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REVISIONES

Administration of corticosteroids to patients with severe sepsis and improvement of in-hospital mortality: A systematic review

Administración de corticoides a los pacientes con sepsis grave y mejora de su mortalidad intrahospitalaria: Una revisión sistemática

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ABSTRACT:

Objective: To determine if there is scientific evidence to demonstrate a beneficial effect of corticosteroid treatment in patients with severe sepsis or septic shock. Also, to indicate the best clinical practice in the use of corticosteroids for the treatment of patients with severe sepsis or septic shock. We propose to determine the profile of the septic patient with critical illness that can benefit from the administration of corticosteroids for their treatment.

Methodology: Search in databases of great evidence, establishing criteria of inclusion and exclusion to obtain a greater specificity of the subject. In the selection, the premises of the CASPe program were followed, and 9 articles were included in our systematic review.

Results and conclusions: Most of the evidence shows that the administration of corticosteroids has a benefit in the reversion of shock, but does not decrease the mortality of patients. It was observed that patients who benefit from this type of treatment are those that are more critical, with APACHE II scores higher. On the other hand, the literature shows better results in relation to the benefit of this treatment, if it is started early in patients candidates for such treatment, and the best way to administer them is in a continuous infusion. A possible cause of the heterogeneity in the results regarding the benefits of corticosteroid administration could be related to a genetic variation, as shown by Schäfer et al.

Keywords: severe sepsis; septic shock; corticosteroids; mortality.

RESUMEN:

Objetivo: Averiguar si existe evidencia científica que demuestre un efecto beneficioso del tratamiento con corticoides en los pacientes con sepsis grave o *shock* séptico. También precisar la mejor práctica clínica en el uso de los corticoides para el tratamiento de los pacientes que presentan sepsis grave o

shock séptico. Nos proponemos determinar el perfil del paciente séptico con enfermedad crítica que puede beneficiarse de la administración de corticoides para su tratamiento.
Metodología: Búsqueda en bases de datos de gran evidencia, estableciendo unos criterios de inclusión y exclusión para obtener una mayor especificidad del tema. En la selección se siguieron las premisas del programa CASPe, y se incluyeron 9 artículos en nuestra revisión sistemática.
Resultados y conclusiones: La mayoría de las evidencias muestran que la administración de corticoides presenta un beneficio en la reversión del shock, pero no disminuye la mortalidad de los pacientes. Se observó que los pacientes que se benefician de este tipo de tratamiento, son aquellos que están más críticos, con puntuaciones en la escala APACHE II más altas. Por otro lado, la bibliografía muestra unos mejores resultados en relación al beneficio de este tratamiento, si se inicia de una forma precoz en los pacientes candidatos a recibir dicho tratamiento, y la mejor forma de administrarlos es en bomba de perfusión continua. Una posible causa de la heterogeneidad en los resultados en cuanto a los beneficios de la administración de los corticoides, podría relacionarse con una variación genética, tal y como mostró Schäfer *et al*.

Palabras clave: sepsis grave, *shock* séptico, corticosteroides, mortalidad.

INTRODUCTION

Sepsis is an organic, harmful and deleterious response of the host to an infectious process, which occurs with systemic manifestations produced by the presence of a host immune response to infection, which can lead to severe sepsis and septic shock[1-4].

This severe stage supposes a dysfunction of the organism, triggered by sepsis, which manifests itself with arterial hypotension, lactic acidosis, oliguria, hypoxemia, weak distal pulses, decreased capillary filling, distal coldness and acute neurological alteration[1-5]. Severe sepsis is the intermediate episode between sepsis and septic shock[6].

Septic shock is an advanced stage of severe sepsis that does not respond to fluid treatment, and therefore, requires the administration of vasoactive or inotropic drugs to achieve an average blood pressure greater than 65 mmHg[1,3-5].

Etiopathologically, sepsis can be produced by various infectious agents, where the most frequent are usually bacteria, such as Staphylococcus aereus, Streptococcus pneumoniae or Neisseria meningitidis. It is followed by viruses, with adenoviruses and cytomegalovirus being more frequent, followed by parasites where Toxoplasma gondii stands out. Less commonly fungi are found, such as Candidasp[3, 5].

Sepsis has a high incidence and morbidity and mortality, especially when it leads to shock and multiple-organ dysfunction [7-9]. Thanks to the important advances in its management, mortality has decreased; However, there is an increase in the incidence and sequelae developed by the survivors[10].

The incidence in Spain of severe sepsis is 104 cases per 100,000 inhabitants per year, with a mortality of 20.5%; In relation to septic shock, there are 31 cases per 100,000 inhabitants per year, with a mortality of 45.7% [9]. Therefore, severe sepsis and septic shock become one of the main health problems[1].
In recent years, scientific evidence has been essential for the development of new recommendations and clinical guidelines with the purpose of improving the management of the septic patient. These recommendations include the administration of corticosteroids, where these drugs have exceeded only endocrine use and are used as coadjuvant treatment[8,11].

Glucocorticoids are drugs with anti-inflammatory, anti-allergic and immunosuppressive effects, which are derived from hydrocortisone or cortisol; hormones produced by the adrenal cortex, essential for a correct adaptation to stress. They are drugs that protect the body from the consequences that an indiscriminate inflammatory response can produce.

Currently, glucocorticoids are considered immunoregulatory and not immunosuppressive, since they do not cancel the secretion of some cytokines, but increase the expression of coreceptors for cytokines and optimize the response of T lymphocytes[11].

On the other hand, recent studies on the use of corticosteroids in this type of patients, and their possible reducing effect on mortality and improvement of prognosis, show controversial results, since corticosteroids are associated with immunosuppression and risk of superinfection in Septic patients[8, 10].

That is why we plan to perform a systematic review, in order to find out if there is scientific evidence that demonstrates a beneficial effect of treatment with corticosteroids in patients with severe sepsis or septic shock, as well as establishing, if positive if a more convenient management, according to the evidence, of corticosteroids in this pathology.

METHODOLOGY

Design

The design of the study was that of a systematic review of the evidence present in the scientific literature on the efficacy of the administration of corticosteroids in patients who present septic shock and severe sepsis with the premise of responding to the objectives set.

Ambit

The search for literature took place between February and April 2017, delving into various bibliographic data bases in order to obtain information and review previous studies on the subject exposed. The databases used were Pubmed-Medline, Web of Knowledge (WOK) and SCOPUS, in which the search strategies differed depending on the source used. The key words and the Boolean operators used were "severe sepsis" OR "septic shock" AND "corticosteroids" AND "mortality" described through DeCS (Descriptors in Health Sciences).
In order to obtain a greater update on the subject, the articles edited in the last 5 years was fixed as a temporary filter for the search.

Inclusion and exclusion criteria

The inclusion criteria were:

• Studies of scientific evidence in which corticosteroids have been used as treatment in patients diagnosed with septic shock or severe sepsis.

• Studies should have been conducted in adult humans.

• The language of the publications was English or Spanish.

We would exclude all those articles that did not meet the previously mentioned criteria or that evaluated the use of corticosteroids in another type of pathology or diagnosis different from our objectives, as well as all articles published before 2012, except for those that had special relevance for the topic of interest and that were not included in later ones.

Data collect

For the selection of the articles included, and when making the critical reading, the premises of the CASPe program (Critical Appraisal Skills Program Spanish) were taken into account. It is a skills program for critical reading of the Institute of Health Sciences of Oxford, which aims to help acquire skills in the search for information and critical reading. The general scheme of said program was used, in order to obtain a firm certainty of what are the results of each of the selected articles, their validity and their application in the field we investigated, where the expression of the results was valued and the confidence intervals expressed in each of the selected studies.

The selection was carried out by a single evaluator, who after critical reading of each of the selected articles decided the inclusion or exclusion of each of them in the study. Of the 678 works found, the first discard was produced by reading the title, followed by a reading of the abstracts, which discarded all those articles that did not evaluate the object of our research, such as those that were carried out in children, where 68 articles were selected. After the elimination of duplicate articles, an exhaustive reading of 35 articles was carried out, of which 7 were discarded for using a very small sample or for the suspension of the study. Of the 28 articles, 9 were finally selected (Figure 1) to carry out the systematic review, since the rest, from the point of view of the evaluator, did not provide relevant information on the treated topic and in one of the studies the results were still they are pending to analyze.

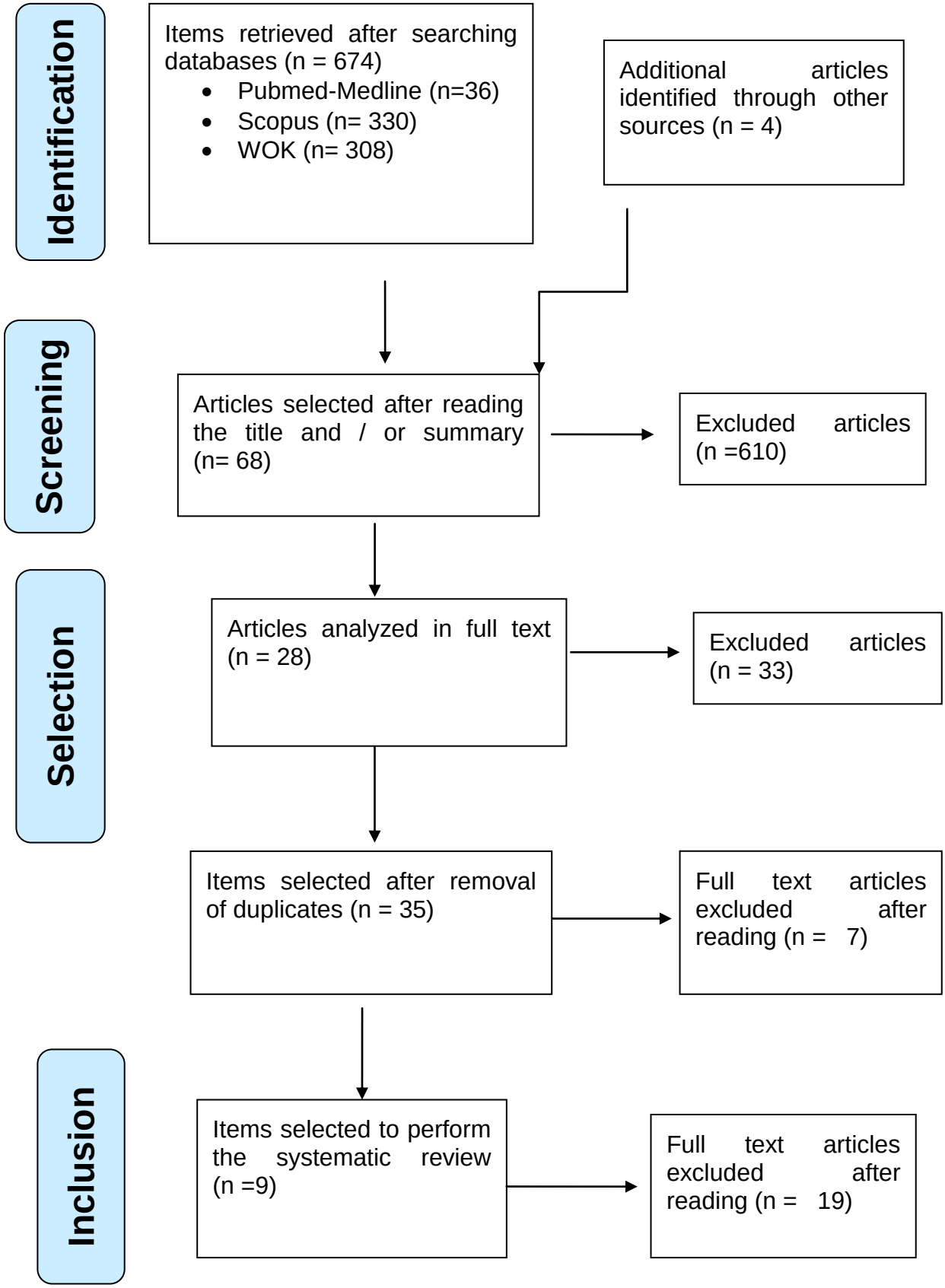
Determination of the level of evidence and degree of recommendation

In our review it was used, to establish the levels of scientific evidence applicable to the selected articles, the classification model of the "US Agency for Healthcare Research and Quality" and to determine the grade of recommendation the classification "Scottish IntercollegiateGuidelines Network" (SIGN) .

Bibliographic management

The program used for the bibliographic management of the references to include in the work was the Mendeley Desktop version 1.17.9.

Figure 1. Flow diagram corresponding to the selection of evidence.



Source: PRISMA 2009 *Flow Diagram*. Modified by the author.

RESULTS

Evidence nº 1

Based on the search, a retrospective analysis published by Park et. al.[12] in 2012 in which they evaluated the influence of early administration of corticosteroids at low doses on mortality in patients diagnosed with septic shock. All patients admitted to the ICU of a Korean hospital, between January 2008 and December 2009, were diagnosed with septic shock who had received low doses (<300 mg / day) of hydrocortisone or similar, obtaining a sample of 112 patients The results obtained were compared among those who received doses of corticosteroids within the first 6 hours of the onset of hypotension derived from septic shock, and those that were administered later at 6 hours after the onset of hypotension. A higher mortality rate was obtained in the second group (p = 0.0107). Among those who survived septic shock, the average time of onset of corticosteroid therapy is lower (6.5h) in relation to those who died (10.4h) (p = 0.0135). The time to initiate the treatment of low doses of corticosteroids was associated with mortality at 28 days (OR = 1.025, p = 0.0075). Although the proportion of patients that showed a reversal of shock was similar in both groups (p = 0.0683), the results of the ICU mortality rate were better in the patients included in the group that received corticosteroids within 6 hours (32% vs. 49%) (p = 0.0243). The subjects included in the group of early onset of corticosteroids had a 28-day mortality rate lower than 37% with respect to those with a later onset and a similar difference in the 90-day mortality rate (32%). vs. 51%, p = 0.0132).

Evidence nº 2

On the other hand, in 2014 Wang et.al.[13], conducted a meta-analysis and systematic review of the literature that existed until then on the use of corticosteroids in septic shock, aimed to evaluate mortality at 28 days after administration of corticoids, and the reversal of shock at 7 and 28 days. Eight publications were included in this meta-analysis, where a total of 1063 participants were analyzed to determine mortality at 28 days. The group that received corticosteroids consisted of 535 participants, and 528 formed the placebo group. Mortality at 28 days in the case group was 227 (42.43%) compared to 237 (44.89%) in the control group. Therefore, no significant difference was obtained in terms of mortality at 28 days (OR = 0.891, p = 0.371). With respect to the results obtained when analyzing the reversal of the shock, 6 articles were included with a total of 964 participants, of which 484 were part of the case group and 480 of the control group. The number of patients in the case group who achieved a shock reversal at 7 days was 307 (63.43%) and 228 (47.50%) of the control group. Therefore, an increase in shock reversion was obtained at 7 days in those patients who were treated with corticosteroids (OR = 2.078, p <0.0001). The analysis of the results of the reversal of shock at 28 days included 6 publications that had a total of 947 participants, 478 belonged to the case group and 469 to the placebo group. Within the case group, shock reversal occurred at 28 days in 328 (68.62%), and in the placebo group occurred in 283 participants (60.34%), so there was also an increase in shock reversal in the subjects who received corticosteroids. (OR = 1495, p = 0.006).

Evidence nº 3

In a cohort study published by Funk et al.[14] in 2014, it was evaluated whether there was a benefit in patients diagnosed of septic shock who received low doses of

corticosteroids within the first 48 hours after their diagnosis, comparing them with other subjects with the same diagnosis that were not treated with corticosteroids. 6,663 patients were recruited, of whom 2031 received intravenous corticosteroids at low doses (150-300 mg / day), and 4632 subjects who did not receive such treatment. The patients included in the case group had an APACHE II (Acute Physiology and Chronic Health Evaluation II) higher than the patients in the control group, as well as presenting a greater multi-organ failure. Mortality was similar in both groups (35.5% vs 34.9%, HR = 0.98, p = 0.77). A greater survival benefit was obtained from the use of corticosteroids in patients who had a greater APACHE II, where the reduction in mortality was 5.2% (62.7% vs. 58.6%, HR = 0.83, p = 0.03). Mortality was analyzed in subjects who had a lower score on the APACHE II scale and had been treated with corticosteroids, and a greater number of injuries were discovered.

Evidence nº 4

In another randomized case-control study published in 2015 by Póvoa et al.[15], the clinical impact of corticosteroids administered alone or in combination with drotrecogin alfa activated (drotAA) in patients with septic shock was evaluated. A total of 1695 patients diagnosed of septic shock were randomly divided into 4 groups, in the first group they would receive steroid therapy together with drotAA (n = 436), in the second drotAA without steroids (n = 414), in the third steroid and placebo (n = 403) and the last placebo and non-steroids (n = 442). Patients who had a higher score on the APACHE II and SOFA (Sequential Organ Failure Assessment) scale, the need for mechanical ventilation and renal replacement therapy were the ones chosen to receive corticosteroid therapy. Some of these patients, depending on whether they were randomly divided, received drotAA or placebo.

The mortality at 28 and 90 days of those who were treated with steroids in relation to those who did not receive them did not differ with those who received drotAA or placebo (p = 0.27). Finally, mortality at 90 days in patients with septic shock treated with drotAA or placebo was similar in those who received steroids or not.

Evidence nº 5

Tagami et al.[16] in 2015, carried out a retrospective study where they used a Japanese national database of patients hospitalized in emergency hospitals of third degree, who had undergone an open abdomen laparotomy that triggered septic shock refractory, which required the use of one or more vasoactive drugs including norepinephrine. We identified 2164 patients, which were divided into two groups, the group cases where corticosteroids were administered at low doses (n = 155) and the control group (n = 2009). Patients who were candidates for treatment at low doses of corticosteroids were those who required more vasopressin, carbapenem or blood transfusions. The results that were obtained do not show a significant difference in in-hospital mortality between the cases and the controls (19.4% vs. 25.1%, -12.8 to 1.3), but they did the propensity score where there were significant differences (17.6% vs. 25%; - 9.9 to -5). The reduction in estimated hospital mortality associated with the reception of corticosteroids was 13.5%.

Evidence nº 6

In a cohort study published in 2016 by Marik et al.[17], they conducted a control case trial, in which they subjected a group of patients diagnosed with severe sepsis or

septic shock admitted in the intensive care unit to treatment with corticosteroids. along with vitamin C and thiamine. On the other hand, we analyzed the results obtained from a group of patients with the same characteristics who were not treated with corticosteroids, to buy them from each other and to know if the patients included in the treated group obtained benefits. Both groups consisted of 47 patients, mortality in the case group was 8.5% and in the control group 40.4% (p = <0.001).

Evidence nº 7

The same year, Tongoo et al.[18] published another randomized double-blind trial. This trial consisted of two groups, of which the case group had 98 participants who received a bolus of hydrocortisone in 10 ml of saline every 6 hours for a period of 7 days, and the control group included 99 patients receiving placebo with the same periodic form (physiological saline bolus). Mortality at 28 days in the intervention group was 22.5%, while in the control group it was 27.3% (p = 0.51, RR = 0.82). Following the same trend, mortality at 60 days was similar, being in the group cases of 34.7% and in the control group of 40.4%, and RR = 0.86 (95% CI: 0.60-1.23) (p = 0.46).

Evidence nº8

In the prospective cohort study published in 2017 by Ibarra-Estrada et al.[19], he investigated the method of administration of corticosteroids in patients with septic shock. They divided the patients into two groups, one consisting of 27 patients who were given corticosteroids in continuous infusion, and another group of 32 patients who administered the corticosteroids with an intravenous bolus. Patients who received bolus corticosteroids were administered 6 hours later after the initiation of continuous perfusion of corticosteroids. The mean number of shock reversal hours in the continuous administration group was 59h, whereas in the intravenous bolus group it was 108 hours (p = 0.001). Mortality at 30 days after the start of corticosteroid administration was 31.2% in the continuous infusion group, while in the bolus administration group it was 55.6% (p = 0.06). The reversal of shock at 7 days in patients who received corticosteroids by continuous infusion was greater than those who received it in bolus (83% vs. 63%, p = 0.004).

Evidence nº 9

We leave for the end of the chapter the exposition of this article that for its genetic interest for the mechanism of action of corticosteroids in sepsis seems to have.

Over the last few decades, studies have shown both negative and positive effects on the mortality of septic shock in relation to the administration of corticosteroids, so in 2014 a randomized clinical trial was published by Schäfer et al.[20], in which who investigated the possible relationship of the systematic response of the organism to the use of corticosteroids if it could be determined by a genetic variation. It is the gene that is responsible for coding the nuclear transcription factor (NF-KB1), which participates in the regulation of the immune system and induces the inflammatory response. This gene has two alleles, the D allele (deletion) and the I allele (insertion). The polymorphism was associated with an increase in the expression of said gene, which leads to a stimulation of lipopolysaccharides, triggering hyperinflammation, which could be inhibited with the use of corticosteroids in patients who presented septic shock. The aim of this study is to show that the NFKB1 promoter polymorphism is associated with hyperinflammation, which can be mediated by corticosteroids. There

are many reasons that made them suspect that the D allele of NFKB1 insertion-deletion polymorphism attenuates hyperinflammation in septic shock, so that corticosteroid therapy could have a great benefit.

They obtained a sample of 160 patients, which were divided into four groups. Mortality at 30 days in the group treated with corticosteroids was 57.6% (34/60) in those with the ID / DD genotype and 24.4% (11/45) in those with genotype II (p = 0.001). In the group of those who did not receive corticosteroids, mortality was 22.2% in those who carried the ID / DD genotype (8/36) and 25% (5/20) those in genotype II. Therefore, the genotype of the NFKB1 ID / DD polymorphism (HR = 1.91, 95% CI: 1.08-336) (p = 0.03) and corticosteroid treatment (HR = 2.15, 95% CI: 1.16-3.98) (p = 0.02) were prognostic factors for survival at 30 days. However, the combination of the ID / DD genotype with the administration of corticosteroids showed the greatest impact (HR = 3.18, IC 95%: 1.61-6.28) (p = 0.001).

Table 1. Description of included studies.

ESTUDIO	TIPO DE ESTUDIO	NE	GR	OBJETIVO	RESULTADOS
Ibarra-Estrada M.A. et al. Febrero 2017	Estudio de cohortes prospectivo N=59	IIa	B	Investigar sobre los patrones de administración de hidrocortisona en el shock séptico.	-Mayor tendencia de mortalidad en el grupo que le administraron la hidrocortisona en bolo(no estadísticamente significativa) -En el grupo de administración continua requerían una dosis menor de norepinefrina a las 12h de iniciar la perfusión, y se asociaba con una recuperación del shock más precoz.
Schäfer S.T. et al. Agosto de 2014	Ensayo clínico aleatorizado N= 160	Ib	A	-El polimorfismo de inserción-supresión de NFKB1 altera la translocación nuclear de la proteína NF-KB1 en los monocitos con y sin administración de hidrocortisona, lo que puede ser asociado con la mortalidad a los 30 días en pacientes con shock séptico que reciben terapia con hidrocortisona.	La mortalidad a los 30 días es peor en los pacientes con shock séptico que recibieron terapia con hidrocortisona y portaban el genotipo ID/DD. Esto podría explicar el porqué de la heterogeneidad de los resultados sobre los beneficios de la terapia con corticoides en el shock séptico, que podría ser debido a una variación genética.
Yun Park H. et al. 2012	Estudio observacional retrospectivo N=178	III	B	Evaluar si el inicio precoz de bajas dosis de corticosteroides se asocia con el riesgo de mortalidad en pacientes con shock séptico.	Mayor tasa de mortalidad en los que se inició la terapia de corticosteroides con mayor precocidad.
Duane Funk M.D. et al. 2014	Estudio de cohortes retrospectivo multicéntrico N= 6663	III	B	Evaluar el beneficio terapéutico del inicio precoz con bajas dosis de corticosteroides en los pacientes con shock séptico	-No se asocia una disminución de la mortalidad a los 30 días con el uso de corticosteroides. -Se observa un beneficio de supervivencia que se limita a los pacientes que recibieron corticosteroides con un APACHE II con alta puntuación.
Changsong Wang M.D. et al. Febrero de 2014	Revisión sistemática y metaanálisis de ensayos controlados aleatorizados N= 1063 (mortalidad 28 días) N=964 (reversión del shock)	Ia	A	Evaluar el beneficio de la administración de corticosteroides en la mortalidad a los 28 días y la reversión del shock a los 7 y 28 días en los pacientes con shock séptico.	-No hay un beneficio significativo en la mortalidad a los 28 días tras la administración de hidrocortisona. -La administración de hidrocortisona aumenta la resolución del shock a los 7 y a los 28 días en los que se administró hidrocortisona.
Tagami T. et al. 2015	Estudio de casos-control N= 2164	III	B	Analizar el papel que juega la administración de bajas dosis de corticosteroides como tratamiento coadyuvante en pacientes con shock séptico abdominal.	-No hay una diferencia significativa en la mortalidad intrahospitalaria entre los casos y los controles. -Se observa que los que recibieron corticoides la retirada de los fármacos vasoactivos fue precoz al igual que la retirada de ventilación mecánica.
Póvoa P. et al. 2015	Estudio prospectivo aleatorizado de cohortes. N= 1695	Ib	A	Evaluar el impacto clínico de la administración únicamente de los corticoides o en conjunto con DrotAA en pacientes con shock séptico.	-La mortalidad a los 90 días por shock refractario en los pacientes que recibieron corticoides o placebo es similar.
Tongyoo S. et al. 2016	Ensayo controlado aleatorizado doble ciego. N= 197	Ib	A	La acción antiinflamatoria de los corticoides puede acelerar la resolución del shock séptico y por lo tanto disminuir la mortalidad.	-Mayor mortalidad a los 28 y 60 días en los pacientes que recibieron placebo, pero no estadísticamente significativa.
Marik P.E. et al. Noviembre de 2016	Estudio clínico casos-control N=94	III	B	-La administración de hidrocortisona, vitamina C y tiamina mejora la supervivencia en los pacientes con shock séptico o sepsis severa	-La mortalidad en los pacientes que no recibieron dicho tratamiento fue mayor que los que recibieron el tratamiento combinado con hidrocortisona, vitamina C y tiamina.

Table 1 shows a summary of the articles included and whose results have been presented in the sequence of evidences exposed in this chapter.
Abbreviations: NE = level of evidence. GR = grade of recommendation

DISCUSSION

According to the different articles found, after being selected and analyzed, a great variability is observed in terms of the results obtained and the conclusions of each one of them. In most of the results analyzed, there was a benefit over the reversal of shock after the administration of corticosteroids, but no decrease in mortality was demonstrated [13, 14,16]. However, other authors did not show a benefit with respect to the survival of patients with septic shock, as in the trial of Póvoa et al.[15] who did not

find any benefit to the use of this therapy, or as in that of Tongyoo et al. .18, in which although it showed that the administration of corticosteroids in patients with sepsis associated with respiratory distress syndrome improves lung function, it also did not have a survival benefit. This trial had a series of limitations, the first and most important was the selection of patients who did not present a high severity.

On the other hand, they did not include longitudinal measurements of the parameters that measured the systemic inflammatory response syndrome and an assessment of adrenal function. Due to this limitation, we thought that they did not obtain any survival benefit since the patients included in the trial did not present an important severity, and the corticoids are more beneficial the more serious the patients present.

Over the last decades there have also been discrepancies in the appropriate time to initiate corticosteroid therapy and how to administer them, whether in bolus or in continuous perfusion, in an early or later. After reviewing the literature, we concluded that the administration time of corticosteroids does affect the benefit of treatment, as recommended by Ibarra-Estrada et al.[19], so that the later the corticosteroids begin, the greater the Mortality, as Park et al.[12] also showed, that within the survivors, the time of onset of the therapy is lower than in those who died, where those who received the corticosteroids within 6 days received the greatest survival benefits. first hours after developing hypotension related to septic shock. This study presented a series of limitations, since being retrospective, there is the possibility of the existence of selection bias. Data on initial resuscitation could not be extracted due to incomplete medical records. Regarding the way of administering corticosteroids, there was a greater recovery of shock and an earlier elimination of vasoactive drugs in those patients who received continuous infusion pump therapy compared to those who received it in bolus, in addition to these The latter developed more hyperglycemia[19]. It was also shown that the strategy of progressively reducing the dose of corticosteroids until their total suppression is unnecessary, since the only thing that produces is the greater risk of developing adverse effects of said drugs. This study presented a series of limitations, where due to their observational and non-random nature, they could not assure a totally homogenous treatment with respect to other variables associated with the improvement of the results. When the appropriate dose, which reverses the shock with greater precocity, Ibarra-Estrada et al.[19], established that it was <0.28 micrograms / kg.

Another issue to be addressed are the characteristics that patients must have in order to benefit from said treatment. There was a greater benefit and a decrease in the mortality of the patients who were more critical, with higher scores on the APACHE II scale. Therefore, the effects of corticosteroids change according to the difference in the severity of each patient, where the most severe obtain benefits, but in the milder the damage with this type of treatment is worse.[14, 16]. This hypothesis was also supported by Póvoa et al.[15], who pointed out that such therapy should be reserved for the most critical patients.

For all this, for future research, it would be interesting to analyze the effects of corticosteroids in patients with different stages of the severity of the disease to be able to observe the different responses to corticosteroids depending on these stages.

Currently it has been investigated on the possibility of administering corticosteroids by combining them with other types of drugs to increase the benefits of these. As is the case of Póvoa et al[15], who evaluated the clinical impact of corticosteroids by

administering them alone or in combination with DrotAA, in which they did not find a significant positive impact of corticosteroids, either alone or administered together with DrotAA. Regarding their limitations, they could not analyze the type, dose and duration of corticosteroids administered since these data were not collected, in addition to the fact that only the prescription of corticosteroid treatment was recorded during the pretreatment period (before the infusion of the drug study).

In the essay by Marik et. al.[17] corticosteroids were administered along with vitamin C and thiamine, where they demonstrated that this combination had a benefit in those who developed septic shock. Patients who did not receive this combination developed a multi-organ failure, while those who received it did not develop it. They revealed the hypothesis that this combination reversed the physiopathological changes of sepsis, since during the development of septic shock the oxidation of cysteine occurs, which decreases the efficacy of corticosteroids, therefore if we administer vitamin C simultaneously it produces the reversal of this process and the function of corticosteroids is restored. With regard to thiamin, during septic shock, the development of insufficiency of this vitamin is frequent, which has been related to an increased risk of death. Therefore, the administration of these three combined drugs that act synergistically is beneficial for the treatment of patients who develop septic shock. However, this study presents a series of limitations, such as, for example, its sample size (n = 94) or the treatment control periods, which were carried out in different seasons of the year.

In relation to the differences found regarding the benefit of administering corticosteroids in patients who develop septic shock. Schäfer et al.[20] gave an explanation to this controversy, describing the relationship between the response of individuals who develop septic shock and the treatment with corticoids received. They demonstrated that genetics influences the response to corticosteroids, where the gene responsible for developing said response is NF-KB1; thus, the existence of a polymorphism of said gene increases its expression and develops hyperinflammation. This response can be inhibited by corticosteroids. In these cases, individuals with this polymorphism would benefit from corticosteroid therapy and develop a good response to this treatment. This would explain the heterogeneous results regarding the benefit of corticosteroids in septic shock. Individuals with a deletion polymorphism (ID / DD) do not benefit from receiving treatment with corticosteroids, while those with the insertion polymorphism II / DD do obtain a benefit after receiving said treatment. With respect to this subject, Marik et al. explained that the administration of corticosteroids and thiamine inhibit the activation of the nuclear factor NF-KB, which would regulate the production of inflammatory mediators[17].

CONCLUSIONS

1. The administration of corticosteroids does not show a significant decrease in in-hospital mortality in patients who present septic shock, but it does improve the reversion of shock, producing an improvement with greater precocity.

2. Early initiation of corticosteroids influences their efficacy, therefore, in patients with corticoid treatment criteria, it is advisable to administer such therapy as soon as possible.

3. The most effective way to administer corticosteroids is at low doses, in continuous perfusion pumps, and alone or in combination with Vitamin C and Thiamine.

4. Patients who are candidates for such treatment are those who are more severe and who do not respond to resuscitation with fluids and vasoactive drugs, the next step in their treatment being corticosteroid therapy.

5. Treatment with corticosteroids in patients who develop septic shock should not constitute a routine action, since if they respond positively to resuscitation with fluids and vasoactive drugs, the administration of corticosteroids does not provide benefits in their state but on the contrary, accentuates the existing damages.

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