Con: Methylprednisolone is Not Indicated for Patients During Cardiopulmonary Bypass

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THE USE OF STEROIDS in the setting of cardiac surgery utilizing cardiopulmonary bypass (CPB) has been a topic of debate for several decades.[1-4] The current perioperative utilization of steroids varies as much among practitioners as do their purported indications; whereas some centers use steroids routinely for cardiac surgery, others have steadfastly avoided their use. The argument opposing the routine use of steroids is largely based on two major premises: (1) there is an overall paucity of data supporting any beneficial effects of this class of drug in cardiac surgery, and (2) the tenet in medicine "of first doing no harm," indicating that when studies show limited benefit coupled with some detriment to a specific therapy, it should not be used. Put another way, making the argument against the routine use of steroids becomes relatively easy as there are no convincing data (ie, randomized, double-blind, placebo-controlled trials) outlining any significant benefits to steroids in cardiac surgery patients and there is data indicating that there may be some harm associated with their use.

Discussions regarding routine steroid use for CPB patients generally center around two hypothetical benefits. The first pertains to attenuating the global systemic inflammatory response to CPB. Indeed, there is a great deal of data suggesting that steroids can effectively blunt CPB-associated inflammation.[5-7] What is missing, however, is the link between this reduced inflammation and improved perioperative outcomes.[4] The second major argument for steroid use relates to suggestions that steroids may possess some specific neuroprotective properties, an argument for which there is neither sufficient experimental nor supportive clinical data in cardiac surgery. Yet they continue to be used, particularly in cases (such as circulatory arrest) where the brain is perceived to be particularly at high risk of injury.

Steroids produce their principle effect by acting on the cell nucleus.[8] By upregulating RNA transcription and thereby modulating protein synthesis, a number of molecular pathways, some of which are beneficial, but some potentially detrimental, are altered. The complex actions of steroids and their effects on the similarly complicated inflammatory cascade may partly explain why the nonspecific blunting of inflammation has not seen significant improvement in meaningful clinical outcomes. The reasons for this missing link between inflammation reduction and outcome improvement are likely complex, but one can speculate that perhaps it is the indiscriminate nature of steroid inflammatory suppression that is potentially harmful. That is, perhaps some aspects of inflammation may be beneficial, and nonspecifically attenuating the entire inflammatory response may be harmful. The two most commonly administered steroids in this setting are methylprednisolone and dexamethasone, both synthetic corticosteroids; subsequent discussions in this text will not discriminate between the two.

Cardiopulmonary bypass is associated with a whole-body inflammatory response, representing a clinical spectrum ranging from subtle physiologic perturbations to more fulminant manifestations characterized as the "systemic inflammatory response syndrome" (SIRS).[9,10] The initiating events for this inflammatory response include: (1) contact of blood components with the artificial surface of the bypass circuit, (2) ischemia–reperfusion injury, (3) direct operative tissue trauma, and (4) endotoxemia. Cardiopulmonary bypass and other perioperative surgical events initiate a complex cascade of events, including complement activation as well as the activation of other blood components, including platelets, neutrophils, and macrophages that culminate in the upregulation of kallikrein, thrombotic, and fibrinolytic systems. A resulting increase in circulating cytokines and endotoxin leads to, among other things, an increased permeability of endothelial barriers, allowing the transmigration of activated neutrophils into surrounding tissues with the subsequent release of further injurious mediators. Although it is difficult to conclusively link increased mortality to this perioperative inflammatory response,[11] it may contribute to the development of numerous postoperative end-organ complications, including respiratory failure, renal dysfunction, bleeding disorders, neurologic dysfunction, altered hepatic function, and if left unabated, may result in multisystem organ failure.

Investigations in recent years have focused on corticosteroids because of their interactions with various immune responses. Indeed, these compounds affect inflammation through their effects on various white blood cells, complement, as well as cytokine and nitric oxide production, and endotoxin release. Steroids may exert a nonspecific anti-inflammatory action by changing the balance of the production of pro-inflammatory cytokines and their various antagonists.[12] Numerous investigators have revealed the ability of steroids to beneficially alter the balance of the mediators in the blood of patients following exposure to CPB by attenuating increases in pro-inflammatory mediators and/or maintaining and augmenting increases in anti-inflammatory mediators.[7]

Corticosteroid pretreatment prior to CPB may blunt the inflammatory response in humans by several distinct mechanisms. Potential anti-inflammatory effects include a reduction in complement activation,[13-15] with parallel decreases in interleukin-6 (IL-6) release,[16-18] IL-8 release,[13,18-20] tumor necrosis factor release,[17,18,20,21] neutrophil integrin CD11b upregulation,[21,22] along with complementary increases in the anti-inflammatory cytokine IL-10.[19,20] Corticosteroids also attenuate post-CPB leukocyte activation,[23] neutrophil adhesion molecule upregulation,[21] and pulmonary neutrophil sequestration.[24] Ad-

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ministration of corticosteroids prior to CPB may also attenuate endotoxin translocation from the gut.[25]

Despite numerous investigations demonstrating the ability of steroids to alter the balance of inflammatory mediators in cardiac surgery patients, the clinical implications of their use has not been fully elucidated, and a clear benefit has yet to be demonstrated. Coupled with the questionable benefits of steroids, significant real and theoretical side effects need to be discussed. One of the principle negative effects of these steroids relates to their glucocorticoid action with consequent hyperglycemia due to their anti-insulin effects.[5,26] Glucocorticoid effects lead to enhanced hepatic gluconeogenesis, as well as decreased peripheral glucose utilization. Indeed, some of the theoretical benefits to steroids (ie, neuroprotection) could potentially be negated by the consequent hyperglycemia that repeatedly has been shown to worsen neurologic outcome in various settings of cerebral ischemia.[27-30] In addition to the impaired glucose tolerance brought about by steroids, impaired wound healing[31] and potentially a higher risk of infection, in part as a result of suppression of T cell function,[32] are also concerns.[33] Although none of these potential complications that have been reported in cardiac surgery have directly implicated steroids,[7] they do represent plausible risks.

Some of the more concerning data about steroids in cardiac surgery that comes from recent well-designed studies associates steroid use to impairments in pulmonary physiology. Pulmonary dysfunction occurring after CPB was one of the first described complications attributed to bypass[34] and can be measured through changes in the alveolar-arterial oxygenation gradient, intrapulmonary shunt, pulmonary edema severity, pulmonary compliance, increased pulmonary vascular resistance, and intubation time (ie, delayed extubation times). Many studies have focused on the pathophysiologic mechanism of lung injury after CPB, which appears to be related to the systemic inflammatory response, and more specifically represents an inflammatory response in the lungs. It shares similarities with what the American-European Consensus Conference on adult respiratory distress syndrome (ARDS) defined as being a mild form of ARDS or acute lung injury (ALI).[35] The risk and severity of ALI has been linked with the duration of CPB. Severe ALI (or ARDS) following CPB is uncommon (1-3%), but has been associated with 50% mortality. Attempts to decrease the pulmonary dysfunction seen in bypass patients on a more regular basis early on in the history of bypass surgery prompted a series of focused investigations. Steroids were an obvious early and promising therapeutic; however, recent publications have highlighted a perplexing paradox in this regard. That is, steroids decrease inflammation, and inflammation can lead to pulmonary dysfunction, yet steroids actually worsen pulmonary function after CPB.

Chaney et al, in two separate studies,[36,37] described how the administration of steroids not only led to hyperglycemia, which itself is an unrelated yet difficult problem to treat successfully,[37] but also caused adverse effects relative to post-bypass pulmonary function. Both studies demonstrated either no improvement or worsening in lung compliance, shunt, A-a oxygen gradient (A-a DO_2), and delays in extubation. These authors speculated that the worsened A-a DO_2 and delayed pulmonary extubation associated with steroid administration was attributable to steroid-induced sodium retention and vasodilation, leading to increased shunt and increased lung water, resulting in pulmonary edema. In a similar recent study, Oliver et al, comparing placebo to either steroids or hemofiltration, noted that steroid-treated patients had larger increases in postoperative alveolar-arterial oxygen partial pressure (A-a DO_2) gradients.[38] Similarly, using a preset mechanical ventilation protocol to guide ventilation or weaning, steroids again failed to reduce the time to tracheal extubation (519 $\pm$ 293 min *v* 618 $\pm$ 405 min, $p = 0.21$), confirming the findings of Chaney et al.[36]

The use of steroids in the setting of neuronal injury saw their most beneficial effect in a study involving patients with spinal cord injury.[39] However, extrapolating the beneficial effect of steroids from the injured spinal cord to the brain injured during cardiac surgery has largely been done in the absence of supporting data. Indeed, there is also no compelling data from the experimental cerebral ischemic literature to suggest that they provide protection to the injured brain.[40] Even in the clinical setting, steroids have not been shown to benefit the hypoxic-ischemia encephalopathy resulting from cardiac arrest-induced brain injury.[41] Furthermore, the administration of steroids after closed head injury has recently been shown to worsen outcome.[42] In the largest (n = 10,008) trial of its kind to date, the CRASH trial, a multicenter study of steroids in head injury, actually demonstrated an increased relative risk of death (1.18 [95% CI, 1.09-1.27], $p = 0.0001$) in those patients receiving high dose corticosteroids within 8 hours of injury.

Despite repeated steroid failures in other neurologic injury settings, their use in cardiac surgery is very common, with the justification of providing neuroprotection frequently used in its defense. The purported reasons to use corticosteroids on brain and cardiac surgery patients relates to two theoretical benefits. First, as mentioned previously, methylprednisolone (30 mg/kg bolus and 5.4 mg/kg/h infusion for 23 hours) had been demonstrated to protect injured spinal cord neurons in the setting of traumatic spinal cord injury. Indeed, this high-dose methylprednisolone regime improved outcome after acute spinal cord injury in a landmark study published by Bracken et al more than 15 years ago.[39] The other theoretical benefits to steroids on the brain are related to the previously described reduction in the inflammatory response. With respect to the specific protection of injured neurons, methylprednisolone, although the standard of care in spinal cord injury, has never been demonstrated to have any other specific neuroprotective effects, specifically in the ischemic brain. Although the etiology of brain injury (ie, cognitive dysfunction as well as stroke) during cardiac surgery is likely multifactorial, it is assumed that cerebral ischemia (due to various embolic phenomena) plays a major pathophysiologic role.

As steroids have never been shown to protect against the injurious effects of cerebral ischemia in other settings, it is unlikely that methylprednisolone would have any direct neuroprotective effect on any bypass-related cerebral ischemia. Alternatively, an argument can be made that inflammation is a major etiologic factor involved in neurologic injury after cardiac surgery. Direct evidence for this seemingly intuitive relationship is lacking, however. There is some indirect evidence, such as data from Hindman et al[43] describing the upregulation of pro-inflammatory cyclooxygenase-2 mRNA in brains of rats