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ORIGINAL ARTICLE

Effect of hydrocortisone on outcome of septic shock patients. A prospective observational study in a tertiary care ICU.

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ABSTRACT

Introduction: Sepsis and septic shock have 10% and 40% mortality in ICU respectively. Early recognition and prompt management of septic shock in ICU can reduce mortality. Further, some studies have suggested that hydrocortisone can impact outcome of septic shock significantly.

Methodology: We designed prospective observational study to evaluate the effect of hydrocortisone in septic shock patients. Septic shock was defined according to definition proposed by international consensus definition of septic shock 2016. We excluded those who were less than 18 years and receiving steroids for some other indication at the time of admission to ICU. Primary outcome was to determine mortality in ICU. Secondary outcome was to evaluate length of stay, vasopressor days, vasopressor free days and dose of norepinephrine.

Results: We studied 208 cases of septic shock. Median age was 61 years. Out of 208 participants, 106 received hydrocortisone. Out of 102 cases who did not receive hydrocortisone, 56.7% died and 42.3% survived (p=<0.001). There was no effect of hydrocortisone on length of stay, vasopressor days, vasopressor free days (OR: 0.7,0.3,1.1), (p=0.98,0.92,0.93) respectively.

Conclusion: We concluded that hydrocortisone reduces mortality in septic shock patients in ICU.

Keywords: Sepsis, hypotension, hypovolemia, septic shock

INTRODUCTION

Sepsis is one of the leading causes of admissions in Intensive Care Units worldwide. Sepsis is defined as life threatening organ dysfunction caused by dysregulated host response to infection. Organ dysfunction is an acute change in total SOFA score ≥2 points consequent to infection. Baseline SOFA score is considered zero. ≥2 points are associated with 10% increase in mortality. Septic shock is a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to cause hypotension (in the absence of hypovolemia) needing vasopressors to maintain MAP≥ 65mmHg and have serum lactate > 2mmoL/L (18mg/dl) despite adequate volume resuscitation. It increases mortality rate from 10% for sepsis to up to 40% for septic shock.

Management of septic shock has always been a challenge to clinicians. Despite many guidelines out there, there is always a challenge for setting hemodynamic targets and applying guidelines to achieve the set target. Role of Antibiotics , Fluids and vasopressors has always been the mainstay of management of septic shock[(1)]. Recommendations regarding the use of steroids are ever changing over the period of 3 decades. In 1987, a prospective, randomized double blind placebo controlled trial was conducted on 382 patients, showed no benefit of steroids in septic shock[(2)]. In 2002 a placebo-controlled, randomized double blind, parallel group trial done on 300 patients over a period of 4 years showed improved outcome with use of low dose steroids and attributed it to ongoing adrenal deficiency in septic shock[(3)]. In 2008 randomized, double-blind, placebo-controlled named CORTICUS trial conducted on 500 patients showed no reduction in 28-day mortality with use of steroids[(4)]. In 2009 a randomized double blind HYPRESS trial, was conducted on 380 patients which showed no effect of hydrocortisone in preventing septic shock from severe sepsis[(5)]. In 2018 a large international double blind randomized controlled trial was conducted enrolling 3800 patients. This trial named ADRENAL trial calculated 90-day mortality in septic shock patient given hydrocortisone. There was no mortality benefit observed in hydrocortisone vs placebo group. However early resolution of shock, increased ventilator free days, and lower blood transfusions was observed in hydrocortisone group[(6)]. On the other hand, another large multicentered double blinded French randomized controlled trial (APROCCHSS) enrolled 1241 patients showed altogether different results than ADRENAL trial. A significant difference in 90 day mortality was seen with an absolute risk reduction of 6.1%[(7)].

No direct study has been done in Pakistan yet regarding effect of hydrocortisone in management of septic shock. However, a prospective observational study was conducted in a tertiary care hospital studying characteristics and outcomes of sepsis. In this study, steroids were used in 6% patients and no association was found in dose and duration on the outcomes of sepsis[(8)]. We designed this prospective observational study to evaluate the effects of hydrocortisone on mortality, length of stay in ICU and vasopressor free days.

METHODOLOGY

It was a prospective observational study conducted in Bahawal Victoria hospital Bahawalpur, Pakistan. It's a 1600 bedded tertiary care hospital which provides care in all discipline of medicine in south Punjab and has 30 beds dedicated for Medical as well as surgical patients. Ethical review of this study was taken from Ethical Review Committee of BVH hospital. Study duration spanned from June 2020 to December 2021. 31st December was last date of follow up. Informed verbal consent was taken from all enrollments. Patients admitted to ICU who consented and with age 18 years and meeting septic shock definition of third international Consensus 3, that is all patients with sepsis and MAP≤ 65 mmHg with lactate >2mmol/l despite adequate volume resuscitation and requiring vasopressors[(9)]. Patients with age <18, who didn't provide consent and already on steroids for some other indications were excluded from our study. We also excluded those who did not meet definition of septic shock. Patients were either admitted to ICU from emergency department or from another surgical/medical ward. Decision of starting hydrocortisone was taken by the rounding ICU consultant who was blind of the objective of the study. Patients were given IV hydrocortisone 50mg iv 6 hourly within 24 hours of onset of septic shock. Onset of shock was defined as need to start vasopressor to maintain MAP ≥ 65mmHg. First vasopressor in our study was Norepinephrine. Vasopressor free days were defined as maintaining MAP≥65 mmHg without any vasopressor and length of stay was defined as time since admission to ICU till discharge from ICU or death. We also recorded variables like age, gender and comorbidities like diabetes

mellitus, Acute kidney injury, ESRD, cirrhosis, HTN and need for hemodialysis. Mortality scores like APACHE II, SOFA and NUTRIC scores were calculated for all patients. Preformed structured questionnaire was used to collect data. All patients were followed till the time of discharge or death during treatment in ICU.

Primary objective of our study was to evaluate outcome of septic shock in cohort given hydrocortisone while secondary objective was to study effect of hydrocortisone on length of stay, norepinephrine dose, days on vasopressors and vasopressor free days.

Statistical analysis: Data was analyzed using SPSS version 25. Categorical variables were presented in percentages and frequencies. Continuous variables were tested for normality using Shapiro wilk test. P value more than 0.5 was used to define normal distribution of data. Non-Normally distributed data was presented in median and interquartile range. Chi-square test was used to analyze categorical variables. Independent t-test was applied to compare means between categorical variables. P value < 0.5 was taken as statistically significant. Logistic regression analysis was used to see impact of hydrocortisone on outcome, length of stay, vasopressor days and vasopressor free days.

RESULTS

We studied 861 patients during total study period and 208 of them met inclusion criteria. Out of 208 cases, 43.75% were males (n=91) and 56.2% were females (n=117). Median age was 61 years (IQR: 54-67). We calculated mortality predictor scores for every patient admitted to ICU. Median score of APACHE II, SOFA and NUTRIC scores were 16, 9 and 5 (IQR: 11-23, 8-11, 5-6) respectively. Median length of stay in ICU was 4 days (IQR: 3-5). Amongst comorbidities, diabetes mellitus was most common comorbid in our study cohort followed by acute kidney injury (n=92). None of comorbid conditions had statistically significant association with mortality and so as was gender difference (p=0.07). Mean score APACHE II was found to be statistically significant high in deceased cohorts (p=0.02). whereas, SOFA and NUTRIC score were not significantly different in both cohorts (p=0.85, 0.08). out of 208 participants, 106 cases received hydrocortisone. Out of 102 cases who did not receive hydrocortisone, We observed 56.7% mortality in those who did not receive hydrocortisone as compared to 43.3% in those who received hydrocortisone (p=<0.001). overall observed mortality in our cohorts was 46.6%.

Characteristics of study population

	Survived (n=111)	Non-survived (n=97)	P value
Gender Male: Female (91:117)	43:68	48:49	0.07
Diabetes Mellitus (n=135)	57%(n=77)	43% (n=58)	0.12
HTN (n=99)	59.6% (n=58)	40.4% (n=41)	0.14
Cirrhosis (n=25)	56% (n=14)	44% (n=11)	0.12
ESRD (n=45)	53.3% (n=24)	46.7% (n=21)	0.16
Neutropenic sepsis (n=46)	52.2% (n=24)	47.8% (n=22)	0.13
Acute kidney injury (n=92)	46.7% (n=43)	53.3% (n=49)	0.17
Hemodialysis (n=81)	54.3% (n=44)	45.6 % (n=37)	
APACHE II (Mean score)	16.7±8.7	19.4±8.17	0.02
SOFA (Mean score)	9.8 ± 8.3	9.9 ± 8.3	0.85
NUTRIC (Mean score)	5.2±1.32	5.5 ±1.22	0.08
Positive Blood cultures (n=160)	51.8% (n=83)	48.2% (n=77)	0.68
GNR in tracheal cultures (n=103)	50.4% (n=52)	49.6% (n=51)	0.24
GPC in tracheal cultures (n=105)	56.2% (n=59)	43.8% (n=46)	
GNR in urine cultures (n=109)	56.9% (n=62)	43.1% (n=47)	0.18
GPC in urine cultures (n=99)	49.5% (n=49)	50.5% (n=50)	
Meropenem (n=205)	53.7% (n=110)	46.3% (n=95)	0.45
Hydrocortisone (n=106)	57.7% (n=64)	43.3% (n=42)	< 0.001
Colomycin (n=117)	50.4% (n=59)	49.5% (n=58)	0.20
Levofloxacin (n=49)	51% (n=25)	49% (n=24)	0.42
Vancomycin (n=197)	52.3% (n=103)	47.7% (n=94)	0.16
Voriconazole (n=69)	50.7% (n=35)	49.3% (n=34)	0.25
Vasopressor free days	3.7 ± 1.4	3.5±1.4	0.23
Mean dose of norepinephrine (µg/kg)	19.7 ± 13.6	19.2 ± 13	0.82
Vasopressor days	3.6 ± 1.5	3.5 ± 1.5	0.51
Length of stay	4.1 ± 1.7	4.6 ± 4.2	0.22

Abbreviations GNR: gram negative rods, GPC: gram positive cocci, ESRD: End stage renal disease, APACHE II: acute physiological assessment of chronic health evaluation, SOFA: sequential organ failure assessment, NUTRIC: nutrition risk in critically ill patients

Table 2: Effect of hydrocortisone on outcome, length of stay, vasopressor days and vasopressor free days

Variable	Odd ratio	P value
Mortality	0.9	0.02
Length of stay	0.7	0.98
Vasopressor days	0.3	0.92
Vasopressor free days	1.1	0.93
Dose of norepinephrine	0.9	0.7

DISCUSSION

We studied 208 cases in total, and results were much promising. Median age was 61 years indicating that it was mainly adult population which participated in our study. Mortality was significantly low in cohort given IV 200mg/day of hydrocortisone(n=106) than those who were not given IV hydrocortisone (n=102) 43.3% vs 56.7%. (p<0.001). we did not notice any relation between comorbidities and outcome. Mean score of APACHE II was significantly high in deceased cohort (19.4 vs 16.7) (p=0.02). There was no effect of hydrocortisone on length of stay, vasopressor free days, vasopressor days and dose of norepinephrine. Our results are somewhat in line with APPROCHS trial which studied the effect of hydrocortisone and fludrocortisone on septic shock. They noticed that death from any cause at the time of ICU discharge was significantly reduced in those who received hydrocortisone and fludrocortisone. They also noticed that vasopressor free days and organ failure free days were significantly low in intervention group. We also noticed mortality benefit of hydrocortisone 43.3% vs 56.7%. (p<0.001). however, our results could not establish the effect of hydrocortisone on vasopressor free days. This is due the fact that APPROCHS trial used both hydrocortisone and fludrocortisone as an intervention and we studied effect of hydrocortisone only due to limited availability of fludrocortisone.

Our results were also in contrast to what was observed in CORTICUS trial[4] which enrolled 500 patients and aimed to calculate 28-day mortality.in this study, 233(46.7%) didn't respond to corticotropin. There was no significant difference seen in 28-day mortality in patients receiving hydrocortisone vs placebo in responders (28.8% vs 28.7%), in non-responders (39.2% v 36.1%) or all patients (34.3% v 31.5%). They also compared variables like age and gender and found n significant difference. Comorbidities like HTN, DM, COPD also showed no statistical significance just like our study. in CORTICUS trial, all patients had to undergo corticotropin stimulation test, but it wasn't the case in our study. CORTICUS trial had to be stopped early due to many reasons hence results of such trials cannot be compared to our results. Another large multicenter trial enrolled 3658 patients. Participants were randomized between 2 groups, considering age above 18, need for mechanical ventilation, documented infection with signs of SIRS and were given 200mg of hydrocortisone per day (n=1832) or matching placebo(n=1826)[10]. Median age was 62.3±14.9 vs 62.7±15.2 years, while mean age in our study was 61 years. Median APACHE II was 24 vs 23 in both groups respectively while in our study median APACHE II score was 16. Their primary outcome was to determine 90-day mortality in both groups which

didn't seem to be different in both groups, however secondary outcomes, including number of blood transfusions, and faster resolution of shock in this trial were observed. In comparison, we did not study the resolution of shock. Moreover, our deceased group had an APACHE II score of 19.4 in comparison to 23 in this trial which means our population had less severity of illness. One large French placebo-control double blind parallel group trial[3], enrolling 300 patients studied the effect of low dose corticosteroid (hydrocortisone 50mg IV 6 hourly per day and fludrocortisone 50mcg/day) in relative adrenal insufficiency for 7-days. They used corticotropin and allocated patients in responders (n=70) (steroids=n36 and placebo=n34) and non-responders (n=299) (steroids=n114 and placebo=n115). One patient withdrawn from trial due to lack of consent. Our study didn't study the effect in responders and non-responders i-e corticotropin stimulation test. We also did not study the effect of fludrocortisone in our cohorts. They observed mortality benefit i-e 28-day mortality in responders (63% died in placebo and 53% died in steroid group. Vasopressor withdrawal was 57% in steroid group and 46% in placebo group. This was a significant result. No significant results were obtained in responders. This study however didn't explain the effect seen in low APACHEE/SOFA score. Surprisingly, there are no local studies which has studied the effects of hydrocortisone on length of stay, vasopressor free days and days on vasopressors. This is the first study of its kind which has studied the effect of hydrocortisone on outcome of septic shock patients, its effect on length of stay, vasopressor days and vasopressor free days.

Keeping in view all the above-mentioned trials and their comparison, there is much need to continue research in this field. As there are no such on-going trials in Pakistan, we need to launch it at a much larger scale and in which all the lags present in our study can be overcome. There are some limitations of our study also. First, it was not double blind randomized controlled trial and secondly, it was a single center study. Its prospective design makes our study robust evidence on use of hydrocortisone in septic shock patients in ICU to reduce mortality.

CONCLUSION

We concluded that hydrocortisone decreases mortality in septic shock patients significantly. Addition of hydrocortisone in septic shock has no impact on length of stay, vasopressor days and vasopressor free days. Randomized controlled trials are needed to further elaborate the effect of hydrocortisone on outcome in septic shock patients.

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