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Efficacy of limited cefuroxime prophylaxis in pediatric patients after cardiovascular surgery

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Abstract:

Purpose. The efficacy of limited cefuroxime prophylaxis in pediatric patients after cardiovascular surgery was evaluated.

Methods. All patients age 18 years or younger who underwent cardiovascular surgery and received postoperative care from the cardiovascular surgery team between February and July 2006 (preintervention group) and between August 2006 and January 2007 (postintervention group) were eligible for study inclusion. Patients were excluded if they did not receive cefuroxime as postoperative prophylaxis, had a preexisting infection, underwent cardiac transplantation or extracorporeal membrane oxygenation, or underwent delayed sternal closure. The preintervention group received prolonged cefuroxime prophylaxis, and the postintervention group received 24 hours of cefuroxime prophylaxis. Data collected included patient demographics and clinical and laboratory markers of infection, as well as microbiological evidence of and treatment courses for documented or presumed infections.

Results. A total of 210 patients were enrolled in the study. The number of patients who required additional antibiotics for suspicion of clinical infection did not significantly differ between the preintervention and postintervention groups (18.6% versus 26.9%, respectively), nor did the rate of documented infection (bacteremia, urinary tract infection, endocarditis, sepsis) (42.1% versus 48.3%, respectively). Moreover, indications for the antibiotics initiated were similar between the preintervention and postintervention groups. Clinical and laboratory signs of postoperative infection were similar between groups. There were no differences in postoperative white blood cell counts, peak serum glucose levels, and platelet nadir between groups.

Conclusion. Limiting postoperative cefuroxime prophylaxis to 24 hours did not increase infectious outcomes in pediatric patients.

The Joint Commission has identified the reduction of surgical-site infections (SSIs) as a major goal for hospital systems in the United States. (1) In order to reduce the risk of infection while preventing the development of resistant organisms, organizations including the American Society of Health-System Pharmacists (ASHP), the Society of Thoracic Surgeons (STS), the Centers for Medicare and Medicaid Services, and the Centers for Disease Control and Prevention have developed guidelines for the selection, initiation, and duration of perioperative antibiotic use. (2-5) When choosing an antimicrobial regimen for SSI prophylaxis, consideration should be given to balancing the prevention of nosocomial infections while avoiding emergence of bacterial resistance, as well as to minimizing drug toxicities and cost. The use of antimicrobials for cardiovascular surgical infection prophylaxis is considered the standard of care, with the goal of preventing SSIs such as wound infection, mediastinitis, and endocarditis.

For patients undergoing cardiothoracic surgery, both cefazolin and cefuroxime are recommended for SSI prophylaxis due to their spectrum of activity against staphylococci and aerobic gram-negative pathogens. (2,3,5) However, the duration of antibiotic use is often debated among

practitioners. The National Surgical Infection Prevention Project (SIP) recommends that antibiotic prophylaxis be continued up to 24 hours after cardiothoracic surgery, while STS and ASHP recommend continuing antibiotics for 48 and 72 hours, respectively. (2-4) Most of these recommendations are based on adult studies and extrapolated to pediatric patients. However, the use of extended antimicrobial prophylaxis in children after cardiothoracic surgery remains current practice among some surgeons. (6-8) The exact reason is unclear but may reflect ongoing practices taught during pediatric cardiovascular surgical fellowship training and individual surgeon practice variation.

At our children's hospital, cefuroxime is the standard antibiotic for SSI prophylaxis in children after cardiothoracic surgery. In August 2006, our hospital changed its practice of not limiting the duration of postoperative prophylaxis to routinely discontinuing prophylactic antibiotics 24 hours after surgery. The primary objective of this study was to compare differences in infectious complications in children who received unlimited cefuroxime prophylaxis after cardiothoracic surgery and those who received cefuroxime for only 24 hours after surgery.

Methods

This retrospective study was conducted after receiving approval from the institutional review board at Indiana University. All patients age 18 years or younger who underwent cardiovascular surgery and received postoperative care from the cardiovascular surgery team between February 2006 and January 2007 at Riley Hospital for Children in Indianapolis, Indiana, were eligible for inclusion in the study. Patients were excluded if they did not receive cefuroxime as postoperative prophylaxis, had a preexisting infection, or underwent cardiac transplantation, extracorporeal membrane oxygenation, or delayed sternal closure. The selected time frame represented six months before and six months after implementation of a change to the standard 24 hours of cefuroxime prophylaxis after pediatric cardiothoracic surgery. In August 2006, cefuroxime prophylaxis was recommended to be limited to 24 hours after cardiovascular surgery. Surgeons received education on the practice change during one of the institution's monthly pediatric cardiovascular quality committee meetings before implementation. This was not an automatic discontinuation of cefuroxime after 24 hours; rather, recommendations were made during daily rounds by either a clinical pharmacist or the pediatric infectious diseases physician. The pediatric cardiovascular surgeon retained responsibility for either continuing or discontinuing prophylaxis and could refuse to discontinue cefuroxime prophylaxis. Before August 2006, no limit was placed on postoperative prophylaxis, and antimicrobials were typically continued until all central i.v. catheters, intracardiac hemodynamic catheters, and chest tubes were removed. Postoperative cefuroxime was given at 50 mg/kg/dose i.v. every 8 hours in patients with normal renal function. Intraoperative antimicrobial prophylaxis was administered in accordance with the SIP project recommendations. (3)

Demographic data collected included age, weight, sex, underlying congenital heart defect and surgical repair, cardiopulmonary bypass, and risk-adjusted classification for congenital heart surgery. (9) Clinical and laboratory data obtained included intraoperative corticosteroid use, white blood cell (WBC) count, serum glucose level, and platelet concentration. The number of postoperative days to reach peak WBC count, peak serum glucose level, and platelet nadir was also recorded. Microbiological data were collected to identify positive blood and urine cultures.

Patients were categorized into two groups: those who required additional courses of antibiotics beyond cefuroxime prophylaxis and those for whom initial prophylaxis was sufficient. Additional antibiotics included those other than cefuroxime (e.g., piperacillin-tazobactam plus vancomycin) that were initiated for empirical treatment. Patients were further categorized by infectious outcomes and local infections: culture-proven bacteremia, urinary tract infection (UTI), endocarditis, culture-negative episode of clinical sepsis, culture-negative rule-out antibiotic course, and culture-negative episode of necrotizing enterocolitis (appendix).

Baseline demographics and clinical characteristics of the preintervention and postintervention groups were compared using the independent-samples t test, chi-square analysis, and Mann-Whitney U test for nonparametric data. Significance was determined using an a priori a of 0.05. Statistical analyses were conducted using Statistical Package for Social Sciences, version 16.0 (SPSS, Inc., Chicago, IL).

Results

Of the 255 patients who met the initial enrollment criteria, 45 were excluded from the final analysis (Figure 1). A total of 210 children were included in the final analysis (102 in the preintervention group and 108 in the postintervention group). Baseline demographics did not significantly differ between groups, except that more patients in the postintervention group had a central i.v. catheter placed intraoperatively compared with the preintervention group ($p = 0.044$) (Table 1).

Additional antibiotics for empirical treatment were initiated in 19 patients (18.6%) in the preintervention group and 29 patients (26.9%) in the postintervention group ($p = 0.156$). Of these, documented infections (bacteremia, UTI, endocarditis, sepsis) occurred in 8 patients (42.1%) in the preintervention group and 14 patients (48.3%) in the postintervention group ($p = 0.675$). Indications for empirical antibiotic therapy were similar between groups (Table 2). Patients for whom empirical antibiotics were initiated were younger (median age, 7.5 months versus 14 months) and weighed less (median weight, 6.8 kg versus 9.1 kg) than patients who did not receive additional antibiotics ($p = 0.002$). Prophylactic cefuroxime was continued for a greater mean [+ or -] S.D. duration in the preintervention group (4.1 [+ or -] 3.4 days versus 1.2 [+ or -] 0.5 days in the postintervention group, $p < 0.005$).

[FIGURE 1 OMITTED]

Clinical and laboratory signs of postoperative infection were similar between the groups. There were no differences in postoperative WBC count, peak glucose level, and platelet nadir between groups (Table 3).

Blood and urine cultures were obtained in 51% (n = 52) and 36.1% (n = 39) of patients in the preintervention and postintervention groups, respectively ($p = 0.03$). The mean [+ or -] S.D. number of total cultures (blood and urine) obtained per patient was significantly greater in the postintervention group (5.2 [+ or -] 3.9 versus 3.7 [+ or -] 2.8 in the preintervention group, $p = 0.034$), as was the mean [+ or -] S.D. number of blood cultures obtained per patient (3.2 [+ or -] 2.9 versus 2.1 [+ or -] 1.6 in the preintervention group, $p = 0.018$). The mean [+ or -] S.D.

number of urine cultures obtained per patient did not differ significantly between groups (p = 0.266). Positive blood cultures were identified in 3 patients (2 in the preintervention group, 1 in the postintervention group, p = 0.207), positive urine cultures in 9 patients (3 in the preintervention group, 6 in the postintervention group, p = 0.803), and positive blood and urine cultures in 2 patients (both in the postintervention group, p = 0.505). One patient in the preintervention group had a urine culture with vancomycin-resistant enterococci (VRE) that was not treated due to presumed colonization.

Discussion

In balancing evidence-based recommendations for postoperative antimicrobial prophylaxis with current practice, our institution changed its long-standing practice of continuing postoperative prophylactic antibiotics until all chest tubes or central i.v. catheters were removed. The new practice is to routinely discontinue prophylactic antibiotics 24 hours after surgery. The results of this study demonstrated that limiting the duration of postoperative cefuroxime prophylaxis to 24 hours after surgery did not increase infectious outcomes or documented postoperative infections.

Surveys of practice have found that the prolonged continuation of prophylactic antibiotics after pediatric cardiac surgery, even for as long as chest tubes or intracardiac hemodynamic catheters remain in place, has existed for decades and has not changed much in the past 30 years. (6-8,10) Our hospital recently surveyed congenital heart surgeons worldwide and found that only 60% of attending surgeons reported discontinuing the designated surgical prophylaxis 24-48 hours after surgery. (10)

The dangers in continuing prophylactic antibiotics for a prolonged period of time are alteration of bacterial susceptibility patterns and emerging resistance. Prolonged use of prophylactic antimicrobials has been associated with increased antibiotic resistance in the targeted organisms but not with any significant difference in the prevention of infection. (11,12) In addition, studies have found that the development of VRE, which is increasingly associated with nosocomial infections, is potentially increased by previous exposure to broad-spectrum cephalosporins during earlier hospital admissions. (13)

The results of this study add to the currently limited and conflicting data regarding the optimal duration of antibiotic prophylaxis after pediatric cardiovascular surgery. Kato et al. (14) found a reduction in postoperative infections in children receiving 48 hours of antibiotic prophylaxis versus prolonged prophylaxis (7-10 days or until chest tube removal). Nasal carriage of resistant Pseudomonas aeruginosa, methicillin-resistant Staphylococcus aureus (MRSA), and Candida species was increased in the prolonged prophylaxis group. A significant increase in SSIs and bloodstream infections was observed when comparing 48 hours of postoperative cefazolin to prolonged cefazolin (until the removal of chest tubes or central venous catheters) in children who underwent cardiac surgery. (15) We did not observe any documented SSIs in our study, though it remains to be seen if this finding will be sustained over time.

Antimicrobial resistance is a growing concern in all hospital systems due to the documented growth of cephalosporin-resistant Enterobacteriaceae and rising rates of MRSA and VRE. (11,16) Continuing prophylactic antibiotics for more than 48 hours increases acquired antibiotic

resistance. (17) This study was not designed to evaluate changes in resistance patterns due to extended durations of prophylactic antibiotic therapy, but we did observe one episode in which a urine culture from a patient in the preintervention group grew vancomycin-resistant Enterococcus faecium. Prolonged exposure to antibiotics contributes to the development of antibiotic resistance in surrounding flora both immediately and during later admissions. Since many cardiac procedures in children are conducted over multiple admissions, the development of resistant organisms is a valid concern. A balance must be struck between sufficient durations of prophylactic antibiotic use and emergence of resistance.

Other variables may have influenced infection rates. As our study was populated with patients from birth through age 18 years, immune function varied widely among patients. The patient's health status before surgery and any risk factor for increased susceptibility to infection could not be completely controlled for in this study. Because only the six months before and after the practice change were evaluated, the long-term benefits of 24 hours of antibiotic prophylaxis in this population could not be evaluated. Further, we could not determine whether these findings would be sustained long term. The lack of a power analysis was another limitation of this study. However, there is no evidence that outcomes will significantly differ from those associated with limitless antibiotic use.

Table 1.
Patient Demographics and Baseline Characteristics (a)

Characteristic	Preintervention (n = 102)	Postintervention (n = 108)
Mean (range) age, mo.	38.3 (0.1-216)	33.8 (0.1-195)
Mean (range) weight, kg	15.3 (2-102.1)	13.4 (2.4-66)
Male, no. (%) pts	56 (54.9)	67 (62.0)
RACHS-1, no. (%) pts		
Category 1	9 (8.8)	8 (7.4)
Category 2	31 (30.4)	34 (31.5)
Category 3	56 (54.9)	52 (48.1)
Category 4	5 (4.9)	12 (11.1)
Category 6	1 (1.0)	2 (1.9)
Cardiopulmonary bypass, no. (%) pts	72 (70.1)	83 (76.9)
Intraoperative corticosteroid use, no. (%) pts	72 (70.1)	83 (76.9)
Intracardiac catheter use, no. (%) pts		
Right atrial	69 (67.0)	75 (69.4)
Pulmonary artery	3 (2.9)	8 (7.4)
Left atrial	15 (14.7)	18 (16.7)
Intraoperative CIV use, no. (%) pts	43 (42.1)	61 (56.5) (b)
CIV site, no. (%) pts		
Subclavian	10 (23.0)	12 (19.7)
Intrajugular	3 (6.9)	6 (9.8)
Femoral	30 (69.8)	43 (70.5)
Foley catheter use, no. (%) pts	99 (97.1)	108 (100)

(a) Differences between groups were not statistically significant unless otherwise noted. RACHS-1 = risk-adjusted classification

for congenital heart surgery, CIV = central i.v. catheter.

(b) p = 0.044.

Table 2.
Indications for Empirical Antibiotic Treatment

	No. (%) Patients (a)	
Indication	Preintervention (n = 19)	Postintervention (n = 29)
Documented infection	8 (42.1)	14 (48.3)
Bacteremia	1 (5.3)	1 (3.4)
UTI	2 (10.5)	7 (24.1)
Endocarditis	1 (5.3)	0
Bacteremia and UTI	0	2 (6.9)
Culture-negative clinical sepsis	4 (21.1)	4 (13.8)
Culture-negative rule-out antibiotic course	11 (57.9)	14 (48.3)
Culture-negative NEC	0	1 (3.4)

(a) None of the differences between groups was statistically significant. UTI = urinary tract infection, NEC = necrotizing enterocolitis.

Table 3.
Signs of Postoperative Infection (a)

	Mean Value	
Variable	Preintervention (n = 102)	Postintervention (n = 108)
Peak WBC count	$16.9 \times 10^3/mm^3$	$18.4 \times 10^3/mm^3$
Platelet nadir	$188 \times 10^3/mm^3$	$168 \times 10^3/mm^3$
Peak serum glucose conc.	173.6 mg/dL	175.9 mg/dL
Postoperative days to reach peak WBC count	3.1	3.4
Postoperative days to reach platelet nadir	2.7	2.6
Postoperative days to reach peak glucose conc.	1.7	1.8

(a) None of the differences between groups was statistically significant. WBC = white blood cell

Conclusion

Limiting postoperative cefuroxime prophylaxis to 24 hours did not increase infectious outcomes in pediatric patients.

Appendix--Six infectious outcomes for which pediatric patients were evaluated after cardiovascular surgery

1. Culture-proven bacteremia

2. Urinary tract infection

3. Endocarditis

4. Culture-negative rule-out antibiotic course, defined as

* Empirical antibiotics initiated for presumed catheter-related bloodstream infection or presumed clinical sepsis,

* Blood culture obtained and no organisms or antigen detected,

* Patient does not meet criteria for clinical sepsis or local infection, and

* Antibiotics discontinued after 72 hours.

5. Culture-negative episode of necrotizing enterocolitis

6. Culture-negative episode of clinical sepsis, defined as one of the following clinical signs or symptoms with no other recognized cause:

Patients age over 1 year

* Fever (>38[degrees]C)

* Hypotension (systolic blood pressure of [less than or equal to] 60-65 mm Hg for patients from birth through age 1 year, [less than or equal to] 70 mm Hg for patients age 1-6 years, and [less than or equal to] 80 mm Hg for patients age 6-17 years)

* Oliguria (urine output of [less than or equal to] 1 mL/kg/hr)

* Junctional ectopic tachycardia

* Supraventricular tachycardia and blood culture not done or no organisms or antigen detected in blood and no apparent infection at another site and treatment initiated for sepsis

Patients age 1 year or younger

* Fever (>38[degrees]C)

* Hypothermia (<37[degrees]C)

* Apnea

* Bradycardia

* Junctional ectopic tachycardia

* Supraventricular tachycardia and blood culture not done or no organisms or antigen detected in blood and no apparent infection at another site and treatment initiated for sepsis

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