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PROPHYLACTIC ANTIBIOTICS AGAINST EARLY AND LATE DEEP INFECTIONS AFTER TOTAL HIP REPLACEMENTS

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A review with a longer observation period is performed of a previously published double-blind investigation of the prophylactic value of cloxacillin against late infections after total hip replacements. In addition, a retrospective patient material is examined. The total material consisted of 1065 total hips. 15.4 per cent deep, late infections were found in the group without prophylaxis and 2.0 per cent in the one with prophylaxis. The frequency of haematogenous deep infection was estimated to be less than 1 per cent.

Key words: infection; prophylactic antibiotics; total hip arthroplasty

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Cumulative experience during recent years has shown that the prophylactic use of antibiotics can substantially reduce the frequency of early postoperative infections after total hip replacements (THR) (Ericson et al. 1973, Fogelberg et al. 1970, Pavel et al. 1974). It is, however, still debatable whether such prophylaxis has any effect on the frequency of so-called late infections. Many orthopaedic surgeons are inclined to doubt whether such precautions as performance of the operation in a sterile box or the peroperative and early postoperative use of antibiotics really can prevent infections appearing months or even years after the operation. Recent investigations, however, have produced evidence strongly suggesting such a preventive effect (Ericson et al. 1973). But corroboration of such an effect requires extensive investigations of several series followed up for a long time, especially since some of the late infections may be haematogenous and not due to implantation of bacteria during the operation.

This paper concerns a) a review of a double-blind investigation earlier published by Ericson et al. (1973), b) estimation of the frequency of deep infection in a 7-year material of THR performed with and without prophylactic antibiotics.

Previous investigation

In 1973, Ericson et al. reported a double-blind investigation of the prophylactic value of cloxacillin used in association with major operations of the hip. The results as regards the THR can be found in Table 1. The result of a retrospective study was also reported. The investigation showed that cloxacillin had a very good preventive effect on early postoperative infections. However, the follow-

Table 1. Incidence of deep, early and late infections in the double-blind investigation.

	Total	Cloxacillin		Placebo		
		Not inf.	Inf.	Not inf.	Inf.	
1–2½ years postoperatively	118	60	0	51	7	($P < 0.05$) *
5–6½ years postoperatively	118	58	2	44	14	($P < 0.01$) *

* chi-square with Yates correction.

up was not long enough to warrant any conclusion as to the effect on the frequency of late, deep infections.

MATERIAL AND METHODS

Only deep infections, both early and late, were considered. Superficial infections which healed without developing into deep infections were not included.

The material consisted of all 1130 hips (476 in men and 654 in women) operated upon with THR between 1968 and 1974 in the Department of Orthopaedic Surgery, University Hospital, Lund (510 hips) and the Department of Orthopaedic Surgery, Malmö General Hospital, University of Lund, Malmö, Sweden (620 hips). The mean age at the time of operation was 64.6 ± 9.3 years (average ± 1 SD). The youngest patient was 19 years and the oldest 87. The patients were reviewed during the first 3 months of 1977, which means between 2 and 9 years after the operation. Sixty-five patients were not included either because it was not possible to ascertain whether prophylaxis had been given or because the patients had not appeared at follow-up or review. Patients who had died within 6 months of the operation without having had any known infection were not included in the investigation. All operations were performed in conventional, modern operating rooms.

The investigation was divided into:

a) a review of the 118 THR in the previously mentioned double-blind investigation of Ericson et al. (1973) in which the patients had been examined after a postoperative interval of 1 to 2½ years. In the present review the reexamination was performed 5 to 6½ years postoperatively. In the investigation by Ericson et al. both superficial and deep infections were considered. In the present study, only the deep ones were included.

b) a retrospective investigation of the 947 other THR; 635 had received prophylaxis and 312 had not. 761 were operated according to Charnley, 183 according to Brunswik and three according to McKee-Farrar.

Prophylaxis

The antibiotic used was cloxacillin (Ekvacillin®, Astra Pharmaceutical, Sweden). The patient was given 1 g intramuscularly 1 hour before the operation and thereafter three times at 6-hour intervals. This was followed by two tablets each containing 0.5 g which were taken in the fasting state with a glass of water. The oral dose was given every 6 hours until the fourteenth day inclusive after the operation. In addition, the patient received oral probenecid in a dose of two tablets, each 0.5 g, twice a day during the same period as the cloxacillin. In the double-blind investigation the placebo was given in the same way as the active substance. The patients receiving placebo instead of cloxacillin were also given probenecid in the same dose. Patients who found it difficult to take the tablets by mouth were given intramuscular injections. The few patients known to be hypersensitive to penicillin or who developed such hypersensitivity during treatment were given lincomycin or cephalosporin, in corresponding doses, instead of cloxacillin. Since January 1974, the prophylaxis at the Orthopaedic Department in Lund has been shortened to 1 week after the operation.

Review

All patients with any symptoms or roentgen changes at the obligatory final follow-up 6 months to 1 year after the operation were reexamined at regular intervals until the cause of the symptoms could be explained or the symptoms had disappeared. It was not difficult to trace the patients with infection because patients operated upon at either of the two departments belonged to the receiving areas of the departments. Therefore, according to the Swedish insurance regulations they could not seek advice at any other hospital before they had first been examined at their local hospital where they were registered and, if necessary, referred

to another hospital for further examination or treatment. The few patients residing outside the receiving area of the hospital were followed up especially for any infection.

Definition of deep infection

Only patients with positive aerobic culture from fistulae or abscesses or with positive aerobic or anaerobic culture from tissue specimens adjacent to the prosthesis or the surface of the cement are included. Furthermore the patients had pain on weight-bearing or during rest, roentgen signs of infection according to Bergström et al. (1974) (radiolucent zone, scalloping and/or periosteal reaction), and an ESR above 35 mm/1 hour without antibiotic therapy.

RESULTS

Review of the patients in the double-blind investigation

As seen in Table 1, two deep, late infections supervened in the cloxacillin group and seven in the placebo group during the 4 years that had elapsed since the preliminary study. The difference between the cloxacillin and the placebo groups is significant. The high frequency of infections in the placebo group may be explained by an epidemic accumulation of infections in Lund during the first half of 1971. The cause of the epidemic is not known.

Retrospective investigation

The distribution of the infected and non-infected cases found in both the double-blind investigation and the retrospective investigation is given in Table 2. The frequency of infection was much lower in the group that had received prophylaxis. The difference is highly significant. The interval between the operation and the review was between 2 and 8½ years in the retrospective study. No serious adverse effects from the cloxacillin were seen during the investigation.

Analysis of the infections that occurred despite prophylaxis

The findings are shown in Table 3. Laboratory studies (ESR, CRP, serum electrophoresis, white blood cell count, differential count and radiographic changes around the prosthesis) proved of little value in tracing the origin of the infection and are therefore not considered here.

Two of the 14 patients belonging to the prophylactic group in Table 2 were excluded from this analysis as it was not quite certain that they had received an adequate prophylaxis.

In Table 3 it can be seen that patients nos. 1–4 had early infections appearing already during the healing of the operation wound. Patients nos. 5–7 were never symptom-free after the operation and had slight pains when walking all the time, but the diagnosis infection was not

Table 2. Distribution of infected and noninfected patients in the two groups with and without prophylaxis.

	With prophylaxis		Without prophylaxis		Total
	Not inf.	Inf.	Not inf.	Inf.	
Prospective study	58	2	44	14	118
Retrospective study	623	12	267	45	947
Total	681	14	311	59	1065
	(2.0 %)		(15.4 %)		

$P < 0.001$ (chi-square with Yates correction)

Table 3. Analysis of infected patients who had received prophylaxis

Pat.	Onset of symptoms	Time of diagnosis of infection	Bacteria	Sensitive to cloxacillin	Comments
1	Immediately postop.	Immediate deep infection after op.	Proteus and enterococci	No	Immediate postop. inf. Culture of biopsy specimen.
2	Immediately postop.	Immediate deep infection after op.	Proteus and Staph. albus	No	Immediate postop. inf. Both proteus and Staph. albus in each of six specimens taken from the tissue adjacent to prosthesis during extraction.
3	Immediately postop.	Immediate deep infection after op.	E. coli	No	Immediate postop. inf. Prosthesis extracted. Repeated cultures from abscess gave abundant E. coli.
4	Immediately postop.	Immediate postop. infection	Anaerobic peptococci and anaerobic streptococci	Yes	The inf. was in the beginning successfully treated with antibiotic, but prosthesis extracted after 2½ years. Culture of biopsy specimen at extraction.
5	Never quite symptom-free	After 2 years 4 months	Propioni-bact acnes	Yes	Culture of six biopsy specimens positive at extraction of prosthesis. Bilat. op., other side not infected. Reported clear difference between sides, became immediately symptom-free in the uninfected hip.
6	Never quite symptom-free	After 2 years 7 months	Propioni-bact acnes	Yes	Culture of biopsy specimen from joint capsule positive. Bilat. op. Other side not inf. Reported clear difference between sides, became immediately symptom-free in the uninfected hip.
7	Never quite symptom-free	After 3 years 4 months	Staph. aureus	Yes	Culture of biopsy specimen positive at extraction of prosthesis. Bilat. op. Reported clear difference between sides, became immediately symptom-free in the uninfected hip. ESR never normalized.
8	3 months postop.	After 6 months	Pseudomonas pyocyanea	No	July 1972 postop. inf. with pseudomonas pycocyanea after nailing of fracture of femoral neck. Jan. 1973 total arthroplasty, 6 months postop. fistula with pseudomonas pyocyanea. ESR never normalized.

Table 3. (continued).

Pat.	Onset of symptoms	Time of diagnosis of infection	Bacteria	Sensitive to cloxacillin	Comments
9	4 months postop.	After 4 months	Staph. aureus	Yes	Aspiration 4 months postop. and biopsy 6 months postop. gave Staph. aureus.
10	6 months postop.	After 6 months. However, antibiotics since second month postop. because of elevated ESR.	Anaerobic streptococci and Gram-neg. rods	Not tested for susceptibility	Aspiration from abscess 6 months after op. gave growth of anaerobic streptococci. Material obtained on extraction of prosthesis 1 year later gave Gram-negative rods. ESR never normalized.
11	1 year postop.	After 3 years and 2 months	Staph. albus	Yes	Culture of two biopsy specimens, both positive. Patient had previously had a Moore prosthesis, which was replaced by a total prosthesis.
12	2 years and 4 months postop.	After 3 years and 4 months	Propioni-bact acnes and Staph. albus	Yes	Culture gave growth of Propionibact. acnes and Staph. albus from biopsy specimen. Staph. albus alone at extraction of prosthesis.

made until after 2–3 years thus called "late". The patients nos. 8–10 probably belonged to the same group but here nothing abnormal had been entered in the patients record. Patients 11 and 12 were quite symptom-free during 1–1½ years postoperatively.

The long interval between the operation and the diagnosis of the infection can in some cases be explained by the difficulty at that time in making a firm diagnosis. In retrospect we can now say that in several of these cases the diagnosis could have been made much earlier.

Staphylococcus albus, Propionibacterium acnes, anaerobic peptococci and anaerobic streptococci were formerly considered "apathogenic" or contaminations but are now known to cause a considerable number of the infections around total arthroplasties (Kamme et al. 1974). In seven cases the infection was caused by microbes sensitive to cloxacillin in spite of the fact that this antibiotic was given prophylactically.

DISCUSSION

It has been clearly shown that antibiotic prophylaxis can substantially reduce the frequency of early infection after THR (Ericson et al. 1973, Fogelberg et al. 1970, Pavel et al. 1974). Yet it is still debatable whether such prophylaxis can prevent so-called late infections. That prophylaxis with cloxacillin has a good preventive effect against late infections around THR caused by the bacteriological flora existing at the two above-mentioned hospitals is however clear from the results of this investigation.

The very high frequencies of post-

operative infection reported from different parts of the world during the first years when total hip replacements were performed has now been considerably lowered through rigorous asepsis, e.g., clean-air operating room enclosures or through the prophylactic use of antibiotics. In this investigation the frequency has been lowered from 15.4 to 2.0 per cent with the use of antibiotics alone. This reduction must depend on a decrease in the number of infections caused by implantation of bacteria during the operation. Otherwise it is difficult to explain why this measure taken at the operation and during the following 1–2 weeks should have an effect for several years.

If this argument is correct, haematogenous infections are to be found among those infections which occur despite the use of prophylactic antibiotics (Table 3). Patients nos. 1–4 had early infections and were thus most probably infected during the operation. Patients nos. 5–7 were never pain-free which otherwise is the rule after a successful THR. In patients 7, 8 and 12 preoperatively low ESR was never restored after the operation which indicates that all these five patients (5, 6, 7, 8, 12) were infected during the operation (Reichelt & Brand 1975). An argument against this is that patients 5–7 were infected with microbes sensitive to cloxacillin.

In the remaining two patients (10, 11) there is nothing to specially indicate peroperative infection. The long symptom-free interval in patient 11 rather indicates that the infection was haematogenous. In the patient group without prophylaxis three patients (0.8 per cent) seemed to have haematogenous infections, two in association with sepsis caused by pneumococci. The third patient had bilateral THR and suffered sudden pains in both hips after 3 years without symptoms and Staphylococcus aureus was found in both hips.

This means that the frequency of haematogenous infections in this material was well under 1 per cent which is in agreement with the figures given by Charnley (1972), 0.30 per cent, and Artz et al. (1975), 0.25 per cent.

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