Review Artical

Role of Steroid in Adult Patients of Septic Shock - A Critical Analysis

Hasan R[1], Kabir H[2], Roy TC[3], Chowdhury JS[4], Yeasmin F[5]

Abstract

" Sepsis and septic shock is the condition which has been with intensive care units from long before. In fact, it is one of the highly ranked diseases causing mortality in ICU patients. There are currently many evidence based practices in the management of septic shock and use of steroid is one of them. The aim of this article is to critically evaluate the evidences regarding the role of steroids in adult patients of septic shock. This article has also evaluated all the current evidences regarding details of the role of steroids including their formulation, dosage, duration and route of administration in patients of septic shock.

Key words: *Steroids and sepsis, Steroids and septic shock, Glucocorticoids and sepsis, Glucocorticoids and septic shock, Corticosteroids and sepsis, and Corticosteroids and septic shock.*

Introduction

American College of Chest Physicians and Society of Critical Care Medicine Consensus Conference (1992) defined sepsis as a clinical syndrome characterized by systemic inflammation due to infection[1]. Sepsis with arterial systolic blood pressure <90 mm of Hg or 40 mm of Hg below patient's normal blood pressure for at least one hour despite adequate fluid resuscitation is defined as septic shock. Even with optimal treatment mortality due to sepsis and septic shock is 40%-50%[2]. There are currently many evidence based practices in the management of septic shock and use of steroid is one of them. In fact steroids have been used in the treatment of septic shock from as early as 1950s. In the earlier years steroids were used in high dosage forms and for shorter duration but such practices failed to show any mortality benefits in clinical trials. Moreover earlier studies even demonstrated the development of infections secondary to steroid use. But recent studies demonstrate that many of the septic shock patients suffer from relative adrenal insufficiency during the period of their acute illness. Interest in the possible therapeutic role of glucocorticoids in severe infections has existed for at least 50 years[3,4,5]. In the following 40 years, the role of steroids in the treatment of septic shock has generated significant interest, with numerous reviews, meta-analyses and even front-page articles in a major newspaper dedicated to the topic. However, from the early 90's there is renewed interest in the use of steroids in patients with sepsis. Dellinger et al (2003) proposed the following guideline regarding use of steroids in patients of sepsis and septic shock based on the current evidence based practice[6]. "Intravenous corticosteroids (hydrocortisone 200-300 mg/day, for 7 days in three or four divided doses or by continuous infusion) are recommended in patients with septic shock who, despite

1. Dr. Rajib Hasan, Incharge, Department of General ICU, KYAMCH, Enayetpur, Sirajgonj.
2. Dr. Humayun Kabir, Medical Officer, Department of General ICU, KYAMCH, Enayetpur, Sirajgonj.
3. Dr. Taposh Chandra Roy, Medical Officer, Department of General ICU, KYAMCH, Enayetpur, Sirajgonj.
4. Dr. Javed Sharoar Chowdhury, Medical Officer, Department of General ICU, KYAMCH, Enayetpur, Sirajgonj.
5. Dr. Farzana Yeasmin, Medical Officer, Department of General ICU, KYAMCH, Enayetpur, Sirajgonj.

Correspondence: Dr. Rajib Hasan, Incharge, Department of General ICU, KYAMCH, Enayetpur, Sirajgonj.
E-mail: drhasanr87@gmail.com

adequate fluid replacement, require vasopressor therapy to maintain adequate blood pressure". The aim of this article is to evaluate the evidence regarding the role of steroids in adult patients of septic shock.

Literature Search

A search of appropriate articles was undertaken based on the search strategies outlined below:

- Search of "PubMed", "Googgle", "Cochrane Library", "MEDLINE", "EMBASE", "SCOPUS" and "TRIP Plus" were used for medical literature published from January 2002 to January 2013.
- Article references were also searched for any other relevant papers.
- Studies were only included if they were published in English language.
- Studies were included if they met all of the following criteria: randomized, controlled trial design, systematic reviews, meta-analyses which enrolls adult patients who met criteria for sepsis or septic shock, defined by the American College of Chest Physicians and Society of Critical Care Medicine Consensus Conference (1992) (Appendix 1).
- In order to include some key studies, three articles published from 1987, 1998 and 1999 were included.

Discussion

Which steroid to use?

Hydrocortisone is the pharmacological form of cortisol. Additional pharmacological steroids include dexamethasone, methylprednisolone, prednisolone etc. Compaired to hydrocortisone, the other pharmacological forms of steroids bind cortisol binding globulin (CBG) poorly, resulting in more free, physiologically active steroid and greater potency at any given dose. The anti-inflammatory and salt retaining effects of some commonly used steroid formulations[7]:

Table: Anti-inflammatory and salt retaining properties of different steroids in comparison to hydrocortisone.

Steroids	Anti -inflammatory Effects	Salt Retaining Effects
Hydrocortisone	1	1
Prednisolone	3	0.75
Methylpr ednisolone	6.2	0.5
Dexamethasone	26	0
Fludrocortisone	12	125

Most of the studies evaluating the effects of steroid in septic shock used hydrocortisone[7,8,9,10,11]. Whether the anti-inflammatory and salt retaining properties of hydrocortisone were considered for its use in these studies is not mentioned. However use of other pharmacological forms of steroids, such as methylprednisolone was associated with increased incidence of steroid induced side effects. Two studies were identified where steroids other than hydrocortisone were used[12,13]. Among them Bone et al (1987) performed the one of the first large prospective, randomized, double-blind, placebo-controlled trial showing the effect of high dose steroid in septic patients. In this trial methylprednisolone was used as the pharmacological form of steroid in patients of severe sepsis and septic shock. Three hundred eighty-two patients were enrolled. Treatment was given either by methylprednisolone or placebo in four infusions, starting within two hours of diagnosis of septic shock. No significant differences were found in the prevention of shock, the reversal of shock, or overall mortality. Among patients treated with methylprednisolone, significantly more deaths were related to secondary infection. This evidence can be labeled as [2- 13].

The other largest randomized, controlled trial on steroid and septic shock however did add fludrocortisone along with hydrocortisone as pharmacological forms of steroids[12]. But it is unknown whether these findings can be generalized to other systemic steroids.

Route of administration

Almost all of the studies evaluating the role of steroid in patients of septic shock used intravenous route as the desired route of drug administration. This could be possibly due to the fact that many of the septic shock patients suffer from gastroparesis which could result in inappropriate systemic drug absorption and bio-availability following oral steroid ingestion.

Which Patients Should Receive Steroid?

Steroids are necessary to survive critical illness[14]. Absolute adrenal insufficiency is rare among critically ill patients, with an incidence estimated to be $\leq$ 3 percent[11]. Suboptimal cortisol production during septic shock has been termed "functional" or "relative" adrenal insufficiency[7,8]. There is no absolute test to diagnose relative or functional adrenal insufficiency. In addition, there is considerable disagreement over what cortisol

level is "normal" or "appropriate" in septic shock, what constitutes an adequate response to ACTH, and what dose of synthetic ACTH should be used for stimulation testing.

However there are currently three widely practiced laboratory methods for the diagnosis of relative or functional adrenal insufficiency in ICUs:

- Measurement of random serum cortisol level
- High dose ACTH test
- Low dose ACTH test

One prospective study was identified which tried to evaluate whether random serum cortisol level was a better discriminator of adrenal insufficiency than high and low dose ACTH test in patients of septic shock[9]. A baseline serum cortisol level was performed followed by a low dose and a high dose ACTH test in fifty-nine patients of septic shock. Patients were considered steroid responsive if the vasopressor agent could be discontinued within 24 hrs of the first dose of hydrocortisone. In the study 47 percent patients died, 22 percent met the diagnostic criteria of adrenal insufficiency by the low dose ACTH test, 8 percent by the high dose ACTH test and 61 percent by random serum cortisol level. Difference between the random serum cortisol level among the steroid responders and the steroid non-responders proved to be statistically highly significant ($p<0.0001$). Baseline cortisol concentration of <25g/dL was found in ninety-five percent of steroid-responsive patients. Diagnostic low-dose test was found in fifty-four percent of steroid responders and 22% had a diagnostic high dose test. A receiver operating characteristic (ROC) curve showed that random serum cortisol concentration of 23.7 µg/dL was the most accurate diagnostic threshold for determining the hemodynamic response to steroid therapy.

Another similar prospective study was identified which tried to evaluate whether low or high dose ACTH test was a better diagnostic tool for evaluating outcome among septic shock patients[10]. In the study 46 patients with septic shock were administered low-dose and high-dose ACTH consecutively. Serum cortisol levels were measured at baseline and after each stimulation test. A positive response to ACTH stimulation was defined as a serum cortisol increase >9 mcg/dL. Patients who responded to low-dose and high-dose ACTH were more likely to survive than those who did not respond to either dose. In addition, a response only to high-dose ACTH stimulation was associated with lower survival than a response to both low-dose and high-dose ACTH stimulation, suggesting that low-dose ACTH stimulation identified a subgroup of patients with inadequate adrenal reserve that would have been missed by high-dose ACTH stimulation alone.

The results of these studies proved to be clinically very important although they are not adequately powered. These two evidences can be labeled as 2+. Larger studies are needed before the implications of the findings from these two investigations can be fully understood.

Dosage, Duration and Outcome of Use

In the early 1980s steroids were given in high dosage and for short duration in patients of sepsis and septic shock. Two prospective, randomized, double-blind, placebo-controlled studies were identified where none of the trials found a mortality benefit and both of them administered high-dose glucocorticoids for a short duration and used early endpoints[13,15]. In the early 1990's, interest in steroids as a therapy in septic shock was renewed, this time using smaller, more physiological doses for longer duration.

A study investigated the effect of hydrocortisone on shock reversal, hemodynamics, and survival in patients of septic shock[16]. It was a prospective, randomized, double-blind, placebo-controlled study where forty-one patients with septic shock were taken from two intensive care units of a University hospital. The patients were given either hydrocortisone (100 mg iv three times daily for 5 days) or matching placebo. The end point of the study was decided to be reversal of shock (stable systolic arterial pressure >90 mm Hg for more than or equal to24 hours without catecholamine or fluid infusion). After 7 days shock reversal was more in the intervention group ($p=0.007$). After 28 days reversal of shock was higher in the hydrocortisone group ($p=0.005$). Shock reversal within 7 days after the onset of corticosteroid therapy was a very strong predictor of survival. The authors concluded "administration of modest doses of hydrocortisone in the setting of pressor-dependent septic shock for a mean of >96 hours resulted in a significant improvement in hemodynamics and a beneficial effect on survival".

Another similar study was identified where the author investigated the effects of stress doses of hydrocortisone on the duration of vasopressor therapy in human septic shock[17]. The study was a prospective, randomized, double-blind, single-center study which included forty septic shock patients of a twenty-bed multidisciplinary intensive care unit in a 1400-bed university hospital. Patients were prospectively randomized to receive either stress doses of hydrocortisone (loading dose of 100 mg given within 30 mins followed by a continuous infusion of 0.18 mg/kg/hr) or placebo. The primary study end point was the time to cessation of vasopressor support.

Final analysis of the results showed infusion of stress doses of hydrocortisone reduced the time to cessation of vasopressor therapy in human septic shock. These evidence can be labeled as 2+. A meta analysis was identified which Peter et al (2004) compaired recent trials of steroid use in septic shock with previous steroid trials. All the studies included were randomized controlled trials of sepsis that examined the effects of glucocorticoid on survival or vasopressor requirements. The 5 trials included which were done in recent years showed a consistent beneficial effect of glucocorticoids on survival ($p = 0.036$) and shock reversal ($p < 0.001$).

These effects were not influenced by the patients adrenal function. On the other hand, 8 trials published before 1989 showed a survival disadvantage with steroid treatment ($p= 0.008$). In contrast to the earlier trials the recent trial started steroid therapy later after the patients had met the enrollment criteria of septic shock (23 hours vs. <2 hours; $p = 0.02$), it was continued for longer periods (6 days vs. 1 day; $p = 0.01$) and at lower total dosages. Limitations of the study include potential bias secondary to nonreporting of negative study results, inclusion of some relatively small studies conducted after 1997 etc. Moreover the beneficial effects of glucocorticoid therapy in the recent trials could also be partially due to time related factors such as, improved ventilator management, fluid therapy, use of vasopressors etc.

In the largest double-blind, placebo-controlled trial performed, 300 patients were randomized within eight hours of the onset of septic shock to receive placebo or replacement dose of hydrocortisone (50 mg intravenously every six hours) plus fludrocortisone (50 mcg enterally once a day) for seven days[12]. Based upon a high dose ACTH test, all patients were classified as having adequate adrenal reserve or responders (maximum increase in serum cortisol of >9 mcg/dL) or inadequate adrenal reserve or non-responders (maximum cortisol increase of 9 mcg/dL). As a result of their analysis Annane and his colleagues showed that hydrocortisone administration was associated with decreased 28-day mortality (53% versus 63%, RR 0.83 with a number needed to treat of 7) and ICU mortality (58% versus 70%, RR 0.82) in patients with inadequate adrenal reserve. There was no significant difference in the responders but the effect on all patients still showed a positive outcome benefit and the 'number needed to treat (NNT)' of [8].

This paper had a number of drawbacks. First of all, use of the induction anaesthetic etomidate within previous 6 hours was used as an exclusion criteria of patients. But in fact, Malerba et al (2005) showed that a single dose of etomidate can inhibit steroid synthesis in the body for as long as 24 hours. The original paper also did not state that how many of the patients recruited in the study did receive etomidate. Secondly, there was high placebo group mortality. Thirdly, a single tailed test was used in the original statistical analysis and finally, use of fludrocortisone was a potential confounder in the study. A meta analysis was identified which showed positive association between glucocorticoid therapy and improved mortality of septic shock patients[20].

The meta-analysis of 15 randomized, controlled trials (2023 patients) examining glucocorticoid administration in severe sepsis and septic shock. Results showed that glucocorticoid therapy was associated with increased shock reversal by 7 days and 28 days. Overall, glucocorticoids did not change mortality. However, when only trials that used low dose glucocorticoids for more than five days were analyzed, glucocorticoid therapy reduced 28-day mortality, ICU mortality, and hospital mortality. This meta-analysis also found that the administration of glucocorticoids was not associated with increases in reported adverse events, including gastrointestinal bleeding, secondary infections or hyperglycemia.

Although some of the recent clinical trials show statistically significant benefit in terms of mortality after administration of low dose steroid for relatively longer duration yet properly designed, sufficiently powered, randomized, multi centre trials are needed in this field.

Conclusion

Identification of the patients who suffer from relative adrenal insufficiency still remains a challenge. Because sufficient adequately powered clinical trials are lacking in depicting that which test should be considered gold standard regarding diagnosis of relative adrenal insufficiency in septic shock patients.

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Appendices

Appendix I.

Consensus Conference of the American College of Chest Physicians and Society of Critical Care Medicine definitions for the various manifestations of infection

- **Systemic Inflammatory Response Syndrome (SIRS):** Manifest by two or more of the following conditions:

1. A temperature >38^{o}C or <36^{o}C
2. An heart rate >90 beats per minute
3. A respiratory rate >20 breaths per minute or a PaCO2 <32 mmHg
4. A white blood cell count >12,000/mm3 or <4000/mm3, or the presence of >10% immature forms.

- ***Sepsis:*** The systemic response to infection, manifested by two or more of the SIRS criteria plus an infection.

- ***Severe Sepsis:*** Sepsis associated with organ dysfunction, hypoperfusion, or hypotension. Hypoperfusion and perfusion abnormalities that may include, but are not limited to lactic acidosis, oliguria or an acute alteration in mental status.
- ***Septic shock:*** Sepsis-induced hypotension despite adequate fluid resuscitation, along with the presence of perfusion abnormalities that may include, but are not limited to lactic acidosis, oliguria or an acute alteration in mental status. Patients who are receiving inotropic or vasopressor agents may not be hypotensive at the time that the perfusion abnormalities are measured. This is a subset of severe sepsis.

Appendix II. Framework for level of evidence. Harbour R and Miller J. (2001)

Level of evidence	Description
1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1-	Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2++	High quality systematic reviews of case-control or cohort studies *or* High quality case-control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal
2+	Well conducted case-control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal
2-	Case-control or cohort studies with a high risk of confounding, bias, or chance
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion