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Author reply to: Perioperative steroids in pediatric cardiopulmonary bypass: we still do not have all the answers

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In regards to perioperative steroids in pediatric cardiac surgery Withington et. al. (1) writes “we still do not have all the answers”; I could not agree more! Almost 50 years ago Drs. Replegle and Gross published the first study comparing 10 children and young adults undergoing cardiac operations with cardiopulmonary bypass who received 9 perioperative doses of dexamethasone to 10 controls (2). They concluded steroid administration resulted in possible lysosome stabilization as evidenced by a reduction in B-Glucuronidase 4 hours after bypass. Although essentially all other laboratory data were similar and there were no data regarding hemodynamics or clinical outcomes the investigators noted “a better general appearance and state postoperatively in those patients who received dexamethasone (2).”

After almost a half of century of debating the role of corticosteroids in pediatric cardiac surgery, we are still no closer to a true answer. Central to our inability to answer this question is the lack of high quality prospective randomized controlled trials (RCTs). Although numerous RCTs have attempted to address this topic we are still faced with the same limitations, namely small sample size and the lack of clinically meaningful study endpoints. It is common for small pediatric cardiac surgery trials to report the combination of a reduction in an inflammatory biomarker coupled with an improvement in a hemodynamic parameter without improvement in length of stay, survival, or neurodevelopmental outcomes as a beneficial effect of steroid administration. Although appropriate outcomes for pilot trials, the widespread use of inflammatory biomarkers, fluid balance or changes in hemodynamic or ventilator parameters, even when combined, are not significantly meaningful outcomes. Without rigorous, larger high quality studies individual and ultimately community biases perpetuate. This results in a lack of equipoise, which further compounds the already significant barriers to conducting RCTs in pediatric cardiac surgery. I strongly believe that given the limited evidence for benefit for corticosteroid administration in pediatric cardiac surgery and the suggestion of potential harms, equipoise should definitely exist on this issue (3–8). However, the evidence from reported clinical practices suggests that it does not (5–8).

I'm currently leading a NHLBI-funded multicenter RCT comparing intraoperative methylprednisolone to placebo in neonates undergoing cardiac operations with

cardiopulmonary bypass with the hopes of definitively answering this question (ClinicalTrials.gov identifier:NCT01579513). We plan to enroll 190 neonates and will use a previously validated composite outcome as the primary endpoint in addition to other clinically meaningful secondary outcomes, such as 1 year neurodevelopmental assessment. If the results from this trial are not definitive, I believe we will have to move beyond our typical way of performing RCTs and use innovative approaches to answer the question. One possibility would be building on the platform of an already-existing high-quality observational registry to perform a “trial within a registry.” This concept has been described as “a disruptive technology, a technology that transforms existing standards, procedures, and cost structures (9)”. This “randomized registry trial” model can: 1) use registry data to ensure the optimal trial design; 2) improve access to study subjects and centers; 3) provide quality control mechanisms to ensure accurate data collection; and 4) provide the infrastructure to compile, analyze, and disseminate trial data efficiently and at low cost. This trial design could overcome the many barriers to ultimately answering the question: do steroids provide a clinical benefit to children undergoing cardiac surgery? Assuming adequate equipoise exists to perform the study.

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