Cefuroxime-impregnated cement at primary total knee arthroplasty in diabetes mellitus

A PROSPECTIVE, RANDOMISED STUDY

F.-Y. Chiu, C.-F. J. Lin, C.-M. Chen, W.-H. Lo, T.-Y. Chaung

From the Taipei Veterans General Hospital and the National Yang-Ming University, Taipei, Taiwan, Republic of China

We have performed a prospective single-blinded randomised study to evaluate the role of antibiotic-impregnated cement in the prevention of deep infection at primary total knee arthroplasty (TKA) in patients with diabetes mellitus. We studied prospectively 78 arthroplasties performed for osteoarthritis in such patients. They were randomly separated into two groups. In group 1 (41 knees), cefuroxime-impregnated cement was used while in group 2 (37 knees) cefuroxime was not added to the cement. The preoperative, intraoperative and postoperative management was the same for both groups. The mean follow-up was 50 months (26 to 88).

There were no cases of deep infection in group 1, but five (13.5%) occurred in group 2 ($p = 0.021$). We conclude that cefuroxime-impregnated cement is effective in the prevention of deep infection at primary TKA in patients with diabetes mellitus.

J Bone Joint Surg [Br] 2001;83-B:691-5.

Received 19 September 2000; Accepted after revision 12 February 2001

A devastating and costly complication of total knee arthroplasty (TKA) is deep infection. Prophylactic antibiotics have been very effective in lowering the incidence of deep infection and recent studies have shown the incidence to be approximately 1% to 2% in general cases.¹⁻⁵ An increased incidence has been reported in patients with diabetes.⁶⁻¹⁶ There are many reports of the use of systemic antibiotics and antibiotic-impregnated cement^{5-11,17-24} in the preven-

tion of infection after arthroplasty, but none has focused on TKA in patients with diabetes. Our aim in this prospective study was to evaluate the effect of cefuroxime-impregnated cement on the prevention of deep infection after primary TKA in these patients.

Patients and Methods

Between 1993 and 1998, 78 consecutive primary TKAs in patients with diabetes were studied. The preoperative diagnosis in all was osteoarthritis. Patients with rheumatoid arthritis, psoriasis, previous knee surgery, any type of infection of the lower limb, osteomyelitis, malignant tumour or who were undergoing immunosuppressive treatment were excluded. All operations were performed in standard operating theatres without routine ultraviolet lights for disinfection, laminar flow or other special air handling. Isolation suits were not worn. All were undertaken using a midline incision and a medial parapatellar approach. In all cases the prosthesis used was the Duracon (Howmedica, Ireland) fixed in a hybrid form, the femoral components being uncemented, and the patellar and tibial components cemented (Simplex P, Howmedica). The same surgeon (F-YC) performed all the procedures.

The patients were separated into two groups according to the number on their medical records. In group 1, cefuroxime-impregnated cement¹³ (2 g of cefuroxime in 40 g of Simplex P cement) was used to fix the patellar and tibial components in patients with odd numbers. In group 2, Simplex P cement without cefuroxime was used to fix the patellar and tibial components in patients with even numbers. For patients undergoing bilateral TKA, cefuroxime-impregnated cement was used on one side (group 1) and not on the other (group 2).

All bilateral TKAs were undertaken in sequence under different anaesthetics. Six patients in group 1 and five in group 2 underwent bilateral TKA. Group 1 therefore comprised 41 knees (35 patients) and group 2, 37 knees (32 patients). The mean age of the patients in group 1 was 72 years (56 to 90). There were 21 left knees and 20 right knees. Group 2 comprised 32 patients with a mean age of 69 years (54 to 81). There were 21 left knees and 16 right knees. In group 1 three patients had insulin-dependent diabetes mellitus (IDDM) and the remainder non-insulin-

F.-Y. Chiu, MD, Attending Surgeon

C.-F. J. Lin, MD, PhD, Attending Surgeon

C.-M. Chen, MD, Chief

W.-H. Lo, MD, Head

Department of Orthopaedics and Traumatology

T.-Y. Chaung, MD, Attending Physician

Department of Physical Medicine and Rehabilitation

Taipei Veterans General Hospital, 201, Sec 2, Shih-pai Road, Taipei, Taiwan 11217, Republic of China.

Correspondence should be sent to Dr F.-Y. Chiu.

©2001 British Editorial Society of Bone and Joint Surgery
0301-620X/01/511737 \$2.00

dependent diabetes mellitus (NIDDM). In group 2 four patients had IDDM and the remainder NIDDM.

Each patient received intravenous cefazolin (500 mg) and gentamicin (80 mg) preoperatively, and cefazolin 500 mg six-hourly and gentamicin 80 mg 12-hourly for 36 hours postoperatively. Thereafter, cefazolin (500 mg six-hourly) was given orally for seven days. Drains (not vacuum) were retained for 36 hours. The patients were maintained on bedrest for the first day after operation, quadriceps exercises and continuous passive motion (CPM) being prescribed immediately. The latter was continued until the day of discharge. Weight-bearing on the operated knee was allowed immediately and crutches used as needed. The mean length of hospital stay for all patients was 8 days (5 to 14).

The patients were reviewed at three and eight weeks and at six months. Thereafter, follow-up was at six-monthly intervals. The mean follow-up period was 50 months (26 to 88). For each patient we recorded the duration and type of diabetes, its treatment, intraoperative tourniquet times, operating times, volume of blood transfusion, pre- and postoperative blood sugar levels, pre- and postoperative knee function, and the incidence of superficial and deep infection (Table I). Radiological evaluation was performed at each review. Functional evaluation began at the third postoperative visit using the Hospital for Special Surgery score (HSS score). Infections were classified according to the system described by McQueen et al,¹³ and confirmed by measurement of the ESR and level of C-reactive protein (CRP) and culture of joint fluid.

The data were analysed by SAS (SAS Institute, Cary,

North Carolina) and represented as the mean and standard deviation for continuous response variables or percentages for discrete variables. Fisher's exact test was used to compare differences between the two groups for each discrete variable, and Student's *t*-test for each continuous variable. Significance was set at $p \leq 0.05$ for each test.

Results

In both groups there was one case each of early superficial wound infection which was satisfactorily treated by wound debridement and antibiotics given intravenously for one week and orally for another week. There was no statistically significant difference between the incidence of superficial infection in the two groups ($p = 0.835$).

There were no cases of deep infection in group 1. In group 2, there were five deep infections (13.5%). All were in patients with unilateral TKA. Before developing deep infection, the wounds had healed at the time of discharge and had remained satisfactory at the first follow-up. The incidence of deep infection between the two groups was significantly different ($p = 0.021$). The relative probability of not developing a deep infection in group 2 was 0.865 times lower than in group 1, with a 95% confidence interval (CI) of 0.769 to 0.973. There were no statistically significant differences in the recorded data between the patients with deep infection and those without (Table II). Apart from two patients with deep infection which was managed by two-stage reimplantation, none had loosening of the implant by the final follow-up.

Table I. Details of both groups. Values are given as mean with SD in parentheses

	Group 1 (n = 41)	Group 2 (n = 37)	p value
Age in years	72 (7.6)	69 (5.9)	0.065*
Duration of diabetes mellitus in years	11 (8.5)	9.5 (7.3)	0.389*
Tourniquet time (minutes)	34 (5.4)	32 (4.7)	0.731*
Operation time (minutes)	60 (4.2)	63 (3.6)	0.625*
Volume of blood transfusion (units)	4 (1.1)	4 (1.3)	0.743*
Preoperative ac† blood sugar (mg/dl)	130 (28)	125 (25)	0.409*
Preoperative pc‡ blood sugar (mg/dl)	172 (40)	164 (32)	0.305*
Postoperative ac blood sugar (mg/dl)	140 (34)	135 (23)	0.447*
Postoperative pc blood sugar (mg/dl)	212 (48)	198 (29)	0.124*
Preoperative knee score (HSS)	51 (7.6)	48 (7.7)	0.108*
Postoperative knee score (HSS)	91 (2.8)	86 (9.2)	0.0093*
Male/female (%)	68/32	67/33	1.00§
Left/right (%)	51/49	56/44	0.638§
NIDDM/IDDM (%)	92/8	89/11	0.695§
Type of treatment (OHA¶/insulin/diet) (%)	87/8/5	81/15/4	0.587§
Superficial infection rate (%)	2.4	2.7	0.835§
Deep infection rate (%)	0.0	13.5	0.021§

* Student's *t*-test

† fasting blood sugar

‡ 2 hours post-meal blood sugar

§ Fisher's exact test

¶ treated with oral hypoglycaemic agent

Table II. Details of knees with and without deep infection. Values are given as mean with SD in parentheses

	Without infection (n = 73)	With infection (n = 5)	p value
Age in years	72 (7.0)	70 (2.8)	0.735*
Duration of diabetes mellitus in years	10 (7.8)	12 (8.7)	0.571*
Tourniquet time (minutes)	33 (4.5)	32 (5.7)	0.332*
Operation time (minutes)	62 (5.3)	59 (4.6)	0.524*
Volume of blood transfusion (units)	4 (1.7)	4 (1.1)	0.625*
Preoperative ac† blood sugar (mg/dl)	129 (27)	120 (25)	0.493*
Preoperative pc‡ blood sugar (mg/dl)	168 (37)	162 (23)	0.695*
Postoperative ac blood sugar (mg/dl)	137 (30)	148 (30)	0.435*
Postoperative pc blood sugar (mg/dl)	205 (42)	206 (30)	0.984*
Preoperative knee score (HSS)	49 (7.7)	52 (7.4)	0.382*
Male/female (%)	67/33	80/20	1.000§
Left/right (%)	52/48	80/20	0.359§
NIDDM/IDDM (%)	92/8	80/20	0.419§
Type of treatment (OHA¶/insulin/diet)	84/11/5	80/20/0	0.577§

* Student's *t*-test

† fasting blood sugar

‡ 2 hours post-meal blood sugar

§ Fisher's exact test

¶ treated with oral hypoglycaemic agent

A comparison of the postoperative HSS knee scores showed statistically significant differences (Table I) caused by the five cases of deep infection in group 2. With the exception of these, all knees were rated as excellent or good at the final follow-up.

In group 2, the first infection developed in a NIDDM 67-year-old man two months after surgery. Culture of joint fluid grew *Staphylococcus epidermidis* which was sensitive to cefazolin and gentamicin. The ESR was 100 mm/hr and the CRP 6.8 mg/dl. The second was in an IDDM 70-year-old man six months after surgery. Culture grew *Staphylococcus epidermidis* which was sensitive to oxacillin and gentamicin. The ESR was 120 mm/hr and CRP 15.0 mg/dl. The femoral component was loose. The third was in a NIDDM 72-year-old man approximately one month after surgery. Joint fluid culture grew *Staphylococcus aureus* which was sensitive to cefazolin and gentamicin. The ESR was 100 mm/hr and CRP 10.0 mg/dl. The fourth developed in a NIDDM 73-year-old man approximately three months after surgery. Culture grew *Staphylococcus aureus*, which was sensitive to oxacillin and gentamicin. The ESR was 110 mm/hr and CRP 9.0 mg/dl. The fifth was in a NIDDM 67-year-old man approximately six months after surgery. Culture of joint fluid grew methicillin-resistant *Staphylococcus aureus* which was only sensitive to teicoplanin and vancomycin. The ESR was 120 mm/hr and CRP 16.0 mg/dl. It was not possible to establish a source for the infection in any of these cases. A satisfactory outcome followed radical debridement, intravenous antibiotics (according to sensitivities) for four weeks and oral antibiotics for two months in the first, third and fourth patients. Two-stage

reimplantation was undertaken for the second and fifth cases. No subsequent late infection has developed.

Discussion

Deep infection is a debilitating complication of TKA and has been cited as the most common cause of failure of an implant.^{5,9,16-18} Many contributory factors have been implicated such as patient factors (local skin condition, systemic medical condition, and prior surgery, etc), operative factors (operating environment, operation course, operation suits, etc), surgical technique (implant selection, antibiotic usage, postoperative wound care, etc), and postoperative factors.¹⁻²⁹

The incidence of superficial wound infection (2.4% for group 1 and 2.7% for group 2) in our study is comparable to that of other reports.¹⁻²⁹ Wounds in patients with diabetes were no less likely to heal than those in non-DM patients.

The major focus of our study was to evaluate prospectively the effect of cefuroxime-impregnated cement on the prevention of deep infection in primary TKA in patients with diabetes. Our patients had poor control of blood sugar and the operating environment was not modern. In such conditions, the incidence of deep infection in group 2 who did not receive cefuroxime-impregnated cement was much higher than that reported by other workers,^{3,6,25,28,29} although these studies were undertaken in developed countries. Under the same conditions, group-1 patients, who did receive cefuroxime-impregnated cement, did not develop deep infection. The results for this group are better than those reported by others. The difference in the incidence of

deep infection in our two groups is statistically significant. Apart from the use of cefuroxime in the cement, no other factor could be found which may have contributed to this difference. The levels of blood sugar alone were not found to contribute to the development of deep infection (Table II). Perhaps the higher rate of deep infection may be due to a combination of poorly controlled blood sugar and an inappropriate operating environment.^{5,17,22,26,28} Comparison of the results of group 1 in our series with those of other series shows that the use of cefuroxime-impregnated cement is effective in preventing deep infection.

In our cases of deep infection, one patient had IDDM and the remaining four had NIDDM. There thus appears to be no higher risk of deep infection occurring in TKA in patients with IDDM compared with those with NIDDM.

The functional results for our series were comparable to those of other series of non-diabetic cases but the follow-up period was too short to allow firm conclusions to be drawn.

Antibiotic-impregnated cement serves as a form of prophylaxis but is only one factor contributing to the prevention of infection in TKA. In this prospective study, no infection developed in patients who had cefuroxime-impregnated cement. This does not suggest that cefuroxime-impregnated cement alone will prevent deep infection; systemic antibiotics were also used in all cases. We used a lengthy, seven-day course of systemic antibiotics because our operating environment was poor and our patients were also in a poor state of hygiene. We are trying to shorten this regime by using antibiotic-impregnated cement.

When performing TKA a surgeon must pay particular attention to asepsis and the administration of antibiotics. The main effect of antibiotic-impregnated cement is to offer local resistance to infection in the postoperative period. Mixing antibiotics with cement is a simple procedure which reduces the incidence of deep infection after TKA. Many antibiotics can be added to cement with only minor adverse effects on the properties of the cement. Up to 2 g of antibiotic powder can be added to a 40 g pack of cement without affecting static tensile and compressive strengths of the material, although the fatigue strength may be reduced, with, however, no adverse effect in clinical use.^{25,29,30-33} The choice of cefuroxime in our series was based on its thermal stability, biological effectiveness in cement and good clinical results from earlier studies.^{1,4,13,23,25,30,31} The addition of 2g of cefuroxime will add approximately 10 US dollars to the cost of TKA.

Our report is the first to evaluate the effect of cefuroxime-impregnated cement on the prevention of deep infection at primary TKA in patients with diabetes. We recommend its use, particularly in patients with poor control of blood sugar or when the operation is undertaken in an inappropriate environment.

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

References

1. Duff GP, Lachiewicz PF, Kelley SS. Aspiration of the knee joint before revision arthroplasty. *Clin Orthop* 1996;331:132-9.
2. Morrey BF, Westholm F, Schoifet S, Rand JA, Bryan RS. Long-term results of various treatment options for infected total knee arthroplasty. *Clin Orthop* 1989;248:120-8.
3. Rand JA. *Total knee arthroplasty*. New York, Raven Press, 1993.
4. Scuderi GR, Insall JN, Windsor RE, Moran MC. Survivorship of cemented knee replacements. *J Bone Joint Surg [Br]* 1989;71-B:798-803.
5. Wilson MG, Kelley K, Thornhill TS. Infection as a complication of total knee-replacement arthroplasty: risk factors and treatment in sixty-seven cases. *J Bone Joint Surg [Am]* 1990;72-A:878-83.
6. Espehaug B, Engesaeter LB, Vollset SE, Havelin LI, Langeland N. Antibiotic prophylaxis in total hip arthroplasty: review of 10 905 primary cemented total hip replacements reported to the Norwegian arthroplasty register 1987 to 1995. *J Bone Joint Surg [Br]* 1997;79-B:590-5.
7. Garvin KL, Salvati EA, Brause BD. Role of gentamicin-impregnated cement in total joint arthroplasty. *Orthop Clin North Am* 1988;19:605-10.
8. Gristina AG, Kolkin J. Total joint replacement and sepsis. *J Bone Joint Surg [Am]* 1983;65-A:128-34.
9. Grogan TJ, Dorey F, Rollings J, Amstutz HC. Deep sepsis following total knee arthroplasty: 10 year experience at the University of California at Los Angeles Medical Center. *J Bone Joint Surg [Am]* 1986;68-A:226-34.
10. Hanssen AD, Osmon DR. Prevention of deep wound infection after total hip arthroplasty: the role of prophylactic antibiotics and clean air technology. *Semin Arthroplasty* 1994;5:114-21.
11. Harris WH, Sledge CB. Total hip and total knee replacement. *N Engl J Med* 1990;323:12:801-7.
12. Hill C, Flamant R, Mazas F, Evrard J. Prophylactic cefazolin versus placebo in total hip replacement: report of a multicentre double-blind randomised trial. *Lancet* 1981;i:795-7.
13. McQueen MM, Hughes SP, May P, Verity L. Cefuroxime in total joint arthroplasty: intravenous or in bone cement. *J Arthroplasty* 1990;5:169-72.
14. Petty RW, Bryan RS, Coventry MB, Peterson LFA. Infection after total knee arthroplasty. *Orthop Clin North Am* 1975;6:1005-14.
15. Poss R, Thornhill TS, Ewald FC, et al. Factors influencing the incidence and outcome of infection following total joint arthroplasty. *Clin Orthop* 1984;182:117-26.
16. Rand JA, Bryan RS, Morrey BF, Westholm F. Management of infected total knee arthroplasty. *Clin Orthop* 1986;205:75-85.
17. Bengtson S, Knutson K, Lidgren L. Revision of infected knee arthroplasty. *Acta Orthop Scand* 1986;57:489-94.
18. Insall JN. Infection in total knee arthroplasty. *Instr Course Lect* 1982;31:42.
19. Bengtson S, Knutson K, Lidgren L. Treatment of infected knee arthroplasty. *Clin Orthop* 1989;245:173-8.
20. Doyon F, Evrard J, Mazas F, Hill C. Long-term results of prophylactic cefazolin versus placebo in total hip replacement. *Lancet* 1987;1:860.
21. Jones EC, Insall JN, Inglis AE, Ranawat CS. GUEPAR knee arthroplasty results and late complications. *Clin Orthop* 1979;140:145-52.
22. Josefsson G, Kolmert L. Prophylaxis with systematic antibiotics versus gentamicin bone cement in total hip arthroplasty: a ten-year survey of 1688 hips. *Clin Orthop* 1993;292:210-4.
23. Kaiser AB. Antimicrobial prophylaxis in surgery. *New Eng J Med* 1986;315:1129-38.
24. Knutson K, Lindstrand A, Lidgren L. Survival of knee arthroplasties: a nation-wide multicentre investigation of 8000 cases. *J Bone Joint Surg [Br]* 1986;68-B:795-803.
25. Marks KE, Nelson CL, Lautenschlager EP. Antibiotic-impregnated acrylic bone cement. *J Bone Joint Surg [Am]* 1976;58-A:358-64.
26. Oishi CS, Carion WV, Hoaglund FT. Use of parenteral prophylactic antibiotics in clean orthopaedic surgery: a review of the literature. *Clin Orthop* 1993;296:249-55.

27. **Papagaelopoulos PJ, Idusuyi OB, Wallrichs SL, Morrey BF.** Long term outcome and survivorship analysis of primary total knee arthroplasty in patients with diabetes mellitus. *Clin Orthop* 1996;330:124-32.
28. **Serna F, Mont MA, Krackow KA, Hungerford DS.** Total knee arthroplasty in diabetic patients: comparison to matched control group. *J Arthroplasty* 1994;9:375-9.
29. **Trippel SB.** Antibiotic-impregnated cement in total joint arthroplasty. *J Bone Joint Surg [Am]* 1986;68-A:1297-302.
30. **Buchholz HW, Engelbrecht H.** Depot effects of various antibiotics mixed with placos resins. *Chirurg* 1970;41:511-5.
31. **Hughes S, Field CA, Kennedy MRK, Dash CH.** Cephalosporins in bone cement-studies in vitro and in vivo. *J Bone Joint Surg [Br]* 1979;61-B:96-100.
32. **Elson RA, Jephcott AE, McGeachie DB, Verettes D.** Antibiotics-loaded acrylic cement. *J Bone Joint Surg [Br]* 1977;59-B:200-5.
33. **Wininger DA, Fass RJ.** Antibiotic-impregnated cement and beads for orthopedic infections. *Antimicrob Agents and Chemother* 1996;40:2675-9.