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ORIGINAL ARTICLE

THE EFFECT OF LOW DOSE HYDROCROTISONE ON DURATION OF VASOPRESSOR THERAPY IN SEPTIC SHOCK

Gagan Deep[1], Krishna Bihari Verma[2], Subarna Ghosh[3], Chandana[4], Shelesh K. Goel[5]

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ABSTRACT: INTRODUCTION: Sepsis is now considered to be the clinical presentation of patients with a serious infection that may or may not be accompanied by positive blood culture with common clinical manifestations, including fever or hypothermia, tachypnea or hyperventilation, tachycardia, leukocytosis, coagulopathy and alteration in mental status. Despite numerous advances in the supportive care of patients, overall mortality has changed little in past 20 years. The recent trials of assessing low does corticosteroids in septic shock have proclaimed positive results. Corticosteroids are clearly indicated for treatment of adreno-cortical insufficiency, but it also shows high mortality rates in patients with septic shock. Who had low cortisol response to corticotropin stimulation test. AIMS: To study the role of low does corticosteroids on duration of vasopressor therapy in patients with septic shock and studied their outcome. **STATISTICAL ANALYSIS:** The statistical analysis was done by using the formulas of two tail t test. **MATERIALS AND METHODS:** 40 patients of 25-75 years age group with septic shock were taken from different ICUs in the department of medicine and were divided into two groups of 20 patients each– hydrocortisone treated and placebo group. Mean values was compared statistically. **RESULT:** The duration of shock in patients with serum cortisol level between 5-25 ugm/dl was significantly ($p<0.10$) lower in the hydrocortisone group than the control group, with no significant ($p>0.10$) change in TLC. **CONCLUSION:** The low dose hydrocortisone therapy reduces the duration of vasopressor therapy in a subgroup of patients with serum cortisol between 5-25ugm/dl. The mortality in this subgroup was also reduced in the patients who received the hydrocortisone therapy.

KEYWORDS: Septic shock therapy, Corticosteroid and septic shock.

INTRODUCTION: The terms sepsis, bacteremia and septicemia have been used interchangeable in the past. Approximately one of every three patients presenting with sepsis have sterile cultures, indeterminate microbiological studies or lack of definite site of infection. Therefore sepsis is now considered to be the clinical presentation of patients with a serious infection that may or may not be accompanied by positive blood culture.[1]

Severe sepsis is a common, frequently fatal and expensive disease. Angus et al suggest that there are at least 750,000 new cases of severe sepsis annually in United States (US).[2] In US severe sepsis is the most common cause of death in non-cardiac intensive care unit and the 11th leading cause of death overall.

Incidence of sepsis is increasing and the numbers of cases of severe sepsis have increased by 139% in recent ten year period. Increase in incidence is probably from an increased awareness of the disorder, the "graying" of the world's population, increased use of invasive procedures for diagnosis and monitoring of critically ill patients. The emergence of antibiotic resistant organisms and increased prevalence of immunocompromised patients (eg. malignancy, AIDS, transplant recipient and debilitating disorders such as DM), alcoholism and malnutrition.

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The common clinical manifestation of sepsis includes fever or hypothermia, tachypnea or hyperventilation, tachycardia, leukocytosis, coagulopathy[3] and alteration in mental status. Organ system dysfunction is a common adverse sequelae of severe sepsis and septic shock and has been reported to be the most common cause of death in the noncoronary intensive care unit.[4]

Prognosis of the patients of septic shock depends on the patients underlying heath 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. The recent trials of assessing low does corticosteroids in septic shock have proclaimed positive results.[5,6,7,8]

Stress does of hydrocortisone infusion reduced the time of cessation of vasopressor therapy in septic shock.[9,10,11,12,13] Corticosteroids are clearly indicated for treatment of adreno-cortical insufficiency.[12,14,15] Several studies have demonstrated high mortality rates in patients with septic shock, who had low cortisol response to corticotropin stimulation test,[16,17] where as high dose corticosteroids do not improve the overall survival of the patients with severe, late septic shock.[18,19,20,21] Due to these dose dependent effects, there were a long and controversial history regarding effects of corticosteroids on septic shock.[21,22] Strict normoglycemia is more easily achieved if the hydrocortisone therapy is given to septic shock patients.[23] We tried the role of low does corticosteroids on duration of vasopressor therapy in patients with septic shock and studied their outcome.

MATERIALS AND METHODS: The study was carried out in 40 patients with septic shock. All patients included in this study were in the age group of 25-75 years. The patients were taken from different ICUs in the department of medicine of Gold Field Institute of Medical Sciences and Research, Faridabad, after consent from the Institutional Ethical Committee.

The study was divided into two groups of 20 patients each. One group received the low dose hydrocortisone in addition to the antibiotics, inotropics and I. V fluids. The other group received only antibiotics ionotropics and IV fluids. Here both the groups received the antibiotics; because, the antimicrobial therapy remains the cornerstone of therapy of patients with sepsis, sever sepsis or septic shock.[24]

INCLUSION CRITERIA: Patients who met the ACCP (American College of Chest Physician)/SCCM (Society of Critical Care Medicine) criteria of septic shock.

Positive blood culture or infection and at least 2 of the following:

1. Fever (temperature >38˚) or hypothermia (temp <36˚)
2. Tachycardia >90 beats/min
3. Tachypnea >20 breaths/min
4. Abnormal WBC count
5. Evidence of organ dysfunction or hypoperfusion
6. Hypotension persisting for 48 hours despite adequate fluid resuscitation or the use of vasopressor or inotropic support.

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EXCLUSION CRITERIA:

1. Patient aged <25 or >75 years
2. Those who are pregnant
3. Who had irreversible underlying disease
4. Those who are treated with vasopressors for greater than 48 hours or with glucocorticoids
5. Organ transplant recipient.
6. Patients with burns or hemorrhage shock
7. Patient who suffered MI in the last six months.

PROCEDURES: The treatment group received hydrocortisone of 100mg every 8 hour for at least 5 days.

When septic shock will be reversed was defined by cessation of vasopressor support with stable systolic BP >90mmHg for at least 24 hours. The dose of hydrocortisone was reduced to 50mg every 8 hours for 3 days, then 25mg for every 8 hours for 3 days then discontinued. The plasma cortisol level was measured for first 72 hours for first 3 days consecutively.

Study drug was discontinued at 5 days if no shock reversal occurs. The control group received antibiotics ionotropics and I. V. fluids without cortical steroids.

Patient was 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 was collected and it was divided into two groups – hydrocortisone treated and placebo group. Mean values was compared statistically.

RESULTS: This prospective study was conducted in patients with septic shock admitted in Gold Field Institute of Medical Sciences and Research, Faridabad over a period of 1 year and 1 month's i. e. January 2014 to February 2015. The cases were selected after the fulfillment of inclusion criteria:

1. A total of 40 patients with septic shock were included in this study. The diagnosis was established on basis of clinical evaluation and biochemical parameters.
2. The mean age of patients was comparable (no significant difference, $p>0.10$) in hydrocortisone group (52.35±15.52) and control group (52.40±11.18). All the patients are in the age group of 25-75 years [Table-1, Fig. 1].
3. In group A the number of female patients is greater than males, but in group B the number of male patients is greater than female patients. There was statistically significant ($p<0.10$) difference in the sex distribution of two groups [Table-2, Fig. 2].
4. The baseline serum cortisol levels were checked. The mean serum cortisol level in hydrocortisone group was 21.32±10.36ugm/dl and in control group was 26.73±14.38ugm/dl [Table-3, Fig. 3]. There were no significant difference ($p>0.10$).
5. The severity of septic shock was determined by SAPS II score. The mean SAPS II score in hydrocortisone group was 65.35±11.90 and in control group was 67.35±13.13. There was no significant difference ($p>0.10$) in severity of septic shock in both the group [Table-4, Fig. 4].
6. The mean duration of shock in house in hydrocortisone group was 64.10±13.59 and in control group was 68.90±9.81 [Table-5, Fig. 5], which is statisticall not significant ($p>0.10$).

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7. The mean duration of shock in subgroup of patients with serum cortisol level between 5-25 ugm/dl in hydrocortisone group was 61.23±15.39 hours and in control group was 72.00±0.00 hours [Table-5a, Fig. 6]. The duration of shock was significantly ($p<0.10$) lower in the hydrocortisone group.
8. In mean change in TLC was -0.39±10.94 in hydrocortisone group and 1.99±12.65 in control group showing mild increase in TLC in control group but statistically change was insignificant ($P>0.10$).

DISCUSSION: Septic shock as per ACCP (American College of Chest Physician) /SCCM (Society of Critical Care Medicine) definition[25] constitutes a subset of patients of severe sepsis with hypotension despite adequate fluid resuscitation[26] along with presence of perfusion abnormalities that may include but are not limited to lactic acidosis, oliguria or an acute alteration in mental status. After volume resuscitation, vasopressors or inotropic therapy or both may be necessary to restore perfusion.[27] Patient receiving inotropic or vasopressor agents may no longer be hypotensive by the time, they manifest hyper perfusion abnormalities or organ dysfunction yet they would still be considered to have septic (SIRS) shock. Authors shows that in septic shock, low-dose steroids induced both gluco- and mineralocorticoid biological effects and seemed to improve renal function. Most of these effects appeared after 2-3 days of treatment and lasted at least until the end of treatment.[28]

An infectious insult results in the stimulation of immune system.[29] This response is normally advantageous, but when uncontrolled or excessive, it becomes deleterious for the organism. This is the situation in septic shock.[30]

In sepsis, the hypothatamic pituatory adrenal (HPA) axis is controlled by systemic and neural pathways. Circulating cytokines like TNF α IL-1, IL-6 activate the HPA axis independently and when combined have synergistic effects.[31,32,33] The second pathways use the neural routes communication between the site of inflammation and the brain. The interruption of vagus has shown to blunt HPA axis and fever responses to intravenous challenge with lipopolysacchnoide (LPS), TNF α or IL-Iβ.[31,34,33]

Hypercortisolemia associated with stress such as septic shock mainly results from increased secretion from HPA axis and decreased clearance.[35]Several authors have hypothesized syndrome of relative adrenal cortical insufficiency in presence of normal or even raised serum cortisol concentration.[36] There are subset of patients with subnormal responses of cortisol rise with ACTH stimulation test[15,37] suggestion an impaired cortisol secretion.[38]

A few uncontrolled studies indicate that stress doses of hydrocortisone improve hemodynamics in patients with hyper-dynamic septic shock which is unresponsive to conventional therapy, because in adequate; endogenous steroid production appears to sensitize patients to hemodynamic effects of therapeutic rice in plasma cortisol levels.[39] Thus, the low dose corticosteroids should be advised to the patients with septic shock empirically but should be discontinued if adrenal insufficiency is not confirmed.[37,40]

Therefore we studied the effect of low dose hydrocortisone on the duration of vasopressor therapy in septic shock and studied their outcome.

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

studies.[11] The baseline serum cortisol levels were checked. The baseline cortisol level was much lower in both the groups when compared to the study done by Boucher with mean cortisol value of 36. 80ug/dl indicating the severe adrenal insufficiency in the present study.

There were no significant difference in mean time of shock in between the two groups, but in case of patients with serum cortisol level of 5-25 ug/dl, the mean time of shock was significantly less in group A than in group B. Thus proving the patients who have moderately low cortisol level are benefited more with hydrocortisone therapy than those with relatively high cortisol level.

When compared with the previous studies[11] in which the time of shock hours in hydrocortisone group was (20.7±3.67 hours) and placebo group was (26.5±4.39 hours) and was much less as compared to the present study indicating the severity of septic shock was much greater than the previous study.[15] But the decreases in time in shock hours in trial groups are similar with pervious study.[11]

When the mean SAPS II score in group A and B were compared to the previous studies.[11] SAPS II score in hydrocortisone group was (55±4.4) and in placebo group was (55±5.0) indicating the severity of septic shock was much greater in the present study.

On comparing the time of shock with survivors, survivors have significantly less time of shock then non survivors in both the groups. In group a it is highly significant.

There were maximum number of blood culture positive in group B and significantly higher number of urine culture positive in group A. E. coli is most common organism isolate cultured followed by staph aureus. Pneumonia was the most common underlying infection in group A and wound infection in group B when compared with the previous studies[11] gram positive organisms and pneumonias are the most common infection whereas gram negative organisms are the most common in the present study indicating difference in local prevalence of the infection.

In the present study it was found that low dose hydrocortisone therapy was effective in subgroup of patients with cortisol levels between 5-25ugh/dl. It decreases the duration of vasopressor therapy by decreasing the time of shock hours. There was significant decrease in mortality in this subgroup of patients who were treated with low does hydrocortisone. Hence low dose hydrocortisone was effective in treating this subgroup of patients with septic shock by decreasing the duration of vasopressor therapy and mortality.[41]

The number of survivors in group A was 25% and group B are 15% and are statistically insignificant but when compared in a group of patients with serum cortisol level (5-25) ug/dl the survival in group A was significantly higher than group B showing the improved outcome in this subgroup of patients. When compared with previous studies[11] the survival in the present study was much less because the patients in the present study group were having more severe septic shock as shown by increase SAP scoring and longtime of duration of shock hours.

CONCLUSION: The low dose hydrocortisone therapy reduces the duration of vasopressor therapy in a subgroup of patients with serum cortisol between 5-25ugm/dl. The mortality in this subgroup was also reduced in the patients who received the hydrocortisone therapy.

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Age (Years)	Group-A	Group-B
26-35	4 (20%)	2 (10%)
36-45	4 (20%)	3 (15%)
46-55	3 (15%)	8 (40%)
56-65	4 (20%)	5 (25%)
66-75	5 (25%)	2 (10%)
Mean ± SD	52.35 ± 15.52	52.40 ± 11.18

Table 1: Age distribution

t-Value = 0. 01, p-Value = >0. 10^{NS}

Sex	Group-A	Group-B
Male	7 (35%)	13 (65%)
Female	13 (65%)	07 (35%)

Table 2: Sex distribution

t-Value = 3. 60, p-Value = <0. 10

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S. Cortisol (µg/dl)	Group-A	Group-B
Upto 10	2 (10%)	5 (25%)
10-20	9 (45%)	3 (15%)
20-30	4 (20%)	2 (10%)
30-40	5 (25%)	8 (40%)
40-50	0 (0%)	1 (5%)
50-60	0 (0%)	1 (5%)
Mean ± SD	21.32 ± 10.36	26.73 ± 14.38

Table 3: Distribution according to serum cortisol

t-Value = 1. 37, p-Value = >0. 10^{NS}

SAPS II Score	Group-A	Group-B
40-49	2 (10%)	2 (10%)
50-59	6 (30%)	3 (15%)
60-69	4 (20%)	7 (35%)
70-79	5 (25%)	3 (15%)
80-89	3 (15%)	5 (25%)
Mean ± SD	65.35 ± 11.90	67.35 ± 13.13

Table 4: Distribution according to SAPS II Score

t-Value = 0. 57, p-Value = >0. 10^{NS}

Time (Hrs)	Group-A	Group-B
26-35	1 (5%)	1 (5%)
36-45	1 (5%)	0 (0%)
46-55	3 (15%)	1 (5%)
56-65	1 (5%)	0 (0%)
66-75	14 (70%)	18 (90%)
Mean ± SD	64. 10±13. 59	68. 90± 9. 81

Table 5: Distribution according to time of shock

t-Value = 1. 29, p-Value = >0. 10^{NS}

Cortisol	Time of shock		Z-value	p-value
	Group-A	Group-B		
5	72± -1	34.00±0.00	-	-
5-25	61.23±15.59	72. 00±00	1.80	<0.10
>25	69.00±7.35	68.00±9.34	0.23	>0.10
t-value	1.15	1.12		
p-value	>0.10	>0.10		

Table 5 (a): Relationship of cortisol with time of shock

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Change in TLC	Group-A	Group-B	t-value	p-value
D_1	20.44±11.48	22.64±10.12		
D_5	20.05±18.87	24.63±14.72		
Change	-0.39±10.94	1.99±12.65	0.23	>. 10^{NS}
t-value	0.26	0.67		
p-value	>. 10^{NS}	>. 10^{NS}		

Table 6: Distribution according to change in TLC from D_1 toD_5

Urea	Group-A	Group-B	t-value	p-value
D_1	135.10±102.57	124.22±55.06		
D_5	134.60±82.70	141.00±50.16		
Change	-0.50±83.75	16.78±52.03	1.78	>0.10^{NS}
t-value	0.11	1.69		
p-value	>. 10^{NS}	>. 10		

Table 7: Distribution according to change in Urea from D_1 toD_5

Change in GCS	Group-A	Group-B	t-value	p-value
D_1	10.25±3.49	10.70±3.51		
D_5	9.50±4.27	9.95±3.46		
Change	-0.75±1.80	-0.75±1.80	0.00	>0.10^{NS}
t-value	1.07	1.23		
p-value	>0.10^{NS}	>0.10^{NS}		

Table 8: Distribution according to change in GCS from D_1 toD_5

Change in pH	Group-A	Group-B	t-value	p-value
D_1	7.33±0.08	7.27±0.16		
D_5	7.29±0.13	7.31±0.18		
Change	-0.04±0.12	0.04±0.24	1.33	>0. 10^{NS}
t-value	1.97	1.81		
p-value	>0.05	>0.10		

Table 9: Distribution according to change in pH from D_1 toD_5

Change in PaO_2	Group-A	Group-B	t-value	p-value
D_1	146.84±116.10	83.05±82.06		
D_5	168.48±182.99	142.79±157.29		
Change	21.65±215.13	59.74±113.04	0.70	>0.10^{NS}
t-value	0.97	1.99		
p-value	>0.10^{NS}	<0.05		

Table 10: Distribution according to change in PaO_2 from D_1 toD_5

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Change in $PaCo_2$	Group-A	Group-B	t-value	p-value
D_1	35.13±11.85	29.08±10.37		
D_5	40.84±9.14	36.82±12.06		
Change	5.71±11.12	7.74±12.3	0.55	$>0.10^{NS}$
t-value	2.13	2.51		
p-value	$>0.05^{NS}$	<0.05		

Table 11: Distribution according to change in $PaCo_2$ from D_1 toD_5

Change in SPO_2	Group-A	Group-B	t-value	p-value
D_1	93.54±116.03	87.88±17.48		
D_5	86.28±19.20	87.89±14.51		
Change	-7.26±24.98	0.01±12.12	1.17	>0.10
t-value	2.03	0.02		
p-value	>0.05	$<0.10^{NS}$		

Table 12: Distribution according to change in SPO_2 from D_1 toD_5

Change in HCO_3	Group-A	Group-B	t-value	p-value
D_1	19.22±7.18	15.45±6.78		
D_2	28.22±30.97	19.29±10.18		
Change	9.00±26.61	3. 84±10.38	0.81	>0.10
t-value	1.97	1.61		
p-value	<0.05	$<0.10^{NS}$		

Table 13: Distribution according to change in HCO_3 from D_1 toD_5

Change in S. K^+	Group-A	Group-B	t-value	p-value
D_1	4.41±1.25	4.44±1.00		
D_5	4.19±1.19	4.16±1.34		
Change	-0.22±1.58	-0.28±1.28	0.13	>0.10
t-value	0.92	1.07		
p-value	$>0.10^{NS}$	$>0.10^{NS}$		

Table 14: Distribution according to change in Serum potassium from D_1 toD_5

Change in S. Na^+	Group-A	Group-B	t-value	p-value
D_1	134.05±8.28	133.80±24.62		
D_5	140.25±7.03	141.95±12.32		
Change	6.20±9.58	8.15±24.80	0.32	>0.10
t-value	3.38	1.86		
p-value	<. 01	<.10		

Table 15: Distribution according to change in Serum sodium from D_1 toD_5

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Culture	Group-A	Group-B	t-value	p-value
Blood	3 (15%)	8 (40%)	1.77	<0.10
ET/Sputum	4 (20%)	3 (15%)	0.42	>0.10^{NS}
Wound	3 (15%)	3 (15%)	-	-
Urine	3 (15%)	0	1.80	<0.10

Table 16: Distribution according to culture isolates

Isolates	Group-A	Group-B
Staph Aureus	3	5
E. Coli	5	5
Non hemolytic streptococci	1	1
Pseudomonas	2	3
Klebsiella	0	1
Enterococci	2	1
Candida	2	0

Table 17: Number of Pathogens

	Group-A	Group-B
Pneumonia	8 (40%)	5 (25%)
Abdominal infection	3 (15%)	5 (15%)
Urogenital tract infection	3 (15%)	3 (15%)
Wound infection	6 (30%)	7 (35%)

Table 18: Underlying infection

Number of organs	Group-A	Group-B
Two	1 (5%)	1 (5%)
Three	7 (35%)	6 (30%)
Four	10 (50%)	11 (55%)
Five	2 (10%)	2 (10%)

Table 19: Number of organ involved

Antibiotics	Group-A	Group-B	t-value	p-value
One	0 (0%)	1 (5%)	1.01	>0.10^{NS}
Two	3 (15%)	3 (15%)	-	-
Three	12 (60%)	8 (40%)	1.27	>0.10^{NS}
Four	4 (20%)	8 (40%)	1.38	>0.10^{NS}
five	1 (5%)	0 (0%)	1.01	>0.10$^{NS`}$

Table 20: Distribution according to Antibiotics

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Outcome	Group-A	Group-B	t-value	p-value
Death	11 (55%)	12 (60%)	0.32	>0.10^{NS}
LAMA	4 (20%)	5 (25%)	0.38	>0.10^{NS}
Survived	5 (25%)	3 (15%)	0.79	>0.10^{NS}

Table 21: Distribution according to Outcome

Cortisol	Outcome			
	Death	LAMA	Survived	Total
<5	0	1	0	1
5-25	7	1	5	13
>25	4	2	0	6

Table 22 (a) : Relationship of cortisol with outcome: Group A

Z-Value = 2.86, p-Value = <0.10.

Cortisol	Outcome			
	Death	LAMA	Survived	Total
<5	0	0	1	1
5-25	6	0	1	7
>25	6	5	1	12

Table 22 (b): Relationship of cortisol with outcome: Group B

z-Value = 1. 04, p-Value = >0. 10^{NS}.

Outcome	Time of shock	
Non survivor (15)	70.80±7.54	
Survivor (5)	44.00±11.23	
	t-value	p-value
Non Survivor v/s Survivor	8.86	<. 001

Table 23 (a): Relationship of time of shock with outcome in Group A

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

Table 23 (b): Relationship of time of shock with outcome in Group B

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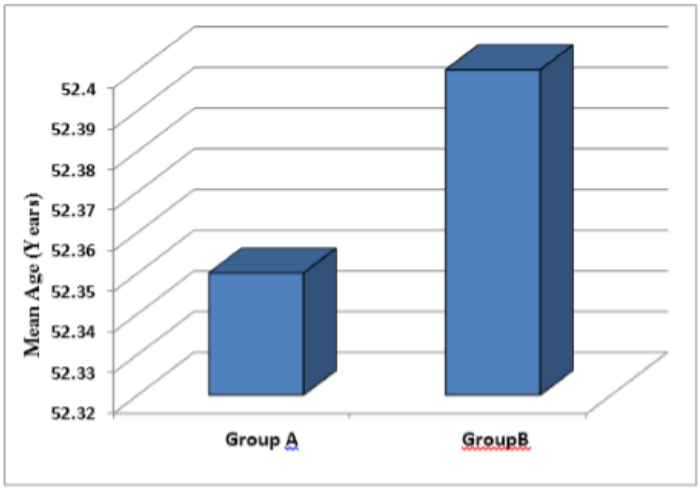

Fig. 1: Age distribution of subjects

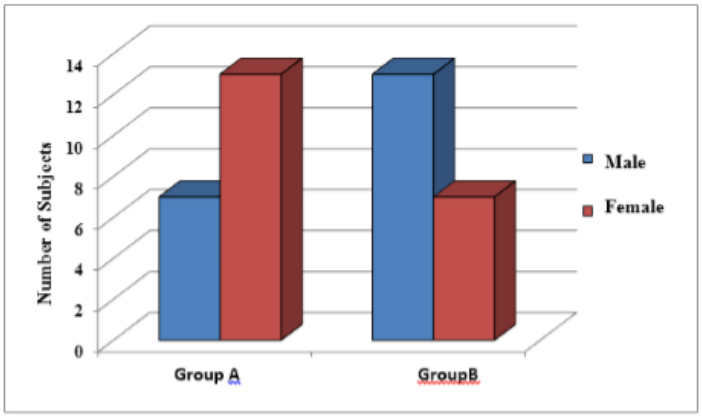

Fig. 2: Sex distribution of subjects

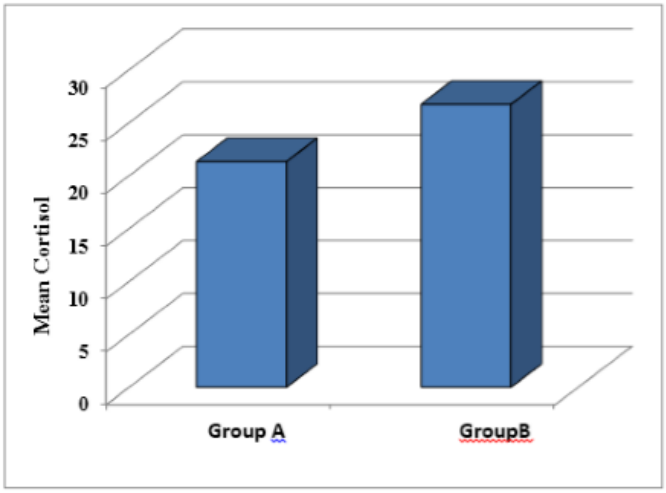

Fig. 3: Mean Cortisol of subjects

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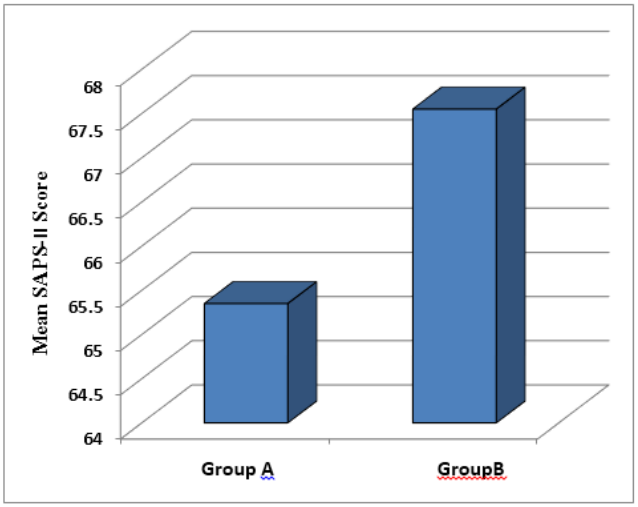

Fig. 4: Mean SAPS-II score of subjects

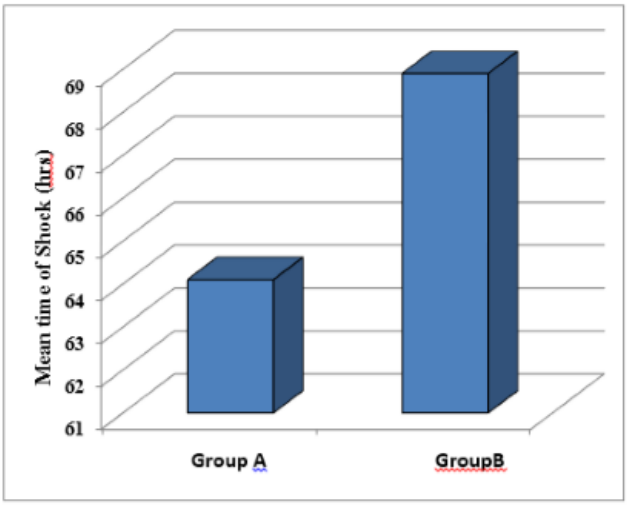

Fig. 5: Mean time of shock of subjects

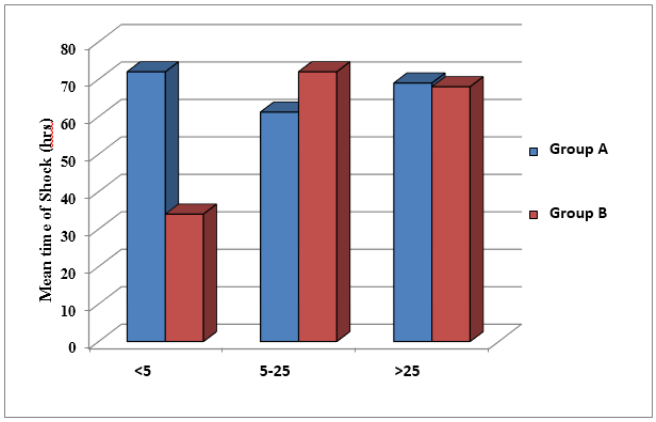

Fig. 6: time of shock in relation to cortisol

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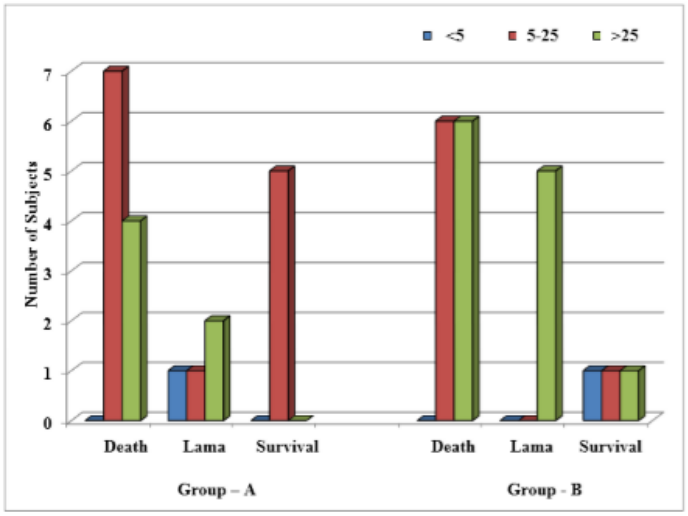

Fig. 7: Relationship of cortisol with outcome

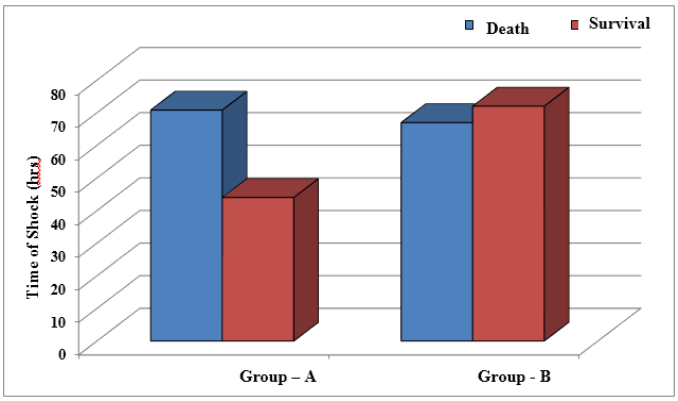

Fig. 8: Time of Shock in relationship of outcome

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ORIGINAL ARTICLE

AUTHORS:

1. Gagan Deep
2. Krishna Bihari Verma
3. Subarna Ghosh
4. Chandana
5. Shelesh K. Goel

PARTICULARS OF CONTRIBUTORS:

1. Assistant Professor, Department of General Medicine, Gold Field Institute of Medical Sciences & Research, Faridabad, Haryana.
2. Assistant Professor, Department of Physiology, Gold Field Institute of Medical Sciences & Research, Faridabad, Haryana.
3. Tutor (Demonstrator) Department of Physiology, Gold Field Institute of Medical Sciences & Research, Faridabad, Haryana.
4. Tutor (Demonstrator) Department of Physiology, Gold Field Institute of Medical Sciences & Research, Faridabad, Haryana.
5. Professor & HOD, Department of Community Medicine, Gold Field Institute of Medical Sciences & Research, Faridabad, Haryana.

NAME ADDRESS EMAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Gagan Deep,
House No. 921/21-C,
Faridabad-121001.
E-mail: gaganricha@gmail.com

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