Integrating Outcome Benefit Into Anesthetic Design: The Promise of Steroids and Statins

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Steroids and statins may facilitate the integration of anesthetic design with clinical outcome. Although steroids clearly benefit adult cardiac surgical patents, the evidence is weaker in pediatric cardiac surgery. Current large randomized trials of steroids likely will determine the future role of steroids in adult cardiac surgery. In the intensive care unit, steroid therapy is indicated in septic shock that is refractory to fluid and pressor therapy. Recent data, however, indicate that liberal steroid therapy for sepsis may have adverse outcome consequences. A 2nd concern in the intensive care unit is acute adrenal suppression secondary to bolus etomidate therapy because it may be deleterious in patients with septic shock. Possible clinical solutions include alternative induction agents, concomitant steroid therapy, and recent etomidate derivatives. Statins also reduce mortality and atrial fibrillation after cardiac surgery. Furthermore, they slow the progression of rheumatic valvular stenosis, an important consideration in the developing world. Statins also may reduce delirium, stroke, and acute renal injury after cardiac surgery, but further randomized trials are required before definitive recommendations can be formulated. Statins are essential in vascular surgery because they reduce mortality, myocardial ischemia, and acute renal injury. As a result, they have been recommended highly for outcome enhancement in recent perioperative guidelines. Although they may improve survival in sepsis, further investigation is indicated to define their therapeutic role.

Key words: steroids, clinical outcomes, atrial fibrillation, mortality, bleeding, transfusion, intensive care unit, length of stay, sepsis, etomidate, septic shock, corticosteroid deficiency, statins, acute renal injury, dialysis, vascular surgery, cardiac surgery, valvular surgery, cardiopulmonary bypass, stroke, delirium, ventilator-associated pneumonia, anesthesia guidelines, clinical trials registry, rheumatic valve disease

STEROIDS AND STATINS offer the perioperative possibility of integrating anesthetic design with clinical outcome. Although the benefits of steroids in adult cardiac surgery are clear in meta-analysis, the evidence is less robust in pediatric cardiac surgery. Current large randomized trials of steroids likely will determine the future role of steroids in adult cardiac surgery. In the intensive care unit, steroid therapy is indicated in septic shock that is refractory to fluid and pressor therapy. Recent data, however, indicate that global compliance with current sepsis guidelines is suboptimal, especially with liberal steroid therapy with possible adverse outcome consequences. A 2nd concern in the intensive care unit is acute adrenal suppression secondary to bolus etomidate therapy because it may be deleterious in critically ill patients, particularly those with septic shock. Possible clinical solutions include alternative induction agents, concomitant steroid therapy, and newer etomidate derivatives with attenuated adrenal suppression.

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Statins also reduce mortality and atrial fibrillation after cardiac surgery, including in high-risk valve surgery. Furthermore, they slow the progression of rheumatic valvular stenosis, a therapeutic intervention that may have enormous potential in the developing world. Statins also may reduce delirium, stroke, and acute renal injury after cardiac surgery, but further randomized trials are required before definitive recommendations can be formulated.

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STEROIDS

Do Steroids Improve Clinical Outcome After Cardiac Surgery?

The adverse clinical outcomes caused by the systemic inflammatory response associated with cardiac surgery and cardiopulmonary bypass provide the therapeutic targets for the immunosuppressive properties of steroids.[1] Although there have been multiple clinical trials, they have been limited by design issues such as surrogate endpoints, sample size, and lack of safety data.[2] Three large recent meta-analyses have shown the clinical outcome benefit of steroids.[3-5] In the 1st meta-analysis (N = 3,205: 44 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 duration of intensive care unit stay (weighted mean difference = 0.23 days; 95% confidence interval, −0.40 to −0.07).[3] There was also a trend toward reduced mortality (relative risk = 0.73; 95% confidence interval, 0.45-1.18).[3] A 2nd meta-analysis (N = 3,323: 50 trials) showed that these clinical benefits are all achieved with steroid below a cumulative dose of less than 1,000 mg of hydrocortisone.[4] In this analysis, steroids were associated significantly with hyperglycemia requiring insulin therapy (relative risk = 1.49; 95% confidence interval, 1.11-2.01; $p = 0.01$) but with no increased risk of perioperative infection (relative risk = 0.93; 95% confidence interval, 0.61-1.41; $p = 0.73$).[4] The 3rd meta-analysis was limited to randomized double-blinded trials (N = 1,974: 31 trials) and confirmed the main findings of the first 2 analyses.[5] This most recent analysis showed the heterogeneity in the type of steroid studied as follows: methylprednisolone (51.4%), dexamethasone (34.3%), hydrocortisone (5.7%), prednisolone (2.9%), and a combination of methylprednisolone and dexamethasone (5.7%).[5]

The clinical benefit of steroids in pediatric cardiac surgery is less impressive. A meta-analysis showed weak evidence that steroid exposure reduces the duration of mechanical ventilation and shortens length of stay in the intensive care unit.[6] A recent massive observational study (N = 46,730: 54% with steroid exposure) showed no clinical outcome benefits because of steroids and raised the possibility that steroids may increase morbidity, especially in lower-risk patients.[7] This analysis of a large pediatric database also revealed the significant variation in steroid practice among the multiple enrolled medical centers.

The benefit of steroids in pediatric cardiac surgery may depend on the level of perioperative risk. A recent observational study of children (N = 221: 2004-2007) undergoing high-risk cardiac surgery revealed that steroid exposure significantly decreased bleeding and the duration of mechanical ventilation and intensive care unit stay. 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 www.aristotleinstitute.org). Further randomized trials are required to delineate the outcome effects of steroids for children undergoing cardiac procedures, especially in high-risk subgroups.

Based on the strong evidence from meta-analysis that steroids improve outcomes after adult cardiac surgery, 2 registered, randomized, controlled trials are currently in progress: the SIRS (Steroids In CaRdiac Surgery) and the DECS (DExamethasone for Cardiac Surgery) trials (full details available at www.clinicaltrials.gov). The SIRS trial is a Canadian multicenter study that aims to enroll 7,500 adults undergoing cardiac surgery with cardiopulmonary bypass. The steroid regimen consists of methylprednisolone with an initial dose of 250 mg upon the induction of anesthesia followed by 250 mg upon the initiation of cardiopulmonary bypass. The primary outcome is mortality at 30 days. This trial was commenced in 2007 and is scheduled to complete enrollment in 2014. The DECS trial is a Dutch multicenter study with a targeted total enrollment of 4,500 adult cardiac surgical patients. The steroid regimen is dexamethasone at a dose of 1mg/kg given on induction of anesthesia. The primary outcome is perioperative mortality. This trial was commenced in 2007 and is scheduled for complete enrollment by 2012. The findings of these well-designed randomized trials likely will determine the future indications for steroid prophylaxis in adult cardiac surgery.

Do Steroids Improve Clinical Outcomes in the Intensive Care Unit?

Recent guidelines from the American College of Critical Care Medicine have focused on critical illness–related corticosteroid insufficiency and the role of steroid therapy in severe sepsis.[8,9] Severe sepsis and shock remain common and important predictors of mortality and major morbidity after cardiac surgery.[10,11] Hydrocortisone therapy is an important consideration in septic shock, especially when refractory to volume and/or vasopressor therapy.[8,9] These guidelines also advise against steroid therapy in sepsis without evidence of shock or steroid deficiency.

Compliance with international guidelines remains a challenge. Recent data from a global sepsis registry (N = 8,968: 79.8% and 34.0% managed with vasopressors and steroids, respectively) revealed significant geographic variation in steroid therapy for sepsis.[12] Furthermore, 14.2% of patients managed with steroids for sepsis were not receiving any vasopressor therapy.[12] After risk-adjusted analysis, steroid therapy remained significantly associated with mortality in this global registry analysis. Thus, the analysis of outcome benefit for steroids in sepsis from global real-world practice is disappointing, with significant geographic variation, noncompliance, and concerns about harm. Further initiatives are required to address these issues.

Acute suppression of adrenal function with resulting acute corticosteroid deficiency remains an outcome concern with etomidate administration for sedation in critically ill patients.[13,14] Recent meta-analysis (21 studies: 1983-2010) revealed that etomidate in critically ill patients was associated significantly with adrenal insufficiency (relative risk = 1.64; 95% confidence interval, 1.52-1.77; $p < 0.0001$) and an increased risk of mortality in septic patients (relative risk = 1.22; 95% confidence interval, 1.11-1.35; $p < 0.0001$).[15]

These outcome concerns with etomidate prompted a multicenter randomized trial across France (N = 655; 12 emergency departments and 65 intensive care units).[16] In this important trial, patients were randomized to etomidate (0.3 mg/kg) or ketamine (2mg/kg) for rapid-sequence intubation. There was no significant difference in intubating conditions ($p = 0.70$). Although adrenal insufficiency was significantly more likely in the etomidate cohort (odds ratio = 6.7; 95% confidence interval, 3.5-12.7), there were no significant differences in mortality or multiple measures of morbidity.[16] The investigators concluded that ketamine is a safe alternative to etomidate for endotracheal intubation in the critically ill, especially in septic patients.[16]

The search for an alternative to etomidate also has included midazolam and mehohexital. A recent trial (N = 122: single US medical center) randomized patients for endotracheal intubation in the emergency department to etomidate or midazolam.[17] In this trial, there were no differences in hospital mortality or the length of stay between groups.[17] A recent small