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Incidence of and risk factors for infectious complications in patients with cardiac device implantation

Hea Won Ann [a,b], Jin Young Ahn [a,b], Yong Duk Jeon [a], In Young Jung [a], Su Jin Jeong [a,b], Boyoung Joung [c], MoonHyoung Lee [c], Nam Su Ku [a,b], Sang Hoon Han [a,b], June Myung Kim [a,b], Jun Yong Choi [a,b,*]

[a] Department of Internal Medicine, Yonsei University College of Medicine, Seoul, South Korea
[b] AIDS Research Institute
[c] Division of Cardiology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea

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SUMMARY

Objectives: The use of cardiac implantable electronic device (CIED; pacemakers, implantable cardioverter-defibrillators [ICD], cardiac re-synchronized therapy [CRT]) implantation, one essential treatment for cardiac arrhythmias, is increasing. Infectious complications related to implants are the main reason for device removal and patient morbidity. We sought to identify the incidence of infectious complications among patients with cardiac device implantation and analyze the risk factors for infectious complications.

Methods: A retrospective analysis was conducted of 1307 patients (61.5±14.2 years-old, 49.6% male) with cardiac device implantation from January 1990 to April 2013. We analyzed the incidence of infectious complications during the follow-up period. To investigate risk factors associated with infectious complications, we conducted a 1:2 matched case-control study of patients with infectious complications and controls without infectious complications who had the same implantation period and physician.

Results: Among 1307 patients, 12 had a confirmed device-related infection: 7 with a pocket infection and 5 with infective endocarditis. Over a total of 9091.9 device-years, the incidence of infectious complications was 1.3/1000 device-years, based on the 12 patients with an infection. ICD (5.1/1000 device-year) had a higher incidence of infectious complications than other cardiac devices, and no infectious complications were observed among patients with CRT implantation. Mean duration from the time of implantation to infection was 2.02±1.65 years. In a multivariate analysis, the number of prior procedures including wound revision or scar revision was an independent risk factor for infectious complications (OR=10.88, 95% CI 1.11->999, p=0.040).

Conclusions: Infection was a rare complication of cardiac device implantation, but repeated procedures were associated with infectious complications.

1. Introduction

The use of cardiac implantable electronic device (CIED; pacemakers, implantable cardioverter-defibrillators [ICD], cardiac re-synchronized therapy [CRT]) implantation, an essential procedure to treat cardiac arrhythmias, is growing. Pacemaker and ICD implantation has increased by 19% and 60%, respectively, from 1997 to 2004 in the United States.[1] A rising trend has been observed globally, including in Korea.[2,3] The reported incidence of cardiac device-related infections ranges from 0.5%-4.8%.[4–7] Although infrequent, infectious complications can cause device removal and even mortality.[8–13] Recent research shows that diabetes mellitus, underlying heart disease, cardiac resynchronized therapy (CRT)/dual chamber devices and use of >1 lead are risk factors for cardiac device-related infection.[11,14,15] Most research on cardiac device-related infections has been conducted in Western countries, and studies in Asian countries are limited. The current incidence of cardiac device-related infections in South

* Corresponding author. Department of Internal Medicine, Yonsei University College of Medicine, 50 Yonsei-ro, Seodaemun-gu, Seoul 120-752, Republic of Korea. Tel.: +82 2 2228 1974; fax: +82 2 393 6884.
E-mail address: seran@yuhs.ac (J.Y. Choi).

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Korea is unknown, although implantation of cardiac devices has been performed there since 1969.[16] There were 5815 cases of cardiac device implantation in 2006 and 9208 cases in 2013 in South Korea.[17,18] A better understanding of the incidence and risk factors of infectious complications in the region would help physicians develop appropriate measures to prevent and treat cardiac device-related infections.

We conducted this study to investigate the incidence and risk factors of cardiac device-related infections in South Korea.

2. Methods

2.1. Study population

The study population was composed of patients who underwent cardiac device (including permanent pacemakers, ICD, CRT) implantation de novo in a 2000-bed, tertiary teaching hospital from January 1990 to April 2013 in South Korea. A retrospective analysis was conducted using the medical records of 1306 patients, aged 18 years or older, for whom clinical observations and laboratory findings were available. We excluded patients who did not receive regular follow-up or who received an implant in another hospital but came to our center with an infection.

2.2. Study design and variables

We analyzed the incidence of cardiac device infections among 1307 patients during the follow-up period. Person-years of follow-up were calculated from the date of cardiac device implantation until the date of cardiac device infection or the date of last follow-up visit at the hospital.

Diagnosis of cardiac device infection was made clinically or microbiologically. We defined clinical evidence of cardiac device infection as one of the following signs: erythema, tenderness, fluctuance, warmth, wound dehiscence, skin erosion or discharge over the generator site.[19] Microbiological diagnosis was made based on positive culture of typical causative agents from the pocket of the device or its leads.[19] We applied modified Duke Criteria for the diagnosis of infective endocarditis for the detection of device-related endocarditis.[20]

In addition, to identify risk factors for cardiac device infection, we performed a matched case-control study. Cases included 12 patients with device-related infections during the study period. The control group consisted of 24 patients who underwent cardiac device implantation during the same period without infections during follow-up. Two controls were matched to each case according to implantation period within a month and the physician who did the procedure.

The following variables were assessed: (1) demographic and clinical characteristics (age at cardiac device implantation, gender, body mass index and Charlson comorbidity index.[21] Presence of arterial hypertension, diabetes, myocardial infarction, heart failure (ejection fraction $< 50\%$), valve disease (significant regurgitation or stenosis in transthoracic echocardiography), chronic obstructive pulmonary disease (FEV1/FVC $<70\%$), renal insufficiency (estimated glomerular filtration rate <60 mL/min/1.73m^2), malignant neoplasm and smoking were assessed.; (2) perioperative circumstances (use of prophylactic antibiotics, presence of signs of infection, anticoagulants use); (3) device characteristics (type of device - pacemaker, implantable cardioverter-defibrillator, cardiac resynchronized therapy, number of intracardiac leads); (4) number of procedures before the infection occurred (generator change, wound revision, lead repositioning and temporary pacemaker use).

2.3. Data analysis

Normally distributed continuous variables were expressed as mean ± standard deviation (SD).

Statistical significance of the comparisons was assessed using the paired t-test and χ^2 test. Uni- and multi-variate logistic regression analyses were used to analyze the cause of device-related infection between cases and controls. Variance inflation factors (VIF) were used to measure co-linearity in the multivariate logistic analysis; parameters with VIF$\geq$10 were considered to be co-linear. Parameters with co-linearity were excluded from the multivariate logistic regression analysis. A p-value <0.05 was considered statistically significant. Analyses were performed using SPSS v19 (SPSS Inc., Chicago, IL, USA) and SAS version 9.2 (SAS Institute Inc., Cary, NC, USA.)

3. Results

A total of 1307 patients underwent cardiac device implantation during the study period. Of these, 49.6% were male, and the mean age was 61.5±14.2 years. There were 1130 patients (86.5%) who received pacemaker implantation, 147 (11.2%) who received an ICD and only 30 patients (2.3%) who received CRT. Over a total of 9091.9 device-years, the incidence of infectious complications was 1.3/1000 device-years (Table 1), based on the 12 patients with an infection. There was a higher incidence of infectious complications with ICD (5.1/1000 device-year) than other cardiac devices, and no infectious complications were observed among the patients with CRT implantation. Of the 12 patients with infection, 7 patients (0.5%) had a pocket infection only and 5 patients (0.4%) had infective endocarditis. The mean duration from the time of implantation to infection (range) was 2.02±1.65 years (6 days to 2481 days) (Table 1).

Table 2 compares demographic and clinical characteristics between patients with and without infections complications. There were no significant differences in gender, echocardiographic findings or lab findings between the two groups. The proportion of patients with renal insufficiency and valvular heart disease was higher in the control group than the case group, and there was no

Table 1
Incidence of infectious complications of cardiac implantable electronic devices

		Device type			
	Total	PM	ICD	CRT	p-value
Number (n,%)	1,307	1,130 (86.5)	147 (11.2)	30 (2.3)	
Age (Years)	61.5±14.2	62.5±13.7	53.6±14.7	64.1±13.6	<0.001
Gender (male; n,%)	634 (49.6)	496 (44.0)	123 (83.7)	15 (50.0)	<0.001
Total FU duration (Device-yr)	9,091.95	8,442.27	579.99	69.68	
No. of infection complications (n,%)	12 (0.9)	9 (0.8)	3 (2.0)		
Incidence (/1,000Device-yr)	1.3	1.0	5.1		
Type of infection					
Pocket infection (n,%)	7 (0.5)	5 (0.4)	2 (1.4)		
Endocarditis (n,%)	5 (0.4)	4 (0.4)	1 (0.7)		

PM: Pacemaker, ICD: implantable cardioverter defibrillator, CRT: cardiac resynchronized therapy, FU: follow-up.

Table 2
Comparison of demographic and clinical characteristics in patients with and without infectious complications: Case control study (1:2 matched)

	Control (n=24)	Case (n=12)	p-value
Age	68.5±12.3	56.7±18.0	0.056
Gender (male; n,%)	13 (45.80)	7 (41.07)	0.819
Device and procedure related factors			
No. of leads	1.5±0.5	1.8±0.5	0.224
No. of prior procedures	0.04±0.21	0.75±1.1	0.056
Hematoma	4.20%	8.30%	0.619
Antiplatelet agent	41.70%	25.00%	0.393
Hospital duration	5.3±1	2.9±1.9	0.078
Underlying disease			
Hypertension (n,%)	16 (66.70)	5 (41.7)	0.16
Diabetes mellitus (n,%)	7 (29.20)	1 (8.3)	0.109
Myocardial infarction (n,%)	1 (4.2)	2 (16.7)	0.314
Heart failure (n,%)	3 (12.5)	1 (8.3)	0.717
Valve disease (n,%)	13 (54.20)	2 (16.7)	0.032
COPD (n,%)	0 (0)	0 (0)	-
Renal disease (n,%)	4 (16.60)	0 (0)	0.043
Cancer (n,%)	0 (0)	0 (0)	-
Charlson comorbidity index	2.1±2.8	0.5±0.80	0.014
Smoking (n,%)	7 (29.20)	4 (33.3)	0.805
Echocardiographic findings			
Ejection fraction	62.9±6.2	64.8±10.3	0.718
E/E'	14.0±5.8	11.0±4.0	0.176
Laboratory findings			
WBC (10^3/uL)	7488.8±3017.8	6876.7±1568.2	0.516
Neutrophil (%)	59.3±14.3	56.9±14.5	0.634
Hemoglobin (g/dL)	13.2±1.6	13.9±1.9	0.262
Platelet (10^3/uL)	234.6±92.5	233.1±46.7	0.958
Hemoglobin A1c (%)	6.7±0.9	6.5±0.6	0.69
Creatinine (mg/dL)	1.1±0.4	0.9±0.2	0.122
eGFR (ml/min/1.73m^2)	72.0±25.5	93.7±28.6	0.031
CRP (mg/L)	24.8	30.7±42.1	0.929
NTproBNP (pg/mL)	1033.9±1546.8	216.4±127.6	0.182
CK (IU/L)	137.4±124.2	78	0.368
CK-MB (ng/mL)	3.7±4.1	1.8±0.3	0.441
TnT (ng/mL)	0.03±0.077	0.01±0.01	0.536
AST (IU/L)	32.4±19.6	21.3±6.2	0.065
ALT (IU/L)	41.1±47.2	20.9±11.7	0.058

COPD: chronic obstructive pulmonary disease, WBC: white blood cell, eGFR: estimated glomerular filtration rate, CRP: C - reactive protein, NTproBNP: N-terminal prohormone of brain natriuretic peptide, CK: creatine kinase, TnT: troponin T, AST: aspartate aminotransferase, ALT: alanine aminotransferase.

significant difference in the prevalence of diabetes mellitus. The Charlson comorbidity index was higher in the control group, but was an insignificant variable in the multivariate analysis (p=0.0936) (Table 3). The multivariate analysis indicated that patients with infection had a greater number of prior procedures including wound revision, generator exchange or scar revision (OR=10.87, 95% CI 1.108->999, p=0.0402) (Table 3).

Table 4 lists the clinical characteristics of each patient with cardiac device infection. The pathogens thereof were identified in six patients, and included *Staphylococcus aureus* (*S. aureus*), two cases of coagulase-negative staphylococcus, *Enterococcus faecium*, and *two cases of gram negative bacilli* (*Enterobacter cloacae, Escherichia coli*). The device was removed in all patients: four through open heart surgery and eight through percutaneous extraction.

4. Discussion

To our knowledge, this is the first report of infections associated with cardiac devices in Korea. The long period of observation allowed us to review long term prognosis of Asian patients with cardiac devices. Device-related infection was a rare complication, and repeated procedures were associated with infectious complications.

According to prior studies, cardiac device-related infection occurs in about 0.5-3.5% of cases, with an incidence that varies from 0.55 to 4.82 per 1000 device-years.[5,8–12] CIED-related infection increased 5.8% from 1996 to 2006 even though CIED implantation only increased 2.6% during the same time period.[15,22] In our study, 0.9% of patients with cardiac devices had infectious complications, and the overall incidence was 1.3/1000 device-years. This low incidence matches those reported in previous studies. Nevertheless. the indications for CIED implantation are widening[23–25] and the number of patients susceptible to infection (due to old age and various underlying diseases) is increasing. Thus, the actual number of cases of CIED infection may greatly expand in the near future. Despite its low incidence, CIED infection is an important complication, the consequences of which are quite serious: endocarditis related with device infection increases mortality,[26,27] and most cases require device removal,[28,29] which involves risks of cardiac perforation or open thoracotomy.[30]

Several earlier studies showed that factors associated with procedures included early intervention, more than two leads, device replacement or revision and placement of temporary pacing wire.[1,8,12,14] Patient-related factors included diabetes, renal failure, heart failure and male sex.[1,12,31] Some researchers have pointed out that corticosteroids or anticoagulation are related to CIED infection.[8,12,28,31,32] There have also been some reports that the number of cardiac device operations is independently related to a higher risk of infection.[12,33]

In our case-control study, repeated procedures were a significant risk factor for infectious complications. This finding is consistent with previous studies. We were unable to analyze the influence of renal dysfunction or heart failure because of the low incidence of these diseases in our study population. Herce et al. evaluated risk factors for infection of implantable cardiac devices with data from a registry of 2469 patients in a French hospital between 1996 and 2007.[1] Their study showed the presence of diabetes and underlying heart disease to be risk factors for infection after cardiac device implantation. Meanwhile, others have reported contrasting results. In a report by Greenspon et al., CIED infection was lower in patients with diabetes (Odds ratio: 0.91; 95% CI: 0.86 to 0.96; p <0.001),[34] and others described diabetes as an insignificant risk factor.[8,32] In our study group, the prevalence of diabetes in the case group (29.2%) was insignificantly higher than that in the control group (8.3%); moreover, the

Table 3
Risk factors for device-related infections by univariate and multivariate conditional logistic regression analysis

	Univariate analysis				Multivariate analysis			
	OR	95% CI		p-value	OR	95% CI		p-value
Age	0.948	0.899	0.995	0.0304	1.02	0.932	1.13	0.72
Gender	0.848	0.162	4.195	1				
Hospital duration	0.73	0.443	1.01	0.0619				
Charlson score	0.6	0.265	1.002	0.0517	0.523	0.103	1.067	0.0936
No. of leads	2.475	0.458	17.784	0.4001				
No. of prior procedures	19.334	1.682	>999	0.011	10.872	1.108	>999	0.0402
Ejection fraction	1.01	0.961	1.068	0.7504				

OR: odds ratio, CI: confidence interval.

Table 4
Clinical characteristics of each patient with a cardiac device infection

	Age	Gender	Local manifestation	Fever	TTE	Device type	Prior procedure	Time interval	Local culture	Lead culture	Blood culture	Outcome	
1	80	F	Inflammation(redness, discharge)	+	-	PM	0	6	Negative	Negative	Negative	Percutaneous extraction	Recurrent skin eruption over the implantation site
2	73	F	Inflammation(hematoma, serosanguineous discharge)	-	-	PM	0	10	Negative	Negative	Negative	Percutaneous extraction	
3	60	M	Inflammation(skin discoloration, tenderness)	-	-	PM	1(wound revision)	34	*Enterobacter cloacae*	*Enterobacter cloacae*	Negative	Percutaneous extraction	Overlying skin thinning and necrosis
4	38	F	Inflammation(redness, local heating, tenderness)	+	Negative	ICD	2(pacemaker revision, scar revision)	65	MRSA	MRSA	MRSA	Surgical removal	Pacemaker insertion under the left pectoralis major muscle via the axillary incision (cosmetic cause)
5	34	M	Inflammation(yellowish pus)	-	-	PM	1(generator repositioning)	191	Negative	Negative	Negative	Percutaneous extraction	
6	73	F	Inflammation(yellowish discharge, skin defect)	-	-	ICD	0	468	Negative	-	Negative	Surgical removal	
7	43	M	erosion, tenderness	-	-	PM	0	566	Negative	Negative	Negative	Percutaneous extraction	
8	57	M	Inflammation(swelling, tenderness)	-	-	PM	1(re-implantation with device protrusion)	611	MRCNS	MRCNS	Negative	Percutaneous extraction	
9	39	F	Inflammation(pus discharge)	-	-	PM	1(generator repositioning)	876	*E. faecium*	Negative	Negative	Percutaneous extraction	
10	69	M	Inflammation(skin erosion, discharge)	-	-	PM	2(wound debridement and revision)	938	MSCNS	MSCNS	Negative	Surgical removal	
11	79	F	Inflammation(skin erosion, wire exposure)	+	Vegetation	PM	0	1013	Negative	Negative	Negative	Surgical removal	Skin erosion by nail scratch, secondary septic pneumonia
12	35	M	Inflammation(wound dehiscence, pus-like discharge)	-	Negative	ICD	1(lead exchange)	2481	ESBL(-) *E. coli*	-	Negative	Percutaneous extraction	

TTE: Transthoracic echocardiography, MRSA: Methicillin-–resistant staphylococcus aureus, MRCNS: Methicillin-resistant coagulase negative staphylococci, MSCNS: Methicillin-sensitive coagulase negative staphylococci, ESBL: Extended spectrum beta-lactamase.

presence of diabetes was not shown to be an independent risk factor for infectious complications in our case control study, even after including diabetes in the multivariate model. Diabetes mellitus is usually related with wound infection, but has no negative influences under tight glycemic control.[35,36] In the present study, diabetes in all enrolled patients was controlled well, with a mean HbA1c of 6.55±0.52%. Thus, we suggest that the burden of repeatedly undergoing medical procedures influences the occurrence of CIED infection much more than patient characteristics, including underlying disease.

In our study, the pathogens of infectious complications were identified in only 6 patients. Previous studies showed that bacterial infection is the leading cause of CIED complication, mostly from skin normal flora,[37] among which *S. aureus* and coagulase negative staphylococcus comprise the majority of infections.[38,39] In our study participants, one case of *S. aureus* and two cases of coagulase negative staphylococcus were observed. The *S. aureus* and one of the coagulase negative staphylococcus cultures were methicillin resistance. Reportedly, the risk of methicillin-resistance is higher within a year of implantation;[40] however, in our study, we could not find a distinct relationship in patients with methicillin-resistant bacteria, due to the small sample size.

We also observed a relatively higher infection rate in patients with ICD implantation (statistically insignificant). The ICD generator is bigger and heavier than pacemakers, and thus requires a longer incision and bigger pocket. Patients with ICD exhibit more tension on covering skin and a chance of bigger dead space. As well, most patients that require ICD are survivors of cardiac arrest. Cardiac arrest and resuscitation cause cardiac stunning and transient multiple organ injury. Although their cardiac dysfunction reversed fully from stress, these systemic effects could have had a negative influence on their general condition and a chance of infection.

All of the patients with device infection had their devices removed. Eight patients underwent percutaneous removal, and the other 4 patients underwent open thoracotomy. There was no CIED infection-related death in our study participants. The reported inpatient mortality related with CIED infection ranges from 4.69% to 17% in cases of endocarditis.[34,41,42]

5. Limitations

This study has several limitations. First, this is a retrospective study. We could not analyze the effect of renal insufficiency or heart failure because there were only few patients with comorbidities. We only included patients from a single referral center, and so our findings may not be broadly applicable. Despite these limitations, this is the first report about the incidence and risk factors of CIED infection in South Korea. And it is meaningful that we saw long term after-effects associated with cardiac device implantation over 23 years of observation (1990-2013).

Our findings could be helpful in the both clinical setting and further research on CIED infections.

6. Conclusions

Even though the incidence of CIED-related infections was low in South Korea, physicians should closely monitor for complications in patients who receive repeated procedures.

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