Permanent Pacemaker and Implantable Cardioverter Defibrillator Infections: Seven Years of Diagnostic and Therapeutic Experience of a Single Center

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ABSTRACT

Background: Increasing evidence-based indications for the implantation of permanent pacemakers (PMs) and implantable cardioverter defibrillators (ICDs) have led to an increase in the rate of device infections. The aim of the present study was to evaluate infection frequency, clinical characteristics, risk factors, and microbiologic and therapeutic features in patients with PM/ICD infections.

Hypothesis: Clinical and demographic characteristics of the patients can affect the PM/ICD infections.

Methods: The PM/ICD infection group consisted of 57 patients diagnosed and treated with PM/ICD infections in our hospital. The control group in this case-control study consisted of 833 patients in whom a PM or ICD had been implanted and no infections were noted.

Results: Patients with PM/ICD infections (median age 65 years; range, 18–104 years) were older than those without PM/ICD infections (median age 58 years; range, 18–86 years; $P = 0.005$). The percentage of generator replacement was higher in the PM/ICD infection group compared with the control group (16% vs 8%, $P = 0.003$). Independent predictors of PM/ICD infections were advanced age (>60 years; odds ratio [OR]: 2.5, 95% confidence interval [CI]: 1.2–4.0, $P = 0.021$) and device revision (OR: 3.8, 95% CI: 1.5–5.5, $P = 0.002$). Primary antibiotic prophylaxis during the procedure reduced the risk for PM/ICD infection (OR: 0.5, 95% CI: 0.4–0.8, $P = 0.011$).

Conclusions: PM/ICD infections occur in a significant number of patients. It is important to be aware of the risk factors for PM/ICD infections so that patients with an increased risk can be identified and preventive measures can be implemented.

Introduction

Permanent pacemakers (PMs) and implantable cardioverter defibrillators (ICDs) have become an essential part of clinical practice, and therefore their indications have progressively expanded.[1] In parallel with this, however, device-related infections that are difficult to treat have also increased. Although advances in surgical technique and development of transvenous devices have led to a decrease in device-related infections, PM and ICD infections are more frequently encountered in clinical practice due to the increase in number of devices used.[1,2]

The incidence of infection following PM and ICD implantation ranges from 0.1% to 20%.[3–5] Infections that occur within the first 2 months after implantation are referred to as acute PM infections.[6] Acute infections constitute 25% of all infections, while the remaining 75% are chronic infections. PM/ICD infections are classified in 2 forms, pocket infections and endocarditis.[7,8] Patients with PM/ICD infections may present with regional or systemic symptoms. Erythema, pain, erosion, redness, increased warmth, purulent drainage, and cellulitis are frequent regional findings in pocket infections. In endocarditis, fever and rash are present in addition to regional findings. Positive surface and blood cultures suggest the presence of a device infection. Some investigators have advocated conservative treatment with antibiotics and generator pocket debridement without hardware removal.[9] Most previously published studies, however, have shown unacceptably high failure rates with conservative treatment.[10,11] Without any doubt, this conservative treatment is not sufficient in the management of PM/ICD endocarditis. The device should be removed in patients with endocarditis, and long-term intravenous antibiotic therapy should be administered. The

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reinfection rate has been reported to be 0.8% if the device is removed and 50% if it is not removed.[10,12] Information about PM/ICD infections is generally based on the studies conducted in the United States and Western Europe, and there were few studies in this field.

The aim of the present comparative study was to evaluate the clinical and demographic characteristics, as well as the risk factors, of patients treated for PM/ICD infections in our tertiary medical care center, which provides services for the entire country.

Methods

Study Population

The PM/ICD infection group consisted of 57 patients diagnosed and treated with PM/ICD infections between January 2000 and December 2007 in our hospital. All patients in whom PM/ICD had been implanted during that same interval and who had not developed infections (n = 833) constituted the control group. Of the 57 patients with PM/ICD infections, 21 (17 PM and 4 ICD infections) had their devices implanted in our hospital and 36 (31 PM and 5 ICD infections) had their devices implanted in other hospitals.

Data Collection

The cases were determined by diagnostic codes for PM/ICD infections used by the Department of Medical Archives and Documentation and the records of the Department of Infectious Diseases. Patient records were evaluated retrospectively. In patients whose devices were implanted in other hospitals, data were gathered from patient records and the attending physician.

Age (at the time of implantation), gender, device type (PM or ICD), characteristics of hospitalization, risk factors, use of antibiotic prophylaxis, growth in blood culture, echocardiographic findings, relapse and reinfection status, removal of device, and reimplantation data were recorded for each patient. The presence of diabetes mellitus (DM), long-term steroid use, femoral venous catheters, postoperative hematomas, anticoagulant use, and malignancies were evaluated as risk factors. A pocket hematoma was defined by 2 investigators as a palpable mass that protruded $\geqslant$2 cm anterior to the pulse generator. Presence of systemic PM/ICD infection was clinically confirmed when valvular or lead vegetations were detected by echocardiography, or if the modified Duke criteria[13] for infective endocarditis were met. Vegetation was defined as an oscillating intracardiac mass on the leads, cardiac valve leaflets, or endocardial surface in the setting of valve or lead infection, confirmed by imaging in more than 1 echocardiographic view and positive blood and/or lead tip cultures. Swelling, redness, and discharge in the pocket region and bacterial growth in the wound cultures were considered as superficial infections.

Relapse was defined as development of infection with the same microorganism within 1 year. Infections that developed 1 year after the initial infection were considered as reinfections. All patients in the PM/ICD infection group were examined by transthoracic echocardiography. Transesophageal echocardiography was performed in patients with high clinical suspicion of device-related infection or in patients with vegetations noted on transthoracic echocardiography (15 patients).

Statistical Analysis

Statistical analysis of the data was conducted using SPSS 15 (SPSS Inc., Chicago, IL). Normally distributed descriptive variables were expressed as the mean $\pm$ SD; variables with skewed distribution were expressed as the median and range (minimum and maximum). Patients with PM/ICD infections and controls were compared in terms of risk factors. Pocket infection and systemic infection subgroups were also compared. The χ^2 and Fischer exact tests were used for categorical variables. The Student t test was used for normally distributed continuous numeric variables. The Mann-Whitney test was used for the comparison of continuous numeric variables with skewed distribution. In order to evaluate the independent effects of clinically significant risk factors (age, gender, etc.) and those that had a significant effect on outcome based on univariate analysis ($P < 0.05$), multivariate logistic regression analysis was performed. The statistical significance level was considered as $P < 0.05$.

Results

Clinical Features

Patients with PM/ICD infections (median age 65 years; range, 18–104 years) were older than those without PM/ICD infections (median age 58 years; range, 18–86 years; $P = 0.005$). There was no significant difference between the PM/ICD infection and control groups in terms of gender (male/female: 36/21 vs 475/358, respectively; $P = 0.490$) and device type (PM/ICD: 48/9 vs 690/143, respectively; $P = 0.350$). The percentage of generator replacement was higher in the PM/ICD infection group compared with the control group (16% vs 8%, $P = 0.003$). This statistical difference was mainly because of a higher generator replacement rate in the pocket infection subgroup (17%) than in the systemic infection subgroup (10%).

The PM/ICD infection rate was 2.45% (21/854) in patients who had undergone PM/ICD implantation in our hospital. The mean follow-up duration of patients was 34.8 months (range, 0–80.4 months).

As previously stated, the 57 patients with PM/ICD infections were further allocated into 2 subgroups: pocket infections and systemic infections. Eighty-two percent (47/57) of the patients with PM/ICD infections had pocket infections, and 18% (10/57) had systemic infections.

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Electrode and valvular vegetations were noted in 5 (9%) and 3 patients (5%) with systemic infections, respectively. The demographic and clinical characteristics of the groups and subgroups are presented in Table 1.

Primary antibiotic prophylaxis was administered in 95% (54/57) of the patients with infections and in 100% (833/833) of those without infections ($P = 0.008$). There was no significant difference between the groups in terms of the duration of antibiotic prophylaxis. When the patients in the PM/ICD infection and control groups were compared in terms of prognosis, 3 of 57 (5%) patients with PM/ICD infections died, and 2 of these deaths were as a consequence of the PM/ICD infection. No device complication-related deaths were noted in the control group. There was no statistically significant difference between the groups in terms of deaths due to all causes.

When the patients were evaluated with respect to signs of infection, erythema (82%) was determined to be the most frequent symptom in general. Among patients with pocket infections, the most common symptom was erythema (93%), whereas in patients with systemic infections, fever (50%) and fatigue (50%) were the most common symptoms. Symptoms in patients with PM/ICD infections are shown in detail in Table 2.

Table 1. Patient Clinical and Demographic Characteristics

Parameter	PM/ICD Infection Group (n = 57)		Control Group (n = 833)
	Pocket Infection (n = 47)	Systemic Infection (n = 10)	
Age, y, median (range)	65 (18–104)[a]	66 (34–88)[a]	58 (18–86)
Gender, n/n	30M/17F	6M/4F	475M/358F
PM/ICD, n/n	40/7	8/2	690/143
Generator replacement, n (%)	8 (17)[b]	1 (10)	63 (8)
Primary antibiotic prophylaxis, n (%)	45 (96)[c]	9 (90)[c]	833(100)
Prophylaxis duration >24 h, n (%)	23 (49)	5 (50)	441(53)
PM/ PM/ICD infection-related deaths, n (%)	0 (0)	2 (20)[c]	0 (0)
Deaths, Deaths, n (%)	1 (2)	2 (20)[c]	25 (3)

Abbreviations: F, female; ICD: implantable cardioverter defibrillator; M, male; PM: permanent pacemaker.
[a] $P < 0.01$ when compared with control group.
[b] $P < 0.05$ when compared with control group.
[c] $P < 0.001$ when compared with control group.

Risk Factors

While postintervention hematomas occurred in 32% of patients with PM/ICD infections (34% in pocket infection and 20% in systemic infection), they occurred in only 3.5% of the controls. There was a statistically significant difference between the groups with respect to hematomas ($P < 0.001$). There was no statistically significant difference between the groups in terms of presence of DM ($P = 0.210$). Anticoagulant use was noted in 29% of patients with pocket infections, 20% in systemic infections and 12% of the controls; the difference between the pocket infection and control groups was statistically significant ($P < 0.01$). Steroid use >1 month was noted in 3 (5%) of patients, all of whom were in the pocket infection group ($P = 0.008$). There was no significant difference between the groups in terms of malignancy or the presence of femoral catheters. A comparison of the groups in terms of risk factors is presented in Table 3.

Variables that were found to be significant risk factors for PM/ICD infection (both pocket and systemic infection subgroups) in univariate analysis were further evaluated by multivariate analysis. There was an increased risk for PM/ICD infections in patients age >60 years (odds ratio [OR]: 2.5, 95% confidence interval [CI]: 1.2–4.0, $P = 0.021$).

Table 2. Symptoms Observed in Patients With PM/ICD Infection

Symptom	Pocket Infection (n = 47)	Systemic Infection (n = 10)
Erythema, n (%)	44 (93)	3 (30)
Swelling, n (%)	42 (89)	3 (30)
Increased warmth, n (%)	43 (85)	3 (30)
Fever, n (%)	37 (79)	5 (50)
Skin ulceration, n (%)	24 (51)	2 (20)
Tenderness, n (%)	24 (51)	2 (20)
Fatigue, n (%)	22 (47)	5 (50)
Purulent discharge, n (%)	20 (43)	0 (0)
Chills, n (%)	17 (36)	4 (40)
Loss of appetite, n (%)	16 (25)	4 (40)
Nausea, n (%)	5 (11)	3 (30)

Abbreviations: ICD, implantable cardioverter defibrillator; n, number of patients; PM, permanent pacemaker.

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Table 3. Comparison of Groups and Subgroups in Terms of Risk Factors

Parameter	PM/ICD Infection Group (n = 57)		Control Group (n = 833)
	Pocket Infection (n = 47)	Systemic Infection (n = 10)	
Hematoma, %	34[a]	20[a]	3.5
Diabetes mellitus, %	28	40	21
Anticoagulant use, %	29[b]	20	12
Steroid use (>1 mo), %	5[b]	0	0
Central venous catheter, %	2	20[c]	3
Malignancy, %	2	10	2

Abbreviations: ICD, implantable cardioverter defibrillator; PM, permanent pacemaker.
[a] $P < 0.001$ when compared with control group.
[b] $P < 0.01$ when compared with control group.
[c] $P < 0.05$ when compared with control group.

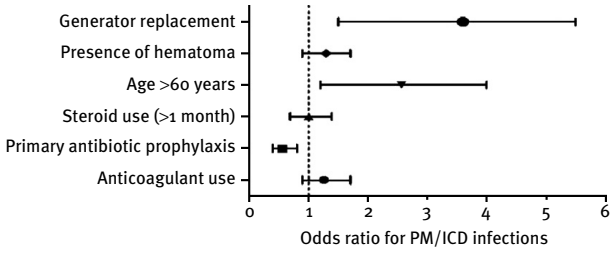

Figure 1. Odds ratios of several risk factors for PM/ICD infections. Abbreviations: ICD, implantable cardioverter defibrillator; PM, permanent pacemaker.

Generator replacement was the strongest independent predictor for PM/ICD infection (OR: 3.8, 95% CI: 1.5–5.5, $P = 0.002$; Figure 1). Primary antibiotic prophylaxis during the procedure reduced the risk for PM/ICD infection (OR: 0.5, 95% CI: 0.4–0.8, $P = 0.011$). Although steroid use >1 month, anticoagulant use, and postintervention hematomas were determined to be significant risk factors in univariate analysis, they were not determined to be significant risk factors in multivariate analysis.

When patients with pocket infections were compared with patients with systemic infections with respect to risk factors, the presence of femoral venous catheters was found to be associated with an increased risk for systemic infections (20% vs 2%; OR: 2.8, 95% CI: 1.2–4.0, $P = 0.01$). Duration of placement of the femoral venous catheter was 7 ± 3.5 days. There was no statistically significant difference between the groups in terms of anticoagulant use, presence of DM, steroid use >1 month, presence of malignancy, and hematoma.

Microbiologic Characteristics and Antibiotic Treatment

All blood cultures were obtained prior to administration of antibiotics. Bacterial growth was observed in blood cultures of 20 patients (35%; 21% in pocket infections and all systemic infections). Gram-positive bacteria were detected in 80% of the positive cultures. *Staphylococcus aureus* in 35% of patients (7/20; methicillin-sensitive *S aureus* in 5 cases and methicillin-resistant *S aureus* in 2 cases) and *Staphylococcus epidermidis* in 30% of patients (6/20; methicillin-sensitive *S epidermidis* in 4 cases and methicillin-resistant *S epidermidis* in 2 cases) were the most frequently isolated microorganisms. *Staphylococcus hominis* was isolated in 2 patients, and *Bacillus* subspecies were isolated in 1 patient with blood cultures positive for gram-positive bacteria. Gram-negative bacteria were isolated in 4 (20%) blood cultures (*Enterobacter cloacae* in 2 patients, *Acinetobacter haemolyticus* in 1 patient, and *Pseudomonas aeruginosa* in 1 patient). A combination of sulbactam plus ampicillin (SAM) was determined to be the most frequently used antibiotic in patients with PM/ICD infections; it was used in 87% (41/47) of patients with pocket infections and in 70% (7/10) of patients with systemic infections. Vancomycin was used in 13% (6/47) of patients with pocket infections and in 50% (5/10) of patients with systemic infections. The duration of antibiotic treatment was longer in systemic infections compared with pocket infections (34.0 ± 6.7 days vs 21.0 ± 4.1 days, $P = 0.001$).

Patient Device Reimplantation and Hospitalization Characteristics

PM/ICD devices were removed from 53% (25/47) of patients with pocket infections and in all patients with systemic infections. Reimplantation was performed after PM/ICD removal in all patients. Lead extraction was performed in 7 patients with pocket infections (6 with manual traction and 1 with laser) and in all patients with systemic infections (6 with manual traction and 4 with laser). Relapse was observed in 15% (7/47) of patients with pocket infections and in 30% (3/10) of patients with systemic infections. Furthermore, reinfection was noted in 1 patient with pocket infection. The rate of successful treatment without relapse or reinfection was 81%. There was no difference in duration of antibiotic treatment (30.1 ± 5.2 days vs 29.0 ± 5.0 days) and proportion of lead extraction (14/47 vs 3/10) between successfully treated patients and patients with relapse, respectively. Two patients with systemic infections who had relapses died. Antibiotic treatment was readministered to patients with relapses or reinfections and their devices were removed. No relapses or reinfections were noted in this group of patients after reimplantation. The rate of

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successful treatment after inclusion of patients with relapses or reinfections was 96.5%.

The median length of hospitalization was 14 days (range, 1–154 days) in patients with pocket infections and 17 days (range, 10–76 days) in patients with systemic infections. The median elapsed time from PM/ICD implantation to the onset of infection was 180 days (range, 3–1453 days) in patients with pocket infections and 764 days (range, 16–2447 days) in patients with systemic infections ($P = 0.001$). The median time until reimplantation was 0 days (range, 0–20 days) in patients with pocket infections and 12 days (range, 0–33 days) in patients with systemic infections. There was no statistically significant difference between the groups ($P = 0.09$).

Discussion

In recent years, there has been a tremendous increase in the use of PMs/ICDs; therefore, PM/ICD-related complications also have been observed to increase.[2,3,14] Voigt et al[14] found that the most significant cause of mortality among PM/ICD complications was PM/ICD-related infections. Studies have been published associated with these infections with rapidly increasing frequency. Varied results have been reported regarding the prevalence of PM/ICD infections.[15,16]

In the present study, the PM/ICD infection rate in our hospital was 2.45% (PM infections 2.4% and ICD infections 2.7%). This result is consistent with infection rates in the literature. Catanchin et al[17] reported that the prevalence of PM/ICD infections was 1.6% in their patients, who were followed up for a mean period of 22 months. Mounsey et al[18] reported that the PM/ICD infection rate was 2.7% in their study, with a mean follow-up duration of 19 months. León et al[19] reported the PM/ICD infection rate to be 1% after 6 months' follow-up, whereas Klug et al[11] reported the PM/ICD infection rate to be 0.7% after a 1-year follow-up. Uslan et al[2] reported a low infection rate of 0.19% in their series consisting of 1524 patients. The low infection rates reported in these studies may be due to short follow-up duration and the exclusion of patients with generator replacement.

It has been shown in several studies that there is an increase in PM/ICD infections with increasing age.[11,20] Duval et al[20] reported that the patients with device infections were older compared with other patients. Moreover, Voigt et al[14] stated that mortality also increases with age in patients with PM/ICD infections. Age >60 years was established to be an independent predictor of PM/ICD infections in the present study (OR: 2.5, 95% CI: 1.2–4.0, $P = 0.021$).

Catanchin et al[17] reported that PM/ICD infection rates were higher in patients with generator replacement compared with controls. In a recent study, Lekkerkerker et al[21] found a strong correlation between generator replacement and PM/ICD infection rates and reported that the increase in infection rates might be due to decreased immunologic defense in the preformed pacemaker pocket and inadequate visualization of the surgical field. In our practice, we did not remove the fibrous capsule of the old pocket. Although there are some who believe removing the capsule decreases risk of infection, this may also increase risk of hematoma, which itself increases risk of infection.[22] In the present study, it was also found that the percentage of patients with generator replacement in the PM/ICD infection group was higher compared with the control group (16% vs 8%, $P = 0.003$) and the generator-replacement procedure was the strongest independent predictor for determining PM/ICD infections (OR: 3.8, 95% CI: 1.5–5.5, $P = 0.002$). This statistical difference was mainly because of a higher generator-replacement rate in the pocket infection subgroup (17%) than in the systemic infection subgroup (10%).

Despite the absence of randomized studies, primary antibiotic prophylaxis prior to PM/ICD implantation has been recommended.[23,24] Bertaglia et al[25] demonstrated that primary antibiotic prophylaxis with a single dose of cefazolin reduces the risk for infection. However, cefazolin is not recommended to be used for more than 48 hours.[26] Generally, a single dose of cefazolin is used for primary antibiotic prophylaxis. An additional dose can be administered during long procedures. Antibiotic administration 1 hour before the procedure is essential in order to achieve adequate tissue concentration.[6] In a meta-analysis of 7 different studies, Da Costa et al[27] found that antibiotic prophylaxis reduced the rate of PM/ICD infections. In their prospective study, Klug et al[11] demonstrated that primary antibiotic prophylaxis led to a decrease in the development of PM/ICD infections. Primary antibiotic prophylaxis appears to be a preventive factor for the development of pocket infections in the present study (OR: 0.5, 95% CI: 0.4–0.8; $P = 0.011$).

Sohail et al[24] found that the presence of central/femoral catheters was an independent risk factor for PM/ICD infections. In agreement with their results, the presence of central/femoral catheters was found to be an independent predictor for systemic PM/ICD infections in the present study (OR: 2.8, 95% CI: 1.2–4.0; $P = 0.01$).

Staphylococci have been reported as the most frequent causative microorganisms of PM/ICD infections in several studies.[24,28,29] Gram-positive bacteria were isolated in 80% of the positive cultures, and *S aureus* and *S epidermidis* were the most frequently isolated microorganisms in our study.

Conclusion

PM and ICD infections have increasingly become more frequent in clinical practice with an increase in the number of devices used. The present comparative study on risk factors in patients with and without PM/ICD infections has revealed that infection-control measures should be carefully executed during the procedure, particularly in

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elderly patients and patients with generator replacement. Primary antibiotic prophylaxis should be administered prior to procedure. Since central/femoral catheters may serve as a major source of infection, redundant catheters should be removed before the procedure. Successful outcome can be achieved in patients with PM/ICD infections by proper diagnostic and therapeutic methods.

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