Comparison of 2-days and 7-days of prophylactic antibiotic therapy in the prevention of surgical site infection in coronary artery bypass grafting: A randomized, double-blind placebo-controlled trial

Mohammad Barary[1], Ghasem Faghanzadeh Ganji[1], Zahra Aliramaji[1], Terence Sio[2], Soheil Ebrahimpour[1], Masomeh Bayani[1], Veerendra Koppolu[3], Mohammad Reza Hasanjani Roushan[1], Mahmoud Sadeghi-Haddad-Zavareh[1], Hamid Reza Vafaei[1], and Mostafa Javanian[1]

[1]Babol University of Medical Science
[2]Mayo Clinic Research in Arizona
[3]AstraZeneca Medimmune

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Abstract

Objectives: The current study aimed to compare the efficacy of the two different prophylactic antibiotic regimens (2-days vs. 7-days) in preventing surgical site infection in coronary artery bypass grafting (CABG). *Methods***:** Patients undergoing CABG were included in this randomized, double-blind, placebo-controlled trial. From 2016 to 2017, 370 cases were allocated to one of two groups. The groups received prophylactic antibiotic therapy for either 2-days or 7-days. All CABG patients were followed for days for surgical site infections. Two of the patients died after surgery, and 3 patients did not show up during the three-month follow-up evaluation and thus did not meet the study criteria. *Results:* Of the remaining 365 patients who participated in the full study, 198 (54.2%) were male, and 167 (45.7%) were female patients. The mean age of these cases was 58.64± 11.4. Of the 365 study participants who received prophylactic antibiotics prior to surgery, 16 patients developed surgical site infections (legs and sternum). Among these 16 patients, nine cases belong to the 7-days prophylactic antibiotic therapy group (2.4%), and seven cases belong to the 2-day prophylactic antibiotic therapy group (1.9%) (P=0.771). *Conclusion:* Comparison of two 2-day and 7-day prophylactic antibiotic regimens showed no significant difference in the incidence of post-surgical infection in the two groups.

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Ghasem Faghanzadeh Ganji[1], Zahra Aliramaji[2], Mohammad Barary[3, 4, 5], Terence T. Sio[6], Soheil Ebrahimpour[2], Masomeh Bayani[2], Veerendra Koppolu[7], Mohammad Reza Hasanjani Roushan[2], Mahmoud Sadeghi-Haddad-Zavareh[2], Hamid Reza Vafaei[1], Mostafa Javanian[2]

1. Department of Surgery, School of Medicine, Babol University of Medical Sciences, Babol, I.R Iran
2. Infectious Diseases and Tropical Medicine Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran
3. Student Research Committee, Virtual School of Medical Education and Management, Shahid Beheshti University of Medical Sciences, Tehran, Iran
4. Student Research Committee, Babol University of Medical Sciences, Babol, Iran
5. Students' Scientific Research Center (SSRC), Tehran University of Medical Sciences, Tehran, Iran

6. Department of Radiation Oncology, Mayo Clinic, Phoenix, AZ, USA
7. Scientist Biopharmaceutical Development Medimmune Gaithersburg, MD, USA – 20878

Correspondence: Mostafa Javanian, Infectious Diseases and Tropical Medicine Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran. Email: dr.javanian1@yahoo.com. Tel: +981132207918

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Results: Of the remaining 365 patients who participated in the full study, 198 (54.2%) were male, and 167 (45.7%) were female patients. The mean age of these cases was 58.64± 11.4. Of the 365 study participants who received prophylactic antibiotics prior to surgery, 16 patients developed surgical site infections (legs and sternum). Among these 16 patients, nine cases belong to the 7-days prophylactic antibiotic therapy group (2.4%), and seven cases belong to the 2-day prophylactic antibiotic therapy group (1.9%) (P=0.771).

Conclusion: Comparison of two 2-day and 7-day prophylactic antibiotic regimens showed no significant difference in the incidence of post-surgical infection in the two groups.

Keywords: Surgical Wound Infection; Coronary Artery Bypass; Antibiotic Prophylaxis

Introduction

Postoperative administration of antibiotics is frequently useless, and even some studies have shown that it is detrimental to the patients. Principals of prophylaxis antibiotics are based on the type of antimicrobial used, time of the first dose, and duration of the prophylactic regimen used [1]. Among the several types of antibiotics, cephalosporins are the preferred choice for many since they are less allergic to recipients than penicillins[2]. Accordingly, first-generation cephalosporins, cefazolin, have been recommended for various surgical procedures due to their significant benefits, especially with anti -*Staphylococcus*effects [3]. Surgical site infections (SSIs) occur more than a month after surgery and affect many tissues at the operation site. About 3% of the surgical patients develop a surgical site infection [4]. Among these infections, prevention of cardiac surgical site infections, including mediastinitis and sternal infection, have become the main sections on improving hospital performance and quality and cost control plans. The incidence of cardiac surgical site infections or coronary artery bypass grafting (CABG) surgery infections ranges from 0.35 to 8.49 cases per 100 operations for sternal sites [5]. A pre-operative antibiotics therapy is an effective strategy to reduce the incidence of SSIs. Despite the generalization that pre-operative antibiotic therapy is beneficial for reducing surgical site infections, there is no consensus on the onset, type, and duration of the antibiotic therapy [6].

According to some studies, the best duration of treatment for antibiotic prophylaxis is short-term, for example, 48 hours prior to surgery[7]. Several reports have indicated that short-term prophylaxis protection lasts only for 4 days and is ineffective in reducing infections. Extended prophylaxis of antibiotic therapy was also found to be associated with a risk of *Clostridium difficile*infection after coronary artery graft bypass surgery in some studies. Therefore, a consensus has emerged in the medical community to standardize the practice associated with prophylactic antibiotic therapy duration, reduce the development of antibiotic-resistant Clostridium difficile infection, and reduce the treatment cost [8]. Due to the incidence of surgical site infections and the lack of definitive guidelines for the duration of antibiotic prophylaxis, we aimed to compare two durations of the regular antibiotic treatment regimens in patients undergoing CABG in Ayatollah Rouhani Hospital, northern Iran.

Materials and methods

This study was performed as a prospective, randomized, double-blind placebo-controlled trial. The study population consisted of all patients who underwent coronary artery bypass graft surgery at Ayatollah Rouhani Hospital, Babol, northern Iran, during 2016-2017. This 511-bed hospital serves more than two million residents of Mazandaran province, North of Iran. Also, over the year, 700 heart surgery operations have been performed in the treatment center. The inclusion criteria were patients' willingness to participate in the study with informed consent and the age range of 18 to 80 years old who underwent coronary artery bypass graft surgery. Patients with the previous infection and antibiotic usage recently (in the last one month), renal failure (creatinine level greater than 2 mg/dL in two repetitive tests), cardiac ejection fraction (EF) less than 30%, liver failure, severe systemic illness or usage of drugs that lead to immunodeficiency, coincidences with other cardiac surgeries (valve surgery), re-surgery in the same area, and history of antibiotic hypersensitivity to the cefazolin and cephalexin antibiotics used in this study were excluded. Moreover, the patients who were under mechanical ventilation for more than 24 hours or stayed in the intensive care unit (ICU) for more than 3 days, along with off-pump surgery, blood transfusion of more than 6 units per day, surgery duration greater than 6 hours, or pump time greater than 120 minutes or aortic clamping time greater than 60 minutes, the need for intra-aortic balloon pump or inotropic doses higher than the median doses, and emergency surgeries were excluded.

Based on the prevalence of CABG infection with antibiotic prophylaxis (6%) [9,10], 370 cases were considered. After obtaining the necessary permissions and registering on the Iranian Registry of Clinical Trials (IRCT201707188968N2), obtaining informed consent from the patients, and applying exclusion criteria, all of the mentioned patients were included in the study.

All patients were showered the night before surgery, and the surgical cutting site was shaved. In the operating room, the incisional site was prepared with iodopovidone solution. Disposable shampoos and sterile operating room appliances were the same for all cases. In terms of ICU, the cardiopulmonary pump, anesthesia, and ward matching technique and equipment were done among the patients.

After entering the operating room, an expert randomly assigned patients to one of the groups (185 cases per treatment). At the time of induction of anesthesia and before surgery, cefazolin (2g, IV) was given. The second dose of cefazolin was given if the duration of the surgery lasted longer than 5 hours. After surgery, they were divided into 2 groups. Both groups, cefazolin (1g, IV), was administered every 6 hours for 2 days. Moreover, group I received placebo capsules (containing starch) every 6 hours for 5 days, and group II received cefalexin 500 mg capsule every six hours for 5 days. Demographic and clinical characteristics of the patients, including age, gender, diabetes, body mass index (BMI), smoking, systemic hypertension, graft number, cardiopulmonary bypass duration, cardiac ejection fraction, ICU duration, time of intubation, creatinine, and blood urea nitrogen (BUN) were entered into the data collection form. Moreover, all patients received training on the symptoms of wound infection.

Patients were evaluated for evidence of SSIs on days 3, 7, 10, 30, and 90 after operation by the surgeon. As an indication of SSI, patients were examined for oozing pus around the incisional site, body temperature above 38 °C, redness, pain, and warmness of the skin. Results were recorded in the data collection forms. In the case of secretion, a sample wound was sent for culture. Surgeons have also warned patients about the complications of surgical site infections (in the sternum and legs). Criteria for superficial SSIs were considered as one of the following: pussy oozing of incisional site, positive microbial culture from a sample collected at the incision site, inflammatory symptoms. Detection of deep SSIs is also based on pussy drainage from deep tissue, re-opening of incision spontaneously or by a surgeon due to fever, or localized pain or tenderness.

In this study, the primary criterion for SSI has wound infection at the incisional site. After collecting and categorizing information, all statistical analysis was done using SPSS v.16.0 (IBM Corp., Armonk, NY, USA). Moreover, it is worth noting that the antibiotic treatment details of the patients were kept as blindness for the statistician to avoid any bias. The comparison of quantitative variables was made by student t-test, whereas Chi-square and Fisher exact tests compared qualitative variables. The level of significance in all

tests was considered to be < 0.05.

Results

This study enrolled 370 patients undergoing coronary artery bypass graft surgery to evaluate the prophylactic antibiotic duration practices post CABG. Among the study participants, five cases were excluded since two patients died and three patients did not fulfill the course of study during 1-month follow-up (Figure1). Of the remaining 365 patients, 198 (54.2%) were male, and 167 (45.7%) were female, and also, the mean age of these cases was 58.64 ± 11.4. One hundred and eighty-two patients in group I received one antibiotic for 2-days, and 183 patients in group II received antibiotics for 7-days. Both the groups did not show a significant difference in sex, mean age, body mass index. In twenty patients (4.5% of total participants), the surgery lasted more than 5 hours and thus received a second dose of intravenous antibiotics. There was no significant difference in the number of operations over 5 hours since13 cases in group I (7%) and seven cases in group II (3.8%) belong to this category (p = 0.251). All subjects' mean body mass index was 25.92 ± 3.41 kg/m^2. The surgery period was variable from 3 hours to 6 hours, and the mean duration of all surgeries was 4.29 ± 0.56 hours (Table 1). The frequencies of comorbidities in these two groups were not significantly different (Table 2). Evidence of SSIs (leg or sternum) was reported in 16 out of 365 patients who have undergone surgery. Nine cases in group II and 7 cases in group I. Relative risk, RR=0.7 (95% Confidence Intervals: 0.22-2.26; p=0.771). The incidence of infection in all subjects in the two groups was 4.3%. One case of mediastinitis was seen (0.21%) in group II. The location, depth, and incidence of surgical site infections in the two groups were also shown in Table 3. Among sixteen patients with evidence of SSIs, 12 patients had positive microbial cultures (75%). Positive cultures were seen in 7 patients in group I and 5 patients in group II, but the frequency of infection in the two groups was not significantly different (p = 0.681). Of these 12 cases, *Escherichia coli* (*E.coli*) was the most common microorganism (7 cases). *Staphylococcus epidermis* in 3 patients and *Pseudomonas aeruginosa* in 2 cases were also isolated. Antibiotic susceptibility showed in Table 4.

Discussion

The use of antibiotics to prevent surgical site infections is shown to be unnecessary after surgery. Many studies have shown that antibiotics are beneficial before surgery, especially for heart surgeries[11,12]. However, the effectiveness of these antibiotics concerning the duration of their use prior to surgery is not very clear. This case has been studied in various sources and numerous clinical trials. Some trials in heart surgery suggested that increasing the duration of antibiotic prophylaxis does not significantly decrease surgical site infections [13].

The duration of antibiotic therapy before surgery, especially in CABG, is still debatable, and for this reason, we examined this critical issue. This study showed no significant difference in the incidence of infection in two groups (antibiotic for 2-days versus 7-days) to prevent postoperative infections in coronary artery bypass graft surgery. These findings are consistent with the findings of Paul et al.[14], which showed that increasing the duration of antibiotic prophylaxis in patients undergoing cardiac surgery does not significantly reduce surgical infections. According to the current study, the incidence of SSIs in 365 patients undergoing surgery was 16 patients. The findings of SSI incidence were also similar to studies by Gelijns et al. [15]. However, in studies by Farrington et al. and Bhatia et al., the rate of occurrence of infection was higher than the current study, with 14.3% 18%rates, respectively[16,17].

Of the 16 patients, 9 cases were in group II, and 7 were in group I, which was not statistically significant. It shows that longer antibiotic use was not beneficial; this may have had harmful effects for the patients. The number of positive microbial cultures in group I was more than group II (7 patients in group I versus 5 cases in group II) with no significant difference between groups, indicating that antibiotic use could only negatively affect culture. Moreover, it suggested that prolonging the antibiotic regimen does not reduce infections, but changing the normal flora may increase the incidence of infection and the emergence of resistant organisms.

Surgical site infections in cardiac surgery, including sternal and mediastinal infections, cause an increase in treatment costs and increased morbidity and mortality. Bhatia and colleagues[17] described sternum and

legs as the most common infection in patients undergoing coronary artery bypass graft surgery, which is consistent with the results of our study. It showed an overall high rate of infection in the lower extremities. Long-term treatment versus short-term is unlikely to cause mediastinitis since only one case was seen with these symptoms. This result is consistent with the study by Lador et al., which showed no association between the increase in antibiotic duration and the reduction of deep infection[18]. As mentioned, infection was mostly found in the foot. The team that removes the veins is separate from the heart surgery team, and the creation of hematoma is considered an important factor in wound infections. Moreover, the time for the discontinuation of the heparin drug is different from the heart surgery team and vascular surgeons, which helps to create an infection, and also because the leg is considered to be the lower extremities and its blood supply is more difficult than other upper organs, the infections are more likely to occur. Therefore, it is suggested that the studies be conducted on the exact time to discontinue heparin treatment. By reducing hematoma, the chance of developing foot infections is also reduced.

The predominant organism responsible for cardiac SSIs is gram-positive staphylococcal species. First-generation cephalosporins are preferred for prophylactic antibiotic therapy [19]. Except in cases with a proven allergy to beta-lactam antibiotics, using cephalosporin (a beta-lactam group antibiotic) as a prophylactic drug for 24 to 48 hours is considered the most logical treatment choice. Gram-negative organisms may cause infections of the sternum wounds after coronary artery bypass graft surgery, possibly due to the transposition of the organism during the removal of the vein. In the **s** tudy by Heydarpour *et al* ., most organisms isolated were gentamicin resistant [20], whereas the current study showed organisms with the highest resistance to ciprofloxacin. Seven cases of 12 positive cultures were resistant to ciprofloxacin, and the organism that showed resistance in both groups was *E.coli* .

This study has not been carried out in large communities, and it is advisable to undertake such studies with a large sample size to confirm that a 2-day antibiotic regimen has a relatively equal effect with longer ones.

Conclusion

This study revealed no significant difference in the incidence of infection in two groups (first-generation cephalosporins for 2-days against 7-days) to prevent postoperative infections in CABG. Such findings can help reduce the overall antibiotic use, cost, and the development of antibiotic resistance.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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conflict of interest disclosure

None to disclose.

Institutional Review Board approval or waiver

This study was performed according to the declaration of Helsinki, and the institutional ethics committee of Babol University of Medical Sciences approved the protocol used in this study (Reference code: MUBABOL.HRI.REC.1396.10).

patient consent statement

A written consent form was obtained from all participants at the time of enrollment.

clinical trial registration

The study protocol was registered on the Iranian Registry of Clinical Trials (IRCT201707188968N2).

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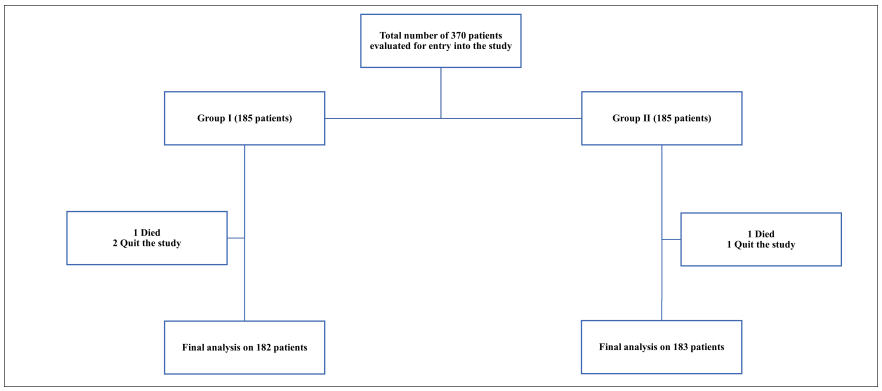
Figure legend

Figure 1. Hospitalization chart of the study participants



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