WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 6.805
Volume 5, Issue 9, 730-743. Research Article ISSN 2277– 7105

# EVALUATION OF THERAPEUTIC EFFECTIVENESS OF ULINASTATIN IN ACUTE PANCREATITIS

**Asif Rasheed*[1], Dr. S. Akbar Hassan[2], Faiq Unnisa[3], Rukhaiya Fatima[4], Sana Tahreem[5], Adiba Saher[6]**

[1]Associate Professor-M Pharm (Department of Pharmacology)-Decccan School of Pharmacy. Hyderabad-500001, Telangana.

[2]Senior Resident Gastroenterology-MBBS, MD, DNB-Princess Esra Hospital, Hyderabad, Telangana.

[3,4,5,6]Intern (Pharm D)- Decccan School of Pharmacy. Hyderabad-500001, Telangana.

Article Received on
22 June 2016,

Revised on 13 July 2016,
Accepted on 02 Aug 2016

DOI: 10.20959/wjpr20169-6872

***Corresponding Author**
**Asif Rasheed**
Associate Professor-M Pharm (Department of Pharmacology)-Decccan School of Pharmacy. Hyderabad-500001, Telangana.

## ABSTRACT

**OBJECTIVES:**

To evaluate the effectiveness of Ulinastatin in Acute Pancreatitis.

To reduce mortality and morbidity in severe pancreatitis.

To reduce hospital stay thereby reducing cost of care.

To spread awareness among the healthcare and allied profesionals on the effectiveness of Ulinastatin.

**METHODS:** An 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 v/s patients not given Ulinastatin but standard treatment only.

**RESULTS:** 60 patients with Acute Pancreatitis following the inclusion criteria set up (n=60). Out of 60 selected patients (n=60), 30 patients in a group were given Ulinastatin while 30 cases were retrospectively collected when ulinastatin was not used (past records). 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.

**CONCLUSION:** This study revealed that the efficacy of the drug Ulinastatin improve serum amylase and lipase levels significantly thus reducing the duration of acute insult and preventing further complications. Out of 30 subjects in Ulinastain group, only 3 patients developed mild complications. The incidence of complications was higher in the group which were

not given the drug compared to the ulinastatin group. This study concludes that the addition of ulinastatin to the standard treatment reduce mortality and severity of the symptoms associated with severe pancreatitis patients thereby reducing hospital stay and cost of care.

**KEYWORDS**: Ulinastatin, Acute pancreatitis, amylase, lipase.

## INTRODUCTION

Atlanta Symposium defines acute pancreatitis, an acute inflammatory process of pancreas with variable involvement of other regional tissues or remote organ systems. It is best defined clinically by a patient presenting with two of the following criteria: symptoms such as epigastric pain consistent with the disease; serum amylase and lipase greater than three times the upper limit of normal; radiologic imaging consistent with the diagnosis usually using computed tomography (CT) or magnetic resonance imaging (MRI).

Acute pancreatitis is a common cause of morbidity and mortality in critically ill patients and its incidence is increasing worldwide annually.[1][2][3][4][5][6]

## TREATMENT

GENERAL CONSIDERATIONS Patients with acute pancreatitis require adequate intravenous hydration and adequate analgesia to eliminate or markedly reduce pain. The patient is usually on nothing per mouth until any nausea and vomiting have subsided. Abdominal pain can be treated with opiate analgesics, often by a patient controlled anaesthesiapump. Opiate dosing is monitored carefully and adjusted on a daily basis according to ongoing needs.

Several studies have shown that there is a decrease in complications in patients treated with Ulinastatin when compared to placebo. On the basis of clinical studies that have shown a trend towards reduced mortality and duration of hospitalization with Ulinastatin in acute pancreatitis, our study aimed aimed to show the effectiveness of ulinastatin in acute pancreatitis by comparing two groups of patient population.

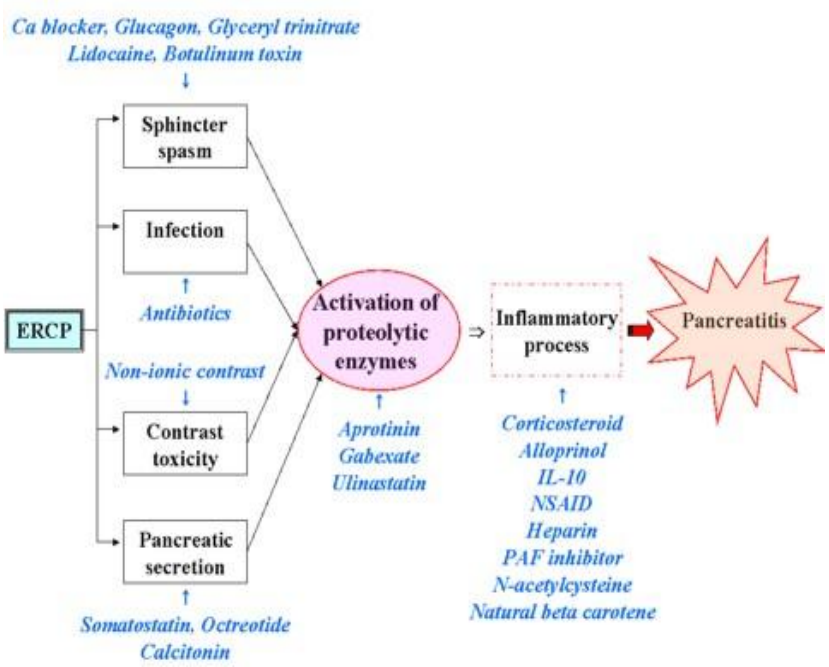


**Figure No.1 ERCP induced pancreatitis**

## MATERIALS AND METHODS

An 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 in patients with acute pancreatitis. For the above study, we developed a patients's data collection form to collect and analyse the patients health status on a daily basis. Adults aged 18-75yrs (both inclusive) with acute pancreatitis admitted to the inpatient ward of Princess Esra Hospital (PEH) between july and December 2014 were eligible for enrollment into the study. Patients meeting the following criteria are enrolled.

Ranson's prognostic criteria (<2 mild-2.5% mortality;>3 severe 6% mortality) Patients with comorbidities Patients who are alcoholics and smokers.

## EXCLUSION CRITERIA

Patients less than 18 yrs of age.

Paediatric patients.

Pregnant and lactating women.

### *STATISTICAL ANALYSIS*

Data analysis was carried out using two way ANOVA (analysis of variance).

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).

- Shi Yao Chen, Ji Yao Wang(2009): A 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.[7]

- Techpool Bio-Pharma Co., Ltd. (2010): A Multicenter, Double-bind, Randomised, Placebo Controlled Study of Ulinastatin in Severe Acute Pancreatitis; this study aims to evaluate the effect of ulinastatin in the treatment and prevention of organ failure in severe acute pancreatitis. Regular treatments plus ulinastatin. Resolved 4 vials of drugs in 100ml physiological saline solution, intravenously infused for 1-2h, tid, for continuous 7 days given in experimental ulinastatin group, resolved 4 vials of drugs in 100ml physiological saline solution, intravenously infused for 1-2h, tid, for continuous 7 days in Comparator placebo group.[8]

## RESULTS

In our study of 'Therapeutic efecttiveness of Ulinatatin in Acute Pancreatitis', We have selected 60 patients with acute pancreatitis following the inclusion criteria setup (n=60). Out of 60 patients, 30 patient were given the ulinastatin drug and the other 30 cases were retrospectively collected when ulinastatin was not used (past records). 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 de-

veloped 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.

**SERUM AMYLASE**

**PATIENTS DATA**

**TABLE NO.1 *ULINASTATIN GROUP (TEST)***

| CASE NO. | AGE | GENDER | | SERUM | AMYLASE | (22-80U/L) |
|---|---|---|---|---|---|---|
| | | M/F | Day1 | Day2 | Day3 | Day4 |
| 01 | 45 | F | 1810 | 115 | 107 | 73 |
| 02 | 22 | M | 740 | 510 | 68 | - |
| 03 | 65 | F | 560 | 602 | 210 | 76 |
| 04 | 45 | M | 600 | 502 | 327 | 110 |
| 05 | 40 | F | 127 | 61 | - | - |
| 06 | 60 | F | 194 | 180 | 70 | - |
| 07 | 29 | M | 700 | 630 | 243 | 51 |
| 08 | 36 | M | 290 | 72 | - | - |
| 09 | 40 | M | 445 | 67 | - | - |
| 10 | 60 | F | 3155 | 250 | 63 | - |
| 11 | 40 | M | 900 | 45 | - | - |
| 12 | 50 | M | 700 | 108 | 39 | - |
| 13 | 52 | F | 1230 | 1009 | 59 | - |
| 14 | 60 | F | 110 | 65 | - | - |
| 15 | 52 | F | 910 | 280 | 95 | 40 |
| 16 | 48 | M | 543 | 65 | 55 | 42 |
| 17 | 48 | M | 342 | 57 | - | - |
| 18 | 75 | F | 210 | 90 | - | - |
| 19 | 40 | M | 1000 | 200 | 57 | - |
| 20 | 65 | M | 132 | 52 | - | - |
| 21 | 60 | M | 800 | 29 | - | - |
| 22 | 35 | M | 3600 | 886 | 72 | - |
| 23 | 50 | F | 340 | 76 | - | - |
| 24 | 44 | F | 210 | 52 | - | - |
| 25 | 45 | F | 120 | 70 | - | - |
| 26 | 54 | M | 165 | 135 | 45 | - |
| 27 | 39 | F | 184 | 179 | 60 | - |
| 28 | 38 | F | 63 | 58 | - | - |
| 29 | 34 | M | 294 | 210 | 81 | - |
| 30 | 40 | M | 440 | 380 | 110 | 78 |

**TABLE NO.2 CONTROL GROUP**

| CASE NO. | AGE | GENDER | | SERUM | AMYLASE | (22-80U/L) |
|---|---|---|---|---|---|---|
| | | | Day1 | Day2 | Day3 | Day4 |
| **01** | 65 | | 1326 | - | - | - |
| **02** | 30 | | 2966 | 1124 | 528 | 183 |
| **03** | 23 | M | 1077 | 1024 | 764 | 121 |
| **04** | 30 | M | 1462 | 1124 | 790 | 261 |
| **05** | 28 | M | 109 | 97 | 94 | 102 |
| **06** | 27 | F | 980 | 1240 | 744 | - |
| **07** | 31 | M | 230 | 119 | 217 | 204 |
| **08** | 29 | M | 1564 | 1170 | 1049 | 1121 |
| **09** | 42 | M | 87 | 84 | 82 | 127 |
| **10** | 37 | F | 341 | 288 | 310 | 307 |
| **11** | 44 | M | 507 | 402 | 347 | - |
| **12** | 32 | F | 774 | 714 | 640 | 504 |
| **13** | 27 | F | 704 | 568 | 511 | 407 |
| **14** | 28 | M | 511 | 407 | 514 | 388 |
| **15** | 55 | M | 141 | 107 | 97 | 94 |
| **16** | 36 | F | 98 | 75 | 76 | 105 |
| **17** | 40 | F | 1149 | 1024 | 427 | 197 |
| **18** | 37 | M | 1275 | 997 | 844 | 741 |
| **19** | 42 | F | 108 | 107 | 97 | 80 |
| **20** | 40 | M | 417 | 407 | 317 | 127 |
| **21** | 38 | M | 180 | 177 | 172 | 77 |
| **22** | 45 | F | 135 | 130 | 130 | 84 |
| **23** | 56 | F | 1314 | 1216 | 974 | 846 |
| **24** | 40 | M | 1660 | 1071 | 827 | 803 |
| **25** | 65 | F | 789 | 642 | 517 | 501 |
| **26** | 67 | M | 118 | 241 | 177 | 84 |
| **27** | 72 | F | 102 | 98 | 92 | 80 |
| **28** | 24 | M | 97 | 92 | 80 | - |
| **29** | 45 | | 184 | 97 | 94 | 83 |
| **30** | 32 | | 180 | 114 | 97 | 80 |

Serum Amylase

Fcal (3,3,0.05) = 9.28

Fcritical (1,3,0.05) = 10.13

Since F value is greater than Fcritical reject null hypothesis (Ho) at 5% L.O.S and conclude that there is significant difference between the two treatment groups w.r.t serum amylase.

**SERUM LIPASE**

**Table No.3 Ulinastatn Group(Test)**

| CASE NO. | AGE | GENDER | | SERUM | LIPASE | Upto38U/L |
|---|---|---|---|---|---|---|
| | (Yrs) | M/F | Day1 | Day2 | Day3 | Day4 |
| **01** | 45 | F | 297 | 70 | 22 | - |
| **02** | 22 | M | 821 | 601 | 32 | - |

| | | | | | | |
|---|---|---|---|---|---|---|
| **03** | 65 | F | 640 | 31 | - | - |
| **04** | 45 | M | 770 | 238 | 140 | 25 |
| **05** | 40 | F | 418 | 37 | - | - |
| **06** | 60 | F | 374 | 292 | 36 | - |
| **07** | 29 | M | 942 | 712 | 296 | 36 |
| **08** | 36 | M | 140 | 25 | - | - |
| **09** | 40 | M | 367 | 58 | - | - |
| **10** | 60 | F | 300 | 100 | 20 | - |
| **11** | 40 | M | 248 | 35 | - | - |
| **12** | 50 | M | 1047 | 37 | - | - |
| **13** | 52 | F | 247 | 800 | 36 | - |
| **14** | 60 | F | 650 | 33 | - | - |
| **15** | 52 | F | 284 | 900 | 33 | - |
| **16** | 48 | M | 137 | 46 | 48 | 40 |
| **17** | 48 | M | 69 | 25 | - | - |
| **18** | 75 | F | 44 | 58 | - | - |
| **19** | 40 | M | 54 | 32 | - | - |
| **20** | 65 | M | 427 | 21 | - | - |
| **21** | 60 | M | 368 | 41 | - | - |
| **22** | 35 | M | 270 | 157 | 31 | - |
| **23** | 50 | F | 321 | 36 | - | - |
| **24** | 44 | F | 137 | 20 | - | - |
| **25** | 45 | F | 902 | 29 | - | - |
| **26** | 54 | M | 660 | 760 | 290 | 34 |
| **27** | 39 | F | 147 | 414 | 115 | 20 |
| **28** | 38 | F | 63 | 35 | - | - |
| **29** | 34 | M | 87 | 25 | - | - |
| **30** | 40 | M | 181 | 30 | - | - |

**Table No. 4 Control Group**

| **CASE** | **AGE** | **GENDER** | | **SERUM** | **LIPASE** | **Upto38U/L** |
|---|---|---|---|---|---|---|
| **NO.** | (yrs) | M/F | Day1 | Day2 | Day3 | Day4 |
| **01** | 65 | M | 902 | - | - | - |
| **02** | 30 | M | 275 | 159 | 82 | 56 |
| **03** | 23 | M | 108 | 144 | 92 | 84 |
| **04** | 30 | F | 417 | 359 | 324 | 221 |
| **05** | 28 | M | 35 | 37 | 35 | 35 |
| **06** | 27 | M | 180 | 117 | 143 | - |
| **07** | 31 | M | 155 | 104 | 98 | 90 |
| **08** | 29 | F | 314 | 288 | 194 | - |
| **09** | 42 | M | 66 | 60 | 64 | 39 |
| **10** | 37 | F | 78 | 109 | 86 | 121 |
| **11** | 44 | F | 118 | 86 | 77 | - |
| **12** | 32 | M | 102 | 46 | 48 | 40 |
| **13** | 27 | M | 97 | 92 | 87 | 64 |
| **14** | 28 | F | 84 | 80 | 89 | 58 |
| **15** | 55 | F | 57 | 77 | 74 | 64 |
| **16** | 36 | M | 130 | 30 | 90 | 85 |
| **17** | 40 | F | 447 | 146 | 87 | 44 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **18** | 37 | M | 342 | 317 | 224 | 207 |
| **19** | 42 | M | 244 | 129 | 84 | 54 |
| **20** | 40 | F | 417 | 179 | 94 | 57 |
| **21** | 38 | F | 265 | 207 | 198 | 114 |
| **22** | 45 | M | 217 | 190 | 84 | 77 |
| **23** | 56 | F | 332 | 246 | 177 | 81 |
| **24** | 40 | M | 88 | 76 | 34 | - |
| **25** | 65 | F | 94 | 57 | 37 | - |
| **26** | 67 | M | 110 | 99 | 86 | 54 |
| **27** | 72 | M | 442 | 246 | 143 | 84 |
| **28** | 24 | M | 265 | 214 | 198 | 77 |
| **29** | 45 | F | 88 | 57 | 36 | - |
| **30** | 32 | F | 275 | 194 | 164 | 98 |

Serum lipase

F cal (3,3,0.05) = 5.45

Fcritical (1,3,0.05) = 10.13

Since F value is less than Fcritical accept null hypothesis (Ho) at 5% L.O.S and conclude that there is no significant difference between the two treatment groups w.r.t serum lipase.

## DISCUSSION

It is an observational 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 (patients data collected retrospectively).

The incidence rate of complications was significantly lower in Ulinastatin group than in control group.In control group, many patients developed pleural effusion, pseudopancreatic cysts and pancreatic pleural fistula.

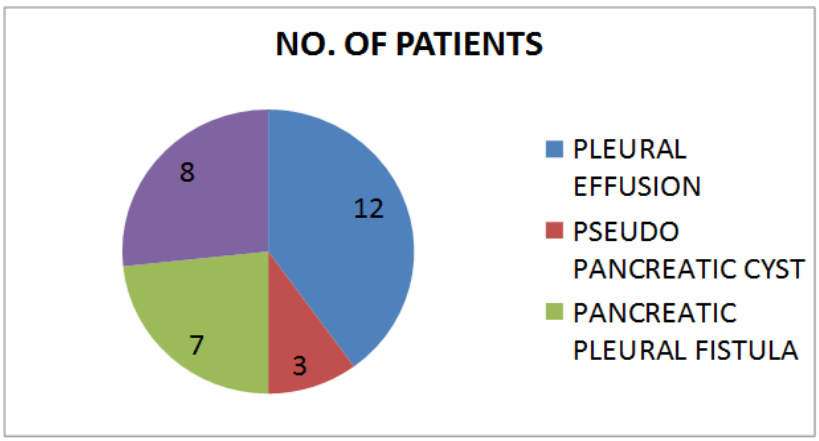


**Figure No.2 Complications In Group Not Treated With Ulinastatin**

*The incidence rate of complications is significantly low in Ulinastatin group.*

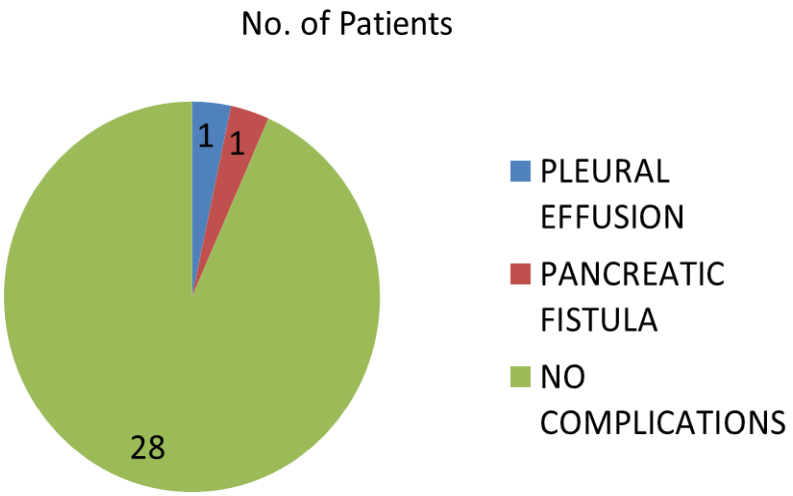


**Figure no.3 complications in ulinastatin group**

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 control 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.

**ULINASTATIN** (or urinary trypsin inhibitor, UTI) is a glycoprotein which acts as a trypsin inhibitor. It may be effective in treatment of acute pancreatitis.

Ulinastatin is an acid-resistant protease inhibitor found in human urine. It is released from the high-molecular weight precursor I alpha T1.

Pancreatitis is a common disease with substantial morbidity and mortality. Pharmacological therapy for the prevention and treatment of pancreatitis is a subject of investigation.

- A Prospective, multicentric, doubleblind, 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

compppleted the study (62 subjects in the mild groupand 67 subjects in the severe group).The 22 day all cause mortalitywas 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 nonserious nature,were less in the study group vs control group(in mild patients 24 vs 34and in severe patients23 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.[9][10][11][12][13][14][15][16][17][18]

Ulinastatin has proved to be effective in treatment of acute pancreatitis by reducing serum amylase and lipase levels thus preventing complications and multiple organ dysfuction.It has also been proved effective in post ERCP pancreatitis.

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.

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.

**FUTURE DIRECTIONS**

Our study aimed to improve the patient's quality of life by reducing the incidence of complications which may lead to multiple organ failure.

Our study may help community know the drug better for the effective treatment of Acute Pancreatitis.

**CONCLUSION**

This study was designed for the group of patients with acute pancreatitis to optimize the treatment regimen.

The present study showed Ulinastain 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 selected based on the criteria setup and all of them 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 Ulinastatin group, 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.

## CONFLICTS OF INTEREST

All authors participated as investigators in the clinical study and also helped in preparing and reviewing the manuscript. Here, we declare that there is no conflict of interest.

## OUTCOMES OBTAINED

1) Improvement in the quality of life.
2) Decrease in serum amylase and lipase levels.
3) Prevention of multiple organ failure.
4) Hospital stay reduced.
5) Prevention of complications in group treated with ulinastatin.

## ACKNOWLEDGEMENT

We would like to express our profound gratitude to Dr. Syed Azeez Basha, M Pharm, PGDPMIR Ph. D, PCCRM, the honourable principal of Deccan School of Pharmacy, Hyderabad for guiding us as well as providing us the support to conduct this project work.

## REFERENCES

1. Badalov N, Baradarian R, Iswara K, et al. Drug induced acute pancreatitis: An evidence based approach. Clin Gastroenterol Hepatol, 2007; 101: 454-76.
2. Besselink MG, Verwer TJ, Nelson DB, et al. Timing of surgical intervention in necrotizing pancreatitis: Arch Surg, 2007; 142: 1194-201.
3. Freeman ML, DiSario JA, Nelson DB , et al. Risk factors for post-ERCP Pancreatitis: A prospective, multicentre study.
4. Gardner TB, Vege SS, Chari ST, et al. Fluid resuscitation in acute pancreatitis: ClinGastroenterol Hepatol, 2008; 6: 1070-6.
5. Gerzof SG, Banks PA, Robbins AH, et al. Early diagnosis of pancreatic infection by computed tomography-guided aspiration. Gastroenterology, 1987; 93: 1315.
6. Isenmann R, Runzi M, Kron M, et al. Prophylactic antibiotic treatment in patients with predicted severe acute pancreatitis: A placebo controlled, double blind trial. Gastrenterology, 2004; 126: 997.

7. Abraham P, Rodriques J et.al. Efficacy and safety of intravenous Ulinastatin versus placebo along with standard supportive care in subjects with mild or severe acute pancreatitis, 2013. http://www.ncbi.nlm.nih.gov/pubmed/24818336
8. Shi Yao CHEN, Ulinastatin in the treatment of acute pancreatitis: A multicenter clinical trial http://onlinelibrary.wiley.com/doi/10.1046/j.1443-9573.2002.00074_3_2.x/abstract
9. Shao Y Zhang L, DengL, YaoH. Clinical study on effects of Ulinastatin on patients with systemic inflammatory response syndrome. Chin Crit Care Med., 2005; 7: 4.
10. Jiang M, Tang J. clinical observation on ulinastatin in treatment of septic shock. Chinese Journal of Practice Medicine, 2004; 3(11).
11. Fang Q, Chen P. A study on clinical efficay of ulinastatin in severe sepsis patients and its mechanism of action.Chinese Journal of Infection and Chemotherapy, Feb 2005; 5: 1.
12. DU HG, Yin LC, HeM, Zhang GJ. Application of ulinastatin in severe craniocerebralinjuries.Chin J Traumatol, Aug 1; 2005: 8(4).
13. Nishiyama T, Yokoyama T, Yamashita K. Effects of protease inhibitor, Ulinastatin on coagulation and fibrinolysis in abdomnalsurgery. JAnesth, 2006; 20(3).
14. Mei Jiang, Jianzhong Tang .Clinical observation if treatment on infectious shock, Chinese Journal of Practice Medicine, 2004; 3: 11.
15. Chen X, LiX, LiuK. Clinical observation of ulinastatin on treatment of SIRS. Chin J Crit Care Med, Now, 2004; 11.
16. 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, Oct, 2004; 24: 1.
17. Pittet D, Thievent B et, al. Bedside prediction of mortality from bacteremicsepsis; a dynamic analysis of ICU patients. Am J Respir Crit Care Med, 1996; 153.
18. Todi S et.al. Epidemiology of severe sepsis in India: an update critical care, 2010.
19. Ulinastatin in Severe Acute Pancreatitis. https://www.clinicaltrials.gov/ct2/show/NCT01132521
20. Department of Gastroenterology, Zhong Shan Hospital, Fudan University, Shanghai, China Chinese Journal of Digestive Diseases, 08, 2009; 3(2): 70-74. http://www.researchgate.net/publication/230098241_Ulinastatin_in_the_treatment_of_acute_pancreatitis_A_multicenter_clinical_trial.
21. Grzegorz Wallner et.al. Morphological changes of the pancreas in course of acute pancreatitis during treatment with Ulinastatin. http://www.degruyter.com/view/j/pjs.2013.85.issue-3/pjs-2013-0020/pjs-2013-0020.xml

22. Selected biochemical parameters and ultrastructural picture of pancreas due to Ulinastatin treatment of experimental acute pancreatitis. http://www.sciencedirect.com/science/article/pii/S0940299304000545.
23. www.bharatserums.com.