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EFFECT OF TREATMENT WITH LOW DOSE CORTICOSTEROIDS ON MORTALITY IN PATIENTS WITH SEVERE SEPSIS AND SEPTIC SHOCK

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ABSTRACT

The benefit and use of low dose corticosteroids in reduction of mortality in patients with severe sepsis and septic shock. Septic shock may be associated with relative adrenal insufficiency. Thus, replacement therapy with low dose steroids has been proposed to treat septic shock. Surviving sepsis guidelines suggests low dose steroids use for septic shock patients poorly responsive to fluid resuscitation and vasopressor therapy.

Objective: To assess whether treatment with low dose steroids (hydrocortisone and fludrocortisone) reduce 28 day mortality in patients with severe sepsis and septic shock. Treatment: patients were divided into two groups randomly. Group 1(placebo group) received only conventional therapy(fluids and vasopressors) and group 2 (steroids) received Hydrocortisone intravenously every 6 hours as 50mg bolus and one tablet containing 50mcg of 9-α-fludrocortisone for 7 days.

Results: 150 patients were included in analysis (75 in placebo group and 75 in steroid groups) 28 day mortality in placebo group was 60.5% and in steroids group was 54.6%. ICU mortality in placebo group was 66.6% and in steroid group was 60%.Hospital mortality in placebo group was 69.3% and in steroid group was 63.5%.

Conclusion: Treatment with low dose corticosteroids significantly reduced 28 days mortality in patients with severe sepsis and septic shock.

Key words: Corticosteroids, Hydrocortisone and fludrocortisone, Septic shock.

INTRODUCTION

The word "sepsis" is derived from the ancient Greek word for rotten flesh and putrefaction. Since then, a wide variety of definitions have been applied to sepsis, including sepsis syndrome, severe sepsis, bacteremia, septicemia and septic shock. [1,2]. The term "*systemic inflammatory response syndrome*" (SIRS) was coined to describe the common systemic response to a wide variety of insults. When SIRS was the result of a suspected or confirmed infectious process, it is termed "sepsis". Severe sepsis was defined as sepsis plus organ dysfunction. Septic shock is a subset of severe sepsis and was defined as "*Sepsis-induced hypotension persisting despite adequate fluid resuscitation*" (figure 1) . While the quantity of fluid that qualifies as "adequate fluid resuscitation" is controversial, we believe septic shock is best defined as a "mean arterial pressure (MAP) less than 65 mmHg after a fluid challenge of 20 mL/Kg body weight (given 30–60 minutes) in patients with sepsis and in the absence of other

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causes for hypotension" . While the use of the SIRS criteria to define sepsis is somewhat controversial [3 – 6], many consider sepsis to be best defined as the" *systemic response to infection with the presence of some degree of organ dysfunction* " [5].

Each year severe sepsis occurs in about three people per 1000 population and accounts for 2% of hospital stays.[7].About 3% of such patients will develop septic shock [8]which itself accounts for 10% of stays in intensive care units.[9] .Overall, hospital mortality is 30% for severe sepsis and 50-60% for septic shock.[7-9]

Researchers have explored the biological mechanisms of septic shock for potential interventions. Corticosteroids have been tested because of their interactions with immune responses.[10].Indeed, these hormones affect inflammation through their effects on white blood cells, cytokines, and nitric oxide production. However, cytokines may suppress the cortisol response to the adrenocorticotropin hormone, causing poor adrenal activity [11] and body tissues may become resistant to corticosteroids [12]. The prevalence of adrenal insufficiency in septic shock is about 50%. For these reasons, it has been anticipated that corticosteroids could be beneficial in septic shock.

Initial studies with corticosteroids in sepsis and septic shock used short courses of high doses. They did not show any evidence of benefit, as shown by two meta-analyses of the randomised trials published during the period 1966-93.[13,14].However, these reviews did not exclude a benefit of longer durations of treatment ($\geq$ 5 days) and lower doses ($\leq$ 300 mg hydrocortisone or equivalent a day), as observed in more recent trials [15-20]. We systematically reanalysed the effects of corticosteroids in severe sepsis and septic shock, considering all currently available data.

Objective

To assess whether low dose corticosteroids improve 28 day survival in patients with severe sepsis and septic shock.

MATERIALS AND METHODS

Materials

All the materials required for the study has been collected form the study site on getting approval from the heads of respective department and on signing of informed consent by the patients enrolled into the study

Study type

Placebo controlled randomized double blinded study.

Patients

All patients 18years and older and age less than 60 years and hospitalised in emergency medicine and critical care unit were prospectively enrolled in the study in Kamineni Institute Of Medical Sciences, Narketpally, (figure 1) if they met following criteria:

a) Documented site of infection or at least strong suspicion of infection with one or more organ dysfunction

b) Patients satisfying SIRS criteria

c) Mean arterial pressure less than 65mmHg in normotensive patients and less than 85mmHg in hypertensive patients (not responding to fluid resuscitation)

d) Arterial lactate levels higher than 2mmol/L

Written informed consent had to be obtained from the patients themselves or their relatives. Patient had to be randomized within 3hrs of onset of shock.

Exclusion criteria:

a) Age more than 60 years

b) Pregnancy

c) Any evidence for acute myocardial infarction

d) Cardiogenic shock

e) Any contraindications for corticosteroids

f) Immunosuppressed patients

g) Patients who received etomidate during the 6hours preceding randamization because it is a selective inhibitor of 11beta hydroxylase and therefore could interfere with cotisol response to corticotropin.

Figure 1.

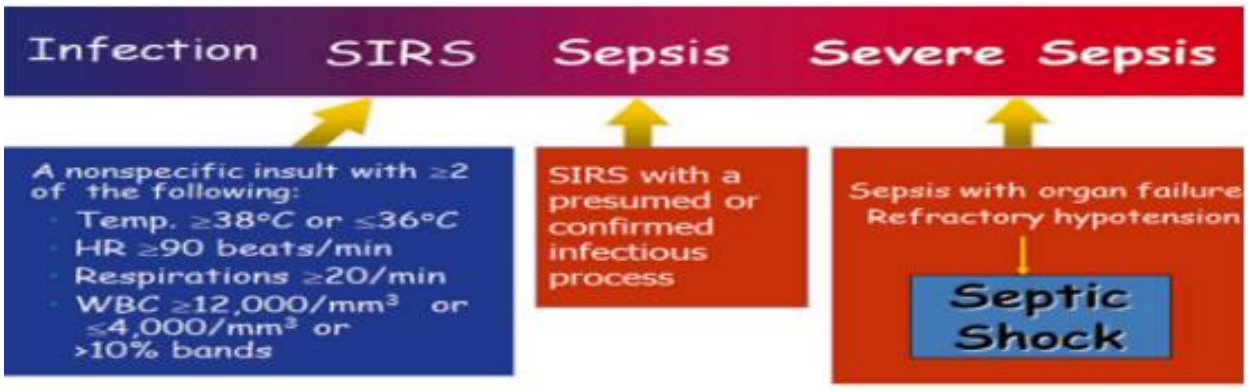


Figure 2.

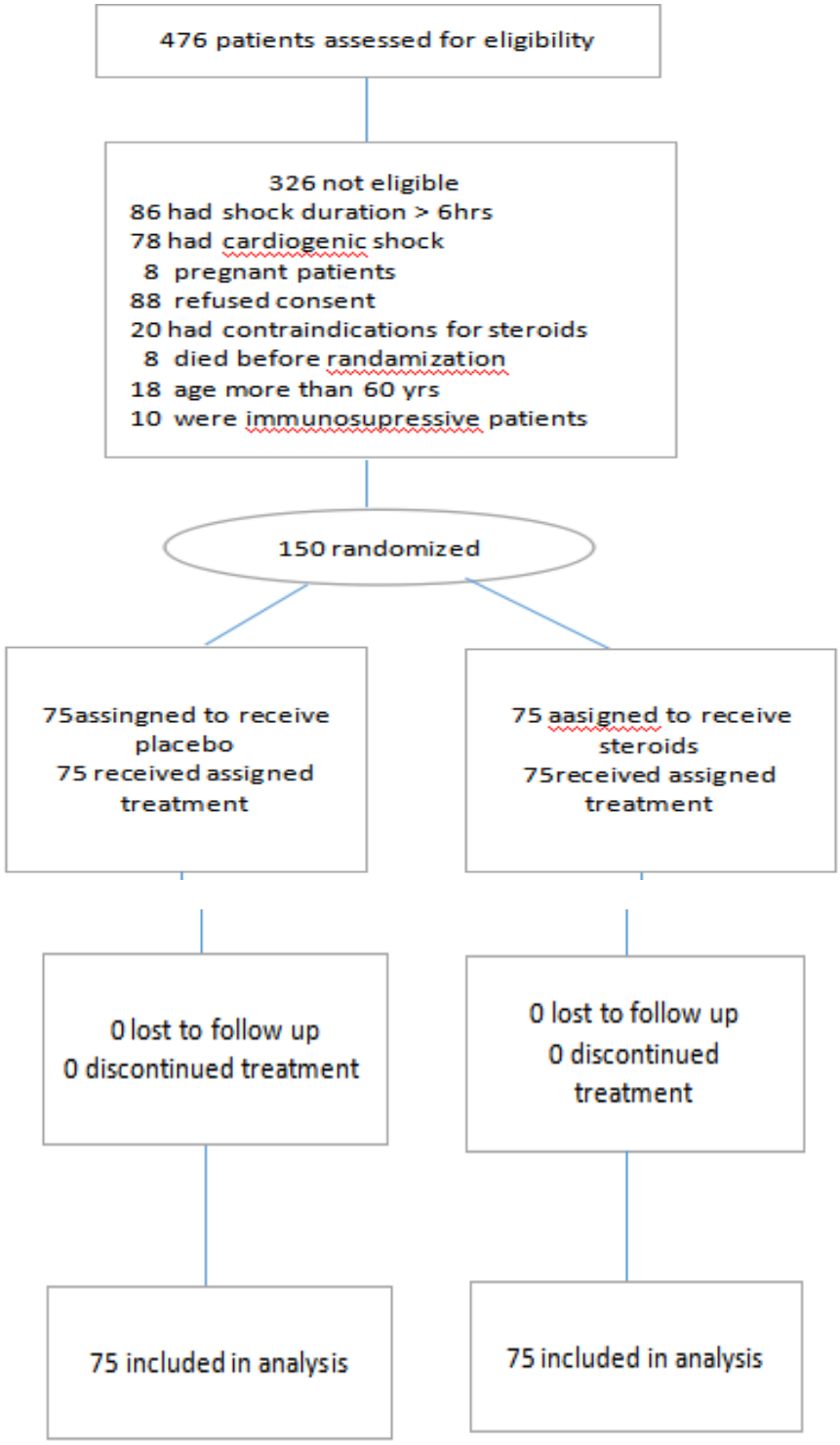

476 patients assessed for eligibility
326 not eligible
86 had shock duration > 6hrs
78 had cardiogenic shock
8 pregnant patients
88 refused consent
20 had contraindications for steroids
8 died before randamization
18 age more than 60 yrs
10 were immunosupressive patients
150 randomized
75assingned to receive placebo
75 received assigned treatment
75 aasigned to receive steroids
75received assigned treatment
0 lost to follow up
0 discontinued treatment
0 lost to follow up
0 discontinued treatment
75 included in analysis
75 included in analysis

Table 1:

	Placebo (n=75)	Steroids (n=75)
Temperature	37.7	37.9
Heart rate	116	117
Map	52	51
Sofa score	16	16
Haemoglobin(gm/dl)	10.4	10.24
Leucocytes $\times 10^3$ /µl	12440	11430
Platelets $\times 10^3$/µl	120	122
Arterial lactate	4.26	4
Fluid loading(ml/kg)	20	20
Vasopressore(µgm/kg/min)		
Dopamine	11(n=18)	10.8(n=22)
Dobutamine	8(n=22)	8(n=22)
Epinephrine	1(n=4)	0.8(n=4)
Nor epinephrine	0.82(n=50)	0.65(n=50)

Table 2:

Variable	Placebo	Steroids	P value
No of patients	75	75	
28 day mortality	46	41	>0.05
ICU mortality	50	45	>0.05
Hospital mortality	52	47	>0.05

Figure 3. Sex distribution of patients: in placebo group 42 are males and 32 are females

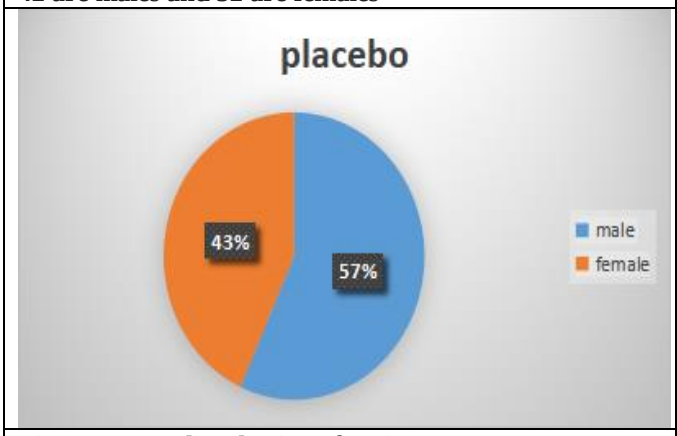


Figure 4. Sex distribution of patients:In steroids group 36 are males and 39 are females

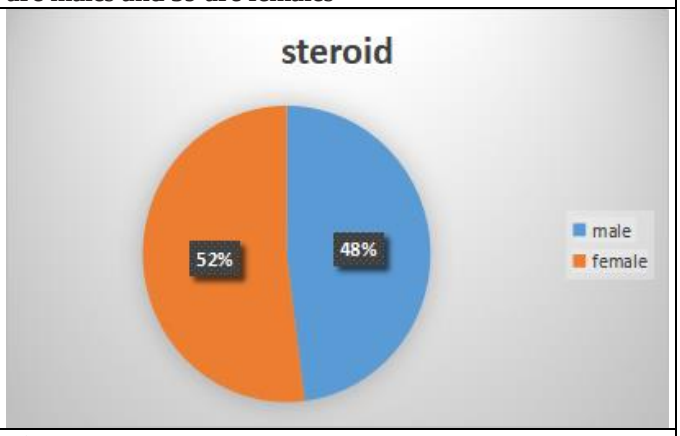


Figure 5. Age distribution of patients

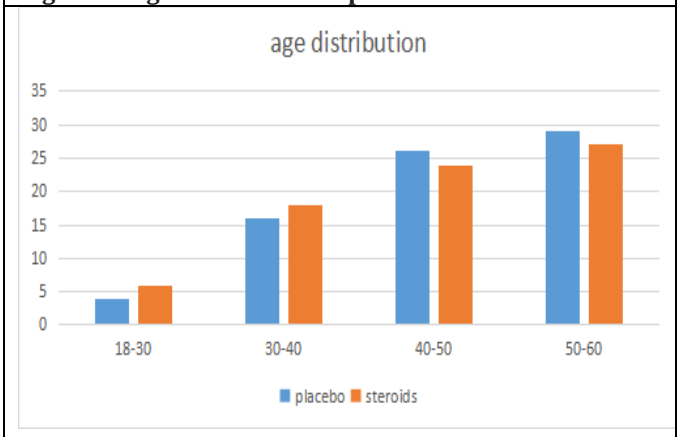
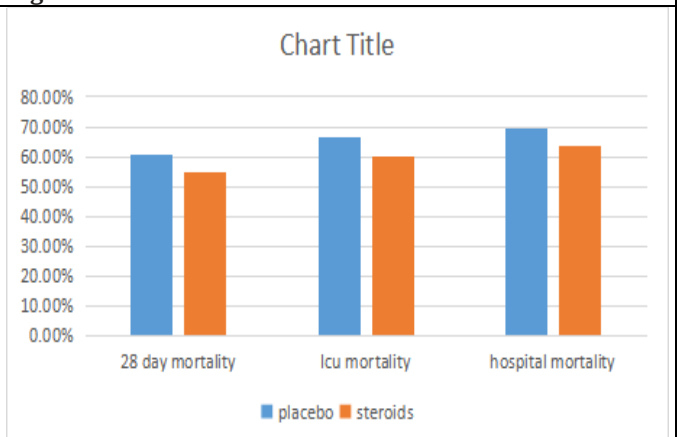


Figure 6.



Treatments

Hydrocortisone came in vials containing 100mg of hydrocortisone powder and 5ml of sterile water for injection, which was administered intravenously every 6 hours as 50mg bolus. One tablet containing 50mcg of 9-α-fludrocortisone was administered daily through a naso gastric tube with 20 to 30 ml of water. Placebo was indiscernible from active treatments. Treatment duration was 7 days.

Data collection at inclusion

Clinical evaluation: The following data were recorded

1) General characteristics including estimated prognosis of any underlying disease and level of activity limitation
2) Severity of illness assessed by vital signs and SOFA (sequential assessment of organ failure) score
3) Interventions including the volume of fluid infusion and the type and doses of vasopressors.

Laboratory variables

Haematological and biochemistry data, arterial lactate and blood gas determination and blood cultures and cultures of specimen drawn from the site of infection were done systematically.

Follow up

Patient's vital signs, laboratory results and culture and sensitivity results were recorded daily during 28 day period following randomization. In addition patients status at discharge from ICU and hospital.

Sample size and statistical analysis

Total of 150 patients were randomized (figure2). Statistical analysis was by using SAS statistical software. Different parameters are compared among two groups (placebo and steroid group). Mean temperature in placebo group was 37.7^0C and in placebo group was 37.9^0C, both the values are compared by paired t test , σ was 1.3030 and t value was -0.485.

Mean heart rate in placebo group was 116bpm and in steroid group was 117 bpm, both the values are compared by paired t test, σ was 7.604 and t value was -0.582. Mean MAP (mean arterial pressure) in placebo group was 52 and steroid group was 51,both the values are compared by paired t test ,σ was 4.028 and t value was 0.785,.Mean SOFA score in placebo group was 16 and in steroid group was 16,t value was 0.Mean haemoglobin levels in placebo group was 10.4gm/dL and in steroid group was 10.24gm/dL,σ was 1.82 and t value was 0.312.Mean leucocyte count in placebo group was 12440 cells/cumm and in steroid group was 11430cells/cumm, both the values are compared by paired t test ,σ was 6014 and t value wsa 0.531.Mean platelet count in placebo group was 120 $\times 10^3/\mu L$ and in steroid group was $122\times 10^3/\mu L$,both the vlaues are compared by paired t test ,σ was 30.9 and t value is -0.204.Mean arterial lactate levels in placebo group was 4.26mmol/L and in steroid group was 4mmol/L,both the values are compared by paired t test,σ was 0.466 and t value was 1.492.

A fluid challenge of 20ml/Kg over 20mins was given in all patients (both placebo and steroid group). In placebo group 11 patients were on dopamine support (mean-11µgm/Kg/min). In steroid group 22 patients were on dopamine support (mean - 10.8µgm/Kg/min).Both the values were compared by levenes test for equality of variance, F value was 1.170 and significance of 0.358.If compared by unpaired t test, if equal variances assumed t value was 0.263 and if equal variance not assumed t value was 0.327.In placebo group 22 patients were on dobutamine (mean-8µgm/Kg/min) and in steroid group 22 patients were on dubutamine (mean-8µgm/Kg/min). Both the values were compared by paired t test and t value was 0. In placebo group 6 patients were on adrenaline support (mean-1µgm/Kg/min) and in steroid group 6 patients were on adrenaline support (mean 0.8µgm/Kg/min),both the values were compared by paired t test and t value was 0.423.In placebo group 50 patients were on nor adrenaline support (mean-0.82µgm/Kg/min) and in placebo group 50 patients were on nor adrenaline support (mean-0.65µgm/Kg/min), both the values compared by paired t test, σ was 0.354 and t value 1.274.

Mortality distribution

In placebo percentage of 28 day mortality was 60.5% and in steroid group it was 54.6%

ICU mortality in placebo group was 66.6% and in steroid group it was 60%

Hospital mortality in placebo group was 69.3% and in steroid group it was 63.6%

P value is calculated by using chi square test.

CONCLUSION

Based on above results, in septic shock patients, a 7 day treatment with the combination of hydrocortisone and fludrocortisone is associated with significant reduction in 28 day mortality. In practice we suggest that all patients with severe sepsis and septic shock should be given low dose steroids (hydrocortisone and fludrocortisone) for 7 days. Further studies are required to better determine the optimal dose and duration of corticosteroids in this setting.

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