Corticosteroids as adjunctive therapy in the treatment of influenza: an updated Cochrane systematic review and meta-analysis.

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Abstract

Objective

Corticosteroids may be beneficial in sepsis but uncertainty remains over their effects in severe influenza. This systematic review updates the current evidence regarding corticosteroids in the treatment of influenza and examines the effect of dose on outcome.

Data Sources

Electronic databases (MEDLINE, EMBASE, CINAHL, LILACS, CENTRAL, Web of Science) and trial registries were searched to October 2018 for randomised controlled trials (RCTs), quasi-experimental designs and observational cohort studies reporting corticosteroid versus no corticosteroid treatment in individuals with influenza.

Study Selection and Data Extraction

Two researchers independently assessed studies for inclusion. Risk of bias was assessed using the Cochrane Risk of Bias tool (RCTs) or Newcastle-Ottawa Scale (observational studies). Where appropriate, we estimated the effect of corticosteroids by random effects meta-analyses using the generic inverse variance method. Meta-regression analysis was used to assess the association of corticosteroid dose and mortality.

Data Synthesis

We identified 30 eligible studies, all observational apart from one RCT. Twenty-one observational studies were included in the meta-analysis of mortality, which suggested an adverse association with corticosteroid therapy (Odds ratio (OR) 3.90, 95% confidence interval (CI) 2.31 to 6.60, 15 studies; adjusted hazard ratio 1.49, 95% CI 1.09 to 2.02, 6 studies). Risk of bias assessment was consistent with potential confounding by indication. Pooled analysis of seven studies showed increased odds of hospital-acquired infection in people treated with corticosteroids (unadjusted OR 2.74, 95% CI 1.51 to 4.95).

Meta-regression of the effect of dose on mortality did not reveal an association, but reported doses of corticosteroids in included studies were high (mostly >40 mg methylprednisolone (or equivalent) per day).

Conclusions

Corticosteroid treatment in influenza is associated with increased mortality and hospital-acquired infection, but the evidence relates mainly to high corticosteroid doses and is of low quality with potential confounding by indication a major concern.

Introduction

Induction of proinflammatory cytokines correlates with symptoms and fever in acute influenza (1), with significantly elevated levels in severe influenza (2-4). Endogenous corticosteroids, produced principally by the adrenal glands and regulated by the hypothalamic-pituitary-axis (HPA), possess anti-inflammatory, immunomodulatory and vascular properties (5-7). However, a combination of proinflammatory cytokine inhibition of the HPA, substrate deficiency, damage to the adrenal glands and peripheral corticosteroid resistance could result in adrenal insufficiency during critical illness (8, 9). Based upon the physiological rationale and evidence from a systematic review incorporating the latest clinical trials (10), a recent 'Rapid Recommendation' makes a weak recommendation to give corticosteroids to people with sepsis, with the proviso that it is also reasonable not to prescribe them due to uncertainty of their benefit. The optimal dose of corticosteroids in sepsis remains uncertain (11).

Although moderate quality evidence from randomised controlled trials (RCTs) suggests reduced mortality in severe community-acquired pneumonia (CAP) treated with corticosteroids (12), their role in influenza virus infections has been highly controversial. During the 2009 pandemic, 9% of hospitalised patients and up to 69% of critically-ill intensive care unit (ICU) admissions with influenza received corticosteroids (13-16); subsequent analysis indicated no benefit or even increased mortality with corticosteroid use.

Meta-analysis of ten studies in the original version of this systematic review, suggested that corticosteroid therapy for presumed influenza-associated complications is associated with increased risk of mortality (17). All included studies were observational with confounding by indication a major concern. In light of the ongoing controversy and subsequent publication of additional individual studies, we have updated this systematic review which, together with evaluation of data on the effect of corticosteroid dose on

mortality, aims to summarise the current evidence, highlight important clinical uncertainties and subsequently inform the design of future studies to help definitively address these areas.

Methods

We conducted this updated systematic review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (18) and Meta-Analysis of Observational Studies in Epidemiology guidelines (19). The original study protocol was registered with the Cochrane Database of Systematic Reviews (http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD010406/abstract).

Study Eligibility

Randomised controlled trials, quasi-experimental designs and observational cohort studies reporting the effect of corticosteroid treatment versus no corticosteroid treatment in people with clinically-diagnosed influenza or influenza-like illness and/or laboratory-confirmed influenza were eligible. The intervention was intravenous or oral corticosteroid of any type, dose or duration, given for any clinical reason but coinciding with influenza confirmed by positive RT-PCR, viral culture or rapid antigen test in respiratory specimens.

The primary outcomes were 30-day mortality and rate of admission to ICUs. Secondary outcomes were 30-day readmission after hospital discharge, the proportion of people requiring mechanical ventilation, length of hospital stay, and adverse events secondary to corticosteroid use, including hospital-acquired infections as defined by individual studies.

Search Methods and Data Extraction

We searched MEDLINE, EMBASE, CINAHL, LILACS , Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science from inception to October 2018, and

the following trial registries (October 2018): ISRCTN (http://www.isrctn.com/); World Health Organization International Clinical Trials Registry Platform (http://www.who.int/ictrp); and ClinicalTrials.gov (www.clinicaltrials.gov). The Cochrane Highly Sensitive Search Strategy was used to identify RCTs (20), and the Scottish Intercollegiate Guidelines Network filter to identify observational studies (21). The search strategy included core search terms relating to influenza and corticosteroids (Supplementary Table 1).

In a three-stage screening process two authors independently assessed the titles, abstracts and full-text of retrieved articles for potential inclusion. Data extraction was done independently by two authors with arbitration by a third author as required. The risk of bias was evaluated at outcome level using the Cochrane Collaboration tool for RCTs and Newcastle-Ottawa Scale (NOS) for observational studies (22, 23). Overall quality of the evidence for the main outcomes of interest was assessed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework (24).

Data Analysis

Dichotomous outcome data from individual studies were extracted as tabulated data from which risk ratios (RRs) or odds ratios (ORs) with 95% CIs were estimated. We extracted adjusted outcome measures as ORs or hazard ratios (HRs) with 95% CIs and presented these separately in pooled analyses. Where appropriate we estimated the effect of corticosteroids by random effects meta-analyses of pooled crude and adjusted ORs and pooled adjusted HRs for each outcome measure compared to no corticosteroids using the generic inverse variance method using Review Manager [Computer program], Version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Heterogeneity was assessed using the I^2 statistic. Publication bias was assessed using funnel plots for meta-analyses containing ten or more studies.

To explore the putative interaction between corticosteroid dose and the magnitude of effect, we performed a meta-regression analysis using post-admission mortality as the dependent variable, and dose of corticosteroids as predictors. We performed random effects meta-regression analyses using the metareg command in Stata version 15.1 (Stata Corp, College Station, Texas).

Results

Study characteristics

We identified 3686 articles; of the 30 articles meeting the inclusion criteria, 21 were included in the meta-analysis of mortality (15, 25-44) and nine were included in the narrative synthesis only (45-53)(Figure 1). There was one RCT and the remainder were observational studies (99,224 individuals). The characteristics of included studies are summarised in supplementary table 2.

The median age of the cohort or corticosteroid-treated groups ranged from 2.5 to 63 years. One study included children only (31), the others included either adults only or people of mixed ages but predominantly adults. Disease severity at baseline was recorded in nine studies (15, 28, 30, 34, 36-38, 42, 49), five of which recorded higher baseline disease severity in the corticosteroid- treated group compared to the untreated group (30, 34, 36-38). Ten studies included only patients admitted to ICU (15, 27, 28, 30, 36-38, 40, 41, 44), with the remaining studies having mixed data for both ICU–admitted and non-ICU hospitalised patients.

Thirteen studies reported the doses or regimens of administered corticosteroids, with median/mean doses ranging from 40 to 141mg/day of methylprednisolone equivalent in ten studies (15, 26, 28, 30, 34, 36, 38, 39, 43, 52), and regimens of 1-6 mg/kg/day in three studies (35, 37, 51). Median duration of corticosteroid therapy in seven studies ranged from 5.1 to 11.0 days.

The risk of bias assessments for 46 reported outcomes from 30 observational studies and the one RCT are summarised in supplementary table 3 and supplementary figure 1. For the RCT (52), the methods of randomisation, allocation concealment and blinding were judged to be adequate. The maximum number of stars for the selection, comparability and outcome domains was achieved in 28, 14 and 36 of the 46 outcomes respectively. A high degree of correlation between corticosteroid treatment and potential confounders such as disease severity and co-morbid conditions was noted in several studies (28, 30, 34, 36, 42).

Effect on mortality

The nineteen studies of influenza A(H1N1)pdm09 conducted solely during the 2009 pandemic (15, 25, 27, 28, 30, 31, 33, 34, 36, 37, 39, 40, 42-44, 46, 48, 49, 51), and five studies of seasonal/mixed seasonal and pandemic strains of influenza (29, 32, 38, 41, 52) reported either no difference or greater mortality associated with corticosteroid therapy. The single study of influenza A(H5N1) found an association between corticosteroid use and increased mortality after adjusting for neutropenia as a marker of disease severity (35). A study of influenza A(H7N9) reported no overall association with 30-day mortality although on subgroup analysis increased mortality and prolonged viral shedding were associated with high doses of corticosteroids (>150mg/day methylprednisolone equivalent) compared to no corticosteroids (26).

Reported timing of mortality from admission was inconsistent so stratification by 30-day mortality was not possible. Meta-analysis of 15 studies (2212 participants) showed significantly greater odds of mortality with corticosteroid use with moderate statistical heterogeneity (OR 3.90, 95% CI 2.31 to 6.60, I^2=68%)(Supplementary figure 2). On subgroup analysis both unadjusted and adjusted OR estimates showed an association between corticosteroid treatment and mortality (unadjusted OR 4.69, 95% CI 2.35 to 9.79, I^2=67%; adjusted OR 2.23, 95% CI 1.54 to 3.24, I^2=0%). An association with corticosteroid use was also found when the results of six studies

reporting adjusted HRs (aHR) were pooled (aHR 1.49, 95% CI 1.09 to 2.02, I^2=68%)(Supplementary figure 3).

Increased risk of mortality in people treated with corticosteroids was observed in subgroup analysis of the ten studies that only included ICU-admitted critically-ill patients (OR 2.43, 95% CI 1.72 to 3.43, I^2=0%, 7 studies, n=1295; adjusted HR 1.70, 95% CI 1.14 to 2.54, I^2=60%, 3 studies, n=2246)(Figures 2a and 2b). The risk was also raised in the subgroup containing eight studies reporting ORs that had a mixed ICU/non-ICU population (OR 4.72, 95% CI 2.07 to 10.77, I^2= 70%), although for the three studies reporting aHR, the risk was not significantly increased (aHR 1.31, 95% CI 0.73 to 2.35, I^2=69%). Three studies analysed patients with acute respiratory distress syndrome (ARDS) separately, with pooled analysis indicating increased risk of death in the group treated with corticosteroids (OR 2.32, 95% CI 1.36 to 3.95, I^2= 0%, n=392)(15, 30, 36). Pooled data for people who did not have ARDS from two of these studies showed a non-significant trend towards increased mortality risk with corticosteroid treatment (OR 2.54, 95% CI 0.77 to 8.39), with no significant subgroup difference between those with ARDS and no ARDS (p=0.89)(supplementary figure 4) A subgroup analysis of patients who were in shock versus those not in shock on admission to ICU was conducted in one study (38), with increased mortality risk associated with corticosteroid treatment in both groups (OR 1.60, 95% CI 1.21 to 2.13 and OR 1.89, 95% CI 1.22 to 2.95 respectively), with no significant difference between the subgroups (p=0.53).

The potential effect of corticosteroids at baseline for the treatment of pre-existing underlying conditions was considered in five studies , and patients were either excluded at the outset if they were receiving corticosteroids for chronic conditions (15, 28, 38) or a separate analysis was done of people who had not received prior corticosteroids (30, 32). Pooled analysis of data from only these patients showed a significant association between adjunctive corticosteroid treatment and risk of mortality (OR 2.01, 95% CI 1.39 to 2.90, I^2=0%, 3 studies; aHR 1.78, 95% CI 1.29 to 2.45, I^2=0%, 2 studies).

Funnel plot analysis did not reveal clear evidence of publication bias in the 21 studies included in the meta-analyses (Supplementary figure 5). We graded the certainty of the evidence specific to mortality as very low (supplementary table 4).

Three studies categorised corticosteroid dose as low or low/moderate and high. One study comparing low-dose (defined as <80 mg/day methylprednisolone equivalent) with higher corticosteroid doses found no difference in mortality risk (p=0.854)(43). A second study (288 participants) reported that compared to controls, patients receiving high-dose corticosteroids (>150 mg/day methylprednisolone equivalent) had increased mortality (HR 3.05, 95% CI 1.28 to 7.25, p=0.012), whereas in those treated with low to moderate dose corticosteroids the risk was not significantly different (HR 1.64, 95% CI 0.79 to 3.39, p=0.183)(26). In the third study (34), a large cohort of 2141 people, no overall effect of corticosteroids on mortality was found (HR 0.80, 95% CI 0.56 to 1.15), although when patients were stratified according to their disease severity as measured by their hypoxic status, low-moderate dose corticosteroids (25-150 mg/day methylprednisolone equivalent) were associated with decreased mortality in hypoxic people (PaO_2/FiO_2 <300mm/Hg), whereas high-dose corticosteroids had no beneficial effect in this group (HR 0.49, 95% CI 0.32 to 0.77, p=0.02 and HR 0.88, 95% CI 0.56 to 1.39, p=0.58 respectively). Neither low-moderate dose nor high-dose corticosteroids had a significant effect on 30-day mortality in non-hypoxic people.

Ten studies with data on corticosteroid dose were included in a random-effects meta-regression analysis (15, 26, 28, 30, 34, 36, 38, 39, 43, 52). Median daily dose was reported in seven of the studies, two reported total daily dose and one reported mean daily dose only. No significant interaction was observed between daily corticosteroid dose and mortality risk (regression co-efficient -0.0032; p=0.745) (Figure 3).

ICU Admission, Mechanical Ventilation, Length of Stay and Hospital-Acquired Infection

Studies reporting these outcomes are summarised in Table 1.

Seven studies presented data on the association between corticosteroid use and hospital-acquired infections. The definition of hospital-acquired infection varied but most studies reporting this outcome broadly defined it as the positive culture of a new pathogen (bacterial or fungal) from lower respiratory tract or blood cultures ≥48 hours after admission, and did not report results for different potential sources of infection separately. On pooled analysis, the overall risk of non-specific hospital-acquired infection was increased in patients treated with corticosteroids (OR 2.74, 95% CI 1.51 to 4.95, n=12,114)(supplementary figure 6), although all included estimates were unadjusted for potential confounders and statistical heterogeneity was high (I^2=90%). Subgroup analysis of three studies which included only ICU-admitted patients showed a trend towards increased risk of infection in corticosteroid treated patients, but was not statistically significant (OR 2.10, 95% CI 0.98 to 4.52, I^2 = 86%, n=1028, p=0.06).

Two ICU-based studies reported ventilator-associated pneumonia (VAP) separately (15, 38). Pooled analysis of unadjusted data suggested a non-significant trend toward increased risk of VAP with corticosteroids (OR 1.44, 95% CI 0.91 to 2.27, I^2=44%, n=2054, p=0.12).

For hospital-acquired infection we graded the certainty of the evidence as very low (supplementary table 4).

Discussion

Our updated systematic review and meta-analysis is, to our knowledge, the most comprehensive analysis to date to investigate the effect of corticosteroids on clinical outcomes in people with confirmed influenza. The majority of the data are from observational studies and although we included one eligible RCT, it was not powered for mortality and had only a very small number of participants with confirmed influenza. Our main finding is that analysis of observational data suggests an association between corticosteroid treatment and increased risk of mortality.

Overall the quality of the evidence is very low and there are important considerations to take into account when interpreting the findings. Firstly, many of the included studies did not specify the indications for corticosteroid therapy. Some studies stated the rationale for giving corticosteroids therapy as adult respiratory distress syndrome (ARDS) and septic shock (15, 30, 43) and it is possible at one extreme that corticosteroids were only given to the sickest patients or those with refractory illness as a final attempt to treat. This is suggested from our subgroup analysis of studies that had separate data for ARDS and non-ARDS patients in which the mortality risk was only significantly elevated in the ARDS subgroup. No significant difference was noted between people who were shocked on admission to ICU and those who were not, although data were very limited with only one included study having separate data for shock. Conversely, corticosteroids may have been used to treat less severe comorbid diseases such as exacerbations of asthma, and although some of the included studies excluded patients who may have received prior corticosteroids for pre-existing conditions, or conducted a separate analysis of such patients, most did not.

A further important consideration relates to the dose of corticosteroid used. In our meta-regression we found no clear evidence of an association between the overall dose of corticosteroid and the risk of mortality. However, dose and duration of corticosteroids were poorly specified in many of the studies, and where reported, median doses were generally considerably higher than the dose typically recommended for the treatment of septic shock or exacerbations of airways disease such as asthma (54-56). Variability in corticosteroid dose and administration schedule are both factors that have been associated with treatment outcomes in the setting of severe sepsis; in particular high doses given in short bursts have not been associated with benefit compared to low doses given for longer duration (≥ 5 days)(57). A recent subgroup analysis of RCTS in sepsis did not find any credible effect modification with corticosteroid dose, although most of the evidence was from studies using hydrocortisone with or without fludrocortisone at low dose (<400 mg/d hydrocortisone or equivalent) and over a long

duration (>2 days)(10). RCTs of corticosteroids in CAP have typically used much lower doses (32mg-40mg methylprednisolone equivalent) (12) than we noted in our included studies. Data from studies using low-dose steroids (≤40 mg/day MP equivalent) were lacking in our review. As the doses in our review were typically high, we cannot exclude the possibility that low-dose corticosteroids may have a different effect on mortality, or that there may be particular patient subgroups in whom their use may indeed be of benefit, as suggested by some of the individual included studies (26, 34). The use of higher doses of corticosteroids may also explain the greater risk from hospital-acquired infections which we noted. Corticosteroid use has been reported to be an independent risk factor for the development of invasive fungal infections in adults admitted to ICUs with influenza (58). Additionally, there is weak evidence from a recent observational study that influenza infection and corticosteroid treatment are both independent risk factors for the development of invasive pulmonary aspergillosis which is itself associated with high mortality (59).

The evidence base from clinical trials of corticosteroids in the setting of sepsis and pneumonia contrast with the findings from our review. Specifically, recent meta-analysis of prolonged low-dose corticosteroids in sepsis (which included two recent large RCTs, the Activated Protein C and Corticosteroids for Human Septic Shock (APROCCHSS) trial(60) and the Adjunctive Glucocorticoid Therapy in Patients with Septic Shock (ADRENAL) trial (61)) concluded that corticosteroids may achieve a small reduction or no reduction in the risk of dying in the short-term with a possible small decrease in longer-term mortality (60 days to 1 year)(10). Thus there is strong evidence from RCTS that corticosteroids in sepsis do not have a large positive effect. In the setting of CAP (not specifically influenza), an association between corticosteroid therapy and decreased mortality, need for mechanical ventilation and hospital length of stay has been shown (62). Other systematic reviews have also demonstrated a beneficial effect of corticosteroids on mortality and other clinical outcomes, but only in people with severe CAP (12, 63-66). Subgroup analyses by individual aetiological pathogens were not

possible in these systematic reviews due to lack of separation of outcome data by pathogen or lack of microbiological confirmation in the included studies. Large trials of corticosteroids in severe pneumonia are currently underway and should provide more robust data in the next few years (67, 68).

Limitations of our review include the current lack of evidence from relevant RCTs. Although we did not restrict our inclusion criteria to particular patient demographics, study settings or influenza subtype, we identified only one RCT which was not directly relevant to our review question. There was a high correlation between corticosteroid therapy and potential confounders for measured outcomes, such as disease severity and comorbid illnesses, so confounding by indication is likely to be a significant bias in studies which only provided unadjusted effect estimates. Additionally, time to hospitalization, antiviral use, presence of respiratory failure prior to corticosteroids, and the rationale for corticosteroid use were sparsely reported across studies. Clinical heterogeneity between the studies was also apparent in the measurement of disease severity with a range of clinical risk scores used, reported timing of mortality, types and doses of corticosteroids, and the consistency of use of co-interventions such as antivirals and antibiotics. Our meta-regression analysis of corticosteroid dose was limited by the lack of studies with data for low-dose corticosteroids, and there was also variation of doses used within the included studies. However, we believe that it is valuable in that it highlights an important gap in the evidence, and particularly so in light of meta-analyses of corticosteroids in sepsis and CAP, where low-dose steroids may have some beneficial clinical effects.

Conclusions

This systematic review highlights that the current evidence base is still not strong enough to make firm recommendations regarding the effectiveness or otherwise of corticosteroids as adjunctive treatment in people with proven influenza. Discrepancies remain between the findings in influenza and other clinical situations, but there are

important differences in terms of study designs and doses of corticosteroids used. The question of whether low doses of corticosteroids may be of some benefit in particular subgroups of patients with influenza requires further study and there is a clear need for well-designed RCTs to examine the effects of corticosteroids on clinical outcomes, particularly addressing the effects of low-dose corticosteroids and to include severely ill patients with influenza complications including primary viral pneumonia, septic shock and ARDS. This supports the updated World Health Organization Research Agenda recommendations for optimising the treatment of patients with influenza (69). In the meantime our results continue to support existing WHO recommendations (70) that systemic corticosteroids should be avoided in influenza patients unless indicated for other reasons or as part of an approved research protocol. In the current absence of finer details regarding the risks associated with subcategories of critically-ill influenza patients, and given the concerns regarding invasive secondary infections, caution should at the very least be applied before offering corticosteroids to anyone with severe influenza and it is not advisable to routinely give them to such patients.

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Figure Legends

Figure 1 Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) flow diagram for the article selection process

Figure 2a and 2b Meta-analysis of studies reporting mortality stratified by ICU admission status.

Figure 2a Odds Ratios (ORs)

Figure 2b Hazard Ratios (HRs)

Footnote for figure 2: Mortality estimates determined using random effects modelling. CI Confidence intervals; CS Corticosteroids; HR Hazard Ratio; OR Odds Ratio; SE Standard Error

Figure 3 Random-effects meta-regression of log of mortality effect size and dose of corticosteroid expressed as methylprednisolone equivalent per day.

Footnote for figure 3: Estimates from each included study are represented as circles. The area of each circle is inversely proportional to the variance of the log effect size, with circle area representative of the weight of each study.

Tables

Table 1 Summary of studies reporting clinical outcomes other than mortality

Supplementary Digital Content legends

Supplementary Table 1 Search Strategy for MEDLINE (OVID)

Supplementary Table 2 Characteristics of Included Studies

Supplementary Table 3 Risk of Bias in observational studies using the Newcastle-Ottawa Scale

Supplementary Table 4 GRADE assessment of outcomes

Supplementary Figure 1 Risk of Bias of included Randomised Controlled Trial

Supplementary Figure 2 Meta-analysis of studies reporting mortality: Odds ratios (ORs)

Supplementary Figure 3 Meta-analysis of studies reporting mortality: Hazard ratios (HR)

Supplementary Figure 4 Subgroup analysis of studies reporting patients with ARDS versus no ARDS

Supplementary Figure 5 Funnel plot analysis for publication bias for 21 studies included in mortality meta-analyses

Supplementary Figure 6 Meta-analysis of studies reporting hospital-acquired infections