The Inflammatory Response to Cardiac Surgery With Cardiopulmonary Bypass: Should Steroid Prophylaxis Be Routine?

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Cardiac surgery with cardiopulmonary bypass (CPB) triggers a vigorous systemic inflammatory response characterized by early and late phases involving both the humoral and cellular pathways. Steroids dampen the immune response to CPB in a multimodal fashion. Perioperative steroid prophylaxis offers the possibility to manipulate the inflammatory response to CPB for outcome benefit. In adult cardiac surgery with CPB, steroids have been rigorously evaluated in multiple randomized clinical trials and meta-analyses. In summary, steroid therapy in this setting can significantly reduce perioperative morbidity. Although the outcome benefits of steroids in adult cardiac surgery with CPB are apparent, multicenter large randomized trials are in progress to determine whether these agents should become a routine component of an anti-inflammatory approach to optimize clinical outcome. The current application of steroids in adult CPB is highly variable, with the highest use likely in high-risk settings such as deep hypothermic circulatory arrest. In pediatric cardiac surgery with CPB, steroids are widely used despite a limited evidence base compared with adult CPB. Recent multicenter observational trials have paved the way for larger more definitive randomized trials targeted to high-risk pediatric CPB including the neonatal period. In conclusion, steroids offer significant potential to improve meaningful clinical outcomes after cardiac surgery with CPB. The results of 2 landmark multicenter randomized trials in adult CPB likely will determine whether steroids should become routine therapy in this setting. It is likely that similar multicenter trials in pediatric CPB will be launched in the near future.

KEY WORDS: steroids, systemic inflammatory response syndrome, contact phase, fibrinolysis, coagulation cascade, complement, ischemia/reperfusion, endotoxin, interleukins, atrial fibrillation, mortality, bleeding, transfusion, intensive care unit, length of stay, randomized clinical trial, meta-analysis, cardiopulmonary bypass, clinical trials registry, Dexamethasone for Cardiac Surgery trial, Steroids In CaRdiac Surgery trial

CARDIAC SURGERY with cardiopulmonary bypass (CPB) triggers a vigorous systemic inflammatory response. This set of inflammatory cascades is characterized by early and late phases that involve both the humoral and cellular pathways. The details of this inflammatory activation are reviewed in the first section of this article as a platform for understanding the dampening effects of steroids on the immune response to CPB. The perioperative management of the inflammatory response to CPB is important because it can improve organ protection and the consequent clinical outcomes after cardiac surgery with CPB in both adults and children.

In adult cardiac surgery with CPB, steroids have been evaluated rigorously in multiple randomized clinical trials and meta-analyses. The results from these trials are discussed in detail in the second section of this article. In summary, steroid therapy in this setting can significantly reduce perioperative morbidity. Although the outcome benefits of steroids in adult cardiac surgery with CPB are apparent, multicenter large randomized trials are in progress to determine whether these agents should become a routine component of an anti-inflammatory approach to optimize clinical outcome. The current application of steroids in adult CPB is highly variable, with the highest use likely in high-risk settings such as deep hypothermic circulatory arrest.

In pediatric cardiac surgery with CPB, steroids are used widely despite a limited evidence base compared with adult CPB. Recent trials have paved the way for larger more definitive randomized trials targeted to high-risk pediatric CPB including the neonatal period. The recent evidence for steroids in pediatric CPB is reviewed in the third section of this article. In conclusion, the current state-of the-art techniques are summarized with conclusions drawn when possible.

STEROIDS AND THE INFLAMMATORY RESPONSE TO CPB

Inflammation is a tissue response to protect itself from harm, with activation of both the humoral and cellular inflammatory pathways. Cardiac surgery with CPB disrupts the array of homeostatic mechanisms to generate a systemic inflammatory response syndrome (SIRS).[1-3] If SIRS is not contained, it may progress to clinically relevant organ dysfunction with consequent perioperative morbidity and even mortality.[2,3] This inflammatory response to CPB typically has an early and late

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phase. The early phase is characterized by the contact of blood with nonendothelialized surfaces. The late phase is characterized by ischemia/reperfusion and endotoxemia. Each phase in CPB-induced SIRS has a set of specific components that merits further discussion. This phase-specific discussion is followed by a review of the effects of steroids on the early and late phases of the inflammatory response to CPB.

The Early Phase of the Inflammatory Response to CPB

The early phase of SIRS caused by CPB results from contact activation of the blood elements because of exposure to the CPB circuit. Contact activation is characterized by a humoral and a cellular response. The humoral response involves the activation of 5 plasma protein systems, namely the contact system, the intrinsic coagulation cascade, the extrinsic coagulation cascade, the fibrinolytic system, and complement.[3-5] The cellular response involves the activation of 5 cell groups, namely endothelial cells, neutrophils, monocytes, lymphocytes, and platelets.[3-5]

Activation of the contact protein cascade generates activated factor XII, which has 3 important consequences: activation of the intrinsic coagulation system, bradykinin release, and kallikrein formation. Bradykinin causes vasodilation and nonvascular smooth muscle contraction. Kallikrein has multiple widespread effects, including neutrophil activation and augmentation of fibrinolysis.[5] The extrinsic coagulation system is principally triggered by vessel trauma during cardiac surgery. The net result of the activated coagulation cascades is the generation of thrombin, which plays a prominent role in the response to CPB, including platelet activation and the stimulation of fibrinolysis.[2] Complement activation takes place principally by means of the alternate pathway.[3] The activated complement cascade causes capillary permeability, vasodilation, and activation of neutrophils and platelets.

Activation of the vascular endothelium is secondary to its contact with blood-borne agonists such as thrombin, complement proteins, and leukocyte-derived cytokines such as interleukins and tumor necrosis factor. Leukocyte activation during CPB is induced by multiple mechanisms including kallikrein and complement activation.[1-5] Neutrophil activation occurs most rapidly, followed by a slower activation over hours of monocytes and lymphocytes. The factors that trigger platelet activation during CPB include tissue trauma, CPB circuit adhesion, hypothermia, complement proteins, leukotrienes derived from activated neutrophils, plasmin, and thrombin.[3-6]

The Late Phase of the Inflammatory Response to CPB

The early phase of the inflammatory response wanes with increasing CPB duration because protein adsorption renders the CPB circuit more biocompatible to reduce the contact activation of blood. The late phase of CPB-induced SIRS then takes effect because of 2 major processes: the reperfusion of ischemic tissue and the release of endotoxins from intestinal microflora.[3] Reperfusion of the ischemic myocardium after unclamping of the ascending aorta during CPB results in an inflammatory reaction characterized by endothelial injury, neutrophil activation, interleukin release, and activation of the complement and coagulation protein cascades.[7,8] Because the specialized CPB technique of deep hypothermic circulatory arrest involves multiple ischemic vascular territories, the inflammatory response is even greater during reperfusion.[8]

Endotoxin is a lipopolysaccharide derived from the cell wall of intestinal gram-negative bacteria and is a potent trigger of SIRS.[9] Endotoxemia during cardiac surgery with CPB occurs mainly because of enteric mucosal ischemia that allows translocation of bacterial products.[10,11] Endotoxin triggers the inflammatory response during CPB by multiple processes including the activation of the complement and the release of proinflammatory cytokines.

The Effects of Steroids on the Inflammatory Response to CPB

The effects of steroid therapy to attenuate SIRS caused by CPB have been documented in multiple studies for more than 20 years.[12,13] Steroids significantly attenuate the CPB-induced surges in proinflammatory mediators such as interleukin-1, interleukin-6, interleukin-8, tumor necrosis factor, leukotrienes, and endotoxin.[11-13] Furthermore, steroid exposure significantly augments the surge in anti-inflammatory mediators during CPB such as interleukin-4 and interleukin-10.[12-15] Steroid therapy has also been shown in multiple studies to attenuate complement and leukocyte activation.[12,13]

It is important to note that the clinical significance of the suppression of SIRS caused by CPB may also depend on patient age, with at least 1 recent study suggesting that the inflammatory response to CPB in infants may not necessarily contribute substantially to perioperative morbidity.[16] Further trials are indicated to explore the modulating effects of perioperative factors in SIRS caused by CPB such as extremes of age, genetic polymorphisms, baseline organ dysfunction, and procedural complexity. Furthermore, the effects of steroids in SIRS caused by CPB could be further clarified in future trials with respect to steroid type, dose, and optimal dosing regimen.

Steroids suppress the inflammatory response to CPB both in the early and late phases. The burning question is whether this suppression of SIRS during CPB significantly improves meaningful perioperative outcomes. The current evidence concerning this question is now reviewed for both adult and pediatric cardiac surgery with CPB to assess whether steroid therapy in these settings has clinical significance.

STEROIDS AND OUTCOME AFTER ADULT CARDIAC SURGERY WITH CPB

The Status of the Current Evidence

Although there have been multiple randomized clinical trials examining outcomes in this setting, they have been limited by design issues such as surrogate endpoints, sample size, dosage selection, clinical confounders, and the lack of safety data.[17-19] In an effort to minimize these limitations, these trials recently have been pooled in a series of 5 meta-analyses.[20-24]

In the first meta-analysis (N = 3,205: 44 randomized trials), steroid exposure significantly reduced atrial fibrillation (relative risk = 0.71; 95% confidence interval, 0.59-0.87), perioperative bleeding (weighted mean difference = −99.6 mL; 95%

confidence interval, −149.9 to −49.3), and the stay in the intensive care unit (weighted mean difference = −0.23 days; 95% confidence interval −0.40 to −0.07).[20] Furthermore, although there was also a trend toward reduced mortality (relative risk = 0.73; 95% confidence interval, 0.45-1.18), there were no adverse events associated with steroid exposure.[20] The second meta-analysis (N = 3,323: 50 randomized trials) showed that a steroid dose below 1,000 mg of hydrocortisone significantly decreased the risk of atrial fibrillation (relative risk = 0.74; 95% confidence interval, 0.63-0.86; $p < 0.01$), the length of intensive care unit stay (weighted mean difference = −0.37 days; 95% confidence interval, −0.21 to −0.52; $p < 0.01$), and the length of hospital stay (weighted mean difference = −0.66 days; 95% confidence interval, −0.77 to −1.25; $p = 0.03$).[21] Furthermore, steroid exposure significantly increased the risk of perioperative hyperglycemia requiring insulin therapy (relative risk = 1.49; 95% confidence interval, 1.11-2.01; $p = 0.01$) with no increased risk of infection (relative risk = 0.93; 95% confidence interval, 0.61-1.41; $p = 0.73$).[21]

The third meta-analysis pooled randomized double-blind trials (N = 1,974: 31 trials).[22] There was significant variation in steroid regimens across the included trials as follows: methylprednisolone (51.4%), dexamethasone (34.3%), hydrocortisone (5.7%), methylprednisolone and dexamethasone (5.7%), and prednisolone (2.9%).[22] In this analysis, steroid prophylaxis reduced atrial fibrillation (odds ratio = 0.56; 95% confidence interval, 0.44-0.72; $p < 0.0001$), blood loss (mean difference = −204.2 mL; 95% confidence interval, −287.4 to −121; $p < 0.0001$), the length of the intensive care unit stay (mean difference = −6.6 hours; 95% confidence interval, −10.5 to −2.7; $p = 0.0007$), and the length of the hospital stay (mean difference = −0.8 days; 95% confidence interval, −1.4 to −0.2; $p = 0.01$).[22] Steroid exposure had no significant effect on mortality, the duration of mechanical ventilation, surgical exploration for bleeding, and infection.[22] The fourth meta-analysis (N = 1,046: 7 randomized trials) showed that steroid prophylaxis significantly decreased the risk of atrial fibrillation (odds ratio = 0.42; 95% confidence interval, 0.27-0.68; $p = 0.0004$).[23] When the analysis was limited to moderate-dose steroid therapy (defined as 200-1,000 mg of hydrocortisone per day), the protective effect of steroids against atrial fibrillation in this setting was strongest (odds ratio = 0.32; 95% confidence interval, 0.21-0.50; $p < 0.000\ 01$).[23]

The fifth and most recent meta-analysis (N = 3,615: 54 randomized trials) showed that steroid exposure had no effect on mortality (odds ratio = 1.12; 95% confidence interval, 0.65-1.92), myocardial infarction (odds ratio = 0.95; 95% confidence interval, 0.57-1.60), or pulmonary complications (odds ratio = 0.83; 95% confidence interval, 0.49-1.40).[24] In this analysis, steroid therapy significantly reduced atrial fibrillation (odds ratio = 0.60; 95% confidence interval, 0.46-0.78) but increased the risk of gastrointestinal bleeding (odds ratio = 2.84; 95% confidence interval, 0.40-20.36).[24]

The Status of Future Evidence

This recent set of meta-analyses strongly suggests that steroid prophylaxis in adult cardiac surgery with CPB reduces perioperative morbidity with a minimal risk of harm. The overall conclusion at this point is that this perioperative intervention should be studied in large adequately powered multicenter trials powered to assess important clinical outcomes (estimated N: 5,000-10,000). Two such randomized controlled trials are in progress: the SIRS (Steroids In CaRdiac Surgery) and the DECS (Dexamethasone for Cardiac Surgery) trials (full details available at http://www.clinicaltrials.gov).

The SIRS trial is a Canadian multicenter placebo-controlled randomized trial that aims to enroll 7,500 adults undergoing cardiac surgery with CPB. The steroid regimen is as follows: 250 mg of methylprednisolone on induction of anesthesia followed by another 250 mg upon the initiation of CPB. The primary outcome is mortality at 30 days. This trial was commenced in 2007, and, as of April 18, 2012, 2,940 patients have been enrolled at 65 medical centers in 134 countries (Dr R. Whitlock [principal investigator of the SIRS trial], personal communication, April 2012). The pilot SIRS trial was published in 2006.[19] Using the same methylprednisolone regimen, this randomized placebo-controlled trial (N = 60: single center) showed that a prophylactic low-dose steroid reduced bleeding, hemodynamic instability, duration of mechanical ventilation, and length of intensive care unit stay (all had $p < 0.05$).[14]

The DECS trial is a Dutch multicenter placebo-controlled randomized trial with a targeted total enrollment of 4,500 adults undergoing cardiac surgery with CPB. The steroid regimen chosen for this trial was dexamethasone at a dose of 1 mg/kg administered upon the induction of anesthesia. It should be noted that 500 mg of methylprednisolone (the SIRS trial steroid total dose) is equivalent to 100 mg of dexamethasone, the dose a 222.2-lb adult would receive in the DECS trial. The primary outcome measure is a composite of mortality, myocardial infarction, stroke, renal failure, and prolonged mechanical ventilation (defined as >48 hours) at 30 days. This trial was commenced in May 2006 and completed enrollment in November 2011. The preliminary findings of the DECS trial were presented on April 28, 2001, in Boston, MA, at the 34th Annual Meeting of the Society of Cardiovascular Anesthesiologists. The definitive findings will be released after completion of the peer-review process (Dr D. van Dijk [principal investigator of the DECS trial], personal communication, April 2012).

The findings of these well-designed randomized trials will likely determine the future indications for steroid prophylaxis in adult cardiac surgery with CPB. The evidence base for steroids in this setting has progressed steadily since 1970.[12,13] The 1970s saw the publication of the first human trials with conflicting results. The 1980s ushered in the mechanistic studies that systematically explored the effects of steroids on the inflammatory response to CPB, with defined biochemical endpoints as described earlier.[12,13] The 1990s saw the advent of the trials that began to consider meaningful clinical outcomes, ultimately leading to the set of 5 meta-analyses 20 years later.[20-24] The landmark multicenter SIRS and DECS trials are in progress and should definitively address the burning question; namely, whether steroid prophylaxis significantly improves meaningful clinical outcomes after adult cardiac surgery with CPB. In the interim, there continues to be considerable use of steroids in adult CPB. The review of this is based on the current published literature including adult CPB with deep hypothermic circulatory arrest.

The Current Use of Steroids in Adult CPB

The use of steroids in adult cardiac surgery is highly variable in procedures requiring CPB with or without deep hypothermic circulatory arrest. In a recent survey of Canadian cardiac surgeons (N = 119: 72% response rate) about the choice of prophylactic strategy for postoperative atrial fibrillation, the penetration of β-blockade, amiodarone, and steroids was 58%, 19%, and 1% despite high-quality evidence.[25] The investigators concluded that larger higher-quality clinical trials are still indicated to change practice. In an accompanying editorial, the commentator concluded that the cardiac community should take atrial fibrillation more seriously and implement proven prophylactic strategies on a more systematic and routine basis.[26] This lack of penetration of effective prophylactic strategies also was shown recently in a survey of cardiothoracic units across the UK.[27]

The 2004 American College of Cardiology/American Heart Association guidelines for coronary artery bypass graft surgery recommend prophylactic steroid therapy in the setting of CPB.[28] Since 2004, the evidence supporting this perioperative intervention has only grown stronger, as discussed in the 5 recent meta-analyses.[20-24] Despite this evidence base, the 2011 update to these guidelines did not address the role of prophylactic steroid therapy in coronary artery bypass graft surgery with CPB.[29] The level of evidence supporting steroids in cardiac surgery with CPB is level A (ie, at the level of multiple randomized trials and meta-analyses). The recommendation for this perioperative intervention is likely at least class II (ie, prophylactic steroid therapy can be considered for cardiac surgery with CPB because the clinical benefit likely outweighs any risks). If the results of the SIRS and DECS trials are strongly positive, this intervention could be upgraded to a class I intervention (ie, steroid therapy for cardiac surgery with CPB should be implemented routinely because the clinical benefits far outweigh the clinical risks).

This approach to steroid prophylaxis recently has been highlighted as part of a multimodal perioperative approach to address SIRS induced by CPB.[30] In this multimodal strategy, aminocaproic acid is used for the dampening of fibrinolysis, steroids for attenuating the release of proinflammatory mediators, and intraoperative ultrafiltration to remove inflammatory mediators that are produced in response to CPB.[30] The authors designed this multimodal attack on SIRS after an extensive literature review with a chosen steroid regimen of 500 mg of methylprednisolone administered after anesthetic induction. This steroid dose has been shown to reduce inflammatory biomarkers without excessive hyperglycemia.[19] Although the 3 components of this elegant immunosuppressive design have been evaluated individually, their synergistic perioperative impact has not yet been evaluated extensively in clinical trials.

In cardiac surgery with CPB and deep hypothermic circulatory arrest, perioperative steroid therapy is an established component of perioperative management despite a limited evidence base.[8,31] Prophylactic steroid therapy has been shown to improve cerebral protection in CPB with deep hypothermic circulatory arrest in both animal and human stuides.[8-32] Considerable uncertainity still exists for steroids in this high-risk perioperative setting.[33] In a survey of the Association of Cardiac Anesthesiologists throughout the UK to assess the selection of pharmacologic agents for cerebral protection in deep hypothermic circulatory arrest, steroids commonly were used despite a consensus that the supporting evidence was limited.[34] Further trials are indicated in this area of adult CPB to assess the clinical outcome effects of steroid therapy given the ongoing high perioperative risk.[35,36]

STEROIDS AND OUTCOME AFTER PEDIATRIC CARDIAC SURGERY WITH CPB

The evidence base related to prophylactic steroids for pediatric cardiac surgery with CPB is far less extensive than in adults. A 2007 Cochrane meta-analysis to evaluate the clinical effects of steroids in this setting included 4 randomized trials (N = 127).[37] This meta-analysis reported weak evidence showing that steroid exposure reduces peak core temperature (weighted mean difference = −0.20°C; 95% confidence interval, −1.16 to 0.77), the duration of mechanical ventilation (weighted mean difference = −0.63 hours; 95% confidence interval, −4.02 to 2.75), and the length of stay in the intensive care unit (weighted mean difference = −0.50 hours; 95% confidence interval, −1.41 to 0.41).[37] The evidence after this 2007 analysis will now be reviewed.

In neonatal cardiac surgery with CPB, 2 small randomized trials recently have been published.[38,39] The first trial randomized 20 neonates undergoing the arterial switch operation for correction of transposition of the great arteries to dexamethasone (1 mg/kg, administered 4 hours before CPB) or placebo.[38] In this trial, steroid exposure significantly reduced proinflammatory cytokines, peak troponin release, and the requirement for perioperative dobutamine.[38] The second trial randomized 76 neonates undergoing various cardiac procedures with CPB to double-dose methylprednisolone (30 mg/kg administered 8 hours before CPB and then again in the CPB prime) or single-dose methylprednisolone (30 mg/kg in the CPB prime).[39] The incidence of low-cardiac-output syndrome, inotropic requirement, intensive care unit stay, and total hospital stay was similar between groups. Double-dose methylprednisolone therapy exacerbated renal dysfunction as reflected by a higher serum creatinine ($p = 0.03$) and postoperative diuresis ($p = 0.05$).[39]

A recent massive multicenter observational study (N = 3,180 neonates undergoing cardiac surgery with CPB: 25 centers, 2004-2008) showed a significant variation in steroid use (ie, 38% received no steroid therapy, 28% received steroid therapy on the day of surgery only, 12% received steroid therapy only the day before surgery, and 22% received steroid therapy the day before and the day of surgery).[40] A multivariate analysis showed no significant mortality or length of stay benefit because of steroid exposure. The risk of perioperative infection was higher with steroid exposure in the lower operative risk cohorts (odds ratio = 2.6; 95% confidence interval, 1.3-5.2).[40] The investigators concluded that the a large randomized trial is required in neonatal cardiac surgery with CPB to evaluate the clinical effects of steroid exposure in this setting.[40]

A similar multicenter observational study in pediatric heart surgery with CPB (N = 46,730: 38 centers, 2003-2008) showed no difference in mortality (odds ratio = 1.13; 95% confidence interval, 0.98-1.30) because of steroid therapy.[41] In this important study, 54% of the cohort had exposure to steroids. Furthermore, multivariate analysis was adjusted for the

propensity score, operative risk, and medical center characteristics. The operative risk was assessed by the Risks Adjustment in Congenital Heart Surgery (RACHS) system.[41,42] The RACHS method has 6 categories of mortality risk, with category 1 having the lowest risk and category 6 the highest risk.[43,44] In this contemporary analysis, steroid exposure was associated significantly with an increased length of stay (least square mean difference = 2.18 days; 95% confidence interval, 1.62-2.74), risk of infection (odds ratio = 1.27; 95% confidence interval, 1.10-1.46), and insulin administration (odds ratio = 2.45; 95% confidence interval, 2.24-2.67).[41] The morbidity associated with steroid exposure was most significant in RACHS categories 1 through 3.[41]

Based on this analysis, the clinical effects of steroids in pediatric cardiac surgery with CPB may depend on the perioperative risk. A recent single-center retrospective analysis of children (N = 221: 2004-2007) undergoing high-risk cardiac surgery with CPB was completed.[45] In this study, high-risk pediatric cardiac surgery was defined as an Aristotle score >10 (definitions and full details of this scoring system are available at http://www.aristotleinstitute.org).[46,47] Nonrandom assignment of steroid exposure was accounted for with propensity modeling. The steroid exposure rate was 61%, with a third of this cohort receiving preoperative steroids as well. Steroid therapy significantly reduced the chest tube output (−5.3 mL/kg, $p < 0.001$), and the length of stay both in the intensive care unit (−2.3 days, $p < 0.001$) and the hospital (−4.1 days, $p < 0.001$).[45] Furthermore, additional preoperative steroid exposure significantly reduced the duration of mechanical ventilation (−1.7 days *v* no steroids and −1.2 days *v* intraoperative steroids, $p = 0.002$). This trial suggests that the benefits of steroids in pediatric heart surgery with CPB are best detected in the high-risk cohorts.[45]

Although the use of steroids in pediatric CPB is more common than in adults, it remains highly variable, as already has been evident in recent multicenter observational trials.[40,41] An international survey of 36 pediatric centers with a cardiac surgical volume of more than 11,000 cases per year showed that 40% administered steroids routinely.[48] Indications for steroid therapy included surgeon preference, neonatal procedures, CPB time >2 hours, and CPB with deep hypothermic circulatory arrest. There was significant variation in steroid type, dosing, route, and timing of administration.[48] A recent survey of pediatric cardiac surgical centers in the UK and Ireland confirmed the widespread variations in steroid use as an anti-inflammatory modality.[49] The evidence from these trials shows the lack of conclusive evidence to guide clinical practice and supports the rationale for multicenter randomized trials to test the clinical effects of steroid therapy in pediatric cardiac surgery with CPB.[50,51]

The evidence from these recent trials clearly lays the groundwork for larger steroid trials in pediatric CPB. A thorough review of clinical trials registries revealed a large single-center double-blind randomized neonatal steroid trial that commenced in May 2012 (full details available at http://www.clincialtrials.gov with trial identifier NCT01579513). The target enrollment is 190, and the trial is scheduled for completion in June 2017. The primary endpoint is a clinical composite of any of the following before hospital discharge: death, cardiac arrest, extracorporeal membrane oxygenation, renal insufficiency (defined as creatinine more than twice normal), hepatic insufficiency (aminotransferases more than twice normal), and lactic acidosis (defined as serum lactate >5 mmol/L). The selected secondary endpoints include the duration of mechanical ventilation, intensive care stay, hospital length of stay, and neurodevelopmental outcome at 1 year. The chosen steroid regimen for this trial is intravenous methylprednisolone as a 30-mg/kg dose administered once during anesthetic induction. Although multicenter steroid trials are being planned in pediatric cardiac surgery, currently none has been indexed in a clinical trials registry (comprehensive survey of global clinical trials registries last done May 1, 2012).[45,46]

CONCLUSIONS

Cardiac surgery with CPB triggers a vigorous systemic inflammatory response characterized by early and late phases involving both humoral and cellular pathways. Steroids dampen the immune response to CPB in a multimodal fashion. Perioperative steroid prophylaxis offers the possibility in cardiac surgery with CPB to improve organ protection and consequent clinical outcomes in both adults and children.

In adult cardiac surgery with CPB, steroids have been evaluated rigorously in multiple randomized clinical trials and meta-analyses. In summary, steroid therapy in this setting can significantly reduce perioperative morbidity. Although the outcome benefits of steroids in adult cardiac surgery with CPB are apparent, multicenter large randomized trials are in progress to determine whether these agents should become a routine component of an anti-inflammatory approach to optimize clinical outcome. The current application of steroids in adult CPB is highly variable, with the highest use likely in high-risk settings such as deep hypothermic circulatory arrest.

In pediatric cardiac surgery with CPB, steroids are used widely despite a limited evidence base compared with adult CPB. Recent multicenter observational trials have paved the way for larger more definitive randomized trials targeted to high-risk pediatric CPB, including the neonatal period. In conclusion, steroids offer significant potential to improve meaningful clinical outcomes after cardiac surgery with CPB. The results of 2 landmark multicenter randomized trials in adult CPB likely will determine whether steroids should become routine therapy in this setting. It is likely that similar multicenter trials in pediatric CPB will be launched in the near future.

REFERENCES

1. Wan S, LeClerc JL, Vintcent JL: Inflammatory response to cardiopulmonary bypass: Mechanisms involved and possible therapeutic strategies. Chest 112:676-692, 1997

2. Levy JH, Tanaka KA: Inflammatory response to cardiopulmonary bypass. Ann Thorac Surg 75:S715-S720, 2003

3. Warren OJ, Smith AJ, Alexiou C, et al: The inflammatory response to cardiopulmonary bypass: Part I—Mechanisms of pathogenesis. J Cardiothorac Vasc Anesth 23:223-231, 2009

4. Day JRS, Taylor KM: The systemic inflammatory response syndrome and cardiopulmonary bypass. Int J Surg 3:129-140, 2005

5. Sainz IM, Pixley RA, Colman RW: Fifty years of research on the plasma kallikrein-kinin system: From protein structure and function to cell biology and in-vivo pathophysiology. Thromb Haemost 98:77-83, 2007

6. Paparella D, Yau TM, Young E: Cardiopulmonary bypass induced inflammation: Pathophysiology and treatment—An update. Eur J Cardiothorac Surg 21:232-244, 2002

7. Jennewein C, Paulus P, Zacharowski K: Linking inflammation and coagulation: Novel drug targets to treat organ ischemia. Curr Opin Anaesthesiol 24:375-380, 2011

8. Svyatets M, Tolani K, Zhang M, et al: Perioperative management of deep hypothermic circulatory arrest. J Cardiothorac Vasc Anesth 24:644-655, 2010

9. Opal SM: The host response to endotoxin, antipolysaccharide strategies, and the management of severe sepsis. Int J Med Microbiol 297:365-377, 2007

10. Rossi M, Sganga G, Mazzone M, et al: Cardiopulmonary bypass in man: Role of the intestine in a self-limiting inflammatory response with demonstrable bacterial translocation. Ann Thorac Surg 77: 612-618, 2004

11. Kats S, Schönberger JPAM, Brands R, et al: Endotoxin release in cardiac surgery with cardiopulmonary bypass: Pathophysiology and possible therapeutic strategies—An update. Eur J Cardiothorac Surg 39:451-458, 2011

12. Chaney MA: Corticosteroids and cardiopulmonary bypass: A review of clinical investigations. Chest 121:921-931, 2002

13. Whitlock RP, Rubens FD, Young E, et al: Pro: Steroids should be used for cardiopulmonary bypass. J Cardiothorac Vasc Anesth 19:250-254, 2005

14. Warren OJ, Watret AL, de Wit KL, et al: The inflammatory response to cardiopulmonary bypass: Part 2—Anti-inflammatory therapeutic strategies. J Cardiothorac Vasc Anesth 23:384-393, 2009

15. Ng CS, Wan S: Limiting inflammatory response to cardiopulmonary bypass: Pharmaceutical strategies. Curr Opin Pharmacol 12: 155-159, 2012

16. Allan CK, Newburger JW, McGrath E, et al: The relationship between inflammatory activation and clinical outcome after infant cardiopulmonary bypass. Anesth Analg 111:1244-1251, 2010

17. Sultzer CF, Mackensen B, Con GHP: Methylprednisolone is not indicated for patients during cardiopulmonary bypass. J Cardiothorac Vasc Anesth 19:255-258, 2005

18. Augoustides JG: Use of corticosteroids to prevent atrial fibrillation after cardiac surgery. JAMA 298:283, 2007

19. Whitlock RP, Young E, Noora J, et al: Pulse low dose steroids attenuate post-cardiopulmonary bypass SIRS: SIRS I. J Surg Res 132:188-194, 2006

20. 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 29:2592-2600, 2008

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

22. Cappablanca G, Rotunno C, de Luca T, et al: Protective effects of steroids in cardiac surgery: A meta-analysis of randomized trials. J Cardiothorac Vasc Anesth 25:156-165, 2011

23. Marik PE, Fromm RF: The efficacy and dosage effect of corticosteroids for the prevention of atrial fibrillation after cardiac surgery: A systematic review. J Crit Care 24:458-463, 2009

24. Dieleman JM, van Paasen J, van Dijk D, et al: Prophylactic corticosteroids for cardiopulmonary bypass in adults. Cochrane Database Syst Rev 5:CD005566, 2011

25. Price J, Tee R, Lam BK, et al: Current use of prophylactic strategies for postoperative atrial fibrillation: A survey of Canadian cardiac surgeons. Ann Thorac Surg 88:106-111, 2009

26. Joyce L: Invited commentary. Ann Thorac Surg 88:110-111, 2009

27. Lutz JM, Panchagnula U, Barker JM: Prophylaxis against atrial fibrillation after cardiac surgery: Effective but not routinely used—A survey of cardiothoracic units in the United Kingdom. J Cardiothorac Vasc Anesth 25:90-94, 2011

28. 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 110:e340-e437, 2004

29. Hillis LD, Smith PK, Anderson JL, et al: ACCF/AHA guideline for coronary artery bypass graft surgery: Executive summary: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Thorac Cardiovasc Surg 143:4-34, 2011

30. Royster RL, Gross Hans DW, Kan ND: A multimodal approach to address the inflammation of cardiopulmonary bypass? J Cardiothorac Vasc Anesth 25:e35, 2011

31. Appoo JJ, Augoustides JG, Pochettino A, et al: Perioperative outcome in adults undergoing elective deep hypothermic circulatory arrest with retrograde cerebrla perfusion in proximal aortic arch repair: Evaluation of protocol-based care. J Cardiothorac Vasc Anesth 20:3-7, 2006

32. Shum-Tim D, Tchervenkov CI, Jamal AM, et al: Systemic steroid pretreatment improves cerebral protection after circulatory arrest. Ann Thorac Surg 72:1465-1471, 2001

33. Shuhaiber JH: Evaluating the quality of hypothermic circulatory arrest aortic surgery. Asian Cardiovasc Thorac Ann 15:449-452, 2007

34. Dewhurst AT, Moore SJ, Liban JB: Pharmacological agents as cerebral protectants during deep hypothermic circulatory arrest in adult thoracic aortic surgery—A survey of current practice. J Anesth 57: 1016-1021, 2002

35. Augoustides JG, Floyd TF, McGarvey ML, et al: Major clinical outcomes in adults undergoing thoracic aortic surgery requiring deep hypothermic circulatory arrest: Quantification of organ-based perioperative outcome and detection of opportunities for perioperative intervention. J Cardiothorac Vasc Anesth 19:446-452, 2006

36. Augoustides JG, Pochettino A, Ochroch EA, et al: Renal dysfunction after thoracic aortic surgery requiring deep hypothermic circulatory arrest: Definition, incidence, and clinical predictors. J Cardiothorac Vasc Anesth 20:673-677, 2006

37. Robertson-Malt S, Afrane B, Elbarbary M: Prophylactic steroids for paediatric open heart surgery. Cochrane Database Syst Rev 4:CD005550, 2007

38. Heying R, Wehage E, Schumacher K, et al: Dexamethasone pretreatment provides anti-inflammatory and myocardial protection in neonatal arterial switch operation. Ann Thorac Surg 93:869-876, 2012

39. Graham EM, Atz AM, Butts RJ, et al: Standardized preoperative corticosteroid treatment in neonates undergoing cardiac surgery: Results from a randomized trial. J Thorac Cardiovasc Surg 142:1523-1529, 2011

40. Pasquali SK, Li JS, He X, et al: Perioperative methylprednisolone and outcome in neonates undergoing heart surgery. Pediatrics 129:e385-e391, 2012

41. Pasquali SK, Hall M, Li JS, et al: Corticosteroids and outcome of children undergoing congenital heart surgery: Analysis of the Pediatric health information systems database. Circulation 122:2123-2130, 2010

42. Jenkins KJ, Gauvreau K, Newburger JW, et al: Consensus-based method for risk adjustment for surgery for congenital heart disease. J Thorac Cardiovasc Surg 123:110-118, 2002

43. Welke KF, Diggs BS, Karamlou T, et al: Comparison of pediatric cardiac surgical mortality rates from national administrative data to contemporary clinical standards. Ann Thorac Surg 87:216-223, 2009

44. Larsen SH, Pedersen J, Jacobsen J, et al: The RACHS-1 risk categories reflect mortality and length of stay in a Danish population of children operated for congenital heart disease. Eur J Cardiothorac Surg 28:877-881, 2005

45. Clarizia NA, Manihiot C, Schwartz SM, et al: Improved outcomes associated with intraoperative steroid use in high-risk pediatric cardiac surgery. Ann Thorac Surg 91:1222-1227, 2011

46. Lacour-Gayet F, Clarke DR, the Aristotle Committee: The Aristotle method: A new concept to evaluate quality of care based on complexity. Curr Opin Pediatr 17:412-417, 2005

47. O'Brien SM, Jacobs JP, Clarke DR, et al: Accuracy of the Aristotle basic complexity score for classifying the mortality and morbidity potential of congenital heart surgery operations. Ann Thorac Surg 84:2027-2037, 2007

48. Checchia PA, Bronicki RA, Costello JM, et al: Steroid use before pediatric cardiac operations using cardiopulmonary bypass: An international survey of 36 centers. Pediatr Crit Care Med 6:441-444, 2005

49. Allen M, Sundararajan S, Pathan N, et al: Anti-inflammatory modalities: Their current use in pediatric cardiac surgery in the United Kingdom and Ireland. Pediatr Crit Care Med 10:341-345, 2009

50. Zimmerman JJ: Development of reliable methods supporting adjunctive therapy for congenital heart surgery. Pediatr Crit Care Med 10:410-412, 2009

51. Kallmann JR, Andropoulos DB, Checchia PA, et al: Report of the pediatric heart network and National Heart, Lung, and Blood Institute working group on the perioperative management of congenital heart disease. Circulation 121:2766-2772, 2010