Association between Pre-Operative Cefazolin Dose and Surgical Site Infection in Obese Patients

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Abstract

Background: A fixed dose of cefazolin results in serum concentrations that decrease as body mass increases. Current national guidelines suggest a pre-operative cefazolin dose of two grams may be insufficient for patients ≥ 120 kg; thus a three gram dose is recommended. These recommendations, however, are based on pharmacokinetic rather than outcome data. We evaluate the efficacy of pre-operative cefazolin two gram and three gram doses as measured by the rate of surgical site infection (SSI).

Patients and Methods: We conducted a retrospective review of adult patients ≥ 100 kg who were prescribed cefazolin as surgical prophylaxis between September 1, 2012 and May 31, 2013 at an academic medical center. Patients were excluded if cefazolin was prescribed but not administered, had a known infection at the site of surgery, or inappropriately received cefazolin prophylaxis based on surgical indication. The SSIs were identified by documentation of SSI in the medical record or findings consistent with the standard Centers for Disease Control and Prevention definition. Inpatient and outpatient records up to 90 days post-operative were reviewed for delayed SSI.

Results: Four hundred eighty-three surgical cases were identified in which pre-operative cefazolin was prescribed. Forty-seven patients were excluded leaving a total of 436 patients for final analysis: 152 in the cefazolin two gram group and 284 in the three gram group. Baseline demographics were similar between groups with a mean follow-up duration of 77 days for both groups. Unadjusted SSI rates were 7.2% and 7.4% (odds ratio [OR] 0.98, $p=0.95$), for the two gram and three gram groups, respectively. When differences in follow-up between groups were considered and logistic regression was adjusted with propensity score, there remained no difference in SSI rates (OR 0.87, 95% confidence interval 0.36–2.06, $p=0.77$).

Conclusion: In otherwise similar obese surgical patients weighing ≥ 100 kg, the administration of a pre-operative cefazolin two gram dose is associated with a similar rate of SSI compared with patients who received a three gram dose.

Keywords: cefazolin; pharmacokinetics; surgical site infection

THE OBESITY EPIDEMIC in the United States has had dramatic effects on patient outcomes and has increased healthcare expenditure [1,2]. Obesity, defined by the World Health Organization as a body mass index (BMI) ≥ 30 kg/m², is a risk factor for many co-morbid conditions, including surgical site infection (SSI) [3,4]. Administration of antibiotic agents prophylactically is the standard of care in an effort to reduce the incidence of SSIs. Prophylactic antibiotic agents suppress bacterial growth at the surgical site when given at the appropriate time: Within 60 minutes before incision followed by intra-operative repeat doses as necessary to sustain target serum concentrations for the duration of the procedure.

Cefazolin is a first-generation cephalosporin antibiotic agent commonly used for surgical prophylaxis across many surgical specialties. As body mass increases, the volume of distribution of cefazolin increases, resulting in a decrease in unbound serum drug concentration [5]. Increased clearance of cefazolin commonly observed among obese patients results in a further decrease in serum concentration [6]. Thus, higher doses of cefazolin are required to achieve comparable serum and tissue concentrations in the obese patient [7,8].

Current American Society of Health-System Pharmacists (ASHP) guidelines suggest a pre-operative cefazolin dose of two grams may be insufficient for patients weighing ≥ 120 kg [9]. These recommendations are the result of a small, single-center

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study. This study demonstrated a two gram pre-operative cefazolin dose did not reliably achieve serum and tissue antimicrobial concentrations in excess of the minimum inhibitory concentration (MIC) for common SSI pathogens [10]. A three gram dose, however, did achieve desired serum and tissue concentrations in a similar patient population [11]. Although pharmacokinetic data provide some dosing guidance, interpretation is confounded by inconsistent definitions of obesity paired with a paucity of outcome data [9–11].

In March of 2012, our institution implemented a Pharmacy, Nutrition, and Therapeutics (PNT) Committee-approved guideline that recommended, but did not mandate, a three gram dose of cefazolin be administered for surgical prophylaxis to patients ≥ 100 kg, whereas those less than 100 kg were to receive the conventional two gram dose. This practice change was implemented before the ASHP guidelines that established the cutoff for the three gram dose to be ≥ 120 kg, although the decision was based on interpretation of the same data set. We seek to compare the efficacy of pre-operative cefazolin two gram versus three gram doses as measured by the rate of SSI in patients weighing ≥ 100 kg, including an a priori subset analysis of those patients weighing ≥ 120 kg.

Patients and Methods

We conducted an Institutional Review Board-approved retrospective review of adult patients weighing ≥ 100 kg who were prescribed cefazolin as surgical prophylaxis between September 1, 2012 and May 31, 2013 at an academic, level I trauma center in which approximately 16,000 surgical procedures are performed annually. Patients were identified using electronic prescribing data with charts reviewed for all surgical, anesthesia, and pharmacy records. Patients were excluded if cefazolin was prescribed but not administered, if they had a known infection at the site of surgery, or inappropriately received cefazolin prophylaxis (rather than a more appropriate drug) based on surgical indication according to current Surgical Care Improvement Project (SCIP) guidelines. Patients were included even if the timing of cefazolin fell outside the SCIP guideline of zero to 60 minutes before incision.

Standard skin preparation included chlorhexidine gluconate and isopropyl alcohol for elective cases and chlorhexidine gluconate alone in emergent cases or where there was an open wound. Multiple surgical encounters were included for a single patient if the surgical sites and date of operation differed, but re-operative cases were excluded.

Service lines were grouped before statistical analysis based on the similarity of procedures and adequate number of data points. Patients undergoing transplantation were assigned to “General and Trauma” based on their surgical procedure. The group designated as “Other” service lines includes between five and 19 data points from each of the following service lines: Gynecology, plastics, surgical oncology, thoracic, urology, vascular, otolaryngology, and ear/nose/throat. Both elective and emergent surgical procedures were included. Wound class was determined retrospectively using our hospital’s standard quality report.

All data points were objectively defined prospectively. Patients were determined to be colonized with methicillin-resistant *Staphylococcus aureus* (MRSA) by either a positive nucleic acid amplified test nasal swab or MRSA infection

within 30 days of operation. Immunosuppressive diseases were defined as: Human immunodeficiency virus and CD4 count < 200 cells/mm³, malignancy, stem-cell transplant recipient, sickle-cell anemia, absolute neutrophil count < 1500 cells/mm³ within 24 hours of operation, or splenectomy. Immunosuppressive medications were defined as: Calcineurin inhibitors, corticosteroids (prednisone ≥ 20 mg/day or equivalent for ≥ 2 weeks immediately before operation), kinase inhibitors, non-biologic or biologic disease-modifying anti-rheumatic drugs, keratinocyte growth factors, anti-metabolites, anti-neoplastics, immune globulins, immunomodulators, monoclonal and polyclonal antibodies, cytotoxic T-lymphocyte-associated protein-4 inhibitors, tumor necrosis factor inhibitors, or other immunosuppressive agents.

Diabetes mellitus was determined by presence of one of more of the following: Diagnosis in the medical history, hemoglobin A1c $\geq 7\%$, or the presence of any insulin or oral hypoglycemic medications in the home medication list. Duration of operation was calculated using incision time to closure time; appropriateness of cefazolin timing was based on the initiation of the infusion relative to incision time. Duration of follow-up was determined as the last documented contact between the patient and any provider within our health system, up to 90 days post-operatively.

The SSIs were identified by documentation of SSI in the medical record (in either the “problem list” or a provider note) or based on symptoms consistent with the standard Centers for Disease Control and Prevention definition characterized as superficial incisional, deep incisional, or organ/space. Inpatient and outpatient notes up to 90 days post-operative were reviewed for delayed SSI. Patients prescribed “prophylactic” antibiotic agents during a surgical follow-up visit for findings related to the surgical site, but not specifically identified as an infection, were designated as having a SSI.

Statistics

Comparison of baseline variables was performed using the t-test for continuous variables, Wilcoxon rank-sum test for categorical variables, and chi-square test for dichotomous variables. Propensity scores are a function of the following variables: Age, weight, BMI, gender, therapeutic antibiotic agent before operation, clipped hair removal, implants, immunosuppressive medication, immunosuppressive disease, service, American Society of Anesthesiologists physical status classification status score, wound class, and prophylactic antibiotic agent initiated zero to 60 minutes before incision. A stratified analysis was performed with patients divided into 10 strata based on calculated propensity scores. Estimates for SSI are reported as odds ratios (ORs) for the two gram group versus the three gram group. In addition, the SSI outcome was weighted by inverse probability of censoring to account for loss to follow-up.

Results

Four hundred eighty-three surgical cases were identified in which pre-operative cefazolin was prescribed to patients weighing ≥ 100 kg. Forty-seven were excluded because of the aforementioned exclusion criteria, leaving a total of 436 patients for final analysis; see Figure 1 for complete details. The majority (65%) of patients received the recommended,

FIG. 1. Patient enrollment.

but not mandated, three gram dose, with the remainder receiving a two gram dose. Baseline demographics were similar between groups with the exception of admitting service and body mass (including BMI and blood volume, which are calculated and derived from body mass).

Table 1 outlines patient demographics. Table 2 outlines case specific characteristics for each group. Patients within the three gram group were more often admitted to the orthopedic or general and trauma surgery service and had a greater body mass. Mean duration for follow-up for both groups was 77 days. Unadjusted SSI rates were 7.2% and 7.4% (OR 0.98, confidence interval [CI] 0.46–2.08, $p=0.95$),

for the two gram and three gram groups, respectively. This did not differ for the subset of patients ≥ 120 kg (SSI 3.7% vs. 7.6%, $p=0.69$).

Table 3 illustrates that surgical service (neurosurgery vs. orthopedic; OR 2.59, 95% CI 1.27–5.30) and wound classification (contaminated vs. clean; OR 4.52, 95% CI 1.16–17.56) were significantly associated with the development of SSI. Table 4 outlines the complete propensity score regression results. Adjustments for differences in follow-up between groups did not demonstrate a difference in SSI rates (OR 0.95, 95% CI 0.44–2.05, $p=0.89$). In addition, when logistic regression was adjusted with propensity score (including surgical service and

TABLE 1. PATIENT DEMOGRAPHICS STRATIFIED BY CEFAZOLIN DOSE

Variable, n (%)	Cefazolin 2 g 152 (35%)	Cefazolin 3 g 284 (65%)	p
Gender (male), n (%)	100 (65.8)	176 (62.0)	0.431
Age, mean years (SD)	51.7 (± 13.9)	49.6 (± 14.7)	0.152
Body mass, mean kg (SD)	112.0 (± 12.3)	123.5 (± 18.5)	<0.001
Height, mean inches (SD)	69.3 (± 3.6)	69.3 (± 3.8)	0.974
BMI, mean kg/m ² (SD)	36.4 (± 5.7)	40.1 (± 7.1)	<0.001
Blood volume, mean L (SD)	6.1 (± 0.6)	6.4 (± 0.8)	<0.001
Diabetes mellitus, n (%)	35 (23.0)	85 (29.9)	0.124
Immunosuppressive disease (excluding diabetes), n (%)	13 (8.5)	37 (13.0)	0.162
Immunosuppressive medication, n (%)	17 (11.2)	31 (10.9)	0.932
MRSA colonization, n (%)	4 (2.6)	6 (2.1)	0.496
Current smoker, n (%)	23 (15.1)	45 (15.8)	0.100
ASA score, n (%)			0.971
1	3 (2.0)	8 (2.8)	
2	49 (32.2)	85 (29.9)	
3	90 (59.2)	176 (62.0)	
4	9 (5.9)	14 (4.9)	
5	1 (0.7)	1 (0.4)	

Blood volume calculated using the Nadler equation: Male blood volume in L = $(0.006012 \times H^3) / (14.6 \times W) + 604$, and female blood volume in L = $(0.005835 \times H^3) / (15 \times W) + 183$, where H = height in inches and W = weight in pounds [12].

SD = standard deviation; BMI = body mass index; MRSA = methicillin-resistant *Staphylococcus aureus*; ASA score = American Society of Anesthesiologists Physical Status Classification Status Score.

TABLE 2. HOSPITAL AND OPERATIVE DEMOGRAPHICS STRATIFIED BY CEFAZOLIN DOSE

Variable, n (%)	Cefazolin 2 g 152 (35%)	Cefazolin 3 g 284 (65%)	p
Admission surgical service, n (%)			0.003
Orthopedic	30 (19.7)	74 (26.1)	
General and trauma	52 (34.2)	125 (44.0)	
Neurosurgery	39 (25.7)	36 (12.7)	
Other	31 (20.4)	49 (17.2)	
Wound class, n (%)			0.469
Clean	118 (77.6)	227 (80.0)	
Clean-contaminated	24 (15.8)	49 (17.2)	
Contaminated	7 (4.6)	5 (1.7)	
Dirty	3 (2.0)	3 (1.1)	
Clipped hair removal, n (%)	67 (44.1)	113 (39.8)	0.386
Implants, n (%)	81 (53.3)	148 (52.1)	0.815
Therapeutic antibiotic agents before operation, n (%)	15 (9.9)	29 (10.2)	0.910
Prophylactic antibiotic agent initiated 0–60 min before incision, n (%)	142 (93.4)	272 (95.7)	0.285
Prophylactic antibiotic agent initiated 0–30 min before incision, n (%)	68 (45)	126 (44)	0.941
Duration of surgery, mean min (SD)	138.9 (±101.1)	135.3 (±91.9)	0.712
Intra-operative antibiotic agent re-dosed ^a (SD)	14/21 (66.7)	20/30 (66.7)	1.000
Duration of follow-up, mean d (SD)	76.3 (± 28.3)	77.4 (±25.6)	0.674

Other: Includes between five and 19 data points from each of the following service lines: Gynecology, plastics, surgical oncology, thoracic, urology, vascular, otolaryngology, and ear/nose/throat.

^aIncludes procedures >4 h where cefazolin re-dosing is indicated per multi-disciplinary guidelines [9].

SD=standard deviation.

wound classification), there remained no difference in SSI rates (OR 0.87, 95% CI 0.36–2.06, $p=0.77$). Table 5 outlines the results of the propensity score adjusted analysis.

Discussion

The results of this retrospective review demonstrate no significant difference in SSI between two gram and three gram

TABLE 3. INCIDENCE OF SURGICAL SITE INFECTION BY GROUP

Group, n (%)	Cefazolin 2 g 152 (35%)	Cefazolin 3 g 284 (65%)	p
All patients	11/152 (7.2)	21/284 (7.4)	0.952
Body mass			
Patients <120 kg	10/125 (8.0)	11/152 (7.2)	0.811
Patients ≥120 kg	1/ 27 (3.7)	10/132 (7.6)	0.470
Surgical service			
Orthopedic	2/ 30 (6.7)	10/ 74 (13.5)	0.322
General and trauma	4/ 52 (7.7)	4/125 (3.2)	0.190
Neurosurgery	2/ 39 (5.1)	6/ 36 (16.7)	0.106
Other	3/ 31 (9.7)	1/ 49 (2.0)	0.127
Surgical site infection			
Superficial incisional	8/ 11 (72.7)	11/ 21 (52.4)	0.266
Deep incisional	3/ 11 (27.3)	10/ 21 (47.6)	0.266
Organ/space	0	0	N/A
Culture-positive			
Gram positive	1/ 1 (100.0)	3/ 5 (60.0)	0.439
Gram negative	0	1/ 5 (20.0)	N/A
Polymicrobial	0	1/ 5 (20.0)	N/A

Other: Includes between five and 19 data points from each of the following service lines: Gynecology, plastics, surgical oncology, thoracic, urology, vascular, otolaryngology, and ear/nose/throat.

N/A=not applicable.

TABLE 4. PROPENSITY SCORE LOGISTIC REGRESSION RESULTS

Variables	OR Estimate (95% CI)
Age	1.01 (0.99– 1.02)
Weight	0.95 (0.92– 0.98)
BMI	0.99 (0.92– 1.07)
Male gender	0.93 (0.47– 1.84)
Therapeutic antibiotic agents before operation	0.86 (0.39– 1.91)
Clipped hair removal	0.92 (0.56– 1.54)
Implants	1.01 (0.62– 1.64)
Immune-suppression medication	1.21 (0.56– 2.59)
Immune-suppression disease (excluding diabetes mellitus)	0.64 (0.30– 1.39)
Admission surgical service	
General and trauma vs. orthopedic	1.04 (0.56– 1.93)
Neurosurgery vs. orthopedic	2.59 (1.27– 5.30)
Others vs. orthopedic	1.61 (0.78– 3.32)
ASA score	
2 vs. 1	1.57 (0.33– 6.75)
3 vs. 1	1.42 (0.30– 6.74)
4 vs. 1	1.67 (0.27–10.37)
5 vs. 1	1.40 (0.05–38.52)
Wound classification	
Clean-contaminated vs. clean	1.23 (0.64– 2.36)
Contaminated vs. clean	4.52 (1.16–17.56)
Dirty vs. clean	3.23 (0.48–21.70)
Prophylactic antibiotic initiated 0–60 min before incision	0.43 (0.17– 1.10)

OR=odds ratio; 95% CI: 95% confidence interval; BMI=body mass index; ASA score=American Society of Anesthesiologists Physical Status Classification Status Score.

TABLE 5. SURGICAL SITE INFECTION
VIA LOGISTIC REGRESSION

<i>Parameter</i>	<i>OR Estimate (95% CI)</i>	<i>p</i>	<i>Adjustment</i>
2 g vs. 3 g	0.98 (0.46–2.08)	0.950	None
2 g vs. 3 g	0.95 (0.44–2.05)	0.890	Follow-up
2 g vs. 3 g	0.81 (0.35–1.88)	0.630	Propensity ^a
2 g vs. 3 g	0.87 (0.36–2.06)	0.750	Follow-up and propensity ^a

^aPropensity scores are a function of the following variables: Gender, therapeutic antibiotic before operation, clipped hair removal, implants, immunosuppressive medication, immunosuppressive disease, service, American Society of Anesthesiologists Physical Status Classification Status Score, wound class, age, weight, body mass index, prophylactic antibiotic agent given zero to 60 minutes before incision.

OR=odds ratio; 95% CI=95% confidence interval.

cefazolin dosing in the setting of obesity. The ultimate goal of antibiotic prophylaxis is the prevention of SSI; however, previous work regarding the need for three gram cefazolin for surgical prophylaxis in the setting of obesity has centered on the results of pharmacokinetic studies. We know antibiotic administration in accordance with SCIP guidelines is a single piece of a much broader initiative aimed at preventing SSI.

Implementation of SCIP guidelines alone is insufficient to decrease overall SSI rates because a multitude of patient and case specific factors contribute to overall risk. We attempted to control for some of these additional influential factors (e.g., diabetes mellitus, immunosuppression) hoping to isolate the effect of cefazolin dosing on the development of SSI. Ultimately, appropriate antibiotic dosing and timing are certainly important, and thus data regarding outcomes must drive recommendations.

This study highlights the difficulties in using pharmacokinetic data for the basis of guidelines. Although pharmacokinetic and MIC data provide a basis for dose and frequency, data regarding the intended clinical outcome should drive recommendations. We know from a previous study that pre-operative cefazolin provides benefit compared with placebo in lowering the rate of SSI and that a two gram dose yields a lower SSI rate compared with a one gram dose in morbidly obese patients undergoing gastropasty, 5.6% versus 16.5%, respectively [13,14].

Edmiston et al. [10] found that incisional skin and closure tissue specimens had similar mean cefazolin concentrations, irrespective of BMI, among morbidly obese patients undergoing Roux-en-Y gastric bypass who received two grams of cefazolin pre-operatively. The researchers, however, were able to demonstrate that cefazolin concentrations in closure adipose and omental tissue decreased as BMI increased resulting in concentrations below the MIC for common pathogens. Another study performed 214 Roux-en-Y gastric bypass procedures using a two gram cefazolin dose that demonstrated a SSI rate of 5.6%; an in-depth review of three study subjects who presented with superficial incisional infections had tissue concentrations that were sub-inhibitory for selected pathogens [10]. This rate is consistent with previous studies; however, the descriptive nature of this study does not evaluate outcomes compared with higher doses of cefazolin three gram.

Pharmacokinetic data suggest a pre-operative cefazolin three gram load followed by an intra-operative infusion results in higher tissue concentrations, with an extended duration of inhibitory activity above the MIC for selected surgical pathogens, although outcome data were not reported [15]. When evaluating two gram and three gram cefazolin prophylactic dosing, our study demonstrates pharmacokinetic data may not correlate with outcome data, and it may not always be necessary to exceed the MIC of pathogens commonly associated with SSI. Given that the intent of pre-operative prophylaxis is to prevent a presumably low inoculum of bacteria from seeding an infection, antibiotic concentration requirements are likely not as high as those necessary to combat an established infection.

The decision to review cefazolin dosing was the result of institutional practice patterns and broad use by multiple specialties. The inclusion of multiple different surgical populations in this study is one of its strengths, because SCIP guidelines are intended to be comprehensive. Although cefazolin is one of the most common surgical prophylaxis antibiotic agents, the findings of this study are not applicable to other prophylactic antibiotic recommendations. Analysis of multiple service lines as a whole provides a global understanding of two gram versus three gram dosing outcomes. Sub-group analysis was conducted to ensure no significant differences existed between individual service lines. Unfortunately, several service lines, grouped as other, had insufficient case numbers to provide reliable isolated analysis.

This study is certainly not without its limitations, foremost being its retrospective nature, which results in difficulty in accurately assessing for SSI. In addition, although this study demonstrates no significant difference in the rate of SSI between the groups, it is possible this could be the result of inadequate sample size. The use of multiple different service lines within this study, while it adds to the generalizability of results, significantly limits the number of patients within any single category and makes it more difficult to control for case variability.

Nearly 5% of patients evaluated did not receive their cefazolin dose at the appropriate time, within zero to 60 minutes before incision. These patients, however, were evenly distributed between groups, and none of them had an SSI develop. Of the remaining patients who did receive their cefazolin appropriately, nearly half received it zero to 30 minutes before incision, suggesting that the entire dose, assuming a 30-minute infusion, may not have completely infused before incision.

There was no difference in SSI for the two gram group based on cefazolin timing (5.8% vs. 8.3%, $p=0.562$ for 0–30 and 31–60 minute groups, respectively), although the three gram patients who received their dose zero to 30 minutes before incision had approximately twice the rate of SSI compared with the 31–60 minute group (10.3% vs. 5.1%, $p=0.093$). Although this failed to achieve statistical significance, it is an interesting finding and warrants further investigation.

Forty-five patients, roughly 10% in each group, had been receiving therapeutic antibiotic agents for another indication at the time of operation, but these patients yielded a SSI rate of 4.4%, which is comparable to that of the group as a whole, and on regression analysis failed to demonstrate an association with SSI (OR 0.86, 95% CI 0.39–1.91). This study also

included all wound classes, retrospectively derived from a standard hospital quality report, including 18 contaminated and dirty cases. Although these accounted for fewer than 5% of all cases, it should be noted that cefazolin was still considered appropriate therapy for these specific cases (14 extremity-related involving debridement or amputation, one neurosurgery, and three other).

Conclusion

In otherwise similar obese surgical patients weighing ≥ 100 kg, the administration of a pre-operative cefazolin two gram dose is associated with a similar rate of SSI compared with patients who received a three gram dose. To our knowledge, this study is the first to evaluate the clinical outcome data between two gram and three gram cefazolin dosing for surgical prophylaxis in the setting of obesity. These clinical findings are consistent with previous cefazolin pharmacokinetic data, demonstrating that a two gram cefazolin dose in patients with BMI 40–50 kg/m² and >50 kg/m² appeared to provide sufficient antibiotic exposure for the majority of surgical procedures of a duration less than five hours [6].

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Author Disclosure Statement

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