Antibiotic Prophylaxis with a Single Dose of Cefazolin During Pacemaker Implantation: Incidence of Long-Term Infective Complications

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BERTAGLIA, E., ET AL.: Antibiotic Prophylaxis with a Single Dose of Cefazolin During Pacemaker Implantation: Incidence of Long-Term Infective Complications. Objective: Systemic and localized infections related to permanent pacemaker implantation are not common, but are serious and potentially life-threatening complications. The aims of this prospective observational study were: (1) to assess the safety and long-term efficacy of a simplified scheme of antibiotic prophylaxis, and (2) to identify the predictors of long-term infective complications, in patients undergoing pacemaker implantation or replacement.

Methods and Results: From October 1998 to July 2001, 852 patients (mean age 77.0 ± 9.2 years; 474 men) who underwent new permanent pacemaker implantation (69.6%) or pulse generator replacement (30.4%) received a mini-bag of 2 g of cefazolin diluted in 50 mL of saline solution, administered intravenously in 20 minutes before the beginning of the procedure. Early (within 2 months of implantation) and late major and minor infective complications were recorded. During the earlier phase, minor complications were observed in 9 patients (1%). During the long-term phase of the surveillance (mean 25.6 ± 11.0 months, range 12–55 months) major infective complications were observed in 6 patients (0.7%). On multivariate analysis, no clinical or procedural variable predicted the occurrence of long-term infective complications.

Conclusions: Our data indicate the safety and efficacy of a single, intravenous 2 g dose of cefazolin in preventing infective complications related to pacemaker implantation or replacement. No clinical or procedural variable predicted the occurrence of long-term infective complications. (PACE 2006; 29:29–33)

Introduction

The use of intracardiac devices such as pacemakers has extended the lifespan and improved the quality of life of patients. However, it is sometimes complicated by localized and systemic infections. Systemic infections are rare, but in some cases severe and potentially life-threatening.1,2

Rates of pacemaker-pocket infection varying between 0.5% and 5.1% have been reported in retrospective and prospective studies,3–6 whereas bacteremia and endocarditis have also been reported in up to 0.5% of patients.1,2 Primary antibiotic prophylaxis to prevent device-related infections is recommended on the basis of the results of studies on surgical wound infection,7–9 but this practice is not supported by the results of individual randomized clinical trials of sufficient size.10–17

A recent meta-analysis of 7 randomized studies examining the impact of systemic antibiotics on the risk of pacemaker-related infections suggested that systemic antibiotic prophylaxis to prevent device-related infections significantly reduces the incidence of serious infective complications after pacemaker implantation.18 However, complex schemes of prophylaxis were proposed in these studies, and the efficacy of antibiotic prophylaxis was rarely evaluated after the first 12 months.

The aims of this observational study were: (1) to assess the safety and long-term efficacy of a simplified scheme of antibiotic prophylaxis, and (2) to identify the predictors of long-term infective complications in patients undergoing pacemaker implantation or replacement.

Methods

Study Population

From October 1998 to July 2001, all patients undergoing implantation of a new pacemaker, pulse generator replacement or upgrading of a pre-existing pacing system in Mirano Hospital received a mini-bag of 2 g of cefazolin diluted in 50 mL of saline solution, administered intravenously in 20 minutes before the beginning of the procedure, to obtain the maximum concentration of the antibiotic during the procedure. In the event of a procedure lasting more than 180 minutes, a further 2 g dose of cefazolin was administered.

Thirty-two patients with a history of intolerance to cefalosporin or penicillin, and 116 patients
already on antibiotic therapy for other reasons, were excluded from the study.

**Implantation Technique**

Written informed consent was obtained before pacemaker implantation or pulse generator replacement in all patients. Only 3 operators (E.B., F.Z., and F.Z.) were involved in the procedures. Povidone iodine 7.5% solution was used for insertion-site skin disinfection, and local anesthesia was administered. New leads were inserted transvenously through the cephalic vein (6%) or through the subclavian vein (94%). Generators were positioned subcutaneously over the greater pectoral muscle. During pulse generator replacement or upgrading, the fibrotic capsule of the old pocket was excised before the new generator was positioned. Drains were never used.

**Follow-Up**

Out-patient visits were scheduled at Mirano Hospital after 1 week, 2 months and, thereafter, every 12 months. Early (within 2 months of implantation) and late infective complications were recorded. Septicemia, endocarditis, pocket abscess, and pocket erosion were regarded as major complications, whereas local signs of inflammation around the pocket (cellulitis, erythema, edema), and skin temperature $>37.5^{\circ}$C for $>2$ consecutive days were considered minor complications.

In the event of death, autopsy results were collected, when available, as well as information on the cause of death from the General Practitioner.

**Statistical Analysis**

Continuous variables are expressed as mean $\pm$ standard deviation (range). Discrete variables are presented as percentages. Univariate comparisons between variables were made by means of Fisher’s exact test or $\chi^2$ test for categorical variables, and unpaired Student’s $t$-test for continuous variables.

The following variables were subjected to multivariate analysis with a logistic regression, using the backward stepwise method according to Wald, to identify significant and independent predictors of long-term infective complications: (1) gender, (2) age (per unit), (3) procedural time (per unit), (4) type of procedure (first implantation or pulse generator replacement), (5) occurrence of pocket hematoma, (6) occurrence of early minor infective complications.

A $P$ value $<0.05$ was considered statistically significant.

Analyses were performed by means of SPSS (version 11.0, Chicago, IL, USA).

**Results**

**Implantation**

From among 1,000 consecutive patients undergoing new permanent pacemaker implantation, pacemaker upgrading or generator replacement from October 1998 to July 2001, 852 patients (mean age $77.0 \pm 9.2$ years; 474 men) were enrolled in the study (Table I). A new permanent pacemaker was implanted in 595 patients (69.6%), while 257 patients (30.4%) underwent pulse generator replacement or upgrading of a pre-existing pacing system. In 22/257 patients (8.6%) who underwent pulse generator replacement or upgrading of pre-existing pacing system, this procedure represented the second or third operation. Mean procedure duration time was 49.6 $\pm$ 30 minutes (range 15–240 minutes), with a significantly longer duration required for pacemaker implantation than for procedures of pulse generator replacement or pacing system upgrading (56.5 $\pm$ 29.7 minutes and 34.4 $\pm$ 25.4 minutes, respectively, $P < 0.0001$). A dual-chamber pacemaker was implanted in 585 patients (68.6%) and a single-chamber pacemaker in 267 patients (31.3%).

No adverse reactions to cefazolin were observed. Pocket hematoma was observed within the first week in 21 patients (2.5%).

**Infective Complications**

During the early phase, no major infective complications were reported. We observed only minor complications in 9 patients (1%): fever in...
8 patients, and skin pocket inflammation in 1 patient, who were treated successfully with empiric antibiotic therapy.

During the long-term phase of the surveillance (mean 25.6 ± 11.0 months, range 12–55 months) 192 patients (22.5%) died, none of infective complications.

Major infective complications were recorded in 6 patients (0.7%). Endocarditis was observed in 1 patient with a prosthetic aortic valve, who presented septic fever for the first time 23 months after the implantation of a single-chamber pacemaker. Transesophageal echocardiography and blood culture proved negative. The fever disappeared after empiric antibiotic therapy, but reappeared 40 months after implantation. This time, however, transesophageal echocardiogram revealed evidence of vegetations on the atrial portion of the ventricular lead. Repeated blood cultures proved negative and no local signs of infection were detected. The generator and lead were extracted and a new contralateral single-chamber pacing system was implanted after 2 weeks of empiric antibiotic therapy. In the following 18 months the patient remained asymptomatic.

Pocket abscess was documented in 1 patient 6 months after generator replacement. Pocket culture proved positive for Staphylococcus aureus. In the absence of signs of systemic infection after 1 week of antibiogram-guided antibiotic therapy, we removed the pulse generator and implanted a new contralateral single-chamber pacing system. During the following 26 months, the patient did not present any other infective complications.

Pocket erosion was observed in 4 patients. In 3 of these patients, this complication appeared 5, 24, and 24 months, respectively, after pulse generator replacement. In the other patient, the pocket erosion appeared 52 months after the implantation of a dual-chamber pacemaker. In all these patients, pocket cultures proved negative. In the absence of signs of systemic infection after 1 week of empiric antibiotic therapy, the pulse generators were removed and new contralateral single-chamber pacing systems were implanted in these patients, too. After a mean follow-up of 32.2 ± 8.6 months, none of them presented infective complications.

**TABLE II.**

Univariate Comparison Between Patients With and Without Long-Term Infective Complications

<table>
<thead>
<tr>
<th>Variable</th>
<th>Infective Complications</th>
<th>No Infective Complications</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>100%</td>
<td>55.6%</td>
<td>0.03</td>
</tr>
<tr>
<td>Age (years)</td>
<td>79.2 ± 8.8</td>
<td>77.0 ± 9.6</td>
<td>0.58</td>
</tr>
<tr>
<td>Pulse generator replacement</td>
<td>66.7%</td>
<td>30.6%</td>
<td>0.05</td>
</tr>
<tr>
<td>Mean procedural time (minutes)</td>
<td>30.0 ± 6.3</td>
<td>49.8 ± 30.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Local hematoma</td>
<td>4.8%</td>
<td>0.6%</td>
<td>0.14</td>
</tr>
<tr>
<td>Early infective complications</td>
<td>0%</td>
<td>1.1%</td>
<td>0.80</td>
</tr>
<tr>
<td>Follow-up (months)</td>
<td>30.3 ± 11.0</td>
<td>25.6 ± 11.2</td>
<td>0.30</td>
</tr>
</tbody>
</table>

**Predictors of Long-Term Infective Complications**

On univariate analysis, patients who developed long-term infective complications were male, had a shorter procedural time, and more often underwent pulse generator replacement. By contrast, local hematoma after the procedure and early minor infective complications did not correlate with long-term infective complications (Table II). On multivariate analysis, none of these variables predicted the occurrence of long-term infective complications.

**Discussion**

**Main Findings**

Our data indicate the safety and efficacy of a single intravenous dose of cefazolin in preventing infective complications related to pacemaker implantation. To the best of our knowledge, these data represent the largest cohort of patients treated with a uniform scheme of antibiotic prophylaxis and followed up for such a long time.

Among several clinical and procedural variables, none correlated with the occurrence of long-term infective complications.

**Previous Studies**

Previous studies have shown that device-related infections occur in 0.5–5% of patients. Data summarized from 7 randomized studies report an incidence of major infective complications of 0.5% among patients who received antibiotic prophylaxis and of 3.7% among control patients. All but one of these studies used complex schemes of antibiotic prophylaxis, often with concomitant administration of more than one agent for up to...
8 days after implantation. Moreover, most of these patients were followed for <1 year. Despite the use of a single administration of cefazolin, our data compared well with those from previous studies, with a final rate of major infective complications of only 0.7% in patients followed up for >1 year.

Predictors of Long-Term Infective Complications

On univariate analysis, patients who developed long-term infective complications were male, had a shorter procedural time, and more often underwent pulse generator replacement. However, the multivariate analysis did not reveal any clinical or procedural variables significantly correlated with the occurrence of long-term infective complications, probably owing to the low rate of major complications observed in our series.

Perhaps the most interesting finding is the confirmation that pulse generator replacement presents the same, or even a higher, risk of major infective complications than first pacemaker implantation. Pocket erosion is the most common complication after pulse generator replacement. Thus, closer attention should be paid to the surgical technique during pulse generator replacement. Subsequently, these procedures should be performed by experienced operators.

The shorter procedural time observed in patients who developed long-term infective complications than in patients who did not is simply related to the fact that most of the former underwent pulse generator replacement, which is obviously a faster procedure.

Another interesting point is the lack of correlation between the incidence of fever during the first days after the procedure and the incidence of long-term major infective complications. In our study group, we recorded a skin temperature >37.5°C for >2 consecutive days in 8 patients, usually within the first week after the procedure; in none of these, however, did major infective complications appear during a mean follow-up of 32.2 ± 8.6 months. It is plausible that the early increase in skin temperature, a rather rare phenomenon, could be the effect of a concomitant disease unrelated to pacemaker implantation.

Conclusions

Our study indicates the safety and efficacy of a single intravenous 2 g dose of cefazolin in preventing infective complications related to pacemaker implantation or replacement. No clinical or procedural variable correlated with the occurrence of long-term infective complications.

Aim of this perspective surveillance was to obtain a reliable rate of long-term infective complications after pacemaker implantation or replacement with the use of intravenous cefazolin in order to design a randomized and placebo-controlled study. However, the extremely low rate of long-term infective complications obtained with cefazolin renders a randomized placebo-controlled no more ethical and suggests the routine use of 2 g of intravenous cefazolin.

Limitations

Our study excluded patients who were already on antibiotic therapy at the moment of pacemaker implantation. In this way we excluded most of the patients with a temporary percutaneous cardiac stimulation, who are those at higher risk of infective complications. Thus, our good results should not be extended to the general population of patients undergoing implantation of a new pacemaker.

References