Antibiotic Prophylaxis for Permanent Pacemaker Implantation

A Meta-Analysis

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Background—Infection remains a serious complication after permanent pacemaker implantation. Antibiotic prophylaxis is frequently prescribed at the time of insertion to reduce its incidence, although results of well-designed, controlled studies are lacking.

Methods and Results—We performed a meta-analysis of all available randomized trials to evaluate the effectiveness of antibiotic prophylaxis to reduce infection rates after permanent pacemaker implantation. Reports of trials were identified through a Medline, Embase, Current Contents, and an extensive bibliography search. Trials that met the following criteria were included: (1) prospective, randomized, controlled, open or blind trials; (2) patients assigned to a systemic antibiotic group or a control group; (3) end point events related to any infection after pacemaker implantation: wound infection, septicemia, pocket abscess, purulent secretion, right infective endocarditis, inflammatory signs, a positive culture, septic pulmonary embolism, or repeat operation for an infective complication. Seven trials met the inclusion criteria. They included 2023 patients with established permanent pacemaker implantation (new implants or replacements). The incidence of end point events in control groups ranged from 0% to 12%. The meta-analysis suggested a consistent protective effect of antibiotic pretreatment ($P=.0046$; common odds ratio: 0.256, 95% confidence interval: 0.10 to 0.656).

Conclusions—Results of the present meta-analysis suggest that systemic antibiotic prophylaxis significantly reduces the incidence of potentially serious infective complications after permanent pacemaker implantation. They support the use of prophylactic antibiotics at the time of pacemaker insertion to prevent short-term pocket infection, skin erosion or septicemia. **(*Circulation*. 1998;97:1796-1801.)**

Key Words: pacemakers ■ meta-analysis ■ prevention

Pacemaker pocket infection remains a serious, potentially life-threatening complication after permanent pacemaker implantation; rates varying between 0.5% and 5.1% have been reported in retrospective and prospective studies.[1–3] Septicemia, endocarditis, or both have also been described in up to 0.5% of patients.[4] In a recent study of 52 patients with pacemaker lead–related endocarditis, hospital mortality was 7.6% and overall mortality was 26.9% after a mean follow-up of 20 months.[5] Many operators routinely prescribe an antibiotic prophylaxis at the time of implantation to prevent such complications, although there is no present evidence that this strategy is beneficial.[6] Indeed, results of individual trials are not convincing and their results are controversial possibly because sample sizes were too small to allow conclusive answers. An appropriate double-blind randomized study is still needed. However, we believed that the time had come to review the present knowledge based on pertinent literature. We thus performed a meta-analysis of available randomized trials to try to evaluate the effectiveness of systemic antibiotic prophylaxis to reduce infection rates after pacemaker implantation.

Methods

We reviewed all published trials and searched all unpublished trials on antibiotic prophylaxis at the time of permanent pacemaker implantation to prevent secondary infections. The hypothesis tested was formulated before data were collected. Patients had to be adult to undergo either a new permanent pacing system implantation or a pulse generator or lead change. Trials that met the following criteria were included (1) prospective, randomized, controlled, open, or blind trials; (2) patients assigned to a systemic antibiotic group or a control group; (3) end point events related to any infection after pacemaker implantation. Data from individual trials were extracted independently by three of us (A.D.C., G.K., F.D.) by using the following end points: all probable or documented infections after pacemaker implantation. In the event of any disagreement about the data extracted, a consensus was obtained among the three readers. Studies were identified by use of the National Library of Medicine Medline from January 1967 to June 1996, Embase (Excerpta Medica) from January 1974 to June 1996, and Current Contents from January

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1967 to June 1996. Abstracts presented at the Scientific Sessions of the American College of Cardiology, the American Heart Association, the North American Society of Pacing and Electrophysiology, and the European Congress of Cardiology were hand screened from 1980 to the present. We also scanned the reference lists in reviews and trials and asked colleagues, investigators, and manufacturers of pacemakers and antibiotics for any unpublished or missing studies. Data concerning study design, baseline patient characteristics, treatment, follow-up, definitions of infection, and results were abstracted from these reports. We searched additional data when necessary from personal communication with trial investigators. We made a special effort to identify multiple reports of the same trial so that the same patients were not counted more than once in the analysis.

Statistical Methods

Outcome was evaluated with major end points mentioned in the original reports. Statistical analysis was done with the use of standard methods because there was no reason to favor a particular effect model. We used various methods based on fixed effect models, that is, the logarithm of the odds ratio method, the Mantzel-Haentzel method, the Peto method, and the risk difference method.[7] These methods required the number of events observed in each trial in the antibiotic group and in the control group. Results obtained from the various methods were similar, the method of the logarithm of the odds ratio gave the most conservative ones (that is, fewer significant results) and was retained for their presentation. The logarithm of the common odds ratio was estimated by a weighted mean of the logarithm of the individual odds ratio.[8] The inverse of the Woolf variance of the logarithm of the odds ratio was used as weight.[9] When no events were reported for a group, a pseudocount was used: a value of 0.25 was added to each cell of the Table 2×2 of each trial.[9] Association and heterogeneity tests were performed for each analysis. The heterogeneity of the treatment effect across the trials was tested with the Cochran Q statistic.[10] A value of $P \leq .01$ from an association test was considered significant. The homogeneity test was considered disclosing heterogeneity at a level of $P \leq .10$.

Results

Characteristics of the Analyzed Trials

We identified 15 studies in which systemic antibiotic prophylaxis was tested.[11–27] Eight were excluded for the following reasons: five were not randomized,[22,23,25–27] the design was not relevant in two (comparison of two antibiotics protocols),[21,24] and local prophylactic antibiotics was compared with systemic prophylactic antibiotics in the last study.[20] We identified seven randomized studies examining the impact of systemic antibiotics on the risk of pacemaker-related infection[11–19] (Tables 1 and 2). No unpublished randomized trial was found. One study was published only as an abstract.[15] Only one study, representing 5% of the patients, was double blind and placebo controlled[16] (Table 1). Results were disclosed on an intention-to-treat basis in five studies; the mode of analysis was not given in two. No patient was reported to be lost to follow-up. Overall, the selected studies included 2023 patients, of whom 1011 received a systemic antibiotic prophylaxis and 1012 none.

Patient Characteristics

No differences were noted between the antibiotic and the control groups for patient age, sex, and pacing mode (Table 2). Procedure time was noted in three studies; no difference was shown between the antibiotic and control groups.[11–13,17,18] When information was available, there was no difference in the proportion of patients with preexisting disorders likely to predispose to infection such as diabetes, corticosteroid treatment, malignancy, anticoagulant therapy, leg ulcer, or a recent operation. Patients with overt sepsis for whom the operator thought antibiotics were clinically indicated and patients who refused consent were said to be excluded in all but, respectively, two trials and one trial. In three studies, patients with overt wound infection at the site of temporary transvenous pacemaker were clearly stated as noneligible.[11,15,16,18]

Protocols

All procedures were undertaken in operating rooms, and skin was assiduously disinfected before surgery. In one study, both groups of patients received intrapocket antibiotic spray containing neomycin, bacitracin, and polymixin.[17] In six studies, the timing of antibiotic administration was recommended within 2 hours preceding incision. In only one were antibiotics administered immediately after the procedure and then for 4 days.[18] In six studies, duration of antibiotic administration after incision was variable, from 6 hours to 8 days.[11–14,16–19] In the last study, antibiotic administration was done only before pacemaker implantation.[15] No study has examined the efficacy of a prolonged antibiotic duration versus a short administration. The antibiotics used were penicillin M (flucloxacillin or cloxacillin) in five studies[11–14,16,17,19] and cephalosporins in two studies: cefazedon and cefazolin, respectively[15,18] (Table 1).

End Points

In two studies, the end point was a repeat operation for an infective complication,[13,17] repeat operation that could be performed either for septicemia, pocket abscess, or erosion of the pulse generator, or electrode through the skin in the study by Mounsey et al.[13] Ramsdale et al[17] considered the following criteria for the diagnosis of pocket infection: (1) an oral temperature ≥37.5°C at two consecutive measurements after the third postoperative day, (2) acute local inflammation associated or not associated with (3) the presence of pus in the generator pocket. Definition of infection was similar in the studies of Glieca et al[18] and Muers et al.[19] In the study of Lüninghake et al,[15] the criteria have been systematically determined: local signs of inflammation around the pacemaker pocket and infection with proven infectious agent. In the remaining study, the criteria for local infection were presence of purulent substance and/or increased local temperature, redness, pain, and swelling.[14]

Length of Follow-up

Follow-up duration ranged from 1 month to 4 years; mean follow-up duration is known in only three studies and ranged from 14 to 23 months. The delay to infection is not clearly stated in two studies[15,18]; it ranged from 5 to 356 days in the other five studies.

TABLE 1. Characteristics of the Studies Included in the Meta-Analysis

Study	Agent/Dose/Regimen	Follow-up in Months Mean (Range)	Blind or Open	No. of Patients Enrolled
Muers et al[19] (1981)	Flucloxacillin 1 g together with benzylpenicillin 600 mg IV 1 hour before, 1 and 6 hours after	23 (9–40)	Open	431
Jacobson et al,[11] Bluhm et al[14] (1983, 1984)	Cloxacillin 2 g IV 1 hour before and 1 g IV every 6 hours for 2 days and by mouth for 8 days after (1 g every 6 hours)	NA (1–43)	Open	100
Ramsdale et al[17] (1984)	Cloxacillin 1 g together with amoxycillin 1 g IV 1 hour before and ampicillin/flucloxacillin (Magnapen) by mouth 500 mg every 6 hours for 48 hours after	NA (3–12)	Open	500
Bluhm et al[16] (1986)	Flucloxacillin 2 g IV 1 hour before and flucloxacillin 1 g by mouth every 8 hours for 5 days	14 (7–35)	Blind	106
Glieca et al[18] (1987)	Cefazolin 4 g IV every day for 5 days	NA	Open	200
Lüninghake et al[15] (1993)	Cefazedon 2 g IV before	NA (12–48)	Open	213
Mounsey et al[12,13] (1993, 1994)	Flucloxacillin 1 g IV before, and 500 mg by mouth every 6 hours for 48 hours	19 (9–26)	Open	473

NA indicates no data available.

Meta-Analysis

The incidence of end point events in control groups ranged from 0% to 12%. Results obtained from the different methods (see "Methods") were similar; therefore only those obtained from the logarithm of the odds ratio method are presented with the corresponding 95% confidence intervals (CI). The meta-analysis suggested a consistent protective effect of antibiotic pretreatment ($P=.0046$; common odds ratio: 0.256, 95% CI: 0.10 to 0.656, Figure). No statistical heterogeneity was observed from the homogeneity test that showed a value of $P=.36$ with a multiplicative model. The additive model was rejected because of significant heterogeneity. Overall mortality rate was not significantly different between the two groups (Table 2).

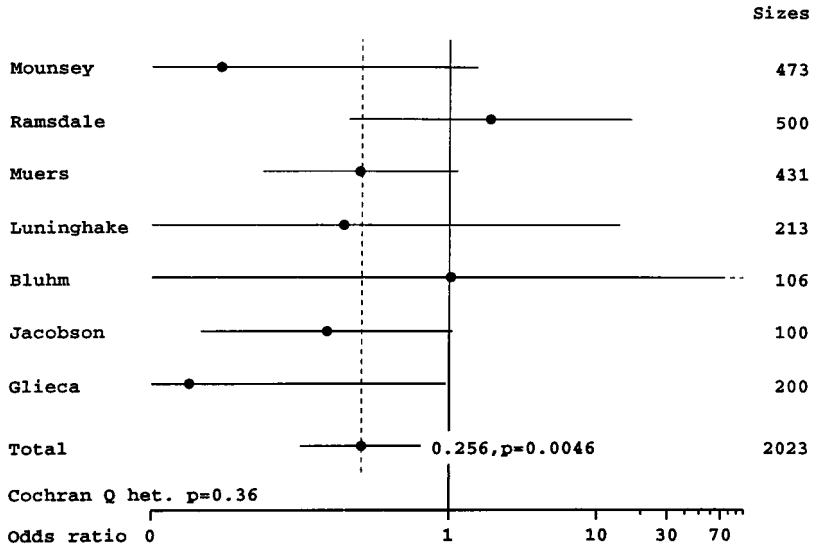
Discussion

Antibiotic prophylaxis is currently widely administered at the time of permanent pacemaker implantation. However, there is no convincing evidence of its usefulness. Its expected efficacy can be questioned, and a suitably powered clinical trial is still needed. Recent controversies have emphasized the need for a reappraisal of the current knowledge.[28,29] Seven controlled, randomized studies have been identified. Despite their relatively limited quality, they represent the only pertinent data available on antibiotic prophylaxis. In four trials, antibiotic prophylaxis was effective to prevent pocket or lead infection.[11–14,18,19] For Mounsey et al,[12,13] erosion was the most common form of infection and never occurred after antibiotic prophylaxis. No efficacy could be observed in the three remaining studies because of the very low infection rates in the control and antibiotic groups.[15–17] We thus performed a meta-analysis of these trials to better estimate the potential usefulness of antibiotic prophylaxis in this setting.[11–19] We found that antibiotic administration at the time of pacemaker insertion significantly decreased the risk of pacemaker or lead infection when data were pooled. Most commonly, wound infection, inflammation, or skin erosion

TABLE 2. Patient Characteristics

Study	Mean Age, y	Sex (% Men)	Antibiotic Group, No. of Patients	Control Group, No. of Patients	Infection (Antibiotic Group) No. of Patients	Infection (Control Group) No. of Patients	Death (Antibiotic Group) No. of Patients	Death (Control Group) No. of Patients
Muers et al	NA	NA	234	197	2	7	NA	NA
Jacobson et al	73	51	50	50	1	7	0	1
Ramsdale et al	72	50	244	256	2	1	19	15
Bluhm et al	75	54	52	54	0	0	1	1
Glieca et al	66	66	100	100	0	12	0	0
Lüninghake et al	NA	NA	107	106	0	1	NA	NA
Mounsey et al	74	55	224	249	0	9	0	0
Total			1011	1012	5	37	20	17

NA indicates no data available.



Antibiotic prophylaxis efficacy for permanent pacemaker implantation. Graphical representation shows odds ratio and 95% confidence interval. Data are based on the longest follow-up. Line graph shows odds ratio and 95% confidence intervals for the reduction of pacemaker infection with antibiotic administration.

were prevented. Uncertainty still remains as to whether antibiotics prevent septicemia or endocarditis, which can occur years after implantation.[4,5] However, in a randomized, controlled study comparing mezlocillin-netilmicin combination with mezlocillin alone, De Lalla et al[30] did not observe any pocket or lead infection in a series of 552 patients during a 29.2-month mean follow-up. These results are in agreement with randomized controlled trials that have shown that prophylactic antibiotics are effective in preventing surgical wound infections.[31–33]

As in most meta-analyses, these results should be taken with care because antibiotic treatments, end points, and lengths of follow-up were not uniformly designed. However, the question was coherent among studies as to whether antibiotics protected against secondary infections. Because early infections appear to be acquired at the time of surgery[6] and staphylococci are associated with the majority of pacemaker infections,[34] antistaphylococcal antibiotics such as flucloxacillin or cloxacillin and cephalosporins were deemed the most appropriate in doses that give high serum and tissue levels during surgery and immediately afterward. In a study on surgical wound infection, Classen et al[31] have shown that the risk of infection is best reduced when antibiotics were administered in the 2 hours before surgery, a recommendation that was followed in six of the seven studies of this meta-analysis. The difference in infection rates in the control groups between studies is puzzling. Good surgical conditions (operating room, experienced surgeons, careful skin preparation, local antibiotics) are probably a key to a low infection rate,[17,20] but this factor cannot be clearly demonstrated from these seven trials that were done in experienced centers aware of these prerequisites.

Although pointing to pacemaker-related infection, end points could vary from one trial to the other. In one study the most common mode of presentation of pacemaker infection was erosion of either the pulse generator or the lead(s).[12,13] Aggarwal et al[28] have criticized such an end point, arguing that erosion might have been caused by mechanical factors. Although the origin of skin erosion has not been clearly established, it is generally believed that infection is secondary to a mechanical process.[35,36] The results of Mounsey et al[12,13] could lead to reevaluation of the responsibility of microorganims in skin erosion because no patient had such a complication in their antibiotic prophylaxis group. In any case, consequences of the differences in the definition of end points across studies are limited because we used relative measures to assess effects of the treatment. This limitation was tested by the heterogeneity test, which failed to detect a difference in the size of effect between the trials.

In the seven trials analyzed in this study, efficacy of antibiotic prophylaxis was not evaluated long term, particularly after 2 years, and most patients probably have not been followed for >1 year. Results of the present meta-analysis thus apply to infections that occur within this delay. Endocarditis occurring late after implantation is a rare but serious life-threatening complication that often requires complex surgical procedures.[4,5,37] Whether such a complication can be obviated by antibiotic prophylaxis at the time of implantation is unknown and requires further study. If confirmed, prevention of late infective complication suggested by De Lalla et al[30] could be per se of high benefit.

Limitations of Meta-Analyses

Limitations of meta-analyses are well known.[7,38,39] Comparative studies that have yielded conflicting results are difficult to evaluate because various factors other than antibiotics can influence sepsis rates, such as different techniques of operation, skin antisepsis, and antibiotic use (topical or systemic).[28,29] As in any meta-analysis, critical attention must be paid to the quality of the primary trials. In terms of study design, all trials were prospective, controlled, and methodologically adequately randomized. However, only one was double blind. All used widely accepted and reasonable definitions of infection that were in agreement with infection criteria used by Choo et al[40] in a landmark study. In only one study erosion of part of the pacing system through the skin was defined as an infec-

tion, but positive culture from the probable infected site was shown in all but two patients.[13] Thus despite different clinical expressions, infection was demonstrated in the majority of end point events, giving validity and consistency to the results of this meta-analysis. Another unavoidable limitation of meta-analysis is that by relying on past information, it may reach conclusions that are correct but not relevant at the time of its publication because of technological or therapeutic progress. In our meta-analysis, despite additional, recent, improved techniques such as surgical and aseptic procedures, smaller pulse generators, and cephalic lead introduction, there was no difference in infection rates between recent and older reports.[11–19] Last, individual patient data were not available for this meta-analysis because most studies were performed more than 10 years ago, thus precluding any subgroup (high-risk patients) analysis.

Clinical Implications

Despite these limitations, carefully designed meta-analyses can give a temporary overview on the present knowledge while awaiting the results of well-designed clinical trials. Infections after pacemaker insertion remain of major concern and can be life threatening or a source of undue morbidity.[4,5] Besides, they increase the real cost of pacemaker implantation. Our conclusions are in strong favor of antibiotic prophylaxis in this circumstance, a finding that carries major clinical implications. Although questionable because of the lack of well-designed randomized studies, they support the use of antibiotic prophylaxis and suggest that it can decrease severe complications. Additionally, cost savings can be anticipated; they have been clearly demonstrated when antibiotic prophylaxis was used in similar situations such as closed fracture surgery.[33]

Conclusions

Comparative studies on the merits of antibiotic prophylaxis have yielded inconclusive results. Results of the present meta-analysis suggest that systemic antibiotic prophylaxis significantly reduces the incidence of serious infective complications after permanent pacemaker implantation. They support the use of prophylactic antibiotics at the time of pacemaker insertion to prevent short-term pocket infection, skin erosion, or septicemia. Efficacy on late septicemia or endocarditis is unknown. These data should be interpreted cautiously until confirmed by suitably powered clinical trials that are undoubtedly needed. However, we believe it is now reasonable to encourage prophylactic antibiotics when implanting a permanent pacemaker.

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