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A comparative study in acute pancreatitis to find out the effectiveness of early addition of ulinastatin to current standard care in Indian subjects

Dr Jenit P. Gandhi
Assistant Professor, Department of Surgery, Smt. B.K.Shah Medical Institute and Research Centre, Sumandeep Vidyapeeth deemed to be university (an Institution), Pipariya Vadodara

Dr Rakesh Jasani
Assistant Professor, Department of Surgery, Smt. B.K.Shah Medical Institute and Research Centre, Sumandeep Vidyapeeth deemed to be university (an Institution), Pipariya Vadodara

Dr Honeypalsinh H. Maharaul
Associate Professor, Department of Surgery, Smt. B.K.Shah Medical Institute and Research Centre, Sumandeep Vidyapeeth deemed to be university (an Institution), Pipariya Vadodara

Dr Kunjan P. Shah
Assistant Professor, Department of Surgery, Smt. B.K.Shah Medical Institute and Research Centre, Sumandeep Vidyapeeth deemed to be university (an Institution), Pipariya Vadodara

Dr Pratik Shaparia
Assistant Professor, Department of Surgery, Smt. B.K.Shah Medical Institute and Research Centre, Sumandeep Vidyapeeth deemed to be university (an Institution), Pipariya Vadodara
Corresponding author email: pratikshaparia@gmail.com

***Abstract*---**Background: Acute pancreatitis is an inflammatory condition of the pancreas which begins in pancreatic acinar cells and triggers local inflammation that may progress to systemic inflammatory response (SIRS) causing distant organ involvement and hampering its function and ending up with multiple organ dysfunction syndrome (MODS). It remains a common disorder with devastating consequences .Although most episodes are mild and self-limiting, up to a one-fifth of patients develop a severe attack that can be fatal.

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Inspite of technical advances in medical and surgical field's acute pancreatitis remains a major cause of morbidity and mortality. Aims and Objectives: Our aim is to find out the effectiveness of early addition of Ulinastatin to current standard care in Indian subjects with acute pancreatitis. The aim of this study is to compare effectiveness of with or without injection Ulinastatin in acute pancreatitis with respect to: 1) Duration of analgesic requirement, 2) Prevention of early sepsis and complication, 3) Duration of hospital stay. Material and methods: This prospective study was conducted between December 2018 to December 2019 on patients admitted to Dhiraj Hospital Piparia Vadodara. 60 patients with episodes of acute pancreatitis were enrolled for the study. Results: Total 60 patients were enrolled with male predominance (43) versus 17 Female. Conclusion: The present study showed Ulinastatin added to current standard care was demonstrated to provide superior safety and efficacy in Acute Pancreatitis patients compared to the group given only the standard treatment.

***Keywords*---**Acute Pancreatitis, Ulinastatin, pain, inflammation, Ranson Score.

Introduction

Acute pancreatitis is an inflammatory condition of the pancreas which begins in pancreatic acinar cells and triggers local inflammation that may progress to systemic inflammatory response (SIRS) causing distant organ involvement and hampering its function and ending up with multiple organ dysfunction syndrome (MODS).

Acute pancreatitis is best defined clinically by a patient presenting with two of the following criteria: symptoms such as epigastric pain, consistent with the disease; a serum amylase or lipase greater than three times the upper limit of normal; or radiologic imaging consistent with the diagnosis, usually using computed tomography(CT) or magnetic resonance imaging(MRI). Premature activation of pancreatic zymogen is likely responsible for protease activated receptor-[PAR-2] which gets activated in the presence of trypsin resulting in production of cytokines and regulation of exocrine function through negative feedback loop. The pathophysiology of acute pancreatitis starts with local acinar injury followed by local inflammatory complications, a systemic response and finally sepsis. Pathophysiological mechanisms include microcirculatory injury, leukocyte chemo-attraction, release of pro and anti-inflammatory cytokines, oxidative stress, leakage of pancreatic fluid into the region of pancreas, and bacterial translocation to the pancreas and systemic circulation.

The release of pancreatic enzymes damages the vascular endothelium, the interstitium, and acinar cells. Acinar cell injury leads to expression of endothelial adhesion molecules (eg.VCAM-1), which further propagates the inflammatory response. Microcirculatory changes, including vasoconstriction, capillary stasis,

decreased oxygen saturation and progressive ischemia, occur early in experimental acute pancreatitis.

These abnormalities increase the vascular permeability and edema of the gland(edematous or interstitial pancreatitis). Vascular injury could lead to local microcirculatory failure and amplification of pancreatic injury. Reperfusion of the damaged pancreatic tissue could lead to release of free radicals and inflammatory cytokines into the circulation, which could cause further injury.

In early stages of human pancreatitis, activation of complement and subsequent release of C5a play significant roles in the recruitment of macrophages and polymorphonuclear leukocytes. Activated granulocytes and macrophages release proinflammatory cytokinesin response to transcription factors such as nuclear factor(NF-Kb). Pro-inflammatory cytokines include TNF, IL-1, IL-6, IL-8, and platelet activating factor (PAF).

Pro-inflammatory cytokines are followed by anti-inflammatory cytokines (IL-2, IL-10, IL-11) that attempt to down regulate the inflammation. Ulinastatin is a protease inhibitor extracted from human urine. Ulinastatin inhibits inflammatory markers: trypsin, pancreatic elastase, polymorphonuclear leukocyte elastase and the endotoxin stimulated production of TNF alpha and interleukin 1,8 and 6. It inhibits coagulation and fibrinolysis and promotes micro-perfusion.

Materials and Methods

Source of data

A current observational study is done to evaluate the effect of early addition of Ulinastatin to the current standard treatment in patients with Acute Pancreatitis. The study subjects consisted of 60 patients with a diagnosis of acute pancreatitis at Dhiraj Hospital, Sumandeep Vidyapeeth Piparia Vadodara.

We developed a patient's data collection form to collect and analyze the patient's health status on a daily basis

This sample size is calculated by using the formula
N = 4PQL/2
Where P is the prevalence,
Q is non-prevalence, Q = 1-PL is probable error, L = 15% of P

Duration of study: 12 Months (Dec 2018 – Dec 2019)

Study Design: Prospective

Methods of collection of data (including sampling procedure, if any)

The method of the study consists of:

- Detail history taking and clinical examination as per the proforma
- Investigations after taking written informed consent

- Patients will be explained about usage of injection Ulinastatin(uses&side effect & cost effectiveness)
  –Time latent for the procedure
  –Documentation of any complication encountered during the injection.
- Complications encountered inthe period (5-14 days)and their management will be observed.
- Patients of both groups will be followed regularly up to 3 months
- Note will be made of any complications, time taken to return to work and patients' satisfaction

Inclusion Criteria:

- Patients with alcoholic pancreatitis, in gastroenterology ward, with comorbidities, history of acute pancreatitis, who are alcoholics and smokers.
- Patients meeting following criteria-Ransons prognostic criteria (<2-mild, 2.5% mortality, >3 severe, 62% mortality).
- Clinical diagnosis of severe acute pancreatitis, severe acute pancreatitis adapted from the Atlanta classification:
- Admission within 72h after onset of symptoms of pancreatitis
- 18-75 years old
- Signed the informed consent form

Exclusion Criteria:

- Pre-existing chronic renal insufficiency requiring hemodialysis or peritoneal dialysis
- Pre existing heart dysfunction or NYHA classification score above III
- pregnancy or lactating women
- Allergy for Ulinastatin
- Serious mentally-ill patients including dementia
- On the verge of death (estimated to be mortal in 12h).

At admission suspected cases were checked for BP, pulse rate, oxygen tension [PAO2], heart rate and temperature along with biochemical parameters serum amylase, serum lipase, S. sodium, S. potassium, S. chloride, S. creatinine, CBP, CT abdomen if necessary [plain], X-ray chest and ECG whenever required as per the age. History of alcoholism, gallstone disease, smoking, hypertriglyceridemia, hypercalcemia, CRF, history of pancreatitis were recorded wherever present. Biochemical parameters were recorded everyday till they touched normal.

Written informed consent was obtained from all the patients before their enrolment in the study. The study protocol was approved by the SV ethical committee. Patients were randomly distributed into two groups of (TEST and CONTROL) 30 each by sealed envelope method. One group was subjected to TEST - injection Ulinastatin and the other to CONTROL – without injection Ulinastatin.

Out of 60 patients: Test group(n=30) received Ulinastatin 1lakh IU in 100 ml dextrose/ NS-over1 hour period twice a day for a period of 5 days along with

standard medication, antibiotics, IV fluids, tramadol for pain, ryles tube aspiration, nil by mouth, PPI twice a day .

Observation and Results

Thirty patients were randomized to each group. The results were,

Patients' demographics:

1. Sex distribution

Table 1

Sex	TEST	CONTROL
Male	18	25
Female	12	05

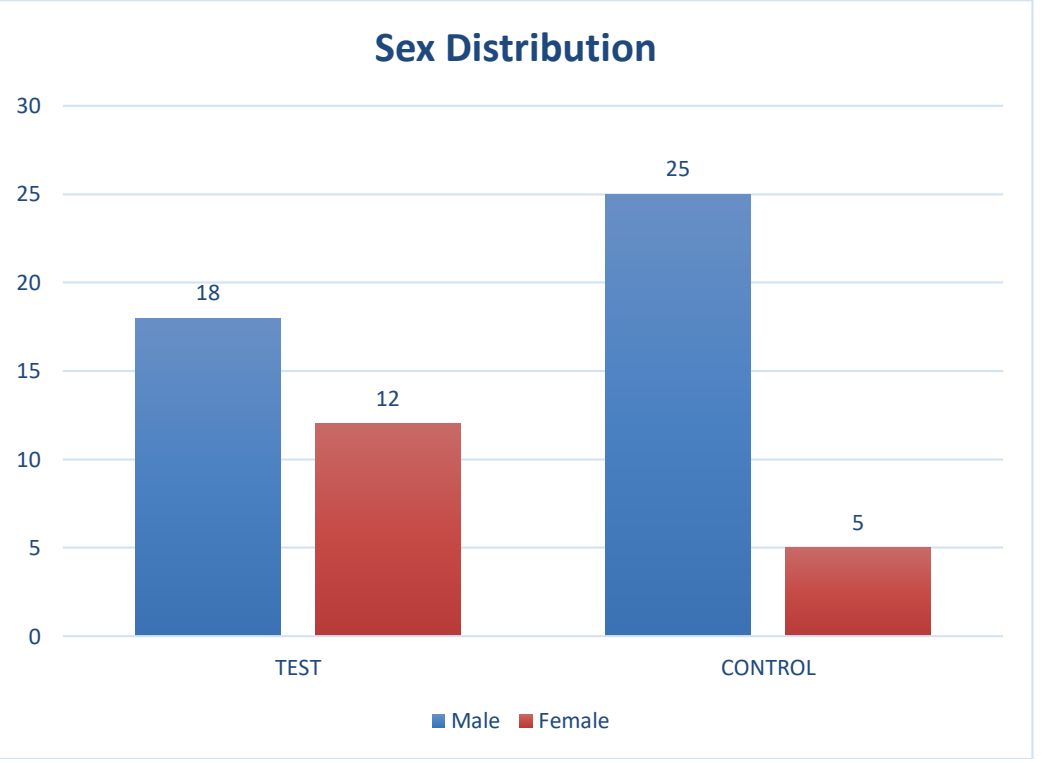

Figure No- 1

25 patients of Control and 18 patients of Test were males. Among Control group 05 were females and among Test group 12 were females.

2. Age distribution

Table 2

Age in years	TEST	CONTROL
< 30	04	06

31 - 40	06	12
41 - 50	08	06
51 – 60	06	02
61 – 70	04	02
>70	02	02

P value > 0.025
(Chi Square test)

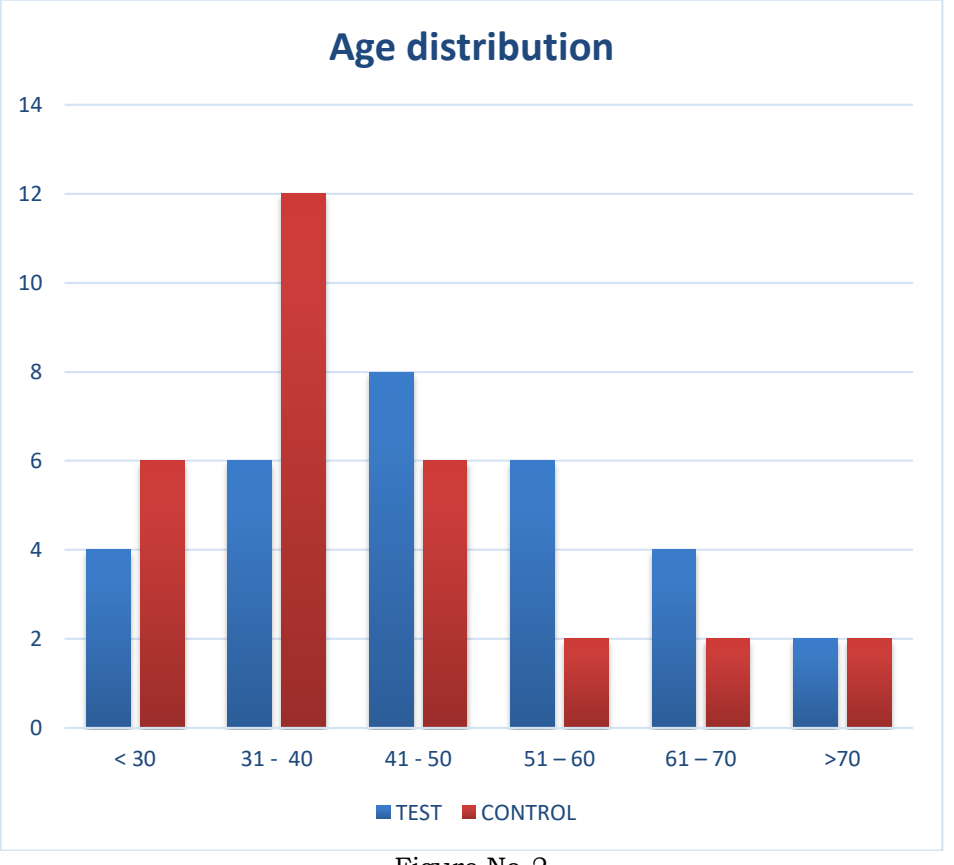

Figure No-2

The median age (range) of patients were 42 (18-72) and 34(20-71) years in TEST and CONTROL groups respectively. The difference was not found to be statistically significant.

3. Pain score and medication

Table -3

	TEST	CONTROL	P value
VAS (Grades 0-5) (Range)	Grade 2 (0-3)	Grade 3 (1-5)	P=0.024 (S)
Duration of pain (days)	02	04	P=0.001

(Range)	(1-5)	(2-10)	(S)
Analgesic used for (days) (Range)	3 (2-6)	6 (2-10)	P=0.016 (S)

* Wilcoxon rank sum test

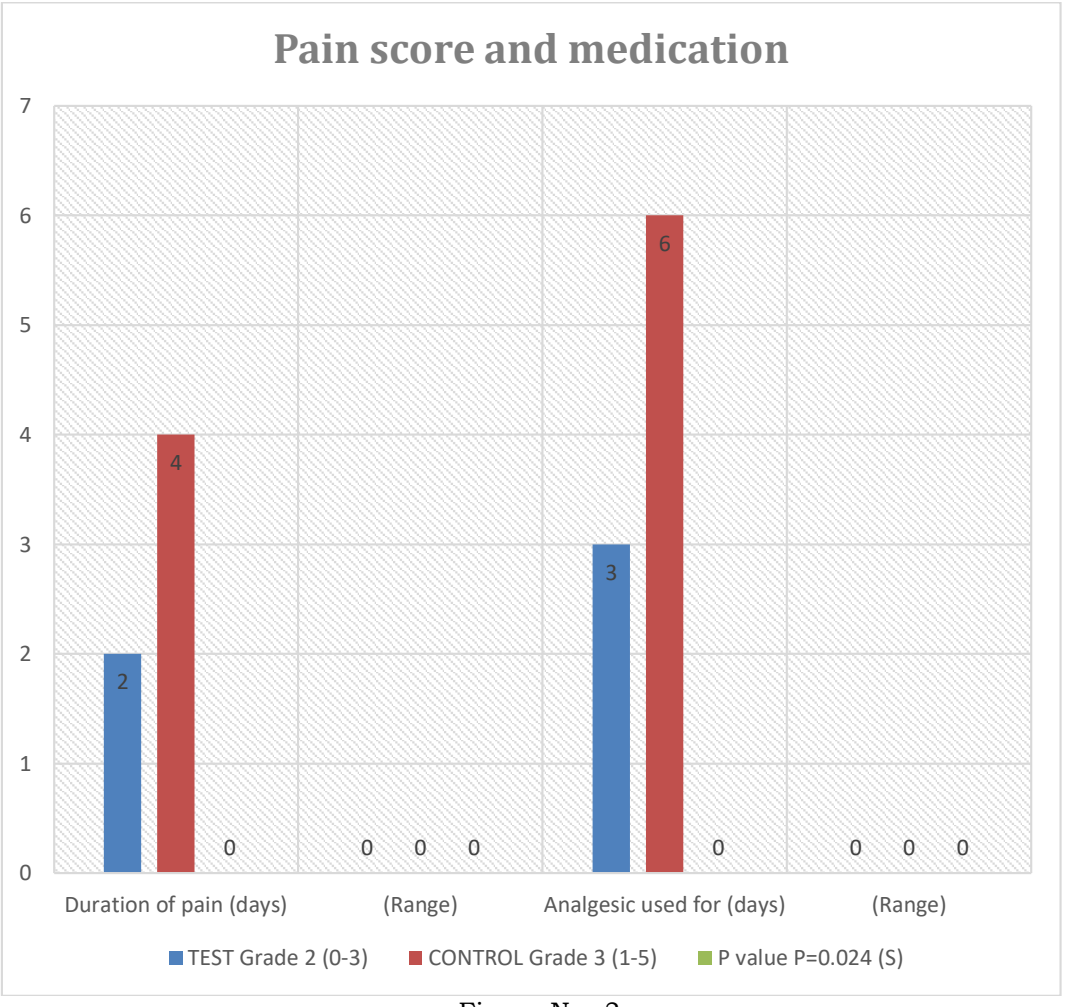

Figure No- 3

The VAS was median Grade3 in CONTROL group as compared to median Grade2 in TEST group, p=0.024. The pain was more in the initial 2 days in both groups and it lasted for median duration of 4 days in CONTROL group compared to 2 days in TESTgroup, p=0.001.

The Analgesic were used for more days in CONTROL group (median-6days) compared to TEST group (median-3days), p=0.016.

4. Complications

Table -4

	TEST	CONTROL
Pleural effusion	2	8
Need for ICU/SIRS/MODS/AKI	1	01 +02=03
DVT	0	0
Pseudo-pancreatic cyst with splenic artery aneurysm	1	1
Portal vein thrombosis & splenic vein thrombosis	0	2
pseudocyst	0	4
Pancreatic pleural fistula	0	0

p value >0.05(chi square test)

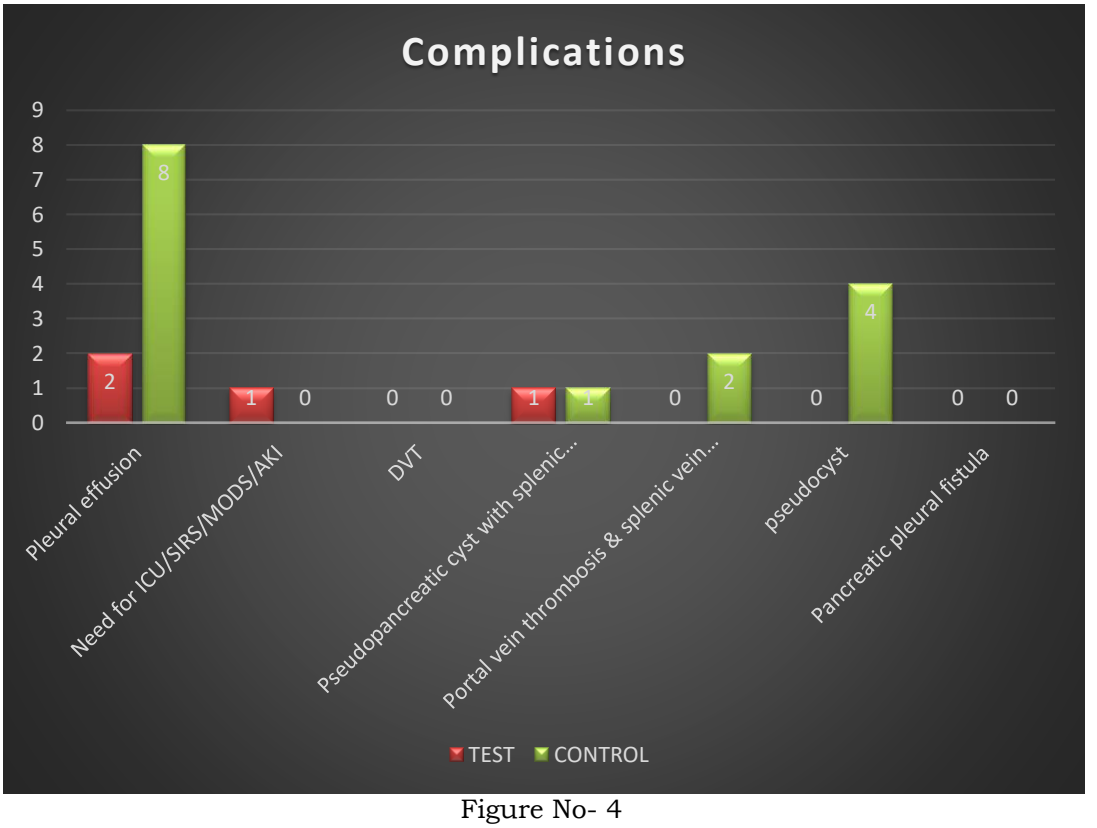

Figure No- 4

Complications in the control group:08 - patients developed pleural effusion, 04- Pseudopancreatic cyst,02 – patients developed portal vein and splenic vein thrombosis, 02 patients – ventilator with ARDS which were treated symptomatically; whereas in test group: 02 - patients developed pleural effusion and 01 – pseudo-pancreatic cyst with splenic artery aneurysm, 01 – patient with AKI and MODS symptomatically treated.

5. Recovery

Table 05

Recovery	LC	OC	P Value*
Duration of hospital stay (in days)+	4	7	P=0.001
	(2-7)	(4-10)	(S)
Time taken to return to normal work (in days)+	5	9	P=0.018
	(3-10)	(5-14)	(S)

+Values are in median (range)
* Wilcoxon rank sum test

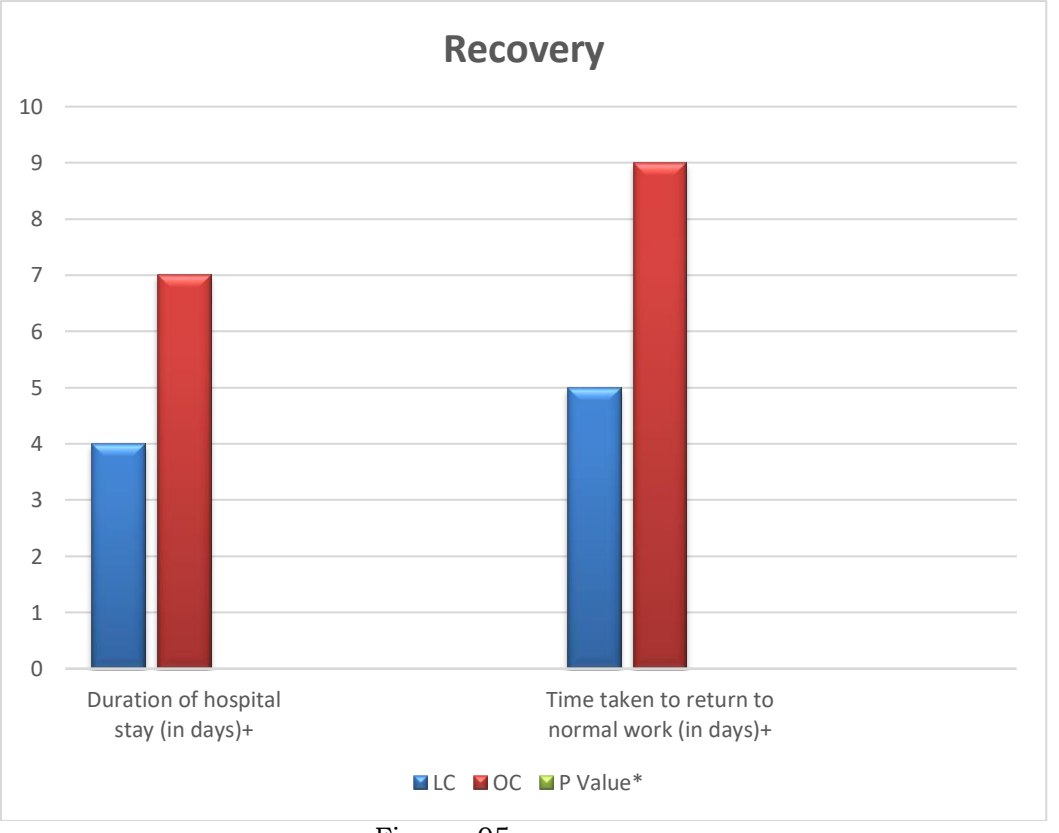

Figure- 05

The duration of hospital stay was for a median period of 4days (2-7days) in TEST group and 7days (4 – l0 days) in CONTROL group. The difference was statistically significant, p=0.001. It was more in CONTROL group due to increased pain,and less mobilization due to pain. All patients who underwent TEST were able to return to normal work on an average of 5 days compared 9 days in CONTROL group. The difference was statistically significant, p=0.0l8.

Discussion

It is a current observational study of Ulinastatin in patients with acute pancreatitis which showed that IV administration of Ulinastatin has better effect

on pain reduction and with low significance of complications compared to control group. A few small studies published in Chinese journals have shown lower mortality in patients treated with Ulinastatin. Treatment with Ulinastatin was independently associated with decreased mortality.

Compared to treatment with placebo group considering the baseline characteristics including age, gender, Glasgow coma scale, specific organ failure, no.of organ failure and need for mechanical ventilation. Our results further collaborate these studies and suggest that treatment with Ulinastatin may reduce mortality in acute pancreatitis in humans.

In a study conducted in India for pancreatitis concluded that, at 22ndday allcauses of mortality in subjects with pancreatitis receiving Ulinastatin was lower than those receiving placebo resulting in a 16% absolute reduction in death risk and relative reduction of 85%.

Our study aimed to show the effectiveness ofearly addition of Ulinastatin in acute pancreatitis by comparing the two groups of patient population in which one group was given the drug and other group was not. 60 patients with acute pancreatitis following inclusion criteria set up (n=60). Out of 60 enrolled patients, 30 patients were given Ulinastatin while 30 patients were not given the drug.

Our study was conducted in the Gastroenterology department of BGS Gleneagle Global Hospital in Bangalore. Subjects enrolled were diagnosed with acute pancreatitis. This study clearly documents the effect of Ulinastatin on pain reduction and analgesic requirement and complication encountered with duration of stay in hospital.

No adverse effects were observed in any of the treatment groups.
Abraham P, Rodriques J et.al[4]has studied the efficacy and safety of intravenous Ulinastatin versus placebo along with standard supportive care in subjects with mild or severe acute pancreatitis. Of 135 randomized subjects, 129 completed the study. Pancreatitis was due to alcohol intake in a majority (81%) of subjects. Efficacy was evaluated in subjects who had received at least 3 days (6 doses) of Ulinastatin /placebo. They have concluded that adverse events were significantly lower in subjects with severe pancreatitis in the Ulinastatin group as compared to the placebo group (p = 0.00001),median hospitalization was shorter by one day in the Ulinastatin group, there was no infusion-related adverse event and Ulinastatin prevents new organ dysfunction and reduces mortality in subjects with severe pancreatitis.

Shi Yao Chen,Ji Yao Wang[5]done multicenter randomized controlled clinical trial was performedto assess the effectiveness of Chinese – manufactured Ulinastatin in the treatment of patients with acute edematous pancreatitis (AEP) and acute hemorrhagic and necrotic pancreatitis (AHNP). A total of 94 patients with acute pancreatitis were enrolled in the study (50 males; 44 females). The study showed that the global effective rates of Ulinastatin and Cabexate in treating AEP were 100%whereas the cured rate for Ulinastatin was 83.3%, which was a little higher than that for Cabexate (71.4%), but this difference was not statistically significant. Ulinastatin was shown to be effective in treating AEP and AHNP with

few adverse effects.Efficacy of Ulinastatin regarding the Prevention of Post-ERCP Pancreatitis: A first multicenter randomized placebo-controlled trial on Ulinastatin for the prevention of post -ERCP pancreatitis was conducted. A series of 406 patients, who underwent diagnostic or therapeutic ERCP for the first time, was finally evaluated. Ulinastatin was administered intravenously immediately before ERCP for 10 minutes. The incidence of hyperenzymenia was significantly lower in the Ulinastatin group than in the placebo group (amylase, P=0.011; lipase, P=0.008). In addition, Ulinastatin significantly reduced the rate of post-ERCP pancreatitis (6/204, 2.9%vs. 15/202, 7.4%; P=0.041). Using multivariate analysis, we found that therapeutic ERCP and the absence of Ulinastatin administration were significant risk factors for the occurrence of post-ERCP pancreatitis.

Ji Won Yoo, MD, et.al[6] in their Prospective, Randomized, Placebo -Controlled Trial. Preventive Effects of Ulinastatin on Post Endoscopic Retrograde Cholangiopancreatography Pancreatitis in High -Risk Patients: A total of 227 patients (mean age, 63 years; 54% men) were randomized to receive placebo (n = 108) or active drug (n = 119) immediately after ERCP and received active drug (100,000 U of Ulinastatin) or placebo. Occurrence of post -ERCP pancreatitis and hyperamylasemia were compared between the 2 groups. It was concluded that low-dose prophylactic treatment with Ulinastatin immediately after ERCP did not show a beneficial influence on the incidence of post -ERCP pancreatitis and hyperamylasemia in high risk patients.

Grzegorz Wallneret.al[7]morphological changes of the pancreas in course of acute pancreatitis during treatment with Ulinastatin. Evaluation of the histological preparations of various time groups showed significantly improved results after application of Ulinastatin, depending on the duration of the inflammation and the number of doses of the drug. It was concluded that application for the treatment of UTI leads to inhibition of the inflammatory process at the stage of pancreatic edema and in cases of severe necrotizing course limits the progression of the disease which gives grounds for its clinical use in humans.

R. Maciejewskia, b et.al[8]selected biochemical parameters and ultrastructural picture of pancreas due to Ulinastatin treatment of experimental acute pancreatitis. They have combined the experimental model of severe, hemorrhagic form of acute pancreatitis, and pharmacological treatment with a protease inhibitor. Subjects in the last group were administered UTI intraperitoneally 1 h after pancreatitis induction in an average standard dose of 3000 units/animal. Statistically significant differences in the serum amylase and lipase activity between the UTI- treated and non - treated subjects were found. In the group of non - treated animals, there a profound destruction of cellular organelles was observed with a total degradation of nuclei, endoplasmic reticulum and zymogen granules. However, in the UTI - treated subjects, pathological processes proceeded with the significantly slower pace and in much smaller quantities.

Minoru Ohwada et.al[9] s comparative study was conducted to evaluate the effectiveness of contrast medium containing Ulinastatin(UST) and water-soluble Prednisolone(PDN) in preventing and decreasing the incidence of post ERCP pancreatitis. The post ERCP serum amylase level in somepatients in the PDN and

UST/PDN groups was lower than the pretreatment value. The results suggests that the use of contrast media containing PDN and UST/PDN is extremely effective in patients withchronic pancreatitis.

Chen Et al[10]debated he role of prophylactic Ulinastatin in the prevention of post - endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis. A meta - analysis of all published randomized clinical trials was performed to evaluate the efficacy of Ulinastatin on post -ERCP pancreatitis. The incidence of post - ERCP pancreatitis was reduced by Ulinastatin. Subsequent sensitivity and subgroup analyses produced conflicting results. Ulinastatin shows to be of value on preventing post -ERCP pancreatitis and hyperamylasemia for patients in average risk, when given intravenously at a dose of not less than 150,000 U, just before ERCP. More high -quality trials are needed for further confirmation. A Prospective, multicentric, double blind, randomized phase III clinical study was conducted to compare the safety and efficacy of IV Ulinastatin vs placebo along with supportive care in subjects with Acute or mild Pancreatitis. Of the 135 randomized subjects, 129 completed the study(62 subjects in the mild group and 67 subjects in the severe group).The 22 dayall-cause mortality was reduced significantly from 18.8%in the placebo group to 2.8%in the Ulinastatin group in severe pancreatitis subjects. New onset organ failure decreased from 90% in placebo group to 34% in the Ulinastatin group this was statistically significant. Hospital stay was shorter in Ulinastatin group. The reduction of serum CRP was comparable in the two treatment groups.

There was only one incidence if infusion related toxicity(transient rash).The number of adverse events. All of non-serious nature, were less in the study group vs control group(in mild patients 24 vs 34and in severe patients 23 vs 45). Thus, treatment with Ulinastatin effectively reduced mortality and morbidity in patients with severe pancreatitis when use as an adjunctive therapy in addition to standard therapy. The reduction in mortality was accompaniedby a shorter stay in the hospital and less complications[11].

Conclusions

The present study showed Ulinastatin added to current standard care was demonstrated to provide superior safety and efficacy in Acute Pancreatitis patients compared to the group given only the standard treatment. Patients with Acute Pancreatitis (n=60) were enrolled based on the criteria setup and all of the completed the study.

The strength of our study is the efficacy of the drug Ulinastatin to improve significant reduction of pain and analgesic requirement and duration of hospital stay and efficiently thus reducing the duration of acute insult and preventing further complications.

Out of 30 subjects in Ulinastatingroup,only 4 patients developed mild complications. Subjects (n=26) showed significant improvement in laboratory assessments. The incidence of complications was higher in the group which were not given the drug compared to the Ulinastatin group. Hospital stay was shorter in the Ulinastatin group.

These laboratory observations were accompanied with better symptom control preventing the progression to multiple organ dysfunction. Early addition of the drug to the standard treatment significantly reduces the risk of episodes of worsening of the condition,providing sustained effect there by reducing hospital stay.

The overall results of our study suggests that Ulinastatin in the dose of 5,00,000IU twice daily via NS result in 24 h consistent and sustained improvement for acute pancreatitis patients clinically.

Thus, the study concluded that early addition of Ulinastatin tocurrentstandard treatment of Acute Pancreatitis is effective in reducing morbidity and mortality in Indian subjects.

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