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Original Research Article

THE EFFICACY OF ULINASTATIN COMBINED WITH DEXAMETHASONE IN THE TREATMENT OF SEPSIS PATIENTS

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Abstract: *This study aims to evaluate the efficacy and application of ulinastatin combined with dexamethasone in treating sepsis. A retrospective study was conducted in Nishtar Medical Hospital from 5th July 2021 to 5th July 2022. It included 80 patients divided into Group A and Group B, with 40 patients each. In Group A, patients were included who were administered dexamethasone monotherapy. In Group B, 40 patients were administered ulinastatin combined with dexamethasone. Adverse effects, treatment efficacy and a related score of both groups were analyzed. Serum inflammatory factors were measured using ELISA. After the treatment, APACHE II scores were 17.43±5.33 and 12.48±2.42 in Groups A and B, respectively. Similarly, SOFA scores were 7.78±2.43 and 5.28±1.32 points, respectively. The adverse effects were in 13 (32.5%) patients in Group A and in 4 (10%) patients in Group B. from the results of current analysis it can be concluded that a combination of Ulinastatin and dexamethasone effectively treats sepsis.*

Keywords: Sepsis, Ulinastatin, Dexamethasone

Introduction

Sepsis, the body's abnormal response to infection, leads to organ failure (Shrestha et al., 2017). The risk of functional defects and death persists even after treatment. There are reports that even all the newly developed treatments may be resisted by sepsis (Cohen et al., 2015). Dexamethasone is a glucocorticoid used for treating immunosuppressive and inflammatory diseases (Ayroldi et al., 2018). Additionally, dexamethasone inhibits inducible nitric oxide synthase synthesis, thus treating sepsis (Spanier and McDonough, 2000). According to research, the survival rate during sepsis can be improved by dexamethasone, and in sepsis-associated encephalopathy, autophagy has a regulatory role (Spanier and McDonough, 2000). Additionally, as an adjunct therapy, dexamethasone is effective in meningococcal disease and has no adverse effect (Tolaj et al., 2017). Ulinastatin is a urinary trypsin inhibitor; it decreases pro-inflammatory cytokines and mediators (Chen et al., 2009). Randomized controlled trials have proved the effectiveness of ulinastatin in reducing mortality and organ failure in sepsis patients (Yu et al., 2017). In animal models, it has diminished systemic and local inflammation, increased anti-inflammatory cytokines, inhibited lymphocyte apoptosis, and increased survival (Qiu et al., 2020). This study aims to evaluate the efficacy and application of ulinastatin combined with dexamethasone in treating sepsis.

Methodology

A retrospective was conducted in Nishtar Medical Hospital from 5th July 2021 to 5th July 2022. It included 80 patients divided into Group A and Group B. The sample size was calculated by using EPI Info 7. Group A included 40 patients (21 males and 19 females) who were administered dexamethasone. Group B also contained 40 patients (25 males and 15 females) who were helped with ulinastatin combined with dexamethasone. Subjects diagnosed with sepsis were included in the study. Included subjects were informed about the study, and consent was taken. The study design was approved by ref# 35/43 dated 03-03-21 from the hospital's ethical committee. Subjects were excluded if they were minors or aged above 50, allergic to drugs used in the study, or had mental disorders, functional insufficiency, or malignant tumour. Subjects in Group A were administered 5 mg of dexamethasone through IV

injections. The drug was added to 100 ml of 5% glucose and injected twice daily. The subjects in Group B were given combination therapy; based on Group A, 50,000 units of IV ulinastatin were added to 100 ml of 5% IV glucose and administered twice daily. Drugs were administered for 6 days. Both groups assessed and compared the general clinical efficacy, SOFA score (9) and APACHE II score(10). 5 ml fasting blood of subjects before and after therapy was taken to quantify the serum concentrations of CK (creatine kinase), BUN (urea nitrogen), Cr (creatinine), IL-6 (interleukin 6), TNF-α (tumour necrosis factor) and IL-10 (interleukin 10) through ELISA. Treatment efficacy in both groups was compared. Effective treatment was defined as an APACHE II score of ≤20 points and major improvement in clinical condition. Ineffective treatment was defined as an APACHE II score of > 20 points, deterioration of disease and insignificant improvement in clinical symptoms. SPSS 21.0 was used for statistical analysis. Intergroup comparison was made using a t-test, and measurement data were represented as (x±sd). Count data were expressed as n (%), chi-square test was used for comparing data. $P < 0.05$ was considered statistically significant.

Results

General patient characteristics in both groups did not differ significantly. Before the treatment, APACHE II scores in Group A were 22.24±9.29 and in Group B were 23.44±10.09. After the treatment, APACHE II scores in Group A were 17.39±5.33 and in Group B were 12.39±2.42. SOFA scores before treatment in Group A were 14.46±4.29, and in Group B were 15.19±3.99 points, respectively. After the treatment, SOFA scores were 7.68±2.43 and 5.28±1.32 issues, respectively. Before treatment, urine volumes in Group A were 25.37±4.21 ml/h, and Group B was 26.17± 4.31 ml/h, respectively. After the dose administration, corresponding urine volumes were 93.23±13.55 ml/h and 142.77±16.23 ml/h. The antibiotic use time, ICU occupancy time and mechanical ventilation time in Group A were 15.33±2.21 d, 16.36± 4.23 and 14.44±3.59 d, respectively and in Group B were 12.58±1.55 d, 12.69±2.25 d, 11.35±2.53 d respectively.

Before treatment, serum tumour necrosis factor-α levels in Group A were 68.36±7.24 µg/L and in Group B were 69.08±7.22 µg/L. After treatment, levels were 37.39± 6.56 µg/L in Group A, and 28.37± 4.34 µg/L in Group B. Before treatment, serum interleukin-6 levels in Group A were 206.09± 10.52 µg/L and 207.19± 10.35 µg/L in Group B. After treatment, these decreased to 168.27± 7.30 µg/L and 131.35± 6.23 µg/L respectively. Before treatment, serum interleukin-10 levels in Group A were 40.52± 12.53 µg/L and 41.11± 12.23 µg/L in Group B. After treatment, these results were 24.46±9.55 µg/L and 16.43±8.32 µg/L. This indicates that serum inflammatory markers decreased significantly in Group B compared to Group A.

Serum Creatinine in Group A was 127.29±17.32 µmol/L, and 128.09± 17.46 µmol/L in Group B After treatment; corresponding values were 56.60± 13.75 µmol/L and 45.18±13.56 µmol/L. Before treatment, serum blood urea nitrogen contents in Group A were 10.43±2.46 mmol/L and 10.75±2.64 mmol/L in Group B; after treatment, these decreased to 6.28±2.53 mmol/L and 3.09±1.65 mmol/L. Before treatment, heart rates in Group A and B were 135.57±16.77 beats/ min and 136.42±16.67 beats/min, respectively; after treatment, corresponding heart rates were 104.49±9.55 beats/min and 87.50±10.48 beats/min. Before treatment, systolic blood pressures in Group A were 72.14±1.26 mmHg and 72.25±1.16 mmHg in Group B; after treatment, corresponding values were 81.32±3.54 mmHg and 89.32± 3.33mmHg. Before treatment, diastolic blood pressures in Group A were 51.58±1.14 mmHg and 51.42±1.32 mmHg in Group B; after treatment, corresponding values were 57.11±3.64 mmHg and 61.43±3.24 mmHg. The adverse effects incidence was lower in Group B than in Group A (Table and Figure 1). Treatment efficacy was more significant in Group B than in Group A (Table 2).

Table 1 Comparison of Adverse Reactions in Both Groups

Adverse reaction rate	**Group A (n=40)**	**Group B (n=40)**
Muscle weakness	3	1
Nausea	1	0
Diarrhea	1	0
Convulsion	3	1
Abdominal discomfort	2	0
Fever	1	2
Hemorrhage	2	0
Total Adverse **rate**	13 (32.5%)	4 (10%)

Table 2 Comparison of Treatment Efficacy in Both Groups

Efficacy	**Group A (n=40)**	**Group B (n=40)**	**p-value**
Effective	27 (67.5%)	35 (87.5%)	0.010
Ineffective	13 (32.5%)	5 (12.5%)	

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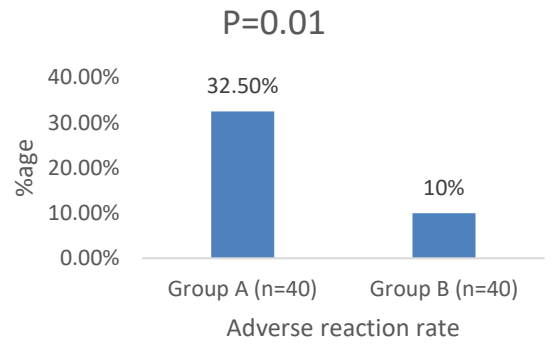

figure 1 Comparison of combined adverse effects between the groups

Discussion

Sepsis is systemic inflammation resulting in response to infection (Angus and Van der Poll, 2013), and recurrent and persistent inflammatory injuries cause endothelial injury (Bone, 1991). Sepsis exacerbates immune response, resulting in multiple organ failure (Kakihana et al., 2016). TNF-α is secreted in sepsis and triggers septic shock (Gil et al., 2016). IL-6 is an inflammatory mediator having specificity and sensitivity for sepsis (Hou et al., 2015). A study has shown that a rapid decline in IL-6 concentration after 48 hours signifies successful antibiotic treatment and chances of survival (Thao et al., 2018). In our study, the serum level of inflammatory cytokines was significantly lower in patients treated with ulinastatin than without it. It may be because ulinastatin reduces exacerbated inflammatory response by decreasing the release of oxygen free radicals and consumption of superoxide dismutase (Chen et al., 2013). Serum Cr indicates renal insufficiency(Schmidt et al., 2017). When renal injury accompanies sepsis, there is a significant increase in the risk of death, and a slight increase in serum Cr indicates a poor prognosis (Doi et al., 2009). CK protein indicates muscle necrosis, increase in its concentration indicates muscle necrosis (Brancaccio et al., 2007). Study shows that a deranged CK system is associated with kidney, heart, brain and muscle disease (Wyss and Kaddurah-Daouk, 2000). Therefore, serum BUN is a clinical indicator of renal function. In our study, serum BUN, CK and Cr levels were higher before treatment but dropped significantly after treatment in both groups. Serum levels in patients supplemented with ulinastatin were much lower than those without it. This is due to the activation of platelets and macrophages and the inhibition of polymorphonuclear leukocyte-derived elastase (Atal and Atal, 2016). In this study adverse effects, general clinical efficacy and relevant score were recorded in both groups. It was observed that efficacy and scores were better in Group B as compared to Group A.

Our study has some limitations. The sample size is small. A multicenter study with a large sample size may yield more beneficial results in the efficacy of these drugs.

Conclusion

A combination of Ulinastatin and dexamethasone is more effective in treating sepsis than dexamethasone alone.

Conflict of interest

The authors declared absence of conflict of interest.

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