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CARDIAC IMPLANTABLE ELECTRONIC DEVICE INFECTION: PREVALENCE AND RISK FACTORS (A SINGLE CENTER EXPERIENCE)

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ABSTRACT

Background: The number of cardiac implantable electronic device implantation procedures has increased dramatically in recent decades due to population aging and expansion of indications. At the same time, the number of cardiac implantable electronic device associated complications has increased too. Infection is a very important and heavy complication of cardiac implantable electronic device implantation, which significantly increases mortality and morbidity.

This study aimed to estimate the risk of cardiac implantable electronic device infection in a group of patients who received an aggressive scheme of postoperative antibiotic therapy and compare this with the risk of infection in another group, where a mild antibiotic therapy scheme was used.

Methods: A retrospective, observational study was performed. The study sample included 355 patients. Two antibiotic prophylaxis and wound follow-up protocols (mild and aggressive) were used. In this study the effectiveness of both methods to prevent a cardiac implantable electronic device related infection was compared.

Results: The prevalence of infection was 3.5% in the group with mild scheme and 1.13% in the group with the aggressive scheme. The difference in two subgroups was not significant (p=0,149).

According to this study severe renal failure, chronic obstructive pulmonary disease and thyroid dysfunction were found as significant predictors for having cardiac implantable electronic device infection. In participants who underwent a reimplantation and in those with postoperative hematoma the odds of having infection was higher, compared to patients with primary implantation and absence of hematoma. Age of participants with cardiac implantable electronic device infection was younger compared to patients without infection.

Conclusion: According to this study there is no statistically significant difference on cardiac implantable electronic device infection between mild and aggressive antibiotic therapy schemes.

KEYWORDS:*CIED implantation. iInfection. Aantibiotic prophylaxis.*

INTRODUCTION

Due to the aging population and the expansion of indications of cardiac implantable electronic device (CIED) implantation in recent decades, the number of implantation procedures has increased dramatically. At the same time, the number of CIED-associated complications has increased too [*Mond HG et al., 2008, Johansen JB et al., 2011, D. Z. Uslan DZ et al., 2012*]. One of the most severe complications of cardiac implantable electronic device implantation is infection, which sig-

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nificantly increases mortality and morbidity [*Greenspon AJ et al., 2011, Ahsan SY et al., 2014 Blomström-Lundqvist C et al., 2020*].

Since 1994, more than 17 studies have been conducted on this topic in different countries. Although the prevalence of cardiac implantable electronic device-infection and risk factors for their develomment remain controversial [*Joy PS et al., 2017, Krahn AD et al., 2018, Biffi M et al.,2019*].

Cardiac implantable electronic device infections can occur with two significant mechanisms. The most common mechanism is contamination of pulse generator and/or leads during the implantation or following manipulation [*Da Costa A et al., 1998*]. Late device erosion following interventions may be caused by or result from pocket infection.

Infection in the blood stream is the second possible mechanism. In cases of bacteraemia caused by a distant infectious focus, such as localized septic thrombophlebitis, pneumonia, osteomyelitis, contaminated vascular catheters, surgical site infections or bacterial entry through the mouth, skin, urinary or gastrointestinal tract direct lead seeding may take place[*Da Costa A et al., 1998*] .

Gram-positive bacteria particularly Coagulasa negative Staphylococcus (37.6% of the isolates) and Staphylococcus aureus (30.8%), which are far more likely to stick to non-biological material have been the most often isolated microorganisms (70–90% of the isolates) [*Bongiorni MG et al.,2012, Hussein AA et al., 2016*]. Methicillin-resistant staphylococci were found in 49.4% of all staphylococcal infections or 33.8% of CIED infections, and their prevalence varied by country and hospital [*Jan E et al.,2012, Hussein AA et al.,2016, Wang R et al.,2017*]. Methicillin resistance rates appear to have increased over the last ten years compared to earlier reports [*Hussein AA et al.,2016*]. 8.9% of samples had Gram-negative bacteria isolated, while anaerobes, streptococci and fungus were isolated less frequently [*Hussein AA et al.,2016*] .

Risk factors for CIED associated infections can be categorized into three different groups: patient-, device-, and procedure-dependent, which can be modifiable or not modifiable [*Blomström-Lundqvist C et al., 2020*]. Identifying modifiable risk factors is very important, because risk-reducing preventive measures can be used. Also, patients with non-modifiable risk factors may be treated with alternative, less risky interventions [*Johansen JB et al., 2011*].

According to the meta-analysis published in EP Europace Journal in 2015, the risk factors include comorbidities, such as end-stage renal disease, chronic obstructive pulmonary disease (COPD), diabetes mellitus, heart failure, skin disorders, malignancy, use of some drugs, such as corticosteroids and anticoagulants, as well as anamnesis of previous CIED-related infection and fever [*Polyzos KA et al., 2015*].

In the Danish registry young age, long procedure duration, cardiac resynchronization therapy deffbrillator (CRT-D) implantation and reimplantations were assessed as risk factors [*Olsen T et al., 2019*].

In another multicenter study malnutrition was identified as a significant risk factor for device-infection [*Joy PS et al., 2017*]. Antibiotic therapy, used immediately prior the procedure, reduces the relative risk of infection for 70% [*Polyzos KA et al, 2015*] . Although postoperative antibiotic therapy and local antibiotic-application in the pocket are not recommended according to European Heart rhythm Association (EHRA) and American Heart Association (AHA) [*BaddourLM et al.,2010, Joy PS et al., 2017, Blomström-Lundqvist C et al., 2020*].

The presence of post procedural hematoma increases the infection risk for 9 times [*Essebag Vet al, 2016, Joy PS et al., 2017*].

Another large multicenter study found that early reinterventions and a temporary pacemaker placement increase the risk of infection [*Polyzos KA et al., 2015*]. Physician's experience has also a significant impact on the outcome [*Al-Khatib SM et al., 2008*]. According to another comparative study replacement of the device generator doubled the infection risk [*Polyzos KA et al., 2015*]. Device-dependent factors associated with CIED infection are fewer. According to the Danish registry complex devices and those with more leads are associated with a higher risk [*Olsen T et al., 2019*].

To overcome it is possible, due to the uniting the knowledge and will of all doctors in the world

Another significant risk factor is the presence of the an abdominal pocket [*Polyzos KA et al., 2015*].

Study aim and objectives

This study aimed to estimate the risk of CIED-infection in a subgroup of patients who received an aggressive scheme of antibiotic therapy and compare this with the risk of infection in another subgroup, where a mild antibiotic therapy scheme was used.

The study objectives were

√ Assess the incidence and prevalence of CIED-related infection in patients operated in a tertiary cardiovascular center.

√ Assess the risk of CIED-infection in two subgroups with mild and aggressive schemes of antibiotic therapy.

√ Identify infection-related risk factors.

Research design and methods

A retrospective, observational study was performed. The participants were all patients in whom CIED related procedure (de novo implantation, revision, replacement) was performed in a tertiary cardiovascular center between 12.2017 and 07.2020. The patients who have died in this period and pediatric patients were excluded.

A retrospective review of the patient's medical histories from the above-mentioned cohort was performed. Modified Duke criteria was used to identify a CIED-related infection. The study involved pocket infections and systemic infections as well.

The following clinical and demographic data were collected: age, gender, presence of heart failure, presence of ischemic heart disease or cardiomyopathy, previous cardiac surgery or coronary angioplasty, some comorbidities such as chronic obstructive pulmonary disease, diabetes mellitus, hypertension, thyroid disfunction, renal disease, transient ischemic attack/stroke and use of any anticoagulant drugs. The device and procedure-related information, such as the type of the device, type of intervention, number of leads, presence of post-procedural hematoma, and previous temporary pacing was collected too. The study aimed to determine whether the above-mentioned factors were related to CIED-infection and which of them can be considered as a risk factor.

Two antibiotic prophylaxis and wound follow-up protocols were performed during this period (Table 1). In this study was compared the effectiveness of both methods to prevent a CIED related infection.

Statistical analysis. Data entry and statistical analyses were performed with SPSS version 23 software.

First, descriptive statistics with the use of $\chi 2$ test for categorical variables and the *t-test* and Mann-Whitney U test test for continuous variables for normal and abnormal distribution respectively were performed. Then the binomial logistic regression analyses were performed for adjusted analyses. *P* values below 0.05 were considered statistically significant.

Results:

Administrative results

The study sample included 355 patients, whom CIED-related procedure was performed between

Table1.

Antibiotic prophylaxis and wound follow up protocols

Antibiotic prophylaxis	Wound follow-up
Mild scheme	
Pre-procedural- 1*g* Ceftriaxone iv	1. Day of discharge
Post-procedural- 2 doses of 750 *mg* Ceftriaxone iv	2. After 7-10 days
After discharge-Ciprofloxacin 500 *mg* b.i.d. for 7-10 days	3. After 1 month
Aggressive scheme	
Pre-procedural- 1*g* Ceftriaxone iv	1. Day of discharge
Post-procedural- 750 *mg* Ceftriaxone iv every 8 hours for 1-2 days and Ciprofloxacin 750 *mg* b.i.d.	2. 2-3 times during the first week
After discharge-Ciprofloxacin 750 *mg* b.i.d. for 14 days and Azithromycinum 500 *mg* q.d. for 3-6 days	3. Once a week during the following 3 weeks
Intra-procedural- 80 *mg* Gentamycinum local in the pocket	

01.12.2017 and 30.07.2020. The patients who have died in this period and pediatric patients were excluded. From the whole sample 85 patients have recieved a mild and 270 patients an agrresive antibiotic therapy. Overall there were 375 patients, who underwent CIED-implantation procedure between the above mentioned period.

Descriptive statistics

Research data in 2 subgroups (patients with and without CIED-related infection) are presented in Table 2. In contrast to pre-existing research data, the groups were not different in presence of diabetes mellitus (p=0.714) and severe heart failure of NYHA class III/IV (p=0.132). The use of anticoagulant and antiplatelet drugs where not associated with increased infection risk (p=0.385). Presence of complex devices such as CRT-D, number of leads and a previous temporary pacing also did not differ in two subgroups (p=0.072, p=0.086, p=0.106 respectively). Age of participants with CIED-infection (mean age=52.5) was younger compared to patients without infection (mean age=61.2, p=0.039).

Table 2.

Descriptive characteristics of study participants

Patient's characteristics	Infection groups		P value
	No CIED	CIED	
Demographic data			
Age(years) mean(SD)	61.92	52.5	0.039
Gender (%)			0.706
male	76.8	83.3	
female	23.2	16.7	
Clinical characteristics			
Heart failure (%)			0.132
NYHA class I/II	63.3	33.3	
NYHA class III/IV	36.7	66.7	
Ejection fraction (%)			0.375
EF<30%	48.4	66.7	
EF>30%	51.6	33.3	
Dilated CMP (%)	22.9	33.3	0.55
Ischemic CMP (%)	48.8	66.7	0.383
Previous MI(%)	51.9	66.7	0.472
Previous CABG(%)	19.2	16.7	0.876
Previous PCI(%)	44.9	66.7	0.290
Previous cardiac other surgery (%)	10.6	0	0.399
COPD(%)	5.7	66.7	0.005
Diabetes milletus(%)	26.6	33.3	0.714
Hypertension(%)	70.2	66.7	0.851
Thyroid disfunction(%)	6.6	33.3	0.011
Severe renal failure(%)	0.6	16.7	0.000
Previous stroke(%)	11.2	0	0.385
Anticoagulant use(%)	96.8	83.3	0.069
Reimplantation(%)	7.4	33.3	0.02
Device and procedure-related data			
Hematoma(%)	2	50	0.000
Temporary PM(%)	3.7	16.6	0.106
CIED type(%)			0.072
PM	33.8	16.6	
ICD	50.7	33.3	
CRT	15.4	50	
Number of leads(%)			0.086
1	6.6	0	
2	77	50	
3	16.3	50	

Bynary logistic regression analysis

According to this study severe renal failure, COPD, thyroid disfunction, a presence of hematoma, reimplantations and a younger age were significant predictors for CIED-related infection risk. A bynary logistic regression model was used to test for association between the probability of CIED-infection and the above mentioned factors. The results are shown in Table 3. The odds of having infection was 32.6 times higher by the presence of severe renal failure with glomerular filtration rate (GFR)<30 *mL/min* (CI=2.5-420.8, p=0,008), 8.2 times higher by the patients with COPD (CI=1.4-47.6, p=0.019), and 7.065 times higher with the presence of thyroid disfunction (CI=1.2-40.6, p=0.028). In participants who underwent a reimplantation and in those with postoperative hematoma the odds of having infection was respectively 6.2 fold (CI=1.086-35.5, p=0.04) and 48,8 fold(CI=8.4-285.9, p=0.028) higher compared to patients with primary implantation and absence of hematoma.

Table 3.

Bynomial logistic regression of the probability of CIED-infection

Variable	Odds Ratio (CI=95%)	P value
Presence vs absence of thyroid dysfunction	7.1 (1.2-40.6)	0.028
Presence vs absence of COPD	8.2 (1.4-47.6)	0.019
Presence vs absence of severe renal failure	32.6 (2.5-420.8)	0,008
Reimplantation vs de novo implantation	6.2 (1.086-35.5)	0.04
Presence vs absence of hematoma	48.9 (8.4-285.9)	0.028

Risk of infection

Comparison of the risk of CIED-related infection in two subgroups with mild and aggressive antibiotic therapy was performed, according the main aim of the project. The prevalence of infection was 3.5% in the group with mild scheme of antibiotic therapy and 1.13% in the group with the aggressive scheme. The difference in two subgroups was not significant (p=0,149). In the whole sample the prevalence of infection was 1,69%.

DISCUSSION

It is well known that the number of CIED-associated complications has increased over the past years parallel with increasing number of cardiac implantable electronic device (CIED) implantation procedures. Infection is a very important and heavy complication of CIED implantation, which significantly increases mortality and morbidity.

Since 1994, more than 17 studies have been conducted on this topic in different countries. Although the prevalence of cardiac implantable electronic device-infection and risk factors for their develomment remain controversial.

This study aimed to assess the incidence and prevalence of CIED-related infection in patients operated in a tertiary cardiovascular center, identify infection-related risk factors as well as assess the risk of CIED-infection in two subgroups with mild and aggressive schemes of postoperative antibiotic therapy.

The limitations of this study are small sample sizes and quantitative and qualitative discrepancy between the two groups. Also as antibiotic therapy is not proven to be better than “no antibiotic therapy”, the present comparison between less intense and more intense antibiotic therapy schemes does not hold significant value. However the absence of statistically significant difference on CIED infection between mild and aggressive antibiotic therapy schemes in our center makes us highly skeptical of the unjustified prescription of antibiotics.

According to this study comorbidities, such as severe renal failure, COPD and thyroid disfunction are associated with significantly increased risk of CIED-infection. By patients with such or other comorbidities the benefits and risk of CIED-implantation must be thorougly assessed. If possible, an intervention with lower risk (for example leadless pacemakers or S-ICD) should be chosen. Also by risky patients more aggressive methods of prevention such as absorbable antibacterial envelope may be useful.

CONCLUSION

According to this study the risk of infection in this tertiary cardiovascular center is not high compared to recorded prevalence in other countries. Also there is no statistically significant difference on cardiac implantable electronic device infection between mild and aggressive antibiotic therapy schemes.Thus the routine use of aggressive antibiotic therapy is not justified and carries a risk of microbial resistance, as well as additional healthcare costs.

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CONTENTS

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