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ORIGINAL ARTICLE

A PROSPECTIVE, RANDOMIZED STUDY USING ULINASTATIN FOR THE TREATMENT OF PATIENTS WITH SEVERE SEPSIS

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ABSTRACT: A prospective, randomized study was conducted on patients of severe sepsis using ulinastatin for treatment. Total of 50 patients were taken up for this study who were randomly assigned in two groups: 25 patients in group A who were given ulinastatin and 25 patients in group B who were given placebo. Patients were evaluated clinically using Acute physiology and chronic health evaluation(APACHE), Multiple organ failure (MOF) and Glasgow coma score (GCS), at the time of admission and after therapy on the 3rd, 8th and 28th day. **RESULTS**: There was a significant difference between the two groups regarding the organ failure scores. Patients in group A showed a better performance in APACHE II, MOF and GCS as compared to patients in group B on 3rd, 8th and 28th day of admission. **CONCLUSION:** Ulinastatin has a beneficial role in the treatment of patients with severe sepsis.

KEYWORDS: Ulinastatin, Severe sepsis, Organ failure scores.

INTRODUCTION: Sepsis is defined as the presence (probable or documented) of infection together with systemic manifestations of infection [sepsis guidelines 2012]. Severe sepsis is defined as sepsis plus sepsis induced organ dysfunction or tissue hypoperfusion.[8] Sepsis has been reported to be the most common cause of death in non-coronary ICUs. Even with optimal treatment, mortality due to severe sepsis or septic shock is approximately 40% and can exceed 50% in the sickest patients.[3,10,15,21]

During sepsis bacterium leads to a decrease in both number and function of circulating lymphocytes through the mechanism of cell apoptosis with resultant immunosuppression. Initially there is an increase in the concentration of cytokines like IL-Iβ, IL-6 and TNF-α.[5] Increased expression of CD64 on polymorphonuclear leukocytes indicates cellular activation[evaluation of sepsis].Therapies like high dose steroids and TNFα antibodies have been tried but proved to be ineffective.

Ulinaststin, a protease inhibitor (kunitz-type) has an anti-inflammatory and anticoagulant action. It is extracted from human urine. It inhibits inflammatory markers: trypsin, pancreatic elastase and the endotoxin stimulated production of TNFα and interleukin 1, 8 and 6. It inhibits coagulation and fibrinolysis and promotes microperfusion. Thus, ulinaststin is an effective agent for immune modulation to prevent organ dysfunction and promote homeostasis.

Present study was conducted to see the effect of ulinaststin for treating severe sepsis.

MATERIAL AND METHODS: The study was conducted in the department of Anaesthesiology and Critical care GMC Srinagar from July 2013 to July 2014. Fifty patients with the diagnosis of severe sepsis were taken up for the study. Exclusion criteria were:

- Age<18years or>80years.

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- Chronic compensated organ dysfunction.
- Incurable malignancies.
- Patients on treatment with immunosuppressive drugs.

The patients were randomly assigned to two groups of 25 patients each, clinically evaluated and investigated. After obtaining informed consent, patients in group A received 2 lakh IU of ulinastatin two times a day and an equal amount of normal saline (NS) was given to patients in placebo group for a period of 7 days. Patients in both the groups received treatment as per the ICU protocol regarding IV fluids, antimicrobial therapy, cardiovascular\ respiratory support and surgical intervention.

Monitoring of vital signs like heart rate, blood pressure, oxygen saturation, temperature and end tidal CO2 was done continuously. GCS of the patients was assessed from time to time. Besides, biochemical and hematological tests were done at the time of admission and on 3rd, 8th and 28th day. These laboratory values and organ specific parameters were used to calculate APACHE II and MOF.

Statistical Analysis: The data collected was tabulated and analyzed by Graph Pad instat 3. Data was expressed as means and standard deviation (SD), medians and ranges or number and percentages. For statistical comparison student's paired and un-paired t-test was applied. P value < 0.05 was considered as significant.

RESULTS:

Patient characteristics on Admission: On admission, mean age, sex (M/F), body weight (kg), mean APACHE II score, MOF scores and Glasgow score were recorded. This distribution, as well as the demographic characteristics, the severity of sepsis at study entry were well-balanced across the two treatment groups (P >0.05). Treatment with UTI was found to be well-tolerated and safe without adverse events (Table 1 & 2).

Demographic characteristics	Group A (n=25)	Group B (n=25)	P-Value
Age (Years, mean±SD)	50±4.25	52±6.49	0.3647
Gender (M/F)	15/10	16/9	
Weight (Kg, mean±SD)	72±6.97	74±7.34	0.2166

Table 1: General characteristics of the two groups

Parameters	Group A	Group B
APACHE II (mean±SD)	15.2±3.39	15.28±3.28
MOF (mean±SD)	12.4±3.27	12.72±4.46
GCS (mean±SD)	8.64±2.54	8.24±1.71

Table 2: APACHE II, MOF and GCS (Glasgow) scores on admission

Effects of UTI in patients with severe Sepsis: APACHE II and MOF were reduced significantly after therapy on the 3rd, 8th and 28th day in Group A (P=0.0091, 0.0001, 0.0001 and 0.010, 0.0001, 0.0001 respectively), so did in Group B only after therapy on 28th day when compared with that on admission (P=0.029, 0.017, respectively). (Tables 3, 4)

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	Group A	Group B
On admission	15.2±3.39	15.28±3.28
Day 3	10.12±3.34	12.96±3.51
Day 8	6.52±2.14	10.15±3.00
Day 28	5.36±1.49	9.88±2.78
P-value	Day3 =0.0091; Day 8 =0.0001; Day 28 =0.0001	Day 28 =0.029

Table 3: APACHE II scores over treatment

	Group A	Group B
On admission	12.4±3.27	12.72±4.46
Day 3	9.96±2.97	10.12±3.14
Day 8	6.84±1.90	9.76±2.55
Day 28	3.16±2.28	7.84±2.35
P-value	Day 3 =0.0100 Day 8 =0.0001 Day 28 =0.0001	Day 28 =0.017

Table 4: MOF scores over treatment

For GCS P =0.0030, 0.0001 on 8th and 28th day in Group A, P=0.027 on 28th day in Group B.(Table 5)

	Group A	Group B
On admission	8.64±2.54	8.24±1.71
Day 3	9.92±3.22	8.48±1.78
Day 8	11.75±3.11	9.76±0.83
Day 28	13±2.55	10.08±1.18
P-value	Day 3 =0.1261; Day 8 =0.0030; Day 28 =0.0001	Day 28 VS 0 =0.027

Table 5: Glasgow scores over treatment

There were significant differences in APACHE II, MOF, and Glasgow scores after therapy on the 8th day between Group A and Group B (P =0.020, 0.024 and 0.007, respectively).

DISCUSSION: Sepsis is a clinical syndrome characterized by systemic inflammation due to infection. There is a continuum of severity ranging from sepsis to severe sepsis and septic shock. Besides the conventional treatment, new therapies for sepsis have been tried from time to time including monoclonal antibodies, NSAIDS and high dose steroids, but have failed to show good results.[5]

It has been shown that levels of proteases such as elastase are typically increased in cases of inflammation and/or infection and any substance that can inhibit this protease results in an anti-inflammatory effect.[10] α1-protease inhibitor (α1-PI) and ulinastatin are intrinsic physiologic protease inhibitors which suppress PMNE activity. In inflammatory tissues, α1-PI loses its ability to function in acidic conditions, but ulinastatin can continue to inhibit PMNE.[14]

Our study attempted to address the beneficial role of ulinastatin in organ failure scores in patients of severe sepsis. We compared difference in APACHE II, MOF and GCS among the two groups on 3rd, 8th and 28th day of admission.

There was a significant improvement in organ failure scores in group A as compared to group B.GCS improved on 8th day of admission in group A, whereas it improved on 28th day of admission in group B.

Ulinastatin, clinically used for the treatment of circulatory shock, hemorrhagic shock in trauma patients,[7] septic shock, burn sepsis,[19] acute pancreatitis,[9] ARDS[1,14,19] has a variety of therapeutic mechanisms:

1. Suppression of protease secretion from neutrophils via stabilization of lysosomal membranes.
2. Activity inhibition of neutrophil elastase and other proteases.
3. An inhibitory effect on the production of cytokines and adhesion molecules.
4. Anti-inflammatory effect and
5. Antioxidation.[2,4,6,12,13,20]

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