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Evaluation of therapeutic effectiveness of ulinastatin in acute pancreatitis

[1]Syed Ibrahim Hassan[*], [2]Syed Mohd Akbar Hassan

[1]Professor and HOD, Department of gastroenterology, Deccan College of medical sciences, Hyderabad, India
[2]Senior resident, Department of gastroenterology, Deccan College of medical sciences, Hyderabad, India

ABSTRACT

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) and causing distant organ involvement and its function and ending up with multiple organ dysfunction syndromes (MODS). **Aim:** To find out the effectiveness of addition of Ulinastatin to standard care in Indian subjects with acute pancreatitis. **Methodology:** A concurrent observational study is done to evaluate the effect of addition of Ulinastatin to the standard treatment and its efficacy to reduce the serum amylase and lipase levels in patients with Acute Pancreatitis. patients of both the genders i.e. male and female. **Results:** In the control groups 43 were males and 57 were females. In the test group 47 were males and 53 females. Majority were in the age group between 30- 70 yrs of age with >50% in the 30-50 yrs age group in both tests and control group. Serum amylase the mean S.amylase: levels in control group was 686.16 units/l (day1), 515.72U/l (day2), 400.27 U/l (day 3), 296.42 U/l (day 4). whereas in the test group the mean amylase levels were 687.14 u/l (day 1), 233.83 u/l (day 2), 103.58 u/l (day3), 67.14 u/l (day 4) suggesting that after 5 days of therapy the amylase levels in the test groups touched normal values whereas in the control groups they were still high (>3 times) the normal (n-60 units/1l). The mean serum lipase levels in the control group at day 1 was 224.8 u/l, 142.93 u/l (day 2), 111.34 u/l (day3) and 82.78 u/l (day4).Where as in a test group the mean serum lipase level was 380.42 u/l (day1), 191.92 u/l (day 2), 91.58 u/l (day 3), 31u/l (day 4). The difference in the mean values between the control and test group for both serum amylase and serum lipase levels were found to be statistically very significant. On follow up after 5 days for a period of 2 weeks none of the patients in the test group developed any complication. Where as in the control group 12 patients developed pleural effusion, 8-Pseudopancreatic cyst, 7- developed pancreatic pleural fistula which were treated symptomatically whereas in test group one patient developed pleural effusion and another pancreatic fistula symptomatically treated. **Conclusion:** The study concluded that addition of Ulinastatin to standard treatment of acute Pancreatitis is effective in reducing morbidity and mortality in Indian subjects.

Keywords: Ulinastatin, Acute Pancreatitis, Complication.

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) and causing distant organ involvement and its function and ending up with multiple organ dysfunction syndrome (MODS).Atlanta symposium definition of acute pancreatitis, which is an acute inflammatory process of the pancreas with variable involvement of other regional tissues or remote organ systems. 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 feed back loop. The pathophysiology of acute pancreatitis starts with local acinar injury that, if unchecked, leads

**Correspondence*
Syed Ibrahim Hassan
Professor and HOD, Department of gastroenterology, Deccan College of medical sciences, Hyderabad, India

to local inflammatory complications, a systemic response and sepsis. Pathophysiological mechanisms include microcirculatory injury, leukocyte chemoattraction, 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 statis, decreased oxygen saturation and progressive ischemia, occur early in experimental acute pancreatitis. These abnormalities increase 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[1].

In early stages of human pancreatitis, activation of complement and subsequent release of C5a play significant roles in the recruitment of macrophages and polymorpho nuclear leukocytes. Active granulocytes and macrophages release proinflammatory cytokines in response to transcription factors such as nuclear factor(NF-Kb). Proinflammatory cytokines include TNF, IL-1, IL-6, IL-8, and platelet activating factor (PAF). Proinflammatory cytokines are followed by anti inflammatory cytokines (IL-2, IL-10, IL-11) that attempt to down regulate inflammation[2].Ulinastatin is a protease inhibitor extracted from human urine. Ulinastatin inhibits inflammatory markers: trypsin, pancreaticelastase. polumorphonuclear leukocyte elastase and the endotoxin stimulated production of TNF alpha and interleukin 1 ,8 and 6. It inhibits coagulation and fibrinolysis and promotes microperfusion[3].Our aim is to find out the effectiveness of addition of Ulinastatin to standard care in Indian subjects with acute pancreatitis.

Materials and methods

A concurrent observational study is done to evaluate the effect of addition of Ulinastatin to the standard treatment and its efficacy to reduce the serum amylase and lipase levels in patients with Acute Pancreatitis. It was done in inpatients of princess esra hospital and it was done in 6 months. We developed a patient's data collection form to collect and analyse the patient's health status on a daily basis.

Inclusion Criteria: Patients of both the genders i.e. male and female. Patients with age of 18-75 years. 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).

Exclusion criteria were patients less than 18 years and more than 75 years of age, paediatric patients and pregnant and lactating women.

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 abd[plain], X-ray chest and ECG whenever required as per the age.

History of alcoholism, gallstone disease, smoking, hypertriglyceraedemia, hypercalcaemia, CRF, history of pancreatitis were recorded wherever present. Biochemical parameters were recorded everyday till they touched normal. Out of 200 patients test group patients (n= 100) received ulinastatin 1lakh IU in 100 ml dextrose/ NS- over 1 hr 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 CT abdomen was done on day 0 and after completion of therapy (day 6).

Results

In our study total 60 patients are enrolled with acute pancreatitis following the inclusion criteria setup (n=60).Out of 60 patients,30 patient were given the drug and the other 30 were not given the drug. The patients who were given the drug showed sudden fall in their serum amylase and serum lipase levels showing the effective response of the drug. The other 30 patients who were not given the drug gradually developed complications with no appropriate effect on serum amylase and lipase levels and evaluated the efficacy of Ulinastatin based on the results on these 60 patients. The serum amylase and lipase levels are obtained once before the initiation of the drug to reach diagnosis and then after the addition of Ulinastatin to the ongoing standard therapy of Acute Pancreatitic patients. The after serum amylase and lipase levels were taken after the use of Ulinastatin for a period of atleast 3-4 days. To know the efficacy of Ulinastatin with respect to serum amylase and serum lipase, we have applied Analysis of Variance(ANOVA) as the data collected fitted into the criteria of ANOVA and the results of which would fall under any one of the following hypothesis; Null Hypothesis(H_0) : Addition

of Ulinastatin to standard care has no effect because of no significant change (calculated F value is less than the table F value). Alternative Hypothesis: Addition of Ulinastatin to standard care has significant effect because of significant change (calculated F value is greater than the table F value).

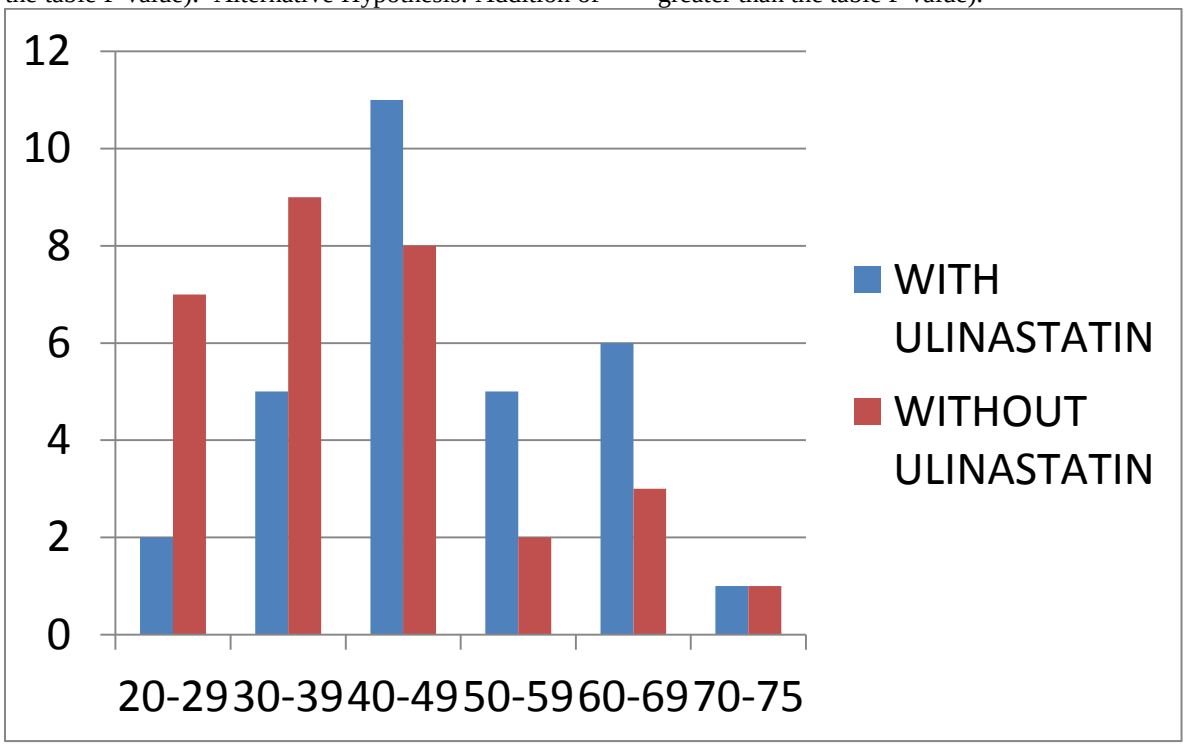

Fig 1: Age Distribution

Table 1: Amylase and lipase ranges in ulinastatin group (test) and control group

Number of cases	Age range in yrs	Gender	Day 1	Day 2	Day 3	Day 4
Serum Amylase (22-80 U/L)						
Test group: 30	22-75	M/F:50/50	63-3600	29-1009	39-327	40-110
Control group: 30	24-72	M/F:55/45	87-2966	75-1240	76-1049	77-1121
Serum Lipase (Upto 38 U/L)						
Test group: 30	22-75	M/F:50/50	44-1047	20-900	20-296	20-40
Control group: 30	24-72	M/F:55/45	87-2966	75-1240	76-1049	77-1121

Table 2: Mean serum amylase and lipase on the days of treatment

serum amylase	D1	D2	D3	D4	Row Total
Control	686.16	515.72	400.27	296.42	1898.57
Test	687.14	233.83	103.58	67.14	1091.69
Total	1373.3	749.55	503.85	363.56	2990.26
serum lipase					
Control	224.8	142.93	111.34	82.78	561.85
Test	380.42	191.4	91.58	31	694.42
Total	605.22	334.33	202.92	113.78	1256.25

Table 3: shows ANOVA-serum amylase and lipase

Source of variation	Sum of squares (SS)	Degrees of freedom (df)	Mean sum of squares(MSS)	F ratio
ANOVA-serum amylase				
Days (DSS)	299202.49	3	99734.16	10.44
Treatment (TSS)	81381.92	1	81381.92	8.52
Error (ESS)	28646.70	3	9548.9	
TSS	409231.11	7		
ANOVA-serum lipase				
Days (DSS)	68824.59	3	22941.53	5.45
Treatment (TSS)	2203.13	1	2203.13	1.90
Error (ESS)	12616.13	3	4205.37	
TSS		7		

The above results showed a significant change in serum amylase levels which is analysed using Analysis of Variance(ANOVA). The calculated F value for serum amylase (n=60) obtained from the data collected during the study period from patients laboratory investigations reports amylase readings 10.44 and 8.52 w.r.t days and treatment. The calculated F value for serum amylase is greater than the table value for 60 subjects i.e,serum amylase F value 10.44 greater than table value 10.13,thus showing that there is a significant change in serum amylase levels in Ulinastatin group and therefore the null hypothesis can be rejected and alternate hypothesis can be accepted for our study. The calculated F value for serum lipase(n=60) obtained from obtained from the data collected during the study period from patients laboratory investigations reports lipase readings 5.45 and 1.90 w.r.t days and treatment. The calculated F value for serum lipase is less than the table value for 60 subjects i.e,serum lipase F value 5.45 less than table value 10.13,thus showing that there is no significant change in serum lipase levels in Ulinastatin group and therefore the null hypothesis can be accepted . Based on the above significant improvement in serum amylase and lipase,it can be concluded that addition of Ulinastatin to the standard care of Acute Pancreatitis is efficacious.

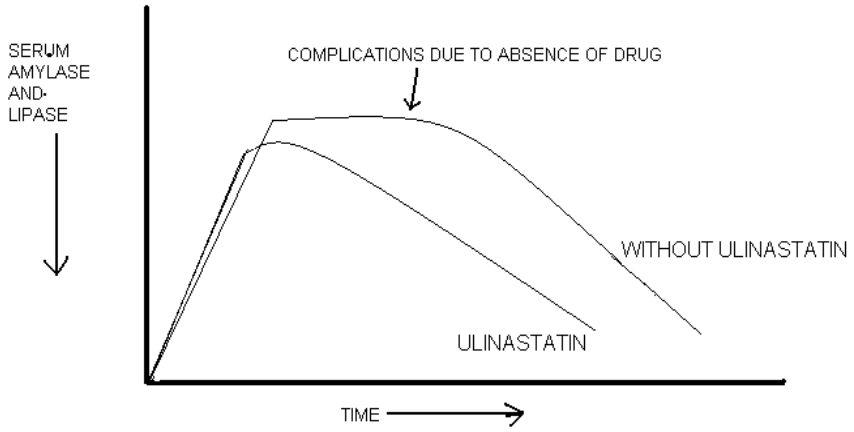

Fig 2: Subjects in Ulinastatin group showing rapid response in their amylase and lipase levels while the subjects without the drug showed gradual decrease with complications arising during that period

Discussion

It is a concurrent and interventional study of ulinastatin in patients with acute pancreatitis which showed that IV administration of ulinastatin has better effect on serum amylase and lipase levels 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 organs failed,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, 22-day all cause 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 of ulinastatin in acute pancreatitis by comparing 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 a multispeciality hospital in Gastroenterology department. Subjects enrolled were diagnosed with acute pancreatitis with high serum amylase and lipase levels. This study clearly documents the effect of ulinastatin on serum amylase and lipase levels. The patients given the drug showed quick decrease in their sr.amylase and lipase levels compared to group which was not treated with the drug. 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 performed.to assess of the effectiveness of Chinese-made 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 into 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 hyperenzymemia 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 Wallner et.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 nuceli, endoplasmatic 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]is 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 some patients 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 with chronic 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 Ulinastain vs placebo along with supportive care in subjects with Acute or mild Pancreatitis. Of the 135 randomised subjects, 129 completed the study(62 subjects in the mild groupand 67 subjects in the severe group).The 22 day all 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 a 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 accompanied by a shorter stay in the hospital and less complications[11].

Conclusion

The present study showed Ulinastatin added to 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 serum amylase and lipase levels efficiently thus reducing the duration of acute insult and preventing further complications. Out of 30 subjects in Ulinastatingroup ,only 3 patients developed mild complications. Subjects (n=27) 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. Addition of the drug to the standard treatment significantly reduces the risk of episodes of worsening of the condition,providing sustained effect thereby 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 addition of Ulinastatin to standard treatment of Acute Pancreatitis is effective in reducing morbidity and mortality in Indian subjects.

References

1. Badalov N, Baradarian R, Iswara K, et al.Drug induced acute pancreatitis:An evidence based approach. ClinGastroenterolHepatol 20007101:454-76.
2. Shao Y Zhang L,DengL,YaoH.Clinical study on effects of Ulinastatin on patients with systemic inflammatory response syndrome.ChinCrit Care Med 2005 vol17 No4.

3. NishiyamaT, YokoyamaT, Yamashita K. Effects of protease inhibitor ,Ulinastatin on coagulation and fibrinolysis in abdominal surgery. J Anesth 2006:20(3).
4. Abraham P et al: Efficacy and safety of intravenous ulinastatin versus placebo along with standard supportive care in subjects with mild or severe acute pancreatitis. J Assoc Physicians India. 2013;61(8):535-8.
5. Shi Yi-ni,et.al.Clinical study of the therapeutic value of the ulinastatin in systemic inflammatory response syndrome.China Chin J Crit Care Med.2004;24(1):1
6. JW Yoo et al :Preventive Effects of Ulinastatin on Post-Endoscopic Retrograde Cholangio pancreatography Pancreatitis in High-Risk Patients: A Prospective, Randomized, Placebo-Controlled Trial.Pancreas.2008; 37 (4): 366-370
7. Grzegorz wallneret. Al . Morphological changes of the pancreas in course of acute pancreatitis during treatment with ulinastatin: PJS: 2013.85.3
8. R. Maciejewski et al. Serum amylase activity in experimental operated groups of the control value from unoperated animal course of experimental pancreatitis. Experimental and Toxicologic Pathology/2005; 56 :305–311.
9. Ohwada M.et al: New endoscopic treatment for chronic pancreatitis, using contrast media containing ulinastatin and prednisolone. J Gastroenterol. 1997 ;32(2):216-21.
10. Chen YK, Tarnasky PR, Raijman I, et al. Peroral pancreatoscopy (PP) for pancreatic stone therapy and investigation of susptected pancreatic lesions: first human experience using the spyglass direct visualization system (SDVS) Gastrointest Endosc. 2008;67:AB108.
11. Gress F, Schmitt C, Sherman S, Ciaccia D, Ikenberry S, Lehman G: Endoscopic ultrasound-guided celiac plexus block for managing abdominal pain associated with chronic pancreatitis: a prospective single center experience. Am Gastroenterol. 2001;96:409–416.

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