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Predicting AKI after Pediatric Cardiac Surgery: Are Steroids Muddying the Water?

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Acute kidney injury (AKI) after cardiac surgery is associated with poor outcomes including longer hospital length of stay, increased risk for development of chronic kidney disease and higher long-term mortality (1, 2). Growing evidence suggests that AKI is a frequent complication after pediatric cardiac surgery with reported estimates ranging from 28–42% (3–5). Ischemic kidney injury is an important cause of AKI. The pathogenesis of renal ischemia following cardiac surgery is multifactorial and can be attributed to the loss of autoregulation during periods of hemodynamic instability, administration of medications that impact renal blood flow, reperfusion injury, and the systemic inflammatory response related to cardiopulmonary bypass (6).

As AKI is increasingly recognized as a major health burden, recent work has focused on identifying biomarkers that predict its development. The traditional reliance on rising creatinine levels or oliguria to diagnose AKI is flawed in that these indices signify loss of renal function – a late consequence of actual structural kidney damage. It is hypothesized that being able to predict or diagnose “early-stage” AKI via novel biomarkers will allow for timely therapeutic interventions to reverse inciting causes and prevent injury progression. Several AKI biomarkers have been identified over the past decade with one of the most promising and widely studied being neutrophil gelatinase-associated lipocalin (NGAL). NGAL is a protein that can be measured in plasma or urine and has been shown to be up-regulated shortly after various types of renal insults including exposure to cardiopulmonary bypass (3, 4). However, NGAL is also a constituent protein of neutrophil specific granules and has been demonstrated to be released during periods of systemic inflammation such as sepsis. Given the well-described systemic inflammatory response to cardiopulmonary bypass and the widespread use of steroids for its reduction, clarifying the source of plasma

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NGAL following cardiac surgery is critical prior to its validation as a biomarker for AKI in this population.

In this issue of *Pediatric Critical Care Medicine*, Pesonen and colleagues (7) sought to determine if perioperative methylprednisolone would decrease plasma concentrations of NGAL and lactoferrin (a marker of neutrophil degranulation) in pediatric cardiac surgery utilizing a secondary analysis of two separate double-blinded, randomized controlled trials. The study demonstrated that preoperative administration of methylprednisolone reduced postoperative plasma NGAL levels by over 40% compared to controls and there was a positive correlation between NGAL and lactoferrin concentrations in a subgroup of patients studied. However, despite the significant reduction in plasma NGAL, there were no differences in the prevalence of AKI, change in serum creatinine or urine output between steroid recipients and non-recipients. The authors conclude that activated neutrophils, not necessarily injured renal epithelial cells, may be a significant source of plasma NGAL following pediatric cardiac surgery. Consequently, preoperative steroid administration appears to be a confounding factor when interpreting plasma NGAL as a kidney injury marker in this population. The strengths of this study include a novel hypothesis and an experimental design that was thoughtfully conceived and well executed. In light of the widespread use of steroids in pediatric cardiac operations, the study findings are especially significant as we consider the candidacy of NGAL for clinical use.

Despite several adult studies touting the high sensitivity and specificity of plasma NGAL, its ability to predict AKI in pediatric cardiac surgical patients has not been well established. Dent and colleagues (4) performed a prospective, uncontrolled cohort study enrolling 120 children undergoing cardiopulmonary bypass and found a strong correlation between plasma NGAL levels and AKI development with a sensitivity of 0.84 and specificity of 0.94. In contrast, Parikh and colleagues (8) recently conducted a prospective, multicenter cohort study involving 311 children undergoing cardiac surgery and found that plasma NGAL levels were not associated with severe AKI and only weakly associated with mild AKI. Neither of these studies commented on the use of perioperative steroids in their respective study populations. As mentioned in the current study, the potential confounding effect of steroids on NGAL levels may explain these contradictory findings, should be considered in future research and warrants secondary analyses of prior studies.

Similar to other studies, this work demonstrates that preoperative steroids reduce the inflammatory response following cardiac surgery yet the evidence to support an association with improved clinical outcomes remains unclear (9–13). As such, the intriguing question regarding the role steroids may play to attenuate the potentially deleterious inflammatory effects of cardiopulmonary bypass remains unanswered. With specific regard to AKI, there is a paucity of data in children and the adult studies examining the effect of perioperative steroids have been inconclusive. Scarscia and colleagues (14) performed a meta-analysis of randomized controlled trials that included 14 trials and 931 adult cardiac surgical patients. The analysis found no difference in the incidence of worsening renal dysfunction in patients who received steroids versus placebo. Jacob and colleagues (15) recently published a post hoc analysis of a large placebo-controlled randomized trial of dexamethasone in 4465 adult patients undergoing cardiac surgery. They found that the use of intraoperative

dexamethasone resulted in a relative risk reduction of 56% in the development of postoperative severe AKI that required renal replacement therapy. While these results are impressive, they are confounded by the relative small number of patients that developed severe AKI and inclusion of patients who had evidence of AKI prior to surgery. With specific attention to congenital heart surgery, we recently examined the Pediatric Heart Network's Single Ventricle Reconstruction Trial public database and found that intraoperative steroid use did not alter the prevalence of postoperative renal failure in neonates undergoing the Norwood procedure (16).

In conclusion, Pesonen and colleagues provide important information that preoperative steroids are likely a confounding factor when interpreting plasma NGAL as a biomarker for AKI. This work highlights the need to rigorously validate potential biomarkers in the specific populations where they will be used. More work is needed to determine whether prediction or earlier detection of AKI permits treatment that impacts clinical outcomes. Finally, the potential contribution of inflammation and the ability of steroids to mitigate the deleterious effects on clinical outcomes including AKI highlight the need for a contemporary multicenter randomized controlled trial comparing steroids with placebo in neonatal cardiac surgery (e.g. [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study?term=NCT01579512) identifier: NCT01579512).

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