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The Efficacy of Ulinastatin in Surgical Sepsis at Tertiary Care Institute

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ABSTRACT

Surgical Sepsis is a life-threatening complication that can lead to organ failure and death. Ulinastatin is a broad-spectrum serine protease inhibitor with anti-inflammatory and immunomodulatory properties. It has been shown to be effective in reducing mortality in patients with severe sepsis. The objective of this study is to evaluate the efficiency of Ulinastatin in improving clinical outcomes in patients with Surgical Sepsis. A retrospective study was conducted on 200 patients diagnosed with surgical sepsis. The patients were divided into two groups: a treatment group (N=100) who received Ulinastatin in addition to standard therapy and a control group (N=100) who received standard therapy alone. The primary outcome measure was the rate of mortality. Secondary outcome measures included the length of hospital stay, the incidence of organ failure, and the need for mechanical ventilation. We also changed the antibiotic class as per culture reports. The mortality rate was significantly lower in the treatment group (8%) compared to the control group (20%) (P=0.03). The treatment group also had a shorter length of hospital stay (12 days vs. 16 days, P=0.02) and a lower incidence of organ failure (12% vs. 24%, P=0.04). it was also noticed that the amount and number of days for which the antibiotic was given, was significantly reduced. There was no significant difference in the need for mechanical ventilation between the two groups. Ulinastatin appears to be a safe and effective treatment for Surgical Sepsis. It significantly reduces mortality, shortens hospital stay, and reduces the incidence of organ failure. Further research is needed to confirm these findings and explore the optimal dosing and timing of Ulinastatin administration in Surgical Sepsis patients.

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Key Words
Sepsis, ulinastatin, effectiveness, mortality

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INTRODUCTION

Sepsis is a systemic inflammatory response syndrome to infection, leading to significant morbidity and mortality, especially in elderly and critically ill patients[1]. A recent scientific publication estimated that in 2017, there were approximately 48.9 million cases of sepsis worldwide, leading to 11 million sepsis-related deaths. This accounted for nearly 20% of all global deaths. In the same year, almost half of all global sepsis cases occurred in children, with an estimated 20 million cases and 2.9 million deaths among children under 5 years of age[2].

Sepsis primarily arises from inflammation triggered by the activation of the body's innate immune system[3]. Two key findings characterize the innate immune response in sepsis. The first key finding in sepsis is that, the innate immune response is triggered by simultaneous recognition of infection-derived microbial products and endogenous danger signals by various cell-surface receptors. This activates a complex signalling system involving complement, Toll-like receptors and other receptors, leading to inflammation[4].

The second key finding in sepsis is that, multiple signalling pathways are activated by recognizing pathogens and tissue damage, leading to inflammation and immune responses[5]. These pathways trigger the expression of genes involved in inflammation, immunity and metabolism, resulting in a common yet finely regulated response to different infections and tissue injuries[6].

Mechanism of Action of Ulinastatin:

- Urinary trypsin inhibitor (UTI), found in human urine, blood and tissues, serves as a vital protease inhibitor.
- UTI exhibits dual roles: it diminishes p38 mitogen-activated protein kinase (p38-MAPK) phosphorylation and inhibits nuclear factor-κB (NF-κB) activation, thereby exerting anti-inflammatory effects.
- Additionally, UTI safeguards mitochondria and scavenges oxygen free radicals, demonstrating anti-apoptotic properties[7,8].
- Ulinastatin is effective for alleviating inflammation and regulating immune function and its role in the clinical treatment of sepsis has become increasingly prominent[9].

Advances in sepsis management, including early fluid resuscitation, prompt antibiotic administration and improvements in supportive care like lung-protective mechanical ventilation, have contributed to a decreasing risk of sepsis-associated death. Despite these advances, the mortality rate of sepsis remains high. Therefore this study aims to find the efficiency of Ulinastatin in Surgical Sepsis.

MATERIALS AND METHODS

In this prospective study, we examined total of 200 cases diagnosed with the surgical sepsis. We included patients aged 18-80 years who met the criteria of The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). These patients had confirmed or suspected infection and experienced a sudden increase in total Sequential Organ Failure Assessment (SOFA) score by $\geq$2 points. The study excluded patients below 18 and above 80 years of age, as well as those with Class IV chronic heart failure or myocardial infarction within the previous 3 months, uncontrolled blood loss, cardiogenic shock, or advanced pulmonary fibrosis.

We categorized patients in two groups,

Group A: A treatment group (n=100) who received Ulinastatin in addition to standard therapy and.

Group B: control group (n=100) who received standard therapy alone.

Statistical Analysis: The data were recorded in a Microsoft Excel spreadsheet. All statistical analyses were conducted using IBM SPSS Statistics version 20.0. Descriptive statistics are presented as mean±standard deviation. A two-tailed unpaired Student's t-test was utilized to compare continuous variables between two groups, while the chi-square test was employed for categorical variables. A $p<0.05$ was considered statistically significant.

RESULTS AND DISCUSSIONS

In the Ulinastatin group, there were 65 males and 35 females, while the Control group also had 65 males and 35 females. The mean age in the Ulinastatin group was 58.7 years with a standard deviation of 16 years, and in the Control group, it was 58.7 years with a standard deviation of 16 years.

The Ulinastatin Group had a mean ICU stay of 14 days (±3.15) compared to 18 days (±3.44) in the Control Group, with a statistically significant difference

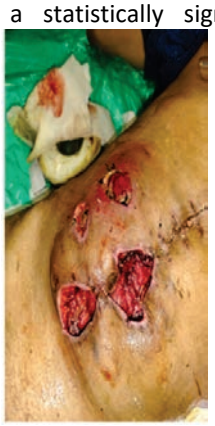

Fig. 1: Start of Burst Abdomen, Sutures were removed Ulinatstatin started (DI of drug)

Fig. 2: Presence of necrotic peritoneal fluid
Day 3 of Ulinatstatin
Drug administered for 5 day

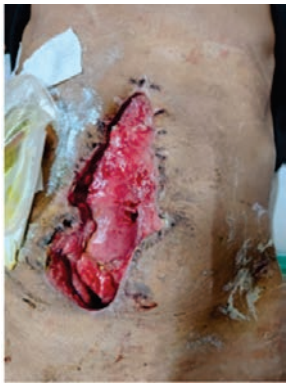

Fig. 3: Wound granulating, settling of SSI
Day 7 post ulinastatin

Fig. 4: Healthy granulating wound
Day 12 post Ulinastatin

Fig. 5: Day 1, post debridement
Day 1 of Ulinastatin

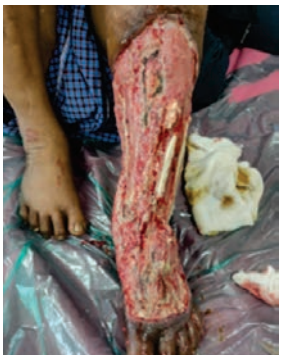

Fig. 6: Day 3 post Ulinastatin

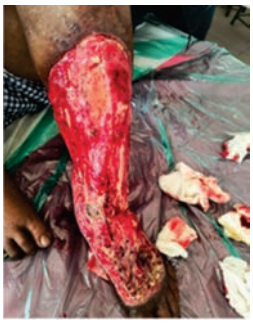

Fig. 7: Day 7 post Ulinastatin

Fig. 8: Day 1 post debridement
Day 1 of Ulinastatin

Fig. 9: Day 3 of Ulinastatin

Fig. 10: Day 5 of Ulinastatin

Fig. 11: Day 2 after stopping Ulinastatin

Fig. 12: Day 1 post debridement and day 1 of Ulinastatin

Fig. 13: Day 3 of Ulinastatin

Fig. 14: Day 5 of Ulinastatin Drug stopped here

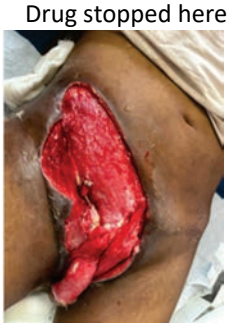

Fig 15: Day 2 post stopped the Drug

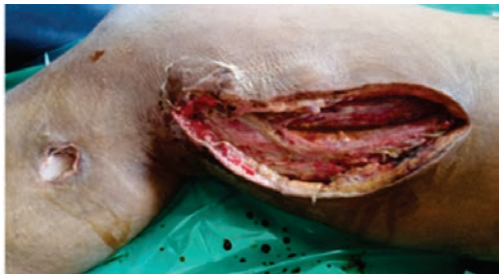

Fig. 16: Day 1 post debridement Day 1 of ulinastatin

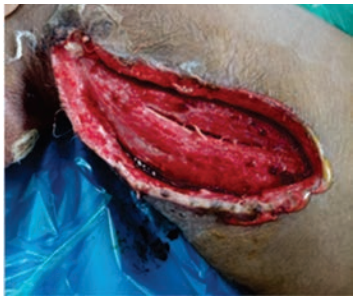

Fig. 17: Day 3 of ulinastatin

Fig. 18: Day 5 of ulinastatin

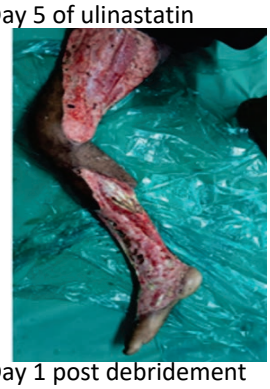

Fig. 19: Day 1 post debridement Day 1 of ulinastatin

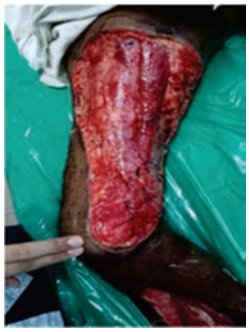

Fig. 20: Day 3 of ulinastatin

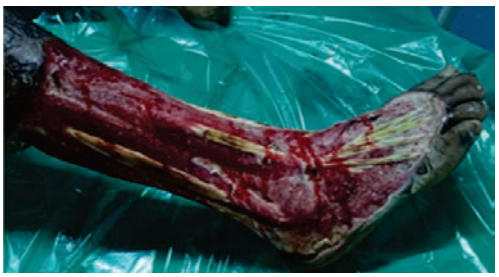

Fig. 21: Day 5 of ulinastatin

Table 1: Age and sex distribution.

Sex	Ulinastatin Group	Control Group
Males	65	65
Females	35	35
Total	100	100
Mean Age	58.7+/-16	58.7+/-16

Table-2: Comparison of Hospital Stay between the groups.

	Ulinastatin Group N=100	Control Group N=100	p-value
Mean ICU Days	14 ± 3.15	18 ± 3.44	<0.0001
Total Days	14	18	-

Table-3: Apache II and Sofa score

Scores	Ulinistatin Group N=100	Control Group N=100
Apache II	72	68
Sofa score	28	28
Gcs	60	60

Table 4: Complication in case and control group.

Underlying Disorder	Ulinistatin Group	Control Group	Chi square (P value)
Diabetes	60	56	2.761,
Hypertension	48	40	(p=0.09)
CKD	24	16	
Others	40	48	

Table 5: Comparison of treatment outcome after 30 days.

Outcome	Ulinistatin Group N=100	Control Group N=100	p-value
Recovered	92	80	P=0.014
Mortality	8	20	

(P<0.0001). The total hospital stay was 14 days in the Ulinastatin Group and 18 days in the Control Group.

The above table showed that, the Ulinistatin and control groups, the Apache II scores were 72 and 68, respectively. Both groups had identical SOFA scores (28) and GCS scores (60), indicating similar baseline severity and clinical status.

The above table showed that, the Ulinastatin and control groups for underlying disorders, the Ulinastatin group had slightly higher numbers of participants with diabetes (60 vs. 56), hypertension (48 vs. 40) and chronic kidney disease (24 vs. 16), while the control group had more participants with other underlying disorders (48 vs. 40). The difference in diabetes distribution approached significance (Chi-square =2.761, p=0.09)

The above table showed that, Ulinastatin showed a higher recovery rate (92%) compared to the control group (80%), with lower mortality (8% vs. 20%). The difference in outcomes was statistically significant (p=0.014).

Some Images of Patients: A 75 year old male presented with acute small bowel obstruction. Laparotomy was done and double barrel stoma was also brought out. On POD5, patient had developed 'burst abdomen and sepsis. Patients was started Ulinastatin immediately and patient was discharged purely on conservative basis management

A 60 Year old male, a/c/o left lower limb necrotising fascitis, one cleaning and debridement done and patients was immediately started on Ulinastatin. A 55 year male presented with septic shock and necrotising fascitis of right thigh region

A 44 year old male, a/c/o Synergistic gangrene presnted with septic shock

A 62 year old female presented with necrotising fascitis of left thigh

A 67 year old male presented with septic shock and necrotising fascitis of right lower limb

Sepsis is a life-threatening condition characterized by a dysregulated host response to infection, leading to organ dysfunction. Despite advancements in medical care, sepsis remains a major cause of morbidity and mortality in critically ill patients worldwide. Ulinastatin, a broad-spectrum serine protease inhibitor, has been investigated for its potential therapeutic role in sepsis. In this study, we included 200 patients in which they were divided into 2 groups the cases group and control group. The mean age of treatment group and control group was 58.7+/-16 and 58.7+/-16 respectively. The Ulinastatin group had a mean ICU stay of 14 days and the control group had 18 days which shows the statistical significance (P=0.002).

In both, the Ulinastatin Group and the Control Group, patients had similar scores for Sofa and GCS i.e. the Sofa score was 7(28%) with 28 % of patients scoring at or below 7. The median GCS score was 15 (60%), indicating that 60% of patients had a GCS score of 15 or lower. The Apache II score was 18 (72%), indicates that 72% of patients scored at 18 or below for Ulinastatin group and for control group with 68% of patients scoring at or below 17.

In the Ulinastatin Group, 92 patients (92%) recovered, while 8 patients (8%) succumbed within 30 days. While, in the Control Group, 80 patients (80%) recovered and 20 patients (20%) succumbed within 30 days. The chi-square test showed no significant difference in treatment outcomes between the two groups (p=0.22).

Our results are in line with previous studies on the effects of Ulinastatin in sepsis patients. Karnad[10] studied 122 sepsis patients with organ failure, finding a 28-day all-cause mortality rate of 7.3% (4 deaths) in the Ulinastatin group compared to 20.3% (12 deaths) in the control group (P=0.045). Zheng[11] conducted a meta-analysis of 16 studies and found that, Ulinastatin

in combination with Xuebijing reduced mortality (RR 0.54, 95% CI: 0.41-0.70., P<0.001), APACHE II score on day 7 (SMD=-1.21, 95% CI: -1.62-0.80, P<0.01), duration of mechanical ventilation (SMD=-1.21, 95% CI: -1.62-0.80., P<0.01) and length of ICU stay (SMD =-1.21, 95% CI:-1.62-0.80., P<0.01) in sepsis patients.

In this study diabetes was the most common comorbidity, followed by hypertension and chronic kidney disease. The chi-square test indicated no significant difference in diabetes prevalence between the two groups (p=0.87).

Meng[12] in their study stated that, the intervention group showed significant improvements compared to the control group in APACHE II (P<0.01), multiple organ failure (MOF) (P<0.01), Glasgow Coma Scale (GCS) (P<0.01), CD3+ (P=0.03), CD4+ (P=0.03) and CD4+/CD8+ (P<0.01) levels. This suggests that Ulinastatin may be effective in treating patients with SS. In terms of safety, there were no significant differences in adverse events between the two groups, indicating an acceptable safety profile for Ulinastatin in surgical sepsis treatment.

In one another study done by Wang[13] with systematic treatment, the APACHE II score dropped significantly in both the UTI group and the control group. However, in the UTI treatment group, the APACHE II score decreased by an additional 4.72 points compared to the control group (mean=-4.72, 95% CI [-6.54,-2.91]., p<0.00001). Based on these results, it can be concluded that UTI treatment can improve the severity of sepsis, which aligns with its efficacy in improving the 28-day survival rate.

CONCLUSION

This study compared the effects of Ulinastatin in a group of 200 patients with a control group of 100 patients. We can draw the following conclusions. There was a significant reduction in the dosage and number of days of administration of antibiotics in the group that received Ulinastatin. The Ulinastatin group had a lower mean ICU stay and a shorter total hospital stay compared to the control group, both of which were statistically significant. Ulinastatin group had a higher recovery rate and a lower mortality rate compared to the control group, but this difference was not statistically significant. Therefore we suggest further research on the use Ulinastatin in patients with sepsis.

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