with counts and percentages, ordinal variables with medians and 95% CI, and interval variables with mean and 95% CI

STATISTICAL ANALYSIS

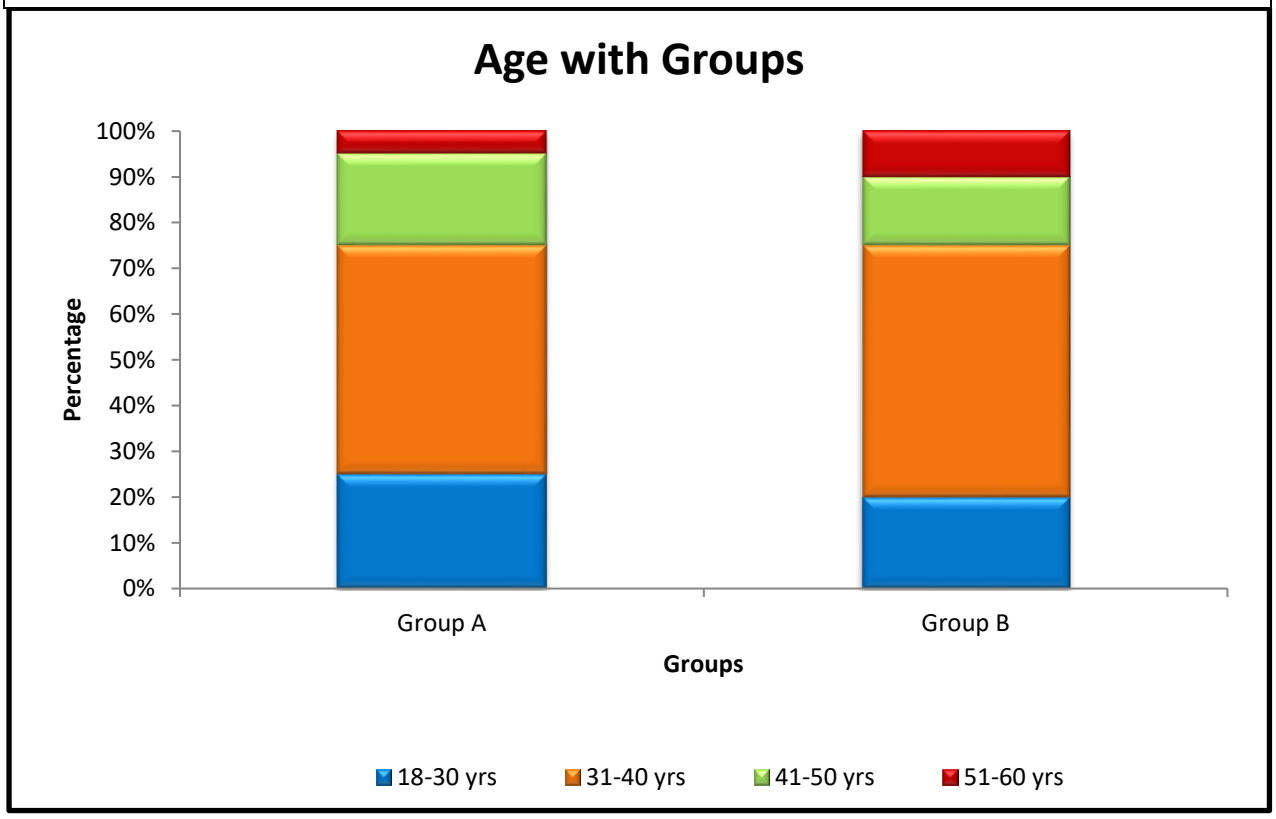
Statistical analysis will be performed on the efficacy parameters. The analysis will include data from subjects who complete both the periods of the study. Data of subjects who are excluded will also be excluded from statistical analysis.

Biostatistician will perform the statistical evaluation using appropriate statistical tests. Statistical analysis will include descriptive statistics for demographics.

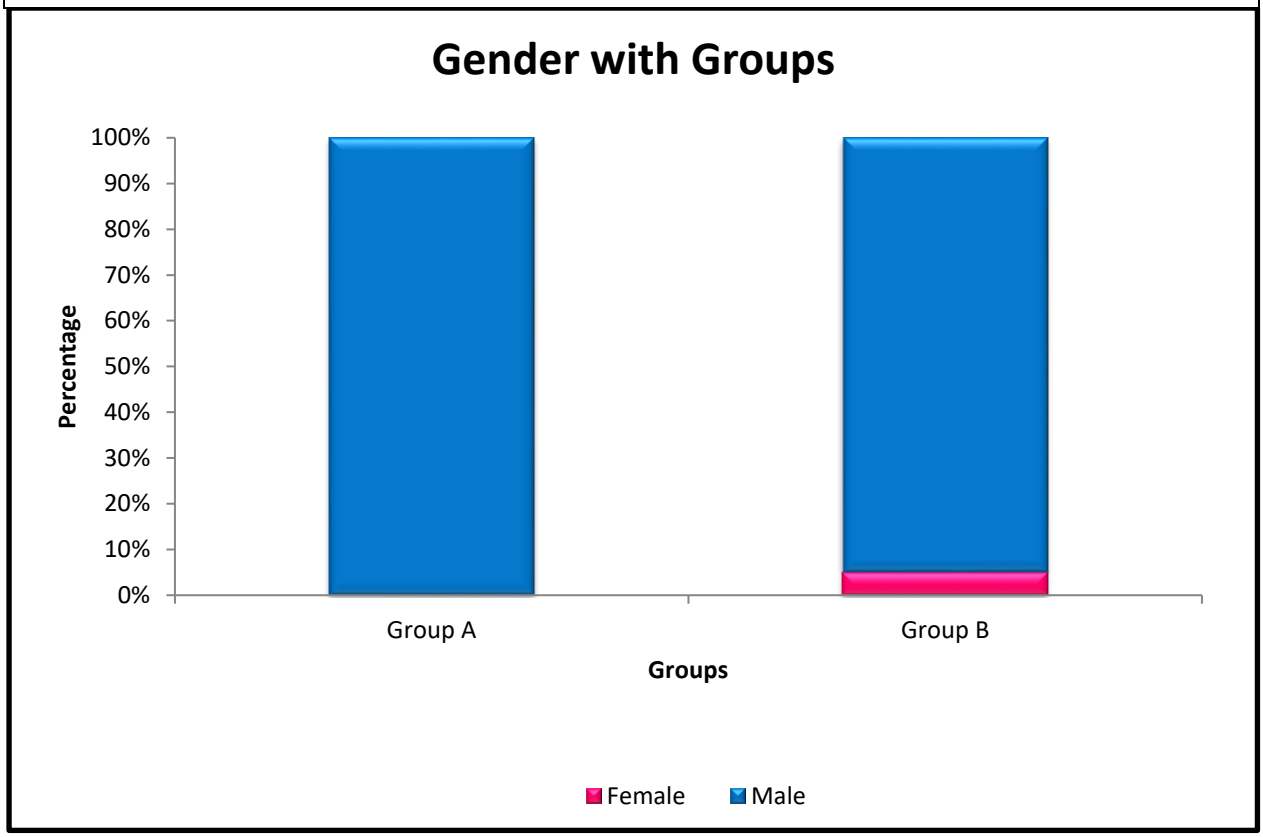
Qualitative data (e.g., pathology, clinical findings, etc.) will be presented in the form of frequency and percentage and compared between the two groups by Pearson's chi-square test with continuity correction where necessary. Normally distributed quantitative data will be represented in the form of mean (SD) as per the distribution of the variable. Comparison of quantitative variables between the two groups will be done using unpaired t test for normally distributed variables and by Mann – Whitney test for data not normally distributed.

The collected data were analysed with IBM.SPSS statistics software 23.0 Version.To describe about the data descriptive statistics frequency analysis, percentage analysis were used for categorical variables and the mean & S.D were used for continuous variables.To find the significance in categorical data Chi-Square test was used similarly if the expected cell frequency is less than 5 in 2×2 tables then the Fisher's Exact was used. In both the above statistical tools the probability value .05 is considered as significant level.

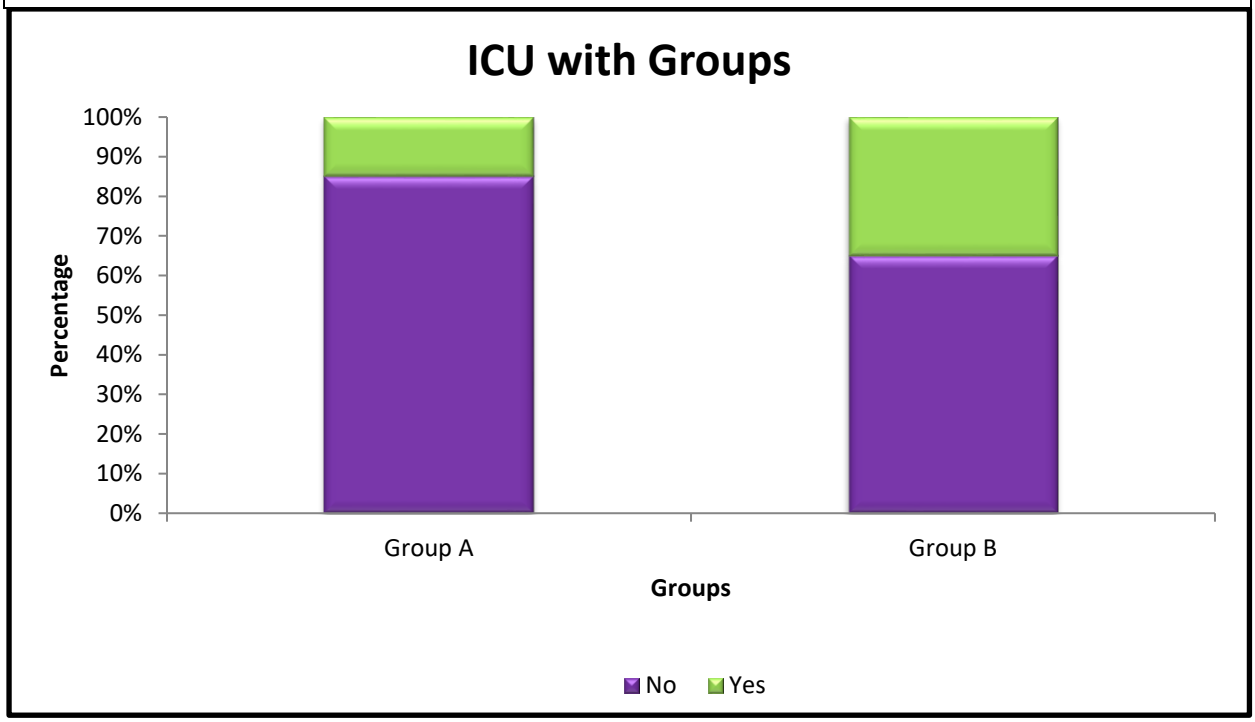
Comparison between Age with Groups							
			Groups		Total	χ 2 - value	P-value
			Group A	Group B			
Age	18-30 yrs	Count	5	4	9	0.635	0.888 #
		%	25.0%	20.0%	22.5%		
	31-40 yrs	Count	10	11	21		
		%	50.0%	55.0%	52.5%		
	41-50yrs	Count	4	3	7		
		%	20.0%	15.0%	17.5%		
	51-60yrs	Count	1	2	3		
		%	5.0%	10.0%	7.5%		
Total		Count	20	20	40		
		%	100.0%	100.0%	100.0%		
# No Statistical Significance at P>0.05 level							



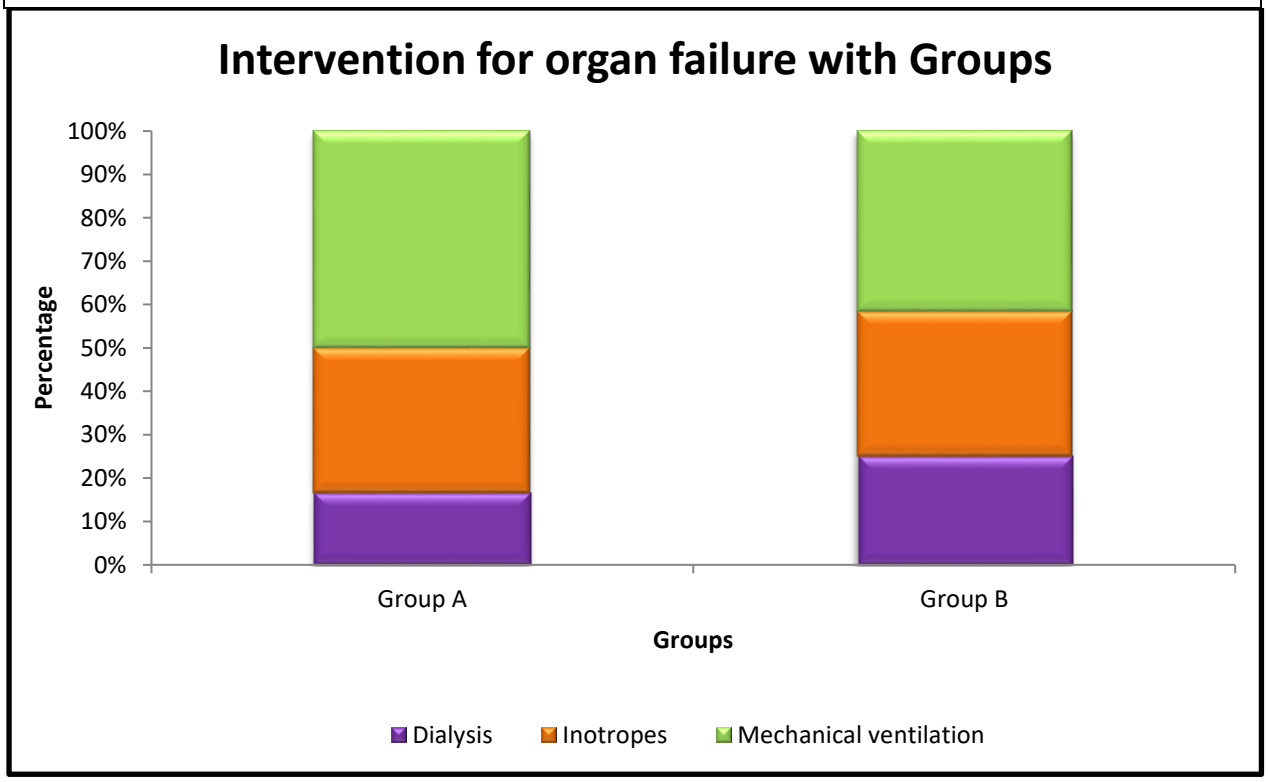
Comparison between Gender with Groups							
			Groups		Total	χ 2 - value	P-value
			Group A	Group B			
Gender	Female	Count	0	1	1	1.026	1.000 #
		%	0.0%	5.0%	2.5%		
	Male	Count	20	19	39		
		%	100.0%	95.0%	97.5%		
Total		Count	20	20	40		
		%	100.0%	100.0%	100.0%		
# No Statistical Significance at P>0.05 level							



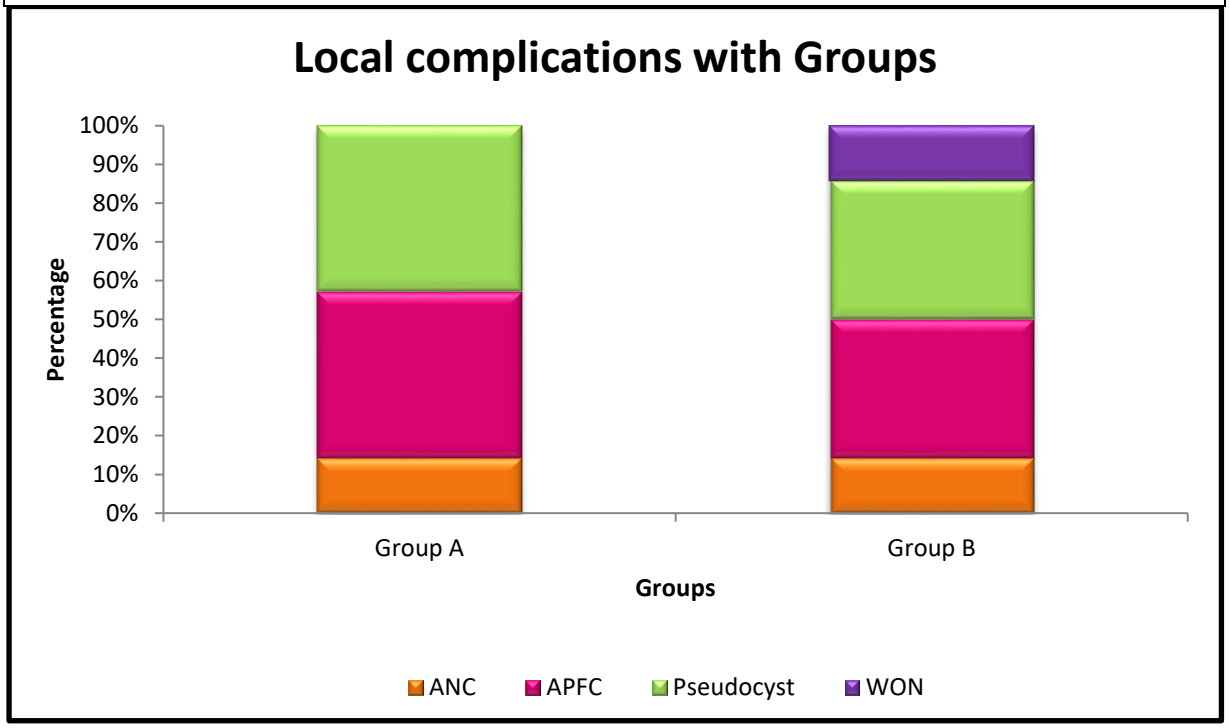
Comparison between ICU with Groups							
			Groups		Total	χ 2 - value	P-value
			Group A	Group B			
ICU	NO	Count	17	13	30	2.133	0.273 #
		%	85.0%	65.0%	75.0%		
	YES	Count	3	7	10		
		%	15.0%	35.0%	25.0%		
Total		Count	20	20	40		
		%	100.0%	100.0%	100.0%		
# No Statistical Significance at P>0.05 level							



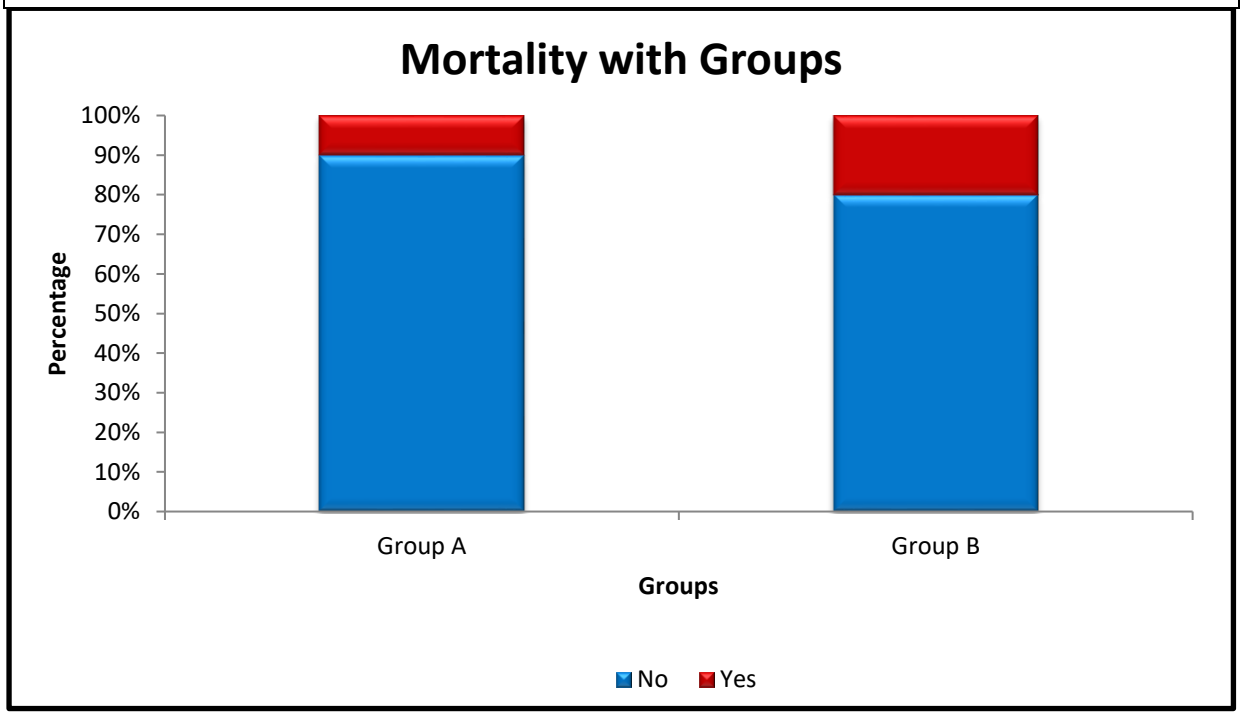
Comparison between Intervention for organ failure with Groups							
			Groups		Total	χ 2 - value	P-value
			Group A	Group B			
Intervention for organ failure	Dialysis	Count	1	3	4	0.188	0.911 #
		%	16.7%	25.0%	22.2%		
	Inotropes	Count	2	4	6		
		%	33.3%	33.3%	33.3%		
	Mechanical ventilation	Count	3	5	8		
		%	50.0%	41.7%	44.4%		
Total		Count	6	12	18		
		%	100.0%	100.0%	100.0%		
# No Statistical Significance at P>0.05 level							



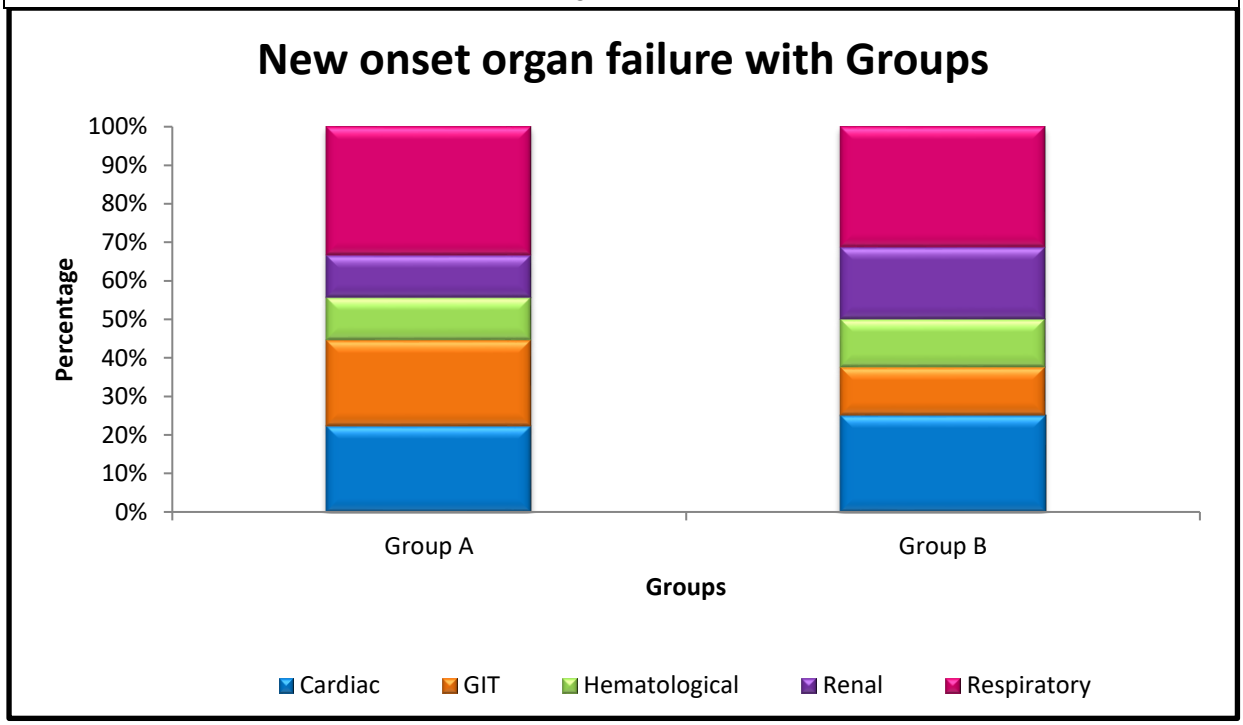
Comparison between Local complications with Groups							
			Groups		Total	χ 2 - value	P-value
			Group A	Group B			
Local complications	ANC	Count	1	2	3	1.125	0.771 #
		%	14.3%	14.3%	14.3%		
	APFC	Count	3	5	8		
		%	42.9%	35.7%	38.1%		
	Pseudocyst	Count	3	5	8		
		%	42.9%	35.7%	38.1%		
	WON	Count	0	2	2		
		%	0.0%	14.3%	9.5%		
Total		Count	7	14	21		
		%	100.0%	100.0%	100.0%		
# No Statistical Significance at P>0.05 level							



Comparison between Mortality with Groups							
			Groups		Total	χ 2 - value	P-value
			Group A	Group B			
Mortality	NO	Count	18	16	34	0.784	0.661 #
		%	90.0%	80.0%	85.0%		
	YES	Count	2	4	6		
		%	10.0%	20.0%	15.0%		
Total		Count	20	20	40		
		%	100.0%	100.0%	100.0%		
# No Statistical Significance at P>0.05 level							

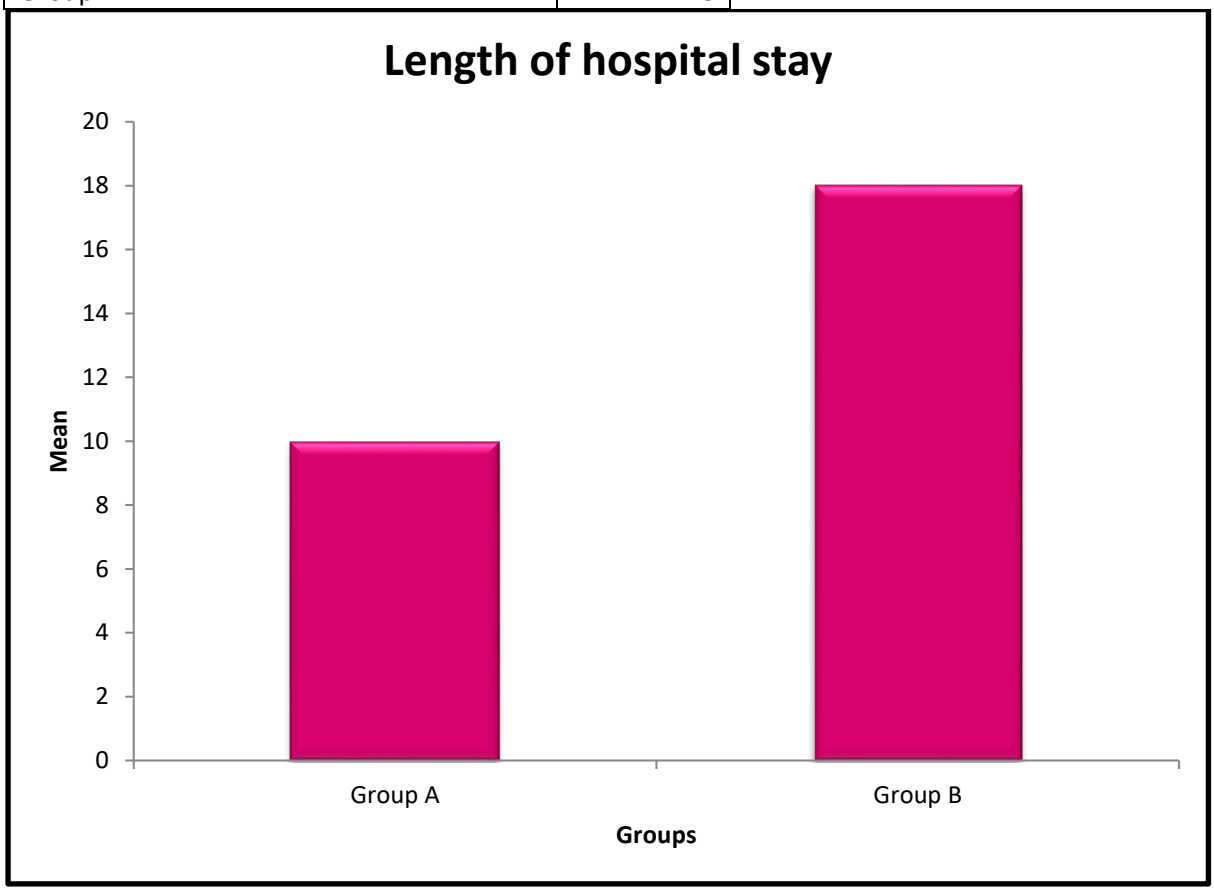


Comparison between New onset organ failure with Groups							
			Groups		Total	χ 2 - value	P-value
			Group A	Group B			
New onset organ failure	Cardiac	Count	2	4	6	0.586	0.965 #
		%	22.2%	25.0%	24.0%		
	GIT	Count	2	2	4		
		%	22.2%	12.5%	16.0%		
	Hematological	Count	1	2	3		
		%	11.1%	12.5%	12.0%		
	Renal	Count	1	3	4		
		%	11.1%	18.8%	16.0%		
	Respiratory	Count	3	5	8		
		%	33.3%	31.3%	32.0%		
Total		Count	9	16	25		
		%	100.0%	100.0%	100.0%		
# No Statistical Significance at P>0.05 level							



length of hospital stay in days:

Group A	10
Group B	18



DISCUSSION

This is a prospective randomised control study, which included 40 patients of moderately severe and severe acute pancreatitis.It is divided into Group A and B. In group A who recieved ulinastatin along with standard treatment, 9 patients had new onset organ failure when compared to group B who recieved only standard treatment where 16 patients had new onset organ failure. In Group A, 3 patients required mechanical ventilation, 1 patient needed dialysis, 2 patients needed inotropes and 7 patients developed local complications. In Group B, 5 patients required mechanical ventilation, 3 patient needed dialysis, 4 patients needed inotropes and 14 patients developed local complications. In Group A, length of ICU stay is 3 days and length of hospital stay is 10 days, whereas in Group B, length of ICU stay is 7 days and length of hospital stay is 18 days. In Group A, 2 patients died in first week after the onset of acute pancreatitis, whereas in Group B , 4 patients died in first week after the onset of acute pancreatitis.

CONCLUSION

Ulinastatin has reduced the morbidity rate by 28 % and the mortality rate by 10% in moderately severe and severe acute pancreatitis. Hence it is proven to be effective in the treatment of moderately severe and severe acute pancreatitis.

MASTER CHART

MORTALITY	GROUP A	GROUP B
DAY 0		
DAY 1	2	2
DAY 2		1
DAY3		
DAY4		
DAY5		1
DAY28		
DAY90		

AGE IN YRS	18-30	31-40	41-50	51-60	61-75
GROUP A	5	10	4	1	0
GROUP B	4	11	3	2	0

GENDER	MALE	FEMALE
GROUP A	20	0
GROUP B	19	1

NEW ONSET ORGAN FAILURE	GROUP A	GROUP B
RESPIRATORY	3	5
RENAL	1	3
CARDIAC	2	4
HEMATOLOGY	1	2
GIT	2	2

INTERVENTION FOR ORGAN FAILURE	GROUP A	GROUP B
MECHANICAL VENTILATION	3	5
DIALYSIS	1	3
INOTROPES	2	4

LOCAL COMPLICATIONS	GROUP A	GROUP B
APFC	3	5
ANC	1	2
PSEUDOCYST	3	5
WON	0	2

	GROUP A	GROUP B
LENGTH OF ICU STAY	3 DAYS	7 DAYS
LENGTH OF HOSPITAL STAY	10 DAYS	18 DAYS

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PROFOMA

Activity	Screening[1] (Day 0)	During hospitalization			Follow up	
		Day 1	Day 2 to 5	Discharge	Day 28	Day 90
Allowed window for visit						
Informed consent						
Subject number allocation						
Medical history						
Inclusion/Exclusion criteria						
Demographic evaluation[2]						
Height						
Weight						
Vital signs[3]						
Physical examination						
Laboratory assessment[4]						
Serum pregnancy test						
Modified Marshall score assessment[5]						
Other investigations[6]						
Study medication						
Adverse events assessment						
Concomitant medication record						
Assessment of survival						

1. Day 0 and Day 1 activities may be completed on same day
2. Date of birth, age, sex
3. Vital signs will include pulse rate, respiration rate, blood pressure, and body temperature
4. Laboratory assessment table provided below[#]
5. Modified Marshall score assessment will be done daily for first 2 weeks, and then weekly
6. Other investigations will be based on institutional practices

Phase	Screening	During hospitalization	At discharge
Serum amylase/lipase			
Serum triglycerides			
Serum Calcium			
CBC			
LFT (serum bilirubin, AST, ALT)			
RFT (serum creatinine, BUN)			
Serum creatinine			

Modified Marshall score details:

Organ system	Score				
	0	1	2	3	4
Respiratory (PaO_2/FiO_2)	>400	301–400	201–300	101–200	≤101
Renal (serum creatinine, mg/dl)	<1.4	1.4–1.8	1.9–3.6	3.6–4.9	>4.9
Cardiovascular (systolic blood pressure, mm Hg)	>90	<90, fluid responsive	<90, not fluid responsive	<90, pH<7.3	<90, pH<7.2

A score of 2 or more in any system defines the presence of organ failure.

A score for patients with pre-existing chronic renal failure depends on the extent of further deterioration of baseline renal function. No formal correction exists for a baseline serum creatinine ≥134 μmol/l or ≥1.4 mg/dl.

Off inotropic support.

INFORMATION SHEET

TITLE: **"A CLINICAL STUDY OF THE EFFICACY OF ULINASTATIN IN TREATMENT OF ACUTE PANCREATITIS"**

Name of Investigator: Dr. K.SURENDAR.

Name of Participant:

Purpose of Research: To determine the efficiency of the index in determining the prognosis of patients diagnosed with peritonitis

Study Design: Randomized Control study (Prospective)

Study Procedures: Patient will be divided into two groups Group A and Group B. Patient will be allotted in one of the group based on double blinding method. Patient in Group A will receive Ulinastatin + standard treatment. Ulinastatin administered by IV infusion in a dose of 200,000 IU administered over 1 hour twice daily (12 ± 2 hours apart) for 5 days (Days 1 to Day 5). Patient in Group B will receive only Standard treatment. Standard treatment therapy for moderately severe or severe acute pancreatitis will be provided based on the International Association of Pancreatology (IAP) treatment guidelines. This will be administered to subjects in both treatment arms as per the institute's practice.

Possible Risks: No risks to the patient

Possible benefits

To patient : Availability of effective drug in the management of moderate and severe acute pancreatitis to reduce morbidity and mortality in acute pancreatitis.

To doctor & to other people: If this study gives positive results, it can help determine the efficacy of ulinastatin in the treatment of patients with moderate and severe acute pancreatitis. This will help in providing better and complete treatment to other patients in future.

Confidentiality of the information obtained from you: The privacy of the patients in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared

Can you decide to stop participating in the study: Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time

How will your decision to not participate in the study affect you: Your decision will not result in any loss of benefits to which you are otherwise entitled.

Signature of Investigator Signature of Participant

Date :

Place :

PATIENT INFORMED CONSENT FORM

TITLE: : **"A CLINICAL STUDY OF THE EFFICACY OF ULINASTATIN IN TREATMENT OF ACUTE PANCREATITIS"**

NAME OF THE INVESTIGATOR: K.SURENDAR

LOCATION: RAJIV GANDHI GOVERNMENT GENERAL HOSPITAL, CHENNAI-600003

I, _____, have been explained the nature and type the study conducted and as I am above the age of 18 years, I give my full and valid consent for the study to be conducted.

o I have read the information in this form (or has been read to me)

o I have read and understood the consent form and the information provided to me.

o I have been explained the nature of the study

o I have been explained about my rights and responsibilities by the investigator.

o I have clearly mentioned my past and current medical and treatment history to the investigator

o I have been clearly explained that there are some risks associated with this study.

Signature/thumb impression

Patient's Name and Address:

Signature of Investigator

Study Investigator's Name: Dr.K.Surendar

URKUND

Urkund Analysis Result

Analysed Document: THESIS URKUND.docx (D58282639)
Submitted: 11/5/2019 9:49:00 AM
Submitted By: dr.k.surendar@gmail.com
Significance: 10 %

Sources included in the report:

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pliag.docx (D31194411)
redo copy new-20 - Copy.docx (D31499545)
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Instances where selected sources appear:

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CERTIFICATE – II

This is to certify that this dissertation work titled "**A CLINICAL STUDY OF THE EFFICACY OF ULINASTATIN IN TREATMENT OF ACUTE PANCREATITIS**" of the candidate **Dr.K.SURENDAR** with registration Number **221711020** for the award of M.S degree in the branch of General Surgery. I personally verified the urkund.com website for the purpose of plagiarism Check. I found that the uploaded thesis file contains from introduction to conclusion pages and result shows 10% percentage of plagiarism in the dissertation.

Guide & Supervisor sign with Seal.

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI 600 003

EC Reg.No.ECR/270/Inst./TN/2013
Telephone No.044 25305301
Fax: 011 25363970

CERTIFICATE OF APPROVAL

To
Dr.K.Surendar
Post Graduate in MS General Surgery
Institute of General Surgery
MMC/Chennai

Dear Dr.K.Surendar,

The Institutional Ethics Committee has considered your request and approved your study titled **"A CLINICAL STUDY OF THE EFFICACY OF ULINASTATIN IN TREATMENT OF ACUTE PANCREATITIS " - NO.22122017**

The following members of Ethics Committee were present in the meeting hold on **12.12.2017** conducted at Madras Medical College, Chennai 3

1. Prof.P.V.Jayashankar	:Chairperson
2. Prof.R.Narayana Babu,MD.,DCH., Dean,MMC,Ch-3	: Deputy Chairperson
3. Prof.Sudha Seshayyan,MD., Vice Principal,MMC,Ch-3	: Member Secretary
4. Prof.N.Gopalakrishnan,MD,Director,Inst.of Nephrology,MMC,Ch	: Member
5. Prof.S.Mayilvahanan,MD,Director,Inst. of Int.Med,MMC, Ch-3	: Member
6. Prof.A.Pandiya Raj,Director, Inst. of Gen.Surgery,MMC	: Member
7. Prof.Shanthy Gunasingh, Director, Inst.of Social Obstetrics,KGH	: Member
8. Prof.Rema Chandramohan,Prof.of Paediatrics,ICH,Chennai	: Member
9. Prof. Susila, Director, Inst. of Pharmacology,MMC,Ch-3	: Member
10.Prof.K.Ramadevi,MD., Director, Inst. of Bio-Chemistry,MMC,Ch-3	: Member
11.Prof.Bharathi Vidya Jayanthi,Director, Inst. of Pathology,MMC,Ch-3	: Member
12.Thiru S.Govindasamy, BA.,BL,High Court,Chennai	: Lawyer
13.Tmt.Arnold Saulina, MA.,MSW.,	:Social Scientist
14.Thiru K.Ranjith, Ch- 91	: Lay Person

We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

Member Secretary - Ethics Committee