Use of Corticosteroids in Cardiac Arrest—A Systematic Review and Meta-Analysis

Kieran Shah, ACPR, PharmD[1]

Anish R. Mitra, MD, MPH[2]

OBJECTIVES: The objective of this systematic review was to evaluate the impact of intraarrest corticosteroids on neurologic outcomes and mortality in patients with cardiac arrest.

DATA SOURCES: We conducted a systematic search using the Cochrane Central Register of Controlled Trials, EMBASE, and MEDLINE databases.

STUDY SELECTION: We included all randomized controlled trials and comparative observational studies. We excluded single arm studies, case reports/series, narrative reviews, and studies irrelevant to the focus of this article.

DATA EXTRACTION: Two reviewers independently assessed trial eligibility. Data were collected for the following outcomes: primary outcomes included good neurologic outcome, survival to hospital discharge, and survival at greater than or equal to 1 year. Secondary outcomes included incidence of return of spontaneous circulation, ICU and hospital length of stay, duration of vasopressor and inotropic treatment, and blood pressure during cardiopulmonary resuscitation and after return of spontaneous circulation.

DATA SYNTHESIS: The pooled estimates from randomized controlled trials for the following subgroups were analyzed using random-effects models: 1) patients with in-hospital cardiac arrest who received vasopressin, steroids, and epinephrine; 2) patients with in-hospital cardiac arrest who used corticosteroids only (i.e., no vasopressin); and 3) patients with out-of-hospital cardiac arrest who used corticosteroids only. Results included an increase in good neurologic outcomes (relative risk, 2.84; 95% CI, 1.36–5.94) and survival to hospital discharge (relative risk, 2.58; 95% CI, 1.36–4.91) in in-hospital cardiac arrest patients receiving vasopressin, steroids, and epinephrine followed by corticosteroids for postresuscitation shock. This was further supported by an increase in return of spontaneous circulation (relative risk, 1.35; 95% CI, 1.12–1.64) and hemodynamics in this population. There was no benefit observed in in-hospital cardiac arrest or out-of-hospital cardiac arrest patients receiving corticosteroids alone.

CONCLUSIONS: Our study found that there are limited high-quality data to analyze the association between corticosteroids and reducing mortality in cardiac arrest, but the available data do support future randomized controlled trials. We did find that corticosteroids given as part of a vasopressin, steroids, and epinephrine regimen in in-hospital cardiac arrest patients and for postresuscitation shock did improve neurologic outcomes, survival to hospital discharge, and surrogate outcomes that include return of spontaneous circulation and hemodynamics. We found no benefit in in-hospital cardiac arrest or out-of-hospital cardiac arrest patients receiving corticosteroids only; however, a difference cannot be ruled out due to imprecision and lack of available data.

KEY WORDS: advanced cardiovascular life support; cardiac arrest; cardiopulmonary resuscitation; corticosteroids; glucocorticoids

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In-hospital cardiac arrest (IHCA) and out-of-hospital cardiac arrest (OHCA) are associated with significant morbidity and mortality. Survival to hospital discharge is approximately 18% and 10% for IHCA (1) and OHCA (2), respectively, and in survivors, the prevalence of severe neurologic deficit is 25–50% (3).

Evidence based therapies for cardiac arrest include cardiopulmonary resuscitation (CPR), defibrillation of shockable rhythms, and antiarrhythmic medication for ventricular fibrillation or ventricular tachycardia (4). Epinephrine has been a central pharmacologic therapy in advanced cardiovascular life support (ACLS) for many years, but a recent study suggests that epinephrine may reduce mortality in OHCA without improving survival to a favorable neurologic outcome (5). No other pharmacologic agent has been shown to improve favorable neurologic outcomes.

Return of spontaneous circulation (ROSC) is associated with adrenal insufficiency, coagulopathies, and elevated proinflammatory cytokines leading to postresuscitation shock (6). Corticosteroids may be an additional or alternative pharmacologic therapy that can improve cardiac arrest outcomes. Exogenous corticosteroids can supplement lower cortisol levels and attenuate systemic inflammatory responses. This has potential to improve hemodynamics, facilitate ROSC, and improve overall survival in patients with cardiac arrest.

However, the benefit of corticosteroids on mortality and neurologic outcomes in patients with IHCA and OHCA remains unclear (4). In two randomized controlled trials (RCTs) of patients with IHCA, the use of combination methylprednisolone, vasopressin, and epinephrine during cardiac arrest and hydrocortisone after ROSC significantly improved survival to discharge, and one of the RCTs demonstrated improved neurologic outcome (3, 7). In contrast, another RCT evaluating corticosteroids as the sole treatment in patients with OHCA demonstrated no improvement in survival to hospital discharge (8). Due to conflicting results, the American Heart Association guidelines state that corticosteroids in patients with OHCA during CPR and in patients with shock after ROSC is of uncertain benefit, and the European Resuscitation Council guidelines recommend against their use entirely (4, 9). Currently, there is no systematic review or meta-analysis that has evaluated the overall impact of corticosteroids in cardiac arrest. Therefore, we performed a systematic review and meta-analysis to evaluate the impact of intraarrest corticosteroids on mortality and neurologic outcomes in patients with cardiac arrest.

METHODS

The study protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) (10). The study is reported in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (11).

Search Strategy

We conducted a systematic search to identify studies comparing corticosteroids with placebo or no corticosteroids as adjunctive therapy in adult patients with cardiac arrest. We combined the following search terms: cardiac arrest, heart arrest, cardiopulmonary resuscitation, advanced cardiovascular life support, ACLS, CPR, corticosteroids, glucocorticoids, methylprednisolone, dexamethasone, and hydrocortisone. We searched the Cochrane Central Register of Controlled Trials (2003 to present) EMBASE (1974 to present), and MEDLINE (1946 to present) databases, for relevant English-language studies.

We included all RCTs and comparative observational studies (retrospective/prospective cohorts, and case-control studies). We excluded any single-arm studies, case reports/series, studies irrelevant to the focus of the paper (with respect to populations, interventions, or outcomes identified), and narrative reviews. Specifically, studies evaluated the use of corticosteroids given during CPR in patients with IHCA and/or OHCA.

Data Collection

Two reviewers independently assessed trial eligibility based on titles, abstracts, and full texts; disagreements were resolved by discussion. The following data were collected in an electronic data extraction spreadsheet: study characteristics (study author(s), publication year, study design, patients and demographics, interventions, number of participants per group, follow-up interval, and outcomes) and results relevant to our predefined outcome measures.

Risk of Bias (Quality) Assessment

We evaluated the risk of bias for RCTs using the Cochrane Risk of Bias 2 Tool (12) and for observational trials using the Cochrane Risk of Bias Assessment Tool: Risk of Bias in Nonrandomized Studies of Interventions-I (13). A third reviewer was used as a tie-breaker in cases where there were disagreements in risk of bias. We rated RCTs as low, high, or some concerns of bias at the study level. We rated observational trials as low, moderate, serious, critical, or unknown risk of bias at the study level (12, 13). We excluded any studies that had abstracts only available from risk of bias assessments.

Outcomes and Subgroups

Primary outcomes included good neurologic outcome (measured using the Glasgow-Pittsburgh Cerebral Performance Category score), survival to hospital discharge, and survival at greater than or equal to 1 year. Secondary outcomes included ROSC, ICU, and hospital length of stay (LOS), duration of vasopressor and inotropic treatment, and blood pressure (systolic blood pressure, diastolic blood pressure, and mean arterial pressure [MAP]) during CPR and after ROSC. Safety outcomes included any adverse events reported, serious adverse events, incidence of infection, and hyperglycemia. Subgroup outcomes were calculated for IHCA patients receiving vasopressin, corticosteroids, and epinephrine (VSE); IHCA patients receiving corticosteroids only; and OHCA patients receiving corticosteroids only.

Statistical Analysis

We presented dichotomous data as relative risk (RR) and odds ratios (ORs) with 95% CIs for RCTs and nonrandomized trials, respectively. When available, we presented data according to the intention-to-treat population. Where insufficient data were reported in original trials for intention-to-treat analysis, we used the per protocol population as presented in the study report. We attempted to contact the trial investigators for any missing data. The pooled estimates from RCTs for the following subgroups were analyzed using random-effects models: 1) patients with IHCA who received VSE, 2) patients with IHCA who used corticosteroids only (i.e., no vasopressin), and 3) patients with OHCA who used corticosteroids only. A combined estimate from observational trials was also analyzed separately. We excluded from the pooled estimates any studies where only the abstract was available.

We assessed statistical heterogeneity with the visual inspection of the forest plot and calculation of the I^2 statistic. As per the Cochrane Handbook, we considered heterogeneity low if the I^2 was less than 25%, moderate if 25–50%, and substantial if greater than 50% (12). If the statistical heterogeneity was substantial, a meta-regression controlled for age, gender, arrest rhythm, duration of arrest before receiving CPR, duration of CPR, study design (RCT vs observational), and IHCA versus OHCA was conducted if there were at least 10 studies available. Publication bias was assessed through visual inspection of a funnel plot for any meta-analysis with at least 10 trials, as this test is considered to be of little value with fewer trials (12). We performed all statistical analyses using Review Manager Version 5.4 (RevMan, The Cochrane Collaboration, 2020).

RESULTS

We identified seven eligible studies (**Fig. 1**) (**Supplementary Table 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/G197): five RCTs (3, 7, 8, 14, 15), one prospective cohort study (16), and one retrospective cohort study (17). Two RCTs compared vasopressin, corticosteroids and epinephrine (VSE) with epinephrine and placebo followed by corticosteroids for postresuscitation shock in IHCA patients (3, 7). One RCT compared corticosteroids with placebo in IHCA patients (14). Two RCTs compared corticosteroids with placebo and no corticosteroids, respectively, in OHCA patients (8, 15). One prospective cohort study compared corticosteroids with placebo and one retrospective cohort study compared corticosteroids with no corticosteroids, both in OHCA patients (16, 17).

Three RCTs were deemed a high risk of bias in the overall assessment (7, 8, 14), and one RCT was rated as a low risk of bias overall (3). One RCT was available as an abstract only and could not be adequately assessed for risk of bias in all domains, and was therefore removed from the risk of bias assessment (15) (**Fig. 2**).

Both the prospective and retrospective cohort studies were rated as a serious risk of bias due to confounding. Other bias domains were not assessable due to lack of information provided (bias due to deviation from intended interventions, missing data, and selective

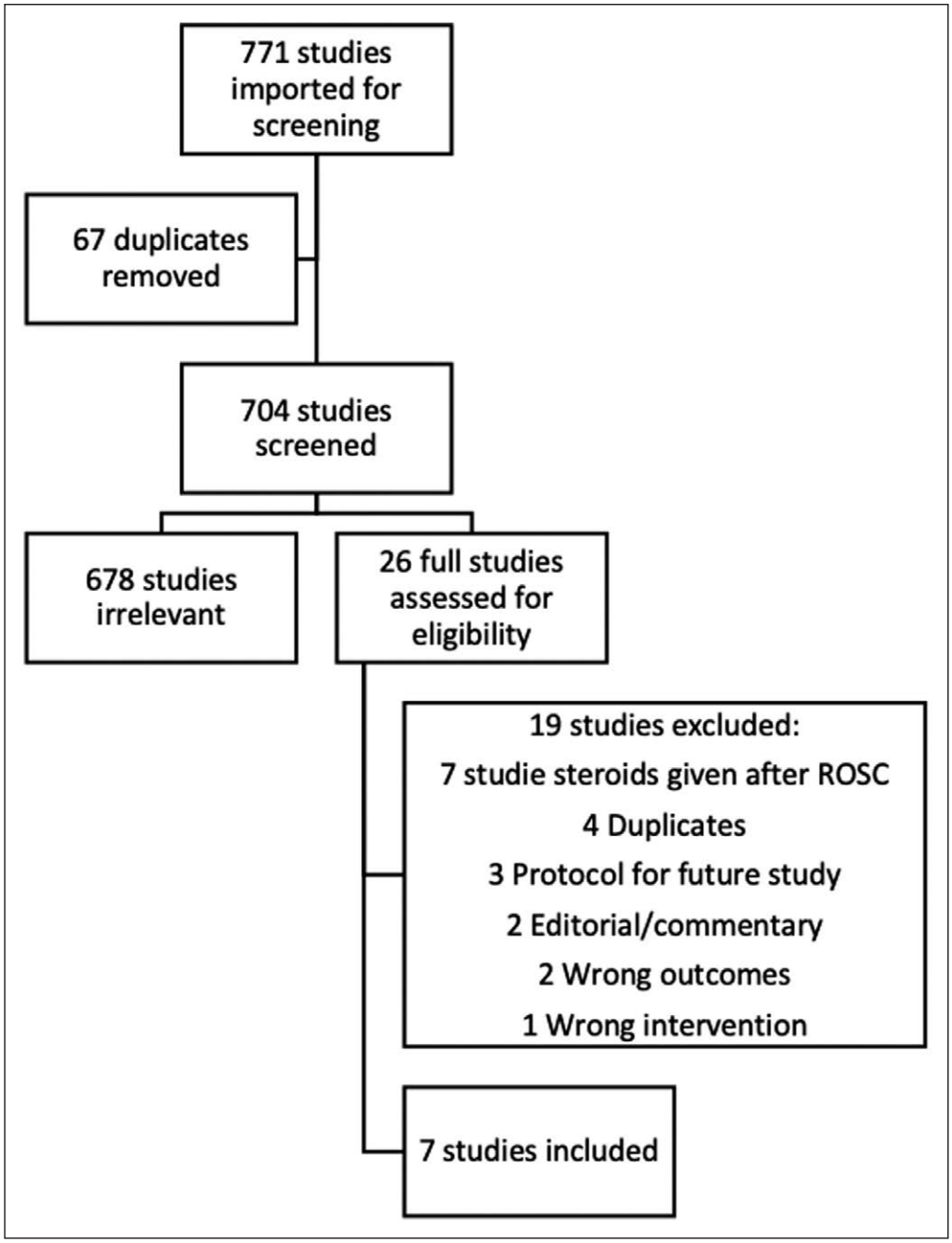

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of included studies. ROSC = return of spontaneous circulation.

reporting) (**Supplementary Table 2**, Supplemental Digital Content 2, http://links.lww.com/CCM/G198).

Primary Outcomes

Good Neurologic Outcome. Five RCTs evaluated the impacts of corticosteroids on neurologic outcome (3, 7, 8, 14, 15). A random-effects analysis of four RCTs demonstrated a statistically significant increase in good neurologic outcome in patients who received corticosteroids (RR, 2.85; 95% CI, 1.39–5.84) (**Fig. 3**). When studies were analyzed within distinct subgroups, only studies evaluating the use of VSE with supplemental corticosteroids for postresuscitation shock in IHCA patients demonstrated a statistically significant increase in good neurologic outcome (RR, 2.84; 95% CI, 1.36–5.94). There was no difference demonstrated in patients with IHCA receiving corticosteroids only (RR, 3.00; 95% CI, 0.13–70.39) or in patients with OHCA receiving corticosteroids only (RR not estimable). Schwitzer et al (15) (abstract only; not included in the forest plot) did not show a difference in good neurologic outcome in patients with OHCA receiving corticosteroids (RR, 1.41; 95% CI, 0.14–13.86).

Nonrandomized trials did not report on the impacts of corticosteroids on neurologic outcomes (16, 17).

Survival to Hospital Discharge. All five RCTs (3, 7, 8, 14, 15) evaluated the effect of corticosteroids on survival to hospital discharge. A random-effects analysis of four RCTs demonstrated a statistically significant increase in survival to hospital discharge in patients who received corticosteroids (RR, 2.61; 95% CI, 1.41–4.85) (**Fig. 4**). When analyzing subgroups, only pooled studies of patients with IHCA receiving VSE and corticosteroids for postresuscitation shock demonstrated a statistically significant increase in survival to hospital discharge (RR, 2.58; 95% CI, 1.36–4.91). There was no statistically

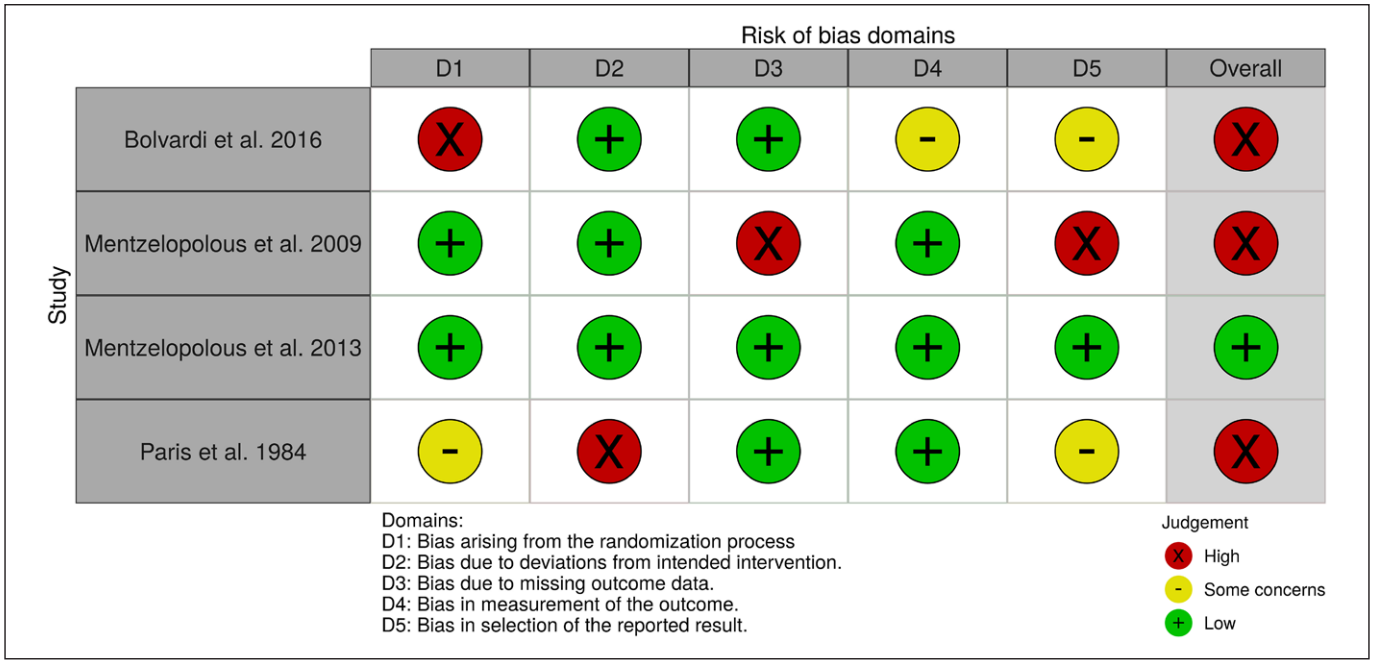

Figure 2. Risk of bias assessment. D = domain.

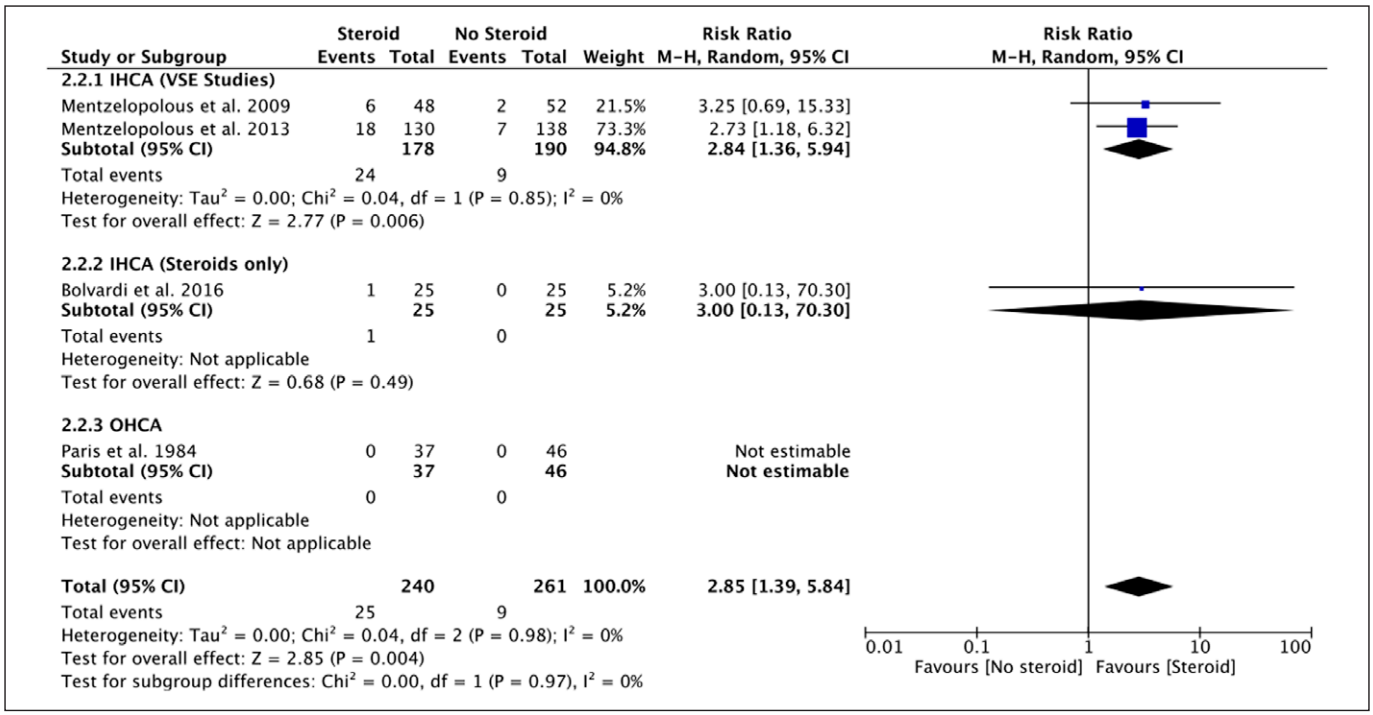

Figure 3. Good neurologic outcome. *df* = degrees of freedom, IHCA = in-hospital cardiac arrest, M-H = Mantel-Haenszel, OHCA = out-of-hospital cardiac arrest, VSE = vasopressin, steroids, and epinephrine.

significant difference in patients with IHCA (RR, 3.00; 95% CI, 0.33–26.92) or OHCA (RR not estimable) receiving corticosteroids only. Schwitzer et al (15) (not included in the forest plot) was unable to demonstrate a benefit in survival to hospital discharge in OHCA patients receiving corticosteroids (RR, 1.41; 95% CI, 0.14–13.86).

A random-effects analysis of nonrandomized studies (16, 17) demonstrated no difference in survival to hospital discharge in patients who received corticosteroids compared with those who did not receive corticosteroids (OR, 1.92; 95% CI, 0.62–5.93) (**Supplementary Fig. 1**, Supplemental Digital Content 3, http://links.lww.com/CCM/G199).

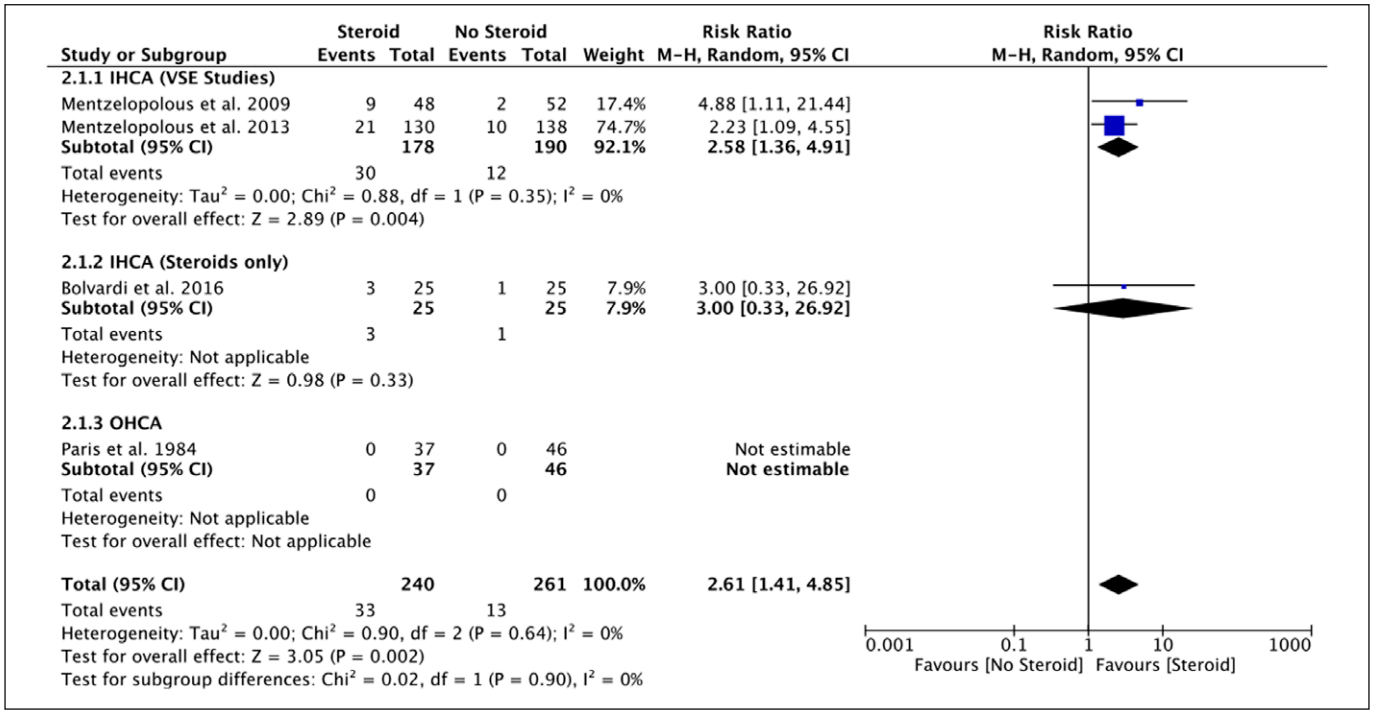

Figure 4. Survival to hospital discharge. *df* = degrees of freedom, IHCA = in-hospital cardiac arrest, M-H = Mantel-Haenszel, OHCA = out-of-hospital cardiac arrest, VSE = vasopressin, steroids, and epinephrine

Survival at Greater Than or Equal to 1 Year. Mentzelopoulos et al (3) is the only study that evaluated survival at greater than or equal to 1 year. In the corticosteroid group, 8.5% of patients survived at 1 year, compared with 3.6% of patients in the placebo group (RR, 2.34; 95% CI, 0.83–6.54).

Secondary Outcomes

ROSC. All five RCTs evaluated the effect of corticosteroids on ROSC (Fig. 4) (3, 7, 8, 14, 15). A random effects analysis of four RCTs (3, 7, 8, 14) demonstrated a statistically significant increase in ROSC in patients who received corticosteroids (RR, 1.32; 95% CI, 1.16–1.50) (**Fig. 5**). IHCA patients receiving VSE had an increase likelihood of ROSC (RR, 1.35; 95% CI, 1.12–1.64). However, there was no increase in ROSC seen in IHCA patients (RR, 1.50; 95% CI, 0.63–3.59) or OHCA patients (RR, 0.62; 95% CI, 0.12–3.21) receiving corticosteroids only. Schwitzer et al (15) also showed no increase in ROSC in OHCA patients receiving corticosteroids (RR, 1.76; 95% CI, 0.41–7.63).

A random effects analysis of nonrandomized studies showed an increased likelihood in ROSC in OHCA patients receiving corticosteroids (RR, 2.70; 95% CI, 2.46–2.96) (Supplementary Fig. 1, Supplemental Digital Content 3, http://links.lww.com/CCM/G199).

ICU and Hospital LOS. Mentzelopoulos et al (3) is the only study that evaluated ICU and hospital LOS. This study demonstrated no statistically significant difference between patients receiving corticosteroids versus placebo in ICU (23.1 d vs 29.3 d; $p = 0.44$) and hospital LOS (48.2 d vs 59.7 d; $p = 0.42$).

Blood Pressure and MAP During CPR and After ROSC. Two studies evaluated the impacts of corticosteroids on hemodynamics including blood pressure and MAP during CPR and after ROSC (3, 7). A random-effects meta-analysis demonstrated increased blood pressure and MAP during CPR and after ROSC in patients receiving corticosteroids (**Supplementary Table 3**, Supplemental Digital Content 4, http://links.lww.com/CCM/G200; and **Supplementary Fig. 2**, Supplemental Digital Content 5, http://links.lww.com/CCM/G201).

Other Secondary Outcomes. No studies reported on duration of vasopressor or inotropes.

Safety

Only three studies reported on safety endpoints (**Supplementary Table 4**, Supplemental Digital Content 6, http://links.lww.com/CCM/G202) (3, 7, 16). Inconsistency in reporting of safety endpoints in included studies precluded meta-analysis. The results

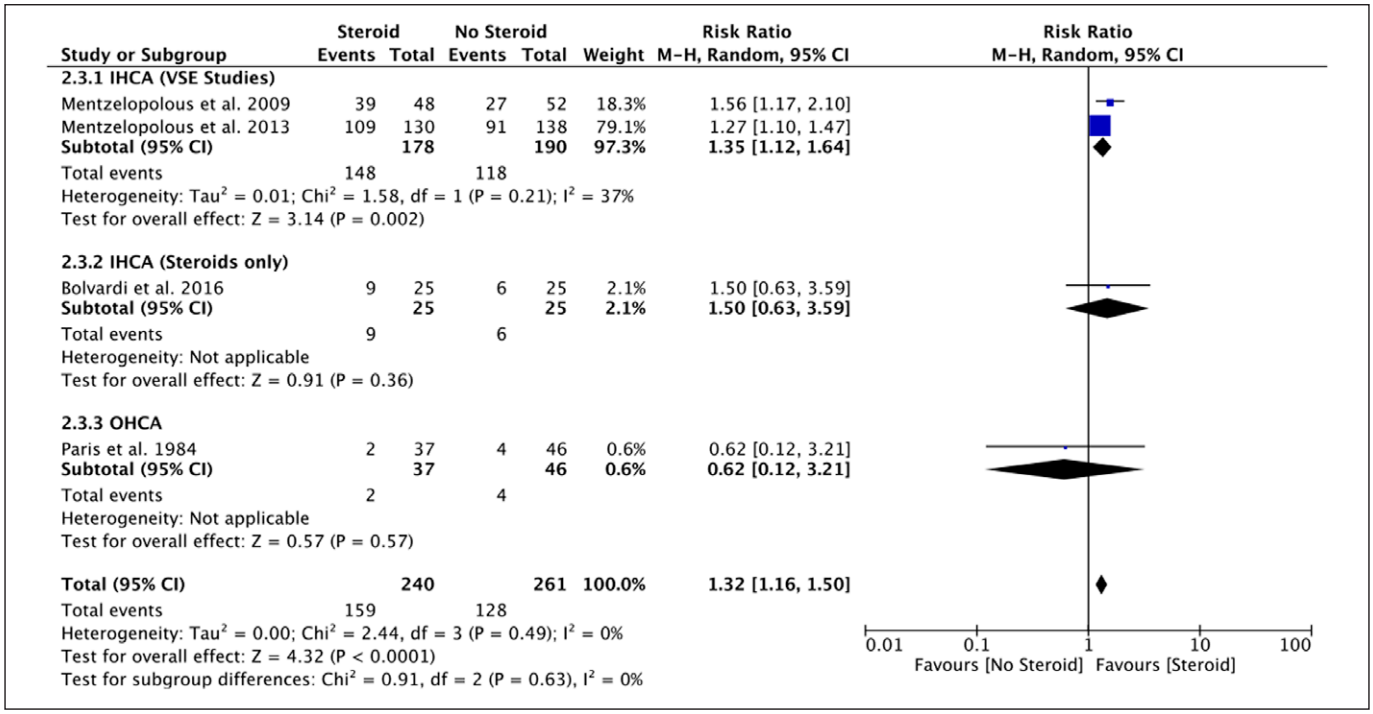

Figure 5. Return of spontaneous circulation. *df* = degrees of freedom, IHCA = in-hospital cardiac arrest, M-H = Mantel-Haenszel, OHCA = out-of-hospital cardiac arrest, VSE = vasopressin, steroids, and epinephrine.

of individual studies are reported. The most common endpoints included in studies were hyperglycemia, infections, weakness, and upper gastrointestinal bleeding. There were no statistically significant differences between corticosteroids and nonsteroid groups for reported safety endpoints.

DISCUSSION

Our analyses found that corticosteroids are associated with improved outcomes in cardiac arrest including good neurologic outcome, survival to hospital discharge, ROSC, and hemodynamics. However, these benefits were driven by data from two RCTs instigating the use of VSE in IHCA patients, which provide 92% of our meta-analysis study data. A causal relationship between steroids and improved outcomes in cardiac arrest is further supported by improvement in ROSC and hemodynamics in these studies.

We did not find high-quality data investigating the use of corticosteroids in OHCA or in IHCA without concomitant vasopressin and epinephrine. The point-estimates for our primary outcomes were similar between the single RCT using corticosteroids in cardiac arrest and the two RCTs using VSE, supporting that future studies should be designed to test the association between corticosteroids and improved outcomes in cardiac arrest and whether concomitant vasopressin is required. OHCA patients may also benefit from corticosteroid administration, but there are fewer available data to support this hypothesis.

The VSE studies administered methylprednisolone during CPR, it is unclear if the improved outcomes were secondary to methylprednisolone specifically or if there is a class effect associated with all corticosteroids. Additionally, the VSE study protocols included stress-dose hydrocortisone for up to 7 days post cardiac arrest, which may have contributed to improved outcomes.

There was inconsistent reporting of safety endpoints in studies. Where safety outcomes were reported, there was no difference identified between corticosteroid groups and noncorticosteroid groups with respects to hyperglycemia, infections, weakness, and upper gastrointestinal bleeding rates. These studies had small sample sizes and were likely underpowered to detect differences in adverse effects.

Our systematic review has several limitations. First, three RCTs contained a high or unclear risk of bias in each domain, and one is only available as an abstract, limiting the inherent validity of results (7, 8, 14, 15).

Both observational studies contained significant methodologic limitations, namely confounding,

which also limits the veracity of their results (16, 17). Variables such as rhythm of arrest, whether or not bystander CPR was given, and quality of CPR are not considered in these studies and could be viewed as potential confounders that limit the applicability of conclusions from these studies.

Second, we observed significant clinical heterogeneity between studies. This includes differences in adjunctive therapies (e.g., VSE, corticosteroids for postresuscitation shock), differences in types of corticosteroids being administered at nonequipotent doses, and different practice settings that span over the course of multiple decades. Of the studies that did show benefit, corticosteroids were employed as part of a VSE regimen as well as for postresuscitation shock in IHCA patients (regimens described in Supplementary Table 1, Supplemental Digital Content 1, http://links.lww.com/CCM/G197) (3, 7). These two studies were similar in design and setting, which limits clinical heterogeneity between them and may support the use of this strategy in IHCA patients. It remains inconclusive whether other corticosteroids and their doses in the absence of supplemental corticosteroids for postresuscitation shock provide benefit.

Third, VSE studies included up to 40% of patients identified to have hypotension and/or respiratory failure as a cause of their arrest. It is postulated that many of these patients were in septic shock, experiencing pneumonia and/or acute exacerbation of chronic obstructive pulmonary disease or asthma, for which corticosteroids may be of additional value. It is unclear if the same benefit applies to patients with IHCA secondary to other causes, such as an acute coronary syndrome. Future studies should be designed to test the association of corticosteroids and outcomes in subgroups based on cause of cardiac arrest.

Fourth, rates of targeted temperature management and percutaneous coronary interventions were reported in the VSE studies only (3, 7). Targeted temperature management occurred in 15–25%. It would be useful to know if VSE and corticosteroids for postresuscitation shock provide additional benefit in IHCA patients in settings where targeted temperature management is used more frequently.

Despite these limitations, given the perceived low risk of administering corticosteroids and potential benefit with regard to good neurologic outcome and survival to hospital discharge, we believe it is reasonable to administer it as part of a VSE regimen in IHCA patients followed by corticosteroids for postresuscitation shock until additional data become available.

CONCLUSIONS

Our study found that there are limited high-quality data to analyze the association between corticosteroids and mortality in cardiac arrest. We did find that corticosteroids given as part of a VSE regimen in IHCA patients and for postresuscitation shock did improve neurologic outcomes, survival to hospital discharge, and surrogate outcomes that include ROSC and hemodynamics. We found no benefit in IHCA or OHCA patients receiving corticosteroids only; however, a difference cannot be ruled out due to imprecision and lack of available data. Given the perceived low risk of administering corticosteroids and potential benefit with regard to good neurologic outcome and survival to hospital discharge, we believe it is reasonable to administer it as part of a VSE regimen in IHCA patients followed by corticosteroids for postresuscitation shock until additional data become available.

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1 *Critical Care, Lower Mainland Pharmacy Services, Fraser Health, Surrey, BC, Canada.*

2 *Division of Critical Care Medicine, Department of Medicine, University of British Columbia, Vancouver, BC, Canada.*

This work was performed at Fraser Health.

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For information regarding this article, E-mail: anish.mitra@fraserhealth.ca

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