Efficacy of Antibiotic Prophylaxis Before the Implantation of Pacemakers and Cardioverter-Defibrillators

Results of a Large, Prospective, Randomized, Double-Blinded, Placebo-Controlled Trial

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Background—Although routinely administered, definitive evidence for the benefits of prophylactic antibiotics before the implantation of permanent pacemakers and implantable cardioverter-defibrillators from a large double-blinded placebo-controlled trial is lacking. The purpose of this study was to determine whether prophylactic antibiotic administration reduces the incidence of infection related to device implantation.

Methods and Results—This double blinded study included 1000 consecutive patients who presented for primary device (Pacemaker and implantable cardioverter-defibrillators) implantation or generator replacement randomized in a 1:1 fashion to prophylactic antibiotics or placebo. Intravenous administration of 1 g of cefazolin (group I) or placebo (group II) was done immediately before the procedure. Follow-up was performed 10 days, 1, 3, and 6 months after discharge. The primary end point was any evidence of infection at the surgical incision (pulse generator pocket), or systemic infection related to the procedure. The safety committee interrupted the trial after 649 patients were enrolled due to a significant difference in favor of the antibiotic arm (group I: 2 of 314 infected patients—0.63%; group II: 11 of 335 to 3.28%; RR = 0.19; P = 0.016). The following risk factors were positively correlated with infection by univariate analysis: nonuse of preventive antibiotic (P = 0.016); implant procedures (versus generator replacement: P = 0.02); presence of postoperative hematoma (P = 0.03) and procedure duration (P = 0.009). Multivariable analysis identified nonuse of antibiotic (P = 0.037) and postoperative hematoma (P = 0.023) as independent predictors of infection.

Conclusions—Antibiotic prophylaxis significantly reduces infectious complications in patients undergoing implantation of pacemakers or cardioverter-defibrillators. (Circ Arrhythmia Electrophysiol. 2009;2:29-34.)

Key Words: antibiotic prophylaxis ■ pacemaker ■ surgical procedures ■ infection

Since the initial use of prosthetic heart valves in 1953,1 the use of cardiac prosthesis and implantable devices, such as conventional pacemakers,2 cardiac resynchronization,3 left ventricular assistance devices,4 and implantable cardioverter-defibrillators,5 has revolutionized the therapeutic options available to patients. The rapid evolution of device-based therapies has resulted in an ever larger number of patients receiving such therapy.6 Not surprisingly, infectious complications have dramatically increased coinciding with this phenomenon. Recent data from Medicare beneficiaries in the United States from 1990 to 1999 have shown an increase in the number of infections from 0.94 per 1000 beneficiaries in 1990 to 2.11 per 1000 beneficiaries in 1999, thus representing an increase of 124%.6

The incidence of infection related to pacemakers varies from 0.13% to 19.9% in prospective and retrospective prior studies.7-9 Serious complications, such as endocarditis and sepsis, occur in almost 0.5% of patients.10,11 In addition, infectious complications have a significant economic impact on the health care system due to the high cost of treatment which ranges from therapy with antibiotics to removal of the entire pacing system with subsequent reimplantation after prolonged treatment with antimicrobials.11-13 The average cost of treatment has been estimated at $25 000 and $50 000 for infections related to pacemakers and defibrillators, respectively.13,14

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Antibiotic prophylaxis has been routinely prescribed to prevent the occurrence of this complication; however, there is insufficient evidence that this strategy is beneficial. A meta-analysis published by Da Costa et al15 in 1998, demonstrated the benefit of the use of antibiotic prophylaxis, but it acknowledged its limitations and reiterated the need of a
large-scale, prospective, randomized, double-blinded and placebo-controlled trial to confirm this hypothesis. Recently, the results of a large, prospective, multicenter registry identified risk factors related to pacemaker and defibrillator infections; the use of antibiotics was negatively correlated with this outcome. However, this study was neither randomized nor blinded, and the use and type of antibiotics was left at the discretion of each center.

Thus, the purpose of this study was to definitively determine whether the use of systemic antibiotic prophylaxis administered before the implantation of pacemakers and defibrillators reduces the risk of infection related to the procedure.

Methods

Patients

We consecutively enrolled all patients who were to undergo device implantation or generator replacement of permanent pacemaker, implantable cardioverter defibrillator, or cardiac resynchronization device at the Heart Institute of São Paulo (InCor) in Brazil beginning on July 1, 2003. This was a double-blinded study in which patients were randomized to 1 of 2 groups. Patients in group I were given antibiotic prophylaxis (cefazolin 1 g) whereas patients in group II received intravenous saline. Patients allergic to penicillin were excluded. Antibiotics or placebo was administered immediately before the procedure. The dose of cefazolin administered was 1 g for all points; the dose was not adjusted for weight. All of the patients signed an informed consent form, according to the local institutional review boards and ethics committee guidelines. The primary end point was the incidence of infection, either localized or systemic, related to the procedure of device implantation at 6-month follow-up. Further analysis was performed to characterize the patient characteristics that correlated with the primary outcome.

Exclusion criteria of patients from the study included the following: antibiotic use for any reason, (including patients who were chronically immunocompromised), patients of remote places that would preclude follow-up at the specified times, patients less than 18-years-old, patients who underwent thoracotomy with implantation of left ventricular leads for cardiac resynchronization, any surgery within the prior 30 days, previous infection treated in the prior 30 days, other antibiotic prophylaxis indications (eg, patients with prosthetics heart valves). A safety committee was created to evaluate the results every 6 months. The study was designed to allow termination of the study by the safety monitoring board if a statistically significant difference in the rate of infection between the 2 groups (P<0.05) was detected. The safety committee members were not involved with the surgery or follow-up of the patients.

Surgical Procedures

All procedures were done in the surgical center of the Heart Institute by 4 cardiac surgeons each of whom had a minimum of 3 years experience of device implantation. A fellow training in electrophysiology assisted in the procedures. Implantation of pacemakers was done with local anesthesia, whereas implantation of implantable cardioverter defibrillator or cardiac resynchronization therapy was done with general anesthesia and mechanical ventilation. All procedures were performed in a surgical operating room; no procedures were performed in a cardiac catheterization or electrophysiology laboratory. Hand washing was done with prepacked sponges soaked either in chlorhexidine or povidone-iodine. Skin preparation of the patients was done at the time of the procedure with 10% povidone-iodine solution and 0.5% alcoholic chlorhexidine. All scrubs were performed as per institutional guidelines which include at least 5 minutes for the first daily scrub and 3 minutes for subsequent hand washings. Hair over the incision site was clipped on the day of the procedure with subsequent washing before arrival to the operating room. Shaving was not done to avoid abrasions with potential skin breakdown over the site. The medical team included for the procedure included the attending surgeon, fellow in training, at least 1 scrub nurse and 1 circulating nurse, and 1 anesthesiologist.

Patients on oral anticoagulation discontinued warfarin and transitioned over to therapeutic dosing of low molecular weight heparin in an outpatient setting before the procedure. Low molecular weight heparin was held at least 24 hours before the procedure. All procedures were performed when the international normalized ratio was ≤1.5. Heparin and warfarin were resumed 24 hours after the procedure and heparin was discontinued when international normalized ratio was >1.5. Monitoring of anticoagulation before and after the procedure was performed in the outpatient setting by an anticoagulation clinic and did not affect the length of hospitalization. As a result, there was no difference in the length of stay for patients on anticoagulation as compared with those not on anticoagulation.

Transvenous leads were introduced either through the cephalic or subclavian vein (or both in some cases). The leads were secured using absorbable suture (vicryl). The pocket for the generator implant was made in the subcutaneous or submuscular plane (for those patients lacking an adequate amount of subcutaneous tissue for proper closure). The pocket was not flushed with antibiotic solution. The subcutaneous tissue was closed with absorbable threads (vicryl), with continuous stitches in 2 planes. The skin was closed with separate stitches of 5.0 nylon thread. After suturing the skin, steri-strips were applied and gauze was placed to cover the wound. The bandage was not removed until 48 hours after the procedure after which time patients were allowed to shower. The steri-strips were removed once bathing was permitted, and the wound was allowed to become wet. The intravenous antibiotic or placebo was administered immediately before the beginning of the surgery by an anesthetist in the operating room.

Simple generator changes were discharged 8 hours after the procedure. Patients who received pacemaker implants remained hospitalized for 24 hours. Patients implanted with an implantable cardioverter defibrillator and/or cardiac resynchronization device implant were hospitalized for at least 48 hours. Antibiotics were not given after the procedure. Patients initially included in the study who subsequently underwent the second procedure for lead revision specifically due to lead dislodgement within the 6 months of follow-up were subsequently excluded from the study.

Follow-Up and Assessment

Postprocedure, patients followed up in the pacemaker clinic of the Heart Institute at 10 days, 1, 3, and 6 months to evaluate the site of the operation for signs of infection. Patients were instructed to contact the clinic concerning any aspects of care, including any suspicion of infection.

Infections were classified in 1 of the following 3 categories:

1. Superficial infections were characterized by localized inflammation (swelling, warmth, or erythema) and pus in the surgical incision, without evidence of pocket extension or systemic manifestation.
2. Pocket infection, without systemic manifestation, was diagnosed by the following criteria: Purulent discharge with microorganisms demonstrated by culture from the surgical wound or pocket with at least 2 of the following clinical indicators: pain, warmth, erythema, or local fluctuance.
3. Systemic infections were considered when there was pocket infection associated with at least 2 of the following criteria: fever (>38°C) or hypothermia (<36°C), tachycardia (>90 bpm), tachypnea (>20 respirations per minute), leukocytosis (>12 000 cells/mm) or leukopenia (<4 000 cells/mm).

A diagnosis of endocarditis was made using the Duke modified criteria. All patients who had undetermined origin of fever or pocket infection had blood cultures drawn (2 samples) in addition to undergoing both transthoracic and transesophageal echocardiography to diagnose endocarditis. Patients diagnosed with infection were treated with antibiotics based on sensitivities of the isolate.

The presence of hematoma was defined as swelling of the pocket site without obvious signs of infection. Postprocedure hematomas...
were treated with pressure dressing only. No additional antibiotics were given simply based on the presence of hematoma. Antibiotics were only administered when the criteria for infection was met, thus reaching an end point.

Statistical Analysis

The sample size (500 patients per group) provided 90% power to detect a 2% difference in infection rate (assuming an α-error of 5%). The classifying variables were compared by utilizing the χ² test or Fisher’s exact test (sex, cardiac failure functional class, diabetes mellitus, hypothyroidism, chronic obstructive pulmonary disease, systemic arterial hypertension, chronic renal failure, corticosteroids use, chronic kidney disease, oral anticoagulants use, previous use of temporary pacemaker, antibiotic prophylaxis, type of procedure, complexity of procedure, and occurrence of pocket hematoma). The quantitative variables were presented by the mean ± standard deviation and compared with Student’s t test (paired and unpaired) or with Wilcoxon rank-sum test (age, left ventricular ejection fraction, and duration of the procedure). The variables that presented a statistically significant difference in the univariate analysis were used to adjust the model of multiple logistic regressions (stepwise). Values of P < 0.05 were considered statistically significant. The authors had full access to and take responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Patient Characteristics

Between July 1, 2003 and October 31, 2005, 649 patients were included in the study. Baseline characteristics of the study patients and the surgical procedures are summarized in Table 1. This included 303 males and 346 females with an average age of 64.2 ± 15.3 years and ranging from 18 to 96 years of age. Characteristics of the 2 groups were similar except for a significantly greater use of oral anticoagulant therapy in group 2 (P = 0.005). A total of 314 patients received cefazolin, whereas 335 patients received placebo. The study was interrupted by the safety committee after 26.5 months due to a significant difference in the infection rate between the 2 groups. The primary end point of infection was reached in 2 (0.64%) patients in the cefazolin group and 11 (3.28%) patients in placebo group (P = 0.016).

Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total n=649</th>
<th>Group I (Cefazolin) n=314</th>
<th>Group II (Placebo) n=335</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, M ± SD, years</td>
<td>64 ± 15</td>
<td>64.1 ± 15.9</td>
<td>64.3 ± 14.8</td>
<td>0.831</td>
</tr>
<tr>
<td>Gender, M, n/ %</td>
<td>303/46.7</td>
<td>140/44.6</td>
<td>163/48.6</td>
<td>0.290</td>
</tr>
<tr>
<td>NYHA class (I/II/III/IV)</td>
<td>292/247/43/1</td>
<td>157/112/16/0</td>
<td>135/135/27/1</td>
<td>0.052</td>
</tr>
<tr>
<td>LVEF, %, M ± SD</td>
<td>57 ± 26</td>
<td>57 ± 15</td>
<td>56 ± 33</td>
<td>0.826</td>
</tr>
<tr>
<td>Diabetes, n/ %</td>
<td>101/15</td>
<td>44/14.0</td>
<td>57/17</td>
<td>0.292</td>
</tr>
<tr>
<td>Hypothyroidism, n/ %</td>
<td>29/4.4</td>
<td>13/4.1</td>
<td>16/4.8</td>
<td>0.695</td>
</tr>
<tr>
<td>Chronic pulmonary disease, n/ %</td>
<td>10/1.5</td>
<td>5/1.6</td>
<td>5/1.5</td>
<td>0.53</td>
</tr>
<tr>
<td>Corticosteroids use, n/ %</td>
<td>6/0.9</td>
<td>3/0.9</td>
<td>3/0.9</td>
<td>1.000</td>
</tr>
<tr>
<td>Anticoagulant use, n/ %</td>
<td>51/7.8</td>
<td>15/4.7</td>
<td>36/10.7</td>
<td>0.005</td>
</tr>
<tr>
<td>Temporary PM, n/ %</td>
<td>88/13.5</td>
<td>38/12.1</td>
<td>50/14.9</td>
<td>0.294</td>
</tr>
<tr>
<td>Implants/replacements, n</td>
<td>303/346</td>
<td>140/174</td>
<td>163/172</td>
<td>0.299</td>
</tr>
<tr>
<td>PM/CRT/ICD, n</td>
<td>591/850</td>
<td>287/225</td>
<td>304/25</td>
<td>0.439</td>
</tr>
<tr>
<td>Duration of procedure, minutes, M ± SD</td>
<td>70 ± 35</td>
<td>68 ± 27</td>
<td>73 ± 41</td>
<td>0.094</td>
</tr>
<tr>
<td>Chronic kidney disease, n/ %</td>
<td>7/1.1</td>
<td>3/1.0</td>
<td>4/1.2</td>
<td>0.619</td>
</tr>
</tbody>
</table>

M ± SD indicates mean ± standard deviation.

Analysis of Variables

Table 2 shows the univariate analysis results. Predictors of infection included prolonged duration of procedure, primary implants as opposed to generator replacements, the development of pocket hematoma postprocedure, and the lack of antibiotic prophylaxis before the procedure.

On multivariable analysis, independent predictors of infection included the development of pocket hematoma and the lack of antibiotic prophylaxis. Two patients (one patient in each group) developed a pneumothorax; both required insertion of a chest tube, and neither developed an infection. Nine patients originally included from the study were excluded due to lead dislodgements that required lead revision within the 6-month follow-up period. Four patients were in the cefazolin group, and 5 were in the placebo group. All hematomas were treated conservatively with pressure dressing only. No patients with postprocedure hematoma required drainage. There was no significant difference in the rate of infection between the type of device implanted (implantable cardioverter defibrillator versus pacemaker versus cardiac resynchronization, P = 0.9).

Infectious Complications

Of the 649 patients included in the study, 13 developed infection (2%). Five patients had superficial infections, 4 patients had pocket infections, and 4 patients had pocket infections associated with systemic manifestations. The management of the thirteen patients who developed infection is shown in the Figure. Patients with superficial infections were treated orally with cephalexin for 10 days. Compliance with oral antibiotics in this small group of patients was completely based on intense follow-up of the infected patients.

Patients with pocket infection, with or without systemic manifestations, had the entire system removed and were treated with intravenous antibiotics. Cefalothin was used for 10 days in patients who had pocket infections without systemic manifestations. One patient with pocket infection...
refused to be admitted to the hospital for removal of the pacing system and was treated with cephalexin, resulting in eradication of the infection. Vancomycin was used for 10 days on patients who had pocket infections with systemic manifestations. Cultures of the secretion taken from the incision or aseptically from the pocket were positive for bacteria in all 13 patients. Blood cultures were positive in 20% of the patients who had isolated pocket infections and in 50% of the patients who had pocket infections with systemic manifestations. No patients developed endocarditis as determined by the Duke criteria, although the transesophageal echocardiogram showed filament adhering to the ventricular lead of the pacemaker in one patient who had a pocket infection with systemic manifestations. The cultures of the leads were positive in all of the patients with isolated pocket infection and in 75% of the patients who had systemic manifestations.

One patient with infection (from the placebo group) developed acute renal failure that required treatment with pressor support in the intensive care unit; the patient had a full recovery with antibiotics and supportive care. Among the 5 patients who had superficial infections only one developed pocket infection despite oral administration of cephalexin. Removal of the pacing system and use of systemic antibiotics were required for complete eradication of the infection.

Characteristics of the Patients Who Developed Infection

The characteristics of the 13 patients who developed infection related to the procedure are shown in Table 3. The time of onset of clinical signs and symptoms of infection ranged from 11 to 33 days confirming the likelihood that the procedure was the causal agent. Infections occurred in 10 primary implants and in 3 generator replacements. The bacteria isolated in all cases of infection was "Staphylococcus." Eight were S. aureus, 3 S. epidermidis, 1 S. coagulase negative, and 1 S. simulans. There were 4 cases of oxacilin resistance (1 was due to S. aureus, 2 S. epidermidis, and 1 S. simulans). Two of the 13 patients had developed a hematoma postprocedure.

Clinical Course of Infected Patients

<table>
<thead>
<tr>
<th>Clinical Course of Infected Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>N(%) Superficial 5(38.4)</td>
</tr>
<tr>
<td>Culture at incision</td>
</tr>
<tr>
<td>Blood culture</td>
</tr>
<tr>
<td>Transesophageal echocardiography</td>
</tr>
<tr>
<td>System explant</td>
</tr>
<tr>
<td>Culture of leads</td>
</tr>
</tbody>
</table>

Figure. Clinical outcome of infected patients and results of subsequent workup. #Superficial infection that evolved to pocket infection. ¥Did not fulfill Duke modified criteria for endocarditis. *One patient refused explant of the system. +, positive; -, negative.
Mortality
In the entire study population, there were 15 deaths (2.31%) during the follow-up period. None of them were caused by the infection or directly related to the procedure involving the implantation of the device. There were 6 deaths in the cefazolin group (1.9%) and 9 in the placebo group (2.7%).

Discussion
Our findings firmly confirm the benefit and safety of the use of antibiotic prophylaxis during implantation of percutaneous pacing devices with a single dose of 1 g of cefazolin given intravenously immediately before the surgical procedure. This result is from the largest prospective, double-blinded, randomized, placebo-controlled study to date. It reaffirms the results from the meta-analysis by Da Costa et al15 which pooled together 7 trials with a total of 2023 patients to show the beneficial effects of this strategy. This important study utilized the available published data to reach its conclusions. However, only 1 trial (representing 5% of the total number of patients) was double blinded and placebo controlled. Importantly, the authors discussed the need of a large, double-blinded, randomized, placebo-controlled study, to confirm their findings due to the inherent limitations of a meta-analysis. Specifically, it included a heterogeneous group of patients utilizing different antibiotic treatments that varied in the time, dose, and route of administration. Among the 7 randomized studies included in this meta-analysis only 4 suggested that antibiotic prophylaxis was beneficial with the other 3 studies showing no difference (likely due to the low rate of infection in both groups).

Another inherent limitation in the studies analyzed in the meta-analysis was the wide range of criteria used for the diagnosis of infection. The present study utilized a predetermined set of criteria for the diagnosis of infection that was assessed and diagnosed by a physician. Indeed, given the vigilance inherent in the study design of the present study, all cases of infection were diagnosed within 33 days of the surgical procedures. This finding also reinforces the likelihood that infection was directly related to contamination during the surgery.

We did not have any cases of endocarditis or deaths related to infection, which suggests that early diagnosis and adequate treatment of the infection, including extraction of the entire pacing system when needed, results in eradication of the pathogen. Indeed, while 20% of patients with pocket infection had positive blood cultures, the tips of the leads in all 4 patients in whom the system was explanted revealed progression of the infection. However, patients with prosthetic heart valves were not included in this study thus potentially excluding those at higher risk for endocarditis. Other high-risk patients that were excluded from the study included those whose initial procedure required lead revision due to dislodgment. It is likely that these patients with early reinterventions would also be at higher risk for infection. Indeed, the recent report by Klug et al16 found that early reinterventions for hematoma or lead dislodgement were the leading risk factors of infection among 6319 patients undergoing primary implants or replacements of pacing devices. No cases of superficial infection occurred among the patients who received antibiotic prophylaxis. This finding is consistent with the results published by Monsey et al18 in which skin erosion was the most common presentation.

Of note, we observed that primary implants were indicators of infection as compared to replacements. This finding was related to the longer duration of the primary implant procedures. Another possibility may be due to a difference in technique employed by our laboratory. For generator replacements we enlarge the pacemaker pocket to allow for proper apposition of the new generator. This technique may diminish the occurrence of infectious complications caused by ischemia and necrosis, and even by extrusion of the generator due to tension within the pocket. However, we cannot make any definitive conclusions based on these groups as the actual number of infections was very low.
The presence of hematoma in the pocket increased the incidence of infection by 7 times, independent of the use of antibiotic prophylaxis (OR, 6.72; 95% CI, 1.32 to 34.04, \( P = 0.03 \)). Although the placebo group had a significantly greater number of patients on oral anticoagulation, those who developed infection post procedure were not more likely to be taking oral anticoagulation. However, there were only 16 total hematomas postprocedure, only 3 of whom developed an infection. As a result, this subset of patients is small, and caution should be taken when making conclusions from this group. In addition, the specific management of anticoagulation at our institution may differ from that of other practices as overlap with heparin likely increases the risk of hematoma and length of stay.

Prophylactic antibiotics were not given to any patient with or without hematoma after the procedure although this is routinely done at many institutions. We do not routinely do so, although it is not known if we may have further decreased the incidence of infection had this intervention been performed. In addition, because all procedures were performed in a single medical center by experienced cardiac surgeons in an operating room rather than a cardiac catheterization/electrophysiology laboratory, it is possible that the rate of infection may be lower than expected.

**Limitations**

Our study subsequently excluded those patients who needed early reintervention due to lead dislodgement. Such patients are at high risk for infection. Follow up after the procedure involved evaluation of the site of the procedure at several time intervals within the 6 months. In addition, the predefined duration of follow up of 6 months may have resulted in the exclusion of late infections, but all 13 cases were found within 33 days postprocedure. Drawing definitive conclusions from analysis of the group of infected patients (n = 13) should be taken with caution given the small size of this group. Finally, although the strict requirements from the safety committee required the review of the data every 6 months, the result was still statistically significant even when accounting for interim analysis.

**Conclusions**

The results of this study confirm the benefit of antibiotic prophylaxis with a single dose of 1 g of cefazolin to reduce the incidence of infectious complications during implantation of pacemakers and cardioverter-defibrillators. In addition, the occurrence of pocket hematoma, identified patients with high risk of postoperative infections.

**Acknowledgments**

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**Disclosures**

None.

**References**

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