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Abstract

Background

This study investigated the efficacy of first-generation (cefazolin) and third-generation (ceftizoxime) prophylactic antibiotics in patients undergoing cardiac surgery and the incidence of surgical site infections, hospital stay lengths, and medical costs.

Methods

All adult patients (≥20 years) undergoing cardiac surgery (coronary artery bypass surgery, valve operation, or combined surgery) at one hospital from January 01, 2009 to December 31, 2016 were included in this study. A single prophylactic antibiotic was administered at a dose of 1 g within 1 hour of surgical incision and for three days after surgery at eight-hour intervals. After the propensity score matching, 194 patients in each antibiotic prophylaxis groups (first-generation vs third-generation) were analyzed. Among the 388 patients, the incidence of surgical site infection were compared according to the type of prophylactic antibiotics and risk factors were evaluated by chi-squared tests followed by multivariate logistic regression analysis. A Student's *t*-tests were analyzed to compare hospitalization and medical costs.

Results

The incidence of deep surgical site infections significantly lower in first-generation group (5.7%) than third-generation group (16.5%). The pathogens isolated from surgical infection sites were similarly distributed in both groups, but gram-positive bacteria were more highly infectious than gram-negative bacteria (67% vs 23%). Preoperative hospitalization duration, mean operation time, and ventilator use time were similar in both groups but the postoperative hospitalization duration was significantly shorter in the first-generation group (25.5 days) than third-generation (29.8 days). In addition, the medical cost lower in the first-generation group (20,594 USD) than third-generation (26,488 USD).

Conclusion

In conclusion, the first-generation (cefazolin) is better than the third-generation (ceftizoxime) as a prophylactic antibiotic in reducing surgical site infection rates, hospitalization lengths, and medical expenditures.

Attachments

PDF	PDF	DOCX	DOCX	FILE
PLOSONE_Table.pdf	PLOSONE_supporting i...	PLOSONE_Table.docx	PLOSONE_supporting i...	Table_Fig_plosone-1....
335KB	77KB	21KB	20KB	696KB

Introduction

In a placebo-controlled trial, the placebo group showed an increased incidence of surgical site infections, by 20%–50%, which demonstrates the validity of prophylactic antibiotic use in cardiac surgery [1-3].Surgical site infections (SSIs) are common hospital infections that increase the morbidity and mortality of patients, treatment duration, and socioeconomic costs. According to the National Centers for Disease Control and Prevention (CDC) National Nosocomial Infections Surveillance (NNIS) report, surgical site infections account for 14%– 16% of hospital infections among hospitalized patients [4]. The SSIs increase the average number of days of hospitalization by 6.5 days, with additional hospitalization costs of $18,900, while the cost of patient mortality is $60,547 more than patient survival[5]. Korean studies show that the additional days of hospitalization due to surgical site infections increase by 5.2 days, with an additional cost of more than $1,800 per incident[6]. Therefore, surgical site infections lead to mental, physical, and economic losses to patients, worsen quality of life, waste healthcare resources, and increase financial burden on medical institutions.

The results of the 2006 Survey on Antibiotic Usage at the National Health Insurance Review & Assessment Service (HIRA) showed that the use of prophylactic antibiotics in Korean surgeries differed from that in the Guideline for Guidance and has classified as an abuse of antibiotics [7, 8]. The choice of prophylactic antibiotics is less methicillin-resistant *Staphyloccus sp* and can be covered by gram-positive bacteria and provides safe and cost-effective guidelines but fails to reflect the domestic medical environment because it refers to guidelines from foreign clinical studies. In recent studies, sufficient medical institutions and research subjects are not available, which limits research results [9, 10]. Since the start of the national hospital evaluation program (NHEP) in 2008, evaluation of prophylactic antibiotics for surgery was started as a comprehensive measure of antibiotic resistance management. In this evaluation program, unfavorable antibiotic choice were defined as over third-generation cephalosporin, aminoglycoside, combination of β-lactam with aminoglycoside, combination of vancomycin with other antibiotics. The following procedures performed from 2008 were included for assessment in the NHEP and the result of clinical performance were officially reported to public as well as to each hospital. As the hospital assessment progressed, we were forced to abandon the use of antibiotics to cover both gram-positive and gram-negative bacteria and changed third-generation cephalosporin.

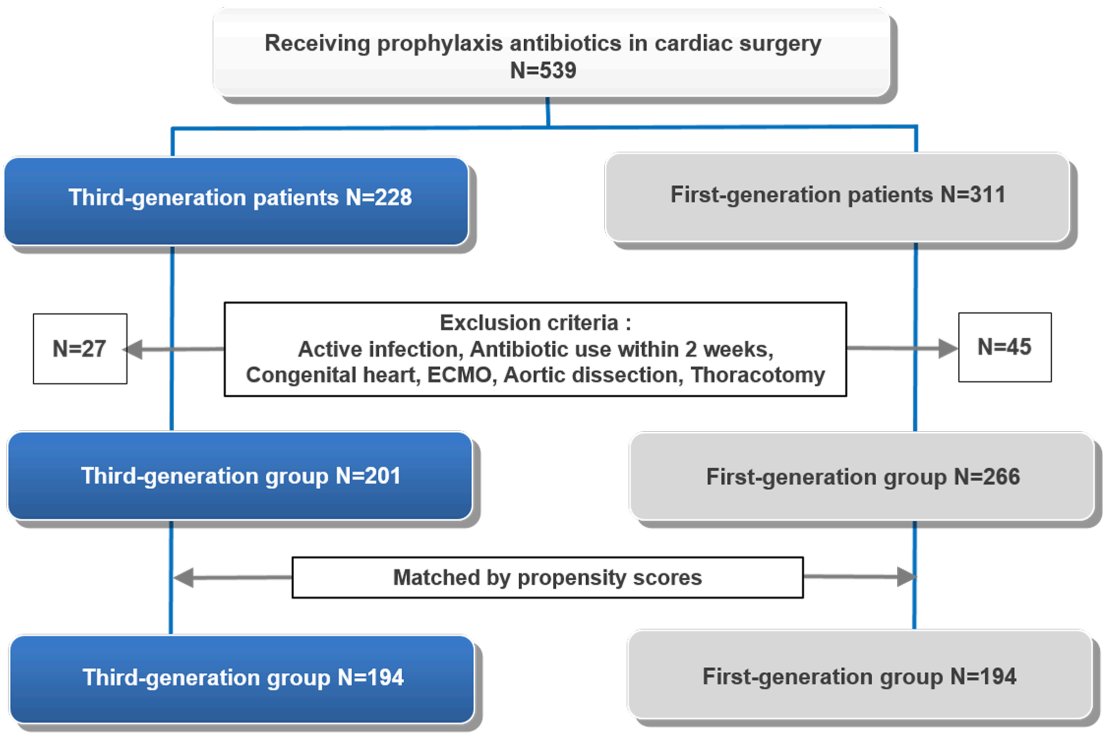
The third-generation prophylactic antibiotic, which was used from 2009 to 2012, were changed to the first-generation prophylactic antibiotic because of evaluation of prophylactic antibiotics. The use of prophylactic antibiotics has been evaluated since 2012 to promote the prevention of SSIs. The benefit of university hospital institution due to prophylactic antibiotic changes has not been identified. Therefore, we performed a comparative study of cephalosporin first-generation (cefazolin) and third-generation (ceftizoxime) antibiotics. The purpose of this study was to investigate the use of prophylactic antibiotics and the prevention of surgical site infections by analyzing the relationships between the use of prophylactic antibiotics and surgical site infection rates.

Materials and methods

Study population

This study was a retrospective review of the electronic medical records of all patients who underwent cardiac surgery from January 01, 2009, to December 31, 2016, at a single university hospital. All patients had undergone a full median sternotomy and cardiopulmonary bypass (CPB). The inclusion criteria were coronary artery bypass grafting (CABG) and valve surgery. Patients with current active infections, those for whom antibiotics had been administered within two weeks of surgery, immunotherapy patients, patients with congenital heart disease or cardiac assistive devices or extracorporeal membrane oxygenation (ECMO), and patients who had undergone aortic dissection or thoracotomy surgeries were excluded from the study. Of the 539 patients who underwent cardiac surgery, 228 received third-generation antibiotics (ceftizoxime) and 311 received first-generation antibiotics (cefazolin). According to the exclusion criterion, 27 patients in the third-generation group and 45 patients in the first-generation group were excluded. The final study included 201 patients in the third-generation group and 266 in the first-generation group. Following propensity score matching, a total of 194 patients were categorized into the two groups (Fig. 1). The cephalosporin-based prophylactic antibiotics used were cefazolin (first-generation) and ceftizoxime (third-generation).

Fig 1. Selection of study subjects and the propensity score matching process. We reviewed the medical records of 539 individuals. After propensity score matching, 388 patients remained in the final analysis.



Antibiotic regimen and surgical preparation

A single cephalosporin antibiotic was administered, at least 1 gram intravenously over 15 to 20 minutes, within one hour before a skin incision was made at the sternum, and additional doses were administered at eight-hour intervals for three days, postoperatively. Because the timing of prophylactic antibiotic administration is important in preventing surgical site infections, we defined the antibiotic drug regimen as optimal prophylaxis if the antibiotic was administered within one hour before the first surgical incision. All preoperative procedures were conducted in the same way. The patients were given a chlorhexidine shower to reduce bacterial proliferation and prevent infection before surgery. The surgical site was disinfected with a 7.5% povidone-iodine (Polydine Cleanser, Dr Fisher), and hair was removed with a hair removal cream (Silk Plus Hair Removal Cream, Nimson). In the operating room, on the day of surgery, all operative sites were scrubbed with 7.5% povidone-iodine soap solution and painted with 3M DuraPrep surgical solution (0.7% iodine-povacrylex, 3M Health) again. All surgical procedures were done under conventional cardiopulmonary bypass conditions and moderate hypothermia (30℃-32℃) with a heater-cooler unit. All operations were performed by two experienced cardiac surgeons. The surgical procedures have not been changed to date.

Surgical site infection

The sternal incision sites were evaluated daily by cardiac surgeons and four times a week by an infection management nurse. The diagnosis of identified surgical site infections was based on positive cultures, dehiscence of the sternotomy, high fever, local pain, redness, purulent drainage, and sternal instability. All patients were followed-up one week hospital discharge and all patients visited an outpatient department every week. The duration of the surgical site infection assessments was within 30 days from the beginning of follow-up to the end of follow-up, based on the surgical site infection guidelines from the Centers for Disease Control and Prevention (CDC)[11]. Nosocomial surgical site infections (SSIs) were defined according to the CDC criteria and mediastinitis was defined according to the Society of Thoracic Surgeons (STS) criteria [12, 13]. Wound cultures were obtained and clinically processed in the microbiology laboratory according to standard procedures.

Pre- and intra-operative covariates

Comprehensive information on data collection requirements and definitions of variables were gathered after hospital admission and the following variables were analyzed : preoperative variables of sex, age, body mass index (BMI), smoking, hypertension, diabetes mellitus (DM), hemoglobin A1C levels 6.5% or higher [14], hypercholesterolemia, neurologic dysfunction, left ventricular (LV) dysfunction (EF < 20%), renal dysfunction, peripheral vascular disease (PVD), chronic obstructive pulmonary disease (COPD) defined by the World Health Organization (WHO) [15], and the intraoperative and postoperative European System for Cardiac Operative Risk Evaluation (EuroSCORE) scores [16].

Costs

Total hospital charges included all medical costs covered by health insurance, self-pay, optional care, and other medical costs. To investigate the costs related to surgical site infection, the pre-cardiac surgery examination costs, admission fees, surgical costs, and material costs were excluded from the total medical cost. All admission fees were reimbursed based on the admission fee for a six-person room. Hospital charges included medication and injection fees, examination fees and radiology fees.

The daily weighted average costs for prophylactic antibiotics were 5.16 US dollars (USD) – 5.20 US Dollar (USD) for third-generation (ceftizoxime) and 1.08 USD – 1.24 USD for first-generation (cefazolin) antibiotics. The exchange rate was based on that for November 20, 2019 (1 USD= 1,175 Korean won {KRW}).

Statistical analysis

The general characteristics of the study subjects were analyzed to determine the distribution of surgical site infections. The continuous variables and categorical variables were analyzed by t-tests and chi-squared tests. Propensity score matching was used to control selection bias according to group selection. This matching method is designed to compare the individual characteristics of two groups, based on propensity scores and conditional probabilities. The first-generation and third-generation groups were matched in a 1:1 ratio using the Greedy matching method [17]. Greedy matching is a method of setting a range of constant propensity scores around a treatment group using a caliper, and selecting the closest objects in the control group corresponding to this range. Incidence score matching eight covariance was selected according to sex, age, hypertension, obesity, diabetes, smoking, harvested internal thoracic arteries, and transfusions[18].

All variables were entered into the Student's t-tests and logistic regression analysis with matched data to determine the effect of surgical site infection. We conducted Student's t-tests to compare the medical-cost expenditures and hospitalization duration between the two groups. The multivariate analysis was performed using the inverse stepwise method with a *p*-value of 0.05. The adjusted odds ratios and 95% confidence intervals (CI) were calculated to investigate the independent effect of prophylactic antibiotics on the surgical site infection parameters using logistic regression. All data analyses were performed using the statistical program SAS version 9.4 (SAS Institute Inc., Cary NC, USA).

Ethics statement

The present study protocol was reviewed and approved by the Institutional Review Board of Inje university Sanggye Paik Hospital (approval No. 2017-05-011-003). Informed consent was presented by all patients enrollment. Before the start of the study, the research ethics review committee in the hospital received the review. Throughout the research period, the related laws and regulations were followed and studied.

Results

Among the 539 heart surgery procedures performed between January 2009 and December 2016, the general characteristics of the study subjects were compared before propensity score matching 467patients and after matching 388patients. Before matching, gender (p=.028), obesity(p=.024), hypertension(p=.042), EuroSCORE risk assessment (p<.001) were significantly different between the two groups, but there were no statistically significant differences after PSM that match is balanced. And the goodness-of-fit test statistics of Hosmmer-Lemeshow model were high (c-statistic=0.63 95% CI:0.54-0.88) (Table 1).

Table 1.General characteristics of study subjects receiving 3rd generation or 1st generation prophylactic antibiotics.

		Total population			Propensity matched population		
		3rd generation (n=201)	**1st generation (n=266)**	**P value**	**3rd generation (n=201)**	**1st generation (n=266)**	**P value**
Preoperative							
Gender	Male	121(60.2)	186(69.9)	0.028*	124(63.9)	129(66.5)	0.682
	Female	80(39.8)	80(30.1)		70(36.1)	65(33.5)	
Age, years		63.4±11.4	64.2±11.9	0.446	63.4±10.8	63.6±12.8	0.596
	<70year	122(60.7)	153(57.5)	0.281	119(61.3)	118(60.8)	0.841
	≥70year	79(39.3)	113(42.5)		75(38.7)	76(39.1)	
Obesity	BMI <25	149(74.1)	184(69.2)	0.024*	135(73.7)	136(74.3)	0.955
	BMI ≥25	52(25.9)	82(30.8)		48.(26.2)	47(25.7)	
Smoker		76(37.8	110(41.3)	0.086	74(41.1)	69(38.3)	0.211
Hypertension		139(69.2)	204(76.7)	0.042*	125(69.4)	131(72.8)	0.224
Diabetes mellitus(DM)		57(28.3)	90(33.8)	0.112	53(29.4)	52(29.9)	0.918
Hypercholesterolemia		22(11.0)	34(12.8)	0.441	20(11.1)	19(10.5)	0.868
Dialysis		10(4.9)	18(6.8)	0.404	9(5.0)	10(5.5)	0.644
Chronic obstructive pulmonary disease		14(6.9)	21(7.9)	0.702	13(7.2)	14(7.8)	0.851
Peripheral vascular disease		12(6.0)	22(4.7)	0.343	9(5.0)	14(7.8)	0.546
LV dysfunction	EF <30% poor	21(10.5)	25(9.4)	0.481	18(9.8)	20(10.9)	0.657
	EF 30-50% moderate	51(25.40	80(30.1)		48(26.2)	56(30.6)	
	EF>50%	129(64.2)	161(60.1)		117(63.9)	107(58.5)	
EuroSCORE risk index	Category1(≤2)	105(52.2)	137(51.5)	<0.001**	95(51.9)	94(51.4)	0.559
	Category2(3-5)	52(25.9)	102(38.4)		48(26.2)	68(37.2)	
	Category3(≥6)	44(21.9)	27(10.1)		40(21.9)	21(115)	
Intraoperative							
Surgical emergency		22(10.9)	19(7.1)	0.150	17(9.5)	14(8.2)	0.549
Type of surgery	CABG	105(52.2)	151(56.7)	0.382	99(54.1)	108(59.0)	0.676
	Valve surgery	91(45.3)	112(42.1)		81(44.2)	72(39.3)	
	Combined CV	5(2.5)	3(1.1)		3(1.6)	3(1.6)	
Internal thoracic artery	Harvested No	78(38.8)	111(41.7)	0.187	68(37.2)	72(39.4)	0.430
	Harvested left only	99(49.3)	111(41.7)		94(51.4)	82(44.8)	
	Harvested both	24(11.9)	44(16.6)		21(11.5)	29(15.8)	
Time on CPB (hour)		2.27±4.6	2.18±5.3	0.084	2.13±2.3	2.18±2.1	0.389
Duration of operation	< 4hour	47(23.4)	46(17.3)	0.078	47(25.7)	46(25.1)	0.172
	≥ 4hour	154(76.6)	220(82.7)		136(74.3)	136(74.9)	
Postoperative							
RBC transfusion(packed)		5.4±7.2	4.9±5.3	0.061	4.7±5.3	4.9±7.2	0.356
PC transfusion(packed)		4.3±7.8	4.1±8.4	0.624	4.0±7.8	4.0±8.4	0.819
Duration of ventilation(hour)		32.5±53.1	28.5±44.2	0.382	29.2±52.9	28.5±50.5	0.686

Values are presented as number (%) and mean ± standard deviation. * p<0.05, **p<0.001
Abbreviations: BSA, body mass index; LV, left ventricle; EF, ejection fraction; EuroSCORE, European System for Cardiac Operative Risk Evaluation; CABG, coronary artery bypass graft; CV, combined coronary and valve operation; CPB, cardiopulmonary bypass; RBC, red blood cell; PC, platelet concentration;

Comparing sternal wound infection rates in the two groups, the incidences of superficial SSIs were 9.8% in the first-generation group and 10.3% in the third-generation group (*P* = 0.86). However, in deep SSIs rates, 5.7% and 16.5% (*P* <0.001), were significantly lower in the first-generation. And in multiple analysis, after adjusting for the variables of sex, age, diabetes, obesity, smoking, emergency, ITA use, ventilator, year and ICU stay, deep SSIs were significantly lower in first-generation than in third-generation (adjusted OR 1.25, 95 % CI 1.07 - 1.91) (Table 2). Pathogens isolated from SSIs resulted in that a common infection with β-lactam-resistant gram-positive cocci (eg methicillin-resistant *S aureus*and methicillin-resistant *Enterococci*) were significantly less frequent among patients who received first-generation group (24 of 194 patients 12.4% third-generation, vs 11 of 194patients 5.6% first-generation, p<0.01).Also methicillin-susceptible *S aureus* and coagulase-negative *Staphylococci* were significantly less frequent among patients who received first-generation group (25 of 194 patients 7.7% third-generation vs 9 of 194 patients 4.4% first-generation, $p = 0.028$). (S1 Tables)

Table 2. Clinical outcomes in patients receiving 1st generation prophylactic antibiotics compared with 3rd generation.

	3rd generation (n=194)	1st generation (n=194)	Crude OR (95% CI)	Adjusted OR (95% CI)
All surgical site Infection	52(26.8)	30(15.4)	1.19 (1.01-1.71)	**1.10 (1.01-1.62)***
Superficial surgical Site Infection	20(10.3)	19(9.8)	0.91 (0.71-1.30)	0.87 (0.62-1.11)
Deep SSI/ Mediastinitis	32(16.5)	11(5.7)	1.36 (1.11-2.08)	**1.25 (1.07-1.91)****

Values are presented as number (%).* p<0.05, **p<0.001
Variables of adjustment : age, sex, DM, obesity, smoking, emergency, ITA harvested, ventilator time, duration of ICU, enrollment.

The preoperative hospitalization duration and ventilator use time were similar in the two groups, 8.48.6 days for the third-generation group and 7.87.6 days for the first-generation group (p= 0.262), 1.2±2.2 days for the third-generation and 1.2±2.1days for the first-generation (p= 0.679). However, a significant difference was found in the ICU stay duration, with 4.1±3.8 days for the third-generation group and 2.9±2.7 day for the first-generation group (p=0.008). The total hospitalization duration increased significantly in third-generations to between 29.8±18.7 days for the third-generation group and 25.5±20.1 days for the first-generation group (p=0.025) (Table 3).

Table 3. Comparison of ICU, hospitalization duration of 1st generation and 3rd generation.

Duration	3rd generation (n=194)		1st generation (n=194)		P-value
Hospitalization duration (d)	**29.8±18.7**		**25.5±20.1**		**0.038**
Preoperative hospitalization (d)	8.4±8.6		7.8±7.6		0.262
Ventilation use time (d)	1.2±2.2		1.2±2.1		0.679
ICU Stay (d)	**4.1±3.8**		**2.9±2.7**		**0.008**
All-infection ICU stay (d)	n=52	**8.9±4.8**	n=30	**7.1±4.7**	**0.027**
Non-infection ICU stay (d)	n=142	2.6±1.2	n=164	2.3±2.0	0.088

Values are presented as mean ± standard deviation. *p*-value for t-test Abbreviations: ICU, intensive care unit; d, day;

Compared to medical costs in the two groups, total medical cost of daily expenses *(p<0.001)* and total hospitalization expenses *(p<0.001)* increased significantly in the third-generation. Medical cost for non-infected group were not statistically different (*p=0.092*) but statistical difference was observed in medical cost among all-infected group (*p<0.05*). As a result, medical cost were reduced in the first-generation group, at 5,894 USD (Table 4).

Table 4. Comparison of medical-cost expenditures of 1st generation and 3rd generation.

Cost	3rd generation (n=194)		1st generation (n=194)		P-value
Antibiotics cost for prophylaxis	USD 125 ±92		USD 80 ± 13		<0.001
Total medical cost/day	**USD 1,408 ±760**		**USD 959 ±738**		**<0.001**
Total medical cost/admission	**USD 26,488±18,402**		**USD 20,594±17,206**		**<0.001**
All-infection ICU stay (d)	n=52	USD 46,154±34,821	n=30	USD 27,191±27,190	**<0.05**
Non-infection ICU stay (d)	n=142	USD 21,251±10,594	n=164	USD 18,443±11,701	0.092

Values are presented as mean ± standard deviation. *p*-value for t-test. Abbreviations: ICU, intensive care unit; d, day;

Discussion

The results of this study showed a significantly higher incidence of deep-SSIs and all-SSIs in the third-generation group. The first-generation group showed excellent antimicrobial effects on β-lactam-resistant gram-positive cocci and remained stable for a long time at infection rates. As a result of comparing hospitalization between the two groups, preoperative hospitalization duration, mean operation time, and the ventilator time were similar in both groups, but hospitalization duration after surgery was significantly shorter in the first-generation antibiotic group.

This study was conducted to identify the use of prophylactic antibiotics and the source of infections and provide basic data for establishing antibiotic use guidelines. In a previous study, no differences were found in SSI rates after cardiac surgery between the third-generation and first-generation antibiotic groups, although a difference was found in antibiotic dosage and usage [19, 20]. However, in this study, while no differences in superficial SSI rates were observed between the third- and first-generation groups, significantly lower were found in the rates of

all SSIs and deep SSIs/mediastinitis rates were found in the first-generation group. Superficial SSIs may have been caused by impaired cutaneous circulation, whereas deep SSIs may reflect the relationship between tissue perfusion and infection, including muscle, bone, and the mediastinum in the surgical site and are less frequent than superficial SSIs but have a shorter duration to diagnosis and higher mortality and morbidity. Deep SSIs are one of the most destructive of cardiac surgery complications in patients and are different than superficial SSIs. Because the potential infection associations are substantially different, different treatment methods and strategies should be established. Therefore, the high incidence of deep SSIs in the third-generation group is confounded by complex complications and surgical treatment, which leads to increased ICU stays and re-admission rates and double the risk of mortality [21]. The effect of SSIs is influenced by antibiotic resistance and the number of infections [22]. Gram-positive bacteria and gram-negative bacteria were cultured from the SSIs of 67% and 23% of the patients in the third-generation group and from 62% and 24% of the patients in the first-generation group, respectively. *S aureus* and coagulase-negative S*taphylococci*, known to be important pathogens responsible for SSIs in heart surgery, are frequently resistant to β-lactam antibiotics [23, 24]. We found that the patients who received third-generation antibiotics for prophylaxis became significantly more colonized with methicillin-resistant coagulase-negative bacteria and *S aureus*than the first-generation group. We observed a trend toward more SSIs in the patients who received third-generation antibiotic prophylaxis. Thus, SSIs caused by methicillin-resistant gram-positive cocci were more common among patients who received third-generation antibiotics.
Considering that the antimicrobial characteristics of the two antibiotics differ, it is appropriate to use first-generation antibiotics because they have excellent antimicrobial activity against gram-positive bacteria and maintain a narrow range of antimicrobial activity. In addition, first-generation antibiotics are more effective in reducing medical costs and increasing safety because they have been used for a long time and are inexpensive. Bratzler et al.[21, 25] warned that the use of prophylactic antibiotics that are incompatible with guidelines is not only less effective in reducing SSIs, but the use of antibiotics over excessively broad antimicrobial ranges may increase the tolerance of other organisms. Barie et al.[26] reported that the choice of the appropriate prophylactic antibiotic is important to cover the range of surgical wound infection organisms and the use of inappropriate prophylactic antibiotics is not effective in reducing surgical wound infection rates. According to Bratzler et al.[21] prophylactic antibiotic selection recommends the use of narrow antibiotic ranges and long-used antibiotics due to factors such as cost, half-life, safety, and antibiotic resistance. Therefore, the newer and broader range of antibiotics should be avoided, as they may increase tolerance. This study did not show any clear advantage of newer and broader range third-generation antibiotics in reducing SSI rates and methicillin-resistant infections in cardiac surgery. In addition, the preoperative conditions, surgical procedures and technique, and antibiotic administration were similar in both groups but differed significantly in the effectiveness to prevent infection. Considering the stability, resistance and efficacy of the antibiotics, first-generation (cefazolin) antibiotics are suitable prophylactic drugs for heart surgery.
The duration of hospital stay in the first-generation group was significantly shorter than in the third-generation group. The preoperative hospital stay, operating time, and duration of ventilator use did not differ between the two groups. However, in the first-generation group, the duration of ICU stay and hospitalization were both significantly shorter than in the third-generation group. In addition, in the ICU stay comparison between the all-infection group ($n = 82$) and the non-infection group ($n = 306$), the mean duration of ventilator use was 2.5 ± 3.7 days vs 0.99 ± 1.4 days ($p<0.001$), the mean ICU stay duration was 7.3 ± 4.8 days vs 2.4 ± 1.4 days ($p<0.001$) respectively, were significantly higher in all-infection group. This result may reflect the increased susceptibility to surgical site infections with the long-term use of ventilators and increased ICU stay duration, leading to increased treatment due to infection. Lola et al.[27] reported that patients using ventilator for more than 48hours in the ICU had five-

fold higher SSI rates and were eight-fold more likely to be readmitted to the ICU due to complications. Therefore, the significant difference in the hospitalization duration between the two groups suggests that long-term ventilator use and ICU stay duration were the independent risk factors of SSIs. More effective effort and attention are, therefore, needed for ventilator management and hand hygiene promotion activities in the ICU to prevent infections.

Prophylactic antibiotic prices vary slightly from manufacturer to manufacturer, but the first-generation is the oldest drug in the cephalosporin family and has the lowest cost. The costs of prophylactic antibiotics may be reflected in the overall cost of patient care and treatment. The total medical care expenditure was about 5,800 USD higher in the third generation group, excluding pre-surgery examination fees, cardiac surgery costs, and material cost for the treatment. In particular, while no difference was observed in total medical expenditures between patients in the non-SSIs group, a significant difference was found in the all-SSIs group. Third-generation antibiotic prophylaxis affected the length of hospitalization and increased the cost of medical care. This was reflected in increases in the SSI rate, hospitalization duration, and the medical expenditures for additional treatments [28]. In addition, if indirect costs that were not evaluated in this study, were added, SSI could result in significant economic losses. Therefore, the active promotion of SSI prevention activities is necessary.

This study had several limitations as a prophylactic antibiotic study. First, the SSI rate was higher than that of a previous study [20]. The patients were followed-up within 30 days of surgery, and SSIs were judged according to the findings of the clinical physician, rather than the infection specialist physician. As such, the clinical physician might overestimate wound infections. Second, while all patients underwent the same surgical procedure, the enrollment period was eight years. After adjusting the enrollment period to confirm the SSI rates and errors due to long-term studies, and this study was able to reduce some of the distortion (S2 Tables). Third, the long-term enrollment results numbers of patients with SSIs are insufficient. Further studies are needed to identify additional interrelated risk factors, including various variables that can affect SSIs. The prophylactic antibiotic treatment duration and the incidence of SSIs need to be established through randomized clinical trials. In addition, further scientific results from investigations, such as accurate confirmation of the occurrence of SSIs and determining the appropriate dose period, are needed.

Conclusion

The results of this study showed that the use of third-generation prophylactic antibiotics increased the surgical site infection rate and the length of hospital stay compared to the use of first-generation antibiotics. In addition, the microbial cultures showed that the numbers of gram-positive bacteria and antibiotic resistant organisms at the surgical site were high. It is, therefore, important to select suitable prophylactic antibiotics. The selection of first-generation prophylactic antibiotics, with their long-term safety and low cost, was effective in reducing the rate of surgical site infections and decreasing hospitalization and medical expenditures.

Supporting information

S1 Tables. Microorganisms isolated according to surgical site infections and prophylactic antibiotics.
S2 Tables. Clinical outcomes in two yearly impact of surgical site infections.

Author Contributions

Conceptualization: Bae SJ, Kim I.
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Supporting information

S 1 Tables. Microorganisms isolated according to surgical site infections and prophylactic antibiotics.

S 1 Tables. Microorganisms isolated according to surgical site infections and prophylactic antibiotics.

	3rd generation				1st generation			
	Superficial SSIs	**Deep SSIs**	**Mediastinitis**	**Total**	**Superficial SSIs**	**Deep SSIs**	**Mediastinitis**	**Total**
	n=20	**n=24**	**n=8**	**n=52**	**n=19**	**n=6**	**n=5**	**n=30**
Coagulase-Negative *Staphylococci*								
All	8 (15.4)	9 (17.3)	5 (9.6)	22 (42.3)	8 (26.7)	3 (10.0)	4 (13.3)	15 (50.0)
Methicillin-resistant	4 (7.7)	4 (7.7)	4 (7.7)	12 (21.1)	4 (13.3)	1 (3.3)	2 (6.7)	7 (23.3)
Methicillin-susceptible	4 (7.7)	5 (9.6)	2 (3.8)	10 (19.2)	4 (13.3)	2 (6.7)	2 (6.7)	8 (26.7)
Staphylococcus aureus								
All	6 (11.5)	8 (15.4)	3 (5.8)	17 (32.7)	3 (10.0)	1 (3.3)	1 (3.3)	5 (16.7)
Methicillin-resistant	3 (5.8)	5 (9.6)	2 (3.8)	10 (19.2)	1 (3.3)	1 (3.3)	1 (3.3)	3 (10..0)
Methicillin-susceptible	2 (3.8)	2 (3.8)	1 (1.9)	5 (9.6)	1 (3.3)			1 (3.3)
Enterococci	1 (1.9)	1 (1.9)		2 (3.8)	1 (3.3)			1 (3.3)
Gram-negative bacilli								
All	4 (7.7)	7 (13.5)		11 (21.2)	6 (20.0)	2 (6.7)		8 (26.7)
Klebsiella species	2 (5.8)	3 (5.8)		5 (9.6)	3 (10.0)	1 (3.3)		4 (13.3)
Enterobacter species		1 (1.9)		1 (1.9)				
Acinetobacter species	1 (1.9)	2 (3.8)		3 (5.8)	2 (6.7)	1 (3.3)		3 (10.0)
Pseudomonas species	1 (1.9)	1 (1.9)		2 (3.8)	1 (3.3)			1 (3.3)
Culture Negative	2 (3.8)			2 (3.8)	2 (6.7)			2 (6.7)

Values are presented as number (%).

S 2 Tables. Clinical outcomes in two yearly impact of surgical site infections.

S 2 Tables. Clinical outcomes in two yearly impact of surgical site infections.

	All SSIs (n=82)	**Superficial SSIs (n=39)**	**Deep SSIs/ Mediastinitis (n=43)**
	OR (95% CI)	OR (95% CI)	OR(95% CI)
Enroll period			
2014-2016years	Ref	Ref	Ref
2012-2014years	0.84 (0.56-1.41)	0.79(0.42-1.22)	1.02(0.67-1.46)
2010-2012years	**1.12 (1.00-2.03) ***	0.87(0.55-1.56)	**1.21(1.07-2.23)***
2009-2010years	**1.31(1.11-2.48)****	1.02(0.91-1.45)	**1.56(1.22-2.67)****

- p<0.05, **p<0.001.

Variables of adjustment: age, sex, DM, obesity, smoking.