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Haemodynamic effects of prophylactic post-operative hydrocortisone following cardiopulmonary bypass in neonates undergoing cardiac surgery

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Abstract

Multiple studies have endeavoured to define the role of steroids in paediatric congenital heart surgery; however, steroid utilisation remains haphazard. In September, 2017, our institution implemented a protocol requiring that all neonates undergoing cardiac surgery with the use of cardiopulmonary bypass receive a five-day post-operative hydrocortisone taper. This single-centre retrospective study was designed to test the hypothesis that routine post-operative hydrocortisone administration reduces the incidence of capillary leak syndrome, leads to favourable postoperative fluid balance, and less inotropic support in the early post-operative period. Data were gathered on all term neonates who underwent cardiac surgery with the use of bypass between September, 2015 and 2019. Subjects who were unable to separate from bypass, required long-term dialysis, or long-term mechanical ventilation were excluded. Seventy-five patients met eligibility criteria (non-hydrocortisone group = 52; hydrocortisone group = 23). For post-operative days 0–4, we did not observe a significant difference in net fluid balance or vasoactive inotropic score between study groups. Similarly, we saw no major difference in secondary clinical outcomes (post-operative duration of mechanical ventilation, ICU/hospital length of stay, and time from surgery to initiation of enteral feeds). In contrast to prior analyses, our study was unable to demonstrate a significant difference in net fluid balance or vasoactive inotropic score with the administration of a tapered post-operative hydrocortisone regimen. Similarly, we saw no effect on secondary clinical outcomes. Further long-term randomised control studies are necessary to validate the potential clinical benefit of utilising steroids in paediatric cardiac surgery, especially in the more fragile neonatal population.

Neonates that are undergoing cardiac surgery with the use of cardiopulmonary bypass carry the highest risk of developing post-operative complications, including myocardial dysfunction and low cardiac output syndrome.[1,2] Cardiopulmonary bypass provokes a systemic pro-inflammatory response that is characterised by the release of many neurohumoral substances that ultimately lead to capillary leak and multiorgan dysfunction.[1,3–5] This inflammatory response, which involves a series of complement activation, cytokine release, and endothelial cell activation, is significantly exaggerated in neonates due to their higher metabolic demands, reactive pulmonary vasculature, and immature organ systems.[1,6–8]

Corticosteroids are potent anti-inflammatory agents that have been strategically utilised in paediatric cardiac surgery to blunt this inflammatory response.[9–13] Multiple studies have demonstrated that corticosteroids are significantly effective in reducing post-bypass inflammation through gene modification resulting in the upregulation of anti-inflammatory cytokine (Interleukin-10) synthesis and the downregulation of pro-inflammatory cytokine (tumor necrosis factor-alpha, interleukin-1 beta, interleukin-6, and interleukin-8) synthesis, nitric oxide synthesis, and complement activation.[8,10,14] Despite what we know about corticosteroids and their effects on inflammation, there remains a considerable degree of uncertainty regarding their impact on post-operative clinical outcomes.[3,6,12,13,15–17]

Several randomised control trials have sought to assess the effects of corticosteroids on short-term and longer-term clinical outcomes in paediatric patients that have undergone cardiac surgery.[2,6,17–30] Recent meta-analyses by Gibbison et. al and Bronicki et. al found evidence to suggest that corticosteroids reduce the duration of post-operative mechanical ventilation and favourably impact post-operative fluid balance.[6,30] They also noted that corticosteroids had minimal to no impact on mortality which was consistent with the previous literature.[6,17,30,31] In lieu of these findings, it is worth noting that the patient selection criterion for the studies

included in these systematic reviews were widely diverse, with several studies excluding neonates altogether.[20,22,25]

This retrospective review was designed to test the hypothesis that routine post-operative hydrocortisone administration reduces the incidence of capillary leak syndrome in neonates who have undergone cardiac surgery with the use of cardiopulmonary bypass and leads to favourable postoperative fluid balance and less inotropic support in the early post-operative period. Additionally, we further sought to determine the impact of post-operative hydrocortisone administration on volume resuscitation, diuretic use, and various clinical outcomes including ICU length of stay, hospital length of stay, duration of mechanical ventilation, and time from surgery to initiation of enteral feeds.

Materials and method

Study design

In September, 2017, our institution implemented a standardised protocol requiring that all neonates undergoing cardiac surgery with the use of cardiopulmonary bypass receive a five-day post-operative hydrocortisone taper. This change in clinical practice was implemented in response to the published results of Robert et al's randomised control trial that demonstrated a significant reduction in the incidence of low cardiac output syndrome with their described steroid regimen.[2] Prior to this protocol change, corticosteroid use at our institution was managed independently by the attending physician on service. This retrospective chart review was conducted at a single-centre university hospital in Jackson, Mississippi. After receiving approval from the University of Mississippi Medical Center Institutional Review Board (reference #2020V0211), data were collected on all term neonates undergoing cardiac surgery with the use of cardiopulmonary bypass between 1 September, 2015 and 1 September, 2019, providing a two-year comparison.

Patient selection

Term and near-term neonates (>36 weeks gestational age) who underwent cardiac surgery with the use of cardiopulmonary bypass within the first 28 days of life were eligible for inclusion. We excluded infants < 36 weeks gestational age, infants weighing less than 2000 grams at birth, infants who were unable to separate from bypass, and infants who required long-term postoperative dialysis or long-term mechanical ventilation (home ventilator).

Data extraction

All information was collected from electronic medical records and entered into a Research Electronic Data Capture database (University of Mississippi Medical Center, Jackson, MS).[32,33] Data pertaining to patient demographics (sex, gestational age, age at surgery, and weight), intraoperative parameters (bypass, cross-clamp, deep hypothermic circulatory arrest, and antegrade cerebral perfusion times), and type of surgery were collected. Post-operative data, including daily net fluid balance, urine output, intravenous diuretic requirements, and daily fluid requirements, were recorded and trended for every patient beginning at the time of arrival to the cardiac ICU through post-operative day seven. A vasoactive-inotropic score, as described by Gaies et al. (See Appendix A), was used as a means of comparing total inotropic support between groups.[34–37] Following admission to the ICU, a vasoactive-inotropic score was abstracted at three random time points per day for post-operative days zero through four. Secondary clinical outcomes included post-operative duration of mechanical ventilation, ICU length of stay, hospital length of stay, and time from surgery to initiation of enteral feeds.

Pre-operative and intraoperative management

All patients received a routine single dose of intraoperative intravenous methylprednisolone (20 mg/kg/dose with a maximum dose of 200 mg). Pre-operative steroids were not routinely administered at our institution. The cardiopulmonary bypass circuit prime consisted of plasmalyte, Heparin, packed red blood cells, fresh frozen plasma, 0.45% normal saline, sodium bicarbonate, calcium chloride, and mannitol. For arch reconstructions, patients were cooled to 25 degrees Celsius and given a dose DelNido cardioplegia. Intermittent ultrafiltration was used to remove extra fluid volume, and zero-balance ultrafiltration was used after antegrade cerebral perfusion to reduce any lactate created during lower body circulatory arrest. We used blood to increase the hematocrit to desired levels upon rewarming and post-clamp (above 24 degrees Celsius), calcium was administered to achieve normal levels.

Post-operative management

Prior to September, 2017, post-operative steroid administration was at the discretion of the attending physician. Some patients did receive hydrocortisone; however, the dose, duration of therapy, and patient selection criteria were highly variable. Patients who were intubated for prolonged periods of time or patients with known airway difficulties typically received a prophylactic four-dose series of dexamethasone to prevent post-extubation airway oedema and extubation failure. This standard of practice was the same for both the pre-protocol and post-protocol groups. All doses of hydrocortisone given in the post-operative period were recorded for both the pre-protocol and post-protocol groups.

Hydrocortisone protocol

Beginning 7 September, 2017, all neonates undergoing cardiac surgery with the use of cardiopulmonary bypass received a bolus of intravenous hydrocortisone (4 mg/kg) upon returning to the cardiac ICU, followed by a bolus regimen that was tapered over five days as follows: 1 mg/kg every 6 hours × 48 hours, 1 mg/kg every 8 hours × 24 hours, 1 mg/kg every 12 hours × 24 hours, then stopped.

Statistical methods

The Statistical Product and Service Solutions (IBM SPSS statistics for windows version 27 Armonk, NY: IBM Corp) was used to analyse the data. For normally distributed data, a two-tailed independent t-test was used to analyse continuous variables between the groups. A Fischer exact test was used for categorical values and dichotomous response variables. For non-normally distributed data, the Wilcoxon rank sum test was used. To evaluate the statistical dispersion, the interquartile range was utilised. An alpha of 0.05 was used to determine significance. The 95% confidence intervals were calculated when appropriate.

Results

Between 1 September, 2015 and 1 September, 2019, ninety-seven neonates underwent cardiac surgery with the use of cardiopulmonary bypass. Of these ninety-seven patients, seventy-five (77%)

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met eligibility criteria. The non-hydrocortisone group consisted of fifty-two patients (69%), all of whom had undergone surgery prior to September, 2017 and did not receive a standardised post-operative hydrocortisone tapered regimen. Several patients in this group did receive several doses of hydrocortisone; however, the amount of hydrocortisone used in this group was significantly less ($p < 0.001$) (see supplemental materials). The hydrocortisone group consisted of twenty-three patients (31%), all of whom had undergone cardiac surgery after September, 2017 and received a five-day long tapered hydrocortisone regimen in the immediate post-operative period. All patients in hydrocortisone group completed a full five days of therapy.

A demographic comparison of the groups is shown in Table 1. The study groups were statistically homogenous with no major differences in sex, age, weight, or intraoperative risk factors. The average gestational age for both groups was around 38 weeks and the average age at time of surgery was between eight and nine days old. The major types of surgeries that were performed are listed in Table 1. Surgeries listed as "Other" included the following procedures: unifocalisation procedure, pericardial tumor resection, Yasui procedure, right ventricular outflow augmentation, pulmonary valvectomy and main pulmonary artery plication, and right pulmonary artery reimplantation.

A graphical comparison of median values for our primary outcomes which included a vasoactive-inotropic score and net fluid trends for both groups (post-operative days 0–4) is depicted in Figure 1. Patients in the hydrocortisone group had a more-positive net fluid balance for post-operative days 0–1 and a more-negative fluid balance for post-operative days 2–3 in comparison to the non-hydrocortisone group. Net fluid balance was almost equal for both groups on post-operative day 4. Similarly, the median vasoactive-inotropic score for the hydrocortisone group was higher for post-operative days 0 and 1, but lower for post-operative days 3 and 4 in comparison to the non-hydrocortisone group. Individually, none of these differences were found to be statistically significant.

Intravenous furosemide and bumetanide use were similar for both groups for post-operative days 0–7; however, chlorothiazide use in the hydrocortisone group was significantly higher (almost doubled) in comparison to the non-hydrocortisone group (4.4 mg/kg/day versus 1.95 mg/kg/day; $p < 002$) (Table 2). Additionally, the average amount of fluid or blood product that was administered during post-operative days 0–7 was also similar for both groups (Table 3).

Secondary clinical outcomes including ICU length of stay, hospital length of stay, time on the ventilator, and time from surgery to initiation of enteral feeds were similar between groups (Table 1). Overall hospital survival was also similar between groups.

Discussion

The use of prophylactic perioperative steroids in paediatric cardiac surgery has become a common practice in many programs, yet an explicit understanding of their utility remains a topic of much debate. Multiple studies have made a concerted effort to define the role of steroids and assess their impact on post-operative clinical outcomes; however, confounding variables including widely diverse dosing strategies and inclusion/exclusion criteria have made this a challenging endeavour.[6,17,30,38]

There have been only two randomised control trials in the last forty years that have studied the effects of prophylactic steroid administration in neonates undergoing cardiac surgery, specifically in the post-operative period.[2,29] Both Ando et al.[29] and Robert et al.[2] evaluated the impact of a five-to-seven day long tapered hydrocortisone infusion versus normal saline placebo administered after the discontinuation of cardiopulmonary bypass. Specifically, both studies sought to examine the effects of hydrocortisone on treating adrenal insufficiency that may ensue after neonatal open-heart surgery. Despite slightly differed steroid regimens, both studies demonstrated improved fluid balance and urine output with steroid treatment.[2,29,38] Additionally, the larger and more recent of the two studies demonstrated a significant reduction in the incidence of low cardiac output syndrome with their described steroid regimen.[2,38]

Although low cardiac output syndrome has been historically difficult to define, we used negative fluid balance as a surrogate parameter for decreased capillary leak syndrome and an indirect marker of improved cardiac output.[39] We also used vasoactive-inotropic score as a marker of cardiovascular dysfunction, as proposed by Gaies et al.[34] Our study was unable to demonstrate a significant difference in net fluid balance with the administration of a tapered post-operative hydrocortisone bolus regimen. Additionally, we saw no major difference in vasoactive-inotropic score between treatment and non-treatment groups. Although our outcome measures and results differ considerably from the aforementioned randomised control trials, there are several differences in study design that are worth expanding on.

First, our study group included neonates with very complex, critical congenital cardiac anatomy requiring higher risk surgeries. Sixty-four percent of our study participants underwent either a Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery (STAT) 4 or STAT 5 category cardiac operations. Of these operations, forty-one percent were Norwood procedures. This is similar to Robert et al.'s study, but contrasts with Ando et al's study population, which excluded patients with single ventricle anatomy/physiology and only included neonates undergoing complete biventricular repair.[29] Additionally, none of our participants received pre-operative steroids; instead, all patients received a ubiquitous single dose of intravenous methylprednisolone in the operating room, upon induction of anesthesia. This is very different from Robert et al.'s study[2], in which all patients routinely received two doses of preoperative steroids (methylprednisolone 10 mg/kg/dose at 8 hours and 1 hour prior to their surgery) and none of their patients received intraoperative steroids. Lastly, our study examined the effects of a tapered bolus regimen rather than a tapered continuous infusion. Given the long duration of action of hydrocortisone, it is unlikely that tapered bolus dosing and tapered continuous infusion are significantly different. Nonetheless, further studies are needed to determine if there are clinical effects related to preoperative steroid administration or postoperative dosing techniques.

Regarding secondary clinical outcomes, we found that post-operative bolus dose hydrocortisone administration had no impact on intensive care or hospital length of stay, duration of mechanical ventilation, hospital mortality, and time from surgery to initiation of enteral feeds. This is consistent with what was noted in several prior studies.[6,17,30,31]

Our study certainly has limitations; the most significant being the retrospective nature of the study, and the inability to definitively establish true cause-and-effect relationships. Furthermore, this was a single-centre study with a small sample size, limiting the overall power and statistical analysis. Additionally, there was a significant study population size difference between comparison

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Table 1. Descriptive Statistics and Clinical Outcomes

Variable:	Non-hydrocortisone Group (n = 52)		Hydrocortisone Group (n = 23)		P-value
Male, n (%)	24	46%	15	65%	0.142
Female, n (%)	28	54%	8	35%	0.142
Gestational age (weeks)	38.4 ± 0.9 [36–40]		38.7 ± 0.9 [36–40.3]		0.196
Age at operation (days)	8.9 ± 6.6 [2–28]		8.1 ± 5.2 [1–24]		0.698
Birth weight (kg)	3.1 ± 0.4 [2.2–4.2]		3.4 ± 0.5 [2.2–4.7]		0.090
Surgical weight (kg)	3.3 ± 0.4 [2.4–4.2]		3.5 ± 0.6 [2.5–4.9]		0.130
Surgical Details					
Total CPB time (min)	145 ± 59 [44–274]		145 ± 39 [71–236]		0.890
Total cross-clamp time (min)	66 ± 41 [0–163]		80 ± 25 [22–120]		0.110
Total DHCA time (min)	1.5 ± 6.7 [0–45]		1.8 ± 7.3 [0–35]		0.890
Total ACP time (min)	25.8 ± 25 [0–76]		20.5 ± 25.4 [0–79]		0.420
Surgery Type					
BT shunt placement	5	1.9%	0	0%	
Central shunt placement	4	7.6%	0	0%	
Norwood/Sano or BT shunt	13	25%	7	30%	
ASO	3	5.7%	6	26%	
Arch augmentation + ASO	2	3.8%	0	0%	
Arch augmentation + PA band	4	7.6%	0	0%	
Arch augmentation + AV repair	2	3.8%	1	4.1%	
Arch augmentation + MV repair	5	9.6%	2	8.7%	
Aortic arch repair	4	7.6%	2	8.7%	
Truncus repair	3	5.7%	0	0%	
TAPVR repair	2	3.8%	2	8.7%	
DKS + RV-PA conduit	0	0%	2	8.7%	
Other	5	0.9%	1	0.4%	
STAT Category 5	16	30%	9	39%	
STAT Category 4	32	62%	7	30%	
STAT Category 3	3	6%	6	26%	
STAT Category 2	1	2%	1	4%	
ICU LOS (days)	15 ± 26 [3–177]		17.3 ± 23 [3–100]		0.97
Hospital LOS (days)	33 ± 33 [5–198]		30 ± 24 [7–110]		0.42
Time on the ventilator (days)	9.6 ± 23 [1–164]		9.0 ± 12 [1–52]		0.62
Time to enteral feeds (days)	3.4 ± 1.7 [1–10]		3.6 ± 2.1 [1–10]		0.97
Hospital survival, n (%)	47	90%	22	96%	0.660

Note. – Data are shown as n (%), mean + standard deviation [range]. ACP = antegrade cerebral perfusion; ASO = arterial switch operation; AV = aortic valve; BT = Blalock-Taussig; CPB = cardiopulmonary bypass; DHCA = deep hypothermic circulatory arrest; DKS = Daymus–Kaye–Stansel procedure; LOS = length of stay; MV = mitral valve; PA = pulmonary artery; RV-PA = right ventricle to pulmonary artery; STAT = The Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery; TAPVR = total anomalous venous return.

groups which may have led to skewed results. We attribute this population difference to a change in cardiothoracic surgeons that took place in 2017 leading to fewer patient referrals and thus fewer neonatal surgeries. With a retrospective analysis, some data may be incomplete or inaccurate. The ongoing Steroids to Reduce Inflammation After Infant Heart Surgery (STRESS trial) by Hill et al.[40] studying efficacy, safety, pharmacokinetics and pharmacodynamics of methylprednisolone in 1200 infants undergoing congenital heart surgery with primary end point of mortality and length of hospital stay may help standardise the treatment regimen in near future.

In conclusion, we found that the routine administration of a tapered post-operative hydrocortisone bolus regimen in full-term neonates that had undergone cardiac surgery, including single ventricle palliative procedures, with the use of cardiopulmonary bypass had no significant impact on net fluid balance or total

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Table 2. A Comparison of Post-operative Intravenous Diuretic Use for Post-operative Days 0–7

Diuretic:	Non-HC Group (n = 52)	HC Group (n = 23)	P-value	95% Confidence Interval
Furosemide (mg/kg/day)	2.76	3.04	0.169	−0.1176/0.6682
Bumetadine (mg/kg/day)	0.03	0.18	0.267	−0.119/0.4271
Chlorothiazide (mg/kg/day)	1.95	4.4	0.002	0.9357/3.9652

Note. – Data are shown as mean values. Non-HC = non-hydrocortisone, HC = hydrocortisone.

Table 3. Comparison of Fluid Requirements and between Groups for Post-operative Days 0–7

Variable:	Non-HC Group (n = 52)	HC Group (n = 23)	P-value
Fluid or blood product given (mL/kg/day):			
Packed red blood cells	1.85 (IQR, 1.65, 10.95)	5.51 (IQR, 2.4, 66.05)	0.472
Platelets	1.16 (IQR, 0.55, 1.67)	1.49 (IQR, 0.491, 4.71)	0.81
Fresh frozen plasma	1.1 (IQR, 0.2, 4.73)	6.22 (IQR, 0, 45.77)	1.0
Cryoglobulin	0.31 (IQR, 0.143, 1.02)	0.29 (IQR, 0, 2.13)	0.936
Albumin	4.55 (IQR, 3.61, 12.25)	5.22 (IQR, 5.18, 9.04)	0.576
Normal saline	0.41 (IQR, 0.194, 2.69)	2.11 (IQR, 1.5, 2.25)	0.379

Note. – Data are shown as median values with IQR (25, 75). HC = hydrocortisone; IQR = interquartile range; Non-HC = non-hydrocortisone.

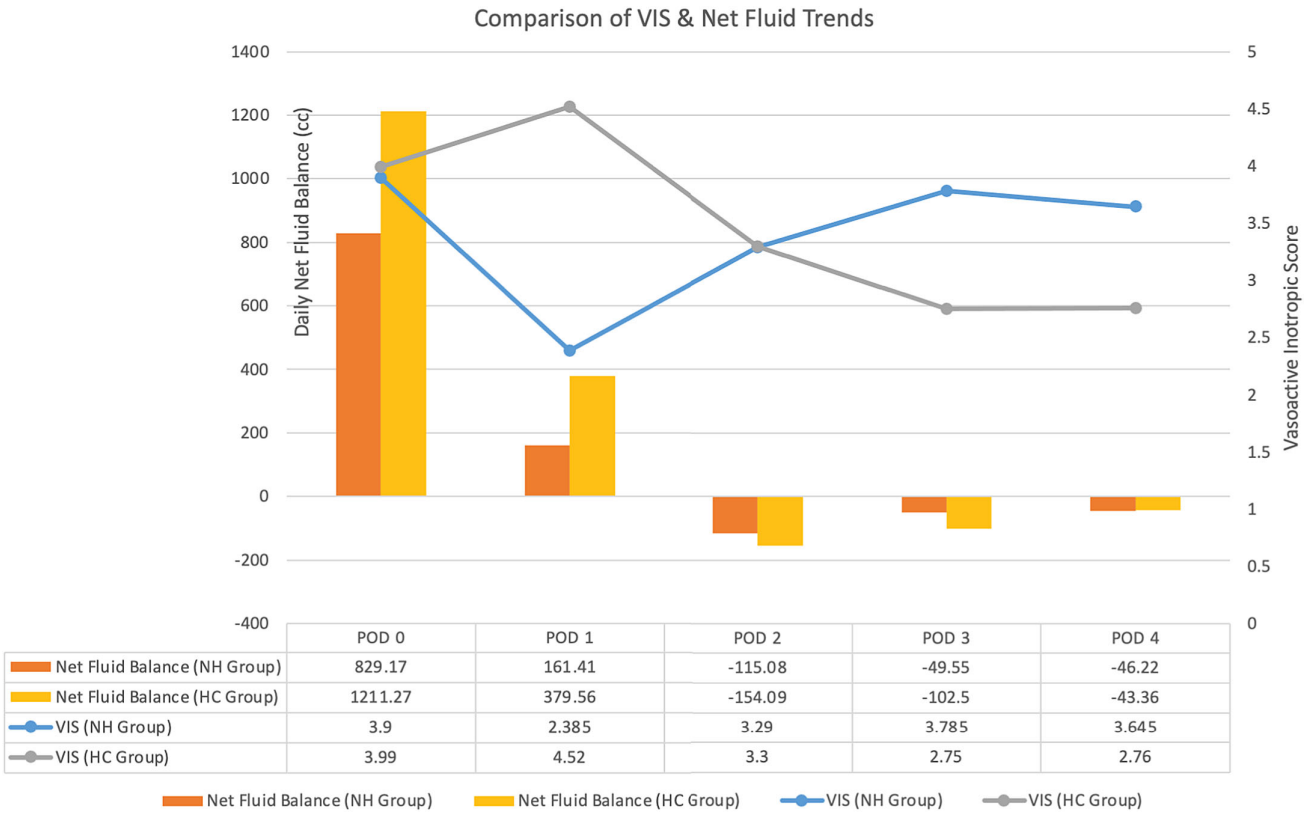

Figure 1. A Combined Comparison of Vasoactive-Inotropic Scores & Net Fluid Trends for Both Groups (Post-operative Days 0–4).
Note. – Data are shown as median values. HC = Hydrocortisone; NH = Non-hydrocortisone; POD = post-operative day; VIS = Vasoactive-Inotropic Score.

amount of required inotropic support in the early post-operative period. Additionally, we saw no difference in secondary clinical outcomes including duration of mechanical ventilation, length of stay, or hospital mortality. Our study demonstrates that further long-term randomised control studies are necessary to validate the potential clinical benefits and/or risks associated with the use of steroids in paediatric cardiac surgery, especially in complex neonatal surgeries. Additionally, further clinical studies looking

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at specific steroid combinations are needed to continue to strengthen our treatment strategies for this very fragile patient population.

Supplementary material. For supplementary material accompanying this paper visit https://doi.org/10.1017/S1047951123000537

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References

1. Kozik DJ, Tweddell JS Characterizing the inflammatory response to cardiopulmonary bypass in children. Ann Thorac Surg 2006; 81: S2347–S2354. doi: 10.1016/j.athoracsur.2006.02.073.
2. Robert SM, Borasino S, Dabal RJ, et al. Postoperative hydrocortisone infusion reduces the prevalence of low cardiac output syndrome after neonatal cardiopulmonary bypass. Pediatr Crit Care Med 2015; 16: 629–636. doi: 10.1097/PCC.0000000000000426.
3. Fudulu D, Lightman S, Caputo M, et al. Steroids in paediatric heart surgery: eminence or evidence-based practice? Indian J Thorac Cardiovasc Surg 2018; 34: 483–487. doi: 10.1007/s12055-018-0670-y.
4. Brix-Christensen, V. The systemic inflammatory response after cardiac surgery with cardiopulmonary bypass in children. Acta Anaesthesiol Scand 2001; 45: 671–679. doi: 10.1034/j.1399-6576.2001.045006671.x.
5. Seghaye MC. The clinical implications of the systemic inflammatory reaction related to cardiac operations in children. Cardiol Young 2003; 13: 228–239. doi: 10.1017/s1047951103000465.
6. Bronicki RA, Flores S, Loomba RS, et al. Impact of corticosteroids on cardiopulmonary bypass induced inflammation in children: A meta-analysis. Ann Thorac Surg 2021; 112: 1363–1370. doi: 10.1016/j.athoracsur.2020.09.062.
7. Anand KJ, Hansen DD, Hickey PR. Hormonal-metabolic stress responses in neonates undergoing cardiac surgery. Anesthesiology 1990; 73: 661–670. doi: 10.1097/00000542-199010000-00012.
8. Hall RI, Smith MS, Rocker G. The systemic inflammatory response to cardiopulmonary bypass: pathophysiological, therapeutic, and pharmacological considerations. Anesth Analg 1997; 85: 766–782. doi: 10.1097/00000539-199710000-00011.
9. Pasquali SK, Hall M, Li JS, et al. Corticosteroids and outcome in children undergoing congenital heart surgery: analysis of the Pediatric Health Information Systems database. Circulation 2010; 122: 2123–2130. doi: 10.1161/CIRCULATIONAHA.110.948737.
10. Bronicki RA, Hall M. Cardiopulmonary bypass-induced inflammatory response: pathophysiology and treatment. Pediatr Crit Care Med 2016; 17 (8 Suppl 1): S272–S278. doi: 10.1097/PCC.0000000000000759.
11. Paparella, D. Cardiopulmonary bypass induced inflammation: pathophysiology and treatment. An update. Eur J Cardiothorac Surg 2002; 21: 232–244. doi: 10.1016/s1010-7940(01)01099-5.
12. Fudulu DP, Gibbison B, Upton T, et al. Corticosteroids in pediatric heart surgery: myth or reality. Front Pediatr 2018; 6: 112. doi: 10.3389/fped.2018.00112.
13. Fudulu DP, Schadenberg A, Gibbison B, et al. Corticosteroids and other anti-inflammatory strategies in pediatric heart surgery: A national survey of practice. World J Pediatr Congenit Heart Surg 2018; 9: 289–293. doi: 10.1177/2150135118762392.
14. Celik JB, Gormus N, Okesli S, et al. Methylprednisolone prevents inflammatory reaction occurring during cardiopulmonary bypass: effects on TNF-alpha, IL-6, IL-8, IL-10. Perfusion 2004; 19: 185–191. doi: 10.1191/0267659104pf733oa.
15. Checchia PA, Bronicki RA, Costello JM, et al. Steroid use before pediatric cardiac operations using cardiopulmonary bypass: an international survey of 36 centers. Pediatr Crit Care Med 2005; 6: 441–444. doi: 10.1097/01.PCC.0000163678.20704.C5.
16. Allen M, Sundararajan S, Pathan N, et al. Anti-inflammatory modalities: their current use in pediatric cardiac surgery in the United Kingdom and Ireland. Pediatr Crit Care Med 2009; 10: 341–345. doi: 10.1097/PCC.0b013e3181a3105d.
17. Scrascia G, Rotunno C, Guida P, et al. Perioperative steroids administration in pediatric cardiac surgery: a meta-analysis of randomized controlled trials*. Pediatr Crit Care Med 2014; 15: 435–442. doi: 10.1097/PCC.0000000000000128.
18. Toledo-Pereyra LH, Lin CY, Kundler H, Replogle RL Steroids in heart surgery: a clinical double-blind and randomized study. Am Surg 1980; 46: 155–160.
19. Bronicki RA, Backer CL, Baden HP, et al. Dexamethasone reduces the inflammatory response to cardiopulmonary bypass in children. Ann Thorac Surg 2000; 69: 1490–1495. doi: 10.1016/s0003-4975(00)01082-1.
20. Lindberg L, Forsell C, Jögi P, Olsson AK Effects of dexamethasone on clinical course, C-reactive protein, S100B protein and von Willebrand factor antigen after paediatric cardiac surgery. Br J Anaesth 2003; 90: 728–732. doi: 10.1093/bja/aeg125.
21. Malagon I, Hogenbirk K, van Pelt J, et al. Effect of dexamethasone on postoperative cardiac troponin T production in pediatric cardiac surgery. Intensive Care Med 2005; 31: 1420–1426. doi: 10.1007/s00134-005-2788-9.
22. Amanullah MM, Hamid M, Hanif HM, et al. Effect of steroids on inflammatory markers and clinical parameters in congenital open heart surgery: a randomised controlled trial. Cardiol Young 2016; 26: 506–515. doi: 10.1017/S1047951115000566.
23. Heying R, Wehage E, Schumacher K, et al. Dexamethasone pretreatment provides antiinflammatory and myocardial protection in neonatal arterial switch operation. Ann Thorac Surg 2012; 93: 869–876. doi: 10.1016/j.athoracsur.2011.11.059.
24. Keski-Nisula J, Pesonen E, Olkkola KT, et al. Methylprednisolone in neonatal cardiac surgery: reduced inflammation without improved clinical outcome. Ann Thorac Surg 2013; 95: 2126–2132. doi: 10.1016/j.athoracsur.2013.02.01.
25. Keski-Nisula J, Suominen PK, Olkkola KT, et al. Effect of timing and route of methylprednisolone administration during pediatric cardiac surgical procedures. Ann Thorac Surg 2015; 99: 180–185. doi: 10.1016/j.athoracsur.2014.08.042.
26. Suominen PK, Keski-Nisula J, Ojala T, et al. Stress-dose corticosteroid versus placebo in neonatal cardiac operations: A randomized controlled trial. Ann Thorac Surg 2017; 104: 1378–1385. doi: 10.1016/j.athoracsur.2017.01.111.
27. Graham EM, Martin RH, Buckley JR, et al. Corticosteroid therapy in neonates undergoing cardiopulmonary bypass: randomized controlled trial. J Am Coll Cardiol 2019; 74: 659–668. doi: 10.1016/j.jacc.2019.05.060.
28. Checchia PA, Backer CL, Bronicki RA, et al. Dexamethasone reduces postoperative troponin levels in children undergoing cardiopulmonary bypass. Crit Care Med 2003; 31: 1742–1745. doi: 10.1097/01.CCM.0000063443.32874.60.
29. Ando M, Park IS, Wada N, et al. Steroid supplementation: a legitimate pharmacotherapy after neonatal open heart surgery. Ann Thorac Surg 2005; 80: 1672–1678. doi: 10.1016/j.athoracsur.2005.04.035.
30. Gibbison B, Villalobos Lizardi JC, Avilés Martínez KI, et al. Prophylactic corticosteroids for paediatric heart surgery with cardiopulmonary bypass. Cochrane Database Syst Rev 2020; 10: CD013101. Published 2020 Oct 12. doi: 10.1002/14651858.CD013101.pub2.
31. Pasquali SK, Li JS, He X, et al. Perioperative methylprednisolone and outcome in neonates undergoing heart surgery. Pediatrics. 2012; 129: e385–e391. doi: 10.1542/peds.2011-2034.
32. Harris PA, Taylor R, Thielke R, et al. Research electronic data capture (REDCap)–a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009; 42: 377–381.

33. Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: building an international community of software platform partners. J Biomed Inform 2019; 95: 103208. doi: 10.1016/j.jbi.2019.103208.
34. Gaies MG, Gurney JG, Yen AH, et al. Vasoactive-inotropic score as a predictor of morbidity and mortality in infants after cardiopulmonary bypass. Pediatr Crit Care Med 2010; 11: 234–238. doi: 10.1097/PCC.0b013e3181b806fc.
35. Kumar M, Sharma R, Sethi SK, et al. Vasoactive Inotrope Score as a tool for clinical care in children post cardiac surgery. Indian J Crit Care Med. 2014;18(10):653–658. doi: 10.4103/0972-5229.142174.
36. Koponen T, Karttunen J, Musialowicz T, et al. Vasoactive-inotropic score and the prediction of morbidity and mortality after cardiac surgery. Br J Anaesth 2019; 122: 428–436. doi: 10.1016/j.bja.2018.12.019.
37. McIntosh AM, Tong S, Deakyne SJ, et al. Validation of the vasoactive-inotropic score in pediatric sepsis. Pediatr Crit Care Med 2017; 18: 750–757. doi: 10.1097/PCC.0000000000001191.
38. Graham EM The role of prophylactic postoperative steroids in pediatric cardiac operations. Pediatr Crit Care Med 2015; 16: 676–677. doi: 10.1097/PCC.0000000000000465.
39. Alten JA, Gaies M. Defining low cardiac output syndrome: an ode to justice Potter Stewart. Pediatr Crit Care Med 2017; 18: 85–87. doi: 10.1097/PCC.0000000000000989.
40. Hill KD, Baldwin HS, Bichel DP, et al. Rationale and design of the STeroids to REduce Systemic inflammation after infant heart Surgery (STRESS) trial. Am Heart J 2020; 220: 192–202. doi: 10.1016/j.ahj.2019.11.016.

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