Cefuroxime for prevention of postoperative coxitis

One versus three doses tested in a randomized multicenter study of 2,651 arthroplasties

Ate Wymenga[1], Jim van Horn[1], Ad Theeuwes[2], Harry Muytjens[3] and Tom Slooff[1]

Infection prophylaxis in hip replacement with one perioperative dose of cefuroxime was evaluated in a randomized controlled multicenter study using a three-dose regimen as a control. All the operations were performed in conventionally ventilated operating theaters. Of the 2,796 hip replacements entered in the study, 145 replacements were excluded because of protocol violations. The remaining 2,651 hip replacements were analyzed: 1,327 and 1,324 in the one- and the three-dose group, respectively.

There were no differences between the one-dose and the three-dose groups as regards the incidence of postoperative wound-healing problems, and urinary tract or other distant infections. The use of additional antibiotics after the perioperative prophylaxis did not differ between the treatment groups.

After a mean follow-up period of 13 months, joint sepsis was diagnosed in 11 of the patients in the one-dose group (0.83 percent) and in 6 of the patients in the control group (0.45 percent). This difference was not significant. Because the estimated difference between the one-dose and the three-dose group was 0.38 percent, we could not confirm that the efficacy of one dose was equal to three doses. An extended follow-up study, with more cases of joint sepsis, may provide more conclusive data. Until then, a three-dose regimen is recommended.

Departments of [1]Orthopedics, [2]Medical Statistics and [3]Microbiology, University Hospital Nijmegen, P.O. Box 9101 6500 HB Nijmegen, The Netherlands. Tel +31–80 614148. Fax +31–80 540555
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Perioperative systemic antibiotics in hip replacement reduce the incidence of joint sepsis (Fogelberg et al. 1970, Ericsson et al. 1973, Hill et al. 1981, Lidwell et al. 1982). There is, however, no consensus on the optimal administration of antibiotic prophylaxis in joint replacement surgery (Pollard et al. 1979, Heydeman and Nelson 1986, Gatell et al. 1987, Evrard et al. 1988). A duration of 24 hours is currently recommended (Norden 1985), but there is a trend towards further reduction to a single dose in orthopedics (Hirschman 1984), as well as in other surgical fields (Pollock 1988, DiPiro et al. 1986).

To establish the efficacy of a single perioperative antibiotic dose for infection prophylaxis in joint replacement, a randomized controlled multicenter study was performed. Cefuroxime, a second generation cephalosporin with a half-life of 70 minutes, was chosen because this antibiotic provides a broad spectrum of activity against the organisms that cause joint infection after arthroplasty (Sanderson 1988).

Patients and methods

Assuming that the incidence of joint sepsis is 1 percent with a three-dose regimen, we estimated that at least 1,250 patients were needed in each treatment group to detect a 1 percent difference on the basis of a one-sided Type I error of 0.05 percent and a Type II error of less than 20 percent (one-tail test). A difference less than 1 percent (which is less than twice the incidence in the three-dose regimen) would mean that the single dose was equally effective.

A study population of 1,250 hip replacements per treatment group was sufficient to ensure that the upper 95 percent confidence limit (one-sided) for the difference between joint sepsis rates was almost certainly less than 1 percent (80 percent probability), given a joint sepsis rate of 1 percent in both groups (Mackuch and Simon 1978). Using these criteria, only rather large relative differences can be detected; but given the low incidence of joint sepsis, a detectable difference of 1 percent was considered to be adequate for estimating the efficacy of a single dose. If we were to employ a smaller detectable difference, the trial would require several thousand more operations in each group.

Twenty-seven Dutch hospitals participated in the study from 1 July 1986 to 1 July 1988. Only centers with conventionally ventilated operating theaters took part. Local ethics committees approved the protocol.

Patients undergoing a total hip replacement, a hemiarthroplasty of the hip, or a total knee arthroplasty were eligible for the study. The exclusion criteria were allergy to cephalosporin, penicillin anaphylaxis, the use of antibiotics less than 48 hours before the operation, the use of perioperative antibiotics other than cefuroxime, malignancy, former or current sepsis in the joint, and the use of gentamicin-impregnated bone cement for prosthetic fixation.

Randomization of the prophylaxis regimen was performed using a computerized list in blocks of 10 numbers. For eligible patients, envelopes containing a self-adhesive label with the prescribed dosage were opened sequentially. The label was placed on the patient's records and the anesthesia list. Thus, the treatment was not blinded. For logistic reasons, a number of centers randomized all their patients and exclusions were performed after the operation.

Cefuroxime at a dose of 1,500 mg was given intravenously to both groups upon inducing anesthesia 30 minutes before the operation. In the three-dose group, second and third injections of 750 mg cefuroxime were given after 8 and 16 hours. In three centers, the surgical wound was rinsed with a fluid containing an antibiotic, whereas two centers used povidone iodine to rinse the wound.

Definitions

The clinical end point of the study was joint sepsis, reoperation, or death.

Confirmed joint sepsis was defined as a positive bacteriologic culture at reoperation or a draining sinus.

Strong evidence of sepsis was defined as four or more possible signs of infection. These two groups of conditions were analyzed together (Category I). In patients who only showed two or three possible signs of sepsis (Category II), a definite diagnosis could not be made. Patients with one or no signs of infection (Category III) were not suspected of having joint sepsis.

The conditions that were defined as being *possible infections* at the follow-up examination were pain during weight bearing and/or at rest, tenderness of the wound, fever, an abnormal radiograph, ESR more than 20 mm above the preoperative value or more than 35 mm, positive culture from joint fluid aspirate, positive arthrogram, bone scan showing typical signs of infection, or increased C-reactive protein.

Wound infection in the postoperative period was defined as erythema more than 1 cm from the incision.

Minor postoperative wound-healing problems were defined as erythema of the wound less than 1 cm from the incision, pus suture, small wound dehiscence, necrosis of the wound edge, and blisters.

Distant infections were usually diagnosed on the basis of positive cultures. A urinary tract infection was defined as bacteriuria of more than 10^5 bacteria/mL. Blood cultures of *Staphylococcus epidermidis* were only considered positive when cultured at least twice. A few pulmonary, skin, and other infections were diagnosed clinically.

Additional antibiotics prescribed after the perioperative period for wound and/or distant infections or other reasons were also recorded. The amount of antibiotic was expressed in Defined Daily Doses, which is based on the main indication and expressed as the weight of active substance (Anonymous 1985).

Patients undergoing knee replacement were also eligible for the study, and were stratified by the randomization procedure. A total of 455 operations were recorded, 58 of which were excluded (13 percent) and 35 withdrawn (9 percent), leaving 362 operations in 328 patients for analysis. Joint sepsis was diagnosed at follow-up in three out of the 175 (1.7 percent) operations in the single-dose group and in 6 out of the 187 operations (3.2 percent) in the three-dose group. Because these data differed considerably from those obtained from the hip operations, the knee arthroplasties cohort was analyzed separately.

The primary variable was joint sepsis (Category I). Confidence limits (one-sided) were calculated for the differences, i.e., the ratio of the crude rates in both groups. Other outcome variables were compared by using a chi-square test (two-sided) with continuity correction.

From 1 July 1986 to 1 July 1988, 3,074 operations were recorded. A total of 278 (9 percent) operations did not meet the criteria in the protocol and were excluded. The most common reason for exclusion was the use of gentamicin bone cement, which was often used in high-risk patients. Some centers did not enter their high-risk patients into the study or they used gentamicin bone cement, whereas other hospitals entered all the consecutive patients.

From the remaining 2,796 operations, 145 (5 percent) were withdrawn, leaving 2,651 operations (2,547 patients) for analysis (Table 1). A separate follow-up of all the withdrawn patients showed that all of them were free from joint infection. Data on 15 patients were lost during follow-up. The mean follow-up period was 13 months for both prophylaxis groups.

The two trial arms were well-matched with respect to the general and orthopedic diagnoses (Table 2). The incidence of rheumatoid arthritis, diabetes, use of

Table 1. Inclusion criteria, exclusions, and withdrawals (hip replacements). Number, *percentages*

	One dose	Three doses	Total
Randomized	1,600	1,599	3,199
Operations recorded[a]	1,540	1,534	3,074
Exclusion protocol	141 *9.2*	137 *8.9*	278 *9*
Follow-up	1,399	1,397	2,796
Withdrawn from analysis			
other type of antibiotic	17	16	33
died within 7 days	4	8	12
wrong dose or administration	42	35	77
second hip replacement[b]	9	14	23
total	72 *5.1*	73 *5.2*	145 *5.2*
Suitable for analysis	1,327	1,324	2,651

[a]In some patients the operation was cancelled or a different procedure was performed.
[b]During one hospital admission.

Table 2. General and orthopedic characteristics (hip replacements). *SD*

	One dose	Three doses
Mean age	69 *11*	69 *11*
Male/female	287/1040	266/1058
Operated on side (left/right)	649/678	611/713
Mean quetelet index (kg/m^2)	26.2 *3.8*	26.5 *4.0*
missing values	216	220
Physical condition (moderate/poor)	206/19	184/17
Steroid use	36	33
Diabetes[a]	42	58
Cardiac disease[a]	191	171
Pulmonary disease[a]	86	87
Preoperative infections	64	67
No concurrent diseases[a]	823	843
Diagnosis:		
arthrosis	959	954
rheumatoid arthritis	83	77
fracture (recent)	138	120
other	35	31
failed prosthesis	26	40
osteotomy	42	56
fracture osteosynthesis	33	30
other earlier operations	11	16
Type of replacement and use of bone cement		
total hip cement a+, f+	863	859
a–, f+	164	152
a+, f–	4	4
a–, f–	183	188
hemiarthroplasty +/–	79/8	71/10
revisions (various procedures)	26	40
Approach (anterolateral/posterolat.)	439/888	422/902
Surgeon status (staff/resident)	1,245/82	1,242/82
Mean blood loss in mL	686 *422*	705 *482*
missing values	55	37
Mean operation time, minutes	88 *31*	89 *32*
missing values	28	16
Breakdown of sterility (90 percent glove rupture)	75	82

[a]More than one concurrent illness possible.
a Acetabular component.
f Femoral component.
+ Fixation with bone cement.
– Fixation without bone cement.

steroids, and prosthetic failure was low. As for the operative procedure, there were no decisive differences between the groups.

Only 5 patients in our study group (0.2 percent) had allergic reactions associated with cefuroxime; 2 were withdrawn from the analysis because they did not receive the full three doses. Anaphylactic shock was not recorded.

Results

Joint sepsis was recorded in 11 patients (0.83 percent, 95 percent confidence limits 0.33–1.32) in the one-dose group and in 6 patients (0.45 percent, 95 percent confidence limits 0.08–0.81) in the three-dose group (Table 3). This difference was not significant ($P < 0.05$). The estimated difference in incidence of sepsis between the one-dose group and three-dose group was 0.38 percent (95 percent upper confidence limit 0.9 percent). The estimated ratio was 1.83 with an upper confidence limit of 4.2.

Joint sepsis was confirmed by a positive culture at reoperation and/or a draining sinus in 14 patients. Three patients showed clear signs of joint sepsis; two underwent reoperation for infection, but their perioperative cultures were negative. The joint aspirate from the third patient was found to contain *Staphylococcus aureus*.

Joint sepsis occurred in 9 patients within 1 month after surgery. Five of these patients underwent early reoperation, either evacuation of an infected hematoma or excision of a sinus; 4 of these patients were well at the 1-year follow-up without signs of joint sepsis. One case of joint sepsis was diagnosed after 4 months, 1 after 5 months, 2 after 11 months, 2 after 14 months, 1 after 18 months, and 1 after 24 months. There were two sepsis-related deaths, one in each prophylaxis group: after 1 month (one-dose group) and after 5 months (three-dose group).

After reoperation for mechanical reasons (n 64), 4 additional patients developed joint sepsis, 3 in the one-dose group and 1 in the three-dose group. These cases of joint sepsis were omitted from the analysis because reoperation was defined as an end point in the study.

No differences were found between the groups with respect to postoperative wound infection, minor wound-healing problems, hematoma and wound drainage, the amount of additional antibiotics prescribed for

Table 3. Joint sepsis, wound healing, distant infections (hip replacements). *Percentages*

	One dose n 1,327		Three doses n 1,324		*P*-value X^2-test
Joint sepsis (Category I)	11	*0.8*	6	*0.5*	0.17[a]
Some signs of possible sepsis (Category II)	7	*0.5*	9	*0.7*	0.37[b]
Postoperative wound infection	25	*1.9*	31	*2.3*	0.50
Minor wound-healing disturbances	169	*12.7*	166	*12.5*	0.89
Hematoma: light	127	*9.6*	145	*11.0*	0.09
moderate	99	*7.5*	82	*6.2*	
severe	28	*2.1*	44	*3.2*	
Any wound drainage	166	*12.5*	178	*13.4*	0.51
Postoperative distant infections:					
urinary tract	201	*15.2*	194	*14.7*	0.72
pulmonary tract	18	*1.4*	20	*1.5*	0.88
skin	31	*2.3*	26	*2.0*	0.59
septicemia	5	*0.4*	4	*0.3*	0.99

[a]One-sided.
[b]Categories I + II analyzed together, one-sided.

Table 4. Additional postoperative antibiotics usage expressed in defined daily doses (DDD) with number of replacements (n). *Percentage of replacements*

Indication	One dose (n 1,327)			Three doses (n 1,324)			*P*-value X^2-test
	DDD	n		DDD	n		
Wound problems	1,241	48	*3.6*	1,281	40	*3.0*	0.45
Fever for unknown reasons	416	18	*1.4*	356	18	*1.4*	1.00
Distant infection	2,040	196	*14.8*	2,072	198	*15.0*	0.94
Other reasons	164	35	*2.6*	57	24	*1.8*	0.15

Table 5. Complications, adverse effects, and mortality (hip replacements). *Percentages*

	One dose n	%	Three doses n	%	*P*-value X^2-test
Orthopedic complications	48	*3.6*	46	*3.5*	0.92
Orthopedic reoperation (also in follow-up)	33	*2.5*	31	*2.3*	0.91
Nonorthopedic complications	47	*3.5*	45	*3.4*	0.92
Nonorthopedic operations	18	*1.4*	7	*0.5*	0.046
Invasive diagnostic procedures	12	*0.9*	5	*0.4*	0.15
Adverse reactions with cefuroxime	1	*0.1*	2	*0.2*[a]	0.99
Died in hospital	11	*0.8*[b]	5	*0.4*[b]	0.21
Died during follow-up < 1 year	43	*3.2*	30	*2.3*	0.20
> 1 year	18	*1.4*	13	*1.0*	

[a] Two additional patients in the three-dose group suffered from adverse reactions (withdrawn from analysis).
[b] Four additional patients in the one-dose group and 8 in the three-dose group died within 7 days (withdrawn from analysis, see Table 1).

wound problems, and fever of unknown reasons (Table 3).

The incidence of distant infections was not influenced by the method of prophylaxis (Table 3). Most postoperative distant infections occurred in the urinary tract. In 9 patients, septicemia was documented during the hospitalization, but only 1 patient developed joint sepsis. The amount of additional antibiotics prescribed for distant infections in both prophylaxis groups did not differ (Table 4).

The number of nonorthopedic and orthopedic complications was similar in the groups (Table 5). The

number of invasive diagnostic procedures, such as gastroscopy, cystoscopy, as well as operations performed for general complications, was slightly higher in the one-dose group. There was no difference between the number of patients who died in the hospital. During follow-up, the number of patients who died of cardiopulmonary disease was higher in the one-dose group, but no relation to sepsis was found.

Discussion

A low number of high-risk patients were included in this series because of the inclusion and exclusion criteria. The latter mainly applied to the use of gentamicin-impregnated bone cement. The follow-up was relatively short. These factors may have influenced the infection rate, which was lower than the expected 1 percent. Nevertheless, our overall incidence of 0.64 percent compares well with the 0.8 percent and 0.7 percent joint sepsis reported by Hill et al. (1981) and Lidwell et al. (1982) in patients operated on in conventionally ventilated operating theaters and receiving prophylactic antibiotics.

The incidence of joint infection in the single-dose group was almost twice as high as that in the three-dose group, but the numbers were small and the difference was not significant. However, the one-sided 95 percent confidence limits of the difference between the single-dose group and the control group had a range of up to 0.9 percent and a ratio of up to 4.2. Thus, ultimately, more than a doubled incidence could occur in the one-dose group. This was, by the criteria set before the trial started, defined as unacceptable. The equal efficacy of the single dose of cefuroxime compared with three doses could therefore not be confirmed despite the not significant statistical difference. Our trial sample with a low incidence of joint sepsis was too small to draw definite conclusions. An extended follow-up, with probably more low-grade infections diagnosed (Lidwell et al. 1985), may provide more conclusive data. We are now planning a 3-year follow-up evaluation.

The wound-healing problems were similar to those reported in other series (Hill et al. 1981, Lidwell et al. 1984, 1985), although the definitions varied to some extent. In this study, the incidence of postoperative minor wound-healing problems, wound drainage, and wound infection, as well as the amount of antibiotic prescribed for wound problems and fever for unknown reasons, was not influenced by one dose or three doses of antibiotic prophylaxis.

The urinary tract was the most frequent site of distant infection, and the 15 percent incidence was somewhat higher than the 4–9 percent reported in other studies (Hill et al. 1981, Evrard et al. 1988, Surin et al. 1983). This may be related to the large proportion of patients who had a urinary catheter postoperatively (Garibaldi et al. 1980). In one study, in which a 5-day regimen was compared with a placebo, the incidence of urinary tract infection was 6 percent and 10 percent, respectively (Hill et al. 1981). In our series, no difference in the incidence of various postoperative distant infections was found between the single-dose regimen and the triple-dose regimen. The amount of additional antibiotics prescribed for distant infections and for other reasons was also similar in both groups. Adverse effects associated with cefuroxime were reported in only 5 patients (0.2 percent).

We were thus unable to confirm that a single perioperative dose of cefuroxime was as effective as a three-dose regimen, because a considerable possibility remained that more than twice the incidence of sepsis could occur when more operations are performed; the number of joint infections was too small in our study to permit reliable conclusions. A three-dose regimen of cefuroxime is therefore recommended in hip replacement surgery until further data become available from an extended follow-up study.

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