Journal of Intensive Medicine 5 (2025) 100–107

Contents lists available at ScienceDirect

Journal of Intensive Medicine

journal homepage: www.elsevier.com/locate/jointm

Systematic Review & Meta-Analysis

Influence of hydrocortisone infusion method on the clinical outcome of patients with septic shock: A systematic review and meta-analysis

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ARTICLE INFO

Managing Editor: Jingling Bao/ Zhiyu Wang

Keywords:
Sepsis
Time
Norepinephrine
Septic shock
Treatment outcome

ABSTRACT

Background: The effect of the modality of hydrocortisone administration on clinical outcomes in patients with septic shock remains uncertain. This systematic review and meta-analysis evaluate the impact of intermittent bolus and continuous infusion of hydrocortisone on these outcomes.

Methods: We searched the PubMed, Embase databases, and Cochrane Library for randomized controlled trials (RCTs) and cohort studies published from inception to January 1, 2023. We included studies involving adult patients with septic shock. All authors reported our primary outcome of short-term mortality and clearly compared the clinically relevant secondary outcomes (ICU length of stay, hospital length of stay, vasopressor-free days, hyperglycemia, hypernatremia, and ICU-acquired weakness [ICUAW]) of intermittent bolus and continuous infusion of hydrocortisone. Results were expressed as odds ratio (OR) and mean difference (MD) with accompanying 95% confidence interval (CI). The PROSPERO registration number is CRD42023392160.

Results: Seven studies, including 554 patients, were included. The primary outcome of this meta-analysis showed no statistically significant difference in the short-term mortality between intermittent bolus and continuous infusion groups (OR=1.21, 95% CI: 0.84 to 1.73; P=0.31; Chi^2=9.06; I^2=34%). Secondary outcomes showed no statistically significant difference in the ICU length of stay (MD=−0.15, 95% CI: −2.31 to 2.02; P=0.89; Chi^2=0.95; I^2=0%), hospital length of stay (MD=0.63, 95% CI: −4.24 to 5.50; P=0.80; Chi^2=0.61; I^2=0%), vasopressor-free days (MD=−1.18, 95% CI: −2.43 to 0.06; P=0.06; Chi^2=2.48; I^2=60%), hyperglycemia (OR=1.27, 95% CI: 0.80 to 2.02; P=0.31; Chi^2=5.23; I^2=43%), hypernatremia (OR=0.93, 95% CI: 0.44 to 1.96; P=0.85; Chi^2=0.37; I^2=0%), or ICUAW (OR=0.83, 95% CI: 0.36 to 1.94; P=0.67; Chi^2=0.90; I^2=0%) between the two groups.

Conclusions: This meta-analysis indicated no significant difference in short-term mortality between intermittent bolus or continuous hydrocortisone infusion in patients with septic shock. Additionally, the hydrocortisone infusion method was not associated with ICU length of stay, hospital length of stay, vasopressor-free days, hyperglycemia, hypernatremia, or ICUAW.

Introduction

Septic shock, one of the most challenging problems in intensive care medicine, is a life-threatening condition with a mortality rate that can exceed 30 %.[1,2] Patients with septic shock have the clinical picture of sepsis; persistent hypotension requires vasopressors to maintain mean arterial pressure (MAP) ≥65 mmHg and serum lactate levels >2 mmol/L (18 mg/dL) despite adequate volume resuscitation.[3] The cornerstones of septic shock treatment include early recognition, prompt antibiotic treatment, source control, and hemodynamic stability through fluid resuscitation and vasopressors.[4] However, even if shock is managed using these strategies, people with sepsis may still die from multiple organ dysfunction.

Septic shock is a response to a severe infection that activates pro-inflammatory mediators. Interacting with the endothelium, causing microvascular damage and capillary leakage. Several studies have shown that patients with septic shock may experience corticosteroid insufficiency, commonly referred to as critical illness-associated corticosteroid insufficiency (CIRCI).[5,6] CIRCI causes an imbalance between pro-inflammatory and anti-inflammatory mediators, yielding an increased inflammatory response. Consequently, recent clinical practice guidelines recommend the use of intravenous hydrocor-

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https://doi.org/10.1016/j.jointm.2024.05.001
Received 1 March 2024; Received in revised form 15 April 2024; Accepted 16 May 2024
Available online 25 June 2024

tisone (200 mg/day) for adults with septic shock who continue to require vasopressors.[7] While not strongly recommended, corticosteroids may be useful due to their anti-inflammatory properties and ability to maintain cardiovascular homeostasis through salt and water retention.[8] Two randomized trials of hydrocortisone for septic shock (ADRENAL and APROCCHSS) reported different results for 90-day mortality; however, it exhibited beneficial effects on shock reversal and relief from mechanical ventilation.[9,10]

However, the optimal method of administering hydrocortisone remains unclear. Controversies on the administration strategy (intermittent bolus or continuous infusion) always exist. A study in Qatar showed that the majority of surgical intensive care unit patients received continuous hydrocortisone infusion, while the majority of medical intensive care unit patients received intermittent bolus hydrocortisone infusion. Overall, patients who received intermittent hydrocortisone infusion were more than those receiving continuous infusion.[11] Physiologically, cortisol is released in a pulsatile form, following the dynamic rhythm of the classical circadian rhythm. Intermittent push injection, which better replicates these oscillations, is the "best" method of hydrocortisone supplementation. However, intermittent injections of hydrocortisone expose patients to high blood glucose levels, high doses of insulin, and an increased workload, potentially leading to worse outcomes.[12] Additionally, administration strategies may be associated with adverse effects, including hypernatremia, hyperglycemia, and neuromuscular weakness.[13]

Given the controversy surrounding the optimal modality of hydrocortisone administration, we conducted a meta-analysis, extracting results from published randomized controlled trials (RCTs) and cohort studies to evaluate the impact of the hydrocortisone infusion method on clinical outcomes and adverse effects in patients with septic shock.

Methods

This systematic review and meta-analysis is reported according to the updated Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[14] The study is registered at PROSPERO (ID: CRD42023392160).

Search strategy

We manually searched the PubMed, Embase databases, and Cochrane Library for studies published in English from inception to January 1, 2023, using the following search terms: "hydrocortisone," "corticosteroid," "corticosteroids," and "septic shock." The search was slightly adjusted according to the requirements of the different databases. The authors' personal files and reference lists of relevant review articles were also reviewed. We have searched gray literature, which is produced on all levels of government, academics, business, and industry in print and electronic formats. However, it is not controlled by commercial publishers to reduce bias. We excluded two reports that were not retrieved as full text and three reports for incomplete outcomes.[15–19] The search strategy for each database is shown in Supplementary Table S1. The flowchart of the search strategies is summarized in Figure 1.

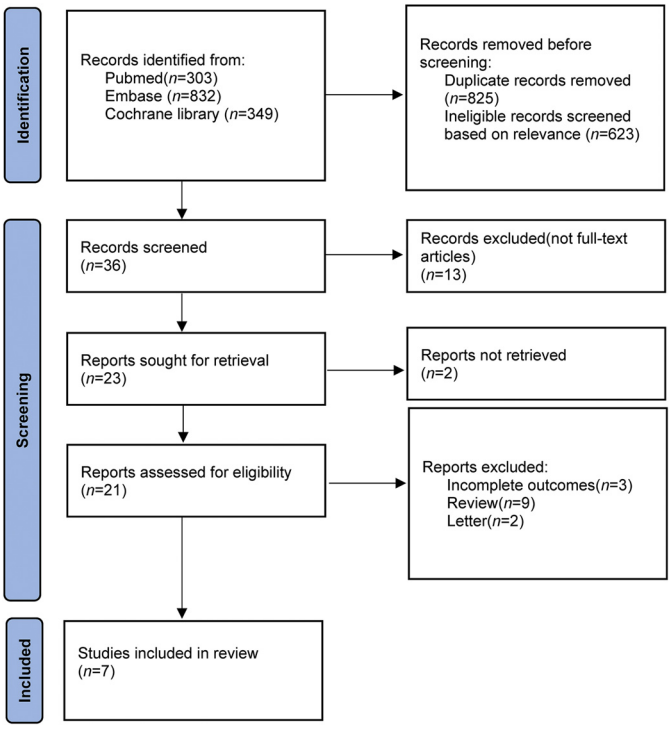

Figure 1. Flowchart of literature selection.

Types of outcome measures

The primary outcome was short-term mortality, including ICU mortality, hospital mortality, 28-day mortality, and 30-day mortality. Secondary outcomes were ICU length of stay, hospital length of stay, vasopressor-free days, hyperglycemia, hypernatremia, and ICU-acquired weakness (ICUAW). The secondary outcomes were defined according to the secondary outcomes defined in the original trials. Weighted means were calculated based on the number of patients in each study. Hyperglycemia is defined as a blood glucose reading >180 mg/dL or 10 mmol/L.[11] Hypernatremia is defined as a serum sodium concentration exceeding 145 mmol/L.[20]

Study selection

The inclusion criteria were as follows: (1) RCTs as well as prospective and retrospective cohort studies published in English; (2) adult patients with septic shock; (3) all authors reported short-term mortality as the primary outcome; (4) clear comparison of clinically relevant secondary outcomes of intermittent bolus *vs*. continuous infusion of hydrocortisone. We excluded studies that did not include estimable data or provide clear comparisons of the outcomes. Additionally, we excluded letters and reviews.

Quality assessment

Two reviewers (YL and YW) independently performed a quality assessment. If the views of two reviewers are very different, the third reviewer(DZ) would be invited to provide input as an aid to decision-making. The quality of studies was assessed using the revised Cochrane Risk-of-Bias tool (RoB 2) for randomized

trials[21]; the Risk Of Bias In Non-randomized Studies-of Interventions (ROBINS-I) tool was used for cohort studies.[22] The bias domain of RCTs included (1) the randomization process, (2) deviations from intended interventions, (3) missing outcome data, (4) measurement of the outcome, (5) selection of the reported result, and (6) overall bias. The low risk of bias, some concerns, and high risk of bias of each domain from the tool are denoted by green, yellow, and red colors, respectively. The risk of bias summary for included RCTs is presented in Supplementary Figure S1; the risk of bias graph for included RCTs is presented in Supplementary Figure S2.

Bias domains in ROBINS-I include bias due to confounding, selection of participants into the study, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of the reported result. The domain-level and overall risk of bias include low risk of bias, moderate risk of bias, serious risk of bias, critical risk of bias, and no information. The quality of the included cohort studies is presented in Supplementary Table S2.

Statistical analysis

Statistical analyses were performed using Review Manager Version 5.3 (RevMan, The Cochrane Collaboration, Oxford, UK). The odds ratio (OR) with 95% confidence intervals (CIs) was calculated for dichotomous variables. For the continuous variables, mean difference (MD) and 95% CI were estimated as the effect result. A random-effects model was used considering the assumed differences across the study populations.[23] The random-effects model was more suitable because there were differences in the results of various studies.

We designed a data extraction table. For the dichotomous variables, we extracted the sample size and the number of events in the intermittent bolus and continuous infusion groups. For the continuous variables, we extracted the sample size, mean, and standard deviation in the intermittent bolus and continuous infusion groups. After the data were extracted, it was verified and collated by another researcher to ensure data accuracy and completeness. Discrepancies in data extraction were also handled by this researcher. Most of the continuous variables in the original literature did not conform to the normal distribution; the data were represented by the median (interquartile range). However, meta-analysis requires continuous variables to be analyzed in the form of mean ± standard deviation. Consequently, missing data included mean and standard deviation. We calculated their mean and standard deviation according to the sample size, median, and interquartile range with a calculator for further meta-analysis.[24] A P-value <0.05 was set as the threshold of statistical significance.

Heterogeneity across studies was assessed using I^2 in the forest plot generated by RevMan software. The I^2 statistic was interpreted as follows: 25%>I^2≥0% indicates low heterogeneity; 50%>I^2≥25%, mild heterogeneity; 75%>I^2≥50%, moderate heterogeneity; and 100%≥I^2≥75%, severe heterogeneity.[25] Usually, heterogeneity is acceptable if I^2 is not greater than 50%. Reasons for high heterogeneity may include differences in study methodology, study subjects, interventions, exposure factors, as well as in study quality and publication bias. To reduce heterogeneity among studies, we performed a subgroup analysis of the primary outcome. We divided RCTs and cohort studies into two subgroups for meta-analysis to improve comparability between different studies and reduce heterogeneity.

Results

Study characteristics

The search strategy identified 1484 studies; eventually, data from 3 RCTs and 4 cohort studies, comprising 554 patients, were included. The characteristics of the included studies are shown in Table 1.[11,26–31] Seven eligible studies were published between 2007 and 2022. The included studies were conducted in various countries: two in the USA, one in Finland, one in Mexico, one in Tunisia, one in Qatar, and one in India. Among these, three were single-center studies, while the remaining four were multicenter studies. Three of these studies were single-center studies, while four were multicenter studies.

Primary outcome

The short-term mortality was about 46.2% (49.8% [151/303] in the intermittent bolus group and 41.8% [105/251] in the continuous infusion group). However, the overall results showed no statistically significant difference in the short-term mortality between the two groups (OR=1.21, 95% CI: 0.84 to1.73; P=0.31; Chi^2=9.06; I^2=34%). The total number of patients in RCTs and cohort studies was 227 and

Table 1
The basic characteristics of studies included in meta-analysis.

Author	Year	Country	Study period	Short-term mortality	Study design	Number of patients		
						Total	Intermittent bolus	Continuous infusion
Loisa et al.[26]	2007	Finland	July 2005–April 2006	ICU	Multicenter, RCT	45	23	22
Ibarra-Estrada et al.[27]	2017	Mexico	June 2015–July 2016	30-day	Multicenter, prospective cohort study	64	32	32
Hoang et al.[28]	2017	USA	August 2014–April 2016	28-day	Multicenter, retrospective cohort study	51	33	18
Tilouche et al.[29]	2019	Tunisia	April 2013–June 2016	28-day	Single center, RCT	70	33	37
Mitwally et al.[11]	2021	Qatar	June 2015–December 2017	Hospital	Multicenter, retrospective cohort study	108	76	32
Coles et al.[30]	2021	USA	January 2013–September 2014	Hospital	Single center, retrospective cohort study	104	52	52
Ram et al.[31]	2022	India	June 2021–May 2022	Hospital	Single center, RCT	112	54	58

RCT: Randomized controlled trial; ICU: Intensive care unit.

327, respectively. The number of deaths/total number of patients for RCTs was 29.1% (32/110) in the intermittent bolus group and 35.0% (41/117) in the continuous infusion group. Subgroup analysis of RCTs showed no statistically significant difference in the short-term mortality rate between the two groups (OR=0.75, 95% CI: 0.42 to 1.37; P=0.35; Chi^2=2.72; I^2=27%). The number of deaths/total number of patients for cohort studies was 61.7% (119/193) in the intermittent bolus group and 47.8% (64/134) in the continuous infusion group. Subgroup analysis of cohort studies showed that the short-term mortality of the intermittent bolus group was higher than that of the continuous group (OR=1.60, 95% CI: 1.01 to 2.54; P=0.04; Chi^2=2.47; I^2=0%) (Figure 2).

Secondary outcomes

ICU length of stay

Five of the included studies were analyzed to assess the ICU length of stay (day). No statistically significant difference was found in the ICU length of stay between the two groups (MD=−0.15, 95% CI: −2.31 to 2.02; P=0.89; Chi^2=0.95; I^2=0%) (Figure 3).

Hospital length of stay

Five of the included studies were analyzed to assess the hospital length of stay (day). No statistically significant difference was detected in the hospital length of stay between the two groups (MD=0.63, 95% CI: −4.24 to 5.50; P=0.80; Chi^2=0.61; I^2=0%) (Figure 4).

Vasopressor-free days

Two of the included studies were analyzed to assess the vasopressor-free days (day). No statistically significant difference was found in the vasopressor-free days between the two groups (MD=−1.18, 95% CI: −2.43 to 0.06; P=0.06; Chi^2=2.48; I^2=60%) (Figure 5).

Hyperglycemia

Four of the included studies were analyzed to assess hyperglycemia. No statistically significant difference was detected in the hyperglycemia between the two groups (OR=1.27, 95% CI: 0.80–2.02; P=0.31; Chi^2=5.23; I^2=43%) (Figure 6).

Hypernatremia

Two of the included studies were analyzed to assess hypernatremia. No statistically significant difference was found in

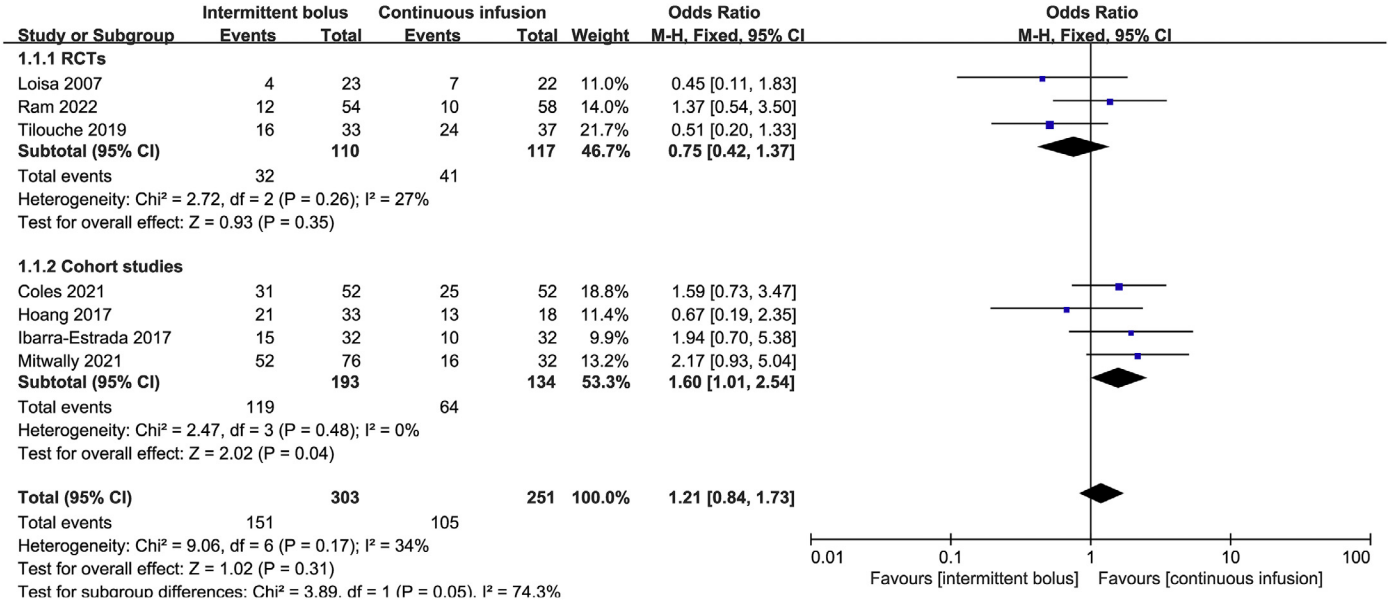

Figure 2. Forest plot for short-term mortality.
CI: Confidence interval; RCTs: Randomized controlled trials.

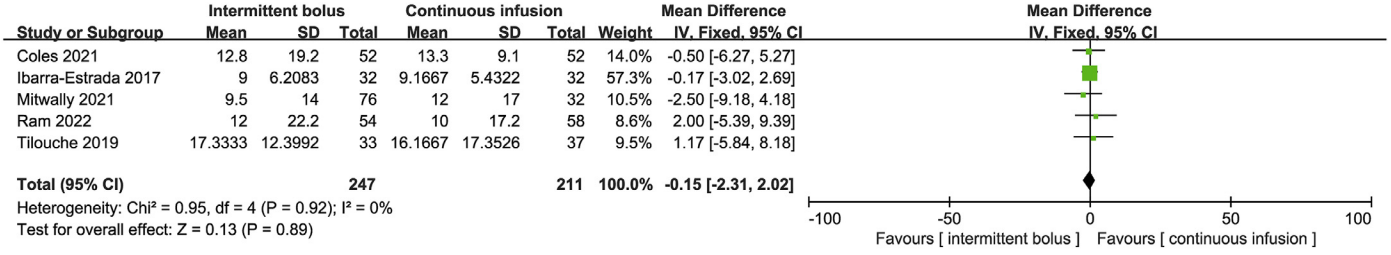

Figure 3. Forest plot for ICU length of stay.
CI: Confidence interval; ICU: Intensive care unit; SD: Standard deviation.

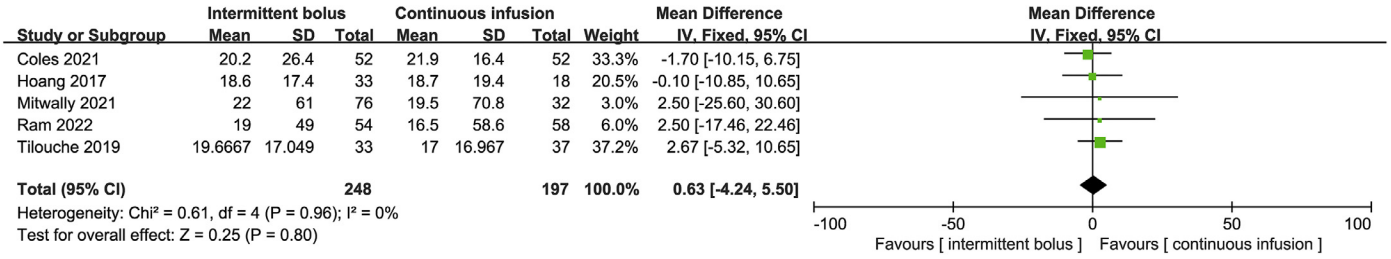

Figure 4. Forest plot for hospital length of stay.
CI: Confidence interval; SD: Standard deviation.

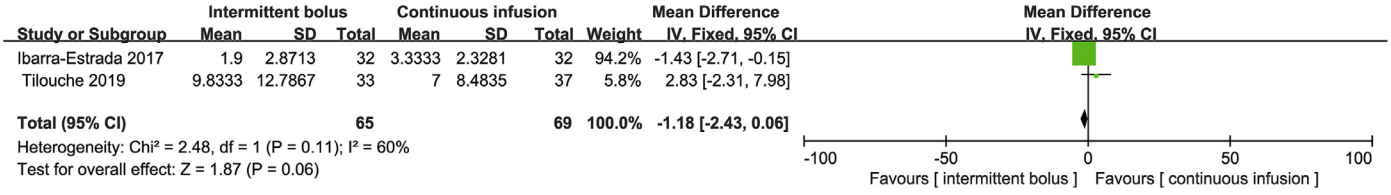

Figure 5. Forest plot for vasopressor-free days.
CI: Confidence interval; SD: Standard deviation.

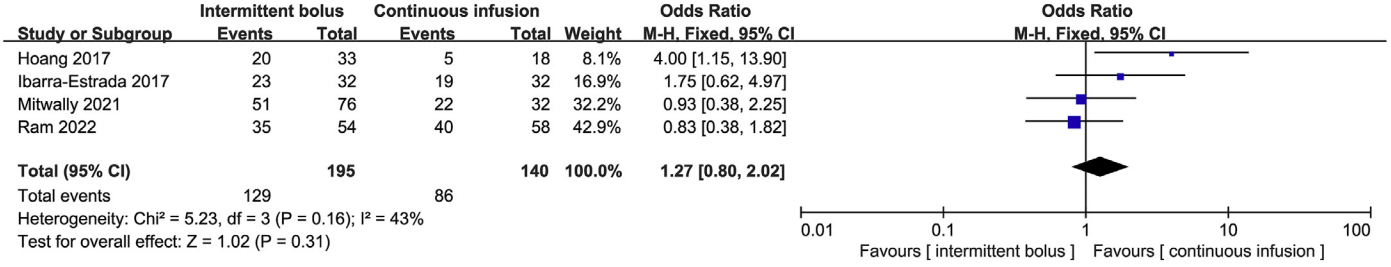

Figure 6. Forest plot for hyperglycemia.
CI: Confidence interval.

the hypernatremia between the two groups (OR=0.93, 95% CI: 0.44–1.96; P=0.85; Chi^2=0.37; I^2=0%) (Figure 7).

ICUAW

Two of the included studies were analyzed to assess ICUAW. No statistically significant difference was found in the ICUAW between the two groups (OR=0.83, 95% CI: 0.36–1.94; P=0.67; Chi^2=0.90; I^2=0%) (Figure 8).

Discussion

Sepsis may be complicated by impaired corticosteroid metabolism, suggesting potential benefits from corticosteroids.[32] The most recently updated guidelines also suggest administering corticosteroids to adult patients with septic shock.[33] However, the effects of continuous *vs*. intermittent bolus administration of corticosteroids remain uncertain. This systematic review and meta-analysis of seven studies, including 554 patients, compared intermittent bolus with continuous infusion of hydrocortisone in patients with septic shock. To our knowledge, this might be the first meta-analysis aiming to discuss the influence of the hydrocortisone infusion method on the clinical outcome of patients with septic shock. The overall short-term mortality rate was about 46.2%, without a statistically significant difference between the two groups. Subgroup analysis of cohort studies showed that the short-term mortality rate of

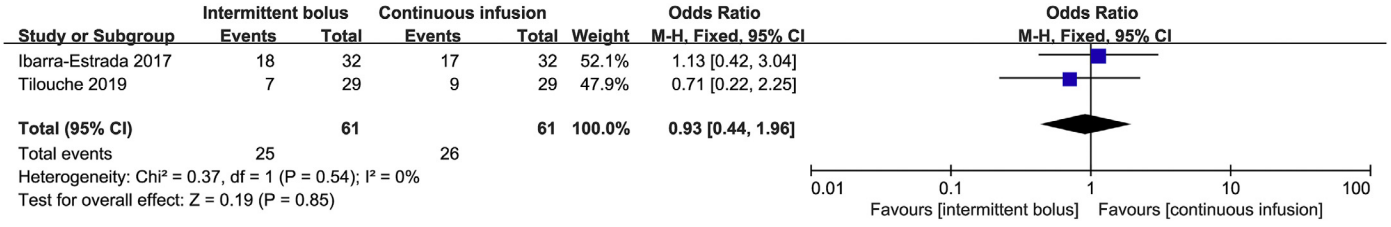

Figure 7. Forest plot for hypernatremia.
CI: Confidence interval.

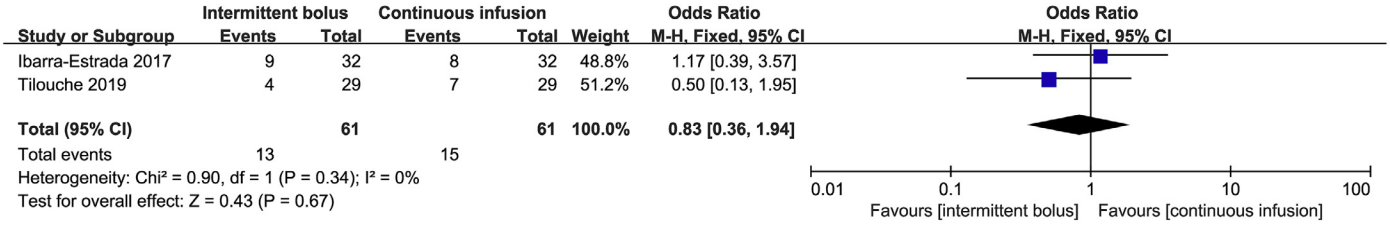

Figure 8. Forest plot for ICUAW.
CI: Confidence interval; ICUAW: ICU-acquired weakness.

the intermittent bolus group was higher than that of the continuous group; however, there was no difference in a subgroup analysis of RCTs. Due to differences in study design and sample size, subgroups may interact. Consequently, larger studies are still needed to confirm this result.

The analysis of secondary outcomes showed no statistically significant difference in the ICU length of stay or hospital length of stay. In the 2016 surviving sepsis campaign guidance, the accumulated evidence did not support a recommendation for corticosteroid use if adequate fluid resuscitation and vasopressor therapy could restore hemodynamic stability.[34] Therefore, the latest surviving sepsis campaign guidelines consider using hydrocortisone for fluid and vasopressor-resistant shock as a weak recommendation based on moderate-quality evidence. Additionally, the clinical practice guidelines did not recommend a specific administration method for hydrocortisone due to insufficient evidence to prove the association between the hydrocortisone infusion method and the patient's clinical outcomes.[7] No clear evidence indicated that a corticosteroid drug or administration strategy is more likely to be effective in reducing mortality, ICU length of stay, or hospital length of stay in septic shock.

Secondary outcomes also demonstrated no statistically significant difference in the vasopressor-free days between the two groups. Studies have shown that people with septic shock have lower cortisol levels.[35] Hydrocortisone may be useful because it counteracts the uncontrolled inflammatory process of septic shock and restores cardiovascular homeostasis through salt and water retention. Hydrocortisone has been shown to be effective in reducing the time to shock reversal with standard treatment. However, the CORTICUS study showed that hydrocortisone did not improve survival or cause reversal of shock in patients with septic shock, either overall or in patients who did not have a response to corticotropin. However, hydrocortisone hastened the shock reversal in responsive patients.[6] Our results suggest that different infusion methods of hydrocortisone have little effect on the shock reversal time in patients with septic shock.

Hyperglycemia, one of the most common side effects of corticosteroid treatment, is associated with a higher incidence of mortality in critically ill patients.[36] In septic shock, continuous hydrocortisone infusion may reduce the number of hyperglycemic episodes during intensive insulin therapy. Continuous hydrocortisone infusion may also reduce the nursing workload needed to maintain tight blood glucose control.[26] However, our results showed no statistically significant difference in the hyperglycemia between the two groups, indicating that many patient factors other than the hydrocortisone infusion method may affect blood glucose readings. These factors include stress, history of diabetes, older age, obesity, pancreatic function, renal function, etc.

Hypernatremia and ICUAW are other common side reactions of corticosteroid treatment. A systematic review revealed that glucocorticoid therapy was associated with hypernatremia among patients with refractory septic shock.[37] Glucocorticoid treatment increases the levels of blood urea nitrogen (BUN) via catabolism. Overproduction of BUN plays an important role in osmotic diuresis. A nested case-control study showed a significant association between high-dose glucocorticoids and ICU-acquired hypernatremia.[38] The incidence of ICUAW has been reported at 25%–100%. Risk factors include sepsis, immobility, persistent systemic inflammation, multiple organ system failure, hyperglycemia, glucocorticoids, and neuromuscular blockers. The clinical features may be neuropathic, myopathic, or both. ICUAW is a devastating and debilitating condition that can leave patients with permanent activity restrictions. Electromyography and nerve conduction studies remain the "gold standard" for diagnosing ICUAW.[39] Our results showed no statistically significant difference in hypernatremia or ICUAW between the two groups.

Our meta-analysis has several limitations. First, the number of included studies is small. Further large-scale RCTs should be conducted to confirm the results. Second, many secondary outcomes, such as ICU length of stay, hospital length of stay, vasopressor-free days, hyperglycemia, hypernatremia, or ICUAW, were not included in all the studies examined in this meta-analysis. Third, although we had performed a subgroup analysis of RCTs and cohort studies, substantial heterogeneity existed among the included studies. Very heterogeneous populations were included in both randomized and observational studies. Furthermore, the inclusion/exclusion criteria and comorbidities varied significantly among the studies, posing a challenge to interpreting the results. Therefore, our findings should be interpreted with caution.

Conclusions

This meta-analysis indicated no significant difference in short-term mortality between patients with septic shock receiving intermittent bolus or continuous infusion of hydrocortisone. Additionally, the hydrocortisone infusion method was not associated with ICU length of stay, hospital length of stay, vasopressor-free days, hyperglycemia, hypernatremia, and ICUAW. The simplicity of continuous infusion does not add to the nursing workload. This meta-analysis clinically implies that it will facilitate the administration of hydrocortisone among different facilities, eliminating the need for practitioners to alter

their administration methods. Further large-scale RCTs are still required to confirm these results.

CRediT Authorship Contribution Statement

Yuting Li: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Youquan Wang:** Data curation, Software, Writing – review & editing. **Jianxing Guo:** Data curation, Formal analysis, Software, Writing – review & editing. **Dong Zhang:** Project administration, Supervision, Writing – original draft, Writing – review & editing.

Acknowledgments

None.

Funding

This work was supported by institutional research funding provided by the National Key R&D Program of China, Ministry of Science and Technology of the People's Republic of China (grant numbers: 2022YFC2304605, 2022YFC2304604), Clinical Applied Research and Medical Training Fund of China Primary Health Care Foundation (grant number: so20220722jl), and Wu Jieping Medical Foundation (grant number: 320.6750.2023-03-11).

Ethics Statement

Ethics committee approval was not required since the article was based on previously conducted studies and did not contain any new studies with human participants or animals.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

All data generated or analyzed during this study are included in this published article.

Supplementary Materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jointm.2024.05.001.

References

[1] Sterling SA, Puskarich MA, Glass AF, Guirgis F, Jones AE. The impact of the sepsis-3 septic shock definition on previously defined septic shock patients. Critical Care Medicine 2017;45(9):1436–42. doi:10.1097/CCM.0000000000002512.
[2] Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. Intensive Care Medicine 2017;43(3):304–77. doi:10.1007/s00134-017-4683-6.
[3] Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (sepsis-3). JAMA 2016;315(8):801–10. doi:10.1001/jama.2016.0287.
[4] Castellanos-Ortega A, Suberviola B, García-Astudillo LA, Holanda MS, Ortiz F, Llorca J, et al. Impact of the Surviving Sepsis Campaign protocols on hospital length of stay and mortality in septic shock patients: results of a three-year follow-up quasi-experimental study. Critical Care Medicine 2010;38(4):1036–43. doi:10.1097/CCM.0b013e3181d455b6.
[5] Katsenos CS, Antonopoulou AN, Apostolidou EN, Ioakeimidou A, Kalpakou GT, Papanikolaou MN, et al. Early administration of hydrocortisone replacement after the advent of septic shock: impact on survival and immune response*. Critical Care Medicine 2014;42(7):1651–7. doi:10.1097/CCM.0000000000000318.
[6] Sprung CL, Annane D, Keh D, Moreno R, Singer M, Freivogel K, et al. Hydrocortisone therapy for patients with septic shock. The New England Journal of Medicine 2008;358(2):111–24. doi:10.1056/NEJMoa071366.
[7] Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Intensive Care Medicine 2021;47(11):1181–247. doi:10.1007/s00134-021-06506-y.
[8] Annane D. Corticosteroids for severe sepsis: an evidence-based guide for physicians. Ann Intensive Care 2011;1(1):7. doi:10.1186/2110-5820-1-7.
[9] Venkatesh B, Finfer S, Cohen J, Rajbhandari D, Arabi Y, Bellomo R, et al. Adjunctive glucocorticoid therapy in patients with septic shock. The New England Journal of Medicine 2018;378(9):797–808. doi:10.1056/NEJMoa1705835.
[10] Annane D, Renault A, Brun-Buisson C, Megarbane B, Quenot JP, Siami S, et al. Hydrocortisone plus fludrocortisone for adults with septic shock. The New England Journal of Medicine 2018;378(9):809–18. doi:10.1056/NEJMoa1705716.
[11] Mitwally H, Saad MO, Mahmoud S, Mohamed A. Hyperglycemia risk evaluation of hydrocortisone intermittent boluses vs continuous infusion in septic shock: a retrospective study. The Indian Journal of Critical Care Medicine 2021;25(1):29–33. doi:10.5005/jp-journals-10071-23501.
[12] Weber-Carstens S, Deja M, Bercker S, Dimroth A, Ahlers O, Kaisers U, et al. Impact of bolus application of low-dose hydrocortisone on glycemic control in septic shock patients. Intensive Care Medicine 2007;33(4):730–3. doi:10.1007/s00134-007-0540-3.
[13] Lamontagne F, Rochwerg B, Lytvyn L, Guyatt GH, Møller MH, Annane D, et al. Corticosteroid therapy for sepsis: a clinical practice guideline. BMJ 2018;362:k3284. doi:10.1136/bmj.k3284.
[14] Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. The Journal of Clinical Epidemiology 2021;134:178–89. doi:10.1016/j.jclinepi.2021.03.001.
[15] Weber-Carstens S, Deja M, Hokema F, Dimroth A, Kaisers U, Falke K, et al. Impact of continuous versus bolus low-dose hydrocortisone application on blood glucose in septic shock patients. Critical Care 2005;9:389. doi:10.1186/cc3452.
[16] Badugu S, Udassi S, Shih A, Kaliki-Venkata G, Lopez-Colon D, Udassi J. Dexmedetomidine administration during CPR decreases the sympathetic response after return of spontaneous circulation. Critical Care Medicine 2012;40:21. doi:10.1097/01.ccm.0000424331.10013.8e.
[17] Liszewski A, Bidwell K, Hockman R, Enfield K, Zomp A. Outcomes in septic shock patients treated with continuous versus bolus stress-dose hydrocortisone. Critical Care Medicine 2014;42:1. doi:10.1097/01.ccm.0000458483.09531.27.
[18] Keh D, Sprung CL. Use of corticosteroid therapy in patients with sepsis and septic shock: an evidence-based review. Critical Care Medicine 2004;32(11):S527–33 Suppl. doi:10.1097/01.ccm.0000142983.15421.11.
[19] Kaufmann I, Briegel J, Schliephake F, Hoelzl A, Chouker A, Hummel T, et al. Stress doses of hydrocortisone in septic shock: beneficial effects on opsonization-dependent neutrophil functions. Intensive Care Medicine 2008;34(2):344–9. doi:10.1007/s00134-007-0868-8.
[20] Qi Z, Lu J, Liu P, Li T, Li A, Duan M. Nomogram prediction model of hypernatremia on mortality in critically ill patients. Infection and Drug Resistance 2023;16:143–53. doi:10.2147/IDR.S387995.
[21] Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019;366:l4898. doi:10.1136/bmj.l4898.
[22] Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 2016;355:i4919. doi:10.1136/bmj.i4919.
[23] Biggerstaff BJ, Jackson D. The exact distribution of Cochran's heterogeneity statistic in one-way random effects meta-analysis. Statistics in Medicine 2008;27(29):6093–110. doi:10.1002/sim.3428.
[24] Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Medical Research Methodology 2014;14:135. doi:10.1186/1471-2288-14-135.
[25] Huedo-Medina TB, Sánchez-Meca J, Marín-Martínez F, Botella J. Assessing heterogeneity in meta-analysis: q statistic or I^2 index? Psychological Methods 2006;11(2):193–206. doi:10.1037/1082-989X.11.2.193.
[26] Loisa P, Parviainen I, Tenhunen J, Hovilehto S, Ruokonen E. Effect of mode of hydrocortisone administration on glycemic control in patients with septic shock: a prospective randomized trial. Critical Care 2007;11(1):R21. doi:10.1186/cc5696.
[27] Ibarra-Estrada MA, Chávez-Peña Q, Reynoso-Estrella CI, Rios-Zermeño J, Aguilera-González PE, García-Soto MA, et al. Timing, method and discontinuation of hydrocortisone administration for septic shock patients. World Journal of Critical Care Medicine 2017;6(1):65–73. doi:10.5492/wjccm.v6.i1.65.
[28] Hoang H, Wang S, Islam S, Hanna A, Axelrad A, Brathwaite C. Evaluation of hydrocortisone continuous infusion versus intermittent boluses in resolution of septic shock. P T 2017;42(4):252–5.

[29] Tilouche N, Jaoued O, Ali HBS, Gharbi R, Fekih Hassen M, Elatrous S. Comparison between continuous and intermittent administration of hydrocortisone during septic shock: a randomized controlled clinical trial. Shock 2019;52(5):481–6. doi:10.1097/SHK.0000000000001316.
[30] Coles LL, Forehand CC, Quidley AM. Hydrocortisone continuous infusion versus bolus dose on glycemic control in critically ill subjects. The Journal of Pharmacy Practice 2021;34(1):35–9. doi:10.1177/0897190019850937.
[31] Ram GK, Shekhar S, Singh RB, Anand R, De RR, Kumar N. Hyperglycemia risk evaluation of hydrocortisone intermittent boluses versus continuous infusion in septic shock: a prospective randomized trial. Anesthesia, Essays and Researches 2022;16(3):321–5. doi:10.4103/aer.aer_115_22.
[32] Annane D, Bellissant E, Bollaert PE, Briegel J, Keh D, Kupfer Y, et al. Corticosteroids for treating sepsis in children and adults. The Cochrane Database of Systematic Reviews 2019;12(12):CD002243. doi:10.1002/14651858.CD002243.pub4.
[33] Chaudhuri D, Nei AM, Rochwerg B, Balk RA, Asehnoune K, Cadena R, et al. 2024 focused update: guidelines on use of corticosteroids in sepsis, acute respiratory distress syndrome, and community-acquired pneumonia. Critical Care Medicine 2024;52:e219–33. doi:10.1097/CCM.0000000000006172.
[34] Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. Critical Care Medicine 2017;45(3):486–552. doi:10.1097/CCM.0000000000002255.
[35] Annane D. Adrenal insufficiency in sepsis. Current Pharmaceutical Design 2008;14(19):1882–6. doi:10.2174/138161208784980626.
[36] Falciglia M, Freyberg RW, Almenoff PL, D'Alessio DA, Render ML. Hyperglycemia-related mortality in critically ill patients varies with admission diagnosis. Critical Care Medicine 2009;37(12):3001–9. doi:10.1097/CCM.0b013e3181b083f7.
[37] Annane D, Bellissant E, Bollaert PE, Briegel J, Keh D, Kupfer Y. Corticosteroids for treating sepsis. The Cochrane Database of Systematic Reviews 2015;2015(12):CD002243. doi:10.1002/14651858.CD002243.pub3.
[38] Imaizumi T, Nakatochi M, Fujita Y, Yamamoto R, Watanabe K, Maekawa M, et al. Glucocorticoid treatment is associated with ICU-acquired hypernatremia: a nested case-control study. Clinical and Experimental Nephrology 2021;25(2):131–9. doi:10.1007/s10157-020-01967-9.
[39] Zorowitz RD. ICU-acquired weakness: a rehabilitation perspective of diagnosis, treatment, and functional management. Chest 2016;150(4):966–71. doi:10.1016/j.chest.2016.06.006.