

Role of steroids in critically-ill sepsis patients: a review article and literature to review

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ABSTRACT

Sepsis, a life-threatening condition, commonly affecting critically ill patients, is a major cause of death worldwide. It is thus of great importance to determine the optimum management to cure this condition. This review article summarizes the role and effects of corticosteroids in the treatment of sepsis and septic shock, and to determine its mortality benefits. We used PubMed, Google scholar, Scopus, and Embase databases for literature review, and terminologies commonly searched were 'sepsis', 'septic shock', 'therapeutic use' and 'corticosteroids'. In this review article, we reviewed a total of eight different articles being done in last 10 years, relevant to the clinical outcome and effects of corticosteroids. Among those, two demonstrated improved clinical outcomes, two showed both improved clinical outcomes and decreased mortality, three showed increased adverse effects, and the remaining one showed unequivocal results.

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1. Introduction

Sepsis is defined as life-threatening condition causing multi-organ dysfunction by a dysregulated host response to infection. Septic shock is a subset of sepsis with circulatory and cellular or metabolic dysfunction associated with a higher risk of mortality [1]. The strongest predictor of death is determined by Sequential Organ Failure Assessment (SOFA) score among sepsis patients [2]. Mortality rates in sepsis patients are high up to 40% within 1 year and 80% within 5 years of hospital discharge [3]. Sepsis is said to effect the hypothalamic pituitary adrenal axis, causing a relative adrenal insufficiency resulting in cardiovascular instability, metabolic disorders, and a sustained pro-inflammatory state [3]. The initial management requires forming a probable diagnosis, obtaining cultures, and initiating appropriate empirical antimicrobial therapy and source control. Intravenous antibiotic therapy should be started as early as possible and should cover all possible pathogens [4]. Aside from early hemodynamic stabilization, respiratory resuscitation procedures, and appropriate antimicrobial therapy, there are no approved adjuvant therapies for use once septic shock has occurred. Patients who advance to septic shock can be identified by a need for vasopressor therapy to maintain a mean arterial pressure ≥ 65 mmHg and by a serum lactate level > 2 mmol/L in the absence of hypovolemia [5,6]. The role of pro-inflammatory pathways suggests a potential use for corticosteroids as an adjuvant therapy in the treatment of

sepsis and septic shock [7]. The Surviving Sepsis campaign guidelines recommend that patients should be loaded with crystalloid fluid unless there is any contraindication followed by vasopressors. If adequate fluid resuscitation and vasopressors have not restored the hemodynamic stability, it was postulated in limited data to use hydrocortisone, at a dose of 50 mg IV every 6 h, or 100 mg IV bolus followed by an infusion of 10 mg/h for 7 days [5]. Optimization of initial management of patients with sepsis prevents brain injury and subsequent declines in cognitive functioning of the patient [3]. Ultimately reducing short term and long-term modalities with reduction in hospital stay [3].

There are several researches exploring whether corticosteroids should be used in the treatment of sepsis and septic shock, but due to the limitation in the data, results are still inconclusive. Recent clinical trials and studies of corticosteroid therapy have been reviewed in this article to best direct the informed management of septic shock patients among those who are resistant to IV fluids and vasopressors treatment [7].

2. Objectives

The objective of this study are to determine the role of steroid in IV fluids and vasopressor-resistant sepsis patients, its short- and long-term mortality benefits and impact on the length of hospital stay.

3. Methods

Literature was reviewed on PubMed, Google Scholar, Embase, and Scopus databases and the keywords searched were 'Sepsis', 'Septic shock', 'Therapeutic use' and 'Corticosteroids'. An extensive literature search for last 20 years starting year 2000 till date were included in our study, most of the data were studied on septic patients being admitted to ICU. Information was gathered from eight most relevant articles and was arranged in ascending order of the year of publication. Information was further tabulated for ease of understanding of outcomes.

4. Literature review

4.1. Annane et al, (2006) [8]

This retrospective, placebo-controlled, randomized, double blind trial, assessed the role of corticosteroids in septic shock patients with or without early Acute Respiratory Distress Syndrome (ARDS). The study was divided between two groups of patients based on ARDS criteria. Out of 300 total patients, 177 met the ARDS criteria, out of which 85 were given steroids while 92 were started on placebo for 7 days. The steroid of choice in this trial was dexamethasone. The study was further divided between responders and non-responders as the patients underwent a short corticotropin test with tetracosactrin (250 µg IV) and were graded as non-responders if the cortisol increase was ≤ 9 microg/dL. There were 129 non-responders (placebo given to 67, corticosteroids to 62) and 48 responders (Placebo given to 25, corticosteroids to 23). In non-responders, there were 50 deaths (75%) in the placebo group and 33 deaths (53%) in the steroid group ($p = 0.013$). The average days off mechanical ventilation was 2.6 in the placebo group and 5.7 in the corticosteroid group ($p = 0.006$). There was no significant difference between groups in responders and further in the two subsets without ARDS. In conclusion to this study, there was a better outcome in non-responders in the steroid group on patients with ARDS, and there was no significant difference between the adverse effects in patients with or without ARDS.

4.2. Arabi et al. (2010) [9]

The aim of this randomized double-blind placebo-controlled trial was to evaluate the role of low dose hydrocortisone in cirrhotic patients with septic shock. 75 adult patients were enrolled, 39 were given hydrocortisone treatment and 36 were placebos. Enrolled patients underwent corticotropin test and were randomized. Hydrocortisone was given every 6 h in an

IV bolus injection of 5 mL normal saline containing 50 mg of hydrocortisone or placebo in full dose until resolution of septic shock was achieved without the use of vasopressors for 24 h and was then tapered off by 1 mL reduction every 2 days until discontinued. Though hydrocortisone was associated with a significant improvement in the hemodynamic response with increased shock reversal compared with the placebo group (24 [62%] v. 14 [39%]; $p < 0.05$), there was increased relapse occurrence in the treatment group (13 [34%] v. 5 [14%]; $p = 0.03$) and no significant difference was seen in the 28-day mortality between the two groups (33 [85%] v. 26 [72%]; $p = 0.19$). There was no difference in mechanical ventilation-free days, renal replacement therapy-free days, length of stay at the hospital. Higher rates of severe hyperglycemia ($p = 0.06$) as well as significant increased risk of gastrointestinal bleeding ($p = 0.01$) was also reported in the treatment group. This study concludes that though initially the effects of hydrocortisone therapy were in favor and improved the hemodynamic state, it did not reduce mortality and was also associated with an increased risk of adverse effects with no mortality benefits.

4.3. Casserly et al, (2012) [10]

In this retrospective study, the Severe Sepsis Campaign (SSC) database was analyzed from January 2005 through March 2010 to note the effects of low dose corticosteroids [LDCS] (50 mg IV q6H or 100 mg IV TDS) on adult patients with septic shock. Out of a total of 17,847 patients, eligibility for LDCS was based on patients who were on vasopressor therapy despite fluid resuscitation and based on the eligibility criteria, 8992 patients (59.4%) received LDCS. Among the patients who received corticosteroids, 3662 (41%) died in the hospital, while 3094 (35%) of patients that did not receive steroids died in the hospital (41% vs 35%, $p < 0.001$). Patients who received low-dose steroids and had multi-organ dysfunction demonstrated an increased adjusted hospital mortality compared to patients who did not receive low-dose steroids ($p = 0.001$). This study claims lack of benefits of low dose steroid therapy in critically ill patients with septic shock since the hospital mortality was higher in the treatment group. This may reflect the study's limitation as an observational design, as it is possible that only the most severely ill patients in septic shock received steroid therapy.

4.4. Nazer et al (2015) [11]

The objective of this three-year duration study was to identify the effectiveness and safety of low-dose hydrocortisone on adult cancer patients with septic

shock. 96 patients were given hydrocortisone (200 mg/day) compared to a control group of 62 patients receiving placebo, in a comprehensive cancer hospital in Amman, Jordan. Resolution of septic shock was noted in 46 patients (47.9%), ICU mortality in 62 patients (65.26% vs 32.3% in control group) and 28-day mortality in 64 patients (66.7% vs 38.7% in control group). Hyperglycemia in the treatment group was noted in 72 patients (75% vs 61.3%) ($p = 0.067$) and was prominently higher than the control group. Secondary infection was also higher in the treatment group (44.8% vs 27.4%; $p = 0.028$). The study concluded that even though there was significant reversal of septic shock, the use of hydrocortisone caused increase ICU mortality and 28-day mortality. Also, contributed to adverse effects, especially secondary infections. The limitations of this study include lack of comparison arm and being a single center study, which may have affected the generalizability.

4.5. Tongyoo et al, (2016) [12]

In this randomized controlled trial conducted over the course of 4 years in Bangkok, the effects of low dose steroid therapy on 28-day mortality of patients with sepsis associated with ARDS were determined. Within 12 h of meeting the ARDS criteria, patients were randomly assigned either hydrocortisone (50 mg/6 h) or placebo for 7 days. Out of a total of 197 patients, 98 were given hydrocortisone and 99 were given placebo. According to this study, although in the treatment group there was significant improvement in the ratio of partial pressure of oxygen in arterial blood to fraction of inspired oxygen and lung injury score ($p = 0.01$), the 28-day survival benefit was not notable ((65.3% vs. 55.6%; $p = 0.19$). After hydrocortisone was stopped, the improved lung physiology was maintained. Statistically there was no increased risk of complications, except hyperglycemia (80.6% vs 67.7%; $p = 0.04$), which did not affect the outcome.

4.6. Gibbison et al, (2017) [13]

This study compared the data of 22 randomized controlled trials to analyze the effects of giving hydrocortisone, dexamethasone, methylprednisolone, or prednisolone to patients in septic shock. There is weak evidence that boluses of dexamethasone may reduce the risk of in-hospital mortality as well as increase the risk of superinfection compared with placebo. There is strong corroboration that boluses of methylprednisolone are less likely to reverse shock than hydrocortisone boluses and infusions. There is also evidence that hydrocortisone increases the likelihood of shock reversal compared with placebo when

given as a bolus or infusion and no drug except hydrocortisone showed astonishing results in shock reversal or reducing mortality and side effects. Limitations of this study include a source of bias as data was used from the last 50 years, during which time the ICU patient population has changed in terms of patient condition, age, and treated comorbidities. There were few direct comparisons of treatment regimens.

4.7. Annane et al, (2018) [14]

This is a more recent trial by Annane et al conducted from September 2008 through June 2015, including 1241 patients to compare the effect of hydrocortisone and fludrocortisone against placebo. Hydrocortisone was administered at 50 mg IV bolus 6 hourly and fludrocortisone as a 50 µg tablet though nasogastric route once daily for 7 days without tapering. 614 patients were in the trial group, out of which, 90-day mortality was seen in 264(43%) and 308(49.1%) from the 627 in the placebo group ($p = 0.03$). It was also noted that in the treatment group, mortality was significantly lower at ICU discharge ((35.4% vs. 41.0%, $P = 0.04$), hospital discharge (39.0% vs. 45.3%, $P = 0.02$), and day 180 (46.6% vs. 52.5%, $P = 0.04$). Mortality was significantly lower in the hydrocortisone plus fludrocortisone group and shorter time to wean off the mechanical ventilator, to vasopressor, and vasopressor free days (17 vs 15; $p < 0.001$). The common adverse affect in the drug group was hyperglycemia, which was significantly higher than the placebo group ($p = 0.002$). Other risk was not remarkably higher between the two groups. According to this trial, Hydrocortisone and fludrocortisone therapy accelerated the resolution of organ failure in adults with septic shock, lower 90-day mortality, and improvement in the hemodynamic state.

4.8. Venkatesh et al, (2018) [5]

This randomized controlled trial was conducted from March 2013 through April 2017, involving 3658 patients with septic shock undergoing mechanical ventilation who were randomly given either hydrocortisone (200 mg per day IV continuous infusion) or placebo for one week. Out of 3658 subjects, 1832 received hydrocortisone and 1826 were given placebo. Hydrocortisone group had faster resolution of septic shock (3 days vs 4 days; $p < 0.001$), shorter duration of mechanical ventilation (6 days vs 7 days; $p < 0.001$) and fewer blood transfusions were required, however it did not result in lower 90-day mortality than placebo, or rate of recurrence of shock, number of days alive, duration of recurrence of mechanical ventilation or incidence of secondary infection. Adverse

effects were also seen more in the hydrocortisone group compared with the placebo but they did not have a significant effect on the outcome. Therefore, although there was quicker resolution of septic shock, there were no significant difference in mortality.

5. Discussion

The aim of this article is to present concise data on the use of corticosteroids in patients with sepsis and septic shock, which has been a topic for debate for several decades without discovering a definitive conclusion. The prolongation of extremely poor outcomes in half of the sepsis cases warrants the need for improved therapies. Sepsis is said to have an effect on the Hypothalamic-Pituitary-Axis, causing a relative adrenal insufficiency by a progressive decline in the ACTH concentrations, as well as marked over-expression of the inducible NO synthase (iNOS), triggered by cytokines particularly IL-1 and TNF. The overproduction of NO contributes to further tissue damage and hemodynamic instability, by triggering NO-induced neuronal apoptosis. Corticosteroid resistance in the body has also been noted due to marked reduction in the cortisol-binding globulin (CBG) and albumin, leading to the net effect of reduced cortisol delivery at the inflammation sites [15]. It also causes decreased corticosteroid receptors and reduced binding capacity of the remaining receptors due to effects of the increased NO [7]. This hypothesis provides potential benefits for the use of corticosteroids in patients with septic shock unresponsive to vasopressor therapy. Several trials have shown that moderate doses of corticosteroids decrease circulating levels of most pro-inflammatory cytokines and help treatment of sepsis. Corticosteroids also improve cardiovascular function by restoring effective blood volume through increased mineralocorticoid activity and by increasing systemic vascular resistance, an effect that is partly related to endothelial glucocorticoid receptors [15]. They also decrease organ failure by reducing inflammation and inhibition of iNOS activation. Majority of the trials that were studied in this article demonstrated that although none of the newly published trials proved any mortality benefits in septic shock after administration of low-dose hydrocortisone, there were significant improvements in the hemodynamic stability in patients with septic shock. Two of the studies discussed in this article, Venkatesh et al. and Tongyoo et al. showed faster improved hemodynamic response and shorter duration of mechanical ventilation, with no survival benefit. Both the Annane et al., trials in 2006 and 2018 exhibited an improvement in the hemodynamic status as well as a decrease mortality rate. The 2018 Annane et al. study stated that the administration of Fludrocortisone with hydrocortisone showed no

benefits of the added drug. The other three studies emphasized more on the adverse effects of steroids which were mostly hyperglycemia, gastrointestinal bleeding, and secondary infections. Patients who had been assigned to receive hydrocortisone had a shorter stay in the ICU and earlier discontinuation of initial episode of mechanical ventilation than did those who had been assigned to receive placebo [5]. Casserly et al. evaluated data from SSC database and demonstrated significantly increased mortality ($p < 0.001$) as well as multi-organ dysfunction due to hydrocortisone and therefore does not support the use of corticosteroids for septic shock. In many older studies, high dose corticosteroids were administered in critically ill patients which had significantly higher adverse effects, the newer trials with low dose hydrocortisone have shown to be well tolerated. The Gibbison [13] study concluded that the low dose corticosteroid of choice preferred is hydrocortisone. Majority of the trials in this review indicate the therapeutic benefit in improvement of septic shock reversal which supports the Surviving Sepsis Campaign guidelines that recommend against using corticosteroids as routine therapy in patients responsive to fluids and vasopressors, and only low doses in non-responders [7].

6. Conclusion

This review article consists of outcomes obtained from eight articles based on the role of low dose corticosteroids in management of sepsis, which is potentially a fatal condition requiring prompt diagnosis and treatment. Majority of the articles highlighted that low dose corticosteroids have shown to provide better hemodynamic response in patients with septic shock, unresponsive to fluids or vasopressor therapy. It should not be administered as a routine or sole treatment for sepsis, but the data available to date is limited, we recommend an extensive research in the upcoming future to determine the definitive conclusion on the role of low dose corticosteroids for the treatment, particularly in slightly healthier patients as majority of the articles were based on critically ill patients in the ICU.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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