Systematic Review

Effect of corticosteroid administration on cardiac arrest: a systematic review and network meta-analysis of the timing of administration

Youngchan Pyo, Tae Nyoung Chung

Department of Emergency Medicine, CHA Bundang Medical Center, CHA University School of Medicine, Seongnam, Korea

Corticosteroids may have a beneficial effect on the outcome of cardiac arrest (CA); however, it is not known whether the timing of corticosteroid use affects the outcome. We performed a systematic review and network meta-analysis to compare the efficacy of corticosteroid administration according to the timing. A favorable final outcome, as the primary study outcome, was defined as a combination of survival with good neurologic outcome and survival for 1 year. The secondary outcome was survival to discharge. Nine clinical studies were included. Corticosteroids administered during cardiopulmonary resuscitation (CPR; odds ratio [OR], 1.29; 95% confidence interval [CI], 1.11–1.51) and post-CA (OR, 1.47; 95% CI, 1.30–1.66) had a positive effect on the favorable final outcome compared to the control protocol (no corticosteroid administration), while those used prior to CA had a negative effect. Corticosteroids administered post-CA had a positive effect on survival to discharge compared to the control protocol (OR, 1.82; 95% CI, 1.02–3.27), while those used prior to CA and during CPR had no significant effect. Post-CA was evaluated to be the best administration timing for both outcomes. In conclusion, the timing of corticosteroid administration may be an important factor for the prognosis of CA. Corticosteroids administration post-CA and during CPR may have beneficial effects on CA outcomes.

Keywords Heart arrest; Cardiopulmonary resuscitation; Adrenal cortex hormones; Steroids; Network meta-analysis

---

Capsule Summary

What is already known
Use of corticosteroids for the treatment of cardiac arrest may be beneficial in terms of return of spontaneous circulation, survival with good neurologic outcome, and long-term survival. However, the optimal timing for corticosteroid administration is unknown.

What is new in the current study
The timing of administration may affect the effect of corticosteroids on the prognosis of patients with cardiac arrest. Corticosteroids may be best administered after the return of spontaneous circulation regardless of whether they were administered during cardiopulmonary resuscitation or not.

INTRODUCTION

Cardiac arrest (CA) is referred to as the abrupt loss of heart mechanical activity, as confirmed by the absence of signs of circulation. Out-of-hospital CA and in-hospital CA are important causes of mortality and morbidity worldwide, and it is estimated that 360,000 and 290,000 cases occur annually in the United States, respectively, with only 10% to 12% and 25% to 40%, respectively, of patients surviving.[1,2]

Currently, epinephrine is considered the only essential pharmaceutical therapy except for antiarrhythmic drugs in CA according to the current advanced cardiac life support (ACLS) guidelines.[3,4] Several studies have previously shown that relative adrenal insufficiency is common in patients after CA, and higher cortisol levels are associated with lower mortality from circulatory shock in animal models and humans.[5-8] These results suggest that the use of corticosteroids after CA can suppress inflammatory reactions, regulate catecholamine synthesis, and protect against ischemia-reperfusion injury.[9] Based on this concept, there have been various clinical studies that assess the effect of corticosteroid administration on CA, which showed inconsistent results.[10-18] Moreover, even the results of recent meta-analyses that included those clinical studies were inconsistent.[19-22] The designs of the clinical studies mentioned above are quite different, especially in terms of the timing of corticosteroid administration; in some cases, corticosteroids were administered during cardiopulmonary resuscitation (CPR) or after the return of spontaneous circulation (ROSC), while other patients had a history of recent corticosteroid use prior to CA. We hypothesized that this difference in timing caused the discrepancies observed in the results of existing clinical studies and meta-analyses.

We aimed to assess the effect of corticosteroid administration on CA and whether the timing of administration affects the outcome. Hence, we performed a network meta-analysis of clinical studies that assessed the effect of corticosteroid administration on CA with a head-to-head comparison of the outcomes according to the timing of corticosteroid administration and prior corticosteroid use.

METHODS

Protocol

This study followed the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) statement extension for network meta-analysis guidelines[23,24] and was prospectively registered in PROSPERO (international prospective register of systematic reviews; No. CRD42022331973).[25]

Search strategy and inclusion criteria

Two reviewers independently searched for studies published in English before May 2022 using PubMed, Embase, Scopus, Web of Science, and Cochrane Central Register of Controlled Trials. We combined the following search words: "cardiac arrest," "heart arrest," "cardiopulmonary arrest," "cardiopulmonary resuscitation," "ventricular fibrillation," "CPR," "advanced cardiovascular life support," "ACLS," "steroid," "glucocorticoid," "hydrocortisone," "adrenal cortex hormones," "methylprednisolone," and "dexamethasone." We also searched for unpublished trials and ongoing studies at ClinicalTrials.gov (The US National Institutes of Health Ongoing Trials Register).

The studies with the following characteristics were enrolled: (1) population: adults (≥ 18 years) with CA, regardless of the CA location, with an initial presenting rhythm of CA; (2) intervention: steroid use during and/or after CA; (3) control: no steroid use (i.e., placebo or conventional ACLS therapy); (4) outcome: survival to discharge and ROSC; and (5) design: randomized controlled trial (RCTs), case-control studies, and cohort studies. In addition, the intervention group of some studies was administered additional drugs, such as vasopressin.

We excluded animal studies, case reports or series without a control group, study protocols, commentaries, review articles, and irrelevant studies (i.e., insufficient information or not in the field of interest).

Data collection and quality (risk of bias) assessment

Two reviewers independently extracted data from a data-collection form, including study title, name of author(s), publication year, country, study design, patients and demographics, interventions, timing of corticosteroid administration, and outcomes.

Risk of bias was assessed by using the Revised Cochrane risk of bias tool (RoB 2) for RCTs and GRACE (Good Research for Comparative Effectiveness) ver. 5.1 checklist for observational studies.[26,27]

Any discrepancies were resolved by discussion and consensus between two authors. In the case of a sustained disagreement, a third expert acted as a moderator.

Outcomes and intervention groups

Primary outcome was the favorable final outcome, which we defined as cerebral performance category 1 or 2 at the time of discharge or 1-year survival after CA. The secondary outcome was the survival to discharge. The timing of corticosteroid administration was categorized as administration prior to CA, during CPR, or post-CA. We classified all the cases in which corticosteroids were administered after ROSC into the post-CA group regardless of whether corticosteroids were administered during CPR or not. This was be-

cause our interest lay in whether corticosteroids were administered post-CA, when the patient is in a sepsis-like condition. Every "prior to CA" classification was based on the subject's history before the CA event in the observational study, not the timing of the actual intervention in the trial.

Statistical analysis

We calculated and presented odds ratios (ORs) with 95% confidence intervals (CIs) for each outcome and each intervention. Only the number of subjects who achieved ROSC was used as the overall count of each intervention group for the studies that enrolled whole CA patients, in order to match the conditions with those enrolled only post-CA patients. A frequentist random-effects network meta-analysis was conducted using multivariate meta-analysis and meta-regression.[28,29] The design-by-treatment model was used to confirm the consistency of the entire network.[30] The node-splitting method was also used to check the inconsistency between direct and indirect estimates of the effect.[31,32] Ranking probabilities were estimated by the surface under the cumulative ranking curve for each outcome. We used STATA ver. 17 (Stata Corp., College Station, TX, USA) for statistical calculations.

RESULTS

Study search results and characteristics

We identified 6,173 records through a database search and screened 5,018 after duplicates were removed (Fig. 1). Among these, 114 articles went through a full-text review, and 10 articles were finally selected by applying the inclusion criteria, including one case-control study,[33] five RCTs,[10-13,15] one prospective cohort study,[18] and three retrospective cohort studies (Supplementary Table 1).[14,16,17] Characteristics of the included studies are summarized in Table 1.[10-18,33]

Risk of bias in the enrolled studies

Most of the trials and all the cohort studies reviewed in the current meta-analysis were classified as those with good quality, according to RoB 2 assessment, except one trial with a high risk of bias (Supplementary Fig. 1). One case-control study was classified as a study with an uncertain risk of bias because of its lack of detailed information.[33]

Favorable final outcome

Nine studies were included for the analysis to determine the favorable final outcome.[10-13,15-18,33] The network plot of the analysis for the favorable final outcome is depicted in Fig. 2A. We did not find any inconsistency in the entire network (Supplementary Table 2). There were significant positive effects on the favorable final outcome associated with corticosteroids administered during CPR (OR, 1.29; 95% CI, 1.11–1.51) and administered post-CA (OR, 1.47; 95% CI, 1.30–1.66), compared to the control protocol (no corticosteroid administration), while there was a negative effect
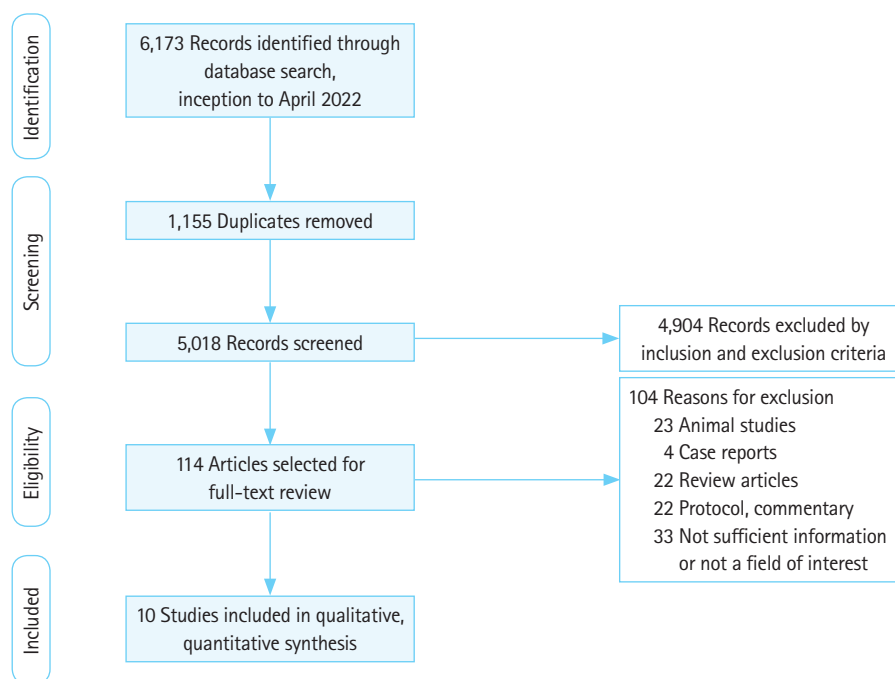

Fig. 1. PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) flowchart and study selection.

Table 1. Characteristics of the enrolled studies

Study	Design	Subject	Administration timing	ROSC	GNO	SD	S1Y	Enrolled analysis
Schwitzer et al.[33] (1983)	CC	OHCA	During CPR	7	3	3	NA	SD, FFO
Paris et al.[15] (1984)	RCT	OHCA	During CPR	6	0	0	0	SD, FFO
Tsai et al.[18] (2007)	PC	OHCA	During CPR	46	1	9	NA	SD, FFO
Mentzelopoulos et al.[13] (2009)	RCT	IHCA	During CPR and post-CA	66	NA	11	NA	SD, FFO
Mentzelopoulos et al.[12] (2013)	RCT	NS	During CPR and post-CA	200	25	31	NA	SD, FFO
Bolvardi et al.[11] (2016)	RCT	NS	During CPR	15	1	NA	NA	FFO
Tsai et al.[17] (2016)	RC	NS	Prior to CA and during CPR	NA	NA	5,471	4,891	SD, FFO
Niimura et al.[14] (2017)	RC	OHCA and IHCA	Post-CA	NA	NA	253	NA	SD
Tsai et al.[16] (2019)	RC	NS	Prior to CA and post-CA	NA	NA	3,552	2,204	SD, FFO
Andersen et al.[10] (2021)	RCT	IHCA	During CPR	186	38	NA	NA	SD, FFO

ROSC, return of spontaneous circulation; GNO, good neurologic outcome; SD, survival to discharge; S1Y, 1-year survival; CC, case-control study; OHCA, out-of-hospital cardiac arrest; CPR, cardiopulmonary resuscitation; NA, not available; FFO, favorable final outcome; RCT, randomized control trial; PC: prospective cohort study; IHCA, in-hospital cardiac arrest; CA, cardiac arrest; NS, not specified; RC, retrospective cohort study.
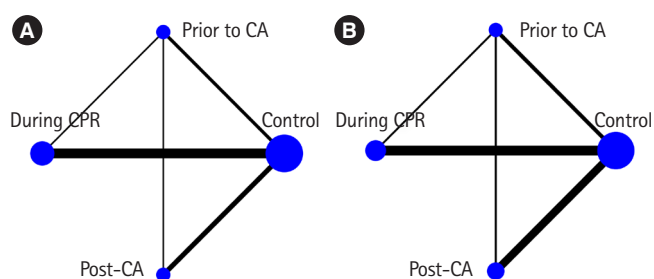

Fig. 2. Network maps of (A) the analysis for the favorable final outcome and (B) the survival to discharge. Network plot includes history of recent corticosteroid use prior to cardiac arrest (CA), corticosteroid administration during cardiopulmonary resuscitation (CPR), and corticosteroid administration post-CA.

Table 2. Ranking of the timing of corticosteroid administration

Variable	Favorable final outcome			Survival to discharge		
	SUCRA	PrBest	Mean rank	SUCRA	PrBest	Mean rank
Placebo	33.3	0	3.0	40.1	0.9	2.8
Prior to CA	0	0	4.0	20.2	1.1	3.4
During CPR	70.0	10.1	1.9	44.8	10.7	2.7
Post-CA	96.6	89.9	1.1	94.9	87.3	1.2

SUCRA, surface under the cumulative ranking curve; PrBest, probability for the best timing; CA, cardiac arrest; CPR, cardiopulmonary resuscitation.

associated with their administration prior to CA (OR, 0.70; 95% CI, 0.64–0.77). Corticosteroids administered during CPR and post-CA showed a significant positive effect on the favorable final outcome compared to that administered prior to CA (OR, 1.85; 95% CI, 1.56–2.18 and OR, 2.10; 95% CI, 1.85–2.39, respectively). Corticosteroids administration post-CA did not have a significant effect on the favorable final outcome compared to administration during CPR (OR, 1.14; 95% CI, 0.94–1.38) (Fig. 3).[10-13,15-18,33] Post-CA was shown as the best timing for corticosteroid administration to achieve a favorable final outcome with a probability of 89.9% (Table 2).

Survival to discharge

Nine studies were included for the analysis of survival to discharge.[10,12-18,33] The network plot of the analysis for the survival to discharge is depicted in Fig. 2B. We found an inconsistency in the network (P < 0.001), and the node-splitting method detected an inconsistency between corticosteroid administration prior to CA

and during CPR (Supplementary Table 3). There was a significant positive effect on survival to discharge when corticosteroids were administered post-CA compared to the control protocol (OR, 1.82; 95% CI, 1.02–3.27), while there was no significant effect associated with administration prior to CA (OR, 0.83; 95% CI, 0.45–1.55) or during CPR (OR, 1.02; 95% CI, 0.51–2.05). Corticosteroid administration post-CA showed a significant positive effect on survival to discharge compared to administration prior to CA (OR, 2.19; 95% CI, 1.04–4.63), but no significant effect of administration during CPR existed (OR, 1.23; 95% CI, 0.55–2.72). Corticosteroid administration post-CA did not have a significant effect on survival to discharge compared to administration during CPR (OR, 1.79; 95% CI, 0.72–4.47) (Fig. 4).[10,12-16,18,33] Post-CA was shown as the best timing for corticosteroid administration to achieve survival to discharge with a probability of 87.3% (Table 2).

DISCUSSION

To the best of our knowledge, this was the first network meta-analysis ever performed regarding the effect of corticosteroid administration on CA. The results of our current network meta-analysis suggest that the timing of corticosteroid administration may
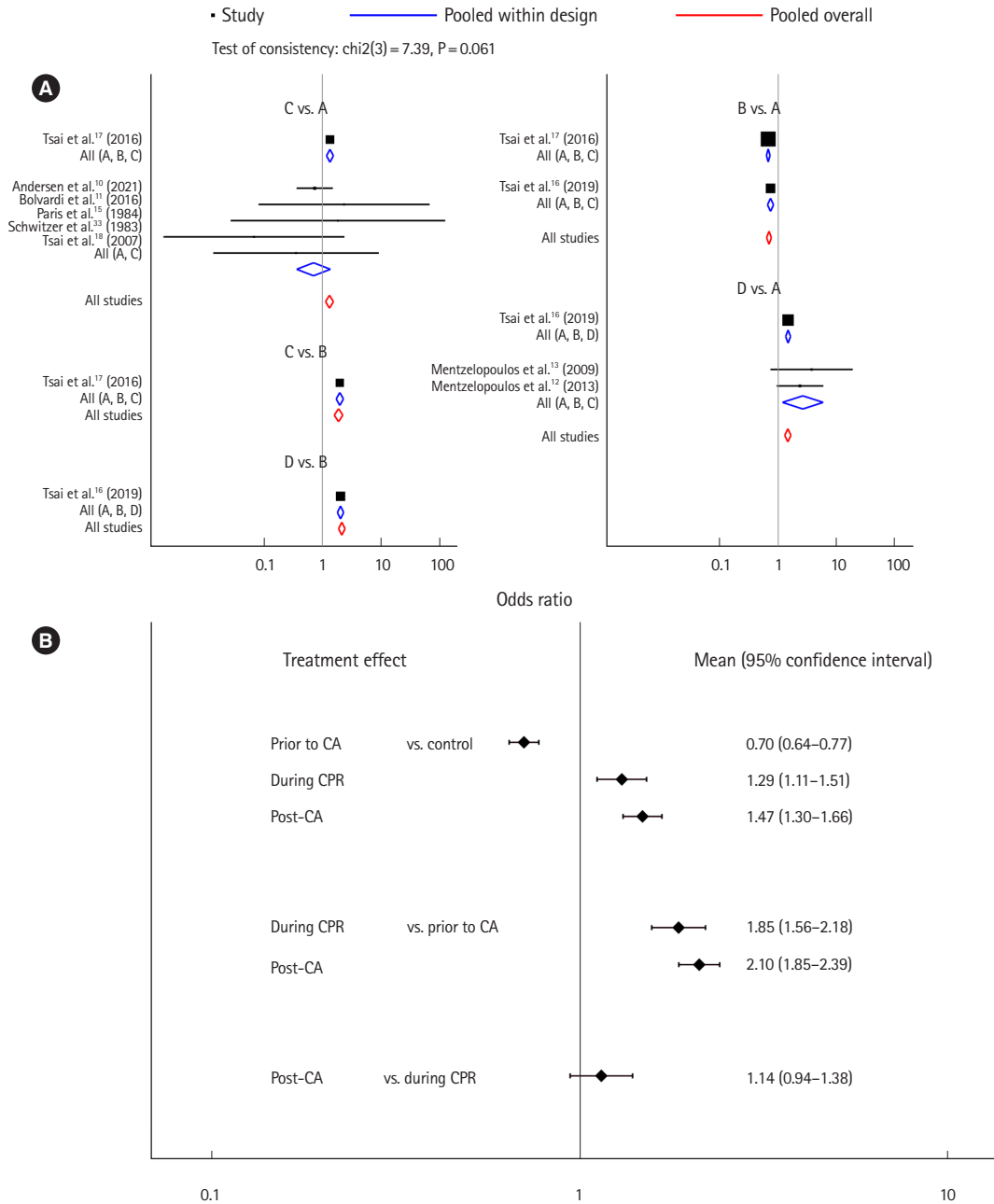
Fig. 3. The analysis for the favorable final outcome. (A) Forest plot and (B) interval plot. In treatment arm: A, control; B, history of recent corticosteroid use prior to cardiac arrest (CA); C, corticosteroid administration during cardiopulmonary resuscitation (CPR); and D, corticosteroid administration post-CA.

affect the outcome of CA patients. They also suggest that the discrepancy among the results of previous clinical studies assessing the effect of corticosteroid administration on CA may be due to differences in the study setting regarding the timing of administration. We can assume that the discrepancy among the meta-analyses that enrolled those studies could be due to differences in the setting of enrolled studies in each meta-analysis.

CA is a devastating medical condition that leads to high socio-

economic costs from which only a small portion of patients can achieve meaningful recovery. Its poor prognosis results from global cerebral ischemia-reperfusion injury, systemic inflammatory response, activation of the apoptotic pathway, free radical production, and myocardial injury.[34-37] It also causes disorders of the immune system and hemodynamic instability with increased levels of endotoxins and cytokines, i.e., a so-called sepsis-like syndrome.[34] One study showed that the serum cortisol level was de-
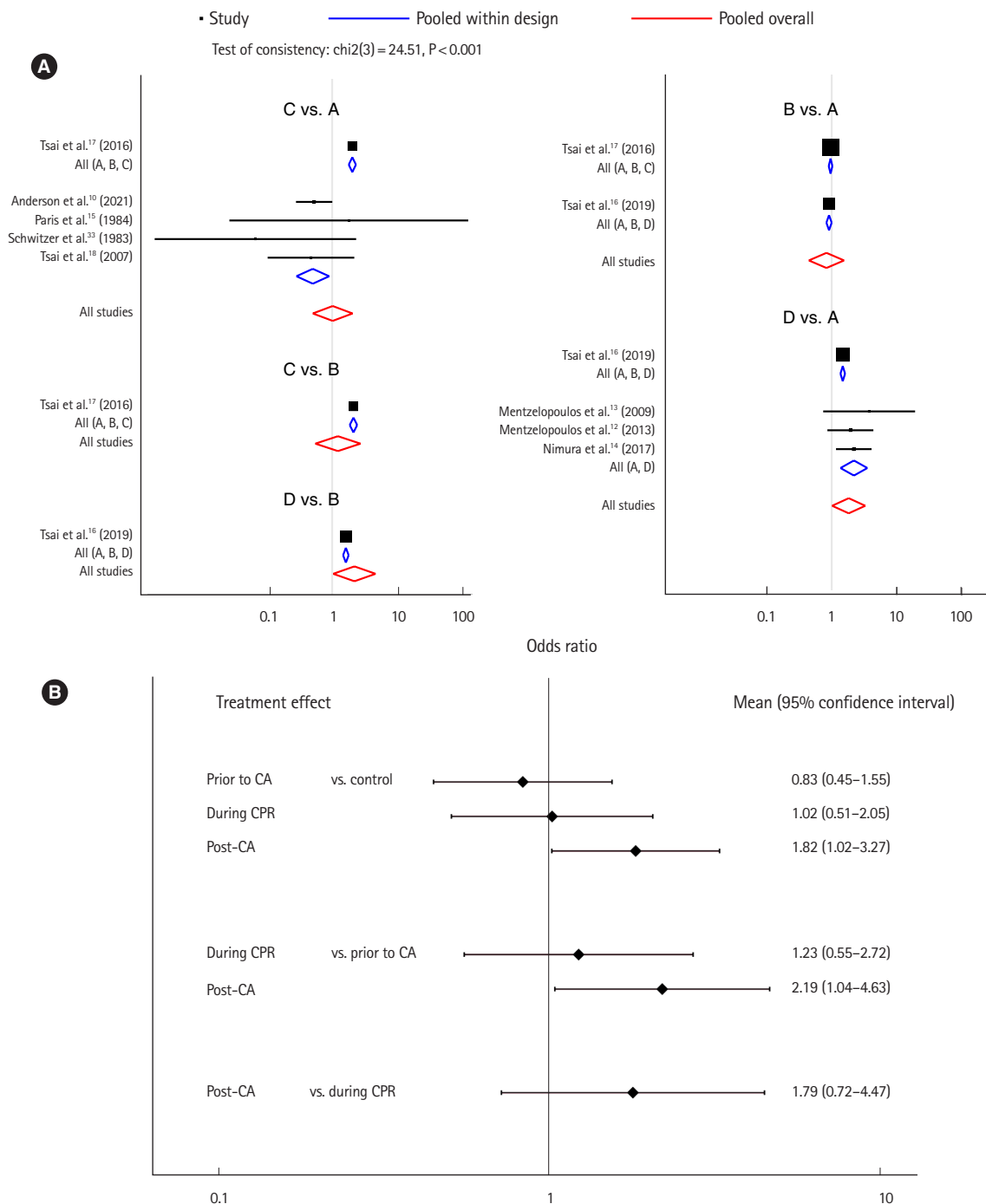
Fig. 4. The analysis for survival to discharge. (A) Forest plot and (B) interval plot. In treatment arm: A, control; B, history of recent corticosteroid use prior to cardiac arrest (CA); C, corticosteroid administration during cardiopulmonary resuscitation (CPR); and D, corticosteroid administration post-CA.

creased after ROSC and was associated with short-term survival.[38] These results initiated studies evaluating the effect of corticosteroid administration on CA. As a result, it was known that corticosteroid administration in CA improves cardiovascular stability through control of the systemic inflammatory response and improvement of the vascular response to vasopressors by lower-

ing the catecholamine reuptake; it also helps to reduce myocardial and cerebral injury by reducing oxidative stress.[39-43]

Many clinical studies that assessed the effect of corticosteroids on CA showed inconsistent results; therefore, the use of corticosteroids for the treatment of CA is recommended in a limited fashion with uncertain value in current guidelines for CPR.[3] Our current

study suggests that the timing of administration may be an important factor in the effect of corticosteroids on CA. Based on this, further research directly comparing the effects on CA according to the timing of corticosteroid administration is necessary to establish a clinical guideline for corticosteroid use during CA treatment.

One of the most interesting findings in our research was that the outcomes of CA were significantly worse in patients to whom corticosteroids were administered prior to CA compared to controls; otherwise, the outcomes were significantly better than control group outcomes if corticosteroids were administered during CPR or post-CA. Considering that patients administered corticosteroids prior to CA, when included in our network meta-analysis, included those in whom a history of corticosteroid administration was identified during a short-term period before the CA event, it is likely that this group included chronic corticosteroid users. Adrenal insufficiency associated with chronic corticosteroid use may explain the worse prognosis in this group.[44] However, this result would better be accepted as a phenomenon showing that the prognosis is worse than that of the control group in a situation where relative adrenal insufficiency is suspected rather than as a recommendation for the timing of administration, considering that the "prior to CA" classification in original studies was not based on an actual timing of intervention but instead was a result of retrospective observation.

The results of our study also suggest that the effect of corticosteroids on CA may be better when they are administered after CA than when administered during CPR. We failed to identify a statistically significant difference in the indirect comparison of the effects of corticosteroids administered during CPR and those administered after CA, although there were consistent tendencies showing a relative superiority of their administration after CA. However, the results of the ranking probability tests for both outcomes support the better effect of corticosteroid administration after CA. Moreover, corticosteroid administration during CPR did not even show a significant difference in the comparison with the control protocol for survival to discharge. Considering the sepsis-like condition of post-CA patients, timely administration of corticosteroids targeting this condition may explain the better effect. Recent studies showing that corticosteroid administration after cerebral ischemia-reperfusion reduces neurological damage through the inhibition of apoptosis and inflammatory responses may also support this finding.[45,46]

The results of the inconsistency test using the design-by-treatment model showed that the analysis of the primary outcome met the assumptions about consistency and homogeneity to some extent.[28] Therefore, it showed that our result from the analysis for the favorable final outcome could be reliable. On the other hand,

the result of the analysis for survival to discharge, the secondary outcome, which did not meet those assumptions, may be difficult to accept. However, it could be adopted as a supportive result for the analysis of the favorable final outcome, considering that the results of both analyses showed a similar trend.

Our network meta-analysis had a few limitations. First, we used a newly defined outcome measure, the favorable final outcome, as a primary outcome, instead of a widely used one, such as survival with good neurologic recovery. This was because information regarding neurologic recovery was not available in two studies with the largest effect sizes.[16,17] Those studies used 1-year survival as an outcome measure reflecting long-term prognosis. Hence, we had to define a new outcome measure that can reflect the ultimate prognosis as much as possible, which was a combination of survival with good neurologic function and 1-year survival. Second, the design and quality of the studies included in our analysis vary compared to their number, and this may compromise the consistency and homogeneity, which are important for the reliability of a network meta-analysis. Hence, caution in adopting the results of our study despite our efforts to overcome this limitation, such as the use of design-by-treatment model or publication bias assessment, should be taken. Third, the analysis for the secondary outcome, survival to discharge, did not meet the consistency assumption of a network meta-analysis. Hence, one should be careful to adopt the result of the analysis for survival to discharge, especially for the comparison between corticosteroids administered prior to CA and those administered during CPR, which showed inconsistency. Fourth, we also classified studies with co-administered drugs such as vasopressin into the corticosteroid administration group, as in most of the prior pairwise meta-analyses dealing with the effect of corticosteroids on CA[19,21,22]; therefore, the possibility of errors due to differences in the intervention regimen cannot be excluded. Hence, caution is required in adopting our results because there might be an interaction of co-administered drugs that affects the efficacy of corticosteroids on CA. Fifth, our post-CA classification included cases of corticosteroid administration during CPR as well as after ROSC. Therefore, we could not rule out the possibility that our results, which showed that post-CA could be a better timing of corticosteroid administration, were attributable to the effect of repeated administration. Finally, our results did not contain enough direct comparisons for checking inconsistencies. Further research to directly compare the effects of corticosteroid administration according to the timing of administration is necessary.

In conclusion, the timing of corticosteroid administration may be an important factor for the prognosis of CA. Corticosteroids administration post-CA and during CPR may have beneficial ef-

fects on the outcomes of CA compared to the control protocol. Corticosteroids administration post-CA may have better efficacy than administration during CPR. Also, our data suggest that corticosteroid use prior to CA may be associated with poor outcomes.

SUPPLEMENTARY MATERIAL

Supplementary Table 1. Search strategy
Supplementary Table 2. Pairwise and loop inconsistency estimates of the analysis for the favorable final outcome
Supplementary Table 3. Pairwise and loop inconsistency estimates of the analysis for the survival to discharge
Supplementary Fig. 1. Risk of bias assessments.
Supplementary materials are available at https://doi.org/10.15441/ceem.22.371.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

FUNDING

None.

AUTHOR CONTRIBUTIONS

Conceptualization: TNC; Data curation: all authors; Formal analysis: all authors; Investigation: all authors; Methodology: TNC; Project administration: TNC; Resources: TNC; Software: TNC; Supervision: TNC; Validation: TNC; Visualization: all authors; Writing–original draft: all authors; Writing–review & editing: TNC.
All authors read and approved the final manuscript.

ORCID

Youngchan Pyo https://orcid.org/0000-0002-8128-1929
Tae Nyoung Chung https://orcid.org/0000-0003-3537-4136

REFERENCES

1. Holmberg MJ, Ross CE, Fitzmaurice GM, et al. Annual incidence of adult and pediatric in-hospital cardiac arrest in the United States. Circ Cardiovasc Qual Outcomes 2019;12:e005580.
2. Virani SS, Alonso A, Aparicio HJ, et al. Heart disease and stroke statistics: 2021 update: a report from the American Heart Association. Circulation 2021;143:e254-743.
3. Panchal AR, Bartos JA, Cabanas JG, et al. Part 3: adult basic and advanced life support: 2020 American Heart Association Guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation 2020;142(16_suppl_2):S366-468.
4. Oh J, Cha KC, Lee JH, et al. 2020 Korean Guidelines for Cardiopulmonary Resuscitation. Part 4: adult advanced life support. Clin Exp Emerg Med 2021;8(S):S26-40.
5. Hekimian G, Baugnon T, Thuong M, et al. Cortisol levels and adrenal reserve after successful cardiac arrest resuscitation. Shock 2004;22:116-9.
6. Miller JB, Donnino MW, Rogan M, Goyal N. Relative adrenal insufficiency in post-cardiac arrest shock is under-recognized. Resuscitation 2008;76:221-5.
7. Tavakoli N, Bidari A, Shams Vahdati S. Serum cortisol levels as a predictor of neurologic survival in successfully resuscitated victims of cardiopulmonary arrest. J Cardiovasc Thorac Res 2012;4:107-11.
8. Tsai MS, Huang CH, Wang CH, et al. Post-cardiac arrest hydrocortisone use ameliorates cardiac mitochondrial injury in a male rat model of ventricular fibrillation cardiac arrest. J Am Heart Assoc 2021;10:e019837.
9. Varvarousi G, Stefaniotou A, Varvaroussis D, Xanthos T. Glucocorticoids as an emerging pharmacologic agent for cardiopulmonary resuscitation. Cardiovasc Drugs Ther 2014;28:477-88.
10. Andersen LW, Isbye D, Kjaergaard J, et al. Effect of vasopressin and methylprednisolone vs placebo on return of spontaneous circulation in patients with in-hospital cardiac arrest: a randomized clinical trial. JAMA 2021;326:1586-94.
11. Bolvardi EH, Seyedi ES, Seyedi MO, Abbasi AA, Golmakani RE, Ahmadi KO. Studying the influence of epinephrine mixed with prednisolone on the neurologic side effects after recovery in patients suffering from cardiopulmonary arrest. Biomed Pharmacol J 2016;9:209-14.
12. Mentzelopoulos SD, Malachias S, Chamos C, et al. Vasopressin, steroids, and epinephrine and neurologically favorable survival after in-hospital cardiac arrest: a randomized clinical trial. JAMA 2013;310:270-9.
13. Mentzelopoulos SD, Zakynthinos SG, Tzoufi M, K et al. Vasopressin, epinephrine, and corticosteroids for in-hospital cardiac arrest. Arch Intern Med 2009;169:15-24.
14. Niimura T, Zamami Y, Koyama T, et al. Hydrocortisone administration was associated with improved survival in Japanese patients with cardiac arrest. Sci Rep 2017;7:17919.
15. Paris PM, Stewart RD, Deggler F. Prehospital use of dexamethasone in pulseless idioventricular rhythm. Ann Emerg Med 1984;13:1008-10.

16. Tsai MS, Chuang PY, Huang CH, et al. Postarrest steroid use may improve outcomes of cardiac arrest survivors. Crit Care Med 2019;47:167-75.

17. Tsai MS, Chuang PY, Yu PH, et al. Glucocorticoid use during cardiopulmonary resuscitation may be beneficial for cardiac arrest. Int J Cardiol 2016;222:629-35.

18. Tsai MS, Huang CH, Chang WT, C et al. The effect of hydrocortisone on the outcome of out-of-hospital cardiac arrest patients: a pilot study. Am J Emerg Med 2007;25:318-25.

19. Liu B, Zhang Q, Li C. Steroid use after cardiac arrest is associated with favourable outcomes: a systematic review and meta-analysis. J Int Med Res 2020;48:300060520921670.

20. Saghafi F, Bagheri N, Salehi-Abargouei A, Sahebnasagh A. Efficacy of combination triple therapy with vasopressin, steroid, and epinephrine in cardiac arrest: a systematic review and meta-analysis of randomized-controlled trials. J Intensive Care 2022;10:5.

21. Shah K, Mitra AR. Use of corticosteroids in cardiac arrest: a systematic review and meta-analysis. Crit Care Med 2021;49: e642-50.

22. Wongtanasarasin W, Krintratun S. Clinical benefits of corticosteroid administration during adult cardiopulmonary resuscitation: a systemic review and meta-analysis. World J Crit Care Med 2021;10:290-300.

23. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71.

24. Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Ann Intern Med 2015;162:777-84.

25. Chung TN, Pyo Y. Effect of corticosteroids during and after cardiac arrest: a systematic review and network meta-analysis of administration timings. Record no.: CRD42022331973 [Internet]. York: PROSPERO; 2022 [cited 2022 Aug 2]. Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022331973.

26. Dreyer NA, Bryant A, Velentgas P. The GRACE checklist: a validated assessment tool for high quality observational studies of comparative effectiveness. J Manag Care Spec Pharm 2016; 22:1107-13.

27. Higgins JP, Thomas J, Chandler J, et al. Cochrane handbook for systematic reviews of interventions version 6. 3 (updated February 2022) [Internet]. London: Cochrane; 2022 [cited 2022 Aug 2]. Available from: www.training.cochrane.org/handbook.

28. White IR, Barrett JK, Jackson D, Higgins JP. Consistency and inconsistency in network meta-analysis: model estimation using multivariate meta-regression. Res Synth Methods 2012;3: 111-25.

29. White IR. A network meta-analysis. Stata J 2015;15:951-85.

30. Higgins JP, Jackson D, Barrett JK, Lu G, Ades AE, White IR. Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. Res Synth Methods 2012;3: 98-110.

31. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557-60.

32. Lu G, Ades AE. Assessing evidence inconsistency in mixed treatment comparisons. J Am Stat Assoc 2006;101:447-59.

33. Schwitzer KW. Dexamethasone therapy in bradyasystolic prehospital cardiac arrest, abstract. Ann Emerg Med 1983;12: 252.

34. Adrie C, Adib-Conquy M, Laurent I, et al. Successful cardiopulmonary resuscitation after cardiac arrest as a "sepsis-like" syndrome. Circulation 2002;106:562-8.

35. Tsai MS, Huang CH, Tsai CY, et al. Ascorbic acid mitigates the myocardial injury after cardiac arrest and electrical shock. Intensive Care Med 2011;37:2033-40.

36. Hou X, Li C, Gu W, Guo Z, Yin W, Zhang D. Effect of Shenfu on inflammatory cytokine release and brain edema after prolonged cardiac arrest in the swine. Am J Emerg Med 2013;31:1159-64.

37. Nolan JP, Neumar RW, Adrie C, et al. Post-cardiac arrest syndrome: epidemiology, pathophysiology, treatment, and prognostication: a scientific statement from the International Liaison Committee on Resuscitation; the American Heart Association Emergency Cardiovascular Care Committee; the Council on Cardiovascular Surgery and Anesthesia; the Council on Cardiopulmonary, Perioperative, and Critical Care; the Council on Clinical Cardiology; the Council on Stroke. Resuscitation 2008;79:350-79.

38. Schultz CH, Rivers EP, Feldkamp CS, et al. A characterization of hypothalamic-pituitary-adrenal axis function during and after human cardiac arrest. Crit Care Med 1993;21:1339-47.

39. Oppert M, Schindler R, Husung C, et al. Low-dose hydrocortisone improves shock reversal and reduces cytokine levels in early hyperdynamic septic shock. Crit Care Med 2005;33:2457-64.

40. van Leeuwen HJ, van der Bruggen T, van Asbeck BS, Boereboom FT. Effect of corticosteroids on nuclear factor-κB activation and hemodynamics in late septic shock. Crit Care Med 2001;29:1074-7.

41. Liakopoulos OJ, Teucher N, Muhlfeld C, et al. Prevention of

TNFα-associated myocardial dysfunction resulting from cardiopulmonary bypass and cardioplegic arrest by glucocorticoid treatment. Eur J Cardiothorac Surg 2006;30:263-70.

42. Hall ED. Neuroprotective actions of glucocorticoid and non-glucocorticoid steroids in acute neuronal injury. Cell Mol Neurobiol 1993;13:415-32.

43. Katz L, Vaagenes P, Safar P, Diven W. Brain enzyme changes as markers of brain damage in rat cardiac arrest model. Effects of corticosteroid therapy. Resuscitation 1989;17:39-53.

44. Sahebnasagh A, Nejad PS, Salehi-Abargouei A, Dehghani MH, Saghafi F. A characterization of cortisol level and adrenal reservation in human cardiopulmonary arrest: systematic review and meta-analysis. Syst Rev 2021;10:266.

45. Sun WH, He F, Zhang NN, Zhao ZA, Chen HS. Time dependent neuroprotection of dexamethasone in experimental focal cerebral ischemia: the involvement of NF-κB pathways. Brain Res 2018;1701:237-45.

46. Xin N, Lu J, Zhou Y, Cheng Y. Dexamethasone Protects against ischaemic brain injury via inhibiting the pAkt signalling pathway through increasing Hap1. Neurotox Res 2021;39:191-7.