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Original article:

Ulinastatin compared with Octreotide in severe acute pancreatitis: A Prospective observational study

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Abstract

Background: Severe Acute pancreatitis (SAP) is a pancreatic inflammatory disease that has a high mortality. Ulinastatin, a urinary trypsin inhibitor that can be used in SAP. However, there are limited studies comparing Ulinastatin and octreotide in SAP. This study was done to study the efficacy of Ulinastatin in SAP patients in comparison with Octreotide.

Methods: A prospective observational study was conducted among 49 SAP patients in the surgical in-patient unit at Goa medical college from January to March 2021. Patients either received Ulinastatin or Octreotide as part of their routine care and the institutional protocol. Various clinical outcomes, blood, and urine amylase levels were compared between two treatment groups. For statistical analysis SPSS version 20 was used.

Results: The mean age of the patients was 40.31 ± 9.45 years. The cause of pancreatitis was alcohol usage in 42(85.71%), gallstones in 4 (8.16%), and pseudocyst in 3 (6.12%). Among the study population**,** 29 (59.18%) patients received Ulinastatin, and 20 (40.82%) received Octreotide. The mean blood amylase was 1452.11 ± 716.54 units per liter before treatment and 945.15 ± 397.03 after treatment. The mean urine amylase was 2432.37 ± 765.22 units per liter before treatment and 1064.7 ± 495.12 after treatment. The differences in the blood and urine amylase levels before and after treatment was statistically significant (P-value <0.001).

Conclusion: This study has shown that Ulinastatin has better outcome than Octreotide in treatment of patients with severe acute pancreatitis.

Keywords: Severe Acute pancreatitis; ulinastatin; multiple organ dysfunction syndromes; Octreotide.

Introduction:

Severe Acute Pancreatitis (SAP) is a common condition of the gastrointestinal tract [1,2]. In this condition, autodigestion of the pancreas occurs which causes injury to the pancreas. This pancreatic autodigestion leads to glandular dysfunction and systemic consequences [3]. Globally, the pooled incidence of SAP is 34 cases per

100,000 people per year, equally affecting both genders. It is common in middle-aged or older aged people [4]. The definitive cause can be detected among 75%-85% of affected patients. In developed countries, the common causes of SAP are stones obstructing the common bile duct (38%) and alcohol abuse (36%) [5,6]. Most acute pancreatitis episodes are mild with self-limiting local inflammation and only require a short hospital stay (~48 h). However, 15%–25% of patients present with systemic involvement, tissue necrosis, or infection [7–9]. The disease's mortality rate is diverse, ranging from almost 0% in mild pancreatitis up to 80% in severe necrotizing pancreatitis [10]. The revised Atlanta classification of 2012 documented this heterogeneity and defined two types and three levels of severity for SAP. It recognizes oedematous interstitial and necrotizing SAP, distinguished by using contrast-enhanced imaging. The three levels of severity are mild (absence of organ failure and local complications), moderately severe (presence of local complications and/or transient organ failure <48 h), and severe (persistent organ failure >48 h) [7,11–13].

The main drugs used for acute pancreatitis are Ulinastatin and Octreotide [7]. The presence of immunosuppressive reactions in the early stages of patients with acute pancreatitis may seriously affect the prognosis of the disease [14]. Ulinstatin is found in the urine and blood of humans and is a glycoprotein that inhibits the serine protease enzyme. By action of neutrophilic elastase on inter-alpha-trypsin inhibitors, Ulinastatin gets released in the body. These trypsin inhibitors reduce the proteolytic activity of trypsin, producing an anti-inflammatory effect. Ulinastatin diminishes the rise of neutrophil elastase release, thereby decreasing the upsurge of pro-inflammatory cytokines and preventing the secretion of pro-inflammatory cytokines such as IL-6 and IL-8 [15]. At present, there are only a few studies on the effects of Ulinastatin or Octreotide on the clinical outcome of patients with acute pancreatitis [16,17]. There are no studies that compare the efficacy of Ulinastatin with Octreotide. Hence, this study was conducted to compare the efficacy of the main drugs for severe acute pancreatitis.

Study Objectives:

The objective of this study was to compare the clinical efficacy of Ulinastatin with Octreotide in the treatment of severe acute pancreatitis.

Materials And Methods

Study center: This study was carried out at Surgical Wards at Goa Medical College from Jan 2021 to March 2021. Approval for the study was obtained from the Institutional Ethics Committee. (Dated 12/10/2019)

Study design This is a prospective observational study done on patients admitted to the surgical wards. SAP patients were divided into two groups based on whether the patient received Ulinastatin or Octreotide. Based on the patient's affordability, the drugs were administered as part of medical management.

Patients: All adult patients up to 70 years of age, diagnosed with SAP with one or more end-organ dysfunction, were identified from surgical wards at Goa Medical College. Patients who received Ulinastatin infusion along with the standard treatment formed the ulinastatin group. Those patients who received the same standard of care and Octreotide in place of ulinastatin constituted the Octreotide group. Patients requiring endoscopy or surgical intervention and those who were on drugs like somatostatin were excluded from the study.

Study intervention: The use of Ulinastatin for the treatment of SAP is approved in India. However, this being a new drug the availability is poor and is also expensive. Based on patients' affordability, they were offered a choice to receive Ulinastatin in addition to the standard care, considering the novelty of the drug, as it is not a

part of our standard treatment protocol. Patients in the Ulinastatin group received ulinastatin as an intravenous infusion at a dose of 1 million units intravenously 8 hourly for a minimum of two days and a maximum of eight days based on the severity of disease addition to the standard care. Octreotide was given at a dosage of 100 micrograms Iv 8 hourly for a minimum of two days and a maximum of eight days based on the severity of disease days. In this study, a total of 29 patients received ulinastatin, and 20 patients received Octreotide.

Sample size calculation: The expected mean and standard deviation of the blood amylase in the Octreotide treatment group as μ_1,σ_1(119.57,2.5) and in the Ulinastatin treatment group as μ_0, σ_0(117.33,2.2) as per the previous study by Hai Wang He et al. [17] The other parameters considered for sample size calculation included were 80% power of the study and 5% two-sided alpha error [18]. As per the data mentioned above, the required sample size was 20 (18 and 10% lost to follow-up 2 cases) in each group. Our study included 29 in the Ulinastatin group and 20 in the Octreotide group in the final analysis.

Statistical methods: Distribution of all qualitative explanatory and outcome parameters reported as count and proportions. Quantitative parameters like age, days of stay were reported as mean and standard deviation with range. Blood and urine amylase were compared before and after periods using paired t-test. All quantitative parameters like age, blood & urine amylase, etc., were compared between two drug treatment groups using an independent sample t-test, non-normally distributed parameters like duration of stay and duration of drug therapy were compared using the Mann-Whitney U test. Categorical parameters were compared using Chi-square Test. P-value < 0.05 was considered statistically significant. SPSS 20 was used for statistical analysis [19].

Result:

A total of 49 subjects were included in the final analysis.

The mean age was 40.31 ± 9.45 years ranged from 24 to 64 years. The cause of pancreatitis was alcohol usage in 42(85.71%), gallstones in 4 (8.16%), and pseudocyst in 3 (6.12%). The mean duration of drug intervention was 2.73 ± 1.4 days ranged from 1 to 8 days. The mean duration of stay in hospital was 3.33 ± 1.66, ranging from 1 to 11 days. Mean blood amylase before treatment initiation was 1665.31 ± 697.95 units per liter ranging from 471 to 3047 units., After treatment, blood amylase levels reduced to 645.15 ± 397.03 units per liter ranged from 154 to 1452. The mean urine amylase before treatment was 2263.53 ± 741.96 units per liter ranged from 478 to 3010. After treatment, urine amylase level reduced to 1064.7 ± 495.12 units per liter, ranging from 145 to 2154. Among the study population**,** 29 (59.18%) patients received Ulinastatin, and 20 (40.82%) received Octreotide. At the end of treatment, 44 (89.80%) patients were discharged, and 5 (10.20%) were discharged against medical advice. (Table 1)

In the Ulinastatin group, the mean blood amylase was 1360.5 ± 710.17 units per liter before treatment and 660.63 ± 354.3 after treatment. In the Octreotide group, the mean blood amylase was 1585.36 ± 738.53 units per litter before treatment and 622.64 ± 469.69 after treatment. The difference in blood amylase was 699.88 (417.78 to 981.97) and 962.73 (463.13 to 1462.33) before and after treatment, and the difference was statistically significant (P-value 0.05). In the Ulinastatin group, the mean urine amylase was 2663.75 ± 471.48 units per liter before treatment and 1115.5 ± 458.05 after treatment. In the Octreotide group, the mean urine amylase was 2095.82 ± 989.32 units per litter before treatment and 990.82 ± 559.05 after treatment. The difference in urine

amylase was 1548.25 (1308.31 to 1788.19) and 1105.00 (657.83 to 1552.17) before and after treatment, and the difference was statistically significant (P-value 0.05). (Table 2)

There was no statistically significant difference between the Ulinastatin arm and octreotide arm with baseline characteristics and outcome (like age, age, cause of pancreatitis, days of drug therapy, days of stay, final outcome, blood amylase, and urine amylase) (P-value >0.05). (Table 3)

Tables:

Table 1: Summary of baseline characteristics in the study population (N=49)

Parameter	Summary	Median (IQR)
Age (in years) (Mean ± SD)	**40.31 ± 9.45 (range 24 to 64)**	**40 (35, 45)**
Cause of Pancreatitis		
Alcohol	**42(85.71%)**	
Gallstone Pancreatitis	**4 (8.16%)**	
Pseudocyst	**3 (6.12%)**	
Days of drug intervention (Mean ± SD)	**2.73 ± 1.4 (Range 1 to 8)**	**3 (2,3)**
Days of stay (Mean ± SD)	**3.33 ± 1.66 (Range 1 to 11)**	**3 (2,4)**
Blood amylase (units per liter)		
Before	**1665.31 ± 697.95 (Range 471 to 3047)**	**1654 (969,2172.50)**
After (N=27)	**645.15 ± 397.03 (Range 154 to 1452)**	**514 (420,981)**
Urine amylase (units per liter)		
Before	**2263.53 ± 741.96 (Range 478 to 3010)**	**2451 (1631,2951.50)**
After (N=27)*	**1064.7 ± 495.12 (Range 145 to 2154)**	**987 (678,1457)**
Drug		
Ulinastatin	**29 (59.18%)**	
Octreotide	**20 (40.82%)**	
Final outcome		
Discharged	**44 (89.80%)**	
Discharged against medical advice	**5 (10.20%)**	

27 patient's data only available

Table 2: Comparison of mean blood and urine amylase before and after in study group individually

	Blood Amylase		Urine Amylase	
Group	**Before**	**After**	**Before**	**After**
Ulinastatin (mean ± SD) (N=16)	**1360.5±710.17**	**660.63±354.3**	**2663.75±471.48**	**1115.5±458.05**
Mean difference (95 % CI and P value)	**699.88 (417.78 to 981.97 and <0.001)**		**1548.25 (1308.31 to 1788.19 and <0.001)**	
Octreotide (mean ± SD) (N=11)	**1585.36±738.53**	**622.64±469.69**	**2095.82±989.32**	**990.82±559.05**
Mean difference (95 % CI and P value)	**962.73 (463.13 to 1462.33 and 0.002)**		**1105.00 (657.83 to 1552.17 and <0.001)**	

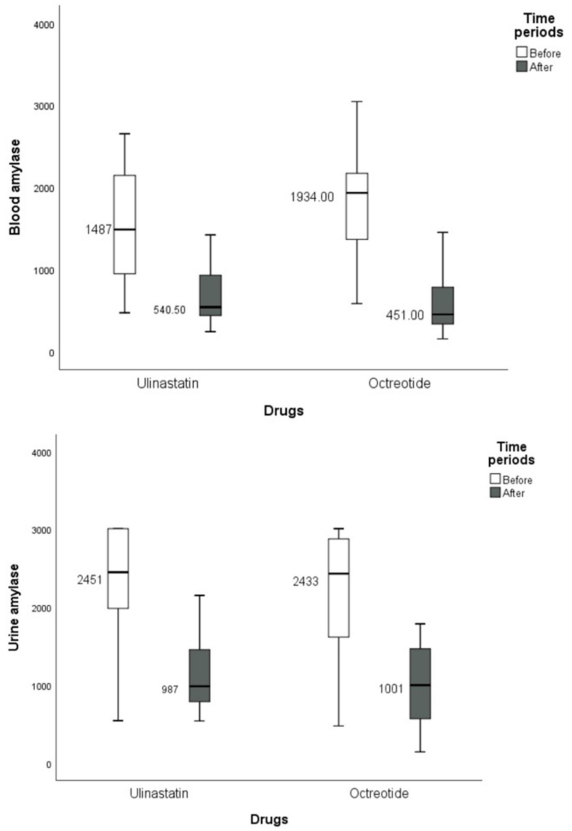
Table 3: Comparison of mean of baseline characteristics and outcome between drug groups (N=49)

Parameter	**Drug**		**P value**
	Ulinastatin (N=29)	**Octreotide (N=20)**	
Age (Mean± SD)	**39.55 ± 8.23**	**41.4 ± 11.12**	**0.507***
Cause of pancreatitis			
Alcohol	**26 (89.66%)**	**16 (80%)**	**0.577†**
Gallstone Pancreatitis	**2 (6.9%)**	**2 (10%)**	
Pseudocyst	**1 (3.45%)**	**2 (10%)**	
Days of drug therapy Median (IQR)	**2 (2,3)**	**3 (2,3.75)**	**0.388‡**
Days of Stay Median (IQR)	**3 (2,4)**	**3 (2.25,4)**	**0.337‡**
Final outcome			
Discharge	**27 (93.1%)**	**17 (85%)**	**0.387§**
DAMA	**2 (6.9%)**	**3 (15%)**	
Blood Amylase Before (Mean± SD) units per liter	**1550.14 ± 696.92**	**1832.3 ± 682.12**	**0.167***
Urine Amylase Before	**2451 (1732.5,3010)**	**2433 (1536.5,2879)**	**0.373‡**

Median (IQR) units per liter			
	(N=16)	**(N=11)**	
Blood Amylase After (Mean± SD) units per liter	**660.63 ± 354.3**	**622.64 ± 469.69**	**0.812***
Urine Amylase After Median (IQR) units per liter	**987 (733.5,1457)**	**1001 (451,1487)**	**0.805‡**

***- independent sample t-test, †- chi-square test, ‡-Mann Whitney u test, §-* Fisher exact test**

Figure 1: Comparative box plot of median blood amylase and urine amylase in before and after treatment with drugs (N=27)



Discussion:

This study was done to compare the treatment outcomes in SAP patients treated with Ulinastatin and Octreotide. The study's results show a statistically significant difference in the level of blood amylase and urine amylase before and after treatment with Ulinastatin compared to Octreotide.

Ulinastatin acts by inhibiting serine proteases, thereby producing inflammation and deregulated coagulation. Various serine proteases consist of trypsin, thrombin, chymotrypsin, kallikrein, etc. By its action on inhibiting these enzymes, Ulinastatin can have a favorable effect on the evolution of acute pancreatitis. It prevents organ dysfunction and promotes hemostasis by the action of immune modulation [20–22].

Ulinastatin acts by reversing the histological damage like interstitial edema, necrosis, and vacuolization as shown in various pancreatitis models by Tani et al. [23] and Hirano et al. [24]. Ulinastatin's role in the lysosome and mitochondrial stabilization, its inhibiting potential of intracellular digestion, autolysis, and tissue injury were proved by experimental studies. These studies have also shown that Ulinastatin role in pancreatic energy metabolism [23,24]. More current experimental studies [25,26] have also proved the favorable effects of Ulinastatin in SAP.

A recent meta-analysis was done among Asian patients with acute pancreatitis. It proved evidence that the serum levels of inflammatory markers such as CRP, IL-6, and TNF-α were significantly reduced following Ulinastatin treatment in AP patients [27]. A randomized controlled trial by Abraham et al.[16] among 70 SAP patients had a significantly lower mortality rate of 2.8% among the Ulinastatin group compared to 18.7% in the placebo group.

In this current study, the etiology of pancreatitis among the study participants was alcohol usage in 42(85.71%), gallstones in 4 (8.16%), and pseudocyst in 3 (6.12%). This indicates that alcohol usage among the study participant was the commonest etiology of SAP. This was similar to the study done by Prasad ML et al., where alcohol was the most common causative factor of SAP [28].

Ulinastatin can efficiently improve the blood and urine amylase levels in the early stages of SAP. Among the Ulinastatin group, 93.1% of the patients were discharged after successful treatment. The current study findings prove that Ulinastatin therapy in patients with severe acute pancreatitis reduces the blood and urine amylase levels compared to Octreotide.

The limitation of the current study is its relatively small sample size and the study's observational nature, limiting the generalizability of the results. In the future, a large-scale randomized controlled trial is recommended to establish the efficacy and safety of Ulinastatin.

Conclusion:

The most common cause of severe acute pancreatitis in India remains to be alcohol abuse. The current study's findings showed that Ulinastatin, a protease inhibitor can reduce the blood and urine amylase levels thereby improving the outcomes of SAP patients compared to Octreotide therapy.

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