

Antibiotic prophylaxis in permanent pacemaker implantation: a prospective randomised trial

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Abstract

Background—Pacemaker pocket infection is a potentially serious problem after permanent pacemaker implantation. Antibiotic prophylaxis is commonly prescribed to reduce the incidence of this complication, but current trial evidence of its efficacy is conflicting. A large prospective randomised trial was therefore performed of antibiotic prophylaxis in permanent pacemaker implantation. The intention was firstly to determine whether antibiotic prophylaxis is efficacious in these patients and secondly to identify which patients are at the highest risk of infection.

Methods—A prospective randomised open trial of flucloxacillin (clindamycin if the patient was allergic to penicillin) *v* no antibiotic was performed in a cohort of patients undergoing first implantation of a permanent pacing system over a 17 month period. Intravenous antibiotics were started at the time of implantation and continued for 48 hours. The trial endpoint was a repeat operation for an infective complication.

Results—473 patients were entered into a randomised trial. 224 received antibiotic prophylaxis and 249 received no antibiotics. A further 183 patients were not randomised but were treated according to the operator's preference (64 antibiotics, 119 no antibiotics); these patients are included only in the analysis of predictors of infection. Patients were followed up for a mean (SD) of 19(5) months. Among the patients in the randomised group there were nine infections requiring a repeat operation, all in the group not receiving antibiotic ($P = 0.003$). In the total patient cohort there were 13 infections, all but one in the non-antibiotic group ($P = 0.006$). Nine of the infections presented as erosion of the pulse generator or electrode, three as septicaemia secondary to *Staphylococcus aureus*, and one as a pocket abscess secondary to *Staphylococcus epidermidis*. Infections were significantly more common when the operator was inexperienced (≤ 100 previous patients), the operation was prolonged, or after a repeat operation for non-infective complications (principally lead displacement). Infection was not significantly more common in patients identified preoperatively as being at high risk (for example patients with diabetes mellitus, patients receiving

long term steroid treatment), although there was a trend in this direction.

Conclusions—Antibiotic prophylaxis significantly reduced the incidence of infective complications requiring a repeat operation after permanent pacemaker implantation. It is suggested that antibiotics should be used routinely.

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Pacemaker pocket infection remains a potentially serious complication after permanent pacemaker implantation. Many operators routinely use antibiotic prophylaxis to reduce the incidence of this complication, but the trial evidence that this strategy is beneficial is not convincing. The two largest trials to date^{1,2} have conflicting conclusions. Muers *et al*¹ showed a small benefit of antibiotic prophylaxis in reducing pacemaker pocket and wound sepsis, whereas Ramsdale *et al*² saw no such benefit.

With these conflicting studies in mind, we elected to perform a large prospective randomised trial of antibiotic prophylaxis. We hoped to establish firstly whether the incidence of serious infection, which we defined as infection requiring a repeat operation, was reduced. These serious infections have been reported to occur in up to 5% of implants.³ They are unambiguous as an endpoint and their prevention should be the main goal of antibiotic prophylaxis. The secondary purpose of the trial was to identify patients at high risk of infection in whom antibiotic prophylaxis may be most efficacious, if the trial did not produce a statistically significant result in favour of the use of antibiotic prophylaxis.

Methods

PATIENTS

All adult patients (older than 18 years) who underwent elective implantation of a new permanent pacing system at the Northern Region Cardiothoracic Centre, Freeman Hospital, Newcastle upon Tyne, between 1 October 1991 and 28 February 1993 were eligible for inclusion in the trial. The trial was approved by the Northern Regional Health Authority ethical committee. Patients undergoing pulse generator or electrode changes were not studied. Patients with overt sepsis in whom the operator thought antibiotics were clinically indicated were excluded. Also excluded were

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patients who refused consent and those whom it was inappropriate to approach for informed consent because of, for example, dementia. Those patients who refused consent and those who were not approached received antibiotics if it was the operator's usual practice to use them, and the antibiotic regimen was, where given, identical to the trial regimen.

Patients who gave informed consent were randomly allocated to receive or not receive antibiotic prophylaxis immediately before the operation. The antibiotic regimen was flucloxacillin 1 g intravenously immediately before surgery, followed by 500 mg by mouth every six hours for 48 hours. Patients allergic to penicillin received clindamycin 600 mg intravenously immediately before surgery, followed by 300 mg by mouth every six hours for 48 hours.

OPERATION

All implantations were performed under local anaesthesia after premedication with diazepam by mouth. All procedures were carried out under full operating theatre conditions. Standard operating packs were used. Hand cleansing was with prepacked sponges soaked either in chlorhexidine or povidone iodine. Skin preparation at the time of the operation was with 10% povidone iodine solution or 0.5% alcoholic chlorhexidine.

Standard transvenous electrodes were introduced either via the cephalic vein, the subclavian vein, or occasionally via the internal jugular vein. Electrodes were secured using either silk or absorbable (vycryl, Ethicon) sutures. Subfascial pockets were fashioned by blunt dissection and standard pulse generators were used. Wound closure was with interrupted or continuous absorbable sutures to the subcutaneous tissues. Some patients also received a continuous subcuticular suture using an absorbable suture; in others, final skin closure was with Steristrips. All wounds were dressed in the theatre using an adhesive dressing.

Patients were normally discharged from hospital on the first postoperative day after technical checks, a chest radiograph, and wound inspection. Routine technical follow up was at four to six weeks after discharge and every six to 12 months thereafter. The

patients were not routinely followed up in the cardiac clinic.

DEFINITION OF INFECTION

The endpoint of the trial was a repeat operation for an infective complication. All pacemaker complications with the potential to require a repeat operation were referred back to the Freeman Hospital for assessment and treatment. Patients with superficial wound infections which required only local treatment or antibiotics by mouth were not deemed to have an infective complication in the analysis of this study.

A repeat operation was performed either for septicaemia, pocket abscess, or erosion of the pulse generator or electrode through the skin. In patients without systemic infection the pulse generator was, where technically feasible, cleaned with alcoholic betadine and resited at a single operation. In other patients the infected system was explanted with, if necessary, connection of the electrode to an external pulse generator. In these patients a new, contralateral pacing system was implanted at a later date. All repeat operations were performed under general anaesthesia with antibiotic cover guided, where available, by microbiological culture results. We have described the procedure and outcome for primary resiting of eroded pulse generators elsewhere.⁴

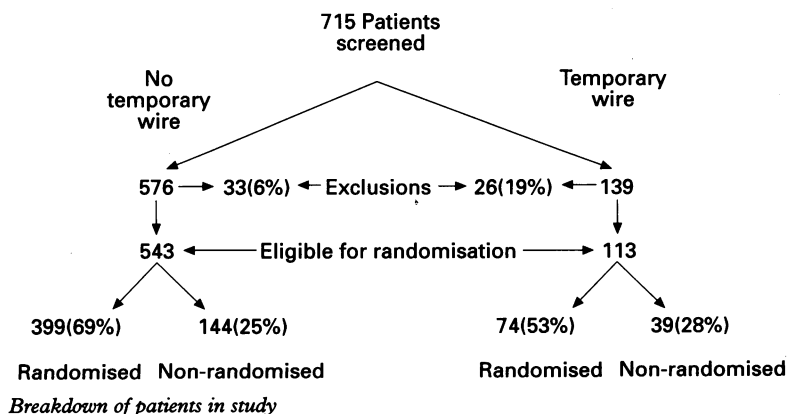
DATA ANALYSIS

Student's *t* test, Fisher's exact test, and the χ^2 test with, where appropriate, Yates's correction were used for statistical analysis. Significance was assumed to be $P < 0.05$.

Results

PATIENT COHORT

The figure shows a breakdown of the patient cohort. A total of 715 patients was screened for inclusion in the trial. One hundred and thirty nine (19.4%) of these had temporary pacing electrodes in situ; 576 (80.6%) did not. In the group without temporary electrodes, 33 (6%) were excluded, 399 (69.2%) were entered into the randomised trial, and 144 (25%) were not randomised. Among patients with temporary electrodes, 26 (19%) were excluded, 74 (53%) were entered into the randomised trial, and 39 (28%) were not randomised. Thus a total of 473 patients were randomised; 224 (47%) of these received antibiotics and 249 (53%) did not. Data for the primary endpoint—that is, pacemaker infection requiring a repeat operation—will be presented for randomised patients separately. A total of 183 patients was not randomised, 64 (35%) of whom received antibiotics and 119 (65%) did not. Thirteen of these patients (7%) were not approached for consent because of dementia or other psychiatric illness; the remainder did not consent. These non-randomised patients, who received antibiotic prophylaxis or not according to the operator's usual practice, will be included in the analysis of predictors of pacemaker infection. Flucloxacillin was the antibiotic used in



89% of patients. The remaining 11% received clindamycin.

This report is based on data analysis up to 1 November 1993 so the follow up period ranges from nine to 26 months (mean (SD) 19 (five) months, identical for treated and untreated groups).

COMPARISON OF TREATED AND UNTREATED GROUPS

Table 1 shows the baseline characteristics of the patient cohort, including randomised and non-randomised patients. There was no significant difference in baseline characteristics between randomised and non-randomised patients. There was no significant difference between the antibiotic and non-antibiotic groups of patients with respect to age, sex, pacing mode, procedure time, or perioperative blood loss (calculated from the weight of blood saturated swabs). A similar proportion of pacemakers in each group was implanted by junior operators with 100 cases or less previous pacing experience. There was no difference in the proportion of patients in each group who had one or more preexisting disorders likely to predispose to infection—for example, diabetes, corticosteroid treatment, malignancy, or a recent operation.

Twenty eight patients (4.3%) had a repeat operation for non-infective complications. This rate was similar in the treated and untreated groups (table 1). Twenty patients (3.0%) had one or both electrodes repositioned less than 14 days after the initial operation and six patients (0.9%) had electrodes repositioned or replaced 14 days to six months after implantation. Two patients (0.3%) required early pulse generator changes because of generator failure (six days and 49 days after implantation). All patients who received antibiotic prophylaxis at implanta-

tion had antibiotics either continued or prescribed again at the time of the repeat operation. Four patients who did not receive prophylaxis at implantation received antibiotics at the time of the repeat operation. In each of these early repositioning of a displaced electrode was carried out.

PACEMAKER INFECTIONS

Table 2 shows observed infection rates for antibiotic and non-antibiotic groups. Among the randomised patients there was a total of nine infections requiring a repeat operation, two of which occurred in patients with temporary electrodes. All infections were in the non-antibiotic group and this represents a statistically significant benefit for antibiotic prophylaxis ($P = 0.003$).

In the total patient cohort, including non-randomised patients, there were 13 infections, all but one in the non-antibiotic group. This difference was also statistically significant. Nine of these infections occurred in patients without temporary electrodes, all in the non-antibiotic group, and this difference was also statistically significant. Among patients with temporary electrodes antibiotic prophylaxis did not confer a benefit. There were four infections in this group, which represents an overall infection rate of 3.5%. One of the patients had received antibiotics and the difference between the antibiotic and non-antibiotic groups was not statistically significant.

MODES OF PRESENTATION OF INFECTED PACEMAKERS

Table 3 gives details of the patients who became clinically infected. The most common mode of presentation of pacemaker infection was erosion of either the pulse generator or the pacing electrode. This occurred in nine patients 171 (77) days after implantation (range 97–346 days). Bacterial pathogens were identified in two patients (*Staphylococcus aureus* and *Enterococcus faecalis*), skin or mixed faecal flora in five patients, and there was no bacterial growth in two patients.

Three patients presented with septicaemia. In each instance the patient presented within 10 days of the operation and the organism responsible was *Staphylococcus aureus*. One patient presented with a closed pocket abscess. This patient also presented early and the organism was *Staphylococcus epidermidis*. None of the patients died as a result of pacemaker infection.

PREDICTORS OF PACEMAKER INFECTION

Table 4 gives the factors which were of significance in the prediction of pacemaker infection. A significant excess of pacemakers which became infected were implanted by inexperienced operators who had previously performed less than 100 pacemaker implantations. Conversely, no infection occurred in patients where the operator had previously performed more than 500 operations. The mean operation time was significantly prolonged in patients who developed infections.

Table 1 Comparison of patient characteristics and operative details for treated and untreated groups

Patient characteristic	AB+ (n = 288)*	AB - (N = 368)*	P Value
Mean (SD) age (years)	74.3 (11.8)	74.2 (12.6)	1.0
Sex (% male)	55	55	1.0
Preoperative high risk	19	14	0.1
Pacing mode			
Single chamber atrial	9	9	
Single chamber ventricular	50	57	
Dual chamber	41	34	0.2
Inexperienced operator (<100 patients)	30	31	0.8
Mean (SD) Duration of operation (minutes)	55 (24)	53 (27)	0.3
Mean (SD) Blood loss (ml)	31 (41)	28 (36)	0.4
Repeat operation, non-infective complication	4	4	0.9

* The percentage of patients with the designated characteristic is shown unless otherwise stated.

Table 2 Outcome: infection rates

Patient group	AB + *	AB - *	P Value
Randomised patients	0/224 (0%)	9/249 (4%)	0.003
Total cohort	1/288 (0.3%)	12/368 (3%)	0.006
Patients with no temporary wire	0/234 (0%)	9/300 (3%)	0.012
Patients with temporary wire	1/53 (2%)	3/60 (5%)	0.6

* Patients receiving antibiotics are designated AB + and those not receiving antibiotics AB -.

Table 3 Infections after pacemaker implantation

Patient No	Age (years)	Mode	Implantation					Repeat operation			
			AB*	Experience* of operator	Operation time (min)	Blood loss (ml)	Lead redo	Interval (days)	Presentation	Swab culture	Treatment
<i>Patients without temporary electrodes</i>											
1	75	AAI	-	I	60	15	N	346	Erosion	Faecal flora <i>E coli</i>	Reimplantation × 2, ciprofloxacin, good result
2	72	DDD	-	I	137	20	N	97	Erosion	<i>S aureus</i>	Reimplantation × 2, flucloxacillin, chronic wound sinus
3	79	VVI	-	I	115	30	N	198	Erosion	Skin flora	Reimplantation, flucloxacillin good result
4	92	VVI	-	E	80	45	Y	115	Erosion	Skin flora	Reimplantation, flucloxacillin, good result
5	79	DDD	-	I	120	30	Y	116	Erosion	No growth	Reimplantation, flucloxacillin, good result
6	82	VVI	-	E	38	20	N	106	Erosion	Skin flora	Reimplantation, flucloxacillin, good result
7	86	VVI	-	I	55	25	N	135	Erosion	No growth	Reimplantation, flucloxacillin, good result
8	66	AAI	-	E	101	135	Y	8	Septicaemia	<i>S aureus</i>	Intravenous flucloxacillin, pacemaker explanted, contralateral new system, good result
9	70	DDD	-	E	65	15	N	5	Septicaemia	<i>S aureus</i>	Intravenous flucloxacillin, pacemaker explanted, contralateral new system, good result
<i>Patients with temporary electrodes</i>											
10	78	VVI	-	I	70	5	N	231	Erosion	<i>E faecalis</i>	Reimplantation, explanted 29 days later contralateral new system good result
11	56	AAI	-	I	40	5	N	199	Erosion	Skin flora	Reimplantation, flucloxacillin, good result
12	65	DDD	+	I	76	25	Y	16	Pocket abscess	<i>S epidermidis</i>	Intravenous flucloxacillin pacemaker explanted, contralateral new system, good result
13	60	DDD	-	E	78	50	N	108	Septicaemia	<i>S aureus</i>	Intravenous flucloxacillin, pacemaker explanted, contralateral new system, good result

* 100 cases or fewer.

Those patients who had a repeat operation for non-infective complications had a significantly higher infection rate. Infection was not significantly more common in patients identified preoperatively as being at high risk of infection, though there was a trend in this direction. There was no difference between infected and non-infected groups for age, sex, or perioperative blood loss. Dual chamber pacemakers were no more likely to become infected than single chamber pacemakers.

Discussion

In this large prospective randomised trial we have shown a highly significant benefit for antibiotic prophylaxis in preventing those

infective complications of permanent pacemaker implantation which require a repeat operation. This finding contrasts with all previous prospective trials of antibiotic prophylaxis, none of which showed such a large benefit of antibiotic treatment.

Two large trials showed no significant benefit for antibiotics. Ramsdale *et al*² reported an overall infection rate of 21/530 patients (3.9%), of whom eight had received antibiotics and only three (0.6%) required an operation (two of these received antibiotics). Bluhm *et al*⁵ observed no infection in 106 patients randomised to receive antibiotics or placebo. In contrast, two large trials have shown a significant benefit for antibiotic prophylaxis. Muers *et al*¹ reported an overall infection rate of 9/431 patients (2.1%), only two of whom received antibiotics. The mode of presentation and subsequent clinical course of the infected patients was not reported. In another, earlier trial from Bluhm's group³ the infection rate was 8/100; one patient had received antibiotics and five required a repeat operation.

The two trials of antibiotic prophylaxis which showed no benefit had low overall rates of serious infection. The British Pacing and

Table 4 Predictors of pacemaker infection. Values are percentage of patients unless stated otherwise.

	Infection (n = 13)	No infection (n = 643)	P Value
Inexperienced operator (less than 100 previous cases)	61.5	29.8	0.03
Mean (SD) operation time (minutes skin-skin)	76 (29)	54 (25)	0.003
Repeat operation (non-infective complication)	30.8	3.7	0.001
Preoperative high risk	30.8	15.8	0.24

Electrophysiology Group have reported a United Kingdom national average pacemaker infection rate of 1.7%⁶ (range up to 5%). These data do not indicate the use of antibiotic prophylaxis or specify the seriousness of the infection. As most units under report infection, however, it is most likely to be an underestimate of the true incidence of serious infection. The British Pacing and Electrophysiology Group infection rate is in accord with our result (overall infection rate 1.9% 13/669 patients) and with Muers *et al.*¹ In contrast, Ramsdale *et al.*² report a serious infection rate of only 0.6%. This low rate may have occurred by chance, but there are two major differences between their practice and ours which may explain the discrepancy.

Firstly, the patients of Ramsdale *et al.*² stayed in hospital longer (three days compared with one day) and were followed up more often than ours (four times in the first year compared with two). It is possible that careful surveillance and antibiotic treatment of wound infections may have resulted in the secondary prevention of serious infection in that trial. We have no data on the incidence of superficial wound infection or of antibiotics prescribed out of hospital, and so cannot speculate whether any serious infections were aborted by early antibiotic treatment in our patient cohort.

Secondly, there was a high incidence of late pulse generator erosion in our series (9/13 infections were erosions), whereas Ramsdale *et al.*² observed none. This striking difference may have been caused by the use of a topical antibiotic spray into the generator pocket in all patients by Ramsdale *et al.*² We prospectively defined erosions as infections for the purposes of this trial because they were a cause for a late repeat operation, possibly of infective origin.⁷ In the event, only seven of nine erosions were overtly infected; the remaining two were microbiologically sterile. It has been argued that sterile erosions may be the result of mechanical factors alone rather than an infective process. In support of this we have previously shown that pulse generator repeat implantation is most often successful when erosions are sterile.⁴ That two sterile erosions occurred in the non-antibiotic group in this trial may be random chance or it may be that all erosions require an underlying infective process to initiate them. Interestingly, to date there have been no erosions in the antibiotic group in our series.

Inexperience of the operators may have contributed to the infection rate in our series. We prospectively defined a learning curve of 100 cases and, by this definition, approximately one third of pacemakers were implanted by inexperienced operators. A significant excess of infections occurred in this group of patients. In Ramsdale *et al.*'s study² two out of five operators were in training (the number of cases previous experience was not specified); Muers *et al.*¹ do not report the proportion of operators in training, though it is probable that some of the operators in their series were, by our definition, in training.

In our series, the duration of the operation and repeat operation for non-infective complications were significantly associated with infection. None of the previous prospective trials specifically addressed either of these factors, though it seems logical that the time the wound was open and reopening the wound predispose to infection. Morgan *et al.*⁸ noted that a repeat operation predisposed to septicaemia in patients with permanent pacemakers. There was a trend towards a higher infection rate in patients identified preoperatively as being at high risk of infection. This did not reach statistical significance, which is in accord with the data of Muers *et al.*¹

Antibiotic prophylaxis was not beneficial in the subgroup of patients with temporary pacing electrodes *in situ*. This subgroup analysis was prospectively defined and, given the known high rate of infection of temporary electrodes,⁹ the absence of benefit is surprising. A relatively small number of patients with temporary electrodes were randomised and exclusions for overt sepsis were common in this series. For these reasons we are not confident that antibiotic prophylaxis is not beneficial in these patients and we would advocate its use on the basis of the highly significant result for the whole cohort. A large trial focused on patients with temporary electrodes would be of interest.

In conclusion, antibiotic prophylaxis significantly reduces the incidence of serious infective complications requiring a repeat operation after permanent pacemaker implantation. Permanent pacemaker infections occur most commonly when the operation time is prolonged, the operator is inexperienced, and after a repeat operation for electrode displacement. We suggest that antibiotic prophylaxis (guided by the sensitivity of local bacterial flora) is used routinely in permanent pacemaker implantation.

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