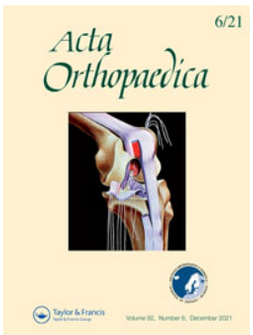

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Antibiotic prophylaxis in total hip arthroplasty

Effects of antibiotic prophylaxis systemically and in bone cement on the revision rate of 22,170 primary hip replacements followed 0–14 years in the Norwegian Arthroplasty Register

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ABSTRACT **We studied the effects of antibiotic prophylaxis, systemically and in bone cement, on the revision rate of cemented total hip arthroplasties (THAs) in data from the Norwegian Arthroplasty Register during the period 1987–2001. To have comparable groups, only THAs performed because of primary osteoarthritis, using cemented implants with documented good results, and high-viscosity cement were included. If systemic antibiotic prophylaxis had been given, only operations with cephalosporin or penicillin were selected.**

Cox-estimated survival relative revision risks (RR) are presented with adjustment for differences among groups in gender, age, cement brand, type of systemic antibiotic prophylaxis, type of prosthesis, type of operating room, and duration of the operation.

Of 22,170 THAs studied, 696 THAs (3.1%) were revised, 440 (2.0%) for aseptic loosening and 102 (0.5%) for deep infection. We found the lowest risk of revision when the antibiotic prophylaxis was given both systemically and in the cement (15,676 THAs). Compared to this combined regime, patients who received antibiotic prophylaxis only systemically (5,960 THAs) had a 1.4 times higher revision rate with all reasons for revision as endpoint ($p = 0.001$), 1.3 times higher with aseptic loosening ($p = 0.02$) and 1.8 times higher with infection as the endpoint ($p = 0.01$).

With the combined antibiotic regime, the results were better if antibiotics were given 4 times on the day of surgery (2,194 THAs), as compared to once (1,424 THAs) ($p < 0.001$), twice (2,680 THAs) ($p < 0.001$), or 3 times (5,522 THAs) ($p = 0.02$). Those who received systemic prophylaxis a single day 1, 2 or 3 times, as compared to 4 times, had a revision rate 1.8–3.5 times higher with all reasons for revision as endpoint, 1.5–3.1 times higher with aseptic loosening, and 2.7–6.8 times higher with infection. When we compared systemic prophylaxis 4 times in 1 day, no further improvement resulted in those given systemic prophylaxis for 2 days (1,928 THAs) or 3 days (717 THAs). In a subset of data including only the Charnley prosthesis, we obtained similar results.

This observational study shows that the best results were recorded when antibiotic prophylaxis was given both systemically and in the bone cement, and if the systemic antibiotic was given 4 times on the day of surgery. ■

Infection is a serious complication of total hip arthroplasty (THA). Thanks to a better surgical technique, stricter pre-and perioperative routines and antiseptic procedures (such as antibiotic prophylaxis), the infection rate has been reduced from 5–10% in the late 1960s to less than 1% (Lidgren 2001). The relative importance of each of the improvements is difficult to assess. In primary THA surgery, systemic antibiotic prophylaxis now

seems to be accepted (Walenkamp 2001), but antibiotic prophylaxis in the bone cement is disputed (van de Belt et al. 2001). In a previous article from the Norwegian Arthroplasty Register, a lower revision rate of primary THAs was found when antibiotic prophylaxis was given both systemically and in the bone cement, as compared to only systemically, in bone cement alone or no antibiotic prophylaxis at all (Espehaug et al. 1997). The present study is a continuation of that article with twice the number of THAs and a 6-year longer follow-up. We have also focused on the effect on the revision rates of the duration of the systemic prophylaxis and on the number of doses of the systemic antibiotic on the day of surgery.

Patients and methods

The Norwegian Arthroplasty Register was established in September 1987. Each THA performed in Norway is reported by the surgeon who fills in a standard form (Havelin et al. 2000). This contains information about the patient's identity, the date of operation, indication for surgery, type of prosthesis, type of cement, duration of surgery, type of operating room, and if systemic antibiotic prophylaxis was given, the type, duration and dosage. Failure (revision) of the implant was defined as surgical removal or change of the whole or part of the implant. Using each Norwegian inhabitant's unique identification number, the information on the primary THA was linked to an eventual revision.

From the start of the Register in September 1987 to the end of December 2001, 84,382 THAs were reported, of these, 71,921 were primary THAs (Havelin et al. 2002). For this study on the effects of antibiotic prophylaxis, we selected solely prostheses and cements with documented good long-term results in the Register. Only primary prostheses in patients with idiopathic osteoarthritis of the hip were included. The following four most commonly used combinations of cemented cup/stem prostheses were included: Charnley/Charnley (DePuy, Leeds, UK), Exeter/Exeter (Howmedica International, Herouville, France), Titan/Titan (DePuy, Chaumont, France) or Spectron/ International Total Hip (ITH) (Smith & Nephew, Memphis, Tennessee). We selected prostheses with high-viscosity cement of the brands Palacos with or without gentamicin (Schering-Plough International Inc., Kenilworth, New Jersey) or Simplex with or without colistin/erythromycin (Howmedica International, London, UK). Lastly, only those who had received systemic antibiotic prophylaxis with cephalosporin (the first-generation cephalotin or the second-generation cefuroxime) or penicillin (cloxacillin or dicloxacillin, both semisynthetic penicillinase-resistant) were included. In this way, 22,170 comparable THAs remained for further analyses.

Statistics

Survival analyses were performed by the Kaplan-Meier method and the Cox regression model (Kaplan and Meier 1958, Cox 1972). Patients who died or emigrated during the follow-up were identified from files provided by Statistics Norway and the follow-up time for the prostheses in these patients were censored on the date of death or emigration. We used a Cox multiple regression model to study relative revision risks (failure-rate ratios) among the different regimes of antibiotic prophylaxis with adjustments for the possible effects of gender, age (< 70, 70–75, > 75 years), brand of cement (Palacos, Simplex), type of systemic antibiotic prophylaxis (penicillin, cephalosporin), type of prosthesis (Charnley, Exeter, Titan, Spectron/ITH), operating room ("greenhouse", laminar air ventilation, ordinary ventilation) and the duration of the operation (< 61, 61–120, > 120 min). Estimates with Cox analyses were used to construct adjusted survival curves. For revisions, the surgeon could record one or more reasons for failure, but if it occurred with an infection this was considered to be the primary cause of revision. Aseptic loosening was otherwise regarded as the principal cause of revision when seen together with other causes.

We used the statistical package SPSS (SPSS Inc. 1999).

Results

The mean age of the patients with the selected 22,170 THAs was 72 (17–97) years, and 71% were

Table 1. Mean age, percentages of women, Charnley prosthesis, Palacos cement (with or without gentamicin), systemic cephalosporin prophylaxis, first systemic antibiotic dose of 1.5 or 2.0 grams, mean duration of surgery (in minutes), and percentage operating room with ordinary ventilation in the various groups of antibiotic prophylaxis

Prophylaxis	Age (years)	Women (%)	Charnley (%)	Palacos (%)	Cephalosporin (%)	1 dose antibiotic (1.5 or 2.0 g) (%)	Mean duration of surgery (min.)	Operation room (ordinary ventilation) (%)
Systemic+cement	72.7	70.6	69.1	91.7	82.8	94.7	99	57
Systemic alone	71.9	70.3	39.4	42.6	93.6	92.3	96	51
Cement	72.9	76.4	74.0	99.6	–	–	97	54
None	71.8	70.7	44.6	42.9	–	–	108	57
1 day 1 dose	73.8	70.4	51.5	97.7	75.1	86.8	95	63
1 day 2 doses	72.0	71.2	70.0	92.6	77.0	94.5	100	71
1 day 3 doses	72.8	71.9	66.2	82.9	88.6	98.5	97	49
1 day 4 doses	72.6	70.8	80.0	98.7	76.4	97.4	102	62
2 days	72.3	68.4	68.7	95.9	89.8	91.6	100	46
3 days	72.0	65.6	90.8	99.0	71.5	90.4	114	65

females. We found no large differences among the groups as regards antibiotic prophylaxis for some relevant variables (Table 1).

AntibŠtic prophylaxis systemically or in cement

A combined antibiotic prophylaxis, both systemically and in cement, was used in 71% of the operations, in 27% only systemic antibiotic was given, in 1.1% antibiotic solely in the cement and in 1.3% no antibiotic prophylaxis was used at all. During the study, the prophylaxis regime was switched almonst entirely to the combined regime after 1998 (Figure 1).

With all reasons for revision as the endpoint, we found the best results of the THAs with combined antibiotic prophylaxis (Figure 2a). Similar results were obtained when the endpoint in the analyses was revision due to aseptic loosening (Figure 2b) or infection (Figure 2c). The revision risk for those who received only antibiotic systemically, as compared to a combined, revision was 1.4 times higher with all reasons for revision as endpoint ($p < 0.001$), 1.3 times higher with aseptic loosening ($p = 0.02$) and 1.8 times higher with infection ($p = 0.01$) (Table 2).

The duratŠn of systemic antibŠtic prophylaxis

98% of the patients received systemic antibiotic prophylaxis. Among these, the prophylaxis was given for only 1 day in 85% of the operations, for

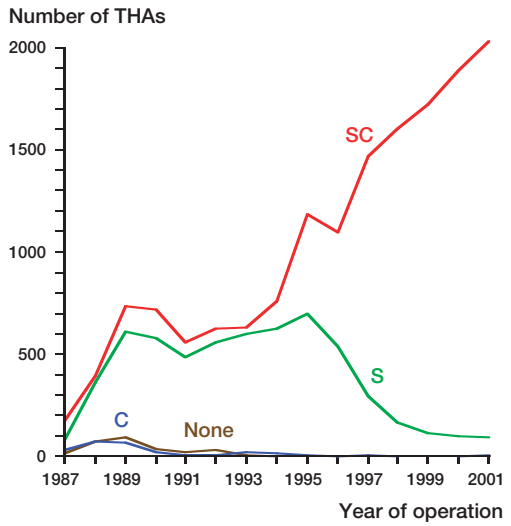
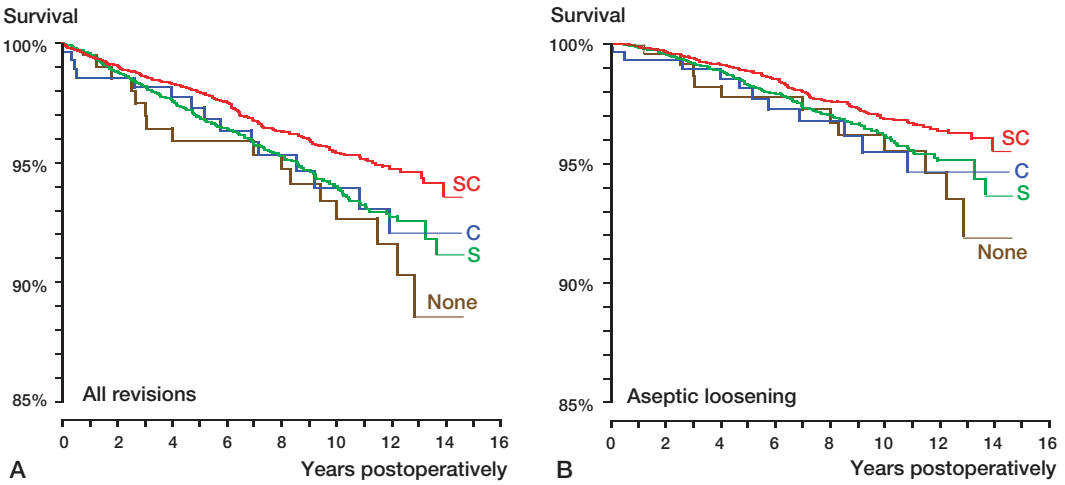


Figure 1. Number of THAs performed annually from 1987 to 2001 in those receiving antibiotic prophylaxis systemically and in cement (SC), only systemically (S), only in cement (C) or no antibiotic prophylaxis (None).

2 days in 11%, for 3 days in 4% and for more than 3 days in less than 1%.

In those who received prophylaxis both systemically and in bone cement (Figure 3), no improvements were obtained by extending the prophylaxis to 2 or 3 days, as compared to 1 day with 4 doses (Table 3). In addition, when 1 day with 4 doses was compared to 3 days with 4 doses on the first day ($n = 271$ with 12 revisions), we found no difference in the results ($p = 0.9$).



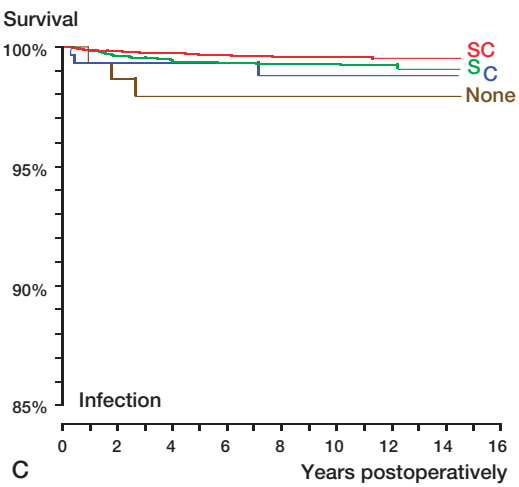


Figure 2. Cox-adjusted survival curves with all reasons for revision (A), aseptic loosening (B), and infection (C), as endpoint for THAs with antibiotic prophylaxis systemically and in cement (SC), only systemically (S), only in cement (C) or no antibiotic prophylaxis (None).

We studied the effect of the number of antibiotic doses in the combined group with systemic prophylaxis only on the day of surgery. Among these, the antibiotic was given once in 11%, twice in 21%, three times in 44%, four times in 17%, and more than four times the day of surgery in 6%. Compared to systemic prophylaxis four times on the day of surgery, three times ran a 1.8 times higher revision risk ($p = 0.02$), twice a 2.5 times higher ($p < 0.001$), and once a 3.5 times higher revision risk ($p < 0.001$) with all reasons for revision as endpoint (Table 3). We obtained similar results with aseptic loosening or with infection as endpoint (Table 3). In Figure 4, the corresponding Cox-adjusted survival curves are shown .

Type of systemic antibŠtic

The systemic antibiotic was a cephalosporin in 86% (cephalothin (n = 15,529) or cefuroxime (n = 3,035)) and a penicillin in 14% (cloxacillin (n = 1,146) or dicloxacillin (n = 1,926)). We found

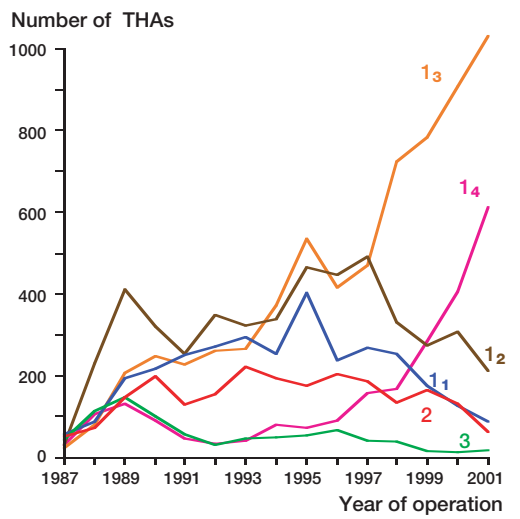


Figure 3. Number of THAs performed annually from 1987 to 2001 in those receiving antibiotic in the cement and antibiotic prophylaxis systemically for 1 day (with number of doses as subscript—i.e.,1 dose (1_1), 2 doses (1_2), 3 doses (1_3) and 4 doses (1_4)), 2 days (2) and 3 days (3).

Table 2. Results of primary THAs with antibiotic prophylaxis systemically + in cement, systemically only, in cement only or no antibiotic prophylaxis. Number of THAs, number of THA revisions, Cox-adjusted 10-year revision percentages, Cox relative revision risk (RR) (with Systemic+Cement as reference value), 95% confidence interval for RR, and p-value estimated with all reasons for revision, aseptic loosening and infection as endpoint in the analyses

Antibiotic prophylaxis regime	THAs	Revisions	10 year-revision [a]	RR [a]	95% CI	P-value
All reasons for revision as endpoint	22,170	696				
Systemic+cement	15,676	391	4.6%	1	–	–
Systemic only	5,960	274	6.0%	1.4	1.1–1.7	0.001
Cement only	254	15	6.1%	1.3	0.8-2.3	0.3
No antibiotic	280	16	7.3%	1.7	1.0–3.1	0.07
Aseptic loosening as endpoint	22,170	440				
Systemic+cement	15,676	245	3.1%	1	–	–
Systemic only	5,960	172	3.8%	1.3	1.0–1.7	0.02
Cement only	254	11	4.5%	1.4	0.8–2.6	0.3
No antibiotic	280	12	4.5%	1.7	0.8–3.3	0.1
Infection as endpoint	22,170	102				
Systemic+cement	15,676	50	0.4%	1	–	–
Systemic only	5,960	46	0.7%	1.8	1.1–3.0	0.01
Cement only	254	3	1.2%	2.7	0.8–8.7	0.1
No antibiotic	280	3	2.0%	4.9	1.2–20.2	0.03

[a] Adjusted in the Cox model for gender, age, cement- and prosthesis-brand, type of operating room and duration of operation. The number of THAs included in the Cox analyses was reduced to 21,717 because of cases with missing values in covariates.

Table 3. Results of primary THAs with antibiotic prophylaxis systemically for 1 day (1 dose, 2 doses, 3 doses or 4 doses), 2 or 3 days combined with antibiotic in the cement. Number of THAs, number of THA revisions, Cox-adjusted 10-year revision percentages, Cox relative revision risk (RR) (with 1 day 4 doses as reference value), 95% confidence interval for RR, and P-value estimated with all reasons for revision, aseptic loosening and infection as endpoint in the analyses

Duration of systemic antibiotic prophylaxis	THAs	Revisions	10-year revision [a]	RR [a]	95% CI	P-value
All reasons for revision as endpoint	14,465	342				
1 day 1 dose	1,424	62	8.8%	3.5	2.1–5.8	<0.001
1 day 2 doses	2,680	83	6.2%	2.5	1.5–4.1	<0.001
1 day 3 doses	5,522	105	3.8%	1.8	1.1–2.8	0.02
1 day 4 doses	2,194	21	2.3%	1		
2 days	1,928	50	3.6%	1.6	0.9–2.7	0.83
3 days	717	21	2.6%	1.1	0.6–2.0	0.80
Aseptic loosening as endpoint	14,465	219				
1 day 1 dose	1,424	37	5.9%	3.1	1.6–5.9	<0.001
1 day 2 doses	2,680	53	4.0%	2.3	1.3–4.2	0.007
1 day 3 doses	5,522	59	2.4%	1.5	0.8–2.7	0.18
1 day 4 doses	2,194	14	1.5%	1		
2 days	1,928	40	3.0%	1.9	1.0–3.6	0.05
3 days	717	16	1.7%	1.0	0.5–2.2	0.90
Infection as endpoint	14,465	46				
1 day 1 dose	1,424	5	0.3%	4.2	0.8–21.7	0.09
1 day 2 doses	2,680	18	0.6%	6.8	1.6–29.3	0.01
1 day 3 doses	5,522	15	0.2%	2.7	0.6–12.0	0.19
1 day 4 doses	2,194	2	0.2%	1		
2 days	1,928	6	0.2%	2.6	0.5–12.9	0.25
3 days	717	0	0%	–	–	–

[a] Adjusted in the Cox model for gender, age, cement- and prosthesis-brand, type of operating room and duration of operation. The number of THAs included in the Cox analyses was reduced to 14,213 because of cases with missing values in covariates.

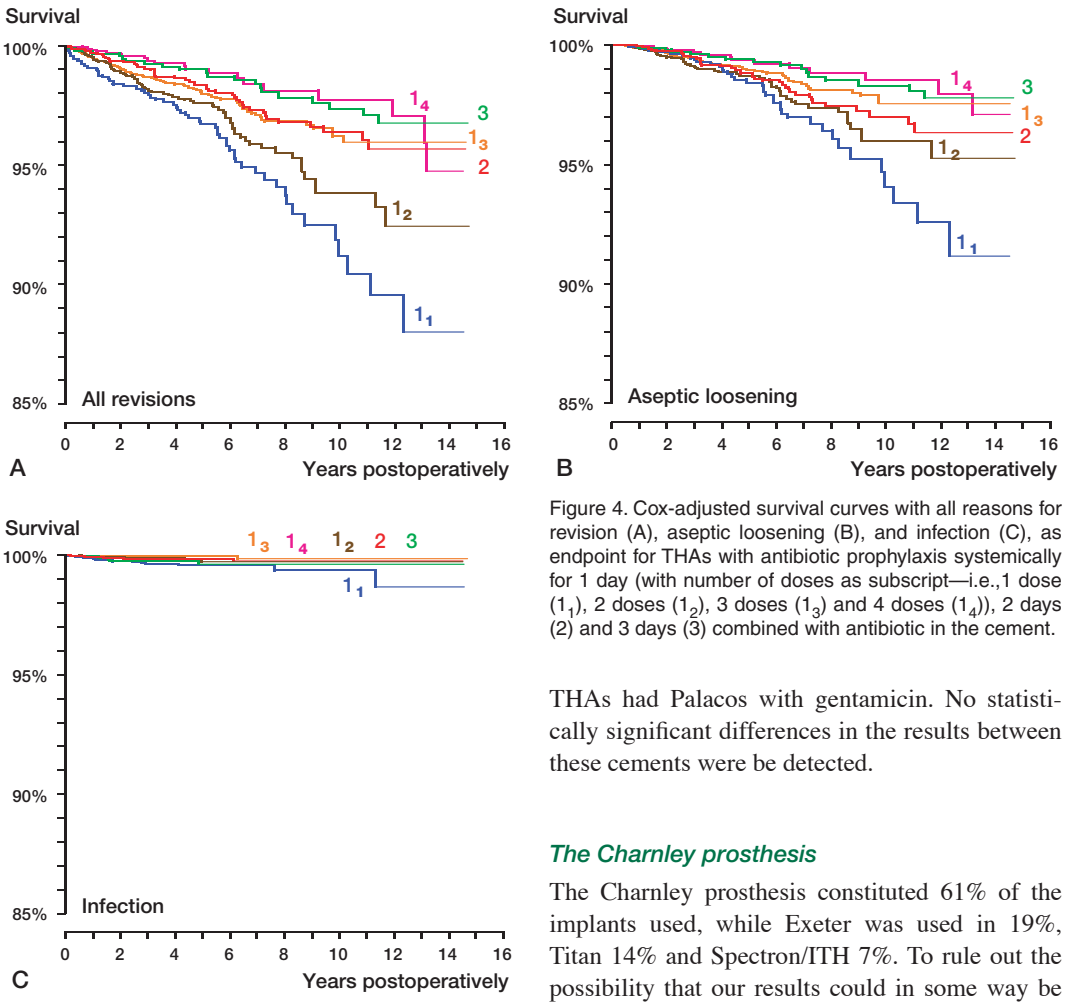


Figure 4. Cox-adjusted survival curves with all reasons for revision (A), aseptic loosening (B), and infection (C), as endpoint for THAs with antibiotic prophylaxis systemically for 1 day (with number of doses as subscript—i.e.,1 dose (1_1), 2 doses (1_2), 3 doses (1_3) and 4 doses (1_4)), 2 days (2) and 3 days (3) combined with antibiotic in the cement.

some changes in the type of antibiotic from 1987 to 2001. From 1987 to 1996 penicillin constituted 20%, but thereafter less than 8%. The systemic antibiotic was given in 84% of THAs in 1987, but after 1992, in more than 99.6%.

The number of doses on the day of surgery and the amount given in each dose of the two antibiotics were very similar—e.g., 2 grams were used as the first dose in 80% in the cephalosporin group and 86% in the penicillin group. No statistically significant differences in revision rate were found between the two types of antibiotic.

Type of antibŠtic in bone cement

In 72% of the THAs, antibiotic-loaded cement was used (n = 15,930). Of these, 1,302 were Simplex with colistin and erythromycin, the remaining THAs had Palacos with gentamicin. No statistically significant differences in the results between these cements were be detected.

The Charnley prosthesis

The Charnley prosthesis constituted 61% of the implants used, while Exeter was used in 19%, Titan 14% and Spectron/ITH 7%. To rule out the possibility that our results could in some way be associated with the type of prosthesis, the survival analyses were also done separately for the Charnley prosthesis. All findings for prophylaxis systemically and in cement, and for the duration of the systemic prophylaxis, were virtually the same as with the four implants together.

Operating room

We also studied the effects of the operating room ("greenhouse", laminar air ventilation, ordinary ventilation), but detected no significant differences. In the analyses of antibiotic prophylaxis systemically/cement and all reasons for revisions as endpoint, the relative revision risk with operations performed in greenhouse as reference, was 1.4 (with confidence interval 0.8–2.3) (p = 0.2) for operations performed in operating rooms with laminar airflow, and 1.4 (CI 0.8–2.2) (p = 0.2) with

ordinary airflow flow. In the analyses of various durations of the systemic antibiotic prophylaxis, the relative revision risk was 1.8 (CI 0.8–4.0) (p = 0.1) for laminar airflow and 1.9 (CI 0.9–4.1) (p = 0.1) for ordinary ventilation.

Discussion

The best results of primary THAs were obtained among patients who received prophylactics antibiotic both in cement and systemically, and if the systemic antibiotic was given four times on the day of surgery.

The endpoint in our analyses is removal or exchange of any of the parts of the prosthesis. If, therefore, debridement and antibiotics with the prosthesis in situ cured an early postoperative infection, the operation would not be reported to our register. Similarly, an infection treated by lifelong suppression with an antibiotic will not be reported. There is, however, no reason to believe that this should affect the relative incidence of infection among the various subgroups studied.

In a previous paper from the Norwegian Arthroplasty Register, we reported similar good results with a combined antibiotic prophylaxis regime (Espehaug et al. 1997). The present report includes, however, twice the number of THAs and the observation period has been increased by 6 years. Although antibiotic-loaded cement is widely used, an article by van de Belt et al. (2001) concluded, "the prophylactic use of antibiotic-loaded bone cements for primary fixation purposes remains to be determined". Our findings indicate that antibiotics should be given in cement as well as systemically. This is also the conclusion in a recently published, randomized study with 340 primary total knee arthroplasties, where a reduced rate of deep infection was found when antibiotic-impregnated cement was combined with systemic antibiotic prophylaxis (Chiu et al. 2002). Good results with the combination of systemic antibiotics (isoxazolyl-penicillin or cefalosporin) and Palacos cement with gentamicin were also reported by the Swedish Hip Arthroplasty Register (Malchau and Herberts 1998).

We found the best results when the systemic antibiotic was given four times on the day of surgery, as compared to fewer times, whether the endpoints in the analyses were all revisions, aseptic loosening or infections. To our knowledge, this has not been previously shown, although Wymenga et al. (1992) found a trend towards fewer infections that was not statistically significant in primary THAs with three doses of cefuroxime, as compared to one dose.

In a comparison of 4 doses of systemic antibiotic prophylaxis only on the day of surgery, no improvement in results was detected if the prophylaxis was given for 1 or 2 more days. On the basis of these findings, and from a financial, microbiological and practical clinical points of view, it seems best to give the antibiotic prophylaxis only on the day of surgery. This conclusion also accords with the prevailing opinion in the literature today (Lidgren 2001, Walenkamp 2001).

It is interesting and somewhat surprising to find that the effect of the antibiotic prophylaxis seems to persist 10-14 years postoperatively, not only for revisions because of infection, but also for aseptic loosening. The reduced infection rate with antibiotic prophylaxis seems to be due to preventing the bacteria from forming a biofilm on the implant (van de Belt et al. 2001, Walenkamp 2001). The explanation of the reduction in revisions due to aseptic loosening, however, is not apparent. A plausible explanation could be that the antibiotic reduces the number of low virulent infections and such infections are peroperatively easily assessed incorrectly by the surgeon and reported as aseptic loosenings. In accordance with this view, modern PCR technique identified bacterial DNA in 22 of 39 revisions for "aseptic" loosening and in 6 of 31 primary THRs, although none of the cultures of specimens from these operations showed bacterial growth (Clarke et al. 2001). Even clean operations, such as THR, are not really clean and bacterial contamination of the surgical field seems to be unavoidable.

At present, aseptic loosening is expected to start with osteolysis at the implant-bone interface. This loosening is explained by accelerated osteoclastic bone resorption due to the action of cytokines produced in response to phagocytosis of implant-derived particles (Spyniewska et al. 2002, Wang et al. 2002). In vivo experiments have shown that bacterial endotoxin adheres to wear particles. The removal of these endotoxins reduces the particle-induced osteoclastic bone resorption by 50–70% (Bi et al. 2001). By destroying the bacteria, the

antibiotic prevents the production of endotoxin, and could therefore also reduce the risk of aseptic loosening of the prosthesis.

Another possible explanation of the reduced aseptic loosening of THAs by antibiotics was presented by Santavirta et al. (1996) who reported a direct inhibitory effect of cephalothin on the enzyme, matrix metaloproteinase, around loose hip prostheses and indicated that cephalotin could, by a nonantimicrobial mechanism, reduce the tissue destruction associated with the loosening of THA implants.

Our observations from the Norwegian Arthroplasty Register consistently show persistent improved results for primary THAs when antibiotic prophylaxis was used both systemically and in bone cement, and when systemic antibiotic prophylaxis was given 4 times on the day of surgery. Ideally, the results of the present register-based study should be confirmed in a randomized double-blind clinical trial. Until such a trial is done, however, this large-scale observational evidence should guide clinical practice.

No competing interests declared.

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