Perioperative Methylprednisolone and Outcome in Neonates Undergoing Heart Surgery

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KEY WORDS

congenital heart disease, heart surgery, outcomes

ABBREVIATIONS

LOS—length of stay

PHIS—Pediatric Health Information Systems

STS-CHS—Society of Thoracic Surgeons Congenital Heart Surgery

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WHAT'S KNOWN ON THIS SUBJECT: Recent studies have called into question the benefit of perioperative corticosteroids in children undergoing heart surgery, but have been limited by small sample size, the lack of placebo control, and the grouping of various steroid regimens together in analysis.

WHAT THIS STUDY ADDS: We evaluated outcomes across methylprednisolone regimens versus no steroids in a large cohort of neonates and found no mortality or length-of-stay benefit associated with any regimen, and a higher risk of infection in certain subgroups.

abstract

BACKGROUND: Recent studies have called into question the benefit of perioperative corticosteroids in children undergoing heart surgery, but have been limited by the lack of placebo control, limited power, and grouping of various steroid regimens together in analysis. We evaluated outcomes across methylprednisolone regimens versus no steroids in a large cohort of neonates.

METHODS: Clinical data from the Society of Thoracic Surgeons Database were linked to medication data from the Pediatric Health Information Systems Database for neonates (≤ 30 days) undergoing heart surgery (2004–2008) at 25 participating centers. Multivariable analysis adjusting for patient and center characteristics, surgical risk category, and within-center clustering was used to evaluate the association of methylprednisolone regimen with outcome.

RESULTS: A total of 3180 neonates were included: 22% received methylprednisolone on both the day before and day of surgery, 12% on the day before surgery only, and 28% on the day of surgery only; 38% did not receive any perioperative steroids. In multivariable analysis, there was no significant mortality or length-of-stay benefit associated with any methylprednisolone regimen versus no steroids, and no difference in postoperative infection. In subgroup analysis by surgical-risk group, there was a significant association of methylprednisolone with infection consistent across all regimens (overall odds ratio 2.6, 95% confidence interval 1.3–5.2) in the lower-surgical-risk group.

CONCLUSIONS: This multicenter observational analysis did not find any benefit associated with methylprednisolone in neonates undergoing heart surgery and suggested increased infection in certain subgroups. These data reinforce the need for a large randomized trial in this population. *Pediatrics* 2012;129:e385–e391

Corticosteroids are administered to children undergoing heart surgery with the aim of reducing the inflammatory response associated with cardiopulmonary bypass.¹ Although previous studies have shown that corticosteroids are effective at reducing levels of various inflammatory markers in this setting, clinical outcomes associated with corticosteroids are less clear.^{2,3} Some analyses have suggested that corticosteroids are associated with improved outcomes, however other recent analyses have called this into question.^{4–6} Many studies have been limited by small sample size and the grouping of various steroid regimens together in analysis.

It has been hypothesized that 2-dose regimens (most often 1 dose given the night before surgery, and 1 dose in the operating room) may be more effective than a single dose.^{4,7} However, a recent single-center trial evaluated the outcomes associated with methylprednisolone (the most common corticosteroid used in this setting) in neonates, and did not find any benefit to a 2-dose regimen.⁸ There were too few deaths to assess mortality, and the study did not include a placebo control group. Thus, the impact of corticosteroid regimen on neonatal outcomes in relation to no treatment remains unclear.

The purpose of this analysis was to evaluate outcomes across regimens of methylprednisolone, in comparison to a no steroid control group, in a large multicenter cohort of neonates undergoing heart surgery. We chose to evaluate neonates because this subgroup is thought to be most likely to benefit from corticosteroids, and it has been the subject of recent analyses.⁸ Evaluation of a large cohort permits analysis of end points, such as mortality and postoperative infection not able to be assessed in smaller studies, in addition to more commonly studied outcomes such as length of stay (LOS).

METHODS

Data Source

The Pediatric Health Information Systems (PHIS) and Society of Thoracic Surgeons Congenital Heart Surgery (STS-CHS) Databases were used for this analysis. Data from 30 centers participating in both databases from 2004 to 2008 were linked by using the method of “indirect identifiers” as previously described and verified.^{9,10} In brief, this method involves matching records on the center where the neonates were hospitalized, date of birth, date of admission, date of discharge, and gender. Overall, data on 90% of 45 830 eligible patients were successfully linked by using this methodology.⁹ Linking these data enables us to capitalize upon the strengths of both data sets and use the detailed diagnosis and procedure information in the STS-CHS Database and medication data from the PHIS Database.^{9,10}

The PHIS Database is a large inpatient administrative database (>4.6 million discharges) of 41 US pediatric hospitals affiliated with the Child Health Corporation of America. Data collected include demographics, International Classification of Diseases, Ninth Revision diagnosis and procedure codes, outcomes data, and resource utilization data including pharmaceuticals, imaging, laboratory studies, and hospital charges. Evaluation of data quality and reliability through systematic monitoring includes bimonthly coding consensus meetings, coding consistency reviews, and quarterly data quality reports.

The STS-CHS Database is the largest pediatric heart surgery registry in the world. It contains data on >180 000 surgeries performed since 1998. Data collected include preoperative, operative, and outcomes data on all children undergoing heart surgery at participating centers. Diagnoses and procedures are coded by clinicians and affiliated

personnel by using the International Pediatric and Congenital Cardiac Code.¹¹ Evaluation of data quality includes the intrinsic verification of data (eg, identification and correction of missing and out-of-range values and inconsistencies across fields), along with a formal process of in-person site visits and data audits conducted by a panel of independent data quality personnel and pediatric cardiac surgeons at 5 randomly chosen institutions each year.¹²

This study was approved by the institutional review boards at Duke University and The Children’s Hospital of Philadelphia with waiver of informed consent.

Study Population

Thirty centers ($n = 41\,371$ patients with successfully linked STS-CHS and PHIS data as described above) were eligible for inclusion. Centers with >15% missing data for any STS-CHS study variable were excluded ($n = 5$ centers). Although the STS-CHS Database contains nearly complete data regarding procedure and in-hospital mortality, not all centers submit complete data for other variables, and it is standard practice to exclude centers with >15% missing data for key study variables, to maximize data integrity and minimize missing data.¹³ This left 25 centers ($n = 32\,660$ patients) eligible for inclusion. Only patients ≤ 30 days of age (neonates) at the time of surgery ($n = 8446$) were included, because this was the subgroup of interest for the current study. Neonates undergoing any surgery classified in the Society of Thoracic Surgeons-European Association for Cardiothoracic Surgery (STS-EACTS) risk stratification system (category 1 = lowest mortality risk; category 5 = highest mortality risk) were included.¹⁴ This system was developed to adjust for case-mix based on empirical data from nearly 80 000 patients.¹⁴ Ninety-eight percent ($n = 8280$) of eligible neonates were classified in the

STS-EACTS system; only the first operation of the admission and surgeries involving cardiopulmonary bypass ($n = 4492$) were included, because corticosteroids are not routinely used in cases not involving cardiopulmonary bypass. Those who received another corticosteroid (other than methylprednisolone) on the day before or day of surgery were excluded ($n = 1001$) because the primary objective of this study was to compare methylprednisolone regimens. From the remaining cohort, patients with missing PHIS medication data or missing weight data ($n = 311$) were excluded, leaving a final study population of 3180 neonates from 25 centers. It is noteworthy that comparison of the included cohort with those excluded because of missing data revealed similar characteristics including age, weight, gender, proportion with prematurity, and overall distribution of STS-EACTS risk categories. The group with missing data tended to have fewer preoperative risk factors.

Data Collection

Data were collected from both the STS-CHS and PHIS Databases including: age (PHIS), prematurity (PHIS), gender (PHIS), race (PHIS), weight (STS-CHS), the presence of any noncardiac/genetic abnormality (STS-CHS), any preoperative risk factor (as defined in the STS-CHS Database), previous cardiothoracic surgery (STS-CHS), STS-EACTS risk category (STS-CHS), and center average annual surgical volume of all STS-EACTS-classified surgeries (STS-CHS).¹⁵

Primary Exposure

The primary exposure was the receipt of methylprednisolone on the day before or day of surgery (or both) as coded in the PHIS Database. A previous query has documented that this captures both methylprednisolone given intravenously or through the bypass circuit in the operating room.⁶ The PHIS database

captures information regarding the day of administration of a medication but not the time of administration.

Outcomes

Primary outcomes included in-hospital mortality (PHIS) and postoperative LOS (combination of STS-CHS/PHIS data). Secondary outcomes included postoperative ICU LOS (combination of STS-CHS/PHIS data), and postoperative infection (sepsis, mediastinitis, wound infection, or endocarditis, as defined in the STS-CHS Database).¹⁵

Analysis

Study variables were described by using standard summary statistics. Unadjusted outcomes were compared across methylprednisolone groups by using χ^2 and Kruskal-Wallis tests. Examination of the distribution of methylprednisolone regimens across centers revealed that the choice of regimen appeared largely center-dependent. We therefore decided to use a model-based analytic approach rather than a propensity adjustment because we were concerned that a single overall propensity model ignoring the center would not fit the data, yet the relatively limited number of patients per center made the estimation of center-specific propensity coefficients infeasible. Thus, multivariable analysis was used to evaluate outcomes associated with methylprednisolone regimens. The method of generalized estimating equations with robust sandwich SE estimators was used to account for unexplained between-hospital variation by treating observations within a hospital as clustered (correlated). Odds ratios and 95% confidence intervals are reported for dichotomous outcome variables from the logistic models. For the linear models, LOS was not normally distributed and was log-transformed for analysis. The residuals from these models were well approximated by a normal distribution. Regression coefficients from the linear

models were exponentiated, and the ratio of LOS between groups with 95% confidence intervals was reported. All models were adjusted for age, gender, weight, race, prematurity, any noncardiac/genetic abnormality or other STS-CHS preoperative risk factor, previous cardiothoracic surgery, year of surgery, STS-EACTS surgical risk category, and mean annual center volume of STS-EACTS-classified cases.

Several sensitivity analyses were performed. First, stratified analyses were performed in STS-EACTS categories 1 to 3 (the “low”-surgical-risk group), and STS-EACTS categories 4 to 5 (the “high”-surgical-risk group) to evaluate whether the impact of methylprednisolone regimen on outcome differed by STS-EACTS risk category. Next, we repeated the overall analysis restricting the population to those with an operating room entry time of 8 AM or earlier. This was done to minimize the possibility that a patient received 2 doses of methylprednisolone on the day of surgery (most regimens involving more than 1 dose used in clinical practice call for administration once in the operating room and once 8 to 12 hours before surgery). Finally, to better assess the generalizability of the results and whether our findings were sensitive to the inclusion of certain centers in the analysis, we removed all center-level exclusion criteria (as described above) and included any patient from any of the 30 centers with complete data and repeated the analysis. All analyses were performed using SAS version 9.2 (SAS Institute, Inc, Cary, NC). A P value <0.05 was considered statistically significant.

RESULTS

Study Population

A total of 3180 neonates from 25 centers (36% South, 32% Midwest, 20% West, 12% Northeast) were included. Twenty-two percent ($n = 686$) received methylprednisolone on both the day of and

day before surgery, 12% ($n = 397$) on the day before surgery only, 28% ($n = 901$) on the day of surgery only, and 38% ($n = 1196$) did not receive any type of corticosteroid on the day of or day before surgery.

Study population characteristics are displayed in Table 1. Age, weight, the proportion with prematurity, a noncardiac/genetic abnormality, and any STS-CHS preoperative risk factor, along with the distribution of STS-EACTS risk categories, were similar between groups. The no-steroid group tended to include fewer white patients and higher-volume centers.

Outcomes

Unadjusted results are displayed in Table 2. There was no difference in the primary outcomes of mortality and LOS between groups, whereas ICU LOS and the proportion with postoperative infection were variable.

Adjusted results are displayed in Table 3. In multivariable analysis, there were no significant differences between the methylprednisolone treatment groups versus the no steroid group for any outcome examined. Several sensitivity analyses were performed (Supplemental Fig 1). First, patients were stratified by surgical risk into low (STS-EACTS categories 1–3) and high (STS-EACTS

categories 4–5) risk groups to assess whether outcomes differed across risk group. Second, we excluded patients with operating room start times later than 8 AM from the overall cohort ($n = 2427$ patients remaining), to minimize the possibility of patients receiving 2 doses of methylprednisolone on the day of surgery. Finally, to better assess the generalizability of our findings we removed all center level exclusions and included any patient with available data. In each of these sensitivity analyses, results did not differ significantly compared with the main results (Supplemental Fig 1). The exception was within the low-surgical-risk group (STS-EACTS categories 1–3) where there was a significant association between methylprednisolone use and postoperative infection consistent across all methylprednisolone regimens (overall odds ratio 2.6, 95% confidence interval 1.3–5.2).

DISCUSSION

In this multicenter observational analysis, we did not find a significant benefit associated with any regimen of methylprednisolone examined in neonates undergoing heart surgery. Corticosteroids are administered to patients undergoing heart surgery with the aim of attenuating the systemic inflammatory response and capillary leak syndrome

that can be triggered by cardiopulmonary bypass.^{1,16,17} Although numerous studies have reported that corticosteroids are effective at reducing levels of certain inflammatory markers in this setting, mounting evidence questions the benefit of corticosteroids in relation to clinical outcomes.^{5,6,8}

In a recent meta-analysis, corticosteroids were not associated with any difference in duration of ventilation or LOS.⁵ However, data from only 4 trials (127 patients) could be analyzed because of heterogeneity between studies.⁵ There were too few deaths to evaluate mortality and or other safety outcomes.⁵ An observational analysis performed by our group supported the findings of the meta-analysis in a large cohort of >45 000 children.⁶ We found no benefit of corticosteroids in relation to duration of ventilation or LOS.⁶ The large sample size permitted analysis of mortality, which did not differ between groups.⁶ This analysis grouped all corticosteroids used in clinical practice together and did not differentiate outcomes according to specific regimens.⁶

Previous studies have suggested that corticosteroid regimens involving more than 1 dose may be more effective.^{4,7,18} Lodge et al found that a 2-dose regimen was more effective in reducing alveolar-arterial gradient, pulmonary vascular

TABLE 1 Study Population Characteristics

	Overall ($n = 3180$)	No Steroids ($n = 1196$)	Methylprednisolone Receipt		
			Day of Surgery ($n = 901$)	Day Before Surgery ($n = 397$)	Both ^a ($n = 686$)
Age, d	6 (4–11)	6 (4–11)	7 (4–12)	7 (4–11)	6 (4–10)
Weight, kg	3.2 (2.8–3.6)	3.2 (2.8–3.5)	3.2 (2.8–3.5)	3.2 (2.8–3.6)	3.2 (2.9–3.6)
Male	1886 (59%)	691 (58%)	533 (59%)	234 (59%)	428 (62%)
Race, white	2128 (67%)	733 (61%)	637 (71%)	252 (64%)	506 (74%)
STA-EACTS category 1–3 (vs 4–5)	876 (28%)	333 (28%)	243 (27%)	110 (28%)	190 (28%)
Noncardiac/genetic abnormality	688 (22%)	246 (21%)	207 (23%)	95 (24%)	140 (20%)
Prematurity	438 (14%)	173 (15%)	130 (14%)	51 (13%)	84 (13%)
Any STS preoperative risk factor	1406 (44%)	514 (43%)	399 (44%)	179 (45%)	314 (46%)
Previous CT surgery	53 (1.7%)	24 (2.0%)	19 (2.1%)	3 (0.8%)	7 (1.0%)
Annual center volume, median operations/yr ^b	393 (341–649)	501 (342–649)	358 (328–574)	368 (341–574)	376 (341–708)

Data are displayed as frequency and percent for dichotomous variables, and median and interquartile range for continuous variables. CT, cardiothoracic; EACTS, European Association for Cardiothoracic Surgery; STS, Society of Thoracic Surgeons.

^a Methylprednisolone received both on the day before and day of surgery.

^b Includes all STS-EACTS-classified operations; not limited to neonatal surgery.

TABLE 2 Unadjusted Postoperative Outcomes

	Overall (<i>n</i> = 3180)	No Steroids (<i>n</i> = 1196)	Methylprednisolone Receipt			<i>P</i>
			Day of Surgery (<i>n</i> = 901)	Day Before Surgery (<i>n</i> = 397)	Both ^a (<i>n</i> = 686)	
In-hospital mortality	367 (11.5%)	125 (10.5%)	123 (13.7%)	44 (11.1%)	75 (10.9%)	.13
Total length of stay, d	14 (9–27)	14 (8–26)	15 (9–27)	14 (9–26)	14 (9–28)	.34
ICU length of stay, d	9 (5–17)	8 (5–15)	9 (6–18)	7 (5–16)	9 (6–19)	.006
Infection	287 (9.0%)	87 (7.3%)	76 (8.4%)	50 (12.6%)	74 (10.8%)	.004

Data are displayed as frequency and percent for dichotomous variables, and median and interquartile range for continuous variables.

^a Methylprednisolone received both on the day before and day of surgery.

TABLE 3 Adjusted Postoperative Outcomes

Outcome	Adjusted estimate	<i>P</i>
In-hospital mortality		
Methylprednisolone receipt	Adjusted OR (95% CI)	
Both day of/before surgery	1.00 (0.66–1.50)	.99
Day before surgery	0.95 (0.60–1.52)	.84
Day of surgery	1.28 (0.93–1.75)	.13
No steroids	Reference	
Total length of stay		
Methylprednisolone receipt	Adjusted ratio (95% CI) ^a	
Both day of/before surgery	0.95 (0.83–1.10)	.51
Day before surgery	0.91 (0.81–1.02)	.10
Day of surgery	0.97 (0.88–1.07)	.56
No steroids	Reference	
ICU length of stay		
Methylprednisolone receipt	Adjusted ratio (95% CI) ^a	
Both day of/before surgery	1.12 (0.87–1.45)	.15
Day before surgery	0.92 (0.75–1.13)	.44
Day of surgery	1.04 (0.84–1.29)	.69
No steroids	Reference	
Infection		
Methylprednisolone receipt	Adjusted OR (95% CI)	
Both day of/before surgery	1.37 (0.81–2.33)	.25
Day before surgery	1.56 (0.96–2.52)	.07
Day of surgery	1.07 (0.66–1.73)	.78
No steroids	Reference	

OR, odds ratio; CI, confidence interval.

^a Adjusted ratio of length of stay between groups.

resistance, and extracellular fluid accumulation in piglets exposed to cardiopulmonary bypass.⁷ Clarizia et al⁴ retrospectively evaluated 221 children undergoing high-risk cardiac operations at their institution and found that a 2-dose regimen was associated with a greater reduction in the duration of ventilation and LOS. Evaluation of mortality was limited because of the small number of events. However, the results of these studies differ from a recent clinical trial. Graham et al⁸ randomly assigned 76 neonates to 2-dose versus

single-dose methylprednisolone. There was no difference in the primary end point of low cardiac output syndrome, or any difference in LOS or duration of ventilation. The 2-dose regimen was associated with higher postoperative serum creatinine and reduced diuresis.⁸ There were too few deaths to assess mortality, and the study did not include a placebo control group.⁸ Thus, it unclear whether both regimens examined were equally effective in comparison with control or whether neither was effective.

The current study builds upon these recent analyses through analyzing a large multicenter cohort of neonates undergoing heart surgery, which enables evaluation of more rare end points. In addition, the inclusion of a control or “no-steroid” group also permits the assessment of outcome associated with various methylprednisolone regimens in relation to no treatment. We did not detect a significant benefit associated with any of the regimens of methylprednisolone examined. It has been previously hypothesized that corticosteroids may not completely address the multifaceted inflammatory response after cardiopulmonary bypass. Several studies have shown that, whereas corticosteroids can reduce levels of certain inflammatory markers, this effect is not universal, and other markers of inflammation may not be impacted.^{2,19} In addition, consistent with our previous analysis of a larger cohort of patients, we found that methylprednisolone was associated with increased postoperative infection.⁶ This effect was seen only in the lower-risk surgical group. These lower-risk operations are generally associated with shorter cardiopulmonary bypass times and reduced inflammatory response such that little benefit from the anti-inflammatory properties of corticosteroids may be expected, and the potential risks of therapy may have a relatively greater impact on outcome.⁶

Finally, this study demonstrates the power of linkage and analysis of large pediatric data sets to answer questions not able to be evaluated by using single-center data, or individual data sets alone.⁹ Multicenter databases can provide adequate power to overcome the rarity and heterogeneity of disease. These data sources also allow analysis of practice variation from center to center, and how practice variation impacts outcome. Many types of outcomes and comparative effectiveness studies can

be conducted (with additional analyses possible when databases are linked), and these databases can also provide information that may aid in better planning future studies. In particular, the study of perioperative corticosteroids highlights many of the difficulties in conducting pediatric clinical research and the limitations of available methodologies, including the heterogeneity of disease, the limitations of single-center studies, and need for multicenter data to provide adequate power. It is also often true, as in this case, that new therapies become widely adopted into routine pediatric practice, based on extrapolation from adults or small pediatric studies, making conducting more rigorous large-scale studies difficult due to the lack of clinical equipoise.²⁰ However, more recent analyses of large data sets have shown that there is in fact widespread variation in the way corticosteroids are used in this setting, and have questioned the clinical benefit associated with corticosteroids.^{1,6} These data support the feasibility and necessity of a large randomized trial.

This study is subject to the limitations of any observational analysis, including selection bias and the potential impact of confounders. We attempted to account for known patient and center confounders, but there may be other unmeasured factors that impact methylprednisolone receipt and/or outcome. Because of the limitations of the data sources, we were

not able to evaluate the specific dose or timing of methylprednisolone in relation to surgery, other than assessment of the day of administration. It is possible that some patients may receive two doses on the day of surgery. If 2 doses were more effective than 1, this could bias our results toward finding a spurious association of regimens involving administration on the day of surgery alone with clinical benefit. However, we found that none of the corticosteroid regimens examined were associated with benefit, and the results of the primary analysis were unchanged when we restricted the cohort to patients who were first cases in the operating room. We were also not able to investigate certain outcomes not collected in detail in the databases, including fluid balance, renal function, blood loss, details and precise duration of mechanical ventilation, and dosage of inotropic agents. In addition, while this represents the largest study of corticosteroids in this population to date, not all US centers were included; and thus the generalizability of these findings requires further study. We did perform a sensitivity analysis within our study cohort and found that our results did not appear to be sensitive to the inclusion of certain patients/centers. In this analysis we also chose to focus on neonates, and our results may not be generalizable to all children undergoing heart surgery. Finally, we were not able to assess the impact of methylprednisolone

on longer-term outcomes because these data are not currently captured in the databases used in this study.

CONCLUSIONS

This multicenter observational analysis of methylprednisolone in neonates undergoing heart surgery, along with other recent studies, calls into question the benefits of corticosteroids in children undergoing heart surgery and furthermore supports the need for an adequately powered clinical trial in this population.

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