Review Article

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Archivos de Medicina
ISSN 1698-9465

2021
Vol.17 No. 8:10178

Corticoids in Sepsis, the Available Evidence

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Received date: August 21, 2021; **Accepted date:** November 16, 2021**; Published date:** November 26, 2021

Citation: Monterrosa-Robles M, Cortazar-Barreto C, Navarro-Alvarez Y, Pérez-Contreras F, Salas-De la Hoz F (2021) Corticoids in Sepsis, the Available Evidence. Arch de Medi. Vol: 17 No: 7.

Introduction

The treatment with corticosteroids in refractory septic shock has historically been of great controversy, taking into account the heterogeneous results found in the different randomized clinical trials. However, in light of the current evidence, it is recognized that, despite not having a significant impact on mortality, it has benefits by reducing the duration of shock, the use of vasopressors, the stay in the intensive care unit and in the days of mechanical ventilation. Methodology: a narrative review about corticosteroids in septic shock was carried out, through a systematic search in PubMed, Medline, Cochrane, and RIMA, for articles in English and Spanish, from January 1, 1980 to August 1, 2021 taking as keywords septic shock, systemic inflammatory response syndrome, corticosteroids. A critical review of the evidence was carried out using the GRADE methodology (Grades of Recommendation, Assessment, Development, and Evaluation), rating the quality of the evidence and the level of recommendation. A total of 20 papers were included. The reference lists of all previously identified studies were checked. Conclusions: The use of corticosteroids could be beneficial in patients with refractory septic shock due to its benefit in reducing days of shock, use of vasopressors, stay in intensive care and days of mechanical ventilation, but its use should be individualized taking into account the side effects associated with their use, such as hypernatremia, hyperglycemia and muscle weakness in critically ill patients.

Keywords: Septic shock; Systemic inflammatory response syn drome; Adrenal hormones. (DeCS)

Sepsis

Sepsis corresponds to an inadequate response to a suspected or confirmed infectious process, which is capable of generating multiple organ dysfunction (DOM) and increasing the risk of mortality [1]. Historically, sepsis was defined as a systemic inflammatory response syndrome (SIRS) associated with an infectious process of any etiology. This is how Bone. In 1992, the consensus document for the definition of sepsis was produced for the first time [2]. In this definition included the term severe sepsis, for all patients who presented arterial hypotension or had at least one laboratory suggestive of organ failure; and the term of septic shock for all patients who presented severe hypotension that was refractory to fluid therapy and required vasopressor support. This definition, despite being very practical, was not perfect. This is because SIRS can be present in conditions other than an active infectious process; such as pancreatitis, burns, multiple trauma [2]. This is evident in different studies; Like Churpek, [3] where approximately 47% of hospitalized patients could present some degree of systemic inflammatory response, without encountering an active infectious process [3]. Like wise, in Kaunuken et al, 12% of the patients who presented sepsis upon admission to the emergency department lacked SIRS [4], thus, they do not have the adequate capacity to accurately discriminate an active infectious process, far from defining the severity and risk of mortality in patients.

In 2016, the third definition of sepsis emerged. In this, the demonstration of DOM associated with a suspected or confirmed infectious process is taken as a starting point [1]. The diagnosis of organ dysfunction is based on the calculation of the SOFA score (System-related Organ Failure Assessment) greater than or equal to 2 points [1]. This score has been endorsed for patients with sepsis for more than 20 years, being very useful to predict mortality risk [5], however, it was not part of the diagnostic algorithm until this consensus [1]. The diagnosis of sepsis based on the SOFA has a good correlation for hospitalized patients.

in the intensive care unit and for those hospitalized in the general ward [6]. The concept of septic shock is based on the demonstration of tissue hypoperfusion; Thus, it is defined as sepsis associated with severe hypotension that requires the initiation of vasopressor support in addition to the elevation of lactate levels above 2.0mmol / L [1].

Within the initial approach to the patient, we have a tool for rapid detection of patients with high mortality risk, the qSOFA. It consists of a score made up of 3 clinical variables: altered state of consciousness, a respiratory rate greater than 22 breaths per minute, and a systolic blood pressure less than or equal to 100mmHg. A score of 2 or more is able to accurately discriminate the patients who could be found with a picture of sepsis and are susceptible to the calculation of SOFA [7]. When evaluating this strategy it was shown that it is more effective to evaluate patients outside of the intensive care unit [6].

There is a group of patients, which presents a torpid evolution, with persistent hypotension despite being receiving infusion of vasopressor drugs and ending in a progressive organic dysfunction that leads to death. This is how refractory septic shock is defined as patients who require a dose of norepinephrine greater than or equal to 0.5mcg / kg / min or an equivalent [8].

Septic patients often develop critically ill-related adrenal insufficiency (CIR CI) [9]; which is defined as a cortisol delta (change in baseline cortisol at 60 min to <9 µg / dL) after the administration of 250 mcg of ACTH or a random plasma cortisol <10µg / dL [10]. This is due to dysregulation of the hypothalamic - pituitary - adrenal axis, alteration in cortisol metabolism (decreased clearance due to suppression of the activity of the type 2 5-alpha reductase enzyme) and peripheral resistance to cortisol [11]. For this reason, corticosteroid therapy has been proposed as an alternative treatment in patients with refractory septic shock and suspected adrenal insufficiency.

In the recommendations of the Surviving Sepsis Campaign 2016 clinical practice guide, the use of corticosteroids is limited to patients with refractory septic shock in whom secondary adrenal insufficiency is suspected to reestablish hemodynamic stability (weak recommendation, low quality of evidence) [12]. Next, we will carry out a historical recount of the scientific evidence and discuss the pros and cons of corticosteroid therapy in septic patients. Similarly, we will mention the recommendations for its use in some of the main infectious foci (pulmonary, urinary, abdominal, meningeal).

Evidence of corticosteroid therapy in the septic patient

Since the 1950s, there has been a special interest in the use of corticosteroids in infectious diseases. in 1984 Sprung et al. conducted a prospective trial of 59 patients with septic shock, who were randomized to receive 30mg / kg of methylprednisolone, 6mg / kg of dexamethasone or placebo. It was found that the groups treated with corticosteroids had a greater reduction in shock within the first 4 hours (P <0.05), there were no statistically significant differences in mortality [13].

In 1987, Bone et al. Conducted a double-blind randomized clinical trial, comparing in a court of 882 patients, the administration of 30mg / kg of methylprednisolone every 6 hours until completing 4 doses with placebo. Their primary endpoints were: shock reversal and 14-day mortality. No statistically significant differences were found in mortality in both groups. In the subgroup of patients who entered the study with creatinine levels> = 2, a statistically significant increase in mortality was observed when methylprednisolone was administered (P <0.01) [14].

That same year, Hinshaw et al. Conducted a multicenter, randomized, double-blind trial, in which 223 were assigned to receive methylprednisolone (30mg / kg bolus, followed by an infusion of 5mg / kg / hour for 9 hours) or placebo. They found no statistically significant differences in mortality at 14 days and the resolution of the infection was faster in the group of patients treated with placebo than in those treated with corticosteroids (P <0.03) [15]. The very high doses of corticosteroids that were used in these studies are striking.

In the 1990s, 3 small clinical trials demonstrated that the use of low doses of hydrocortisone (200–400mg / day) resulted in a more rapid decrease in shock and a lower requirement for vasoactive drugs [16–18].

In 2002, Annane D. et al. Published the Frances trial in JAMA. A multicenter, double-blind, placebo-controlled study. It included 300 patients from 19 centers, who were randomized to receive hydrocortisone plus

fludrocortisone (50mg every 6 hours and 50mcg respectively) or placebo. Therapy was started in the first 8 hours of the shock and continued until 6 days. The adrenal reserve was estimated with the ACTH stimulation test at high doses (250mcg), classifying them as adequate or inadequate reserve (increase in cortisol> 9mcg / dL or <9mcg / dL). In patients with inadequate adrenal reserve, hydrocortisone use was associated with lower 28-day mortality (P = 0.02) and faster reversal of shock. In contrast, in patients with adequate adrenal reserve, there were no statistically significant differences in mortality (P = 0.81) [19]. This trial was criticized for its high mortality in the placebo group, as well as the marked difference in results compared to the CORTICUS study [20].

In 2008, Sprung et al. They performed the CORTICUS trial. A randomized, multicenter, double-blind study that included 499 patients with septic shock (regardless of the dose of vasopressors), who were assigned to receive hydrocortisone (50mg every 6 hours for 6 days) or placebo. The ACTH stimulation test was previously performed, with the same criteria as those used in the French trial to define adequate or inadequate adrenal reserve. No statistically significant differences were found in mortality in both groups, but there was evidence of a shorter duration of shock in the group treated with hydrocortisone [20].

Subsequently, in 2016, the HYPRESS study was published. In which 353 patients with severe sepsis, without septic shock, were randomized to receive hydrocortisone (200mg / day for 5 days) or placebo. It was carried out with the old definition of sepsis that included at least 2 variables of SIRS associated with an active infectious process. No differences were found in 28-day mortality or progression to shock in both groups. However, the group treated with hydrocortisone presented a higher rate of adverse effects (hyperglycemia, muscle weakness and increased infection rates) [21]. The ADRENAL study , It is the largest work done on corticosteroids in patients with sepsis; It was a multicenter, randomized clinical trial that included 3800 patients who were randomly assigned to receive hydrocortisone

(200mg / day for 7 days) or placebo. His End Points were: 90-day all-cause mortality, shock resolution time, recurrence of shock, days of ICU stay, duration of mechanical ventilation, presence of acute kidney injury, appearance of a new in-hospital infection. Although no statistically significant differences were found in mortality at 90 days, a shorter duration of shock was demonstrated (P <0.001), shorter stay in intensive care (P <0.001) and fewer days of mechanical ventilation (P <0.001) in the group treated with hydrocortisone [22]. Like wise, the APROCCHSS study was carried out, a randomized, multicenter trial, which included 1241 patients (medical or surgical) with septic shock, who were assigned to receive Hydrocortisone plus Fludrocortisone (200mg / day and 50mcg / day respectively) or placebo. A benefit was found in reducing mortality in the group treated with corticosteroids [23]. However, when we compare the APROCCHSS trial with the ADRENAL trial, we see that it included patients with less severity, with lower doses of vasopressors, a lower percentage of intra-abdominal infections, and more pulmonary infections. This could mean that the benefit of corticosteroids could depend on the severity of the disease or even on the present infectious focus.

Table1: Summarizes the evidence available in each of the clinical trials of corticosteroids in sepsis.

Year / Author n Characteristics of the patients Intervention Conclusions Observations	Year / Author n Characteristics of the patients Intervention Conclusions Observations	Year / Author n Characteristics of the patients Intervention Conclusions Observations	Year / Author n Characteristics of the patients Intervention Conclusions Observations	Year / Author n Characteristics of the patients Intervention Conclusions Observations	Year / Author n Characteristics of the patients Intervention Conclusions Observations
1984. NEJM	1984. NEJM	1984. NEJM	1984. NEJM	1984. NEJM	1984. NEJM
Charles L. Sprung, MD 59	Charles L. Sprung, MD 59	Charles L. Sprung, MD 59	Charles L. Sprung, MD 59	Charles L. Sprung, MD 59	Charles L. Sprung, MD 59
Patients with septic shock under the following criteria: SBP (Systolic Blood Pressure) <90mmHg or a 50mmg decrease in baseline SBP. Tissue hypoperfusion demonstrated by altered mental status or	Patients with septic shock under the following criteria: SBP (Systolic Blood Pressure) <90mmHg or a 50mmg decrease in baseline SBP. Tissue hypoperfusion demonstrated by altered mental status or	Patients with septic shock under the following criteria: SBP (Systolic Blood Pressure) <90mmHg or a 50mmg decrease in baseline SBP. Tissue hypoperfusion demonstrated by altered mental status or	Patients with septic shock under the following criteria: SBP (Systolic Blood Pressure) <90mmHg or a 50mmg decrease in baseline SBP. Tissue hypoperfusion demonstrated by altered mental status or	Patients with septic shock under the following criteria: SBP (Systolic Blood Pressure) <90mmHg or a 50mmg decrease in baseline SBP. Tissue hypoperfusion demonstrated by altered mental status or	Patients with septic shock under the following criteria: SBP (Systolic Blood Pressure) <90mmHg or a 50mmg decrease in baseline SBP. Tissue hypoperfusion demonstrated by altered mental status or
oliguria (<20cc / hour), persistence of hypotension despite fluid therapy with at least 500cc of NSS, documented bacteremia or suspected apparent focus of infection. 30mg / kg of methylprednisolone or 6mg / kg of dexamethasone	oliguria (<20cc / hour), persistence of hypotension despite fluid therapy with at least 500cc of NSS, documented bacteremia or suspected apparent focus of infection. 30mg / kg of methylprednisolone or 6mg / kg of dexamethasone	oliguria (<20cc / hour), persistence of hypotension despite fluid therapy with at least 500cc of NSS, documented bacteremia or suspected apparent focus of infection. 30mg / kg of methylprednisolone or 6mg / kg of dexamethasone	oliguria (<20cc / hour), persistence of hypotension despite fluid therapy with at least 500cc of NSS, documented bacteremia or suspected apparent focus of infection. 30mg / kg of methylprednisolone or 6mg / kg of dexamethasone	oliguria (<20cc / hour), persistence of hypotension despite fluid therapy with at least 500cc of NSS, documented bacteremia or suspected apparent focus of infection. 30mg / kg of methylprednisolone or 6mg / kg of dexamethasone	oliguria (<20cc / hour), persistence of hypotension despite fluid therapy with at least 500cc of NSS, documented bacteremia or suspected apparent focus of infection. 30mg / kg of methylprednisolone or 6mg / kg of dexamethasone
2002. JAMA	2002. JAMA	2002. JAMA	2002. JAMA	2002. JAMA	2002. JAMA
Annane D. cols 300 Sepsis patients with active systemic inflammatory response . Hydrocortisone + Fludrocortisone (50 mg every 6 hours and 50 mcg respectively) Vs placebo. Treatment was continued for up to 6 days. Adrenal reserve was estimated with ACTH stimulation test. In the group of patients with inadequate adrenal reserve (increase	Annane D. cols 300 Sepsis patients with active systemic inflammatory response . Hydrocortisone + Fludrocortisone (50 mg every 6 hours and 50 mcg respectively) Vs placebo. Treatment was continued for up to 6 days. Adrenal reserve was estimated with ACTH stimulation test. In the group of patients with inadequate adrenal reserve (increase	Annane D. cols 300 Sepsis patients with active systemic inflammatory response . Hydrocortisone + Fludrocortisone (50 mg every 6 hours and 50 mcg respectively) Vs placebo. Treatment was continued for up to 6 days. Adrenal reserve was estimated with ACTH stimulation test. In the group of patients with inadequate adrenal reserve (increase	Annane D. cols 300 Sepsis patients with active systemic inflammatory response . Hydrocortisone + Fludrocortisone (50 mg every 6 hours and 50 mcg respectively) Vs placebo. Treatment was continued for up to 6 days. Adrenal reserve was estimated with ACTH stimulation test. In the group of patients with inadequate adrenal reserve (increase	Annane D. cols 300 Sepsis patients with active systemic inflammatory response . Hydrocortisone + Fludrocortisone (50 mg every 6 hours and 50 mcg respectively) Vs placebo. Treatment was continued for up to 6 days. Adrenal reserve was estimated with ACTH stimulation test. In the group of patients with inadequate adrenal reserve (increase	Annane D. cols 300 Sepsis patients with active systemic inflammatory response . Hydrocortisone + Fludrocortisone (50 mg every 6 hours and 50 mcg respectively) Vs placebo. Treatment was continued for up to 6 days. Adrenal reserve was estimated with ACTH stimulation test. In the group of patients with inadequate adrenal reserve (increase

in cotisol to 9 mcg / dl with ACTH doses of 250 mcg), the administration of corticosteroids was associated with a lower mortality at 28 days (P <0.02). In the group with adequate adrenal reserve, there was no statistically significant difference in mortality (P = 0.81). The high mortality found in the placebo group is striking.	in cotisol to 9 mcg / dl with ACTH doses of 250 mcg), the administration of corticosteroids was associated with a lower mortality at 28 days (P <0.02). In the group with adequate adrenal reserve, there was no statistically significant difference in mortality (P = 0.81). The high mortality found in the placebo group is striking.	in cotisol to 9 mcg / dl with ACTH doses of 250 mcg), the administration of corticosteroids was associated with a lower mortality at 28 days (P <0.02). In the group with adequate adrenal reserve, there was no statistically significant difference in mortality (P = 0.81). The high mortality found in the placebo group is striking.	in cotisol to 9 mcg / dl with ACTH doses of 250 mcg), the administration of corticosteroids was associated with a lower mortality at 28 days (P <0.02). In the group with adequate adrenal reserve, there was no statistically significant difference in mortality (P = 0.81). The high mortality found in the placebo group is striking.	in cotisol to 9 mcg / dl with ACTH doses of 250 mcg), the administration of corticosteroids was associated with a lower mortality at 28 days (P <0.02). In the group with adequate adrenal reserve, there was no statistically significant difference in mortality (P = 0.81). The high mortality found in the placebo group is striking.	in cotisol to 9 mcg / dl with ACTH doses of 250 mcg), the administration of corticosteroids was associated with a lower mortality at 28 days (P <0.02). In the group with adequate adrenal reserve, there was no statistically significant difference in mortality (P = 0.81). The high mortality found in the placebo group is striking.
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2018. NEJM	2018. NEJM	2018. NEJM	2018. NEJM	2018. NEJM	2018. NEJM
Venkatesh B. Finfer S. 3800 Adult patients over 18 years of age with sepsis diagnosed by 2 or more criteria of systemic inflammatory response, on invasive mechanical ventilation, and with at least one vasopressor or inotropic in the last 4 hours Hydrocortisone 200 mg	Venkatesh B. Finfer S. 3800 Adult patients over 18 years of age with sepsis diagnosed by 2 or more criteria of systemic inflammatory response, on invasive mechanical ventilation, and with at least one vasopressor or inotropic in the last 4 hours Hydrocortisone 200 mg	Venkatesh B. Finfer S. 3800 Adult patients over 18 years of age with sepsis diagnosed by 2 or more criteria of systemic inflammatory response, on invasive mechanical ventilation, and with at least one vasopressor or inotropic in the last 4 hours Hydrocortisone 200 mg	Venkatesh B. Finfer S. 3800 Adult patients over 18 years of age with sepsis diagnosed by 2 or more criteria of systemic inflammatory response, on invasive mechanical ventilation, and with at least one vasopressor or inotropic in the last 4 hours Hydrocortisone 200 mg	Venkatesh B. Finfer S. 3800 Adult patients over 18 years of age with sepsis diagnosed by 2 or more criteria of systemic inflammatory response, on invasive mechanical ventilation, and with at least one vasopressor or inotropic in the last 4 hours Hydrocortisone 200 mg	Venkatesh B. Finfer S. 3800 Adult patients over 18 years of age with sepsis diagnosed by 2 or more criteria of systemic inflammatory response, on invasive mechanical ventilation, and with at least one vasopressor or inotropic in the last 4 hours Hydrocortisone 200 mg

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Results of meta-analysis

A 2018 meta-analysis that included 22 trials, 7297 patients showed that, compared with placebo, corticosteroid therapy did not reduce short- or long-term mortality, however, it had a shorter duration of shock (-1.52 days; 95% CI), shorter stay in intensive care (-1.38 days; 95% CI), shorter duration of mechanical ventilation (-0.75 days; 95% CI) [24].

Conclusion

In conclusion, corticosteroid treatment must be individualized for each patient. The patients who benefit the most from this intervention are those with refractory septic shock, and the use of corticosteroid therapy (hydrocortisone 200mg / day for 7 days) could be useful to reduce the requirement of vasopressors, shorten the duration of the shock and the stay in the ICU, as well as the days of mechanical ventilation.

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