Published in final edited form as:

Pediatr Crit Care Med. 2014 June ; 15(5): 492–493. doi:10.1097/PCC.0000000000000139.

The Utility of Steroids in Pediatric Cardiac Operations

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Keywords

congenital heart disease; heart surgery; inflammation; cardiopulmonary bypass; corticosteroids; pediatrics

The clinical appreciation of the post-cardiopulmonary bypass (CPB) inflammatory response and desire to attenuate it with steroids dates back to the 1960's(1). Despite demonstrated benefits of steroids in reducing the post-bypass inflammatory response, data to support an association with improved clinical outcomes have been conflicting in both adults and children undergoing cardiac surgery(2;3).

In this issue of *Pediatric Critical Care Medicine*, Scrascia and colleagues(4) report a meta-analysis of randomized control trials of steroids in pediatric cardiac operations in an effort to overcome previous studies limitations including small sample sizes and wide variability in the type, dosing and timing of steroid administration. Despite being the largest meta-analysis in this population to date, small sample size remains an issue. Only 6 trials with a total of 232 subjects met inclusion criteria for analysis. The inclusion of studies with a widely variable steroid administration further diminishes the ability to draw firm conclusions. For example, in the Toledo-Pereyra study(5), published in 1980 and accounting for 41% of the subjects in the meta-analysis, steroids were administered both preoperatively and postoperatively (6 doses total). The study by Ando and associates(6) only explored postoperative steroids (continuous infusion for a week). Given that the majority of the literature has focused on attenuating the inflammatory response by the administration of preoperative or intraoperative steroids and has reserved postoperative steroids for patients with catecholamine resistant hypotension, the inclusion of these trials in the meta-analysis could be debated. Furthermore, there have been many advances in surgical technique and perioperative management over the last 3 ½ decades since the publication by Toledo-Pereyra that further obscures its relevance in current practice(5). It's not to imply these are flawed or unimportant studies, rather to highlight that these 2 studies with very different dosing regimens accounted for the majority of the substantive findings and the conclusion drawn (7 of the 15 with worsening renal function and 10 of the 15 deaths). Another concern is the

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Disclosure: Dr. Graham receives support from the NIH (R01 HL112968) for an ongoing randomized control trial "Corticosteroid Therapy in Neonates Undergoing Cardiopulmonary Bypass". He has no financial relationships to disclose.

Copyright form disclosures: Dr. Graham received support for article research from NIH (R01 HL112968). His institution received grant support from NIH/NHLBI (RCT to evaluate steroids in pediatric cardiac surgery).

inclusion of the trial by Checchia(7), as 11 of the 28 subjects overlapped with the Bronicki study(8) resulting in these subjects being included twice in this meta-analysis. Finally, the stringent methodology utilized in this meta-analysis, although a strength also resulted in the exclusion of several important studies. These studies should be considered before reaching any definitive conclusion on the utility of steroids in pediatric cardiac surgery and are discussed in the following sections.

Supporting the potential benefits of steroids, Clarizia and associates(9) performed a single center retrospective review of high-risk cardiac operations in 221 children. In propensity score adjusted multivariable regression models, intraoperative steroid use was associated with a reduction of both intensive care unit (ICU) and hospital length of stay. The addition of a preoperative dose was associated with further improvement in both outcomes. A single intraoperative dose of steroids was not found to be associated with a reduction in postoperative duration of mechanical ventilation. However the addition of a preoperative dose was beneficial. The use of steroids was not associated with mortality, inotrope requirements or adverse events(9).

As mentioned in the current article, Pasquali and colleagues(10) utilized the Pediatric Health Information Systems Database to evaluate the outcomes of corticosteroids in children undergoing congenital heart surgery at 38 US centers. Multivariable analysis adjusting for propensity score and individual covariates were performed. Data from 46,730 children were included, 54% of which received steroids. Steroid recipients had longer total and ICU lengths of stay, greater postoperative infection rate, and greater use of insulin. There was no difference in duration of mechanical ventilation or mortality. In multivariable analysis stratified by the risk adjustment for congenital heart surgery (RACHS-1) category, no significant benefit was seen in any group, and the association of steroids with increased morbidities was most prominent in RACHS-1 categories 1 through 3. In a sub analysis restricted to 10,018 neonates, steroids were associated with significantly longer postoperative ICU length of stay and greater use of insulin. There were no other significant differences in outcomes. In this large observational analysis, in contrast to both the previous and current studies, the authors were unable to demonstrate a benefit with steroid administration and found that steroids may be associated with increased morbidity particularly in lower-risk patients(10).

As attention has been drawn to surgical risk groups, neonates have been a particular area of focus. In light of a heightened inflammatory response following CPB, steroids may hold the most benefit in this vulnerable population. In follow up to her previous study, Pasquali and colleagues(11) linked clinical data from the Society of Thoracic Surgeons Database to medication data from the Pediatric Health Information Systems database for neonates undergoing heart surgery from 25 participating centers. Multivariable analysis adjusting for patient and center characteristics and surgical risk category was used to evaluate the association of methylprednisolone regimen with outcome. A total of 3180 neonates were included. In multivariable analysis there was no significant mortality or length of stay benefit associated with any methylprednisolone regimen versus no steroid, and no difference in postoperative infection. In subgroup analysis by surgical risk group, similarly there was no benefit associated with any steroid regimen versus no steroid. However there was a

significant association with infection across all steroid regimens in the lower-surgical risk groups(11).

Finally, in the largest randomized controlled pediatric trial, we prospectively enrolled 76 neonates undergoing cardiac surgery with cardiopulmonary bypass to either a single or two dose steroid groups(12;13). The single dose group received placebo 8 hours prior to surgery and methylprednisolone in the CPB prime. The 2 dose group consisted of methylprednisolone both 8 hours prior to surgery and in the CPB prime. There was no difference in the incidence of low cardiac output syndrome, mortality, inotrope requirement, duration of mechanical ventilation, ICU or hospital stay between groups. These findings are consistent with a similar study design using dexamethasone in a smaller trial(14). In contrast to the findings in the current meta-analysis, plasma creatinine, adjusted fluid balance, and urine output at 36 hours postoperative were slightly worse in the 2-dose steroid group(12). Although limited by the lack of a placebo group these findings are consistent with adult studies(15).

In summary, there is widespread use of perioperative steroids in pediatric cardiac surgery. Although studies have demonstrated that steroids are effective at reducing some inflammatory markers their ability to improve clinical outcomes is less clear and may actually be harmful. Considered in total, the past and present studies continue to highlight the need for a contemporary multicenter randomized controlled trial comparing intraoperative steroids to placebo in neonatal cardiac surgery (e.g., ClinicalTrials.gov identifier: NCT01579513).

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