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A STUDY ON EVALUATION OF THERAPEUTIC EFFECTIVENESS OF ULINASTATIN IN SEVERE ACUTE PANCREATITIS

Medicine

Dr S Thirumuruganand M.S., Associate Professor, Chengalpattu Medical College and Hospital, Chengalpattu 603001.

Dr N Srividhya* M.S., Assistant Professor, Govt Stanley Medical College and Hospital, Chennai 600001. *Corresponding Author

ABSTRACT

BACKGROUND: Ulinastatin is an acid-resistant protease inhibitor found in human urine and released from the high-molecular weight precursor I alpha T1. It inactivates many serine proteases including trypsin , chymotrypsin. Ulinastatin also supresses neutrophil accumulation and activity. Thus ulinastatin plays an important role in the protection of organ injury during severe inflammation in Acute Pancreatitis

METHODS: This is a prospective randomised interventional study conducted in Department of General Surgery in Stanley Medical College and Hospital, Chennai, India on 68 patients diagnosed to have acute pancreatitis and was treated with ulinastatin versus a control group. The duration of hospital stay and ICU, organ function damage, mortality in patients were all considered as outcomes.

RESULTS: The mean duration of symptoms is 2.41 days for the Ulinastatin group. The mean duration of symptoms is 2.35 days for the non-Ulinastatin group. Majority of them were alcoholics in both the groups. The Majority of Acute edematous Pancreatitis in both the groups. The Majority (n=39,N=68) of CTSI Score was 7.0. AKI was found more among the group that was not on Ulinastatin. The mean number of days in ICU was 2.59 with a SD of 1.579 (n=34) among Ulinastatin. The mean number of days in ICU was 3.5 with a SD of 1.895 (n=34) among controls. Three people not on Ulinastatin died while only one patient on Ulinastatin died. The mean number of days in the hospital was 10.82 (SD = 3.996, n=34) for cases. The mean number of days at the hospital was 12.76 (SD= 5.538, n=34) for controls. Significant association was found on day 3 and day 7 for serum amylase and day 7 for serum lipase ($p<0.005$).

CONCLUSIONS: The study found out that the Ulinastatin is effective for treating acute pancreatitis albeit minimal and the effect of addition of ulinastatin to standard care on mortality and morbidity in patients with severe acute pancreatitis is better compared to the control group.

KEYWORDS

Acute pancreatitis, Ulinastatin, Acute severe pancreatitis

INTRODUCTION

Pancreas is an internal organ in the abdomen that lies behind the stomach. It primarily functions to produce enzymes that are released into the gut and helps in digestion. It contains islets which are groups of cells.

Acute pancreatitis is the inflammation of the pancreas due to varied aetiology. It begins in the acinar cells of the pancreas as a local inflammatory response which may lead to multiple outcomes, sometimes, fatal. The Atlanta symposium on pancreatitis defines acute pancreatitis as the inflammatory process of the pancreas where the regional tissues or distant organ systems are involved variably. It is associated with high mortality. The systemic inflammatory response due to the local inflammation may lead to the involvement of non contiguous organs resulting in MODS (Multiple Organ Dysfunction Syndrome).

AIMS AND OBJECTIVES

- To study the effect of addition of ulinastatin to standard care on mortality and morbidity in patients with severe acute pancreatitis
- To find out its efficacy in prevention of multiorgan failure in SAP
- To show its effectiveness in reduced incidence of local complications
- To evaluate its efficacy in reduction of number of days of ICU stay and Hospital stay.

METHODOLOGY

MATERIALS AND METHODS

Place of study:
Department of General Surgery, Stanley medical college and hospital

Duration:
January 2018 to August 2018

Study design:
Prospective Interventional study

Selection of cases
From cases who present with signs and symptoms of acute pancreatitis

Sample size - 68 cases, of which 34 were treated with Ulinastatin and Standard of care and the control group 34 were treated with Standard of care alone.

INCLUSION CRITERIA

- Age group of the patients between 18 and 70 years
- Both males and females can be studied
- Patients with presentation of acute pancreatitis
- Patients must meet the following criteria:
- Ranson signs >=3
- APACHE II Score >=8
- Admission should be done within 72 hours after onset of symptoms of pancreatitis

EXCLUSION CRITERIA

- Age group of the patients < 18 and >70 years
- Women who are pregnant and/or lactating
- Patients with chronic pancreatitis
- Any patient who is a known case of heart dysfunction or NYHA classification score>3
- Any patient who is a known case of chronic renal insufficiency and on haemo or peritoneal dialysis
- Any patient who is allergic to Ulinastatin
- Any patient who is estimated to be mortal in 12 hours

Study group

Methodology

1) The present study was conducted for a period of eight months. This is a prospective randomised interventional study.

2) The following prerequisites were fulfilled;

- Detailed history
- Complete general examination
- Complete physical examination
- Complete systemic examination
- Patients were subjected to relevant investigations.

3) Acute pancreatitis was diagnosed if the patient has at least two of the following criteria:

- epigastric pain
- serum amylase and/or lipase level >3 times upper limit of normal
- imaging findings of acute pancreatitis

4) Subjects were classified as having mild or severe acute pancreatitis on the basis of the following:
a) APACHE II score (<8 mild, ≥8 severe)
b) CT severity index(CTSI) scores on abdominal CT scan were

grouped into three categories--mild-0-3,moderate-4-6 and severe-7-10.

5) At admission, suspected cases were checked for:
- BP
- pulse rate
- oxygen tension [PAO2]
- heart rate
- temperature

Biochemical parameters:
- Serum amylase
- Serum lipase
- S. Sodium
- S. Potassium
- S. Chloride
- S. Creatinine
- C Reactive Protein
- CT abd[plain]
- X-ray chest
- ECG

6) Standard care was given to all subjects as per the protocol.

7) Eligible subjects were randomized to receive intravenous 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 (Standard of care)

IV Antibiotics
IV fluids
Tramadol for pain
Ryles tube aspiration
Nil by mouth
PPI twice a day

8) Baseline characteristics, including demographic information, clinical findings, pre-existing chronic conditions, possible aetiology of pancreatitis, presence and severity of organ dysfunction, laboratory parameters, were assessed.

9) Serum CRP levels on day 1&7, serum amylase and lipase levels were assessed on days 1,3 and 7 and CT abdomen was done within 72 hours of admission.

10) Measures of outcomes:
Primary - Any new onset organ failure.
Secondary :
- Mortality
- Incidence Of Local Complications
- Necrosis
- Abscess,
- Pseudocyst.
- Duration Of ICU and Hospital Stay.

11) Sample size calculation
Taking 20% as P(% reduction in mortality)
Confidence interval at 95%
Power of study at 80%
Margin of Error at 10%
Minimum Sample size calculated is 61%
Expecting a loss of ratio 10%
Minimum Sample size adjusted to Loss is 68%
34 Cases of Pancreatitis & 34 appropriate controls were recruited

STATISTICAL ANALYSIS
The data was analysed using IBM SPSS Version 23 software. Frequencies, percentages and inferential statistics were done.

- Categorial variables were tested using Chi-Square test & Fischers Exact test
- ANOVA was done to understand how the two groups vary
- P Value <0.05 Considered Significant.

RESULTS
The data was analysed using SPSS software analysis. Frequencies, percentages and inferential statistics were done. Following results were obtained.

- The mean age of the ulinastatin group was 40.82 years (S.D=9.94, n=34). The mean age of the non-ulinastatin group was 39.91 years (S.D=11.09,n=34). The Males (82.4%,n=28) was higher compare to Females (17.6%,n=6) in Ulinastatin group and Males (94.1%,n=32) was higher compare to Females (5.9%,n=2) in non-Ulinastatin group.
- The mean duration of symptoms is 2.41 days for the Ulinastatin group vs 2.35 days for the non-Ulinastatin group.
- Majority of them were alcoholics in both the groups. The Majority had Acute edematous Pancreatitis in both the groups. The Majority (n=39,N=68) of CTSI Score was 7.0.
- AKI was found more among the group that was not on Ulinastatin. The mean number of days in ICU was 2.59 with a SD of 1.579 (n=34) among Ulinastatin. The mean number of days in ICU was 3.5 with a SD of 1.895 (n=34) among controls.
- Three people not on Ulinastatin died while only one patient on Ulinastatin died.
- The mean number of days in the hospital was 10.82 (SD = 3.996, n=34) for Ulinastatin group. The mean number of days at the hospital was 12.76 (SD= 5.538, n=34) for controls.
- Significant association was found on day 3 and day 7 for serum amylase and day 7 for serum lipase levels with Ulinastatin administration ($p<0.005$).

Etiology of the disease
The following tables and figure shows the etiology of pancreatitis. Majority of them were alcoholics in both the groups. The chi-square test shows significant result ($p<0.05$) with a value of 14.

ETIOLOGY	ON ULINASTATIN		TOTAL
	NO	YES	
ALCOHOL	26	26	52
DRUG INDUED (PHENYTOIN)	1	0	1
GALL STONE	6	7	13
HYPERTRIGLYCERIDEMA	1	1	2
TOTAL	34	34	68

CTSI Score
The following tables and figures show the CTSI score. The Majority (n=39,N=68) of CTSI Score was 7.0.

CTSI SCORE	ON ULINASTATIN		TOTAL
	NO	YES	
7.0	18	21	39
8.0	15	12	27
9.0	1	1	2
TOTAL	34	34	68

NEW ONSET ORGAN FAILURE
The following figures and tables show the new onset organ failure. AKI was found more among the group that was not on Ulinastatin.

ORGAN FAILURE	ON ULINASTATIN		TOTAL
	NO	YES	
AKI	6	2	8
ARDS	4	2	6
AKI + ARDS	2	1	3
NIL	22	29	51
TOTAL	34	34	68

LOCAL COMPLICATIONS –

LOCAL COMPLICATIONS	ON ULINASTATIN		TOTAL
	NO	YES	
ABSCESS	3	0	3
NECROSIS	12	6	18
NECROSIS WITH ABSCESS	1	0	1
NECROSIS WITH PSEUDOCYST	1	1	2
PSEUDOCYST	6	3	9
NIL	11	24	35
TOTAL	34	34	68

Number of Days in ICU
The graph shows the distribution of number of days in ICU among the Ulinastatin group. The mean number of days in ICU was 2.59 with a SD of 1.579 (n=34)

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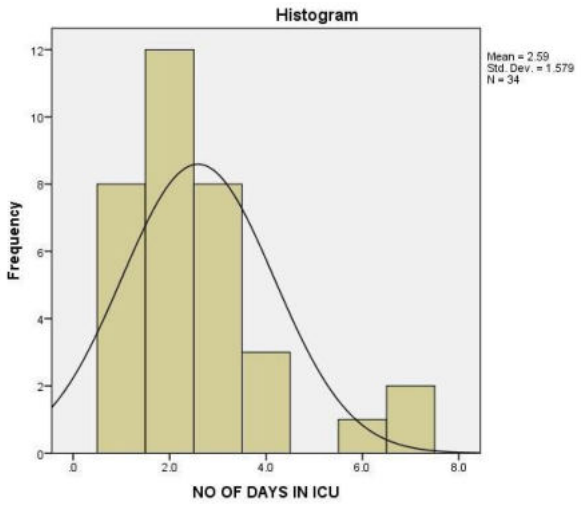
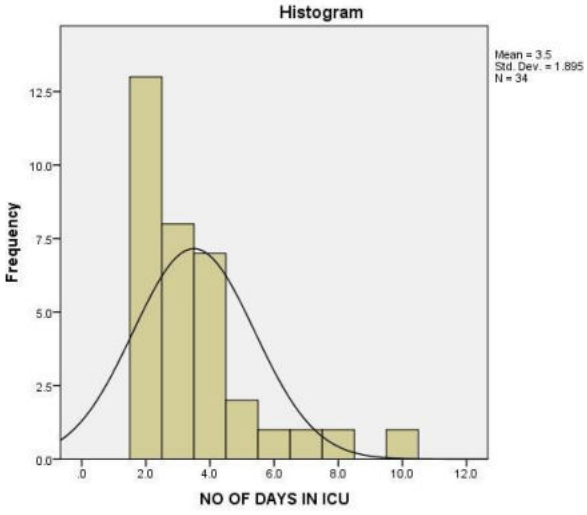
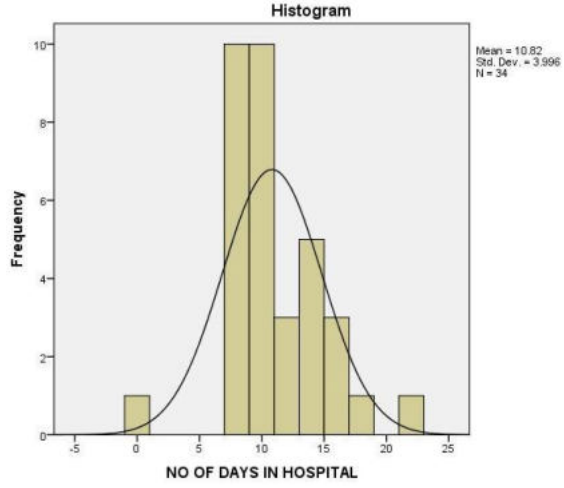


The following graph shows the distribution of number days in ICU among the non-Ulinastatin group. The mean number of days in ICU was 3.5 with a SD of 1.895 (n=34). The chi-square was not significant (p>0.005).

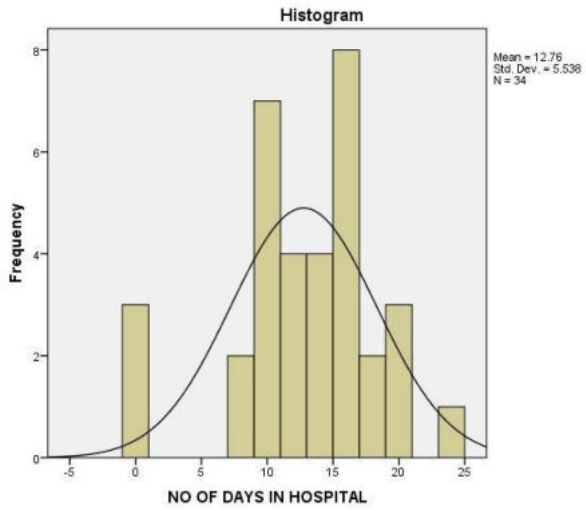


Number of Days in Hospital

In this study, three people not on Ulinastatin died while only one patient on Ulinastatin died. The graph shows the distribution of number of days at the hospital among the Ulinastatin group.The mean number of days in the hospital was 10.82 (SD = 3.996, n=34)



The graph shows the distribution of number of days at the hospital among the non-Ulinastatin group. The mean number of days at the hospital was 12.76 (SD= 5.538, n=34). The chi-square was found to be not significant (p<0.005)



DISCUSSION

A systematic review of literature showed that there are few studies from the Indian scenario to give an idea on how effective Ulinastatin is for treating acute pancreatitis. Studies from different countries also did not reveal much about the variables under study.

Role of Ulinastatin in the treatment of Acute Pancreatitis: Asystematic review

Ulinastatin (UTI) is an urinary trypsin inhibitor that acts against the proteases. It is obtained from the urine of healthy humans. They are protease inhibitor that acts against the pancreatic enzymes thereby reducing the inflammation of the pancreas in acute pancreatitis. The survival rate was seen to increase in Phase 1 trial of the drug (Maciejewski et al, 2005). It is also seen that Ulinastatin can act against the tumor necrosis factor-α and interleukin-1β. It also acts to increase the levels of interleukins 2 and 10. Most of the studies on Ulinastatin has centred around these cytokines.

Wang et al in 2015 showed that the immunological function can be boosted using Ulinastatin by stopping the death of CD4+ T-cells. Hao et al in 2013 demonstrated that ulinastatin can reduce the inflammatory response in patients of cardiopulmonary bypass by expanding regulatory T-cells ($CD4^{+}CD25^{+}$).

Previous Studies of Ulinastatin in the treatment of Acute Pancreatitis

Lagoo et al in 2018 did a retrospective analysis to find the clinical efficacy of Ulinastatin to treat severe acute pancreatitis. The patients were those diagnosed with acute pancreatitis. They were admitted in the Intensive Care Unit of the Surgical unit with complaints of end organ dysfunction. They divided into those who received the drug and those who did not.

Among 48 patients, 25 were in the case group while 23 were controls. The following results were obtained;

- in-hospital mortality was significantly lower in the cases (16% vs 69.6)
- development of new-onset organ dysfunction (24% vs73.9%)
- Resolution of existing organ dysfunctions by day 5 was higher in the ulinastatin group.

They concluded stating that the cases had improved outcomes than controls.

Another study by Abraham et al in 2013 to assess the safety and efficacy of Ulinastatin against a placebo used a double-blinded, randomised and placebo controlled trial that was conducted across 15 different centres in India. The patients were in the age group of 18 to 70 years who had high CRP and acute pancreatitis. The standard inclusion guidelines were followed for admitting the patients.

1) A characteristic epigastric pain that radiates to the back
2) An increase in the serum amylase and lipase level that is three times above the normal
3) Characteristic radiological findings in ultrasonography and

contrast-enhanced computed tomography [CT]/magnetic resonance imaging [MRI]

APACHE II score (< 8 mild, > or = 8 severe) was used to classify the patients into mild. Moderate and severe

Treatment arm received: - intravenous infusion of 200,000 IU ulinastatin
Control arm received: - placebo in 100 mL of 0.9% saline
Both were given over one hour once in 12 hours for 5 days.

A total of 135 patients were enrolled in the study. The study was completed by 129 patients. Out of which, 67 patients had severe pancreatitis and 62 and mild pancreatitis. Alcohol was the major reason in 81% of the subjects.

The following results were obtained;
- Baseline data did not vary between the groups.
- A minimum of 3-day dose was required to evaluate the patients.
- One Vs six was the number of deaths between cases and controls
- Five vs. four was the number in new organ dysfunction with mild pancreatitis
- Twelve Vs twenty nine was the number in new organ dysfunction with severe pancreatitis Ulinastatin registered
- lower adverse events

The study concluded that ulinastatin is effective in preventing new organ dysfunction and reducing the mortality rate.

The results of our study was in line with the above mentioned studies, proving that there is significant reduction in morbidity and mortality with Ulinastatin in patients of severe acute pancreatitis in the Indian scenario as well.

CONCLUSION

1) The present study found out that the effect of Ulinastatin is effective for treating acute pancreatitis albeit minimal.
2) The effect of addition of ulinastatin to standard care on mortality and morbidity in patients with severe acute pancreatitis is better compared to the control group.
3) The efficacy in prevention of multiorgan failure in SAP is more than the control group.
4) The incidence of local complications differs slightly between the two groups that took Ulinastatin and those who did not with lesser complications in those on Ulinastatin.
5) There is a reduction of number of days of ICU stay and hospital stay in patients on Ulinastatin. The mean number of days in ICU was 2.59 with a SD of 1.579 (n=34) in cases. The mean number of days in ICU was 3.5 with a SD of 1.895 (n=34) in controls. The mean number of days in the hospital was 10.82 (SD = 3.996, n=34) for cases and the mean number of days at the hospital was 12.76 (SD= 5.538, n=34) for controls.

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