Effect Of Low Dose Hydrocortisone On Duration Of Vasopressor Therapy In Septic Shock

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Abstracts: **Background & objectives:**Severe sepsis and septic shock are major health problems. Stress dose of hydrocortisone infusion reduces the time of cessation of vasopressor therapy in septic shock. This study was planned to see the role of low dose corticosteroids on duration of vasopressor therapy in patients with septic shock along with their outcome. **Methods:** The study was carried out in 40 patients of septic shock. The patients were randomized into two groups i.e. treatment (Group A) and the placebo (Group B) groups of 20 each. Both groups received antibiotics, vasopressors i.e. Dopamine and Norepinephrine and IV fluids along with low dose hydrocortisone being administered only to Group A. Mean values were compared statistically using t-test and z-test. **Results:** The mean time spent in shock (hours) in survivors was 44.00 ± 11.2 ($p< 0.001$) while in group B was 72.00 ± 0.00 ($p< 0.05$). Also, the number of survivors in group A was more with cortisol levels of 5-25 mcg/ml. **Interpretation & conclusion:**Low dose hydrocortisone reduced the time spent in shock in survivors of group A, thereby reducing duration of vasopressor therapy. It also reduced mortality in subgroup of patients with serum cortisol levels of 5-25 mcg/ml proving that moderately low cortisol levels are benefitted more with hydrocortisone therapy than those with relatively high cortisol levels. [Mahajan B NJIRM 2014; 5(1) : 17-20]

Key Words: Corticosteroids, management, sepsis

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Introduction: A Sepsis is a systemic, deleterious host response to infection leading to severe sepsis (acute organ dysfunction secondary to documented or suspected infection) and septic shock (severe sepsis accompanied with hypotension and not reversed with fluid resuscitation)[1]. Severe sepsis and septic shock are major health problems, frequently fatal killing one in four[2]. Incidence of sepsis is increasing and the number of cases of severe sepsis has increased by 139% in recent ten year period. The incidence of sepsis is increasing dramatically, due to the ageing population[3] and despite the advantages of modern medicine including vaccines, antibiotics and intensive care. Hospitalizations for sepsis have overtaken those for myocardial infarction in the US[4]. International and national surveys indicate that 20-40% of sepsis patients that require treatment in the intensive care unit developed sepsis outside the hospital[5].

The common clinical manifestations of sepsis include fever or hypothermia, tachypnea or hyperventilation, tachycardia, leukocytosis, coagulopathy and alteration in mental status.

Prognosis of the patients of septic shock depends on the patients underlying health status, development of septic insults and prevention of complications. Mortality is significantly high in severe sepsis and septic shock.

Despite numerous advances in the supportive care of patients, overall mortality has changed little in past 20 years. However, the speed and appropriateness of therapy administered in the initial hours after severe sepsis develops are likely to change the outcome of patients[1]. Many studies have shown improved outcome[6] and reduced hospital length of stay[7] with low dose steroids in patients of severe sepsis and septic shock.

Stress dose of hydrocortisone infusion reduces the time of cessation of vasopressor therapy in septic shock[8]. This study was planned to see the role of low dose corticosteroids on duration of vasopressor therapy in patients with septic shock along with their outcome.

Material and methods: The study was carried out in 40 patients of septic shock. The patients were taken from medical ICUs in a tertiary care hospital of North India. Ethical committee approval was

taken and written informed consent was taken from the relatives of the patients.

The patients were randomized into two groups i.e. treatment (Group A) and the placebo (Group B) groups of 20 each. The patients in Group A received low dose hydrocortisone in addition to antibiotics, vasopressors i.e. Dopamine and Norepinephrine (in their standard dose range) and IV fluids. Hydrocortisone was administered in the dose of 100 mg intravenously every 8 hour for at least 5 days. The reversal of septic shock was defined as the cessation of vasopressor support with stable systolic BP > 90 mm Hg for at least 24 hours. After this, the dose of hydrocortisone was reduced to 50 mg every 8 hours for 3 days, then 25 mg for every 8 hours for 3 days and then, it was discontinued. The plasma cortisol levels were measured for first 72 hours i.e. during first three days consecutively of starting hydrocortisone. Study drug was discontinued at 5th day, if no shock reversal occurred. The control group received antibiotics, vasopressors and IV fluids without cortical steroids. The various parameters were recorded to

- study the effect of low dose hydrocortisone on duration of vasopressor therapy in septic shock
- study the outcome in patients of septic shock receiving hydrocortisone

The patients included in the study were those who met the ACCP/SCCM[9] criteria for septic shock i.e. positive blood culture or infection and at least 2 of the following:

- Fever (temperature >38˚C) or hypothermia (temp. < 36˚ C)
- Tachycardia >90 beats/min
- Tachypnea >20 breaths/min
- Abnormal WBC count
- Evidence of organ dysfunction or hypoperfusion
- Hypotension despite adequate fluid resuscitation or the use of vasopressor or inotropic support.

The patients with age <18 and >75 years were excluded. The patients who had irreversible underlying disease, who were treated with vasopressor for greater than 48 hours or with glucocorticoids, organ transplant recipients, patients with burns or hemorrhagic shock and the ones who had suffered myocardial infarction in the last six months were all excluded from the study.

The patients were monitored according to SAPS-II scoring system which consists of 12 physiological variables and 5 other variables. For the 12 physiological variables, the worst value in 24 hours was taken into account. The data were collected based on the treatment and placebo groups. Mean values were compared statistically using t-test and z-test.

Results: The patients in both the groups were in the age group from 25-75 years along with other parameters is shown in (Table1).

Table1: Patient allocation based on various parameters

Parameters	**Group-A** (Mean ± SD)	**Group-B** (Mean ± SD)
Age (years)	52.35 ± 15.52	52.40 ± 11.18
Serum cortisol (mcg/dl)	21.32 ± 10.36	26.73 ± 14.38
SAPS II score	65.35 ± 11.90	67.53 ± 13.13
Underlying infections		
Pneumonia	8 (40%)	5 (25%)
Abdominal infection	3 (15%)	5 (25%)
Urogenital tract infection	3 (15%)	3 (15%)
Wound infection	6 (30%)	7 (35%)

After the enrollment of the patients in the study, the time in shock (hours) was between 66-75 hours for maximum number of patients in both the groups. The number of survivors was more in Group A as compared to Group B with p value >0.10 (Table 2). As the patients who left against medical advice were serious, they were ultimately counted under the category of non-survivors. The outcome of the patients was also affected by the serum cortisol levels (Fig 1).

Table 2: Distribution according to outcome

Outcome	Group A	Group B
Death	11 (55%)	12 (60%)
LAMA	4 (20%)	5 (25%)
Survival	5 (25%)	3 (15%)

The relationship between outcome and time spent in shock is presented in (Table 3).

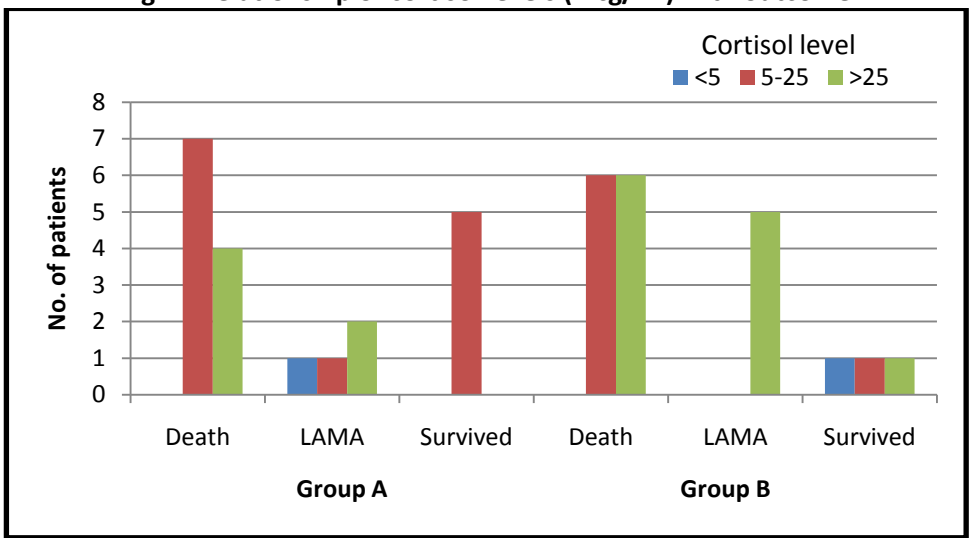
Table 3a: Relationship of time in shock with outcome in group A

Outcome	Time in shock	Non Survivor v/s Survivors
Non Survivors (15)	70.80 ± 7.54	t- value = 8.86 p- value < 0.001
Survivors (5)	44.00 ± 11.23	

Table 3b: Relationship of time in shock with outcome in group B

Outcome	Time in shock	Non Survivor v/s Survivors
Non Survivors (17)	72.00 ± 0.00	t- value = 2.08 p- value < 0.05
Survivors (3)	66.94 ± 10.89	

Fig. 1: Relationship of cortisol levels (mcg/ml) with outcome



Discussion: The hallmark of severe sepsis is uncontrolled systemic inflammation which is responsible for progression of organ dysfunction and death. Homeostasis in the body is maintained by the complex interaction between the neuroendocrine and the immune system[10]. The nuclear factor kappa B (NF-κB) system promotes the release of proinflammatory mediators, whereas the glucocorticoid-glucocorticoid receptor alpha (G-GRα) complex inhibits inflammation. There is uncontrolled inflammation if the imbalance favours NF-κB bioactivity. It has been seen that overactivity of NF-κB in relation to G-GRα in patients with persistent acute respiratory distress syndrome[11] or septic shock[12] can damage cells, tissues and organs.

Glucocorticoids exert their mechanism via both genomic and non-genomic mechanisms. Non genomic effects appear during the first few minutes including decreased platelet aggregation, cell adhesions and intracellular phosphotyrosine kinases and increased annexin 1 externalization[13]. Genomic effects occur after few hours which include sequestration of nuclear transcription factors in the cytosol, prevents reading of genes for most of the proinflammatory mediators[14]. Thus, these molecular mechanisms of action of glucocorticoids can counteract the uncontrolled inflammation that characterized sepsis. Recent critical analysis of available randomized trials have suggested[15] that low-to-moderate doses of corticosteroids improves survival.

The baseline demographic characteristics were similar in two groups. All patients included in this study were in the age group of 25-75 years comparable to the previous study[8].

The time in shock (hours) was significantly less in survivors as compared to non-survivors of Group A (Table 3) indicating that low dose hydrocortisone reduced the time spent by patients in shock. Also, the number of survivors was more in Group A with serum cortisol levels 5-25 mcg/dl (Fig. 1) as compared to Group B proving that the patients who have moderately low cortisol levels are

benefited more with hydrocortisone therapy than those with relatively high cortisol levels.

Conclusion: This study has shown that low dose hydrocortisone therapy was effective in subgroup of patients with cortisol levels between 5-25 mcg/dl. It reduced the duration of vasopressor therapy by decreasing the time in shock. There was also a significant decrease in mortality in patients who received low dose hydrocortisone. Hence, there was a significant decrease in duration of vasopressor therapy and mortality with low dose hydrocortisone therapy.

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