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CASE REPORT

Antibiotic cycling therapy reduces occurrence of surgical site infections after cardiac surgery

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Abstract

Background: The scheduled changing of antibiotics type (antibiotic cycling therapy) has been reported as an effective prophylaxis to reduce the incidence of antibiotic resistant bacteria. In this study, we aimed to clarify the preventive effects of antibiotic cycling therapy on surgical site infections after cardiac surgery.

Methods: 618 patients underwent elective cardiac surgery in our department. We examined the frequency of occurrence of SSI between different groups, Cycling group, using single antibiotics with changing the type every 3 months, and Combined group, using two types of antibiotics together at once.

Result: 284 patients was participated in Cycling group, 334 was in Combined group. 3 patients (1.1%) developed SSI after cardiac surgery in Cycling group, and 13 (3.9%) in Combined group (p= 0.027). Antibiotic cycling therapy was an independent factor of the risk of SSI with an odds ratio of 0.2 (confidence interval [CI]: 0.07–0.9, p=0.030), and the risk of SSI caused by antibiotic–resistant bacteria with an odds ratio of 0.2 (CI: 0.05–1.0, p=0.054).

Conclusion: Antibiotic cycling therapy reduced the incidence of antibiotic–resistant bacteria and SSI after cardiac surgery. The multiple logistic regression analysis showed, antibiotic cycling therapy was an independent factor to lower the occurrence of postoperative SSI and SSI related antibiotic–resistant bacteria.

Key words : Antibiotic cycling therapy, Cardiac surgery, Surgical site infection, antibiotic heterogeneity, postoperative antibiotic prophylaxis

■Introduction

It is well known that overuse of antibiotics can lead to the emergence of antibiotic-resistant bacteria, and the treatment of infection caused by multiantibiotic-resistant bacteria is difficult. The occurrence of hospital-acquired infections caused by multiantibiotic-resistant bacteria is becoming a disturbing problem. Accordingly, proper selection of antibiotics is important. It has been demonstrated that a resistant bacteria may appear when a specific antibiotic is used frequently and that sensitivity for antibiotic is restored when the antibiotic is suspended for a period of time. On the basis of these findings, the concept of antibiotic heterogeneity was established, in which the emergence of antibiotic-resistant bacteria is controlled by the impartial use of various antibiotics. As a means of enabling antibiotic heterogeneity, antibiotic cycling therapy, a method in which different kinds of antibiotics are sequentially used for a certain period, has been proposed and its effectiveness in controlling the emergence of resistant bacteria reported[1~3]. However, since few reports of the efficacy of antibiotic cycling therapy for preventing surgical site infections (SSI) following cardiac surgery have been presented, it effectiveness has not been well established. In the present study, we aimed to clarify the preventive effects of antibiotic cycling therapy on postoperative SSI after cardiac surgery.

■Materials and Methods

A total of 618 patients were enrolled in this study from April 1997 to March 2005. The study population included patients undergoing elective cardiovascular surgery at Toyama University Hospital. Patients for

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whom the administration of antibiotics was suspended or changed due to an allergic reaction to the drugs, and those who underwent surgery for an infectious disease such as infectious endocarditis were excluded. They were divided into two groups in accordance with the postoperative antibiotic prophylaxis, with those given cefotiam (2g/day) which was second-generation cephalosporin and vancomycin (1g/day) concomitantly immediately before and for seven days after surgery classified as the Combined group, and those given antibiotics after surgery for preventing surgical site infection, which was changed every 3 months in an antibiotic cycling therapy protocol, classified as the Cycling group. In the Cycling group, the used antibiotics were penicillin antibiotics, ampicillin sodium combined with sulbactam sodium or first- and second-generation cephalosporin antibiotics, which were administered immediately before and for 5 days after cardiac surgery. The study was approved by our institutional ethics committee, and informed consent was obtained from each patient with respect to the surgical method and postoperative care.

Definitions of SSI

The postoperative SSI[1] was defined as the occurrence of purulent discharge from the surgical wound[2], localized inflammation of the surgical wound[3], systemic inflammatory reaction of hematological examination was increased and associated with fever. Mediastinaitis was defined as criteria reported by Baskett et al[4]. Postoperative infectious complication, such as pneumonia, urinary tract infection, or biliary tract infections were not addressed. Necrosis of the skin due to peripheral circulatory disorder, adiponecrosis, and wound disruption associated with undernutrition were considered to exclude SSI.

Statistical analysis

Results for continuous variables were expected as mean ± standard deviation and categorical variables were expected as number (percent). The unpaired Student *t* test was used to compare the continuous variables and the Pearson χ^2 test was used to compare the categorical variables between the Cycling group and the Combined group.

The multivariate logistic regression analysis was used to assess risk factors for the occurrence of SSI. First, each variable was compared between patients with SSI and patients without SSI by the unpaired Student t test and the Pearson χ^2 test. Variables were considered for the multivariate logistic regression analysis if their univariable p value was less than 0.20. Independent variables were assigned odds ratios with 95% confidence intervals, shown together with the corresponding p value. p value less than 0.05 was considered statistically significant. SPSS version 12.0J software (SPSS Japan, Tokyo, JAPAN) was used for all analyses.

■Results

Comparisons between Combined and Cycling groups

The Combined group consisted of 334 patients (mean age 64.6 ± 10.8 years), of whom 259 underwent an isolated coronary artery bypass surgery, 57 received surgery for heart valve diseases, and 18 had other types of open heart surgeries. The Cycling group consisted of 284 patients (mean age 66.0 ± 10.2 years), of whom 192 underwent an isolated coronary artery bypass surgery, 66 received surgery for heart valve diseases, and 26 had other open heart surgeries. As for preoperative factors, the prevalence of hyperlipemia was significantly higher in the Cycling group (76 patients, 26.8%) as compared to the Combined group (61 patients, 18.3%) (p=0.01). In regard to surgical factors, the use of a cardiopulmonary pump was significantly higher in the Cycling group (98 patients, 34.5% v.s. 90 patients, 26.7%, p=0.04). No significant differences for other factors were observed between the groups (Table 1).

No statistically significant difference was observed for the 30-day mortality between the groups, though the mortality was lower in the Cycling group (2 patients, 0.7% v.s. 8 patients, 2.4%). The incidence of postoperative SSI was significantly lower in the Cycling group (3 patients, 0.7%) than in the Combined group (13 patients, 3.9%) (p=0.027). As for postoperative SSI that spread to the organs and cavity (mediastinitis, infection of replacement valve), no significant difference was observed between the Cycling and Combined groups (4 patients, 1.2% and 2 patients, 0.4%), respectively. The incidence of SSI caused by antibiotic-resistant bacteria was significantly lower in the Cycling group (2 patients, 0.7%, both *methicillin–resistant Staphylococcus aureus*) as compared to the Combined group (10-patients, 3.0%, *methicillin–resistant Staphylococcus aureus* in 8 patients, *methicillin–resistant Staphylococcus epidermidis* in 1 case, *multidrug–resistant Pseudomonas aeruginosa* in

Table 1 Comparison of patient characteristics between combined group and cycling group.

	Combined group n=334	Cycling group n=284	p value
Gender, M / F	247 / 87	201/83	0.378
Age (years)	64.6 ± 10.8	66.0 ± 10.2	0.385
Coronary artery bypass surgery	259 (77.5%)	192 (67.6%)	
Heart valve surgery	57 (17.1%)	66 (19.8%)	
Cardiopulmonary bypass	90 (26.7%)	98 (34.5%)	0.024
Diabetes mellitus	100 (30.0%)	91 (32.0%)	0.573
Hypertension	106 (31.8%)	101 (35.6%)	0.315
Hyperlipidemia	61 (18.3%)	76 (26.8%)	0.011
Previous history of cerebral infarction	46 (13.8%)	32 (11.3%)	0.350
Chronic renal dysfunction	21 (6.3%)	18 (6.3%)	0.979
Hemodialysis	8 (5.4%)	8 (2.8%)	0.742

Table 2 Comparison of post operative outcomes between combined group and cycling group.

	Combined group n=334	Cycling group n=284	p value
Mortality	8 (2.4%)	2 (0.7%)	0.097
Hospital stay (days)	35.7 ± 34.1	31.8 ± 19.1	0.143
Surgical site infection	13 (3.9%)	3 (0.7%)	0.027
Surgical site infection of organ and space	4 (1.2%)	2 (0.4%)	0.533
Respiratory infection	1 (0.3%)	3 (1.1%)	0.242
Infection due to antibiotic-resistant bacteria	10 (3.0%)	2 (0.7%)	0.040

Table 3 Comparison of patient characteristics with surgical site infections and infection due to resistant microbial

	surgical site infections			infection due to antibiotic-resistant bacteria		
	Yes	No	p value	Yes	No	p value
Number	16	602		12	606	
Gender, M / F	11 / 5	437 / 165	0.734	10 / 2	438 / 168	0.400
Age (years)	67.5 ± 12.0	65.2 ± 10.5	0.385	68.0 ± 12.2	65.2 ± 10.5	0.360
Coronary artery bypass surgery	12 (75.0%)	455 (75.6%)	0.957	9 (75.0%)	458 (75.7%)	0.955
Cardiopulmonary bypass	4 (25.0%)	184 (30.6%)	0.633	3 (25.0%)	184 (30.4%)	0.686
Diabetes mellitus	7 (43.8%)	184 (30.6%)	0.260	4 (33.3%)	187 (30.9%)	0.857
Hypertension	8 (50.0%)	199 (33.1%)	0.156	5 (41.7%)	202 (33.4%)	0.548
Hyperlipidemia	2 (12.5%)	135 (22.4%)	0.346	2 (16.7%)	135 (22.3%)	0.641
Previous history of cerebral infarction	4 (25.0%)	74 (12.3%)	0.131	3 (25.0%)	74 (12.4%)	0.193
Chronic renal dysfunction	2 (12.5%)	37 (6.1%)	0.302	1 (8.3%)	38 (6.3%)	0.772
Hemodialysis	1 (6.3%)	15 (2.5%)	0.350	1 (8.3%)	15 (2.5%)	0.206
Cycling therapy	3 (18.8%)	281 (46.7%)	0.027	2 (16.7%)	282 (46.6%)	0.039

1case) (p=0.04) (Table 2).

Univariate analysis of postoperative SSI incidence (Table 3)

Antibiotic cycling therapy (p=0.027), previous history of cerebral infarction (p=0.131), hypertension (p=0.156), and diabetes mellitus (p=0.26) were found to be factors involved in the occurrence of postoperative SSI. In addition, antibiotic cycling therapy (p=0.039), previous history of cerebral infarction (p=0.193), and hemodialysis (p=0.206) were factors involved in SSI caused by antibiotic-resistant bacteria.

The multiple logistic regression analysis

Risk factors for occurrence of postoperative SSI, including age, sex, antibiotic cycling therapy, history of cerebral infarction, hypertension, diabetes mellitus, and use of cardiopulmonary bypass, were examined by

Table 4 Multivariate analysis of surgical site infections

	Odds ratio	95%CI	p value
Antibiotic cycling therapy	0.2	0.07-0.9	0.030
Hypertension	1.8	0.7-5.2	0.248
Previous history of cerebral infarction	1.9	0.6-6.5	0.288
Diabetes mellitus	1.7	0.6-4.9	0.318
Age	1.0	1.0-1.1	0.433
Female	0.8	0.3-2.4	0.670
Cardiopulmonary bypass	1.3	0.4-4.5	0.717

Table 5 Multivariate analysis of infection due to antibiotic-resistant bacteria

	Odds ratio	95%CI	p value
Antibiotic cycling therapy	0.2	0.05-1.0	0.054
Hemodialysis	4.9	0.5-45.3	0.165
Age	1.0	1.0-1.1	0.292
Previous history of cerebral infarction	2.0	0.5-8.0	0.343
Female	2.1	0.4-10.6	0.348
Cardiopulmonary bypass	1.4	0.3-5.9	0.655
Diabetes mellitus	1.0	0.3-3.6	0.979

multiple logistic regression analysis. As a result, only antibiotic cycling therapy was shown to be an independent factor, with an odds ratio of 0.2 (confidence interval [CI]: 0.07-0.9, p=0.030) (Table 4). The same factors were analyzed for the risk of SSI caused by antibiotic-resistant bacteria, antibiotic cycling therapy with an odds ratio of 0.2 (CI: 0.05-1.0, p =0.054), and hemodialysis with an odds ratio of 4.9 (CI: 0.5-45.3, p=0.165), were shown to be significant (Table 5).

■Discussion

The SSI following cardiac surgery is associated with adverse outcomes. When the infection spreads to deeper regions, it becomes as serious as mediastinitis. Further, it has been known that the immune system is suppressed by use of a cardiopulmonary bypass and systemic hypothermia is associated with increased SSI[5]. In 2006, the society of thoracic surgeons recommended that the duration for postoperative administration of prophylactic antibiotics is no longer than 48 hours, and a beta-lactum antibiotics is indicated as a single antibiotic of choice for standard cardiac surgical prophylaxis in usual population[6,7]. However, the patients who have a high incidence of *methicillin–resistant Staphylococcus aureus* and the other antibiotic-resistant bacteria were increasing. The choice of antibiotic prophylaxis is important to prevent postoperative SSI in cardiac surgery.

Antibiotic cycling therapy has been proposed as a method for utilizing antibiotic heterogeneity and its effectiveness in intensive care unit has been reported[2,3]. Kollef et al.[1] introduced antibiotic cycling therapy to the patients undergoing cardiac surgery, in which ceftazidime and ciprofloxacin were changed in turn every 6 months, and reported that the antibiotic cycling therapy reduced the incidence of postoperative ventilator-associated pneumonia attributed to antibiotic-resistant bacteria. Gruson et al.[2] also employed antibiotic cycling therapy, with a beta-lactam antibiotics, amino-glycosidic antibiotics, and newquinolones antibiotics used in turn, based on their analysis of resistance patterns of the antibiotics. They reported a decrease in the incidence of ventilator-associated pneumonia and improvement of drug sensitivity of Gram-negative bacteria. Other studies have reported the inhibitory effects of antibiotic cycling therapy toward infection with Gram-negative bacteria, such as ***P. aeruginosa, Bacillus***, and *glycopeptide–resistant enterococci*[8,9,10]. For resistant Gram-positive bacteria as well, it was reported that the incidence was decreased by introduction of antibiotic cycling therapy[3,10]. In our study, the incidence of postoperative antibiotic-resistant bacteria decreased in significance by antibiotic cycling therapy.

The cycle length in antibiotic cycling therapy varies widely among reports. Toltzis et al.[11] performed antibiotic cycling therapy with a single antibiotic changed every month in a neonatal intensive care unit and reported that the detection rate of Gram-negative bacteria was not different than with the control group. Further, Merz et al.[12] performed antibiotic cycling therapy with a cycle length of 3-4 months in an intensive care unit and reported that no significant effect on infection was observed. It is considered that new tolerance might be acquired in some cases when the cycle length is extended, which would make the therapy ineffective[13]. The view about the cycle length is that less than 1 month is too short, while 3 or 4 months is too long[2,14]. In the present study, we changed the antibiotics every 3 months and obtained effective results. However, additional studies regarding the cycle length in antibiotic cycling therapy are needed.

Study limitations

The present study has a number of limitations. First, our study was retrospective without randomization. Second, there may be problems regarding the unmatched backgrounds of patients contained in the findings. We consider it desirable to conduct a randomized prospective study, in which the types of antibiotics are unified.

■Conclusion

In the present study, we found that the incidence of SSI following cardiac surgery was reduced following the introduction of antibiotic cycling therapy. The multiple logistic regression analysis showed that antibiotic cycling therapy was an independent factor to lower the occurrence of postoperative SSI and incidence of antibiotic-resistant bacteria, and hemodialysis were shown to factors that increased the risk of SSI caused by antibiotic-resistant bacteria.

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