Hosp Pharm 2014;49(3):232–236

www.hospital-pharmacy.com
doi: 10.1310/hpj4903-232

Cardiovascular Therapeutics

Role of Corticosteroids During Cardiopulmonary Bypass

Judith L. Kristeller, PharmD, BCPS[*]*; Arthur Jankowski, PharmD*[†]*; and Travis Reinaker, PharmD*[‡]

Abstract

Corticosteroids are commonly used in the peri-operative setting for patients undergoing cardiac surgery with cardiopulmonary bypass (CPB). The inflammatory response to CPB is associated with organ dysfunction and increased mortality. Corticosteroids reduce biochemical inflammatory markers associated with CPB, however the impact on clinical outcomes is mixed. The purpose of this article is to evaluate the evidence of changes in clinical outcomes associated with the peri-operative administration of corticosteroids in patients undergoing cardiac surgery with CPB. Randomized, placebo-controlled trials and meta-analyses were reviewed for evidence evaluating the impact of corticosteroids on clinical outcomes including mortality, myocardial infarction, atrial fibrillation (AF), duration of intubation, length of intensive care unit (ICU) or hospital stay, hyperglycemia, and gastrointestinal complications. Most of the relevant studies are underpowered to assess major clinical outcomes. Although corticosteroids likely reduce the risk of AF, this needs to be evaluated when used in addition to or in lieu of other anti-arrhythmic agents. Evidence does not equivocally support the use of corticosteroids to improve clinical outcomes in cardiac surgery patients.

Key Words—cardiac surgery, cardiopulmonary bypass, corticosteroids

Hosp Pharm—*2014;49(3):232–236*

Although commonly used in the peri-operative setting of cardiopulmonary bypass (CPB), corticosteroids have limited evidence of improving clinical patient outcomes. The anti-inflammatory effects of corticosteroids are well studied, but they do not necessarily correlate with improved clinical outcomes. In 2004, guidelines from the American Heart Association recommended "liberal prophylactic use" based on the reduction in systemic inflammation, however corticosteroids are no longer recommended in the 2011 guidelines.[1,2]

During CPB, blood is exposed to foreign materials causing the systemic release of inflammatory markers including tumor necrosis factor-α and interleukin-6.[3] These substances have known cardio-depressant effects, although most patients recover normally postoperatively. For some, however, the inflammatory response can cause hypotension and organ dysfunction. Inflammation also causes impaired gas exchange and interstitial damage throughout the lungs.[4] Thus CPB-induced inflammation could lead to worse outcomes including myocardial ischemia, cardiac arrhythmias, and prolonged respiratory failure.

The physiologic effects of corticosteroids can predict the potential benefits and risks. Through multiple mechanisms, corticosteroids minimize the CPB-induced inflammatory response. They decrease capillary wall permeability, preventing migration of inflammatory mediators into the systemic circulation. Corticosteroids also prevent the release of intracellular cytokines and subsequent adhesion to cell surfaces. Conversely, hyperglycemia, a well-known side effect, could contribute to impaired immune function and delays in wound healing. Renal effects can cause electrolyte and fluid imbalances, leading to hemodynamic changes and cardiac instability. Gastrointestinal effects of corticosteroids could cause

[*]Associate Professor, Department of Pharmacy Practice, Wilkes University, Wilkes-Barre, Pennsylvania; [†]Clinical Pharmacist, Geisinger Medical Center, Danville, Pennsylvania; [‡]Critical Care Resident, Department of Pharmacy, York Hospital, York, Pennsylvania. Corresponding author: Judith L. Kristeller, PharmD, BCPS, Department of Pharmacy Practice, Wilkes University, 84 W. South Street, SLC 336, Wilkes-Barre, PA 18766; phone: 570-408-4272; fax: 570-408-7729; e-mail: Judith.kristeller@wilkes.edu

nausea, vomiting, and ulcerative bleeding. While the anti-inflammatory effects are desirable, evidence of improved clinical outcomes is needed before recommending corticosteroids in the peri-operative setting. This review will summarize evidence from randomized controlled studies and meta-analyses that evaluate the impact of peri-operative use of corticosteroids on clinical outcomes.

METHODS

In addition to the Cochrane Review,[5] we searched MEDLINE and EMBASE for randomized controlled trials comparing corticosteroids to placebo in adult patients undergoing cardiac surgery. To search for applicable studies, medical subject headings, including steroid, corticosteroid, glucocorticoid, dexamethasone, prednisolone, prednisone, methylprednisolone, or hydrocortisone, were cross-referenced with cardiac surgery, cardiopulmonary bypass, and heart surgery. Studies or meta-analyses evaluating clinical outcomes including mortality, myocardial infarction, atrial fibrillation (AF), duration of intubation, intensive care unit (ICU) or hospital stay, hyperglycemia, and gastrointestinal complications were considered in this review. For the purpose of this review and similar to other authors,[6] the total daily dose of corticosteroid was classified as low (less than 1,000 mg/day), moderate (1,000-10,000 mg/day), or high dose (more than 10,000 mg/day) of hydrocortisone equivalents.

RESULTS AND DISCUSSION

Mortality and Myocardial Infarction

There are no studies powered to assess mortality or myocardial infarction as primary outcomes. After considering 49 studies including more than 3,200 patients, the Cochrane Review found no benefit of corticosteroids in improving mortality in patients undergoing cardiac surgery (odds ratio [OR], 1.06; 95% confidence interval [CI], 0.58-1.95).[5] The lack of a mortality benefit persists after evaluating subgroups of studies using low doses only, as well as a combination of moderate to high doses of corticosteroids. Similarly, meta-analyses do not suggest any reduction in the risk of myocardial infarction associated with corticosteroids.[5,7]

The recently published Dexamethasone for Cardiac Surgery (DECS) study was a large, multi-center, randomized controlled trial.[8] In this study, 4,494 patients undergoing cardiac surgical procedures using CPB were randomized to receive dexamethasone 1 mg/kg (moderate dose) or placebo. There was no statistically significant difference in the composite primary outcome of death, myocardial infarction, stroke, renal failure, or respiratory failure within 30 days of randomization between the corticosteroid or placebo groups (7% vs 8.5%; relative risk [RR], 0.83; 95% CI, 0.67-1.01; $P = .07$). Unfortunately, after all exclusions, only 20% of eligible patients were randomized, thus limiting the application of the results.

Atrial Fibrillation

AF occurs in 30% to 50% of patients following cardiac surgery and is associated with an increased incidence of stroke and prolonged length of stay. Several trials found that corticosteroids reduce the incidence of new onset AF following cardiac surgery, illustrating a correlation between inflammation and AF. Corticosteroids were evaluated as part of a regimen including beta blockers to prevent AF in 2 studies.[9,10] One randomized, double-blinded, multicenter study of 241 cardiac surgery patients evaluated a low dose of hydrocortisone (100 mg following surgery, then 100 mg every 8 hours for 3 days).[9] Although a power analysis was not described, the incidence of new onset AF during the first 84 hours after cardiac surgery was 48% in the placebo group compared to 30% in the hydrocortisone group (hazard ratio, 0.54; 95% CI, 0.36-0.82; $P = .01$). These results were consistent with a smaller but similar study, also using low dosing of corticosteroids (1,000 mg hydrocortisone prior to CPB followed by dexamethasone 4 mg every 6 hours for 1 day postoperatively).[10]

Two meta-analyses evaluated the dose-dependent effect of corticosteroids on postoperative AF.[6,11] To avoid significant heterogeneity, Marik and colleagues excluded studies using doses less than 200 mg/day and more than 10,000 mg/day of hydrocortisone equivalents.[11] For the 2 studies that evaluated corticosteroids at these low and high ends of the dosing range, neither found significant benefit of corticosteroids in preventing AF.[12,13] Within the remaining doses, corticosteroids reduced the incidence of AF compared to placebo by nearly 70% (OR, 0.32; 95% CI, 0.21-0.50; $P < .0001$) with insignificant heterogeneity between studies. Another meta-analysis showed a more modest reduction in the incidence of AF (25% vs 35%; RR, 0.74; 95% CI, 0.63-0.86; $P < .01$), and no differences between low, medium, or high dose strata.[6] Most of the studies included in either meta-analysis did not describe the use of perioperative beta-blocker therapy.

Even though the optimal regimen is unclear, evidence suggests a beneficial effect of corticosteroids in

preventing postoperative AF in patients undergoing cardiac surgery. Further study is needed to determine if corticosteroids will further reduce the risk of AF when used in combination with or in lieu of other agents commonly used. Additionally, the beneficial risk reduction of AF needs to be weighed against the potential side effects of corticosteroids.

Respiratory Failure

Prolonged intubation following cardiac surgery is associated with an increased risk of infection and a prolonged ICU length of stay. Evidence concerning the effects of corticosteroids on postoperative duration of intubation is conflicting and varies based on the corticosteroid doses studied. One randomized controlled trial of 90 patients undergoing elective cardiac surgery demonstrated prolonged time to extubation in patients receiving a cumulative high dose of 60 mg/kg methylprednisolone compared to those receiving 30 mg/kg or placebo (7.5 ± 2.7 vs 5.9 ± 2.2 vs 5.7 ± 2.3 hours; $P = .04$) despite no changes in fluid balance, patient weight, or pulmonary hemodynamic variables between the groups.[14] Similarly, a meta-analysis found that high doses of corticosteroids were associated with a prolonged intubation by 2.1 hours (95% CI, 1.76-2.52; $P < .01$, without significant heterogeneity).[6]

While high doses may contribute to respiratory failure, evidence about moderate doses is conflicting. Three different randomized, placebo-controlled studies of moderate doses (Liakopoulos et al used methylprednisolone 15 mg/kg/day once prior to CPB; Oliver et al used methylprednisolone 1 g before induction then dexamethasone 4 mg every 6 hours for 4 doses; Yasser et al used dexamethasone 1 mg/kg at induction then 0.5 mg/kg 8 hours later) demonstrated no difference in ventilation time.[15-17] On the contrary, another study of moderate dose (dexamethasone 0.6 mg/kg after induction) in 236 patients undergoing elective surgery showed that whereas duration of ventilation was not statistically different between groups (11.6 ± 11.9 hours dexamethasone vs 13.1 ± 13.8 hours placebo, $P = .074$), the corticosteroid group had a larger percentage of patients with a short (6 hours or less) intubation time (10% vs 26%, $P = .02$) compared to placebo.[18] Most recently, analysis of secondary outcomes in the DECS study described above demonstrated a reduction in respiratory failure, defined as the need for mechanical ventilation for at least 48 hours postoperatively, in the group receiving a moderate dose corticosteroid (dexamethasone 1 mg/kg) compared to placebo (3% vs 4.3%; RR, 0.69; 95% CI, 0.51-0.94; $P = .02$).[8] Although there was little difference in the median time to weaning mechanical ventilation, the average time was higher in the placebo group (11 vs 14.3 hours; $P < .001$) due to a higher number of patients requiring prolonged (>24 hours) intubation in the placebo group (3.4 vs 4.9%; P value not reported).

One factor associated with prolonged duration of intubation is shivering,[18] which can be prevented with dexamethasone.[19] Given that shivering patients are commonly treated with opioid analgesics, a reduction in ventilator time may be related to a reduced need for opioids. One study showed a higher incidence of short (6 hours or less) intubation time in patients without shivering compared to those with shivering (23.6% vs 6.3%; $P = .009$).[18] The potential use of dexamethasone in preventing shivering, reducing opioid use, and shortening the duration of intubation needs further study.

Results of the Cochrane meta-analysis show no overall difference in time of mechanical ventilation with significant heterogeneity (weighted mean difference, -1.8 minutes; 95% CI, -11.5 to 7.8).[5] Taken together, these results suggest the potential for a dose-dependent effect of corticosteroids prolonging intubation at high doses. Considering the conflicting evidence and results from the meta-analyses, corticosteroids may exert a positive effect on duration of intubation, but adequately powered controlled studies would be needed to confirm this.

Length of Stay

Length of ICU or hospital stay has not been a primary outcome in any clinical trial, however they have been addressed in 3 meta-analyses with similar reductions for both parameters.[5-7] The Cochrane meta-analysis found a significant reduction in ICU stay by about 2 hours (95% CI, -2.8 to -1.8 hours) and hospital stay by about half a day (95% CI, -0.65 to -0.15). The results of the 3 meta-analyses are similar, and they all had significant heterogeneity between studies as a result of studies spanning 3 decades, including different corticosteroids at varying dosage regimens in different risk categories of patients. Therefore, any improvement in length of stay needs to be interpreted cautiously.

Hyperglycemia and Infectious Complications

Hyperglycemia is a well-known side effect of corticosteroids. Although changes in blood glucose concentrations represent a biochemical outcome, hyperglycemia is associated with impaired T-cell

function and an increase in patient morbidity and mortality following cardiac surgery.[20] As expected, several clinical trials of corticosteroids have shown an increase in the incidence of hyperglycemia as well as higher insulin requirements.[15,17,18,21,22] The Cochrane analysis did not find an increased risk of infection in 15 studies including infectious complications as secondary outcomes.[5] Given that no study has been sufficiently powered to assess this outcome, there remains a theoretical increased susceptibility to infection and poor wound healing associated with hyperglycemia that has not been elucidated in the existing studies.

Gastrointestinal Complications

Corticosteroids are well known to increase the risk of peptic ulcers and other gastrointestinal complications. Since 1990, only 3 small studies involving a total of 204 patients have included gastrointestinal bleeding as a secondary outcome.[10,12,23] In the Cochrane meta-analysis, these 3 studies showed a trend of increased gastrointestinal bleeding in the corticosteroid groups (OR, 2.85; 95% CI, 0.4-20.36), although significant heterogeneity existed between the studies ($I^2 = 35\%$).[5]

Ongoing Research

One large study is ongoing that is powered to assess major clinical outcomes. The steroids in cardiac surgery trial (SIRS) will enroll 7,500 adult patients and compare methylprednisolone 250 mg during induction and also prior to CPB (500 mg total) versus placebo. The primary endpoint is mortality at 30 days with secondary outcomes of myocardial infarction or mortality at 30 days and mortality at 6 months.

CONCLUSION

Although biochemical evidence of the anti-inflammatory effect of corticosteroids is promising, existing clinical trials have not demonstrated an improvement in mortality or a reduction in myocardial infarction. The beneficial effect of preventing AF with corticosteroids needs to be evaluated in combination with or in lieu of established agents. Any potential effect on shortening the duration of respiratory failure is promising, but requires further study. The result from meta-analyses about shorter length of stay is encouraging, but significant heterogeneity including different drugs, doses, and study design limit the application of this outcome. The risks of corticosteroids related to hyperglycemia or gastrointestinal effects also require further study. The use of corticosteroids in patients undergoing cardiac surgery with CPB has not been shown to improve clinical outcomes beyond the standard of care in adequately powered randomized controlled trials and is not recommended.

REFERENCES

1. Hillis LD, Smith PK, Anderson JL, et al. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Developed in collaboration with the American Association for Thoracic Surgery, Society of Cardiovascular Anesthesiologists, and Society of Thoracic Surgeons. *J Am Coll Cardiol.* 2011;58(24):e123-e210.

2. Eagle KA, Guyton RA, Davidoff R, et al. ACC/AHA 2004 guideline update for coronary artery bypass graft surgery: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1999 Guidelines for Coronary Artery Bypass Graft Surgery). *Circulation.* 2004;110(14):e340-e437.

3. Chaney MA. Corticosteroids and cardiopulmonary bypass: A review of clinical investigations. *Chest.* 2002;121(3):921-931.

4. Asimakopoulos G, Smith PL, Ratnatunga CP, Taylor KM. Lung injury and acute respiratory distress syndrome after cardiopulmonary bypass. *Ann Thorac Surg.* 1999;68(3): 1107-1115.

5. Dieleman JM, van PJ, van DD, et al. Prophylactic corticosteroids for cardiopulmonary bypass in adults. *Cochrane Database Syst Rev.* 2011;(5):CD005566.

6. Ho KM, Tan JA. Benefits and risks of corticosteroid prophylaxis in adult cardiac surgery: A dose-response meta-analysis. *Circulation.* 2009;119(14):1853-1866.

7. Whitlock RP, Chan S, Devereaux PJ, et al. Clinical benefit of steroid use in patients undergoing cardiopulmonary bypass: A meta-analysis of randomized trials. *Eur Heart J.* 2008;29(21):2592-2600.

8. Dieleman JM, Nierich AP, Rosseel PM, et al. Intraoperative high-dose dexamethasone for cardiac surgery: A randomized controlled trial. *JAMA.* 2012;308(17):1761-1767.

9. Halonen J, Halonen P, Jarvinen O, et al. Corticosteroids for the prevention of atrial fibrillation after cardiac surgery: A randomized controlled trial. *JAMA.* 2007;297(14): 1562-1567.

10. Prasongsukarn K, Abel JG, Jamieson WR, et al. The effects of steroids on the occurrence of postoperative atrial fibrillation after coronary artery bypass grafting surgery: A prospective randomized trial. *J Thorac Cardiovasc Surg.* 2005;130(1):93-98.

11. Marik PE, Fromm R. The efficacy and dosage effect of corticosteroids for the prevention of atrial fibrillation after cardiac surgery: A systematic review. *J Crit Care.* 2009;24(3): 458-463.

12. Chaney MA, Nikolov MP, Blakeman B, Bakhos M, Slogoff S. Pulmonary effects of methylprednisolone in patients undergoing coronary artery bypass grafting and early tracheal extubation. *Anesth Analg*. 1998;87(1):27-33.

13. Halvorsen P, Raeder J, White PF, Almdahl SM, Nordstrand K, Saatvedt K, Veel T. The effect of dexamethasone on side effects after coronary revascularization procedures. *Anesth Analg*. 2003;96(6):1578-1583.

14. Chaney MA, Durazo-Arvizu RA, Nikolov MP, Blakeman BP, Bakhos M. Methylprednisolone does not benefit patients undergoing coronary artery bypass grafting and early tracheal extubation. *J Thorac Cardiovasc Surg*. 2001;121(3):561-569.

15. Liakopoulos OJ, Schmitto JD, Kazmaier S, et al. Cardiopulmonary and systemic effects of methylprednisolone in patients undergoing cardiac surgery. *Ann Thorac Surg*. 2007;84(1):110-118.

16. Oliver WC, Jr, Nuttall GA, Orszulak TA, et al. Hemofiltration but not steroids results in earlier tracheal extubation following cardiopulmonary bypass: A prospective, randomized double-blind trial. *Anesthesiology*. 2004;101(2):327-339.

17. Yasser MA, Elmistekawy E, El-Serogy H. Effects of dexamethasone on pulmonary and renal functions in patients undergoing CABG with cardiopulmonary bypass. *Semin Cardiothorac Vasc Anesth*. 2009;13(4):231-237.

18. Yared JP, Starr NJ, Torres FK, et al. Effects of single dose, postinduction dexamethasone on recovery after cardiac surgery. *Ann Thorac Surg*. 2000;69(5):1420-1424.

19. Yared JP, Starr NJ, Hoffmann-Hogg L, et al. Dexamethasone decreases the incidence of shivering after cardiac surgery: A randomized, double-blind, placebo-controlled study. *Anesth Analg*. 1998;87(4):795-799.

20. van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. *N Engl J Med*. 2001;345(19):1359-1367.

21. Fillinger MP, Rassias AJ, Guyre PM, et al. Glucocorticoid effects on the inflammatory and clinical responses to cardiac surgery. *J Cardiothorac Vasc Anesth*. 2002;16(2):163-169.

22. Yared JP, Bakri MH, Erzurum SC, et al. Effect of dexamethasone on atrial fibrillation after cardiac surgery: Prospective, randomized, double-blind, placebo-controlled trial. *J Cardiothorac Vasc Anesth*. 2007;21(1):68-75.

23. Whitlock RP, Young E, Noora J, Farrokhyar F, Blackall M, Teoh KH. Pulse low dose steroids attenuate post-cardiopulmonary bypass SIRS; SIRS I. *J Surg Res*. 2006;132(2):188-194. ■