First nights, the adrenal axis, and steroids

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The scenario is familiar to all who care for patients undergoing congenital heart surgery: It is the first night after surgery and a neonate who has undergone a complex cardiac repair has low cardiac output unresponsive to volume and catecholamines. The first night was highlighted as a critical period by data from the Boston Circulatory Arrest Study,¹ which showed a nadir in cardiac index at 9 to 12 hours after an arterial switch procedure. In the setting of catecholamine-resistant low cardiac output, there are limited therapeutic options available to avoid mechanical support. The use of exogenous glucocorticoids is one of these options. Perioperative steroid supplementation is aimed at blunting the inflammatory response to cardiopulmonary bypass (CPB), improving hemodynamic status and ultimately patient outcomes. The role of steroids in patients with congenital heart disease has been a subject of interest since the 1960s. Fifty years ago, Replogle and Gross² published a study in children and young adults undergoing cardiac operations with CPB in which 10 patients received perioperative dexamethasone (9 doses) compared with 10 control patients. They concluded that steroid administration resulted in possible lysosome stabilization, as evidenced by a reduction in β -glucuronidase after bypass. Although there were no data regarding clinical outcomes, the investigators noted “a better general appearance and state postoperatively in those patients who received dexamethasone.”²

The hypothalamic-pituitary-adrenal axis responds to a variety of stimuli.³ The hypothalamus releases corticotropin-releasing hormone, which leads to the release of corticotropin (ACTH) by the pituitary. ACTH stimulates the synthesis and release of the primary effector glucocorticoid, cortisol, from the adrenal glands. Cortisol has myriad downstream effects important to the maintenance of homeostasis and the response to stress. Cortisol is approximately 90% bound to corticosteroid-binding globulin, and 5% to albumin, so that only 5% is present in the biologically active form, free cortisol. Adrenal responsiveness can be evaluated by the ACTH-stimulation test, which assesses the response of cortisol level to an exogenous dose of synthetic ACTH (cosyntropin).³

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Central Message

After cardiac surgery on a infant with use of preoperative dexamethasone, there is postoperative depression of the adrenal axis, characterized by low adrenocorticotrophic hormone and cortisol levels, with relatively preserved adrenal function (ie, central adrenal insufficiency). However, there is no association of cortisol levels with clinical outcomes.

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The past 15 years have seen numerous studies on the adrenal axis and the effects of steroids in patients with congenital heart disease. Several of the studies have been prospective, randomized controlled trials.⁴⁻⁸ Despite this, the role of perioperative steroids remains anything but clear, in part due to wide variations among the studies. The variations have included the study population (age and complexity), steroid regimen (prophylactic vs targeted), timing of administration (preoperative, anesthesia induction, CPB prime, and postoperative), as well as steroid type, dosing, and route. Further confusion results from the lack of accepted normal ranges for steroid levels in neonates, and of a clear definition of adrenal insufficiency in postoperative patients. There is also variation in the cosyntropin dose used in ACTH-stimulation tests: the standard test uses 125 to 250 mcg, whereas a low-dose test uses 1 mcg. As a consequence, many questions in this area remain unanswered. These include the typical response of the adrenal axis to CPB in infants, and whether there exists a blood test or assay that can identify patients who have adrenal insufficiency and might benefit from steroid supplementation.

Wald and colleagues⁹ from Lurie Children's Hospital and the Mayo Clinic examine the adrenal axis in 68 infants undergoing CPB. They report levels of total cortisol, free cortisol, corticosteroid-binding protein, and ACTH at 3

time points (pre-CPB, intensive care unit arrival, and 24 hours postoperative). In addition, ACTH stimulation tests were performed at the 3 time points. The primary finding is that levels of cortisol (both total and free) as well as ACTH decreased significantly after CPB. The decreases were quite marked, with cortisol falling to 21% and ACTH to 12% of the preoperative values. The cortisol response to ACTH stimulation was normal in only 41% of patients before surgery, but was either maintained or improved during the postoperative period. A subnormal total cortisol response to ACTH stimulation was associated with greater fluid requirement and longer intensive care unit length of stay. However, absolute cortisol levels (total or free) did not correlate with any outcome measure.

This prospective, observational study is well executed and provides a comprehensive look at measures of adrenal function after CPB. The collaboration between 2 well-regarded centers not only increases the number of patients, but strengthens the findings because the results were similar at both centers (personal communication from the authors). No previous study has directly measured free cortisol levels in this setting. So the information on free cortisol levels is new, although it does not seem to add substantively to that provided by total cortisol levels. It is puzzling that only 41% of patients had a normal cortisol response to ACTH before surgery. As the authors note, this may be due to the use of a low dose ACTH (1 mcg) stimulation test. A reasonable interpretation of the data is that these patients had fairly profound postoperative depression of their adrenal axes, characterized by low ACTH and cortisol levels, with relatively preserved adrenal function (central adrenal insufficiency). Nonetheless, there was no clear association of adrenal insufficiency with clinical outcomes, at least on average. This leaves open the possibility that low postoperative levels of cortisol might impair outcomes in individual patients.

The major caveat to this study is that all of the patients received 1 mg/kg dexamethasone before CPB. This makes it impossible to determine whether the postoperative adrenal depression observed was due to the effects of CPB, or to the preoperative dexamethasone. In support of the latter, a previous study examining postoperative cortisol levels with no preoperative steroid exposure found that both cortisol and ACTH levels increased after CPB.¹⁰ Other studies with preoperative steroid dosing found depression in post-CPB cortisol levels similar to the current study.^{5,11,12} A previous study from the Mayo authors¹³ measured postoperative dexamethasone levels in patients who had received 1 mg/kg dexamethasone before CPB. Postoperative dexamethasone levels varied, but remained elevated out to 24 hours. Patients with high postoperative dexamethasone levels had very low cortisol levels, which persisted even after the dexamethasone levels fell to near zero.¹³ This suggests that depression of intrinsic cortisol

levels extends beyond 24 hours after just a single dose of preoperative dexamethasone. It would be of great interest to see the current study repeated in patients with no preoperative steroid exposure. Limiting the patients to neonates undergoing more complex operations, and including postoperative indicators of cardiac output such as mixed venous oxygen saturation and near-infrared spectroscopy could maximize the chances of identifying a subset of patients who would predictably benefit from steroid therapy.

CONCLUSIONS

We offer the following observations:

1. Steroids administered in a variety of fashions result in a reduction in perioperative inflammatory markers. Their influence on meaningful clinical outcomes is less clear.
2. Preoperative prophylactic steroids do not appear to significantly improve outcomes, and can increase morbidity (eg, infection, renal function, and hyperglycemia).^{6,7,14-17} A National Heart, Lung, and Blood Institute-funded multicenter randomized controlled trial comparing prophylactic methylprednisolone to placebo in neonates undergoing cardiac operations with CPB is underway ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01579513) identifier: NCT01579513).
3. In patients with postoperative catecholamine-resistant hypotension, rescue steroid therapy can be effective, regardless of cortisol levels.^{18,19} Targeted steroid use will undoubtedly continue in this situation.
4. A blood test or assay to identify patients who might benefit from prophylactic or targeted steroid supplementation remains elusive.

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