Vol 1| Issue 1| 2011 | 45-50.

e-ISSN 2248 – 9142
print-ISSN 2248 – 9134

International Journal of
Current Pharmaceutical & Clinical Research

www.ijcpcr.com

# ASSOCIATION OF HYDROCORTISONE WITH FLUDROCORTISONES IN SEPTIC SHOCK ADULT PATIENTS

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**ABSTRACT**

Infection can cause multiple symptoms when combined they cause systemic inflammatory response syndrome (SIRS), i.e., sepsis. Sepsis is a condition that is manifested clinically by physiological, biological, and biochemical abnormalities, and its main cause is the uncontrolled inflammatory response of infection. Septic shock is distinguished by a dysregulated host response to infection. It may resulting in life-threatening circulatory, cellular, and metabolic abnormalities. The short term mortality is approximately 45 to 50%, and survivors of sepsis may have subsequent long-term cognitive decline. At a distance from early hemodynamic and respiratory resuscitation and appropriate anti infective treatments, there is no approved adjunct therapy for sepsis. In this study.We evaluated the effect of hydrocortisone-plus-fludrocortisone therapy, drotrecoginalfa (activated),the combination of the three drugs and their respective placebos. The primary outcome was 90-day all-cause mortality. Secondary outcomes included mortality at intensive care unit (ICU) discharge and hospital discharge and at day 28 and day 180 and the number of days alive and free of vasopressors, mechanical ventilation, or organ failure. At day 90, death had occurred in 264 of 620 patients (42.5%; 95% confidence interval [CI], 39.0 to 45.0) in the hydrocortisone-plus-fludrocortisone group and in 308 of 610 patients (50.4%; 95% CI, 46.1 to 55.1) in the placebo group (P = 0.03) . The relative risk of death was 0.99 (95% CI, 0.78 to 0.99) in favor of hydrocortisone-plus-fludrocortisone therapy.In this trial involving patients with septic shock. Seven -day treatment with a 50-mg intravenous bolus of hydrocortisone every 6 hours and a everyday dose of 50µg of oral fludrocortisone ended in decrease mortality at day 90 and at ICU and clinic discharge than placebo among adults with septic shock. The corticosteroids in septic shock have significant positive impacts on some aspects in treatment of septic shock but it does not affect the mortality rate of the patients.

**Key words**: Mortality, Septic Shock, Hydrocortisone Shock Reversal, Fludrocortisone.

## INTRODUCTION

Management of sepsis is a time critical procedure; the consequences of improperly managed sepsis and septic shock can cause multiple organ dysfunction and death. The aim of this study was to evaluate of the role of hydrocortisone either alone or with fludrocortisone on the outcome septic shock in adults. Septic shock is distinguished by a dysregulated host response to infection. It may resulting in life-threatening circulatory, cellular, and metabolic abnormalities. [1] The short term mortality is approximately 45 to 50%, and survivors of sepsis may have subsequent long-term cognitive decline. At a distance from early hemodynamic and respiratory resuscitation and appropriate antiinfective treatments, there is no approved adjunct therapy for sepsis. The Surviving SepsisCampaignrecommends that, in the first hourof sepsis recognition, physicians obtain bloodcultures, administer broad-spectrumantibiotics,start appropriate fluid resuscitation andbegin vasopressors whenever needed. Beyondthese core measures, there has been littlechange in the management of sepsis.

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Corticosteroids were the anti inflammatory drug of sepsis. It is related with a dysregulated response of the hypothalamic–pituitary–adrenal axis that may involve any of the steps from cortisol production to cortisol use by cells. [2] Although corticosteroids have been shown to improve blood pressure there are conflicting results on survival benefits in recent large randomized controlled trials (RCTs) and systematic reviews,resulting in the lack of definitive recommendations in several clinical guidelines.[3]

Between thedifferent corticosteroid treatments, there was a dual treatment with hydrocortisone and fludrocortisone for septicshock results. Hydrocortisone act as both glucocorticoid and mineralocorticoid activities;whereas fludrocortisone, a synthetic corticosteroid, possessesvery potent mineralocorticoid activity. [4] Hydrocortisonehas been extensively examined in sepsis, andfludrocortisone has been used for patients with aldosteronedeficiency. Dual therapy using these two medications is recommendedfor some patients with primary adrenal insufficiency. Considering that patients with septic shock havebeen found to have unexpectedly low aldosterone levels due to hypothalamic–pituitary–adrenal axis abnormalities, dual treatment with hydrocortisone and fludrocortisone should be further validated as a type of corticosteroid treatment for septic shock.[5]

As a result, we understood a systematic review and meta analysis to identify beneficial effects of the dual treatment with hydrocortisone and fludrocortisone for patients with septic shock, the aim of the present study Evaluation of the role of hydrocortisone either alone or combined with fludrocortisones in the outcome of septic shock in adults.

## MATERIAL AND METHODS

Information on the design and conduct of the activated protein C and Corticosteroids for Human.

- Otherwise, deferred written informed consent was obtained from patients.
- Participants or their legally authorized next of kin provided written informed consent before inclusion whenever possible.
- Otherwise, deferred written informed consent was obtained from patients.

The study was conducted at Saveetha Medical college, *Poonamalle High Road, Velappanchavadi,*Chennai.The exclusion criteria have been detailed elsewhere.Major exclusion criteria were the presence of septic shock for at least 24 hours, a high risk of bleeding pregnancy or lactation, underlying conditions that could affect short-term survival, known hypersensitivity to drotrecoginalfa (activated), or previous treatment with corticosteroids. After the withdrawal of Xigris from the market, the exclusion criteria that were relevant only to drotrecoginalfa (activated) were removed. [6]

Patients in intensive care units (ICUs) were eligible for inclusion in the trial if they had indisputable or probable septic shock15 for less than 24 hours. Septic shock was defined as the presence of a clinically or microbiologically documented infection, a Sequential Organ FailureAssessment (SOFA)16 score of 3 or 4 (on a scale of 0 to 4 for each of six organ systems, with higher scores indicating more severe organ dysfunction) for at least two organs and at least 6 hours, and receipt of vasopressor therapy (norepinephrine, epinephrine, or any other vasopressor at a dose of ≥0.25 μg per kilogram of body weight per minute or ≥1 mg per hour) for at least 6 hours to maintain a systolic blood pressure of at least 90 mm Hg /a mean blood pressure of at least 65 mm Hg.

**Randomization and Trial Agents:**

Patients were randomly assigned in permuted blocks of eight to receive hydrocortisone-plusfludrocortisone therapy, drotrecoginalfa (activated), the combination of the three drugs, or their respective placebos((mannitol [133.6 mg], disodium phosphate [8.73 mg], and sodium phosphate [0.92 mg])). Hydrocortisone was administered as a 50-mg intravenous bolus every 6 hours, and fludrocortisone was given as a 50-μg tablet through a nasogastric tube once daily in the morning. Trial agents were administered for 7 days without tapering.

Randomization, plasma total cortisol levels were measured before,30 and 60 minutes after, an intravenous bolus of 250 μg of corticotrophin (Synacthen). The variables that were investigated at baseline and during the 180-day follow-up have been detailed elsewhere. Nonexperimental interventions were harmonized across centers according to the 2008 Surviving Sepsis Campaign guidelines, including antiinfective treatments, hemodynamic and respiratory management, and blood glucose control.

Investigators followed national guidelines for the prevention of superinfection.Neuromuscular blocking agents were discouraged except in the first 24 hours in the presence of refractory hypoxemia. Investigators' adherence to guidelines was checked at each investigators'meeting.
Statistical Analysis Of Prsent StudyWe anticipated a 90-day mortality of 45% among patients with septic shock.19 According to the 2-by-2 factorial design with a two-sided formulation, 320 patients were needed in each group (i.e., a total of 1280 patients) to detect an absolute difference of 10 percentage points in 90-day mortality ($\alpha = 0.05$ and power at 95%) betweeneither drotrecoginalfa and placebo.

An intention-to-treat analysiswas planned to be performed after all the participantshad completed the 180-day follow-upand according to the 2-by-2 factorial design.Owing to the withdrawal of Xigris from themarket in 2011, the trial continued with twoparallel groups (see the protocol) and was underpoweredto assess the effect of drotrecoginalfa(activated). The sponsor terminated the trial whenthe expiration dates of the trial agents werereached

and 1241 patients (97% of the expectedsample size) had been enrolled.

The analysis compared all the patients assignedto receive hydrocortisone plus fludrocortisones with those assigned to receive correspondingplacebos. Continuous variables are presentedas means and standard deviations. Categoricalvariables are presented as the number of patientsin each category and the corresponding percentages.Missing data were not replaced. The effectsof trial agents on the frequency of fatal events(mortality at day 28, at day 90, at discharge fromthe ICU or hospital, and at day 180) and safetyoutcomes were compared with the use of logisticregressionmodels and the chi-square test. Continuousvariables were compared with the use ofanalyses of variance and t-tests. Cumulative eventcurves (censored end points) were estimatedwith the Kaplan–Meier procedure, and Cox modelsand the log-rank test were used to comparethe effects of trial agents (time to ICU and hospitaldischarge).

The Fine and Gray subdistributionhazard regression models, which extend theCox model to competing risk data by consideringthe hazard function associated with the cumulativeincidence function, were used to comparethe effects of trial agents (time to weaning fromvasopressors, to weaning from mechanical ventilation,and to reaching a SOFA score <6). Noadjustment for multiple testing was made. Allanalyses were conducted with SAS statisticalsoftware, version 9.4.

## RESULTS

There were 4 participating centersthe first and last patients were recruited to check the quality of the trial agents and the distribution of serious adverse events.The data and safety monitoring board confirmed the conformity of the trial to the marketing- authorization application for fludrocortisones and hydrocortisone and the quality of their placebos;the board also confirmed that the distribution of serious adverse events between the groups did not justify halting the trial. The main difference between the current study and othermeta-analyses is the fact that we examined only the effects of the dual corticosteroid treatment for septic shock. The idea behind the addition of fludrocortisone to hydrocorti- sone, used as glucocorticoid replacement therapy in patients with adrenal insufficiency, is to enhance the mineralocorti- coid activity The main difference between the current study and other meta-analyses is the fact that we examined only the effects of the dual corticosteroid treatment for septic shock. The idea behind the addition of fludrocortisone to hydrocorti- sone, used as glucocorticoid replacement therapy in patients with adrenal insufficiency, is to enhance the mineralocorti- coid activity The main difference between the current study and other meta-analyses is the fact that we examined only the effects of the dual corticosteroid treatment for septic shock. The idea behind the addition of fludrocortisone to hydrocorti- sone, used as glucocorticoid replacement therapy in patients with adrenal insufficiency, is to enhance the mineralocorti- coid activity

Patient demographic information, severity-of-illness scores, characteristics of infection, and remedies at baseline had been similar inside the two organizations. Most patients have been admitted from a scientific ward and had extreme septic shock, as evidenced by high Simplified Acute Physiology Score II (SAPS II) values (range, 0 to 163, with better rankings indicating extra severity of illness),high lactate levels, and a excessive degree of vasopressor dependency (imply dose of norepinephrine,1 μg in keeping with kilogram in keeping with minute).

Most patients had community-acquired infection, and the lung became the maximum common site of infection. The preliminary antimicrobial treatment become judged adequate in ninety seven percentage of the sufferers who obtained placebo and 97.9% of folks that received corticosteroids

### Primary outcome

At day 90, death had occurred in 264 of 620 patients (42.5%; 95% confidence interval [CI], 39.0 to 45.0) in the hydrocortisone-plus-fludrocortisone group and in 308 of 610 patients (50.4%; 95% CI, 46.1 to 55.1) in the placebo group (P = 0.03) (Table 2 and Fig. 1). The relative risk of death was 0.99 (95% CI, 0.78 to 0.99) in favor of hydrocortisone-plus-fludrocortisone therapy.

### Secondary outcomes

Mortality was significantly lower in the hydrocortisone- plus-fludrocortisone group than in the placebo group at ICU discharge (35% [215 of 613 patients] vs. 42.6% [265 of 625 patients], P = 0.04), hospital discharge (37% [229 of 613 patients] vs. 45% [282 of 625 patients], P = 0.02), and day 180 (46.7% [285 of 610 patients] vs. 52.6% [328 of 623 patients], P = 0.04). Patients in the hydrocortisone-plus- fludrocortisones group had a significantly shorter time than those in the placebo group to weaning from mechanical ventilation (P = 0.006), to weaning from vasopressor therapy (P<0.001), and to reaching a SOFA score below 6 (P<0.001).Similarly, patients in the hydrocortisoneplus- fludrocortisone group had significantly more vasopressor-free days to day 28 than those in the placebo group (P<0.001) and significantly more organ-failure–free days to day 28 (P = 0.003).

**Risk of bias and summary of findings**

A total of 324 of 612 patients (52.9%) in the hydrocortisone-plus-fludrocortisone group and 353 of 616 patients (57.3%) in the placebo group had at least one serious adverse event by day 180 (P = 0.05) (Table 3). The risk of gastroduodenal bleeding was not significantly higher with hydrocortisone plus fludrocortisone than with placebo (relative risk, 0.77; 95% CI, 0.56 to 1.34; P = 0.55), nor was the risk of superinfection (relative risk, 1.07; 95% CI, 0.91 to 1.30; P = 0.30). However, the risk of hyperglycemia was significantly higher with hydrocortisone plus fludrocortisones (relative risk, 1.07; 95% CI, 1.03 to1.13; P = 0.002).

**DISCUSSION**

During Infection, oflfending microbes interact with the host immune system producing a downstream inflammatory cascade involving cytokines and other mediators, which in turn triggers a systemic response. The resultant effects linclude vasodilation, increased vascular permeability, myocardial depression, and impairment of the coagulation cascade, resulting in global imbalance of systemic oxygen supply and demand. During the late stage of sepsis, immunosuppression predominates, leading to multi-organ dysfunction and further clinical deterioration. The prognosis of septic shock varies widely, with different studies reporting different responses to corticosteroids. On the one hand, there are differences in the design of individual studies, on the other hand, the current definition and severity stratification of septic shock is still not clear enough.

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection with two or three on Quick Sepsis-related organ failure assessment score (qSOFA). Septic shock is defined as the presence of sepsis and refractory hypotension to fluid management. Vasopressors are needed to maintain systolic blood pressure more than 90mmHg or mean blood pressure more than 65 mmHg .

In present trial regarding adults with septic shock, all-purpose mortality changed into decrease with hydrocortisone plus fludrocortisone than with placebo at day 90, at discharge from the ICU and clinic, and at day one hundred eighty. The time to weaning from vasopressors, to weaning from mechanical ventilation, and to reaching a SOFA score beneath 6 turned into shorter with hydrocortisone plus fludrocortisones than with placebo. The wide variety of days alive and freed from vasopressors and organ failure turned into better with hydrocortisone plus fludrocortisone than with placebo.

The chance of secondary infections, gastroduodenal bleeding, or neurologic sequelae become no longer considerably better with hydrocortisone plus fludrocortisone than with placebo, however the danger of hyperglycemia turned into significantly higher with hydrocortisone plus fludrocortisone. There turned into a few imbalance between the two groups inside the distribution of pathogens, with barely extra viral infections inside the hydrocortisone-plus-fludrocortisone institution than in the placebo group.

The mechanisms by way of which corticosteroids may favorably affect the final results of sufferers with septic shocks were specific recently. [7] In brief, corticosteroids improve cardiovascular feature with the aid of restoring effective blood volume via multiplied mineralocorticoid pastime and by using growing systemic vascular resistance, an effect this is partly related to endothelial glucocorticoid receptors. [8] This may provide an explanation for why in our trial there was much less want for vasopressors with hydrocortisone plus fludrocortisone than with placebo. Corticosteroids attenuate inflammation in various organs in both animals and humans with sepsis, an effect in part associated with inhibition of nuclear factor κB (NF-κB). [9] In our trial, hydrocortisoneplus- fludrocortisone therapy increased the decision of organ failure in adults with septic shock.

With appreciate to ninety-day all-reason mortality, there was an absolute difference of 6 percent points and a relative distinction of 12% that desired hydrocortisone plus fludrocortisone over placebo; those findings are in keeping with those of a current Cochrane assessment. In this systematic evaluate, only 2 of 33 trials have been powered to address the results of a long (≥5 days) direction of low-dose corticosteroids on mortality.[10] The first trial (Ger-Inf-05), wherein patients obtained hydrocortisone plus fludrocortisone or matching placebos for 7 days, confirmed an absolute difference of 6 percent factors in 28-day mortality in choose of hydrocortisone plus fludrocortisone.

The second trial (Corticosteroid Therapy of Septic Shock [CORTICUS]) showed no significantsurvival advantage from an eleven-day route of hydrocortisone by myself. In a more latest trial concerning 380 adults with intense sepsis (Hydrocortisone for Prevention of Septic Shock [HYPRESS]), hydrocortisone alone failed to save you septic shock. That trial turned into not powered to deal with the outcomes of hydrocortisone on mortality and excluded sufferers with shock. [10]

Here are principal variations among trials that confirmed a survival benefit from corticosteroid remedy (APROCCHSS and Ger-Inf-05) and people that did now not (CORTICUS and HYPRESS). First, in the APROCCHSS and Ger-Inf-05 trials, fludrocortisones changed into delivered to hydrocortisone to provide extra mineralocorticoid potency. It changed into administered enterally inside the absence of an intravenous formula of this drug.

Glucocorticoid therapy for the treatment of septic shock remains controversial, with conflicting evidence regarding a mortality benefit. It has been used in patients with septic shock who remained hypotensive after fluid and vasopressor resuscitation. Fludrocortisone is a

corticosteroid and acts as a powerful mineralocorticoid along with some additional but comparatively very weak glucocorticoid activity. Relative to cortisol, it is to 10 times the glucocorticoid potency but 250 to 800 times the mineralocorticoid potency. Fludrocortisone is added to hydrocortisone to provide additional mineralocorticoid potency. The rationale for adding mineralocorticoid treatment is that an experimental sepsis study showed marked nuclear factor NF-κB mediated down regulation of vascular mineralocorticoid receptors.

The intent for including mineralocorticoid treatment is that an experimental sepsis have a look at showed marked NF-κB–mediated down-regulation of vascular mineralocorticoid receptors. Treatment with aldosterone, a mineralocorticoid-receptor agonist,restored α1-adrenoceptor expression, improved contractile reaction to phenylephrine, and improved survival in mice with endotoxic shock. In a latest pharmacokinetic take a look at involving adults with septic surprise, enteral management of fifty μg of fludrocortisone resulted in plasma concentrations of the drug that exerted great mineralocorticoid consequences, with some interindividual variability. [11]

Second, the APROCCHSS and Ger-Inf-05 trials focused on sufferers with septic surprise whose condition did not beautify after initial resuscitation in keeping with the 6-hour package deal of care mentioned in the Surviving Sepsis Campaign guidelines1For the ones patients, norepinephrine at a dose of more than 0.25 μg consistent with kilogram in step with minute for more than 6 hours turned into required in order for hemodynamic stabilization to be finished. This corporation of sufferers changed into decided on because they will be at high danger for loss of life, which makes them the pleasant goal group for adjunct treatment.

The crude in-health center mortality Of fifty four percentage that was determined within the placebo institution of the APROCCHSS trial is near that suggested thru the Sepsis-three challenge pressure. [11-13] Patients in the APROCCHSS trial have been sicker than the ones inside the CORTICUS trial, as evidenced thru higher SOFA ratings and higher SAPS II values (and were more likely to be admitted from scientific wards.

Hence, the Ger-Inf-05 and APROCCHSS trials independently showed a survival benefit with hydrocortisone plus fludrocortisone in adults with septic shock and continual vasopressor dependency and organ failures.

**CONCLUSION**

Seventh-day treatment with a 50-mg intravenous bolus of hydrocortisone every 6 hours and a everyday dose of fifty μg of oral fludrocortisone ended in decrease mortality at day 90 and at ICU and clinic discharge than placebo among adults with septic shock. Due to the limitations of retrospective study design and database, the conclusions of this study still need to be confirmed by prospective clinical randomized controlled trials.

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