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Original Article

Serum level of prophylactic antibiotics in cardiac surgery and its implication on surgical site infection (SSI)

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Abstract: Background: Surgical site infection in cardiac surgery is still common despite applying preoperative antibiotic prophylaxis as per guidelines. Therefore, the aim of our study was to assess the relationship between perioperative antibiotics serum levels and the incidence of surgical site infection. Methods: This is a prospective study that included all adult patients who underwent elective coronary artery bypass grafting between June and December 2018. The serum antibiotics levels were measured at 4 different time points. The patients were divided into two groups: The group who developed surgical site infection and the group who did not develop surgical site infection. The serum antibiotics levels were compared between the two groups. Results: Eighty-seven consecutive patients were enrolled in the study. The overall rate of infection was 17.95% (14/78 patients). High pre-operative HbA1C levels were associated with a higher rate of SSI (SSI 8.46 ± 2.23 vs no SSI 7.28 ± 1.82, P = 0.04). Patients who developed surgical site infection had longer intervals between administration of prophylactic antibiotics and different parts of the procedure than those who did not develop infection T2 (SSI 3.09 ± 1.12 vs no SSI 2.32 ± 0.98, P = 0.004), T3 (SSI 5.74 ± 1.69 vs no SSI 4.68 ± 1.83, P = 0.024) and T4 (SSI 7.35 ± 1.97 vs no SSI 6.01 ± 2.11, P = 0.015). Conclusion: Prolonging different parts of cardiac surgery procedures could lead to higher risk of infection and better timing of intra-operative re-dosing of prophylactic antibiotics could be guided by measuring intra-operative serum concentrations of these antibiotics.

Keywords: Coronary artery bypass grafting, surgical site infection, prophylactic antibiotics, cefuroxime, serum antibiotic concentration

Introduction

Surgical Site Infection (SSI) is the second most common cause of all nosocomial infections and it ranks third with respect to cost driving [1]. It occurs in 0.4%-4% of cardiac surgery patients in the sternal wound and underlying mediastinum, with more than 50% caused by coagulase-positive Staphylococcus Aureus or coagulase-negative Staphylococcus Epidermidis [2]. It is well known as a significant cause of mortality, morbidity, lengthy hospital stays, decreased patients' quality of life and increased need for antimicrobial therapy [3]. The mortality rate rises from 0.6% without infection up to 22% with SSI in some procedures such as coronary artery bypass grafting (CABG) surgery [4]. There are multiple risk factors for surgical site infection including diabetes mellitus, peripheral vascular disease, older age, inappropriate antibiotic prophylaxis, longer procedures and longer cardiopulmonary bypass time. Some of them are non-modifiable such as age and peripheral vascular disease and the rest are modifiable. Our interest in this study specifically was the appropriate antibiotic prophylaxis, length of the procedures and the length of cardiopulmonary bypass and whether intra-operative redosing is required based on the serum antibiotics level. The importance of prophylactic antibiotics for cardiac surgery has been confirmed in a number of placebo-controlled studies [2]. Since surgical procedures are increasingly performed in elderly population with multiple comorbidities, it is expected that the SSI will increase, unless prevention is improved. For these reasons international practice guidelines were established by the Society of Thoracic Surgeons (STS) [2, 5], American College of Cardiology/American Heart Association (ACC/AHA) [6] and National Surgical Infection Prevention Project (NSIPP) [7]. These guidelines indicate that all patients going for Coronary artery bypass grafting should receive second generation cephalosporines (Cefuroxime) intravenously within 1 hour from making the skin incision and continued for 24-48 hours postoperatively. But despite applying these guidelines in most surgical practices, the surgical community did not notice a decrease in the incidence of SSI. This could be related to multiple factors including deviation from the guidelines [8] or due to failure to achieve therapeutic serum levels of the antibiotics during the procedure [9].

One of the causative factors for failure to achieve therapeutic levels of antibiotics is the dilution effect of Cardio-Pulmonary Bypass (CPB) machine. During CPB, there is a progressive decline in serum concentrations of the cephalosporins [9] due to a mixture of kidney elimination and sequestration in the machine. Several studies have examined intraoperative Cephalosporine [9, 10] pharmacokinetics and documented as much as 50% reduction of first and second-generation cephalosporin concentration after the initiation of CPB with incomplete recovery of serum levels after bypass. Proper perioperative dosing of antibiotics during cardiac surgery represents an exceptional challenge to achieve acceptable tissue levels. These studies did not investigate the relationship between intraoperative antibiotic levels and SSI rates.

Therefore, the aim of our study was to assess the relationship between perioperative prophylactic antibiotics serum levels and the incidence of SSIs. This is a unique study since previous studies focused on studying the relationship between different dosing regimens, rather than the serum antibiotics levels, and the risk of SSI in cardiac surgery patients.

Methods

Study design

This is a prospective study that included: 1) All adult patients, 2) Who underwent elective coronary artery bypass grafting (CABG) surgery between June and December 2018. Exclusion criteria included: (1) Patients who underwent Emergency procedures, (2) Patients with active or treated endocarditis that will require cardiac surgical procedure, (3) Patients with remote infection at the time of surgery likes patients with diabetic ulcers, (4) Patients on immunosuppressive therapy, (5) Patients who were admitted in the hospital for more than 1 week prior to surgery and (6) Patients who had hemofiltration during CPB.

Antibiotics prophylaxis and serum level measurements

The perioperative antibiotics prophylaxis was administered according to the Society of Thoracic Surgeons (STS) Practice Guideline Series [2, 5]. All patients received second generation cephalosporines (Cefuroxime) intravenously within 1 hour from making the skin incision and continued for 24-48 hours postoperatively. The serum antibiotics levels were measured at 4 different time points: 1) Immediately before skin incision (T1), 2) Immediately before starting CPB (T2), 3) One hour after starting CPB (T3), 4) Immediately before skin closure (T4). Blood samples for Cefuroxime concentration were collected in EDTA blood collection tubes, stored on ice, mixed and centrifuged at 5000 rpm for 10 minutes directly after the procedure and plasma stored at -20°C until analysis. We used Monte Carlo simulation method to create a concentration-time profiles for all samples.

Surgical site infection (SSI)

The incidence of SSI was recorded at three time points: during hospital stay, 2 weeks postoperatively and 90 days postoperatively. The Criteria from the Centers for Disease Control and Prevention (CDC) was followed to classify SSIs into superficial incisional, deep incisional and organ SSI. A superficial incisional SSI must occur within first 30 days post-surgery and involves only the skin and subcutaneous tis-

Table 1. Patients' Demographics and Clinical Characteristics

Variable	N = 78 (%)
Sex (male)	59 (75.6)
DM	42 (53.8)
HTN	43 (55.1)
PVD	2 (2.6)
AF	8 (10.3)
Smoking	24 (31.2)
Procedure	
Combined	25 (32.1)
Isolated	53 (67.9)
Age	53.69 ± 13.26
BMI	30.42 ± 16.83
Pre-Operative E.F	46.82 ± 13
Pre-Operative HbA1C	7.49 ± 1.94
BSA	1.75 ± 0.47

DM = Diabetes Mellitus, HTN = Hypertension, PVD = Peripheral Vascular Disease, AF = Atrial Fibrillation, BMI = Body Mass Index, E.F = Ejection Fraction, BSA = Body Service Area.

sue. A deep incisional SSI must occur within 90 days post-surgery and involves deep soft tissue-muscle and fascia. An organ/space SSI must occur within 90 days of procedure and involves any organ or space other than the incision.

Data collection

Seventy-eight patients were included in the study. Data collection included presence of SSI in the sternal wound or the vein harvesting site in the leg as a primary outcome. Infection was documented if at least one of the following endpoints occurred: (1) Wounds requiring incision and drainage. (2) Positive culture from wound's fluid discharge. (3) Cellulitis of the wound requiring starting antibiotics. The patients were divided according to the outcome of developing SSI into two groups: the SSI group (14 patients) and the no-SSI group (64 patients).

Adherence to antibiotics guidelines was assessed using five variables as follows: (1) Antibiotic choice, (2) Timing of antibiotic administration before skin incision, (3) Antibiotic dose, (4) Re-dosing in the operating room and (5) Re-dosing interval.

Ethical approval

The study was approved by the institutional review board (IRB) at the hospital (E-16-1844) and were conducted in accordance with Good Clinical Practice. Written informed consent was obtained from all patients.

Statistical analysis

Continuous variables were compared using the Wilcoxon rank sum test. Categorical variables were compared using Fisher's exact test. A *p*-value of less than 0.05 was considered statistically significant. The Statistical analysis was performed using stata13.1 software. All simulations and graphical representations were performed using the R statistical software.

Results

A total of 78 consecutive patients were enrolled in the study. Fifty-nine patients (75%) were males with a mean age of 53.7 ± 13.3 and BMI of 30.4 ± 16.8. An isolated procedure was performed in 53 (67.9%) patients and Diabetes mellitus and HTN were common in our cohort, 42 patients (53.8%) and 43 patients (55%) consecutively. The mean preoperative HbA1C was 7.49 ± 1.94. The baseline demographic and general clinical characteristics of the patients are shown in **Table 1**.

Surgical site infection

The overall rate of SSI was 17.95% (14/78 patients). The characteristics of patients who developed SSI were compared to those who did not develop SSI in **Table 2**. BMI and Diabetes mellitus were not associated with SSI but high pre-operative HbA1C levels were associated with a higher rate of SSI (SSI = 8.46 ± 2.23 vs no SSI = 7.28 ± 1.82, P = 0.04). Compared with patients who did not develop infection, the infection group had more patients who underwent combined or complex procedures (no SSI = 26% vs SSI = 50%, P = 0.11). However, it did not reach statistical significance. Neither CPB duration nor total surgery time were associated with SSI (SSI = 55.0 ± 55.62 vs no SSI = 135.0 ± 77.79, P = 0.368) and (SSI = 341.5 ± 170.0 vs no SSI = 280.0 ± 144.5, P = 0.17) consecutively.

Table 2. Comparing characteristics of patients who developed surgical site infection (SSI) vs those who did not develop SSI

Patient/Operative Characteristic	SSI N = 14 (%)	No-SSI N = 64 (%)	*P*-value
Age (Mean ± SD)	55.14 ± 14.42	53.38 ± 13.09	0.65
Sex (Male)	9 (64.3)	50 (78.1)	0.28
BMI (Mean ± SD)	31.61 ± 5.54	30.24 ± 18.98	0.79
DM	9 (64.3)	33 (51.56)	0.39
HTN	7 (50)	36 (56.3)	0.67
PVD	1 (7.1)	1 (1.6)	0.24
AF	1 (7.1)	7 (10.9)	0.67
Smoking	12 (85.7)	41 (64.1)	0.12
Pre-Operative HbA1C (Mean ± SD)	8.46 ± 2.23	7.28 ± 1.82	0.04
Pre-Operative Creatinine (Mean ± SD)	75.64 ± 16.49	87.14 ± 31.44	0.19
Procedure Classification			0.11
Combined	7 (50)	18 (28.1)	
Isolated	7 (50)	46 (71.9)	
Total surgery time (Median (IQR))	341.5 (170.0)	280.0 (144.5)	0.17
Total CPB Time (Mean ± SD)	155.0 ± 55.62	135.0 ± 77.79	0.36

DM = Diabetes Mellitus, HTN = Hypertension, PVD = Peripheral Vascular Disease, AF = Atrial Fibrillation, CPB = Cardio-Pulmonary Bypass.

Table 3. Serum Antibiotics concentration levels during different time points

Sample Concentration	SSI N = 14 Median (IQR)	No-SSI N = 64 Median (IQR)	*P*-value
T1	120.0 (92.40)	102.5 (62.20)	0.62
T2	87.50 (43.70)	110.5 (111.1)	0.38
T3	85.80 (66.80)	113.4 (108.0)	0.20
T4	89.50 (59.60)	78.05 (84.20)	0.28

T1: before skin incision, T2: before starting CPB, T3: 1 hour after starting CPB, T4: immediately before skin closure.

Serum antibiotics level

Serum antibiotics levels were compared between the two groups at the specified time points as in **Table 3** and showed no statistical difference between the two groups. Inappropriate perioperative antibiotic prophylaxis occurred in 61 patients (78.2%). The inappropriate timing of administration occurred in 33 patients (42.3%). Lack of re-dosing or inappropriate re-dosing timing had no significant effect on SSI rate (SSI = 50% vs no SSI = 43.8%, *P* 0.67) (**Table 4**).

Timing of antibiotics administration

When comparing the effect of different time intervals from the antibiotics administration time on the risk of infection, the SSI group had longer intervals to starting CPB (Interval to T2) (SSI 3.09 ± 1.12 vs no SSI 2.32 ± 0.98, P = 0.004), longer duration between antibiotic prophylaxis until 1 hour from starting CBP (Interval to T3) (SSI 5.74 ± 1.69 vs no SSI 4.68 ± 1.83, P = 0.024) and longer interval to skin closer (Interval to T4) (SSI 7.35 ± 1.97 vs no SSI 6.01 ± 2.11, P = 0.015) (**Table 5**).

Discussion

The overall rate of SSI was 17.95% in this study, which is higher than the reported prevalence of SSI after cardiac surgery reported in the literature that ranges from 0.4% to 4% [2]. We think this is mainly related to the higher prevalence of risk factors in our patients including DM (53.8%), uncontrolled HbA1C (7.49 ± 1.94) and obesity (BMI = 30.42 ± 16.83). Surgical site infection is well known as a significant cause of mortality, morbidity, lengthy hospital stays, decreased patients' quality of life and increased need for antimicrobial therapy [3]. The mortality rate raises from 0.6% without infection up to 22% with SSI in some procedure such as coronary artery bypass graft (CABG) surgery [4]. Other researchers have suggested an opportunity to reduce occurrence of SSI by targeting patient-specific factors, such

Table 4. Violations to Antibiotics prophylaxis protocol

Lack of Adherence reason	SSI N = 14 (%)	No-SSI N = 64 (%)	*P*-value
Inappropriate prophylaxis	11 (78.6)	50 (78.1)	0.97
Inappropriate timing	5 (35.7)	28 (43.8)	0.58
Lack of re-dosing	4 (28.6)	23 (35.9)	0.61
Inappropriate re-dosing timing	3 (21.4)	5 (7.8)	0.13
Lack of re-dosing or Inappropriate re-dosing timing	7 (50)	28 (43.7)	0.67

Table 5. Comparing Different procedural time intervals between patients who developed surgical site infection (SSI) vs those who did not develop SSI

Covariate	SSI N = 14 (%)	No-SSI N = 64 (%)	*P*-value
Interval to T1 in hours (Mean ± SD)	1.22 ± 0.87	0.97 ± 0.55	0.17
T1 Interval less than 30 Minutes	0 (0)	2 (3.1)	0.51
T1 Interval less than one hour	7 (50)	41 (64)	0.33
T1 Interval less than 1.5 hour	11 (78.6)	59 (92.2)	0.13
Interval to T2 in hours (Mean ± SD)	3.09 ± 1.12	2.32 ± 0.98	0.01
Interval to T3 in hours (Mean ± SD)	5.74 ± 1.69	4.68 ± 1.83	0.05
Interval to T4 in hours (Mean ± SD)	7.35 ± 1.97	6.01 ± 2.11	0.03

T1: before skin incision, T2: before starting CPB, T3: 1 hour after starting CPB, T4: immediately before skin closure.

as weight reduction and preoperative glycemic control.

Another focus for SSI preventive measures is prophylactic antibiotics. Recommendations for SSI prophylaxis include cephalosporins administration within 60 minutes of surgical incision. The focus of the guidelines in terms of proper timing of antibiotic is to allow time for adequate blood and tissue concentrations to exceed minimum inhibitory concentration of the pathogens in order to prevent SSI [2]. Proper perioperative dosing of antibiotics during cardiac surgery gives exceptional challenges to achieve acceptable tissue levels. In this study, significant percentage of patients had longer time interval between administration of prophylactic antibiotics and skin incision. However, that did not translate into different level of serum antibiotics just before skin incision. This lack of correlation between timing of antibiotics administration and serum level of these antibiotics might be explained by the different drug pharmacokinetics in different patients. This finding contradicts the recommendations by the guidelines, which consider the timing as a surrogate for achieving appropriate serum level of antibiotics but seemingly it is not an appropriate surrogate.

Another important finding in this study is the effect of prolonging different time intervals from the timing of antibiotics administration to different parts of the procedure on the incidence pf SSI rather than the CPB duration itself. That increased risk is not related to the complexity of the procedure but rather related to the duration of different time intervals.

Intraoperative Cephalosporin [2, 9] pharmacokinetics had been examined in several studies. During CPB there is a progressive decline in serum concentrations of the cephalosporins due to a mixture of kidney elimination and sequestration in the machine [2]. However, in this study we did not find any difference in serum concentrations between SSI group and the non-SSI group in these time intervals (T2, T3 and T4) despite the longer intervals between administration of antibiotics dose and different parts of the procedure in the SSI group. Again, this lack of correlation between serum levels and duration of time intervals in causing higher risk of infection could be attributed to the dilution effect of CPB on serum concentrations of antibiotics. Previous studies documented an 11% to 41% abrupt decrease in serum concentrations of first- and second-generation cephalosporin concentration after the initiation of CPB with incomplete recovery of serum levels after bypass [2].

Another important finding in our study was the deviation from proper Antibiotics prophylaxis protocols in a significant percentage of both groups. This was a surprising finding since the surgical team felt that they were strictly following the antibiotics prophylaxis regimen. However, this is a well-reported phenomenon and it is related to the busy environment inside the OR that distort the time perception for the surgical team. These deviations were related to either delays in patients' arrival to the operating room, difficult insertion of IV lines, difficult intubation or other administrative issues that resulted in longer periods between antibiotics administration and skin incision. Some deviations were also due to the lack of intra-operative redosing or administering the second dose intra-operatively at in-appropriate time due to the fact that the anesthesia were busy with different parts of the procedure. However, all these deviations did not affect the incidence of postoperative SSI.

Limitations

This is a non-randomized study and included a small number of patients. However, it sheds an important light on some new factors that could be utilized to improve perioperative antibiotics prophylaxis and its titration to prevent SSI.

Conclusion

The timing of prophylactic antibiotics concentration before skin incision is not necessarily a surrogate of achieving adequate serum level of these antibiotics. Prolonging different parts of cardiac surgery procedures could lead to higher risk of infection and better timing of intra-operative re-dosing of prophylactic antibiotics could be guided by measuring intra-operative serum concentrations of these antibiotics.

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Disclosure of conflict of interest

None.

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