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Systematic Review

Impact on Efficacy and Safety of Hydrocortisone in Sepsis and Septic Shock – A Systematic Literature Review and Meta-analysis

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Abstract

Background: Sepsis and septic shock are major causes of morbidity and mortality worldwide, associated with a high economic and social burden on healthcare systems and communities, yet with few definite treatment modalities. The efficacy of steroids in the management of sepsis or septic shock remains a controversy and subject of investigation due to their theoretical beneficial effects.

Methods: This was a systematic literature review and meta-analysis on randomized controlled trials of hydrocortisone usage in sepsis or septic shock as of 2000, following the GRADE methodology, considering a primary outcome of 28 day all-cause mortality.

Results: Ten randomized control trials were included in the review, 9 of which reported 28 day mortality either as a primary or secondary outcome. Relative risk of dying at 28 days was 0.93 in favor of hydrocortisone (95% CI: 0.86–1.01; $P = 0.056$). Other secondary outcomes of the review were similarly statistically insignificant. The quality of evidence was graded as very low to low.

Conclusion: Hydrocortisone, when used in sepsis or septic shock, in critically ill adult patients showed a statistically insignificant trend towards decreasing 28 day all-cause mortality. This warrants consideration of clinical significance for each patient individually.

Keywords: Efficacy, Hydrocortisone, Safety, Sepsis, Septic shock

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Introduction

Sepsis and septic shock remain a global health issue and major causes of morbidity and mortality in the community.[1,2] Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection. It is associated with an in-hospital mortality of greater than 10%. It is clinically characterized by a 2-point increase in Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score.[3] Septic shock, which is manifested in up to 20% of patients of sepsis,[4] is defined as a subset of sepsis with profound circulatory, cellular, and metabolic abnormalities and is clinically characterized by vasopressor requirement to maintain arterial pressure and serum lactate levels in the absence of hypovolemia.[3] Septic shock is reported to be associated with a mortality rate of up to 60% within a short period[5] with a rising incidence.[6]

Despite being such an enormous healthcare problem harboring a tremendous financial burden and resource consumption,[7] no definitive pharmacological therapy was proven to be effective in the management of sepsis and septic shock apart from antibiotic agents, hemodynamic resuscitation using fluids and vasopressors, and respiratory support.[8-11]

The use of steroids in the management of sepsis and septic shock was proposed decades ago[12] and continues to be subject of trials, at least in view of its theoretical potential benefits through various mechanisms,[13-16] however, uncertainty remains about their efficacy and safety,[2] particularly with recent large randomized controlled trials simultaneously reporting opposing results.[2,11] Similarly, well conducted reviews also reported conflicting results. The review by Annane et al[17] reported decreased mortality with the use of steroids in septic shock, whereas the review by Sligl et al[18] reported no such benefit although both reviews confirmed that using low dose hydrocortisone improves shock state reversal. This uncertainty is clearly reflected in the most recent Surviving Sepsis Campaign recommendations,[11] which

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included only a weak recommendation with low quality evidence for not using hydrocortisone in septic shock if hemodynamic stability can be restored by fluid therapy and vasopressors, if not, the recommendation is to use 200 mg hydrocortisone intravenous (IV) per day. Any other recommendations regarding hydrocortisone from the previous version (2012) were removed.

Description of the Intervention

The incidence of adrenal dysfunction is estimated to be as high as 50% during severe sepsis and septic shock, either due to lowered glucocorticoid production or impaired response to cortisol in the systemic circulation.[19] Furthermore, endotoxin induced nitric oxide synthase, results in smooth muscle relaxation with a subsequent vasodilatation, hypotension, and decreased contractility response to vasopressors.[20] Hydrocortisone might counter these effects through restoration of blood volume by mineralocorticoid sodium and water sparing effect[21] and augmentation of systemic vascular resistance by impacting glucocorticoid receptors.[11] Furthermore, hydrocortisone counteracts induction of inflammatory cytokines and nitric oxide through inhibition of nuclear factor kappa B at least partially.[22]

Objectives

Due to inconclusive evidence, we decided to conduct this systematic review and meta-analysis to investigate the effectiveness of hydrocortisone in terms of mortality and its safety in terms of superadded infection and gastrointestinal (GIT) bleeding among patients with sepsis or septic shock.

Materials and Methods

We utilized the PRISMA checklist for minimum items to be reported in a review and meta-analysis.[23]

Studies' Selection Criteria

We included only randomized controlled trials (RCT) with or without blinding, of either two arms design or a 2X2 factorial design, published in English, as of the year 2000 onwards, we did not include abstracts, conference proceedings, short communications, letters to editors, or unpublished data. We assumed that 18 years is a suitable period to have enough publications to conduct our review, furthermore, we believe that from 2000 onwards with the start of the surviving sepsis campaign activities and guidelines (2001), the definitions as well as the management of sepsis and septic shock started to be unified to the extent that we have confidence that control groups in trials were managed almost similarly.

PICO Framework

Population: The selected studies must have recruited adult patients with either sepsis or septic shock, in the setting of an intensive care unit (ICU). We didn't include studies that recruited patients with other clinical diagnoses such as (but not limited to) adult respiratory distress syndrome (ARDS), acute lung injury (ALI), liver cirrhosis, etc.

In our review we considered the criteria for diagnosis of sepsis and septic shock that are identical to or slightly modified from those described by the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)[3] and the International Sepsis Definition Conference by the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM).[24] (Definitions detailed in Supplementary file 1).

Intervention: The considered intervention was the use of systemic hydrocortisone in any form, dose, route, and duration, whether it was used alone or in combination with other forms of steroids, with or without tapering. No other forms of steroids were considered (dexamethasone, methylprednisolone, etc). In case of 2X2 design studies, patients who received hydrocortisone were grouped in a single (intervention) group regardless of the second medication.

Control: Must have received the standard of care of sepsis or septic shock but have not received hydrocortisone. In case of 2X2 design studies patients who did not receive hydrocortisone were grouped in a single (control) group regardless of the second medication.

Outcome: The primary outcome of this review was the dichotomous 28-day mortality. Secondary outcomes included: incidence of superadded-infection, GIT bleeding, ICU length of stay (LOS), hospital LOS, ICU mortality, and hospital mortality.

Identification of Studies

We systematically searched PubMed, and EMBASE databases for eligible studies according to the predefined inclusion criteria using the search terms "steroids" "sepsis" and "septic shock". Furthermore, we reviewed the references list of any literature reviews we encountered in our search for eligible studies. The authors could also present any eligible studies for inclusion. Included studies must have reported at least one of the predefined outcomes of the review (Detailed PubMed search strategy in Supplementary file 1).

Data Extraction

Two authors independently scrutinized each included study to extract data on a data extraction sheet prepared ahead and approved by all authors, that was adopted from the previous work of Annane et al,[17] extracted data included: first author's name, year of publication, study design, participants (number and characteristics), intervention, and outcomes.

Assessment of Risk of Bias

The assigned pair of authors for each included study

independently assessed risk of bias using the modified version of the Cochrane Collaboration tool.[25] The risk of bias assessment tool considers risk of bias in 7 domains, namely: random sequence generation, allocation concealment, blinding of participants, blinding of assessors, attrition bias, selective reporting bias, in addition to other sources of bias. Each of the 7 domains can be described according to a 3-level scale as: low, unclear, or high risk of bias.

Any disagreement between the authors evaluating a study was resolved by a third author.

Assessing Certainty of Evidence

Certainty of evidence was assessed according to the GRADE approach,[26] the GRADE system evaluates certainty of evidence aggregated as: high, moderate, low, or very low, for the studies reporting a particular outcome after consideration of 5 criteria:

1- Individual study risk of bias
2- Directness
3- Consistency
4- Precision
5- Publication bias

And every criterion was evaluated as: not serious, serious, and very serious.

Statistical Method

We presented outcomes as risk ratio (RR) for dichotomous, and mean difference (MD) for continuous outcomes with 95% CI, using DerSimonian and Laird for random-effects model to pool effect sizes for each outcome. Since we indeed expected some heterogeneity among the studies, in terms of at least population and intervention, heterogeneity among studies was evaluated statistically by I^2 and chi-square tests, adopting the scale described by Higgins et al[27] which labels heterogeneity as high, moderate, or low according to values of I^2 of ≥ 75%, ≥50%, or ≥ 25%, respectively.

Subgroup Analysis and Investigation of Heterogeneity

To identify potential causes of heterogeneity among included studies for the primary outcome we sought to conduct a meta-regression in which we utilized the following continuous predictor variables: first 24 hours total hydrocortisone dose, and first 7 days total hydrocortisone dose. Allowing us to construct a model for each variable, in addition to a model including both factors. Furthermore, we conducted subgroup analyses for studies included in the primary outcome, utilizing the following a priori criteria: studies including septic shock patients only, studies with the most consistent dose, studies administering hydrocortisone as boluses rather than infusion, studies tapering hydrocortisone, and studies with only low risk of bias.

Evaluation of Publication Bias

Publication bias was represented as a funnel plot, and its significance evaluated by Egger's test for the primary outcome (for which the null hypothesis of no effect of small studies could be rejected if $P < 0.05$). We performed a sensitivity test reporting risk difference (RD) on all included studies for the primary outcome.

All statistical tests and graphs were generated using STATA 14 software (StataCorp. 2015. *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP) and Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

For continuous variables reported as median and inter-quartile range (IQR), we initially attempted to contact the author of the study to obtain the data as mean and standard deviation (SD). Whenever that was not possible we imputed the data using mathematical methods described in details in Supplementary file 1. The quality of evidence derived from imputed data was downgraded twice.

Assessment of Sparse Data

To avoid type I errors resulting from random errors in studies with small sample size, publication bias, or of low quality we conducted a trial sequential analysis (TSA) for the studies included in the primary outcome.[28] Our TSA was based on the assumption of a two-sided test, with type I error of 5% and type II error of 10% (90% power). Results were expressed as a cumulative Z-curve graph, with monitoring and futility boundaries, according to O'Brien-Fleming alpha and beta spending functions respectively. If the depicted Z-curve crosses the monitoring boundary or enters the futility area, we could conclude that the evidence is conclusive.[29]

Furthermore, we attempted to analyze the risk of bias inherent to the use of ratio measures of effect quantification of a treatment or an intervention, which is particularly evident when the data lack sufficient numbers or few events. A bias preferably termed "Sparse data bias" rather than "small sample bias", as it can still occur in large datasets,[30] deploying data augmentation (penalization) thus leading to shrinkage of coefficient estimates.[31]

We applied data penalization by Firth adjustment – despite not being the most accurate – in view of its ease and feasibility.[30] Accordingly, we will report the percent (%) reduction of coefficient estimates after data penalization for studies included in the primary outcome. The authors have arbitrarily agreed to consider a bias reduction > 10% as substantial.

The protocol of this literature review and meta-analysis is registered at PROSPERO (https://www.crd.york.ac.uk/PROSPERO) under the number: CRD42018100112.

Results

Included Studies

Our search yielded ten studies for inclusion in the review. All ten studies were identified from PubMed search and were duplicates in EMBASE search. No other studies were added from reference lists of review articles or suggested by authors. Figure 1 details PubMed search.

Characteristics of Included Studies

Ten studies were included in our review,[2,4,11,16,32-37] enrolling a total of 6903 patients, of which 3394 received the intervention, while 3422 patients constituted the control. All the studies recruited adult patients, with septic shock except for two studies,[34,37] which recruited patients with severe sepsis. All studies were in a setting of ICU except for Keh et al[34] which recruited patients from both ICU and intermediate care units. All studies were multicenter except three.[35-37] Recruited patients were predominantly Europeans, in addition to patients from Australia, New Zealand, China, and Saudi Arabia. Nine studies reported the primary outcome of this review (28 day mortality), while the tenth[37] did not, but reported secondary outcomes of this review (Table S1 in Supplementary file 1 provides further details).

Risk of Bias Assessment

Risk of bias of included studies was low in the majority of domains. All studies had low risk of bias in the domains of random sequence generation, attrition bias, and other bias. In one study,[37] there was no concealment of study allocation, nor was there blinding to patients, treating personnel and investigators, and that was acknowledged by the authors as a limitation. Reporting bias in the same study was unclear as the study didn't state primary and secondary endpoints. Gordon et al[32] and Oppert et al[36] did not state whether or not outcome assessors were blinded (unclear bias). Figure 2 outlines risk of bias assessment. The overall risk of bias for the primary outcome was low.

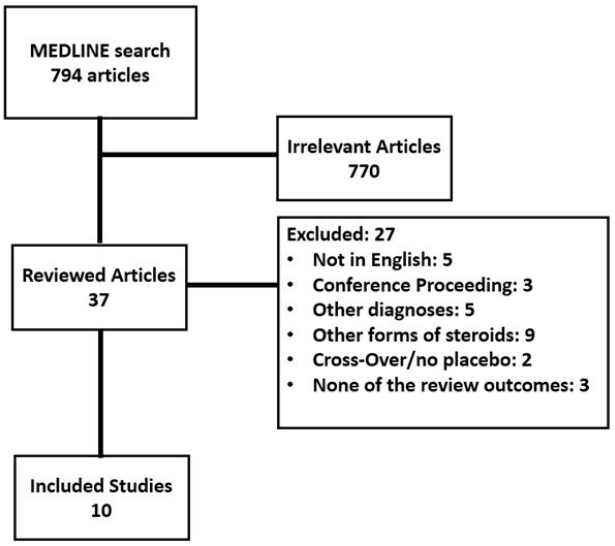

Figure 1. PubMed Search for Included Studies.

Interventions Used

The most prominent discrepancy among the included studies was the regimen of hydrocortisone administered. The most common dose was 50 mg/6 hours in 5 studies[4,11,16,32,33] for 5 to 7 days, although those studies varied regarding tapering, and association with fludrocortisone. One study[34] administered hydrocortisone 50 mg bolus followed by 200 mg/d infusion, another[35] started with 200 mg/d without a bolus, Oppert et al[36] started an infusion after a bolus of 50 mg at a rate of 0.18 mg/kg/hour, whereas, Rinaldi et al[37] started with 300 mg/d infusion. Details of interventions are available in Table S1.

Primary Outcome

Nine studies[2, 4,11,16,32–36] reported 28 day mortality mostly as a secondary outcome, while as a primary outcome in only 3 studies,[4,16,35] the evidence was downgraded to very low quality because of differences in population (inclusion of severe sepsis and septic shock patients), recruitment from intermediate care unit in one study, variable age limits of adulthood, and varying regimens of hydrocortisone (Table S3, Supplementary file 1). The studies included 3334 patients in the intervention groups of which 898 patients died at 28 days (26.9%), and 3353 patients as control of which 970 died at 28 days (28.9%). RR was statistically insignificant at 0.93 favoring the intervention (95% CI 0.86–1.01, P = 0.056) calculated as a pooled random effect size. Heterogeneity among studies was very low (I^2= 0.0%, Chi^2 P = 0.7). Publication bias was not detected (null hypothesis of no effect of small studies failed to be rejected, P = 0.4 for Egger's test). In sensitivity analysis,

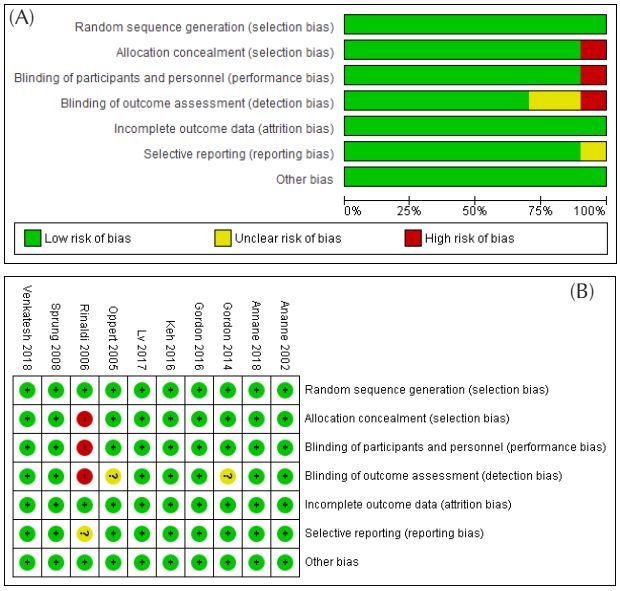

Figure 2. (A) Risk of Bias Assessment Summary, (B) Risk of Bias Graph.

similar insignificant results were found for risk difference (Figure S1, Supplementary file 1). Funnel plot is depicted in Figure 3, and forest plot in Figure 4.

Subgroup Analysis and Investigation of Heterogeneity

A priori defined independent predictors in the models of meta-regression confirmed significant only for the total cumulative 7 days dose, indicating an increase in RR of mortality, as the cumulative first 7 days dose increased (Log RR 0.002 [95% CI 0–0.004], $P = 0.048$), Figure 5.

Whereas, there was no significant interaction between mortality at 28 days and the first 24 hours dose (Log RR = 1 [95% CI 0.99–1.002, $P = 0.9$) when examined alone, or when linked to the cumulative first 7 days dose in the regression model ($P = 0.9$)

Subgroup Analysis

As for the predefined subgroup analyses for the 28 day mortality, predefined subgroups of studies recruiting septic shock patients, studies administering bolus hydrocortisone, hydrocortisone tapering, and studies with the most consistent doses showed insignificant findings. The closest to significance was the subgroup of only septic shock patients (in favor of hydrocortisone administration), (RR = 0.93, 95% CI: 0.86–1, $P = 0.06$). Subgroup of hydrocortisone administered only as boluses also proved insignificant (RR = 0.93, 95% CI: 0.84–1.03, $P = 0.17$), the subgroup of studies with hydrocortisone tapering similarly was insignificant, with RR of 1.08, 95% CI was [0.92–1.28], with an insignificant P value of 0.35, Likewise, the subgroup including studies with the most consistent dose of hydrocortisone had a RR of 0.93 (95% CI: 0.84–1.04, $P = 0.17$).

On the other hand, the subgroup of studies with low risk of bias showed significant reduction of mortality risk in favor of hydrocortisone, RR = 0.92 (95% CI: 0.86–0.99, $P = 0.04$), it is worth mentioning that in this subgroup heterogeneity was very low with $I^2 = 0.0\%$ and Chi^2 P value of 0.69 (Figures S2, S3, S4, S5, and S6 in Supplementary file 1).

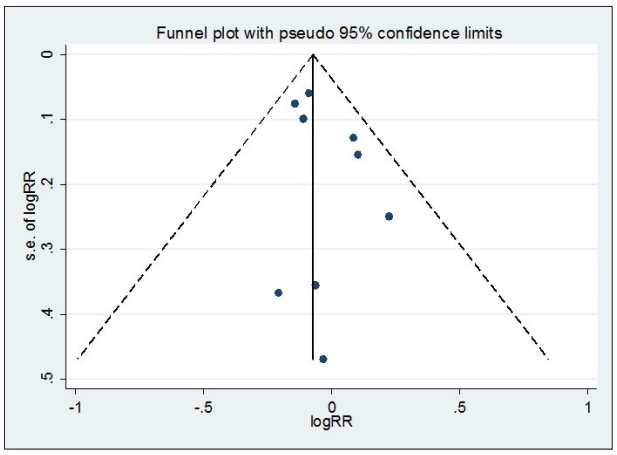

Figure 3. Funnel Plot of Primary Outcome.

Sparse Data Assessment

Our TSA was conducted to maintain a type I error of 5%, and type II error of 10%, on the assumption of occurrence rate of 30% in the control group and risk difference of 5% in the intervention group. As a result, the required information size was 3343 patients. The number of included patients in our meta-analysis surpassed this number; however, the cumulative Z-curve did not cross the monitoring boundary for benefit, which renders the driven evidence inconclusive (Figure 6).

Data Augmentation Analysis

Implementation of data augmentation (firth adjustment)

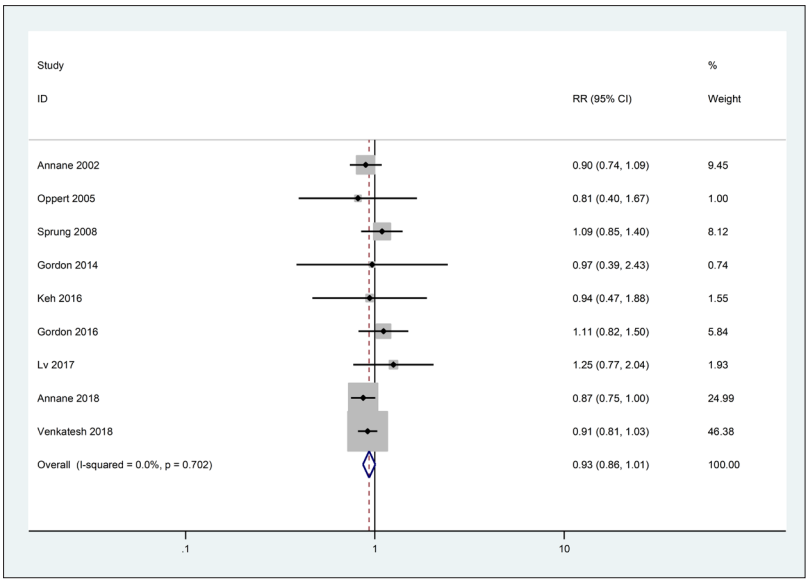

Figure 4. Forest Plot of Primary Outcome: 28-Day Mortality.

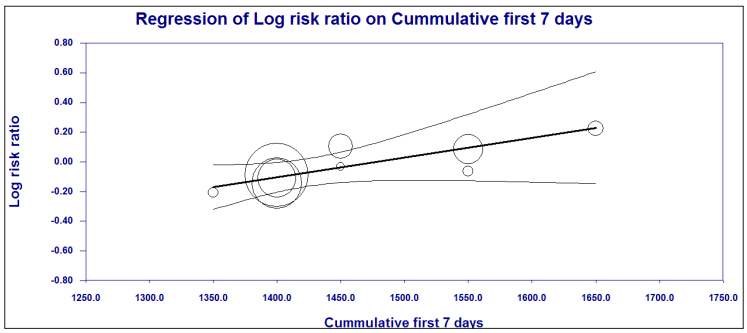

Figure 5. Meta-regression for Cumulative First 7 Days Dose.

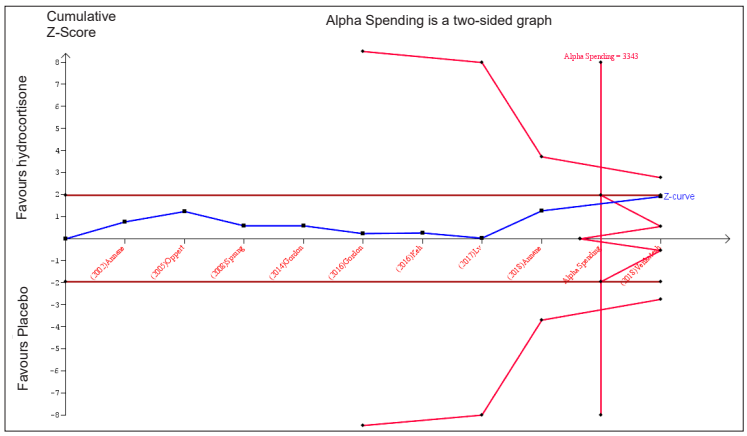

Figure 6. TSA and Cumulative Z Curve.

to studies of the primary outcome resulted in coefficient estimate bias reduction varying between 0.3% for Venkatesh et al[2] since it enrolled the largest number of patients, up to 5.7% bias reduction in the study by Oppert et al[36] which had the smallest sample size. The authors decided that data penalization for the included studies was not substantial. Table 1 provides a summary of data augmentation (Detailed results in Table S3).

Secondary Outcomes

Superadded infection

Five studies[2, 4,11,16,34] reported the incidence of superadded infection, without heterogeneity among studies (I^2 = 0.0%, Chi^2 P = 0.42). RR was statistically insignificant at 1.07 (95% CI: 0.97–1.19, P= 0.17). Evidence was downgraded twice to low quality for indirectness and individual risk of bias (Table 2, Figure S7 in Supplementary file 1).

Table 1. Coefficient Estimate Bias Reduction by Data Augmentation

Study	Log Likelihood	Penalized Log Likelihood	% Bias Reduction
Annane 2018	-811.48	-806.52	0.6%
Annane 2002	-202.91	-199.32	1.8%
Gordon 2014	-32.86	-31.16	5.2%
Gordon 2016	-245.37	-241.63	1.5%
Keh 2016	-99.19	-96.59	2.6%
Lv 2017	-76.41	-73.81	3.4%
Oppert 2005	-27.95	-26.35	5.7%
Sprung 2008	-315.76	-311.75	1.3%
Venkatesh 2018	-1997.6	-1991.81	0.3%

GIT Bleeding/Receipt of Blood Transfusion

The same 5 studies reported GIT bleeding or receiving blood transfusion as an adverse event. Quality of evidence was downgraded twice for indirectness and individual risk of bias. Insignificant RR was found at 1.02 (95% CI: 0.74–1.41, P = 0.9). No heterogeneity among studies (I2 = 0.0%, Chi^2 P = 0.83) (Figure S8, Table 2).

ICU LOS

Mean difference of ICU LOS was statistically insignificant at -1.53 (95% CI: -4.09 to 1.04, P = 0.2), the quality of evidence was downgraded to very low for several reasons, most important was data imputation (Table 2, Figure S9). Heterogeneity among studies was high (I^2 = 73%, Chi^2 P = 0.003). Six studies[2,4,33-35,37] reported this outcome, data was provided as mean ± SD by one author[33] and imputed for 2 studies.[2,34]

Hospital LOS

Four studies reported hospital LOS[33-35,37] data was provided by one author[33] and imputed for one study,[34] resulting in

downgrading of quality of evidence twice, a further one step reduction was decided due to inconsistency and imprecision (Table S2), the MD was not significant at 0.97 (95% CI: -2.18 to 4.11, P = 0.55), but there was very low heterogeneity among studies (I^2 = 0.0%, Chi^2 P = 0.72) (Figure S10 in Supplementary file 1).

ICU Mortality

Mortality in ICU was reported by 6 studies,[4,11,16,34-36] the quality of evidence was downgraded to low for indirectness and individual risk of bias. The resulting RR was not significant at 0.93 (95% CI: 0.85–1.01, P = 0.09), the studies had very low heterogeneity among them (I^2 = 5%, Chi^2 P = 0.38) (Figure S11 in Supplementary file 1).

Hospital Mortality

Similar to other outcomes, hospital mortality – reported in 8 studies[4,11,33-35,37]– was statistically insignificant with RR of 0.94 (95% CI: 0.88–1.01, P = 0.1), with very low among studies heterogeneity (I^2 = 0.0%, Chi^2 P = 0.51) and very low quality of evidence (Figure S12 in Supplementary file 1). Primary and secondary outcomes are outlined in Table 2.

Table 2. Summary of All Outcomes of This Review

Outcome	RR/MD	95% CI	*P* Value
28 day mortality	0.93	0.86–1.01	0.056
Superadded infection	1.07	0.74–1.41	0.9
GIT bleeding / transfusion	1.02	0.74–1.41	0.9
ICU LOS	-1.53	-4.09–1.04*	0.2
Hospital LOS	0.97	-2.18–4.11*	0.6
ICU mortality	0.93	0.85–1.01	0.09
Hospital mortality	0.94	0.88–1.01	0.1

Abbreviations: GIT, gastrointestinal tract; ICU, intensive care unit; LOS, length of stay; RR, risk ratio; MD, mean difference; CI, confidence interval *Mean difference.

Discussion

Several literature reviews evaluated the impact of steroids in septic shock and sepsis,[16,17,38-40] however, we are not aware of one that included only studies utilizing hydrocortisone as the intervention and excluded other forms of steroids. Indeed, this narrowing down of the research question in our review resulted in a more focused scope of the conclusion, which is advocated by the Cochrane handbook.[25] This can be seen reflected in absence of heterogeneity among studies reporting the primary outcome in our review (I^2 = 0.0%, Chi^2 P = 0.7). Further restriction of the inclusion criteria to publications of the year 2000 onward also emphasized that purpose since this meant consistency in the definition and management of sepsis and septic shock apart from intervention. This obvious difference between our review and most of the published reviews should always be observed when comparing our results to those of others.

The primary outcome of this review was all cause 28-day mortality, which had a rate of 28.9% and 26.9% in control and intervention groups, respectively. The RR just missed the level of statistical significance with P value of 0.056 (RR = 0.93 [95% CI 0.86–1.01]) in favor of the intervention, with very low quality of evidence. It is intriguing that the same border line insignificant result is repeatedly found by others. Rochwerg et al[38] reported RR of 0.93 (95% CI, 0.84–1.03), and the interval was even narrower in the review by Ananne[16] with a CI of 0.74 to 1.01. In 2 other reviews, the upper limit of confidence interval was exactly the null value of one.[39,40] This should direct attention to the value of statistical significance as compared to clinical significance when evaluating results of studies or meta-analyses, and the need for further analysis when such marginal results are obtained. This was done by Annane et al[39] where after obtaining a marginally insignificant result, they evaluated the studies of prolonged low dose hydrocortisone where RR of dying at 28 days was statistically significant in favor of the intervention (RR, 0.84; 95% CI, 0.72–0.97; P = .02). In our review, the sensitivity analysis of risk difference similarly produced insignificant results.

Although heterogeneity among studies included in the primary outcome was 0.0%, we proceeded as planned to assess heterogeneity among studies using meta-regression, which proved a significant association of the cumulative first 7 days dose of hydrocortisone with 28-day mortality; when the dose was lower, the mortality was lower. This result may be correlated to a similar finding reported by Annane et al,[40] who reports a trend towards reduced mortality associated with day 1 dose (P = 0.04) and to a lesser extent of total steroids dose (P = 0.05).

A predefined subgroup analysis of studies with low risk of bias showed a significant P value of 0.04 (RR = 0.92 [95% CI: 0.86–0.99]), indicating a reduced mortality risk with administration of hydrocortisone. Other subgroup analyses proved statistically insignificant.

Despite the significant finding in our meta regression of cumulative first 7 days dose of reduced mortality risk with lower hydrocortisone dose, as well as the mortality benefit observed in the subgroup of studies with low risk of bias in favor of hydrocortisone, we are obliged to acknowledge that our findings are inconclusive as evident by the TSA.

In our review, very low to low quality evidence showed statistically insignificant overall effect of hydrocortisone on all of the secondary outcomes, however, with trends of less GIT bleeding and superadded infection, decrease in ICU LOS, ICU mortality, and hospital mortality, but an increase in hospital LOS.

Our results coincide with those reported in other reviews[16,38-40] regarding GIT bleeding and superadded infection, with the same trend. The overall effect on ICU mortality was marginally insignificant, similar to that obtained by Annane et al[39] with RR of 0.81 (95% CI,

0.63–1.04; P = 0.1), however, the impact of steroids on ICU mortality was found to be significant in a more recent review[40] with a P value of 0.045 (RR 0.82 [95% CI, 0.68 to 1.00]) although there was moderate heterogeneity among the studies (I^2 = 30%). Likewise, hospital mortality in our review was not statistically different (RR = 0.94; 95% CI: 0.88 – 1.01, P = 0.1). The same finding was reported by Annane et al[39] (RR = 0.83; 95% CI: 0.68 – 1.00, P = 0.05). This result, however; goes counter to a recent review [40], which reported a significant impact on hospital mortality in favor of hydrocortisone (RR = 0.85; 95% CI: 0.73 – 0.98, P = 0.03), although the aforementioned review had substantial heterogeneity regarding that particular outcome (I^2 = 47%).

As for the impact on ICU and hospital LOS, very low quality evidence indicate that hydrocortisone resulted in a decrease of ICU LOS (MD = -1.5) but this was not statistically significant (95% CI: -4.09 to 1.04, P = 0.2). Furthermore, there was high heterogeneity among studies with a statistically significant P value of Chi^2 test of 0.003, and I^2 = 73%. On the other hand, hydrocortisone appeared to cause an increase in hospital LOS (RR = 0.97), but that was not statistically significant as well (95% CI: -2.18 to 4.11, P = 0.6). Similar insignificant results were reported for both outcomes by other reviews,[16,38-40] except for ICU LOS in the review by Annane et al[40] where steroids resulted in reduction of ICU LOS of about 2 days (RD = -1.68; 95% CI -3.27 to -0.09; P value = 0.04) with some heterogeneity evident across studies (I^2 = 31%).

In conclusion, low quality evidence indicate that hydrocortisone in critically ill adult patients with septic shock or severe sepsis has a statistically insignificant trend to decrease 28 day all-cause mortality. Clinicians are encouraged to consider the clinical significance of hydrocortisone on case-by-case basis. Hydrocortisone seems to be more effective in reduction of mortality when administered to septic shock (rather than sepsis) patients, with a low cumulative first 7-days dose.

Limitation

Our review was limited to trials published in English, possibly resulting in the exclusion of certain populations, which may negatively affect the generalizability of our conclusion. Our sensitivity tests were limited to the fixed effects model. Furthermore, we didn't perform subgroup analyses for secondary outcomes due to limited number of studies fulfilling our inclusion criteria and may have overlooked other subgroup differentiation for the primary outcome, such as different adulthood cutoff values in different studies. Had this differentiation been done, it may have resulted in the identification of a specific subgroup of population that can benefit from hydrocortisone. An additional limitation to our review is the risk of bias involving 3 included studies across 5 categories of assessment, which – although minimal – definitely had its impact on the outcome results.

Authors' Contribution

First and fifth authors: Methodology experts, electronic literature search, and statistical tests. First and last authors: Manuscript writing. All authors: Data extraction, risk of bias assessment, and quality of evidence assessment.

Conflict of Interest Disclosures

All the authors declared no conflict of interest.

Ethical Statement

All authors testify to the authenticity and integrity of the material included within this article. Our institutional Review Board (IRB) approval was obtained (approval number H1RI-08-Apr19-06). No informed consent was required for this work.

Supplementary Materials

Supplementary file 1 contains Figures S1-S12 and Tables S1-S3.

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