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 stud-
ies [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-
Prophylactic antibiotics in cardiac surgery and surgical site infection

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 67.9% patients and Diabetes mellitus and HTN were common in our cohort, 53.8% and 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

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.

Table 1. Patients’ Demographics and Clinical Characteristics

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

DM = Diabetes Mellitus, HTN = Hypertension, PVD = Peripheral Vascular Disease, AF = Atrial Fibrillation, BMI = Body Mass Index, E.F = Ejection Fraction, BSA = Body Service Area.
Table 2. Comparing characteristics of patients who developed surgical site infection (SSI) vs those who did not develop SSI

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

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

<table>
<thead>
<tr>
<th>Sample Concentration</th>
<th>SSI N = 14</th>
<th>No-SSI N = 64</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>Median (IQR)</td>
<td>Median (IQR)</td>
<td>0.62</td>
</tr>
<tr>
<td>T2</td>
<td>120.0 (92.40)</td>
<td>102.5 (62.20)</td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>87.50 (43.70)</td>
<td>110.5 (111.1)</td>
<td>0.38</td>
</tr>
<tr>
<td>T4</td>
<td>85.80 (66.80)</td>
<td>113.4 (108.0)</td>
<td>0.20</td>
</tr>
<tr>
<td>T5</td>
<td>89.50 (59.60)</td>
<td>78.05 (84.20)</td>
<td>0.28</td>
</tr>
</tbody>
</table>

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 CPB (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
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 of 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-gen-
eration 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 follow-
ing the antibiotics prophylaxis regimen. How-
ever, this is a well-reported phenomenon and it
is related to the busy environment inside the
OR that distort the time perception for the sur-
gical team. These deviations were related to
either delays in patients’ arrival to the operat-
ing room, difficult insertion of IV lines, difficult
intubation or other administrative issues that
resulted in longer periods between antibiotics
administration and skin incision. Some devia-
tions were also due to the lack of intra-opera-
tive redosing or administering the second dose
intra-operatively at inappropriate 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 concen-
tration 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-opera-
tive re-dosing of prophylactic antibiotics could
be guided by measuring intra-operative serum
concentrations of these antibiotics.

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Arabia.

Disclosure of conflict of interest

None.
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