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The Role of Prophylactic Postoperative Steroids in Pediatric Cardiac Operations

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Cardiopulmonary bypass (CPB) is known to incite an inflammatory cascade that is believed to contribute to post-operative morbidity. As a result, the empiric use of steroids as prophylactic anti-inflammatory therapy has become a common practice in pediatric cardiac surgery. Most of the early work investigating steroids and pediatric cardiac surgery revolved around steroid administration preoperatively and/or at the induction of anesthesia or in the CPB prime. In the early 2000's, several small pediatric randomized controlled trials of varying type, dose, and timing of preoperative steroids demonstrated a reduction in inflammatory markers albeit with variable improvement in hemodynamic parameters or clinical outcomes (1;2). More recently the literature has given way to larger trials (3;4), meta-analysis (5), and large observational studies (6;7) that suggest no benefit with prophylactic steroids and possibly an association with increased morbidity particularly in lower-surgical risk groups. As such, the utility of preemptive preoperative and intraoperative steroids in pediatric cardiac operations remains highly debated (8).

In contrast, there is a paucity of literature that has explored the risks and benefits of steroids in the postoperative period. In the majority of these studies steroids were administered selectively to surgical (and sometimes nonsurgical) patients with catecholamine resistant hypotension (9-11). These studies suggest an improvement in hemodynamics and a reduction in inotropic requirements when compared to the time preceding selective steroid administration. While encouraging study limitations hinder their generalizability.

In this issue of *Pediatric Critical Care Medicine*, Robert and colleagues (12) performed a double blind randomized control trial of postoperative hydrocortisone versus placebo in infants undergoing cardiac operations with cardiopulmonary bypass to determine if prophylactic hydrocortisone could decrease the incidence of low cardiac output syndrome

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(LCOS). The main findings of the study are that a prophylactic continuous 5 day infusion of hydrocortisone reduced the incidence of LCOS, improved fluid balance and urine output, and attenuates inflammation after CPB compared to placebo. The strengths of this study include an experimental design that was thoughtfully conceived and was well executed. In addition, it is the largest contemporary randomized control trial to evaluate postoperative steroids in pediatric cardiac surgery. In fact, there are only 2 other pediatric randomized controlled trials specifically examining postoperative steroids (13;14). Four decades ago, Toledo-Pereyra and colleagues (13) performed a double blind randomized control trial of 95 children undergoing CPB. Patients were randomized to 6 doses of methylprednisolone (30 mg/kg/dose) or placebo beginning 1 hour preoperatively and continuing every 6 hours for 24 hours postoperatively. In contrast to the current study, they found no difference between groups in any hemodynamic parameters measured. The authors did however observe an improved hospital survival in the steroid group that they found difficult to explain given no other differences between groups.

More recently Ando et al (14) randomized 20 neonates undergoing biventricular repair to a postoperative 7 day continuous hydrocortisone infusion or placebo to determine if adrenal insufficiency exists after CPB. As such it was not powered to detect clinical outcomes, but similar to the current study they found steroid treatment was associated with an improved fluid balance and urine output but was not associated with other important clinical outcomes. Consistent with these findings, a recent meta-analysis (15) that included these studies as well as several others that explored preoperative steroids demonstrated a reduction in the prevalence of “worsening renal function” with steroids but no difference in duration of mechanical ventilation, ICU length of stay, or mortality.

The authors appropriately acknowledge the current study's weaknesses but a few limitations deserve expanding on. First, inherent to any study in the pediatric cardiac surgical population is the large variability in clinical outcomes and lack of validation of surrogate outcomes that makes the choice of a primary outcome challenging. Low cardiac output is common after congenital heart surgery and can contribute to significant morbidity. Low cardiac output is often readily apparent when present clinically yet remains problematic to define for a trial without directly measured invasive hemodynamic data. While any attempts to define LCOS would ultimately be subjective, the authors utilized a clinical definition of LCOS that has been used in other pediatric cardiac surgical trials (3). Unfortunately this definition was recently shown to not be associated with other important short term outcomes in neonates undergoing cardiac operations (16). In light of this and without a significant difference in other important outcomes the enthusiasm for the routine use of postoperative steroids is diminished. Nevertheless, it is interesting that in 24% of the placebo group and none of the hydrocortisone group blinded providers ordered “rescue” steroids, supporting the author's notion of improved hemodynamics with the hydrocortisone infusion.

A second concern arises from the uniform administration of 2 doses of preoperative steroids regardless of study group assignment. The authors' appropriately acknowledge the comparison is between a postoperative hydrocortisone infusion and placebo. While the question of the utility of postoperative steroids is compelling enough to study independently, the study would have been stronger had there been a group that did not receive any open

label steroids. Finally, despite being the largest contemporary trial, small sample size, the universal use of preoperative steroids and relatively frequent use of “rescue” steroids in the placebo group make the assessment of adverse effects difficult.

As we continue to unravel the intertwined and redundant inflammatory cascade and its contribution to complicating postoperative recovery we must remain cognizant of both the risk and benefits of steroids. Similar to the early work examining preoperative steroids, the current study demonstrated an improvement in some clinical outcomes and inflammatory markers with postoperative steroids. While appropriate for a pilot trial reductions in the incidence of LCOS, duration of inotropic requirement, inflammatory markers, or an improvement in fluid balance are not significantly meaningful outcomes in and of themselves without improvements in length of stay, survival, or neurodevelopmental outcomes. In light of the growing evidence suggesting no benefit and possible harm (6;7) with prophylactic preoperative steroid administration, larger studies are needed before we should advocate for the routine use of prophylactic postoperative steroids.

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