

The Infections of Cardiac Implantable Electronic Devices: Four Year Experience of a Single Center

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ABSTRACT

Objective: Cardiac implantable electronic devices (CIED) have been increasingly used in recent years. The incidence of infection has ranged from 0.5 % to 12% in the literature. The purposes of this study was to investigate the frequency of CIED infection and to find the causes of infection.

Patients and methods: Totally, 211 patients with CIED infection were retrospectively evaluated. For each patient, all the following data were recorded; age, sex, CIED type, accompanying diseases, complete blood count, serum biochemistry, echocardiographic findings and whether first implantation or replacement. In addition, wound culture, antibiotic regime, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), glomerular filtration rate (GFR) and anticoagulation test results were recorded in infected patients.

Results: CIED infection was detected in 18 of the 211 patients (8.5%). 15 cases developed infection following the first implantation (10%), and 3 cases after replacement (5%). Infection was detected within 60 days in 5 patients. CIED pocket cultures were positive in 12 patients (66.7%). 13 of 18 infected devices were removed (72.2%). Diabetes mellitus [Odds Ratio, OR: 4.56 (1.449-14.408)] (p=0.010), male sex [OR: 3.84 (1.034-14.232)] (p=0.045) and increasing age [OR: 0.96 (0.932-0.998)] (p=0.038) were found as significant independent variables on development of CIED; but, pacemaker, implantable cardioverter defibrillator and cardiac resynchronization were not independent variables [OR: 1.66 (0.469-5.929)] (p=0.43).

Conclusions: Increasing age, male sex, diabetes mellitus were related to increased frequency of CIED infections. Identification of comorbid conditions prior to CIED implantations may be important in reducing risk of CIED infections.

Key words: Cardiac Implantable Electronic Devices, Staphylococcus Epidermidis, Infection

INTRODUCTION

In the last several years, cardiac implantable electronic devices (CIED) including pacemaker (PM), implantable cardioverter defibrillator (ICD) and cardiac resynchronization therapy (CRT) devices are increasingly being utilized in treatment of a wide range of diseases such as bradyarrhythmias, ventricular tachycardia/fibrillation and heart failure and the frequency of CIED use is increasing. However, infection related complications which are usually observed within 12-months post implantation [5]) with an incidence frequency of 1-7% [1] still remain poorly studied and understood. Besides increased morbidity, up to 16.9% increase in mortality

rates have been recorded within 12 months following diagnosis of the respective inflammatory complications [3]. Recently, in many studies it has been reported that diabetes mellitus, implantation of more than one lead or biventricular pacemakers increased the risk of infections [6-8]. Infections that develop within 60 days after the implantation are classified as early infections [2]. Both local and systemic symptoms are seen in the patients with CIED infections of which 30% also show nonspecific symptoms such as fever and lethargy. In addition, it is common to find infections around the implantation site. Identified CIED infections should be classified according to clinical findings,

Received: 18.05.2018,

Accepted: 28.05.2018

DOI: 10.5799/jcei.433805

blood culture and transesophageal echocardiography results as follows: 1) Pocket infections 2) Bacteremia 3) CIED-associated endocarditis.

The aim of this study was to investigate the frequency of CIED infection, to find the causes of infection, and to improve the long term prognosis of patients with CIED by decreasing the infection related complications.

PATIENTS AND METHODS

Study design and patient cohort

This study was designed in one tertiary center as a retrospective study. The patient cohort in this study consists of 211 patients for CIED implantation (between 2010-2014 years). The patients were followed up for 12 months after the procedure. The patients were categorized into two groups; patients who developed CIED related infections and who did not. Intravenous antibiotic prophylaxis (2 grams of cephazoline) was applied to each patient 30 minutes before operation. All procedures were performed in the cardiac catheterization laboratory. For each patient, skin preparation was made with chlorhexidine and betadine respectively. Skin closure for each patient was performed with subcuticular suture. For each patient, all the following data were recorded; age, sex, CIED type, accompanying diseases, complete blood count, serum biochemistry, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), glomerular filtration rate (GFR) and anticoagulation usage, echocardiographic findings and first implantation or replacement, in addition to these data wound culture and antibiotic regime were recorded in infected patients.

Definition

CIED infections are diagnosed through local and systemic symptoms. Some of the local symptoms include erythema at the implantation site, swelling, rash, sensitivity, heat increase and erosion. On the other hand, some of the systemic symptoms are fever, lethargy, hypotension and endocarditis. Valvular or lead vegetations related to CIED that were verified with echocardiography and found in modified Duke criteria patients were described as related to endocarditis. In addition, CIED infections were diagnosed using wound and/or positive blood culture.

Statistical Analysis

Statistical data in this study were evaluated using SPSS 20. Descriptive variables that display normal distribution were shown as mean \pm standard deviation, whereas the ones that do not display normal distribution were shown as median, maximum and minimum values. In this study, the patients with CIED infection were compared with patients that do not have CIED related infections with regard to risk factors. For categorical variables, both chi-squared and Fisher Exact chi-squared tests were used. In patients with CIED infections, to show the independent

variables Logistic Regression (Hosmer and Lemeshow Test) analysis was done. A p value of less than 0.05 was regarded as statistically significant.

RESULTS

Mean age of 211 patients enrolled in this study were 64 ± 16 years, ranging from 16 to 95 years old of which 61% were male and 39% were female. Of those patients, 105 received PM, 65 received ICD and 41 received CRT implantations. Eighteen patients (8.5% of the patients) were diagnosed with CIED infections; 15 cases developed infection following the first implantation (10%), and 3 cases after replacement (5%). Of those 15 patients, 5 developed infection within 60 days post device implantation/replacement. Overall, 16 patients (88.8%) out of all diagnosed with CIED infections showed normal erythrocyte sedimentation rates and 5 patients (27.8%) showed high CRP level (Table 1). CIED pocket cultures were positive in 12 patients (66.6%). Eleven of 12 patients had coagulase-negative staphylococci (91.6%). One patient had *Rhizopus* species. None had blood culture positivity. Only one patient had oscillating vegetation on the lead. Minimum duration of intravenous antibiotic (daptomycin, ciprofloxacin and ampicillin/sulbactam) use was 14 days, extended maximally to 24 days. Thirteen of 18 infected devices were removed (72.2%) and five of 18 infected devices were not removed which considered as superficial infection.

Table 1. Demographic variables of the patients

Age (year)	64 \pm 16
Sex (M/F)	128 (61%) / 83 (39%)
PM / ICD / CRT	105 (50%) / 65 (31%) / 41 (19%)
Implantation / Replacement	153 (72%) / 58 (28%)
DM (%)	54 (25.5%)
Anticoagulation (%)	21 (10%)
Heart failure (%)	46 (22%)
Renal failure (%)	24 (11%)

PM: Pacemaker, ICD: Implantable cardioverter defibrillator, CRT: Cardiac resynchronization therapy, DM: Diabetes mellitus.

Furthermore, CIED infections were found to be in younger patients (58 ± 12.4) in comparison to the control group (64.9 ± 16.1) ($p=0.04$). In addition, the number of male patients was statistically significantly higher than the number of female patients ($p=0.045$). However, the type of CIED or implantation/replacement did not make a difference between the infection and the control group ($p=0.114$ and $p=0.282$, respectively). When the risk factors between the infection and the control group were compared, diabetes mellitus (DM) ($p=0.055$), heart failure (HF) ($P=0.210$), renal failure ($p=0.182$) and use of anticoagulation ($p=0.320$) did not seem to affect the CIED infection rates. In multi-variant

analysis, DM [4.56 (1.449-14.408)] (p=0.010), male sex [3.84 (1.034-14.232)] (p=0.045) and increasing age [0.96 (0.932-0.998)] (p=0.038) were considered as independent variables, but PM/ICD/CRT [1.66 (0.469-5.929)] (p=0.43) were not considered as independent variable (Table 3). DM and male sex increase the risk of CIED infection while young age reduces the risk of CIED infection.

Table 2. Comparison between CIED infection group and the control group

	CIED Infection Group (n=18)	Control Group (n=193)	p value
Age	58.1 ± 12.4	64.9 ± 16.1	0.040
Sex (M/F)	15 / 3	113 / 80	0.045
PM / ICD / CRT	5 / 9 / 4	100 / 56 / 37	0.114
Implantation / Replacement	15 / 3	138 / 55	0.282
DM (%)	44.4%	23.8%	0.055
Anticoagulation (%)	16.7%	9.3%	0.320
Heart failure (%)	29.8%	21.1%	0.210
Renal failure (%)	27.7%	10%	0.182
High CRP level (%)	27.8%	N/A	-
Normal ESR (%)	88.8%	N/A	-

CIED: Cardiac implantable electronic devices, PM: Pacemaker, ICD: Implantable cardioverter defibrillator, CRT: Cardiac resynchronization therapy, DM: Diabetes mellitus, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate.

Table 3. Independent variables for CIED infections using logistic regression analysis

	Logistic regression Odds Ratio	p value
DM	4.56 (1.45-14.41)	0.010
Young age	0.96 (0.93-0.99)	0.038
Male sex	3.84 (1.03-14.23)	0.045
PM / ICD / CRT	1.66 (0.47-5.93)	0.43

PM: Pacemaker, ICD: Implantable cardioverter defibrillator, CRT: Cardiac resynchronization therapy, DM: Diabetes mellitus

DISCUSSION

CIED infections have been increasing in the last several years. With the increase in the number/type of implantable devices and comorbidities in the patients positively correlate with the increased occurrence of infections. Yet, infection frequency was found to vary in many studies. Da Costa et al [9] recently found that 2.4% of 1326 patients developed CIED related infection. While a study led by Rahman et al [10] showed that 1.9% of 316 patients were diagnosed with CIED infection. In another meta-

analysis of 21 prospective studies, data from 26,172 patients were collected. Accordingly, on average 1.6% of the patients were found to have CIED infections [11]. In conclusion, despite use of preventive actions against infections related to new surgical techniques and prophylactic antibiotics, in many studies it has been shown that CIED infection rates range between 0.5 and 12% [12-14]. In our study, 8.5% of 211 patients developed CIED infections and these numbers were within the range reported in the literature.

When CIED infections were examined for defining microbiological factors, gram positive *staphylococcus* was found to be the major contributing microbial group, especially due to aberrant growth in the normal skin flora. A study by Bongiorno et al [15] demonstrated that in CIED infections, 92.5% of the microbiota were gram positive. Of those 92.5%, 69% were coagulase-negative staphylococci, and 13.8% were *Staphylococcus aureus*. In many other studies, where infection factors were examined, it has been reported that the most common group of bacteria were staphylococci [16-20]. In our study, 91.6% (11/12) of patients had coagulase-negative staphylococci outgrowth.

When comorbid conditions were taken into account, DM, male sex and young age were found to be statistically significant in CIED infection. Da Costa et al. [9] have recently reported that in DM and dialysis patients were statistically found to have increased risk of CIED infections, however in their study, age, sex, cardiomyopathy and antibiotic use were found to be as non-contributing factors [9]. Another study, Bloom et al [21] showed that CIED infections were related to congestive heart failure, DM and anticoagulant treatment. When Qintar et al [22] examined 2792 patients, they found that DM, young age and heart failure were independent factors in development of CIED infections. Yet, there are many conflicting findings regarding relevancy of young age in CIED infections. In a study by Duval et al [23], CIED infections were observed in older patients. In contrast, review by Nielsen et al [24, 25] mentions that there is a positive correlation between DM, male sex, young age and increase in the number of CIED infections. Similarly, a study by National Danish Pacemaker Registry reported that young age, male sex and absence of antibiotic prophylaxis were strongly associated with increased CIED infections [11]. In our study, DM, male sex and increasing age were found to be statistically significant in CIED infection but young age was found reduce the risk of CIED infection.

Diabetes mellitus, which disrupts wound healing, increases skin necrosis risk. In diabetic patients, wound healing disorder is caused by a combination of different mechanisms, such as neuropathic degeneration, vasculopathy, poor wound healing due to damaged collagen production [26]. With increasing age, an increase in the frequency of CIED is observed. Factors such as the presence of less firm subcutaneous connective tissue, which would permit less traumatic formation of the pacemaker pocket,

as well as a less aggressive immune response against low virulence bacteria with increasing age could theoretically play a role.

Limitations of the Study

Our study has some important limitations. Main limitation of our study was its retrospective design. Another important limitation is the relatively small number of patients included in the study. There were variations in generator sizes, lead diameters, and lead materials between various pacemaker devices that depend on the manufacturing company and year of device availability.

CONCLUSIONS

Increase in use of CIED significantly reduced the risk of mortality and morbidity. Yet, factors related to the patients such as increasing age, male sex, DM have been related to increased morbidity due to CIED infections. Identification of comorbid conditions prior to CIED implantations accordingly may be important in reducing risk of developing CIED infections.

Conflict of Interests: The authors declare that they have no conflict of interest.

Financial Disclosure: No financial support was received.

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