ANTIBIOTIC PROPHYLAXIS IN TOTAL HIP ARTHROPLASTY

REVIEW OF 10 905 PRIMARY CEMENTED TOTAL HIP REPLACEMENTS REPORTED TO THE NORWEGIAN ARTHROPLASTY REGISTER, 1987 TO 1995

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We have assessed the effect of different regimes of antibiotic prophylaxis on the survival of total hip implants, comparing antibiotics administered both systemically and in the bone cement, systemically only, in the bone cement only and with no antibiotics given.

We studied 10 905 primary cemented total hip replacements, performed for osteoarthritis of the hip and reported to the Norwegian arthroplasty register between 1987 and 1995. Cox-estimated failure-rate ratios (FRR) are presented with adjustment for gender, age, the brand of cement, the prosthesis, the type of operating theatre and the operating time.

For revisions performed for infection (39 operations), the lowest rate of revision was found among patients receiving antibiotic-containing cement plus systemic antibiotics ($n = 5804$). The revision rate for the 4586 patients receiving systemic antibiotics only was 4.3 times greater (95% CI 1.7 to 11.0, $p = 0.001$); in 239 with antibiotics in the bone cement only it was 6.3 times greater (CI 1.6 to 25.0, $p = 0.003$); and in the 276 who did not receive antibiotics it was by 11.5 times greater (CI 2.1 to 63.0, $p = 0.002$). Adjustment for the total amount of systemic antibiotic administered did not change the results. We also observed an increased revision rate for aseptic loosening (109 operations) comparing the systemic-only (FRR = 1.8, CI 1.1 to 2.9,

$p = 0.01$) and the cement-only regimes (FRR = 2.6, CI 1.2 to 5.9, $p = 0.02$) with the combined dosage.

Our findings show that systemic antibiotics combined with antibiotic-containing bone cement led to fewer revisions than the other methods.

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There is a wide range of options available during total hip replacement (THR).¹ Previous studies have shown that the use of low- and high-viscosity cement, of cemented or cementless prostheses, and the design of the prosthesis may all substantially influence the survival of the implant.²⁻⁸

The use of prophylactic systemic antibiotics is well established both in general surgery and joint replacement,⁹⁻¹² but there are large variations in the dosage and duration of use and in the inclusion of antibiotics in the bone cement. One large, randomised trial compared the effect of antibiotics given either systemically or in the cement. No statistically significant difference was found, but the study suggested that combined use may be preferable to antibiotics administered either only in cement or only systemically.¹³ Further investigations of this issue have been called for.¹⁴

Our study compares the effect on implant survival of the different regimes of antibiotic prophylaxis used for hip arthroplasty in Norway, particularly with regard to the possible benefit of adding antibiotics to bone cement, using information from the Norwegian arthroplasty register which records all THRs carried out in the country since 1987.

PATIENTS AND METHODS

Since September 1987, information on almost all primary THRs and all revisions performed at 68 hospitals in Norway has been recorded in the Norwegian arthroplasty register. After each operation, a standard form is completed by the surgeon and sent to the register. An English translation of the form has been given in a previous report.¹⁵ Revisions, defined as a surgical removal or exchange of a part of or the whole implant, were linked to the data already

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collected on the primary operations by using the unique number assigned to each inhabitant of Norway.

For primary THRs performed from 1987 to 1995, we compared the time until revision for four groups as follows:

- 1) patients receiving antibiotic prophylaxis both systemically and locally in the bone cement (combined regime);
- 2) those receiving antibiotics systemically only (systemic-only regime);
- 3) those receiving antibiotics in the cement only (cement-only regime); and
- 4) those receiving no antibiotic prophylaxis (no antibiotic regime).

A total of 38 835 primary operations had been performed during the study period. To investigate the effect of the use of antibiotics in a relatively homogeneous population, we included only patients operated on for primary osteoarthritis of the hip who had not had a previous operation ($n = 25\,737$). Cement had been used in both components in 86% of these operations. Previous reports based on information from the Norwegian arthroplasty register have shown that particular brands of cement and types of prosthesis have been rarely used or have given poor results.^{6,8} We therefore studied only those THRs in which Charnley (DePuy, Leeds, UK), Exeter (Howmedica International, Herouville, France), Titan (Landos, Chaumont, France) or Spectron/ITH (Spectron acetabulum, ITH femur; Richards, Memphis, Tennessee) components were cemented with high-viscosity Palacos (Schering-Plough International Inc, Kenilworth, New Jersey) or Simplex (Howmedica International, London, UK) cement. Among the 11 998 THRs performed with systemic antibiotic prophylaxis we included only those in which the most commonly used types of systemic antibiotic, namely cephalothin ($n = 6168$), cefuroxime ($n = 1969$), dicloxacillin ($n = 1468$) and cloxacillin ($n = 785$) had been used.

In the procedures performed with antibiotic-containing cement, gentamicin was used in combination with Palacos (0.5 g per 40.0 g polymethylmethacrylate; $n = 5898$) and

erythromycin/colistin with Simplex cement (0.5 g erythromycin and 0.24 g colistin per 40.0 g polymethylmethacrylate; $n = 145$).

For revisions the surgeon could record one or more reasons for failure. When seen in combination with other causes, infection was considered as the primary cause of revision. Aseptic loosening was otherwise acknowledged as the principal cause of revision.

Statistical analysis. In this survey the endpoints for survival were defined as revision for deep infection and aseptic loosening, respectively. Further analyses also used revision for any cause as the endpoint. The Central Bureau of Statistics, Oslo, Norway, provided information on deaths until February 1, 1996. The survival times of THRs in patients who had died without revision were censored. The probability of survival at five years was estimated for the different antibiotic regimes using the product-limit method.¹⁶ Multivariate Cox regression analysis¹⁷ provided effect estimates for the regimes with adjustment for the possible influence of gender, age (<65, 65 to 74, >74 years), cement brand (Palacos, Simplex), prosthesis type (Charnley, Exeter, Titan, Spectron/ITH), operating theatre (an enclosed area with laminar air ventilation and use of body-exhaust systems ('greenhouse')), laminar air ventilation, ordinary ventilation and the duration of the operation (<61 min, 61 to 120 min, >120 min). Cox analyses were also performed with additional adjustment for the total amount of systemic antibiotic prophylaxis given (≤ 1.5 g, 1.6 to 2.0 g, 2.1 to 4.0 g, 4.1 to 6.0 g, >6.0 g). Tests of the proportional hazards assumption were made for all risk factors included in the Cox regression models.¹⁸ To investigate further whether the effect of the use of antibiotics varied with time since the primary operation, Cox analyses were performed with time-dependent risk factors included. In the Cox models, we used score tests to calculate p values, and risk factors with more than two levels were represented with indicator variables to avoid assumptions of linear relationships. Estimates from Cox analyses were

Table I. Characteristics (percentage) of four antibiotic prophylaxis regimes used in cemented primary total hip replacements in Norway from 1987 to 1995

Antibiotic prophylaxis regime	Number	Males	Age (yr)		Prosthesis brand*				Cement brand		Operating theatre†		Median op time (min) (95% CI)
			<65	65 to 74	C	E	T	S	Palacos	Simplex	G	L	
Combined	5804	31	15	49	67	3.6	21	8.4	98	2.5	2.7	32	95 (93.7 to 95.3)
Systemic only	4586	30	17	52	38	44	9.2	9.1	40	60	2.1	47	90 (89.4 to 90.6)
Cement only	239	24	14	50	74	0.8	24	1.3	100	0.0	6.4	40	90 (85.9 to 94.1)
No antibiotic	276	30	17	53	45	4.0	0.7	51	43	57	38	5.8	110 (107.6 to 112.4)
Total	10905	31	16	50	55	20	16	9.6	72	28	3.4	38	90 (89.5 to 90.5)

* C = Charnley; E = Exeter; T = Titan; S = Spectron/ITH

† G = greenhouse; L = laminar air flow

Table II. Characteristics (percentage) of systemic antibiotic prophylaxis regimes used in cemented primary total hip replacements in Norway from 1987 to 1995

Antibiotic prophylaxis regime	Number	Systemic antibiotic		Duration of administration (days)				Daily amount of systemic antibiotic (g)‡		
		Penicillins*	Cephalosporins†	1	2	3	>3	≤2.0	2.0 to 4.0	>4.0
Combined	5804	33	67	70	19	9.6	1.6	13	41	47
Systemic only	4586	7.7	92	90	5.7	2.5	1.5	36	46	18
Total	10390	22	78	79	13	6.5	1.6	23	43	34

* cloxacillin (n = 785) and dicloxacillin (n = 1468)

† cephalothin (n = 6168) and cefuroxime (n = 1969)

‡ calculated as total amount/days of duration

Fig. 1

Cox regression-adjusted survival curves of THRs performed in Norway from 1987 to 1995. The probabilities of survival were calculated with revisions due to infection as the endpoint for patients receiving different antibiotic regimes for prophylaxis. The p value refers to a test of homogeneity showing a statistically significant difference in survival among the regimes.

Fig. 2

Cox regression-adjusted survival curves of THRs performed in Norway from 1987 to 1995. The probabilities of survival were calculated with revisions due to any cause as the endpoint for patients receiving different antibiotic regimes for prophylaxis. The p value refers to a test of homogeneity showing a statistically significant difference in survival among the regimes.

used to construct adjusted survival curves at mean values of the risk factors.

The packages S-PLUS,¹⁹ SPSS²⁰ and BMDP²¹ were used for statistical analyses.

RESULTS

Systemic antibiotics were used in 95% of the operations, 44% of which were performed with systemic antibiotics alone and 56% with a combination of antibiotics given systemically and in the bone cement (Table I). Procedures with antibiotics only in the cement accounted for 2.2% of the operations and no antibiotics were used in 2.5%. The Charnley prosthesis and Palacos cement were more common among patients receiving antibiotic-containing cement

than in those having antibiotics systemically only or not receiving any antibiotics (Table I). Of procedures in which no antibiotics had been given 38% were performed in a 'greenhouse' compared with 2.5% with the other antibiotic regimes (Table I). Cephalosporins were used in 78% of operations performed with systemic antibiotics and 79% received such treatment for one day only (Table II).

Cox-adjusted survival curves for the combined, the systemic only, the cement only and the no antibiotic regimes are given in Figures 1 and 2 with revisions due to infection and revisions due to any cause as the endpoints, respectively. The figures and Table III show that the lowest probability of revision was found among patients receiving systemic antibiotic prophylaxis in combination with antibiotic-containing bone cement. With revisions

Table III. Kaplan-Meier estimated five-year failure probabilities and Cox regression failure-rate ratios (FRR) estimated with infection, aseptic loosening and any revision as endpoints for cemented primary total hip replacements in Norway 1987 to 1995

Antibiotic prophylaxis regime	Number	Number revised	Kaplan-Meier		Cox estimated FRR				
			5-yr failure prob %	95% CI	Unadjusted		Adjusted*		
					FRR	p value	FRR	95% CI	p value
Infection as endpoint									
Combined	5804	8	0.2	(0.1 to 0.4)	1		1		
Systemic only	4586	25	0.8	(0.5 to 1.1)	3.8	0.0004	4.3	(1.7 to 11)	0.001
Cement only	239	3	0.9	(0.0 to 2.0)	6.4	0.002	6.3	(1.6 to 25)	0.003
No antibiotic	276	3	1.2	(0.0 to 2.5)	5.4	0.005	11.5	(2.1 to 63)	0.002
Aseptic loosening as endpoint									
Combined	5804	44	1.0	(0.7 to 1.4)	1		1		
Systemic only	4586	54	1.9	(1.3 to 2.4)	1.5	0.05	1.8	(1.1 to 2.9)	0.01
Cement only	239	7	2.1	(0.0 to 4.1)	2.4	0.03	2.6	(1.2 to 5.9)	0.02
No antibiotic	276	4	1.7	(0.0 to 3.4)	1.1	0.83	2.1	(0.6 to 7.3)	0.25
Any revision as endpoint									
Combined	5804	70	1.6	(1.2 to 2.0)	1		1		
Systemic only	4586	94	3.1	(2.4 to 3.8)	1.6	0.002	1.8	(1.3 to 2.7)	0.002
Cement only	239	10	2.9	(0.5 to 5.2)	2.2	0.01	2.5	(1.3 to 4.9)	0.01
No antibiotic	276	7	2.9	(0.7 to 4.9)	1.3	0.49	2.7	(1.0 to 7.1)	0.04

* the model included antibiotic regimen, gender, age, cement- and prosthesis-brand, type of operating theatre and operating time. The number of operations included in the analysis was reduced to 10 611 due to missing values

performed because of infection as the endpoint (39 cases), the adjusted Cox regression analysis showed that, compared with the combined regime, the revision rate was 4.3 (95% CI 1.7 to 11.0, $p = 0.001$) times higher with the systemic-only regime, 6.3 (95% CI 1.6 to 25.0, $p = 0.003$) times higher with the cement-only regime and 11.5 (95% CI 2.1 to 63.0, $p = 0.002$) times higher when no antibiotics were used (Table III). We also observed an increased rate of revision for aseptic loosening (109 cases) when comparing the systemic-only failure rate (failure rate ratio (FRR) = 1.8, 95% CI 1.1 to 2.9, $p = 0.01$) and the cement-only failure rate (FRR = 2.6, 95% CI 1.2 to 5.9, $p = 0.02$) with the combined failure rate (Table III). Similar results were found with all revisions (181 cases) as the endpoint (Table III).

With revisions due to infection as the endpoint, the effect of the combined regime compared with the systemic-only regime was greatest during the first two years after operation (FRR = 6.0, $p = 0.001$) and less during the next three years (FRR = 3.6, $p = 0.04$), whereas the difference was upheld throughout the first five years with any revision as the endpoint.

A higher daily amount of systemic antibiotics and a longer period of administration were found in the combined regime (Table II). Further adjustment for the total amount of antibiotics administered systemically, however, did not change the results. With revision due to infection as the endpoint and cutpoints set at 1.5 g and 4.0 g, the lowest revision rate was found among patients receiving a combined prophylaxis regimen irrespective of the total amount of systemic antibiotics administered.

When analyses were performed on operations in which systemic antibiotics were given for one day only, the results were similar to those reported for all durations. The same results were also found when restricting the material to

operations performed with a Charnley prosthesis and Palacos cement with or without gentamicin.

The effect of the use of antibiotics was studied separately for operations undertaken in the three different types of operating theatre. The results in each type were similar to those estimated for the total material, and regardless of the antibiotic regime the rates for revision due to infection were not lower in operations performed in the special enclosures compared with those in ordinary theatres.

DISCUSSION

The lowest probability of revision in THRs was found among patients receiving antibiotic-containing cement in combination with systemic antibiotics. Several large studies have reported lower rates of infection for THRs undertaken with systemic antibiotic prophylaxis as compared with a placebo group.²²⁻²⁴ Other investigations have indicated that adding antibiotics to the cement gives better results than using plain cement only.²⁵⁻²⁷ Two randomised trials have compared the effect of antibiotics in the bone cement with antibiotics given systemically,^{13,28-30} but the results were inconclusive, with no difference reported in the smallest study³⁰ and an improvement in the rate of deep infection in the hips with antibiotic-containing cement which was not statistically significant.¹³ In both studies, superficial infections were more common among operations performed with antibiotic-containing cement and a concurrent use of systemic administration was suggested.¹³

We have shown that with revisions performed due to infection as an endpoint, the benefit of systemic antibiotics administered in combination with antibiotic-containing bone cement was highest during the first and the second years after surgery. With any revision as the endpoint the effect was upheld throughout the first five years of follow-

up. Beyond this the numbers were too small to give estimates with sufficient precision. Other studies have also reported that antibiotic prophylaxis prevents both early infections and late hip infections.^{24,31}

The strongest estimated relative difference in rates of failure among the antibiotic prophylaxis regimes was observed with revisions due to infection as the endpoint. A similar pattern of results was seen with aseptic loosening as the endpoint. It had been shown previously that there was less aseptic loosening in operations performed with antibiotic-containing bone cement than in those with plain cement.⁶ Cephalothin has been shown to have an inhibitory effect on matrix metalloproteinase³² and this may reduce the risk of aseptic loosening. A similar effect was not shown for gentamicin,³² however, which was the preferred antibiotic used in bone cement in our study. A more likely explanation is that antibiotic prophylaxis prevents low-grade infection which is unrecognised and possibly misclassified as aseptic loosening.

Concern has been expressed as to whether added antibiotics may lessen the strength of the cement.²⁵ We did not, however, find higher rates of failure due to aseptic loosening among arthroplasties with antibiotic-containing cement compared with those with plain cement, which is in accordance with other clinical studies.^{13,30,33} Experimental studies with mechanical tests of tensile strength have reported inferior results for antibiotic-containing cements,²⁵ but others have shown only negligible differences.³⁴

Palacos cement with gentamicin was used in 98% of all operations performed with antibiotics in the cement. Generalisation of our results to other types of antibiotic and cement is inappropriate,¹⁴ but restricting the analyses to operations performed with Palacos cement, which comprised 72% of the total material, yielded results very similar to those reported.

We found similar patterns of results for operations performed in ordinary operating theatres compared with those designed to lower airborne contamination. Some studies have reported similar results,^{35,36} but others describe an effect of systemic antibiotics in ordinary operating theatres only.²³ A further reduction in rates of infection has been observed when antibiotics are used in combination with ultraclean air and body-exhaust suits.^{35,36} There is as yet no convincing evidence for the beneficial effect of ultraclean-air technology.³⁷ Irrespective of the antibiotic regime used, we did not find lower revision rates due to infection for operations performed in special operating theatres. It should be noted that relatively few operations were performed in an enclosed operating area with laminar airflow and surgeons using body-exhaust systems ('greenhouse').

While patients operated at 14 hospitals received no antibiotic prophylaxis, 92% of such operations were performed at two centres only. At these two hospitals, the combined regime was seldom used. Thus, comparisons between the combined and the no-antibiotic regimes were

based on operations from separate hospitals which possibly confounded the observed differences. Longer operating times were observed for the no-antibiotic regime, but operating times at the two hospitals were equally long for all regimes. Survival analysis within these two hospitals gave the same relation between the systemic-only regimen and the no-antibiotic regimen as was seen in the overall study. Results from multivariate analysis, however, showing the poorest survival among patients not receiving antibiotics, should be interpreted with these concerns in mind. Because this is an observational study, however, suitable blinded, randomised clinical trials are still needed to substantiate our findings further.

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