

SYSTEMATIC REVIEW

Characterization of the use of corticosteroids in the treatment of sepsis or septic shock

Caracterización del uso de corticoides en el tratamiento de sepsis o choque séptico

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ABSTRACT

Introduction: sepsis and septic shock are currently a serious public health problem, as it is a disease with a high rate of complications and because it is one of the main causes of admission to the intensive care unit (ICU). In addition, in recent decades the number of patients diagnosed with sepsis is growing every year.

Objectives: to determine whether the implementation of corticosteroids in the basic treatment of patients who are in sepsis or suffering from septic shock brings benefits or harms.

Method: this systematic review is based on a thorough search in the Medline (Pubmed) and Google Scholar databases, the analysis of the publications was chosen between the years 2010 to 2024.

Result: according to the evidence found in the 20 articles reviewed, the use of corticosteroid therapy reduces the time in some patients who are in shock, mainly those who do not respond adequately to conventional vasopressin fluids and drugs. However, it is still under discussion whether these data can be interpreted as beneficial for patients in terms of mortality. And whether the benefits are the same for septic patients given the potential risks that corticosteroids cause to the immune system and the hyperglycemia evidenced in some studies.

Conclusion: The results of the systematic review and the cohort studies analyzed suggest that there are still many disagreements on the matter, but most recommend the use of corticosteroid therapy as part of the treatment of patients with septic shock and not in sepsis.

Keywords: Corticosteroid; Sepsis; Septic Shock; Hospital Emergency; Treatment.

RESUMEN

Introducción: la sepsis y el shock séptico en la actualidad constituyen un grave problema de salud pública, por tratarse de una enfermedad con gran índice de complicaciones y por ser una de las principales causas de ingreso a la unidad de terapia intensiva (UTI). Además, en las últimas décadas el número de pacientes diagnosticados con sepsis está creciendo a cada año..

Objetivos: determinar si la implantación del corticoide en el tratamiento de base del paciente, que está en sepsis o sufriendo shock séptico, trae beneficios o maleficios.

Método: esta revisión sistemática se basa en la búsqueda minuciosa en las bases de datos Medline (Pubmed) y Google académico, el análisis de las publicaciones fue elegida entre los años de 2010 a 2024.

Resultado: de acuerdo con las evidencias encontradas en los 20 artículos revisados, el uso de corticoterapia disminuye el tiempo en algunos pacientes que se encuentran en estado de shock, principalmente los que no responden adecuadamente a los fluidos y drogas vasopresinas convencionales. Pero todavía sigue en discusión si estos datos pueden ser interpretados como beneficiosos para los pacientes en término de mortalidad. Y si los beneficios son los mismos para los pacientes sépticos dado a los riesgos potenciales que

causa los corticoides en el sistema inmunológico y la hiperglucemia evidenciada en algunos estudios

Conclusión: los resultados de la revisión sistemática y los estudios de cohorte analizados sugieren que todavía hay muchos desacuerdos sobre el asunto, pero en su mayoría recomienda el uso de corticoterapia como parte del tratamiento del paciente en shock séptico y no en sepsis.

Palabras clave: Corticoide; Sepsis; Shock Séptico; Emergencia Hospitalaria; Tratamiento.

INTRODUCTION

The septic condition is the immune imbalance in response to an infection capable of leading to multi-organ failure; worldwide, there are an estimated 6 million deaths due to sepsis.⁽¹⁾ Sepsis is considered a widespread public health problem worldwide.⁽²⁾ In the intensive care unit (ICU), sepsis is a leading cause of death of non-cardiac type, especially in countries with economic decline and poor conditions in the health sector.⁽³⁾ Sepsis is how our body can respond to an infection due to a physiological and chemical disorder that occurs, producing an organic alteration and usually has dire consequences that can even lead to death if not treated adequately; this infection can produce an unfavorable chain reaction, thus causing sepsis.⁽⁴⁾ Septic shock, a severe and potentially fatal manifestation of infection, represents a critical challenge in pediatric care. The pathophysiologic progression of septic shock can lead to circulatory collapse, requiring rapid and precise interventions to restore hemodynamic stability.⁽⁵⁾

Septic shock is a rare condition with a high mortality rate.⁽⁶⁾ Sepsis and septic shock are currently a serious public health problem, being a disease with a high rate of complications and one of the leading causes of admission to the intensive care unit (ICU). Sepsis is a condition of public health relevance due to its high morbidity and mortality worldwide. The Brazilian Journal of Health Review also cited the disease as the second leading cause of death after coronary heart disease in the U.S.⁽⁷⁾

It has been reported in the last decade that sepsis and septic shock suffered a significant increase in prevalence. These increases are related to several factors, such as a more significant number of immunosuppressed people (this is due to an increase in life expectancy over the years), the use of immunosuppressive drugs and chemotherapy, a substantial increase in the use of antibiotics by the world population having as one of the consequences an increase in super bacteria, which facilitates the development of sepsis.

Inflammation is defined as a normal response of an organism suffering an invasion by some microorganism. When the body detects a pathogen, it elaborates a cellular response where defense cells start attacking it, producing proinflammatory cytokines harmful to the microorganism. However, the difference between physiological inflammatory response and sepsis is the excessive production of inflammatory mediators present in the disease, causing an inability of the body to control the inflammation, generating a systemic inflammatory response (SIR) that can ultimately cause organ dysfunction.

Systemic Inflammatory Response Syndrome (SIRS) was proposed to describe the inflammatory reaction triggered by the body to any infectious or non-infectious aggression. The definition of infection is already a microbial phenomenon characterized by an inflammatory response to the presence of a microorganism or an invasion of tissues.⁽⁸⁾

Following the discussion, sepsis is defined according to the Surviving Sepsis Campaign (SSC) as the presence of suspected or confirmed infection associated with an acute increase in the Sequential Sepsis-related Organ Failure Assessment (SOFA) score of 2 points or more. SOFA is a scale that assesses organ dysfunction through the sum of scores obtained from evaluating six organs. Each organ receives a value ranging from zero to four points, graded according to the degree of dysfunction. A patient with an infection and a score ≥ 2 is diagnosed with sepsis.⁽⁹⁾

The SOFA is the most widely used mechanism in the ICU for diagnosing sepsis precisely because it effectively quantifies the severity of organ dysfunction and morbidity and estimates the risk of mortality. The higher the SOFA score, the higher the patient's risk of morbidity and mortality.⁽⁴⁾ Along with the SOFA, a simpler identifying version was developed for clinicians to identify patients at risk without laboratory values, the qSOFA. The qSOFA score is based on clinical criteria but does not require laboratory testing, thus providing a simple and rapid assessment of patients with suspected infection. The criteria used are:

- Systolic blood pressure of 100 mmHg or less
- Respiratory rate of 22/min or greater
- Altered consciousness

Septic shock is already defined as a hemodynamic imbalance where the patient needs vasopressin therapy to maintain mean arterial pressure (MAP) ≥ 65 mmHg associated with a lactate level above two mmol/L or above 18 mg/dL, called septic shock.⁽⁸⁾ A serum lactate level above two mmol/L suggests hypoperfusion, so it is essential to consider this laboratory. In sepsis, macrophages are activated by multiple pathways, such as toxins

and endotoxins, T lymphocytes and gamma interferon, superantigens, etc. For this reason, corticosteroids were evaluated as part of the treatment against sepsis.⁽¹⁰⁾

This is because corticosteroids have a modulating effect, inhibiting the nuclear factor kappa beta (NFkB) and the synthesis of inflammatory cytokines such as tumor necrosis factor-alpha (TNF- α), interleukin 1 (IL-1), 6 (IL-6), etc. In addition, they also act by decreasing the migration of inflammatory cells, thus reducing endothelial adhesion molecules, prostaglandin, and chemokines. However, despite their anti-inflammatory actions, the use of corticosteroids in the treatment of sepsis and septic shock is still in doubt. Several pieces of literature are conflicting on the use, dosage, timing, and type of corticosteroid to be used. Therefore, the main objective of this study is to carry out a systematic review of the use of corticosteroids, dosage, time, and type of corticosteroid to make patient care more beneficial and safer and to reduce the number of deaths.⁽¹¹⁾

Therefore, the objective of this article is to determine whether the implementation of corticosteroids in the primary treatment of a patient who is in sepsis or suffering from septic shock brings benefits or harm.

METHOD

A systematic review was carried out, which was divided into phases: starting by analyzing the reading of the titles and abstracts of the articles found in PubMed and Google Scholar, using the terms “sepsis,” “septic shock,” and “treatment” as a search engine. Focusing on the benefits that corticosteroids can bring to the patient. In this first search, a total of 884,644 articles were found. Then, a new search was performed, adding the words “emergency” and “corticoid,” the results were 18,719 articles. The search was repeated applying the following filters: Case Report, meta-analysis, randomized controlled trial, and systematic review, in the last 14 years, and 28 results were obtained in Pub Med and 5650 in Google Scholar.

In order to limit the number of articles and make the study more specific, studies in adults, humans, male and female, and language in Portuguese, Spanish, and English were added to the search filters. A total of 3028 results were obtained. The inclusion and exclusion criteria mentioned in tables 2 and 3 were used among the results obtained. Among the results obtained, 12 articles were selected where an exhaustive search for information was applied, focusing on the benefits and disadvantages of corticosteroids in the patient’s primary treatment.

Study design

The study design was based on a systematic review of the scientific literature on corticosteroids’ use and their benefits or harm to the patient in sepsis and septic shock. It follows a prospective and comprehensive approach to collect, review, and analyze the information available in various databases and bibliographic resources, using Medline (Pubmed) and academic Google.

Study population

Articles published in PubMed (MedLine) and academic Google, including adult patients exposed to different corticosteroids and in different medical contexts.

Inclusion criteria: article published between 2010- 2024, randomized and controlled clinical studies comparing corticosteroids and placebo treatment, young adults and adults aged 18-60 years, any systemic corticosteroid treatment, language in Spanish, English, and Portuguese.

Exclusion criteria: use of topical or inhalation corticosteroids, articles that did not have keywords in the title or abstract, health commentaries or guidelines, technical reports and articles in which the idea and discussions did not complement this systematic review, clinical studies that combined corticosteroid with vitamin C.

RESULTS

Within the 12 articles analyzed, some articles detail the type of study design, the number of patients included, the condition of the patients, the corticosteroids used, and the maximum and minimum doses. A brief conclusion was also extracted from each article analyzed to facilitate the reader’s interpretation, presented in table below.

DISCUSSION

Recalling that sepsis is nothing more than a response of the organism itself to an invasion of microorganisms, resulting in a generalized infectious process called SIRS (Systemic Inflammatory Response Syndrome). This disease manifests itself with two or more signs:

- 1) Temperature higher than 38°C or lower than 36°C
- 2) HR greater than 90 bpm
- 3) HR greater than 20rpm
- 4) PCo₂ less than 32 mmhg
- 5) Leukocytosis greater than 12 000/mm³ or Leukopenia less than 4 000/mm³

Reference	Year published	Type of study	N° of patients	Disease state	Corticosteroid used	Maximum and minimum dosage	Conclusion
1° Biography	2013	Meta analysis study	46	Main comorbidities: Malignant Neoplasm, Arterial Hypertension, Diabetes Mellitus.	-----	-----	Regarding clinical outcome, 54,4 % of the patients died, most of them in the septic shock group.
2° Biography	2015	Systematic Review	4268	-----	Hydrocortisone or equivalent	>400mg	Moderate-quality evidence suggests that a prolonged course of low-dose corticosteroids reduced 28-day mortality without inducing major complications and led to increased metabolic disturbances.
3° Biography	2014	Clinical Research	170	-----	Hydrocortisone	Early onset/ Late onset	In patients who received hydrocortisone for septic shock, early initiation of treatment was associated with improved survival.
4° Biography	2019	Systematic review and meta analysis	----	Degree of sepsis to patients with major complications	hydrocortisone, methylprednisone to betamethasone, fludrocortison todexamethasone, cortisone, and other corticosteroids	Prolonged/short term use High doses/low doses	Comparison of the findings between the studies confirmed that the prolonged use of low-dose corticosteroids contributes to a reduction in 28-day mortality, ICU mortality of low-dose corticosteroids contributes to a reduction in 28-day mortality, ICU mortality, length of ICU stay, length of hospitalization, and length of stay and the length of stay in the ICU of patients undergoing treatment for sepsis and septic shock.
5° Biography	2018	Systematic review	112/ 1063/2 164/16 95	----- -----	Hydrocortisone or similar/ Hydro	>300 mg in - 6h and/or + 6h/ Low doses with placebo group/ Continuous infusion	Administration of corticosteroids does not shows a significant reduction in in-hospital mortality, but does improve the reversal of shock. Early initiation of corticosteroid influences its efficacy
7° Biography	2020	Literature review	-----	-----	Glucocorticoids	-----	Despite having beneficial effects such as reversing septic shock in less time, improving hemodynamic variables and patient stability. The therapy does not significantly reduces mortality and there are reports of potential adverse effects.
9° Biography	2014	Retrospective and multicenter multicenter	6663	Severe illnesses and stable patients	-----	-----	There may be a beneficial effect of corticosteroids at low doses on mortality in patients with more severe disease severe disease.

11° Biography	2018	Systematic Review and Meta-Analysis	10194	Seriously ill	-----	-----	In critically ill patients with sepsis, corticosteroids may result in a small reduction in mortality.
12° Biography	2012	Systematic Review	-----	-----	Hydrocortisone	<300mg	It is currently recommended only in cases of septic shock, allowing increased vascular sensitivity to vasopressor agents. For other cases it needs further studies.
13° Biography	2015	Systematic Review	-----	-----	Hydrocortisone /fludrocortisone	50mg Hydro EV + Flu VO 50 ug/ Hydro EV only	Evidence consistently suggests that corticosteroids do, in fact, reverse shock more quickly, but it is not yet clear whether or not there is a benefit in terms of shock faster, but it is not yet clear whether or not there is a benefit in terms of mortality.
14° Biography	2023	Integrative and systematic review	-----	Patients in the ICU and in the emergency room	Hydrocortisone alone or in association with Vitamin C.	-----	Hydrocortisone in the management of septic shock in health services is a practice that, although currently used in some sectors, still requires higher levels of evidence.
16° Biography	2021	Systematic Review	12304	Variety of diseases e.g. Pneumonia of the surgical community/in ternation	hydrocortisone, methylprednisolona, betamethasone fludrocortisona and dexamethasone	Hydro> 200 mg/ <200mg flumetaso na (50 µg/day)	The findings demonstrate that corticosteroids failed to reduce 28-day, 90-day, and long-term mortality; however, they may reduce in-hospital and ICU mortality ICU.

Septic shock is a more severe condition. The patient presents a hemodynamic imbalance in which the cardiac output fails to maintain adequate blood pressure ($\text{MAP} \geq 65$ mmHg) for blood perfusion in the tissues, all this because of the existing pathological vasodilatation, in addition to finding a lactate > 2 mmol/L. Thus, the pathognomonic symptom of septic shock is severe hypotension that does not respond to fluid treatments, causing the patient to require increases in treatment such as vasopressors.

For these reasons, corticosteroid therapy was thought to be added to the primary treatment (because it has a faster response than vasopressors) to improve the hypotensive state of the patient and reduce the number of days in the ICU and mortality.

The mechanisms of action of corticosteroids include the following:

- Anti-inflammatory action potential (Interacts with transcription factors IL-6 and nuclear factor kappa beta (NFkB) inhibiting the synthesis of several pro-inflammatory factors (IL-1, IL-2, IL-3, IL-6 and IFN-g, TNF-a).
- Decreases inflammatory cell migration to the tissues.
- Blocks chemokine and prostaglandin synthesis.
- Blocks the anachronic acid cascade along with leukotriene production.
- Vasomotor capacity once it blocks NO (nitric oxide) inhibiting vasodilatation, improving vascular function by increasing perfusion and preload.
- Mineralocorticoid activity
- Helps to attenuate a possible adrenal insufficiency, due to exogenous corticoids that help in low cortisol levels.

Because of these mechanisms of action, corticosteroids were thought to be part of the treatment in managing sepsis. Of the 12 articles analyzed, this work will discuss the use of corticosteroids alone (more specifically, hydrocortisone), the use of hydrocortisone associated with fludrocortisone, hydrocortisone associated with ascorbic acid, and thiamine. Still to be studied was the best time to initiate the medication.

The results were diverse, but what prevailed most was to indicate hydrocortisone at high doses (greater than 400mg) at the beginning of sepsis observed a more significant number of patients with side effects such as hyperglycemia, hypertension, hypernatremia, intestinal bleeding, and secondary superinfections due to the state of immunosuppression induced by the corticoid.

Start using hydrocortisone when the patient evolves to septic shock, in doses of 300 mg of hydrocortisone, equivalent to 75 mg of prednisone or 1 mg/kg in a 75 kg patient in an average time of 7 days. This treatment in most of the articles showed that the patient spent less time in shock, less time in the ICU, and with fewer side effects (where it was found, only in some patients, hyperglycemia or hypernatremia), which are effects that can be effectively controlled in the hospital. However, some of the selected studies pointed out that corticosteroids did not significantly affect mortality. However, it was found that when used in low doses and for a short period, it decreased the number of mortality in patients in the ICU.

The addition of fludrocortisone did not improve hospital mortality. Thus, using fludrocortisone or not does not imply less time in the ICU. The treatment using hydrocortisone associated with ascorbic acid and thiamine has yet to have a good evolution according to the degree of confidence. The three clinical studies mentioned did not show significant clinical differences. However, 1 of the articles presented clinical studies with patients who, six months after septic shock, did not show benefits or had a worsening in cognitive, psychological, and functional aspects when compared to patients who did not undergo treatment with ascorbic acid and thiamine. ⁽¹²⁾

For patients with risk factors, a more selective prescription may be critical to minimize the incidence of cardiac arrhythmias related to the use of macrolides. Regarding when to start treatment, most studies indicate starting when the patient no longer responds to fluid therapy. This way, the patient will have less time in the ICU, less time in recovery, and less risk of organ dysfunction. However, it is still necessary to conduct further research to conclude whether or not its use is beneficial because the current research has mixed results, and there are few studies on these drugs.

CONCLUSION

There is still much disagreement on the matter, but most of them recommend the use of corticosteroids as part of the treatment of the patient in septic shock and not in sepsis. This is because it has been proven that corticosteroids have a tremendous anti-inflammatory mechanism, that their use reduces the migration of inflammatory cells to the tissues, reduces the levels of prostaglandin, cytokines, chemokines, even reducing the organic dysfunction, the patient stays less time in the ICU and therefore has a reversion of the shock in less time.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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