Original Article

Plasma Concentrations of Cefazolin in Pediatric Patients Undergoing Cardiac Surgery

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ABSTRACT

Background: The guideline for antibiotic prophylaxis in pediatric cardiac surgery is currently unavailable, and the effects of cardiopulmonary bypass (CPB) may result in low plasma cefazolin concentrations and subsequent postoperative surgical site infections (SSIs).

Aims: To demonstrate the calculated-unbound plasma concentrations of cefazolin during uncomplicated pediatric cardiac surgery.

Settings and Design: A prospective observational study that included 18 patients <seven years of age, undergoing elective cardiac surgery with CPB.

Materials and Methods: An intravenous infusion of cefazolin (25 $mg.kg^{-1}$) was administered to patients over 30 minutes within 1 hour before skin incision (first dose). Another 25 $mg.kg^{-1}$ infusion was administered to the CPB prime volume (second dose). Blood samples were obtained at eight time points: 15 minutes after the first dose (T1); before aortic cannulation (T2); immediately after CPB initiation (T3); 30 (T4), 60 (T5), and 120 (T6) minutes after CPB; 15 minutes after CPB discontinuation (T7), and at skin closure (T8). The total plasma cefazolin concentrations were measured using liquid chromatography tandem mass spectrometry.

Results: The unbound cefazolin concentrations were calculated assuming 80%-protein binding. The median cefazolin levels were 18.1 (range 4.3-27.0), 11.9 (2.8-24.1), 31.4 (18.3-66.1), 23.4 (13.7-35.9), 20.2 (15.4-24.9), 17.7 (14.8-18.0), 15.6 (9.8-26.2), and 13.3 (8.3-24.6) $\mu g.mL^{-1}$ from T1-T8, respectively. The cefazolin levels remained four times above the minimum inhibitory concentrations (MICs) for Methicillin-sensitive *S. aureus* (MSSA) and *S. epidermidis* in most patients, but they were inadequate for *Enterobacter* and *E. coli.*

Conclusion: This regimen produced adequate plasma cefazolin concentrations for common organisms that cause SSIs after cardiac surgery.

Keywords: Cardiac surgery, cardiopulmonary bypass, cefazolin, pediatric, surgical site infection

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INTRODUCTION

Neonates and pediatric patients undergoing open heart surgery are susceptible to surgical site infections (SSIs) because of their immature immune systems and various insults from cardiopulmonary bypass (CPB). The reported incidences of postoperative superficial and deep sternal wound infections in adults are 1.6-6.4%[1,2] and 1-4%,[2-4] respectively. Postoperative mediastinitis is associated with an approximately 15-40% increased risk of mortality.[4] However, the rate of SSIs in pediatric cardiac have been reported to be between 1.7-8% in several previous studies.[5-7] The risk factors for pediatric patients to develop the SSIs

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include younger age, especially children less than 1 month, longer duration of the CPB, and increased postoperative blood transfusion.[8,9]

Methicillin-sensitive *S. aureus* (MSSA) and *S. epidermidis* are the most common pathogens isolated from infected surgical sites.[1,10] Gram-negative bacteria are also observed but in a lesser extent. Prophylactic antibiotics, such as a first- or second-generation cephalosporins, including cefazolin, are commonly used in cardiac surgery. The re-administration of the antibiotics should be within two half-lives to maintain the serum level above the minimum inhibitory concentrations (MICs), regardless of any influences from the CPB.[5,11] Cefazolin has a half-life of approximately 1.8 hours; therefore, it should be redosing every 3–4 hours according to the guideline for adult patients.[10] However, the drug level may be inadequate after a large amount of CPB volume is added.[12] The plasma levels of the antibiotic should be maintained above the MICs as long as the incisional site remains open because there is a potential for wound infection that leads to unfavorable consequences in these fragile patients.

The standard guideline regarding prophylactic antibiotics for pediatric cardiac surgery is still unavailable, and the antibiotic protocols are varied among institutional standards. According to the author's institution, we generally administer intravenous infusions of cefazolin at an initial dose of 25 $mg.kg^{-1}$ within 60 minutes before the incision and another 25 $mg.kg^{-1}$ mixed with the CPB circuit prime solution. There were two previously published studies regarding plasma cefazolin concentrations: one study conducted in neonates who weighed less than 10 kg,[13] and the other was performed in patients undergoing CPB with deep hypothermic circulatory arrest (DHCA).[6] Therefore, this study aimed to demonstrate the plasma concentrations of cefazolin during uncomplicated pediatric cardiac surgery.

MATERIALS AND METHODS

This prospective observational study was approved by the Institutional Review Board (Ref. 449/2559) and registered in Clinicaltrials.gov (Ref. NCT03141450). The study enrolled patients from neonate to seven years of age who received cefazolin as a prophylactic antibiotic for elective cardiac surgery with CPB from October 2017 to January 2018. Patients who were allergic to penicillin or cephalosporin or who had a positive family history of allergy to the study drug were excluded. We also excluded patients who had a preexisting hepatic or renal dysfunction, had an episode of infection or antibiotic use within the past two weeks, or had a history of a previous sternotomy. Additionally, the operations with an expected CPB time longer than 3 hours were also excluded. Overall, 18 patients were recruited in this study, and written informed consent was obtained from the parent or the legal guardian of the patients.

General anesthesia was conducted and maintained at a discretion of the attending pediatric cardiac anesthesiologist. Patients were monitored with standard monitoring, invasive arterial blood pressure, and central venous pressure. The patients received intravenous infusion of cefazolin at the dose of 25 $mg.kg^{-1}$ over a period of 30 minutes within one hour before the skin incision (first dose) and an additional dose of 25 $mg.kg^{-1}$ mixed with the CPB prime solution (second dose).

Blood samples were drawn from the existing arterial catheter or directly from the CPB circuit during the CPB period. One mL of blood was collected in a lithium heparin tube. The blood samples were obtained at 15 minutes after the end of intravenous cefazolin infusion (T1); before the cannulation of the aorta (T2); immediately after the CPB initiation (T3); at 30 (T4), 60 (T5) and, 120 (T6) minutes after the CPB commenced; 15 minutes after the CPB discontinuation (T7); and at the end of skin closure (T8). The timing of antibiotic administrations and blood sample collections are illustrated in Figure 1. The samples were kept in a refrigerator at 4°C and delivered to the laboratory within 30 minutes after the blood collection. All blood samples were analyzed for total plasma concentrations of cefazolin. The unbound plasma cefazolin concentrations were calculated assuming that the protein binding of cefazolin was 80%.

The patient characteristics including age, body weight, diagnosis, preoperative hematocrit, serum albumin, and serum creatinine were documented. Blood sampling time, CPB time, aortic cross-clamp time, CPB circuit prime volume, the lowest temperature during CPB, and length of intensive care unit and hospital stays were recorded.

Blood sample analysis

Liquid chromatography with tandem mass spectrometry (LC-MS/MS) was developed, and cefoperazone was used as an internal standard. Cefazolin was extracted using the liquid-liquid extraction technique (LLE) with acetonitrile and methyl-t-butyl ether. Chromatographic separation was carried out on LC-MS/MS using a Kinetex C18 column (50 × 2.1 mm i.d., 1.7 μm, Phenomenex Inc., USA) that was equipped with a C18 guard column (4.0 × 2.0 mm i.d., Phenomenex Inc., USA). The column

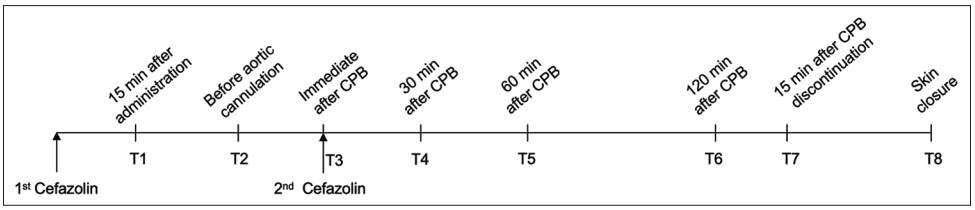

Figure 1: Timing of cefazolin administrations and blood collections

temperature was maintained at 45°C. The mobile phase consisted of a mixture of A: 0.1% aqueous formic acid and B: 0.1% formic acid in acetonitrile, which was delivered at a flow rate of 0.4 mL.min^{-1} in the gradient elution mode.[14,15]

Mass spectra were obtained using a Quattro Premier XE mass spectrometer (Micromass Technologies, UK) that was equipped with an electrospray ionization (ESI) source. The mass spectrometer was operated in the multiple reaction monitoring (MRM) mode. Sample introduction and ionization was electrospray ionization in the positive ion mode. The mass transition ion-pair was selected as m z^{-1} 455.00 to 322.93 for cefazolin and m z^{-1} 646.14 to 530.07 for cefoperazone. Validation of this method was performed as recommended by the USFDA guidelines.[16]

Statistical analysis

This study aimed to evaluate the inappropriate proportion of plasma cefazolin concentrations in pediatric patients during cardiac surgery. The inappropriate plasma cefazolin concentration was defined as the plasma levels that were below the target concentrations for potential organisms causing SSIs. Based on previous studies[6,13] and the authors' experience, the sample size was calculated on the assumption that there would be a 10% incidence of an inadequate plasma cefazolin level. A sample size of 140 samples or 18 subjects was needed to achieve a 95% confidence interval with a 10% margin of error.

Demographic data were analyzed using descriptive statistics. The mean and standard deviation are presented for continuous variables with a normal distribution; otherwise, the median with minimum and maximum values are reported. The statistical analysis was performed using IBM SPSS v 18 Inc., Chicago, IL, USA.

RESULTS

Patient characteristics and demographic data are shown in Table 1. One hundred and twenty-five blood samples were analyzed for plasma cefazolin concentrations. Four samples at T5 and 15 samples at T6 were not drawn due to early CPB termination.

Table 1: Patient characteristics and demographic data

	n=18
Gender:Male	10 (55.6)
Age (mo)	40.0 (2.0,78.0)
Body weight (kg)	13.0±7.1
Diagnosis	
VSD	9 (44.4)
ASD	2 (11.1)
TOF	5 (27.7)
VSD with ASD	1 (5.6)
VSD with subvalvular PS	1 (5.6)
Right atrial mass	1 (5.6)
Preoperative hematocrit (%)	37.6 (30.4,69.0)
Preoperative serum albumin (g.dL^{-1})	4.4 (4.1,4.7)
Preoperative serum creatinine (mg.dL^{-1})	0.3 (0.2,0.6)
Cyanosis	4 (22.2)
Lowest temperature (°C)	32.1 (18.2,33.2)
CPB priming volume (mL.kg^{-1})	58.0 (30.0,125.7)
Operation time (min)	152.4±48.6
CPB time (min)	86.2±38.5
Aortic cross-clamp time (min)	56.5 (28.0,127.0)
ICU LOS (hr)	22.0 (18.0,48.0)
Hospital LOS (d)	6.0 (5.0,13.0)
Interval	
first cefazolin to incision (min)	31.5 (10.0,62.0)
first to second cefazolin dose (min)	60.0 (33.0,87.0)
Reduction of plasma cefazolin concentrations (%)	
T1 to T2	34.5 (-33.5,50.5)
T3 to T7	49.9 (14.3,81.1)
T7 to T8	9.9 (-14.3,55.1)

Data are presented as number (%), mean±SD, or median (range). ASD: Atrial septal defect; CPB: Cardiopulmonary bypass; LOS: Length of stay; ICU: Intensive care unit; PS: Pulmonic stenosis; TOF: Tetralogy of Fallot; VSD: Ventricular septal defect

This study measured total plasma cefazolin concentrations. The calculated unbound plasma cefazolin concentrations are illustrated in Figure 2 and Table 2.

After intravenous cefazolin administration (first dose), the median plasma cefazolin concentrations dropped from 18.1 to 11.9 μg.mL^{-1} at the time of the aortic cannulation. Even so, the level exceeded the desired concentrations in most of the patients. However, this reduction resulted in the concentration that was slightly lower than the suggested effective concentration for MSSA in one patient. Another peak cefazolin level was observed after the CPB was initiated. The median interval between the first and second doses was 60 minutes (range 33.0-87.0). The plasma cefazolin concentrations remained over the target concentrations for MSSA, *S. epidermidis*, and *Enterobacter* until the end of the sternal wound closure.

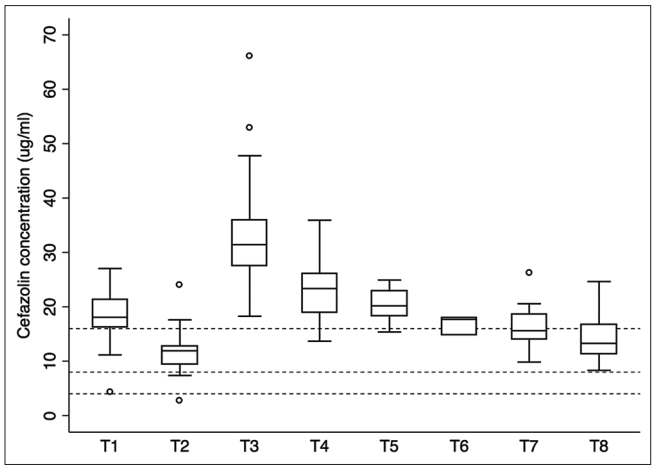

Figure 2: Predicted unbound plasma concentrations, based on measured total and 0.8 fraction bound at different time points. Dashed lines represent target concentrations of 4, 8, and 16 μg.mL^{-1}

Most of the patients showed lower plasma cefazolin concentrations at T2 compared to T1, except for one patient. The T2 concentration was approximately 30% higher than T1 in a 5-year-old boy (weight, 30 kg). Sampling at T2 was performed 25 minutes after T1 in this patient, and he also exhibited high outlying values at T2, T3, and T7. The cefazolin was administered intravenously and added in the CPB prime solution using the dose of 25 mg.kg^{-1} of the actual body weight. Further, there were two other outliers. One exhibited relatively low plasma concentrations at T1 and T2, and the other presented with the highest plasma concentration at T3. There was no remarkable difference observed among these outliers and the rest of the study population.

DISCUSSION

The present study investigated the plasma concentrations of cefazolin in pediatric patients during cardiac surgeries. The plasma cefazolin concentrations were observed after intravenous administration of 25 mg.kg^{-1} dose in all patients. The recommended effective plasma cefazolin concentration is four times above the MICs for target organisms because it produces the highest bactericidal effect.[17] The potential organisms that cause SSIs after cardiac surgery include MSSA, *S. epidermidis*, *Enterobacter*, and *E. coli*. Their MICs are 0.25-1, ≤0.25, ≤2 and 1-4 μg.mL^{-1}, respectively.[17] Thereby, target concentrations of 4 μg.mL^{-1}, 8 μg.mL^{-1}, and 16 μg.mL^{-1} are used as breakpoints for MSSA and *S. epidermis*, *Enterobacter*, and *E. Coli*, respectively.

The plasma concentrations of cefazolin were progressively dropped after the intravenous administration. The apparent decrement in the plasma concentrations was compatible with the short half-life of cefazolin, which was also demonstrated in other studies.[6,18,19] This reduction resulted in cefazolin level slightly below the target 4 μg.mL^{-1} at the T2 measure-point in one patient. This patient also exhibited the lowest cefazolin concentration at T1. Nevertheless, the patient did not show any apparent abnormalities in terms of patient, surgery, or CPB characteristics. Moreover, the interval from the first dose to the measure-point was only 34 minutes, which was less than average among the study group. However, after the supplemental dose of cefazolin, the plasma concentrations remarkably elevated and steadily remained higher than the target concentrations throughout the operative period. This finding signifies the importance of a second dose of cefazolin in the CPB prime volume because the drug concentrations progressively drop and CPB-induced pharmacokinetic alterations may further impact drug concentrations.

Table 2: Plasma concentrations of cefazolin (μg.mL^{-1})

Sample time	*n*	Median	Minimum	Maximum
1	18	18.1	4.3	27.0
2	18	11.9	2.8	24.1
3	18	31.4	18.3	66.1
4	18	23.4	13.7	35.9
5	14	20.2	15.4	24.9
6	3	17.7	14.8	18.0
7	18	15.6	9.8	26.2
8	18	13.3	8.3	24.6

Similar to our study, Himebauch *et al*.[6] administered two doses of cefazolin to patients. The first 25 mg.kg^{-1} dose of cefazolin was intravenously administrated within one hour before incision, and the other 25 mg.kg^{-1} dose of cefazolin was added to the CPB priming volume. All of their subjects (five subjects required CPB only, seven subjects required CPB with DHCA) showed unbound plasma cefazolin concentrations over 4 μg.mL^{-1} throughout the operative period. The median percentages of time that unbound plasma cefazolin concentrations were greater than 16 μg.mL^{-1} were 69.8% for CPB only and 94.4% for CPB with DHCA groups. Similar to our findings, this dosing regimen resulted in adequate plasma levels against MSSA but inadequate plasma levels against gram-negative bacteria at some time points. Their study also measured tissue concentrations and demonstrated that the plasma levels may not be predictive for tissue concentrations. As a result, the interpretation of the sufficient plasma cefazolin concentrations in our study should be applied carefully. Our findings regarding the efficacy of the prophylactic dosing regimen may be misleading because the target tissue concentrations were not measured. Nonetheless, the incidence of SSIs is too low to clinically detect a consequence of low plasma cefazolin levels in the present study.

Haessler *et al*. used a large single dose of cefazolin at 40 mg.kg^{-1} that was infused over a period of 30 minutes at the induction of anesthesia.[13] Similar to our findings, a sharp reduction in plasma cefazolin concentrations was also observed at the time of the aortic cannulation. The cefazolin concentrations progressively decreased, but the levels remained above the target 8 μg.mL^{-1} throughout the entire operation. The use of a single dose regimen has an advantage over two-dose as it may minimize drug error and reduce the potential for forgetting to add the extra dose.

Another study on population pharmacokinetics simulated the cefazolin dose of 40 mg.kg^{-1} prior to the incision with a supplemental dose of 20 mg.kg^{-1} upon the initiation of CPB and another 20 mg.kg^{-1} during rewarming.[20] This dosing scheme provided the most favorable plasma concentrations of cefazolin. The overdosing following this dosing regimen may be of concern regarding the potential toxicity despite the low toxicity profile of cefazolin. However, the risks of subtherapeutic treatment and subsequent SSIs were considered of greater importance. Cies *et al*. recommended tailoring a cefazolin dose individually.[21] As the CPB circuit prime volume is fixed, the dose of cefazolin added in the CPB could be adjusted in order to match the desired target concentrations based on the institutional SSIs epidemiology.

Even though several previous studies have conducted studies that identified the plasma concentrations of cefazolin in pediatric patients undergoing cardiac surgery, the settings, and patients, including their age and body weight, that were used in these studies were different than those used in the current study. Further, the complexity of the operations, CPB materials, and techniques used in previous studies were also different than those used in the current study. This study included pediatric patients with simple cardiac disease who underwent uncomplicated surgery. Overall, this study provides additional data on the use of cefazolin and contributes to the development of a pediatric prophylactic antibiotic guideline in the future.

The limitation of this study is the measurement of total plasma cefazolin concentrations. The alteration of plasma proteins may affect the concentrations of cefazolin-free fraction because cefazolin is extensively bound to plasma proteins. A decrease in plasma proteins as a result of hemodilution upon the initiation of CPB may overestimate the plasma cefazolin concentrations. Besides, plasma concentrations may not accurately represent the true target concentrations of cefazolin compared with tissue concentrations.

In conclusion, the administration of a dose of prophylactic cefazolin (25 mg.kg^{-1}) within 60 minutes before incision and a supplemental dose (25 mg.kg^{-1}) to the circuit prime solution is sufficient to maintain plasma cefazolin concentrations above the target concentrations for MSSA and *S. epidermidis* throughout the operation.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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