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A Single-Center Analysis of Methylprednisolone Use during Pediatric Cardiopulmonary Bypass

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Abstract: Cardiac surgery with the use of cardiopulmonary bypass (CPB) is known to induce an inflammatory response in patients. This response may be even more pronounced in pediatric patients given their small body size compared to adults. Several interventions have been instituted in an effort to attenuate this response, including the use of corticosteroids in the pump prime. However, the clinical effectiveness and potential harmful effects of steroid use have been the source of recent debate. Therefore, our institution made the decision to evaluate the use of methylprednisolone in our CPB prime. This evaluation was performed as a formal quality improvement project at The Children's Hospital of Philadelphia. Methylprednisolone was eliminated from the CPB prime for 6 months. At the end of this time period, The Society of Thoracic Surgeons Congenital Heart Surgery Database was used to evaluate clinical outcomes of patients (n = 222). These outcomes were then compared to patients operated on during the 6 months prior to elimination of methylprednisolone (n = 303). No significant clinical benefit was identified in the group of patients who received methylprednisolone. When compared to the group who did not receive methylprednisolone, significantly more patients in the steroids group had a postoperative wound infection (p = .037) or respiratory failure requiring tracheostomy (p = .035). No other differences in clinical outcomes were identified between the two groups. No significant differences in clinical outcomes were identified between neonates who received methylprednisolone (n = 55) and neonates who did not receive steroids (n = 58). Due to the lack of clinical benefit seen with its use, as well as its potential contribution to the incidence of wound infection, methylprednisolone continues to be excluded from the CPB prime at our institution. Methylprednisolone is still given intraoperatively at the request of the attending anesthesiologist and on bypass during orthotopic transplant procedures according to institutional protocol. **Keywords:** methylprednisolone, pediatric, cardiopulmonary bypass, inflammatory response, outcomes. *JECT. 2015;47:155–159*

It is well-established that cardiac surgery with the use of cardiopulmonary bypass (CPB) initiates an inflammatory response in patients (1–8). The full extent of all contributing factors to this process has not been completely elucidated. While surgical and anesthetic factors certainly play a role in this response, the use of CPB appears to exacerbate it (3). Exposure of blood to foreign surfaces, mechanical shear stress, ischemia–reperfusion, hemodilution, blood product transfusion, and hypothermia are specific variables related to CPB that can lead to systemic inflammatory response syndrome (SIRS) postoperatively (1–6). The manifestation of SIRS can vary from mild capillary leak to clinically relevant organ dysfunction (2,4). This response can be even more pronounced in pediatric patients given the greater degree of hemodilution, increased need for blood product transfusion, and more frequent use of hypothermia.

Modifications to CPB-specific variables have been performed in an effort to minimize the inflammatory response to bypass. Such interventions include: circuit miniaturization, the use of various ultrafiltration techniques, leukocyte filtration, and the inclusion of corticosteroids (most frequently

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methylprednisolone) in the CPB prime (2,4–17). Corticosteroids have the ability to attenuate complement activation and pro-inflammatory mediators (interleukin [IL]-1, IL-6, IL-8, leukotrienes, endotoxin, tumor necrosis factor) while augmenting anti-inflammatory mediators (IL-4, IL-10) (4,7–11). Therefore, in its biochemical aspects, methylprednisolone has the ability to decrease the markers of inflammation associated with the use of CPB (6). Recently, however, research has shown no clinical benefit to the perioperative use of methylprednisolone during pediatric cardiac surgery (13–17). Furthermore, several of these studies found that the use of corticosteroids intraoperatively was associated with a greater incidence of infection postoperatively (13,14,17). In their 2012 study, Pasquali et al. (17) also correlated the use of methylprednisolone with an increased length of stay in pediatric patients. Based on this latest data, our institution decided to discontinue the use of methylprednisolone in the CPB prime for 6 months. The permanent removal of steroids from the pump prime was then re-evaluated after an assessment of several clinical outcome variables.

MATERIALS AND METHODS

This assessment was performed as a rapid cycle quality improvement project; therefore, it did not require institutional review board oversight. Prior to making the decision to stop administering steroids to the CPB prime, methylprednisolone (30 mg/kg up to a maximum dose of 500 mg) was given on 100% of CPB cases at our institution. Starting in November of 2013, methylprednisolone was completely eliminated from the CPB prime for a period of 6 months. Patients undergoing orthotopic heart and/or lung transplantation during this time period still received methylprednisolone on bypass at a dose of 15 mg/kg (maximum dose of 1,000 mg) as per institutional protocol for transplant procedures. Additionally, it was established prior to the cessation date that steroids would still be administered if the anesthesiologist deemed it clinically necessary for any given patient. Data from these latter two scenarios were excluded from analysis. No other significant changes were made to the CPB prime, techniques, or personnel during the time period of this evaluation. Furthermore, surgical and anesthesia processes remained consistent throughout the project's timeframe.

Data Analysis and Statistical Methods

After 6 consecutive months of excluding methylprednisolone from the CPB prime, data from patients during this time period were compared to the previous 6 months of patients who did receive steroids. A sub-analysis of neonates was also performed to evaluate the most sensitive patient population. Patients were classified according to previously established diagnostic criteria that incorporate cardiac anatomy and that have been shown to be predictive of perioperative mortality (18). Class 1 indicates two ventricles with no aortic arch obstruction; class 2, two ventricles with aortic arch obstruction; class 3, a single ventricle with no arch obstruction; and class 4, a single ventricle with arch obstruction. All data were harvested from the Society of Thoracic Surgeons Congenital Heart Surgery Database and JOCAP® XL data management system (MAQUET, Rastatt, Germany).

Standard descriptive statistics were used to summarize the data and expressed as median (range) for skewed continuous variables and count (percentage of total) for categorical variables. Comparisons between groups were made using the Wilcoxon rank-sum test or Pearson's chi-square test as appropriate. A sub-group analysis was performed restricting the cohorts to only neonates (age <30 days). Statistical significance was established a priori at a two-tailed p-value $< .05$. All statistical analyses were performed using STATA v10 (Stata Corp., College Station, TX).

RESULTS

Demographic and clinical data for all patients are presented in Table 1. In the 6 months prior to discontinuing the use of methylprednisolone in the pump prime, 303 patients underwent cardiac surgery with the use of CPB. During the 6 months when steroids were omitted from the pump prime, 244 patients underwent procedures involving CPB. Data from 22 of these patients were excluded from analysis because methylprednisolone was still administered at some point during the intraoperative time period. Nine of these patients had undergone orthotopic organ transplantation and 13 received

Table 1. Demographic and clinical comparison between groups (all patients).

	Steroids (n = 303)	No Steroids (n = 222)	p-Value
Male	176 (58.09%)	128 (57.66%)	NS
Prematurity	23 (14.65%)	23 (13.69%)	NS
Birth weight (kg)	3.04 (1–4.48)	3.09 (1–5.86)	NS
Age (days)	338 (1–12311)	148 (0–11231)	.0008
Height (cm)	82 (42–183)	64 (43–184)	.0007
Weight (kg)	7.8 (1.9–103)	6.0 (2–91)	.008
Chromosomal anomaly	47 (15.51%)	39 (17.57%)	NS
Known syndrome	67 (22.11%)	50 (22.52%)	NS
Single ventricle	102 (35.05%)	59 (26.58%)	.040
Diagnostic class			.046
1	178 (61.17%)	145 (65.32%)	
2	10 (3.44%)	17 (7.66%)	
3	53 (18.21%)	27 (12.16%)	
4	50 (17.18%)	33 (14.86%)	

Data presented as median (range) or count (percentage of total).
Diagnostic class: 1: two ventricles, no aortic arch involvement; 2: two ventricles, aortic arch involvement; 3: single ventricle, no aortic arch involvement; 4: single ventricle, aortic arch involvement.
NS, not significant.

Table 2. CPB data (all patients).

	Steroids (n = 303)	No Steroids (n = 222)	p-Value
CPB time (minutes)	62 (7–315)	60.5 (15–249)	.95
Cross-clamp time (minutes)	32 (2–204)	37 (4–136)	.09
DHCA time (minutes)	31 (2–70)	32 (4–98)	.99
Use of neosynephrine	178 (58.75%)	91 (40.99%)	<.001
CPB neosynephrine dose (mcg/kg)	28.6 (1.3–327)	22.8 (.8–508)	.055

Data presented as median (range) or count (percentage of total).
DHCA, deep hypothermic circulatory arrest.

steroids according to the clinical decision of the attending anesthesiologist. With respect to the latter scenario, reasons for methylprednisolone use included: suspected allergic reaction intraoperatively, concern for airway edema, and the continuation of a preoperative steroid regimen.

The time period in which all patients received methylprednisolone included the summer months, during which the greatest percentage of elective Fontan procedures are performed at our institution. Consequently, patients who received methylprednisolone in their prime were significantly older, bigger, and more likely to have single ventricle physiology (diagnostic classes 3 and 4). There was no significant difference in CPB, cross-clamp, or circulatory arrest times between the two groups (Table 2). Significantly more patients in the steroid group required the use of phenylephrine on bypass ($p < .001$). However, there was not a significant difference in the dose of phenylephrine used to control hypotension on bypass between the groups ($p = .055$).

Table 3 presents clinical outcome data for the steroid and non-steroid groups. Significant differences were seen in the number of patients who had a wound infection ($p = .037$) and the number of patients who required tracheostomy ($p = .035$). Both complications occurred more often in the patients who received methylprednisolone in their CPB prime. No significant differences were seen in any of the other clinical outcome variables.

Demographic, CPB, and clinical outcome data from the neonatal sub-analysis are presented in Tables 4–6. Neonates who did not receive methylprednisolone were slightly younger ($p = .038$), but did not differ in any other characteristic. No significant differences in clinical outcomes were

Table 3. Outcome data (all patients).

	Steroids (n = 303)	No Steroids (n = 222)	p-Value
Any complication	128 (42.24%)	82 (37.10%)	NS
Length of stay (days)	8 (2–424)	8 (2–149)	NS
Unplanned readmission within 30 days	14 (4.62%)	10 (4.52%)	NS
Intubation time (days)	.17 (0–269.42)	.17 (.06–101.68)	NS
Reintubation	30 (10.14%)	14 (6.64%)	NS
Respiratory failure requiring tracheostomy	6 (1.98%)	0 (.00%)	.035
Unplanned open sternum	20 (6.60%)	11 (4.98%)	NS
Arrhythmia	16 (5.28)	5 (2.26%)	NS
Any wound infection	9 (2.97%)	1 (.45%)	.037
Wound infection (superficial)	7 (2.31%)	1 (.45%)	NS
Wound infection (deep)	1 (.33%)	0 (.00%)	NS
Mediastinitis	2 (.66%)	0 (.00%)	NS
Any infection, including sepsis	10 (3.30%)	3 (1.35%)	NS
Unplanned cardiac catherization	16 (5.28%)	10 (4.52%)	NS
Unplanned cardiac reoperation	13 (4.29%)	10 (4.52%)	NS
Postoperative mechanical circulatory support	12 (3.96%)	8 (3.62%)	NS
Cardiac arrest	15 (4.95%)	7 (3.17%)	NS
Seizure	9 (2.97%)	2 (.90%)	NS
Renal failure requiring dialysis	2 (.66%)	0 (.00%)	NS
Death prior to discharge	10 (3.30%)	8 (3.64%)	NS

Data presented as median (range) or count (percentage of total).
NS, not significant.

Table 4. Demographic and clinical comparison between groups (neonates only).

	Steroids (n = 55)	No Steroids (n = 58)	p-Value
Male	35 (63.64%)	36 (62.07%)	NS
Prematurity	6 (17.14%)	3 (5.17%)	NS
Birth weight (kg)	3.1 (.68)	3.2 (.53)	NS
Age (days)	6 (1–26)	4 (0–29)	.038
Height (cm)	48 (42–54)	50 (43–55)	NS
Weight (kg)	3.2 (1.9–4.6)	3.2 (2–4.1)	NS
Chromosomal anomaly	11 (20.00%)	9 (15.52%)	NS
Known syndrome	13 (23.64%)	10 (17.24%)	NS
Single ventricle	21 (38.18%)	15 (25.86%)	NS
Diagnostic class			NS
1	24 (43.64%)	30 (51.72%)	
2	10 (18.18%)	13 (22.41%)	
3	5 (9.09%)	2 (3.45%)	
4	16 (29.09%)	13 (22.41%)	

Data presented as median (range) or count (percentage of total).
Diagnostic class: 1: two ventricles, no aortic arch involvement; 2: two ventricles, aortic arch involvement; 3: single ventricle, no aortic arch involvement; 4: single ventricle, aortic arch involvement.
NS, not significant.

Table 5. CPB data (neonates only).

	Steroids (n = 55)	No Steroids (n = 58)	p-Value
CPB time (minutes)	79 (12–186)	74.5 (23–182)	NS
Cross-clamp time (minutes)	44 (2–149)	43 (13–136)	NS
DHCA time (minutes)	42 (16–70)	39 (11–98)	NS
Use of neosynephrine	15 (27.27%)	12 (20.69%)	NS

Data presented as median (range) or count (percentage of total). CPB, cardiopulmonary bypass; DHCA, deep hypothermic circulatory arrest; NS, not significant.

Table 6. Outcome data (neonates only).

	Steroids ($n = 55$)	No Steroids ($n = 58$)	p-Value
Any complication	38 (69.09%)	34 (59.65%)	NS
Length of stay (days)	19 (5–179)	15 (3–71)	NS
Unplanned readmission within 30 days	0 (.00%)	3 (5.26%)	NS
Intubation time (days)	1.29 (.11–58.27)	1.21 (.1–11.07)	NS
Reintubation	13 (24.07%)	7 (12.96%)	NS
Respiratory failure requiring tracheostomy	0 (.00%)	0 (.00%)	NS
Unplanned open sternum	13 (23.64%)	10 (17.54%)	NS
Arrhythmia	2 (3.64%)	1 (1.75%)	NS
Any wound infection	4 (7.27%)	1 (1.75%)	NS
Wound infection (superficial)	4 (7.27%)	1 (1.75%)	NS
Wound infection (deep)	0 (.00%)	0 (.00%)	NS
Mediastinitis	0 (.00%)	0 (.00%)	NS
Any infection, including sepsis	4 (7.27%)	2 (3.45%)	NS
Unplanned cardiac catherization	9 (16.36%)	7 (12.28%)	NS
Unplanned cardiac reoperation	3 (5.45%)	6 (10.53%)	NS
Postoperative mechanical circulatory support	5 (9.09%)	6 (10.53%)	NS
Cardiac arrest	7 (12.73%)	5 (8.77%)	NS
Seizure	2 (3.64%)	1 (1.75%)	NS
Renal failure requiring dialysis	0 (.00%)	0 (.00%)	NS
Death prior to discharge	4 (7.27%)	6 (10.53%)	NS

Data presented as median (range) or count (percentage of total).
NS, not significant.

evident in neonates who received methylprednisolone when compared to those who did not receive steroids.

DISCUSSION

Cardiac surgery with the use of CPB is known to produce a systemic inflammatory response that can lead to negative clinical outcomes. Corticosteroids have been shown to attenuate this response by inhibiting the production of pro-inflammatory mediators and increasing the surge of anti-inflammatory mediators secreted as a response to CPB (3,4). While our quality improvement study did not examine cellular markers of inflammation, elimination of methylprednisolone from the CPB prime did not negatively affect short-term clinical outcomes. Prior studies have reported on the effects of removal of various components from the CPB prime, but this is one of the first to focus on changes associated with the removal of steroids from the prime in pediatric cardiac surgery (19,20).

Beyond the negligible benefits of routine methylprednisolone use in pediatric cardiac surgery, research has also indicated a potential link between steroid use and increased postoperative infection (13,14,17). Interestingly, our data are consistent with these published findings. Elimination of methylprednisolone from our CPB prime reduced the incidence of postoperative infection. We did not see a difference in length of stay between patients who received steroids and those who did not as was described by Pasquali et al. (17) in their retrospective review. Methylprednisolone has also been associated with increased postoperative blood glucose levels and subsequent insulin use; however, those variables were not examined in this study (6,17).

There was some concern that discontinuing the use of methylprednisolone in the CPB prime would result in airway edema, but our results showed no difference in intubation time or reintubation rate between groups. One limitation to this finding is that patients for which airway edema was of greatest concern still received steroids at the request of the anesthesiologist, thereby excluding their data from analysis.

The neonatal sub-analysis was performed for two reasons. First, the patient characteristics in the overall cohort were significantly different; the steroid group consisted of more single ventricle patients undergoing elective Fontan procedures. Consequently, the patients receiving methylprednisolone were also older and bigger. The neonatal analysis normalized the population with respect to patient size and diagnostic class. Secondly, neonates have been considered most likely to benefit from the routine use of corticosteroids (17). Their size in particular makes them more susceptible to CPB variables known to contribute to the inflammatory response (e.g., hemodilution). It seems understandable, then, that differences in outcomes resulting from the discontinuation of methylprednisolone might be more appreciable in this population.

In their 2012 retrospective study, Pasquali et al. (17) analyzed clinical outcomes in a large cohort of neonatal cardiac surgery patients, 62% of who received methylprednisolone perioperatively and 38% who did not receive methylprednisolone. Once again, methylprednisolone use did not translate into improved clinical outcomes but was associated with increased postoperative infection in the lower surgical risk group. While our sub-analysis of neonates did not demonstrate a statistically significant difference in wound infection rate between groups ($p = .15$), more neonatal patients who received methylprednisolone had a wound infection when compared to neonates who did not receive steroids. More importantly, our results on neonates did not show any improvement in clinical outcomes with the use of methylprednisolone.

This project is not without limitations. First, small sample sizes, particularly with the neonatal analysis, may have limited our ability to detect all meaningful differences in outcomes. Also, this investigation focused on short-term outcomes so any long-term impact, such as neurodevelopment, could not be evaluated. Lastly, this was a quality improvement project isolated to one institution. A prospective randomized controlled clinical trial could reveal more generalizable data.

In summary, this quality improvement study did not demonstrate a clinical benefit to the routine use of methylprednisolone in our neonatal or pediatric cardiac surgery patients. As a result, methylprednisolone continues to be excluded from our CPB prime. Steroids are still administered perioperatively at the discretion of the anesthesiologist and on bypass during orthotopic heart and/or lung transplantation procedures as it continues to be institutional protocol.

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