Increased 3-gram cefazolin dosing for cesarean delivery prophylaxis in obese women

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OBJECTIVE: The purpose of this study was to determine tissue concentrations of cefazolin after the administration of a 3-g prophylactic dose for cesarean delivery in obese women (body mass index [BMI] >30 kg/m^2) and to compare these data with data for historic control subjects who received 2-g doses. *Acceptable coverage* was defined as the ability to reach the minimal inhibitory concentration (MIC) of 8 μg/mL for cefazolin.

STUDY DESIGN: We conducted a 2-phase investigation. The current phase is a prospective cohort study of the effects of obesity on tissue concentrations after prophylactic 3-g cefazolin doses at the time of cesarean delivery. Concentration data after 3-g were compared with data for historic control subjects who had received 2-g. Three grams of parenteral cefazolin was given 30-60 minutes before skin incision. Adipose samples were collected at both skin incision and closure. Cefazolin concentrations were determined with the use of a validated high-performance liquid chromatography assay.

RESULTS: Twenty-eight obese women were enrolled in the current study; 29 women were enrolled in the historic cohort. BMI had a proportionally inverse relationship on antibiotic concentrations. An increase of the cefazolin dose dampened this effect and improved the probability of reaching the recommended MIC of $\geq$8 μg/mL. Subjects with a BMI of 30-40 kg/m^2 had a median concentration of 6.5 μg/g (interquartile range [IQR], 4.18—7.18) after receiving 2-g vs 22.4 μg/g (IQR, 20.29—34.36) after receiving 3-g. Women with a BMI of >40 kg/m^2 had a median concentration of 4.7 μg/g (IQR, 3.11—4.97) and 9.6 μg/g (IQR, 7.62—15.82) after receiving 2- and 3-g, respectively. With 2 g of cefazolin, only 20% of the cohort with a BMI of 30-40 kg/m^2 and none of the cohort with a BMI of >40 kg/m^2 reached an MIC of $\geq$8 μg/mL. With 3-g, all women with a BMI of 30-40 kg/m^2 reached target MIC values; 71% of the women with a BMI of >40 kg/m^2 attained this cutoff.

CONCLUSION: Higher adipose concentrations of cefazolin were observed after the administration of an increased prophylactic dose. This concentration-based pharmacology study supports the use of 3 g of cefazolin at the time of cesarean delivery in obese women. Normal and overweight women (BMI <30 kg/m^2) reach adequate cefazolin concentrations with the standard 2-g dosing.

Key words: cefazolin, cesarean delivery, minimal inhibitory concentration (MIC), obesity, prophylaxis

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Cesarean delivery is the most common major surgical procedure in the United States. With a 32.8% cesarean delivery rate, it can be estimated that nearly 1.3 million cesarean deliveries are performed annually in this country.[1] Cesarean delivery is the single most important risk factor for postpartum infection, placing women at a 5- to 20-fold increased risk when compared with women who undergo vaginal delivery.[2] Surgical site infection (SSI) rates after cesarean delivery are estimated to be as high as 7-20%. Two major factors that increase this risk are unscheduled cesarean deliveries and obesity.[2] Obesity alone may increase the likelihood of the development of a SSI after cesarean delivery 3- to 5-fold,[3,4] and obese parturients are up to 3 times more likely to require a cesarean delivery than nonobese control subjects.[4,5] This additive effect results in an up to 30% wound complication rate in the severely obese population after cesarean delivery, with nearly 1 in 3 superobese women requiring additional care.[6]

There are many potential reasons that this association exists. Obese patients have a higher rate of medical comorbidities that directly affect the healing process. Obesity is associated with longer operative times and higher blood loss.[6,7] Increasing depth of subcutaneous adipose tissue has a higher degree of hypoperfusion, lower tissue oxygenation, less delivery of neutrophils, lower ability to fight infection, and a greater risk of necrosis and ischemia.[7] Finally, it has been shown that tissue

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concentrations of antibiotics are lower in obese patients.[8-10]

Patients who experience health care–associated infections or SSI have a significant increase in perioperative morbidity and mortality rates that lead to increased use of antibiotics, readmissions, prolonged hospital stays, and billions of health care dollars annually.[11-13] Patients who experience SSI have a 2- to 11-fold increased mortality rate[12]; therefore, any measure that can be taken to reduce the incidence of SSI would be invaluable.

We sought to determine pharmacologic outcomes of an increased 3-g dose of cefazolin in the obese population who undergo cesarean delivery. Concentration data from the current investigation were compared with previously published concentrations from a historic cohort who had received the standard 2-g prophylactic dose.[8]

Materials and Methods

This prospective cohort study was conducted at the University of California, Irvine and Miller Children's and Women's Hospital, Long Beach Memorial. The protocol was reviewed and approved by the local Institutional Review Board, and all participants provided informed written consent before enrollment.

Inclusion criteria were identical to that of our pilot study.[8] All obese women who underwent scheduled cesarean delivery at term, >37 weeks' gestation, were screened for enrollment. Exclusion criteria included any chronic medical comorbidity that potentially could affect tissue perfusion, thereby influencing pharmacokinetics; these included chronic hypertension, pregestational diabetes mellitus, and collagen vascular diseases including systemic lupus erythematosus. Other exclusion criteria included patient allergy to cephalosporins, exposure to antibiotics within the 7 days preceding cesarean delivery, multiple gestations, need for emergent delivery, or suspected preexisting infection.

Using accepted World Health Organization classifications for body mass index (BMI) we divided women into 2 categories: obese (BMI, 30-39.9 kg/m^2) and extremely obese (BMI, >40 kg/m^2).[14] Maternal BMI was calculated with the use of recorded height and weight at time of admission for cesarean delivery and calculated with the following formula: weight (kg)/height (m)^2.[14] We did not recruit normal and overweight women (BMI, <30 kg/m^2), given that, in our historical cohort, all of the women met acceptable tissue concentrations after the standard prophylactic 2-g dose.[8]

Three grams of cefazolin was given parenterally 30-60 minutes before skin incision. A primary study nurse and/or the lead research physician was involved in the timing and collection of all serum and adipose samples. Cefazolin was given as a slow intravenous push over an average of 3-5 minutes. Immediately after skin incision and before fascial incision, the initial adipose sample was collected. Serum collection was coordinated to occur at time of skin incision. The second adipose sample was collected after fascial closure and just before skin closure. Both adipose samples were collected from just below the level of the subcutaneous tissue.

Adipose samples were immediately blotted dry and placed in labeled vials on ice. Maternal blood was allowed to clot and centrifuged for 10 minutes at 3200 rpm. Serum then was removed selectively and, along with the 2 adipose samples, was placed in a −80°C freezer until the time of analysis.

Cefazolin concentrations were determined with the use of a validated high-performance liquid chromatography assay, as previously reported,[15,16] at the Center for Anti-Infective Research and Development, Hartford Hospital. The serum assay was linear over a range of 0.5–50 μg/m: (R^2 = 0.998). Intraday (n = 10) coefficients of variation for the low- (1 μg/mL) and high-quality (40 μg/mL) control samples were both <4%. Interday (n = 4) coefficients of variation were 6.9% and 2.8%, respectively. All tissue samples were processed with 1 part tissue and 4 parts saline solution. The tissue assay was linear over a range of 0.5–50 μg/g (R^2 = 0.996). Intraday (n = 10) coefficients of variation for the low- (1 μg/g) and high-quality (40 μg/g) control samples were 4.2% and 4.4%, respectively. Interday (n = 8) coefficients of variation were 5.9% and 3.7%, respectively.

Criteria for meeting acceptable serum and tissue concentrations were based on the Clinical and Laboratory Standards Institute published susceptibilities of cefazolin.[17,18] Minimal inhibitory concentrations (MICs) are now set at 8 μg/mL, based on resistance data for common *Enterobacteriaceae* organisms.[17,18]

Calculations for an a priori power analysis were based on the results of our historic control subjects.[8] Seventy percent of historic obese subjects obtained tissue concentrations of >4 μg/mL, which is the previous accepted breakpoint for cefazolin at the time of power calculation.[8] Assuming that 95% of obese subjects would attain an MIC of >4 μg/mL with an increased cefazolin dose of 3 g, with an alpha of .05 and a power of 0.8, it was estimated that 12 subjects in each BMI category would be needed to detect a significant difference in adipose cefazolin concentrations after a 3-g prophylactic dose. We planned to enroll 14 subjects in each group to account for potential sample storage, processing, or plating complications that could lead to a "no" result.

Statistical analyses were performed with the statistical program R (version 3.03; R Foundation for Statistical Computing, Vienna, Austria, 2014). All tests were conducted at the .05 significance level. The *t*-test on the regression coefficient for the group indicator was used to test for differences in means. Categoric variables were evaluated with the Fisher exact test of association. Linear regressions for log-transformed start adipose concentrations were calculated by dose-specific group.

Results

We enrolled 30 women in this prospective study between August 2013 and January 2014. Two women were excluded from the study before collection of all tissue and serum samples because of inability to achieve skin incision in the required time of 30-60