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Pharmacodynamics of Antimicrobial Prophylaxis (AP) in Cardiac Surgery: Association Between Intraoperative Cefazolin (CFZ) Concentrations and Postoperative Infections

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BACKGROUND

- Surgical site infections (SSIs) are serious and potentially life-threatening complications following cardiac surgery.
- Although the principles of antimicrobial prophylaxis (AP) are founded on maintaining effective antimicrobial concs from incision to wound closure,[1] studies that characterize antimicrobial activity in preventing SSIs are limited. In our previous study of AP in colorectal surgery, gentamicin plasma conc at wound closure was identified as one of the strongest independent risk factors for SSI.[2]
- **GOAL:** To conduct a pharmacodynamic (PD) study of intraoperative cefazolin (CFZ) concs and postoperative infections in patients undergoing cardiac surgery with cardiopulmonary bypass (CPB).

METHODS

- A secondary PD analysis of AP in cardiac surgery was conducted using data from our pharmacokinetic study of CFZ during surgery. Inclusion criteria: adult patients undergoing elective cardiac surgery with CPB, informed consent, SSI follow–up at 30 days post–surgery. Exclusion criteria: known or suspected infection or antimicrobials within 3 days of surgery, liver disease, Cl_{cr} <50 mL/min/72 kg.
- AP was given as per institution protocol: CFZ 1 or 2 g preop within 60 min prior to incision, q4h during surgery and q8h x 48 h post–surgery.
- Blood samples were collected 30 min after the preop dose (peak conc), prior to any repeat doses during surgery (intraop trough conc) and within 15 min of wound closure (closure conc). Whole blood samples were centrifuged to yield plasma and then re-centrifuged in a Centrifree® device to yield protein-free ultrafiltrate. CFZ concs were determined by liquid chromatography with tandem mass spectrometric detection (LC-MS/MS, Shimadzu Nexara®) using $^{13}C_2{}^{15}N$ cefazolin as the internal standard. Assays were validated according to FDA Bioanalytical Methods[2001] over linear ranges of 4 to 100 mg/L (total concs) and 1 to 100 mg/L (free concs).
- Study subject characteristics and details regarding their surgery and CFZ prophylaxis were collected from medical records.
- Subjects were monitored for SSI during hospitalization using the CDC criteria. Subjects who consented were also contacted via phone for follow-up at 30 and 90 days post-surgery to identify clinically significant SSIs (i.e., requiring systemic antimicrobial therapy).
- Univariate analysis was used to examine potential subject–, surgery– and CFZ prophylaxis–related risk factors for SSI. Comparisons were made using two-tailed Student's t-test, Mann Whitney U, or Fisher's exact test, as appropriate. Significant variables (P <0.1) were included in multivariate logistic regression analysis (MVLRA) to assess their conditional significance for SSI following cardiac surgery.

RESULTS

- Forty (n = 40) study subjects were included in the PD analysis.
- Subject characteristics (65±10 years, 88±16 kg) and details regarding their surgery and CFZ prophylaxis are listed in **Table 1**:
  - CABG, valve and mixed surgeries were conducted in 45% (18/40), 30% (12/40) and 25% (10/40) of cases, respectively. The mean duration of surgery was 243 ± 71 min. AP consisted of a preop CFZ dose only in 25% (10/40) of cases. The mean preop CFZ dose was 23.5 ± 5.4 mg/kg administered 35 ± 13 min prior to incision. The median CFZ closure $conc_{total}$ was 88.5 mg/L [IQR 50.4–139.5 mg/L] whereas the minimum $conc_{total}$ (lowest conc during surgery including at wound closure) was 45.9 mg/L [IQR 35.4–52.1].
- Eight (8) cases of superficial SSI of the sternal wound were identified.
- In univariate analysis **[Table 1]**, obesity, duration of CPB and surgery, CFZ closure $conc_{total}$ and minimum $conc_{total}$ were associated with SSI. The distribution of these variables in those with and without SSI is shown in **Figure 1**. In MVLRA **[Table 2]**, duration of surgery (p=0.027) and CFZ closure $conc_{total}$ (p=0.038) were independently associated with SSI. The probability of SSI based on the logistic regression model of CFZ closure $conc_{total}$ and stratified for duration of surgery is depicted in **Figure 2.**
- Significant thresholds identified by Classification and Regression Tree (CART) analysis were duration of surgery <346 min (SSI rate of 14.3% versus 60.0%) and CFZ closure $conc_{total}$ >104 mg/L (SSI rate of 5.9% versus 30.4%).

Table 1: Univariate analysis of factors associated with SSI following cardiac surgery

Study subjects	no SSI (n = 32)	SSI (n = 8)	p-value
Gender (male)	20 (62.5%)	5 (62.5%)	1.0
Age (y)	66.0 ± 9.5	62.5 ± 12.2	0.38
Weight (kg)	86.2 ± 14.4	95.7 ± 21.8	0.14
BMI (kg/m^2)	30.0 ± 4.6	33.5 ± 7.6	0.10
Obese (BMI ≥30 kg/m^2)	14 (43.8%)	5 (62.5%)	0.08
Smoker	3 (9.4%)	1 (12.5%)	1.0
Cl_{cr} (mL/min/72 kg)	78.7 ± 16.5	86.5 ± 25	0.29
Diabetes mellitus	9 (28.1%)	4 (50.0%)	0.40
Charlson comorbidity index	3.0 (2.0, 4.0)	3.0 (2.5, 3.0)	0.75
Prior cardiac surgery	2 (6.3%)	0	1.0
Antibiotics within months	10 (31.3%)	2 (25%)	1.0
Hospitalization within months	3 (9.4%)	0	1.0

Cardiac surgeries	no SSI (n = 32)	SSI (n = 8)	p-value
CABG surgery	13 (40.6%)	5 (62.5%)	1.0
Valve surgery	10 (31.3%)	2 (25.0%)	--
Mixed surgery	9 (28.1%)	1 (12.5%)	--
Number of grafts (n = 21, 6 cases)	2.5 (1.0, 3.3)	4.0 (2.5, 4.0)	0.94
Albumin (g/L)	31.5 ± 3.0	30.9 ± 1.7	0.59
Glucose (mmol/L)	8.2 ± 1.5	8.7 ± 1.5	0.40
Fluid balance (mL)	3422 ± 1188	4169 ± 1207	0.12
Duration of CPB (min)	114 ± 37	151 ± 83	0.07
Duration of surgery (min)	232 ± 57	288 ± 103	0.05
Complications	3 (9.4%)	1 (12.5%)	1.0
Hospital stay post-surgery (d)	5.0 (4.0, 6.3)	4.5 (4.0, 7.3)	0.58

Cefazolin prophylaxis (preop and during surgery)	no SSI (n = 32)	SSI (n = 8)	p-value
Preop dose only	9 (28.1%)	1 (12.5%)	0.65
Preop dose and ≥1 repeat dose	23 (71.9%)	7 (87.5%)	--
Timing of preop dose (min)	34.3 ± 13.9	36.3 ± 6.1	0.70
Dose selection (1 g / 2 g)	8 (25%) / 24 (75%)	2 (25%) / 6 (75%)	1.0
Preop dose (mg/kg)	23.6 ± 5.4	22.9 ± 6.1	0.75
Total dose (mg/kg/h)	9.0 ± 2.3	8.6 ± 2.5	0.67
CFZ closure $conc_{total}$ (mg/L)	105.9 ± 57.8 96.4 (55.4, 142.3)	70.4 ± 35.6 59.2 (46.7, 90.6)	0.08
CFZ closure $conc_{free}$ (mg/L)	35.5 ± 27.9 28.1 (11.9, 46.2)	21.6 ± 14.8 15.2 (11.3, 27.3)	0.15
CFZ minimum $conc_{total}$ (mg/L)	47.5 ± 15.1 47.7 (36.2, 53.8)	38.6 ± 7.8 37.7 (33.4, 45.5)	0.03
CFZ minimum $conc_{free}$ (mg/L)	11.6 ± 4.2 11.2 (9.2, 14.2)	12.2 ± 3.5 11.6 (10.4, 12.9)	0.63

Table 2: MVLR model of risk factors for SSI

Variable	Odds Ratio	95% CI	p-value
CFZ closure $conc_{total}$ (per 10% decrease)	1.36	1.02 - 1.82	0.038
Duration of surgery (per 1 h increase)	2.94	1.13 - 7.64	0.027
Area under the ROC curve (95% CI) = 0.789 (0.583 - 0.996)			
Hosmer-Lemeshow p-value = 0.21			

Figure 1: Distribution of significant factors associated with SSI following cardiac surgery identified by univariate analysis

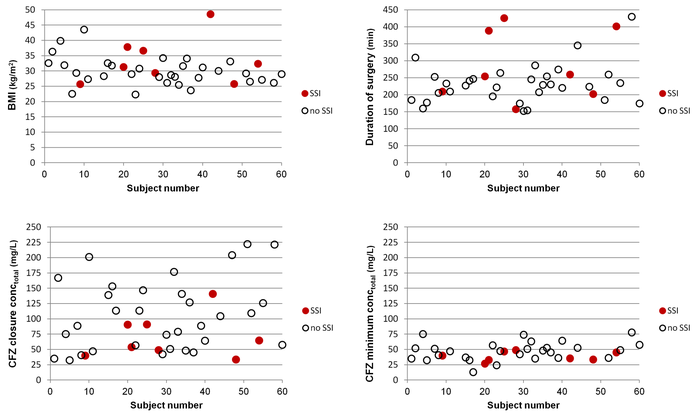
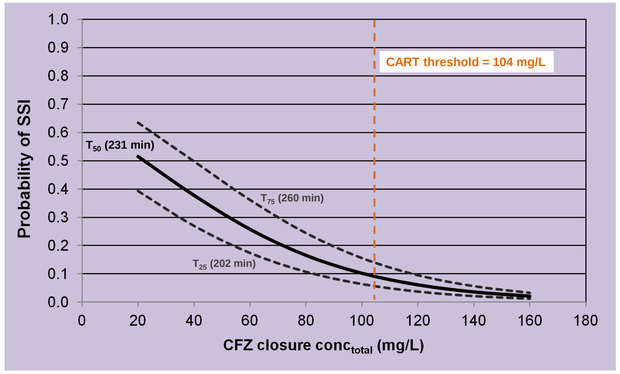


Figure 2: Probability of SSI versus cefazolin closure $conc_{total}$ stratified for duration of cardiac surgery



CONCLUSIONS

- ✓ CFZ plasma $conc_{total}$ at wound closure and duration of surgery were significant risk factors for SSI following cardiac surgery with CPB.
- ✓ CFZ closure $conc_{total}$ was an important finding with its potential influence on the probability of SSI characterized by the logistic regression model shown in Fig 2.
- ✓ Minimum CFZ $conc_{total}$ (lowest during surgery) was not a significant factor likely because intraop trough concs were soon followed by a repeat CFZ dose.
- ✓ The significance of total as opposed to free (active) CFZ concs in AP was an interesting finding that warrants further investigation.
- ✓ Small sample size was a limitation of the study that would have reduced the ability to identify other established risk factors for SSI such as age and diabetes.

REFERENCES: [1] Bratzler DW, Dellinger EP, Olsen KM *et al.* AJHSP 2013, [2] Zelenitsky SA, Ariano RE, Harding GK *et al.* AAC 2002

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