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RESEARCH ARTICLE

THE ASSOCIATION BETWEEN CORTICOSTEROID USE AND PROGNOSIS AND MORTALITY IN CHILDREN WITH SEPTIC SHOCK: A SYSTEMATIC REVIEW

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Abstract

Background/ objectives: The leading factor in pediatric death is septic shock. The use of corticosteroids, however, is still debatable. The management of septic shock has included the adjunct use of several corticosteroids and treatment plans. At the cellular and tissular levels, the various medications and their modes of administration differ qualitatively and quantitatively. This comprehensive analysis looked at the likelihood of mortality and prognosis for children with septic shock who were supplemented with corticosteroids.

Methods: PubMed, Web of Science, Science Direct, and Google Scholarwere systematically searched to include the relevant literature. Rayyan QRCI was used throughout this systematic approach.

Results/ Interpretation: The use of corticosteroids in pediatric septic shock patients is debatable. However, this study supports that corticosteroids are not recommended for children with septic shock. In order to increase generalizability and determine the ideal timing to begin treatment, the ideal dose of hydrocortisone (or an equivalent), and the duration and mode of withdrawal from treatment, additional studies are required to examine the role of prolonged low-dose corticosteroid treatment for septic shock in developing nations.

Introduction:-

A dangerous, sometimes fatal illness known as the pediatric septic shock has a complicated pathogenesis that includes an augmented immune response, numerous organ failures, and inadequate cortisol [1, 2]. Volume replacement, vasoactive-inotropic support, and supplementary corticosteroid therapy should be taken into account during the early stages of recovery, in addition to the administration of antibiotics [3]. It has been suggested that hormone therapy can help a patient's hemodynamic condition. The medication can, however, also drastically lower the immunological response, particularly adaptive immunity. As a result, the use of corticosteroids in patients with septic shock is still debatable [4].

The recovery of hemodynamic instability in septic shock is accelerated by supplementary corticosteroids, according to numerous adult and a few pediatric studies [5, 6]. Mechanistic biological plausibility for this clinical observation is provided by elegant pharmacologic studies serially examining the dose-response relationship between mean

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arterial pressure and norepinephrine infusions in adults and children with septic shock before and after hydrocortisone infusion [7, 8]. Clinicians should be aware that prescribing adjunctive corticosteroids for children with septic shock , because they recall a quicker decline in the need for vasoactive-inotropic support, is an unreliable surrogate outcome because it is not linked to better patient-centered, clinically significant outcomes like survival [9].

According to evolving practitioner attitudes and available empirical data, corticosteroid administration has alternatively been encouraged and discouraged in the management of severe sepsis [10]. Corticosteroid treatment in pediatric septic shock has a broad range of practice variations because of conflicting findings in adult research and scant data on safety and efficacy in the pediatric literature [10–15].

Only patients with absolute adrenal insufficiency, adrenal-pituitary axis failure, and catecholamine-resistant shock should receive hydrocortisone treatment, according to the 2007 revision of the American College of Critical Care Medicine's (ACCM) clinical practice parameters for hemodynamic support of pediatric and neonatal shock [15].

Meta-analyses taking into account carefully planned and sizable RCTs are required because the conclusions are still primarily constrained by small sample sizes and inconsistent methodological quality [16, 17]. However, it is challenging to conduct large-scale RCTs because of the low incidence and urgent etiology [18]. Additionally, following two or more vasoactive infusions in children with septic shock, more than 90% of pediatric intensivists still believe that steroids are necessary [19]. Therefore, this systematic review investigated the prognosis and risk of mortality associated with corticosteroid supplementation for children with septic shock.

Methodology:-

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines were followed for this systematic review [20].

Study Design and Duration

This was a systematic review conducted between June and July 2023.

Search strategy

To retrieve the relevant research, a thorough search was conducted across four major databases, including Google Scholar, PubMed, Web of Science, and Science Direct. We only searched in English and took into account each database's unique criteria. The following keywords were converted into PubMed Mesh terms and used to find studies that were related; "Corticosteroids," "Steroids," "Prognosis," "Mortality," "Children," "Pediatric," "Septic shock," and "ICU," "Saudi Arabia," and "KSA." The Boolean operators "OR" and "AND" matched the required keywords. Among the search results were publications in full English language, freely available articles, and human trials.

Selection criteria

We considered the following criteria for inclusion in this review:

1. Any study designsthe prognosis and mortality risk associated with corticosteroid supplementation for children with septic shock.
2. We did not include case reports and review articles.
3. Only pediatric patients (< 18 years).
4. English language.
5. Free accessible articles.

Data extraction

Duplicates in the search strategy output were found using Rayyan (QCRI) [21]. To determine the titles' and abstract relevance, the researchers used a set of inclusion/exclusion criteria to filter the combined search results. The reviewers carefully read each paper that matched the requirements for inclusion. The authors provided other methods of resolving disputes with some thought. With the use of a previously created data extraction form, the authorized study was uploaded.The authors extracted data about the study titles, authors, study year, country, participants, gender, management, and main outcomes.

Strategy for data synthesis

To provide a qualitative overview of the outcomes and study components, summary tables were made utilizing data from relevant research. The most efficient method for using the data from the included study articles was chosen after the systematic review's data extraction.

Risk of bias assessment

Using the ROBINS-I risk of bias assessment approach for non-randomized trials of therapies, the included studies' quality was assessed [22]. The seven themes that were assessed were confounding, participant selection for the study, classification of interventions, deviations from intended interventions, missing data, assessment of outcomes, and choosing of the reported result.

Results:-

Search results

A total of 550 study articles resulted from the systematic search, and 54 duplicates were deleted. Title and abstract screening were conducted on 496 studies, and 430 studies were excluded. 66 reports were sought for retrieval, and 5 articleswere not retrieved. Finally, 61 studies were screened for full-text assessment; 39 were excluded for wrong study outcomes, and 14 for the wrong population type. Eight eligible study articles were included in this systematic review. A summary of the study selection process is presented in **Figure 1.**

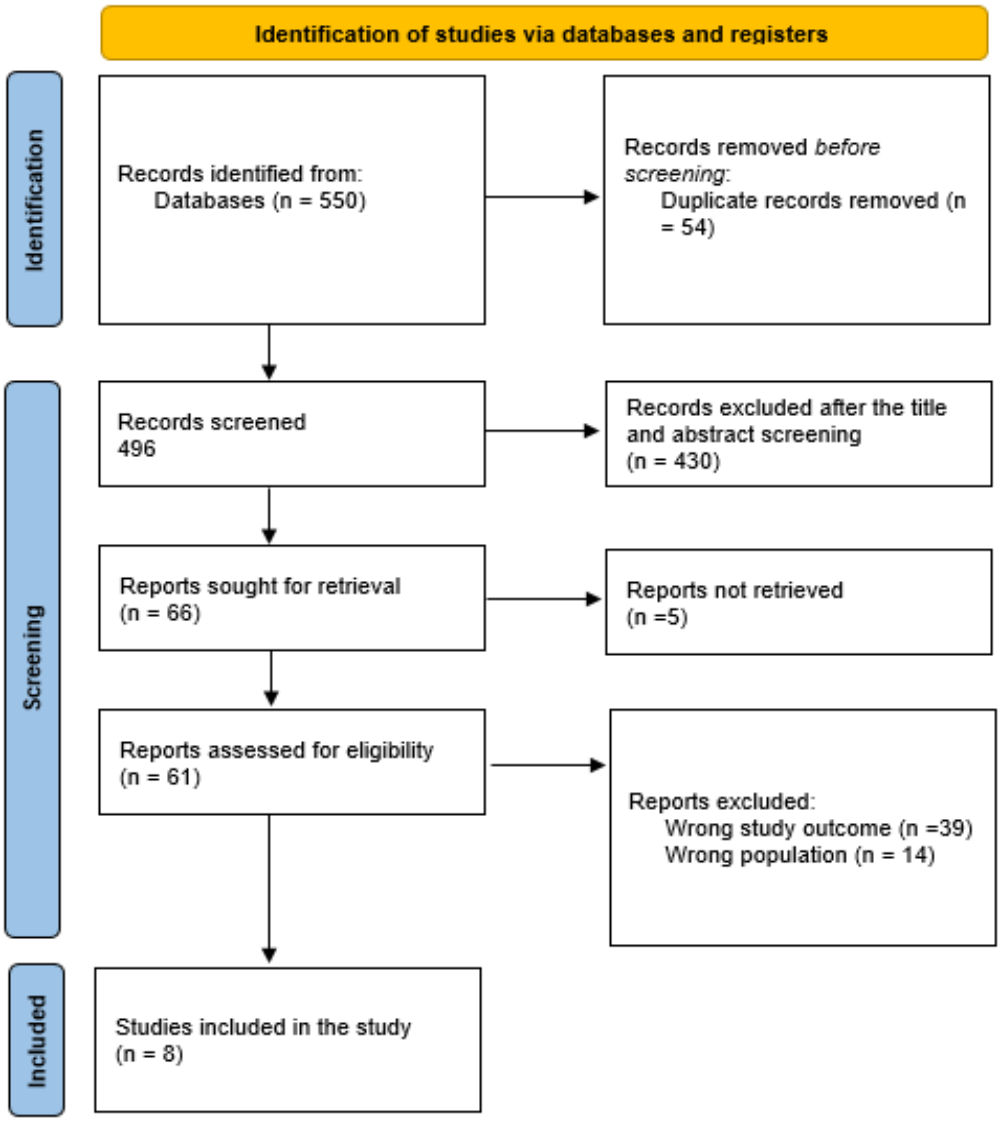

Figure (1):- PRISMA flowchart summarizes the study selection process.

Characteristics of the included studies

Table 1 includes the sociodemographic characteristics of the included study articles. Our results included nine studies with a total of 1872 patients. Three studies were conductedin the USA [26, 27, 29], one in Bangladesh [23], one in Saudi Arabia [24], one in Egypt [25], one in Canada [28], and one in Indonesia [29].Four were retrospective in nature [23, 24, 26, 27], two were prospective in nature [28, 29], one was a prospective randomized control trial (RCT) [25], and one was a cross-sectional study [30].

Table 2 presents the clinical characteristics of the included studies.Three studies demonstrated that the use of corticosteroids in pediatric patients with septic shock increased the mortality rate [23, 28, 30]. Two analyses found no correlation between corticosteroid use and death rate [24, 29]. Additionally, two studies found that corticosteroids were useful for those patients as they decreased the duration of septic shock conditions without increasing mortality or having a superinfection [25, 26].

Table (1):- Sociodemographic characteristics of the included study articles.

Study	Country	Participants	Age range (years)	Males (%)
Chowdhury et al., 2022 [23]	Bangladesh	93	5.85 (Median)	48 (51.6)
Alkhalaf et al., 2023 [24]	Saudi Arabia	182	15 (Median)	105 (57.7)
El-Nawawy et al., 2017 [25]	Egypt	96	1 to 48 (Months)	NM
Atkinson et al., 2014 [26]	USA	496	0.7-7.1	277 (55.8)
Wong et al., 2014 [27]	USA	180	0.8-6.5	109 (60.6)
Klowak et al., 2023 [28]	Canada	461	2-13.6	NM
Kamps et al., 2022 [29]	USA	352	0-17	189 (53.7)
Yunair et al., 2019 [30]	Indonesia	12	11-533 (Months)	8 (66.7)

Table (2):- Clinical characteristics of the included studies.

Study	Study design	Management	ROBIN-I
Chowdhury et al., 2022 [23]	Retrospective analysis	When a severely malnourished under-five infant develops septic shock that cannot be treated with dopamine alone and requires the administration of corticosteroids and fourth-line antibiotics, the likelihood of death increases considerably.	Moderate
Alkhalaf et al., 2023 [24]	Retrospective analysis	No correlation between receiving corticosteroids and mortality was discovered after modifying for baseline characteristics, severity scores, and medical intervention (p=0.492); however, patients who received corticosteroids had a lower risk of an extended stay in the PICU than those who did not (HR: 0.35; 95% CI: 0.13-0.98).	Moderate
El-Nawawy et al., 2017 [25]	Prospective RCT	19% of children brought to the PICU experienced septic shock, and 42% of them passed away. Early corticosteroid use in septic shock patients may reduce the time it takes for the condition to reverse without increasing mortality or superinfection.	NA
Atkinson et al., 2014 [26]	Retrospective analysis	Risk-stratified analysis was unable to show that corticosteroids were beneficial in this group of children with septic shock. Therefore, the growing evidence does not support the routine administration of corticosteroids in children with septic shock in the absence of a randomized trial, with the exception of children receiving chronic steroids and children with "classic" adrenal insufficiency.	High
Wong et al., 2014 [27]	Retrospective analysis	Through the use of a transcriptomics technique, the use of corticosteroids in children with septic shock is linked to further repression of gene programs related to the adaptive immune system. This observation does not appear toresult from the severity of the sickness, differing white blood cell numbers, or the type of pathogen	Moderate

		causing the infection.	
Klowak et al., 2023 [28]	Secondary analysis of prospective data	A correlation between corticosteroid use and increased mortality in pediatric sepsis has been found by prognostic subgrouping using the PERSEVERE-II score. Overall, the use of corticosteroids in pediatric septic shock was not supported by any data found in this investigation.	Moderate
Kamps et al., 2022 [29]	Prospective cohort	After correcting for factors that can obscure the link between these two endpoints, there was no correlation between early corticosteroid therapy and clinically significant endpoints.	Moderate
Yunair et al., 2019 [30]	Cross-sectional	Only a small percentage of children with septic shock received corticosteroid therapy, primarily hydrocortisone. Patientswith corticosteroids had a 100% death rate and short LoS. In the group of patients,they treat who have sepsis, corticosteroids do not appear to be effective.	High

Discussion:-

The use of corticosteroids in pediatric septic shock patients is disputable. Conclusions from meta-analysis findings, recommendations, and clinical practices are frequently inconclusive. The controversy's origins and characteristics, however, are unknown. The goal of almost all meta-analyses and systematic reviews is to use large sample sizes and RCTs that are well-designed to provide more conclusive results. This systematic review studied the recently published literature about the effect of corticosteroids on mortality rate among the pediatric population with septic shock.

Three studies demonstrated that the use of corticosteroids in pediatric patients with septic shock increased the mortality rate [23, 28, 30]. The idea that children may be at baseline at varying risks of mortality from septic shock and respond variably to therapies like corticosteroids is supported by the difference in association with mortality between the entire cohort and those in the high PERSEVERE-II risk group. However, it is not widely known what intrinsic causes cause this variability. Prior research mainly concentrated on the correlation between septic shock mortality and sickness severity scores. These ratings may not be sensitive enough to identify patients at risk of a different result after treatments like corticosteroids, which is why patient-specific biomarkers are needed [31-33].

There is no connection between corticosteroid use and death rate, according to two analyses [24, 29]. Furthermore, according to two trials, corticosteroids were useful to those patients since they reduced the length of time those patients were in septic shock conditions without raising mortality or causing a superinfection [25, 26]. In a prior meta-analysis, **Gibbison** used a network meta-analysis to examine the use of corticosteroids for treating septic shock in adults and children. The results revealed that no single medication significantly decreased mortality, gastrointestinal bleeding, or superinfection occurrence. The shock reversal time was shortened by a hydrocortisone bolus compared to a placebo or methylprednisolone. However, the inclusion of the patients rendered the meta-analysis inapplicable. It was important to conduct independent analyses of adults and youngsters. It is uncertain whether this result applies to youngsters [16]. **Menon and Wong** used qualitative analysis to determine whether giving corticosteroids to children who were in septic shock was helpful or detrimental. Only two early RCTs revealed that steroids helped children survive, and no trials suggested that steroids were hazardous, according to the findings [34].

Pediatricians have been debating the potential advantages and disadvantages of supplementary corticosteroids administered for pediatric septic shock for nearly a century, frequently with a religious fervour. Intellectual integrity requires one to draw the conclusion that the body of published literature does not support this intervention. Children with (severe) sepsis who are not in shock or children with septic shock stabilized with fluid and vasoactive-inotropic support should not undergo empiric corticosteroid therapy, according to the maxim "primum non nocere" initially. It should be noted that science requires testing of its theories to determine if predictions and even prejudices are supported by experiments, assuming that the rational pediatric intensivist operates within the framework of science. What sets (medical) science apart from other creative professions is the testing of theories [35]. There is a scientific, ethical, and health-economic imperative to carry out a high-quality interventional trial to develop evidence to support or refute this frequent sepsis therapy since supplementary corticosteroids may benefit or damage a child

with septic shock. Only within a research protocol created to assess both the dangers and benefits of this practice may corticosteroids be used for kids with septic shock.

Conclusion:-

The use of corticosteroids in pediatric septic shock patients is debatable. However, this study supports that corticosteroids are not recommended for children with septic shock. Current studies should clarify the following: (1) the survival advantages of prolonged low-dose corticosteroid therapy in adult septic shock and possible connection with activated protein C; (2) the function of prolonged low-dose corticosteroid treatment for managing septic shock in children; (3) the function of prolonged low-dose corticosteroid therapy in severe sepsis, especially for patients with community-acquired infections; and (4) the additional function of mineralocorticoid replacement. In order to increase generalizability and determine the ideal timing to begin treatment, the ideal dose of hydrocortisone (or an equivalent), and the duration and mode of withdrawal from treatment, additional studies are required to examine the role of prolonged low-dose corticosteroid treatment for septic shock in developing nations.

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