The use of antibiotic-impregnated cement in infected reconstructions after resection for bone tumours

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We have studied 35 patients with infected reconstructions after segmental resection for bone tumours. Two different regimes of treatment were employed both of which entailed debridement and the use of cement impregnated with antibiotic. In 25 patients gentamicin-PMMA beads were used and in ten an antibiotic-impregnated cement spacer. Better results were achieved with the second procedure in terms of cases healed, the number of operations, time of healing, time of recovery and the functional score. The use of vancomycin in the cement spacer gave better local control.

J Bone Joint Surg [Br] 1998;80-B:1045-50.

Received 24 November 1997; Accepted after revision 3 June 1998

Massive segmental skeletal reconstruction after resection of bone tumours is often followed by complications.¹ Infection is the major cause of early failure and the most challenging for both surgeon and patient.^{2,3}

The essential surgical step in the treatment of chronic osteomyelitis is radical debridement of all infected and necrotic tissue and removal of foreign material.⁴ A combination of continuous irrigation and suction is required to remove necrotic tissue.⁵

Local antibiotic therapy using chains of gentamicin polymethylmethacrylate (PMMA) beads is an established technique in septic bone surgery. Buchholz and Engelbrecht⁶ and Buchholz and Gartmann⁷ reported the efficacy of antibiotic-loaded bone cement in the management of infected total hip arthroplasties and this was confirmed in further pharmacokinetic studies by Wahlig and Buchholz.⁸ They reported local levels of antibiotic 200 times higher than those achieved by systemic administration. Walenkamp et al⁹ showed that the serum and urine concentrations of gentamicin after the implantation of gentamicin PMMA

beads were much lower than those after systemic use. The clinical assessment of this method has been validated in post-traumatic, postoperative and haematogenous osteomyelitis and in infected conventional total hip and knee arthroplasty.¹⁰⁻¹⁴

Since 1981 we have been using gentamicin-PMMA beads in infected reconstructions after resection of bone tumours. Rotation of muscle flaps¹⁵⁻¹⁸ can be used to heal the infection without removal of the prosthesis. When the prosthetic component is to be removed, however, a two-stage procedure has to be considered.¹⁹ Since 1992 we have used antibiotic-impregnated acrylic cement as a block spacer. This technique has proved to be successful in infected conventional knee and hip prostheses,²⁰⁻²³ preserving length and space for later reinsertion of an implant. Our aim in this study was to compare the use of PMMA beads and cement spacers.

Patients and Methods

There were 35 patients in the study divided into two groups. Group 1 consisted of 25 patients in whom gentamicin-PMMA beads were inserted and group 2 of ten patients who had an antibiotic-impregnated cement spacer. Details of both groups are given in Table I.

Group 1. The 25 patients had a mean age of 20 years (11 to 53). The most commonly affected site was around the knee. The type of tumour was an osteosarcoma in 16 patients, a chondrosarcoma in three, Ewing's sarcoma in two, and an adamantinoma, haemangioendothelioma, malignant fibrous histiocytoma and giant-cell tumour in one each. Postoperative antitumour chemotherapy was given in 16 patients.

After the resection, 12 patients with the tumour localised at the distal femur or the proximal tibia had a non-cemented Howmedica Modular Resection System (HMRS) prosthesis (Howmedica International) inserted (Fig. 1). Three (proximal humerus) had a cemented Modular Resection System prosthesis, one (proximal femur) a cemented IOR modular prosthesis (Officine Orthopediche, Rizzoli, Italy), one (total humerus) a cemented custom-made prosthesis, and in five intercalary or articular resections a cement spacer was fixed by a nail (3), plate (1) or external fixator (1). Autogenous bone was implanted in three patients.

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0301-620X/98/68570 \$2.00

Table I. Details of the two groups

	Gentamicin beads	Cement spacer
Number of cases	25	10
Mean age in years (range)	20 (11 to 53)	27 (4 to 70)
Site		
Humerus	4	1
Femur	14	6
Tibia	7	3
Reconstruction		
Prosthesis	16	6
Cemented	5	-
Uncemented	11	6
Grafts	3	3
Temporary spacer	5	1
Postoperative complications	5	3
Risk factors	6	7
Early infections	15 (60%)	5 (50%)
Infection signs		
Sinus	14	7
Swelling	3	2
Wound slough	8	1
Bacteria		
Coagulase-negative <i>Staphylococcus</i>	17 (70%)	6 (60%)
<i>Staph. aureus</i>	9	1
Others	-	3
Negative samples	1	-

Fig. 1a

Fig. 1b

Fig. 1c

Figure 1a – The HMRS non-cemented modular system for reconstruction of the distal femur and proximal tibia. Figures 1b and 1c – Anteroposterior radiographs showing b) an implanted HMRS prosthesis in the distal femur and c) with beads in place.

Six patients had additional risk factors: diabetes, a pathological fracture, contemporary thoracotomy for lung metastases, and oral infection in one each and postoperative direct trauma in two. Postoperative complications were seen in five patients: a haematoma in three, persistent fever after surgery in one, and an external popliteal nerve palsy in one.

Infection developed in 15 patients (60%) within three months, in 12 immediately after surgery, while in the

remaining ten it appeared at a mean of nine months (3 to 61). A draining sinus was detectable in 14 patients and in two was associated with fever. Three patients had local swelling and inflammation, and eight a wound slough. Culture samples grew coagulase-negative *Staphylococcus* in 17 patients (68%), associated with other bacteria in six. In nine *Staphylococcus aureus* was grown, with other organisms in three. In one case culture samples proved sterile in spite of clinical evidence of infection.

Fig. 2a

Fig. 2b

Fig. 2c

Radiographs showing a) infection after reconstruction of the distal femur, b) augmentation of the distal femoral bone with signs of bone involvement and c) the spacer in place; it fractured after four weeks.

In all patients treatment included extensive surgical debridement with intravenous antibiotics for at least five days during the perioperative period. Gentamicin-PMMA beads were inserted using as many chains as possible and were removed or replaced between three and four weeks later. The procedure was repeated several times until no clinical or laboratory signs of infection were present.

Group 2. The mean age of the ten patients was 27 years (4 to 70). The tumour was an osteosarcoma in four, giant-cell tumour in three, Ewing's sarcoma in two and a leiomyosarcoma in one. After operation antitumour chemotherapy was given to seven patients. Reconstruction was performed in six using an HMRS prosthesis (Fig. 2). In three a bone allograft was implanted and an intercalary reconstruction with cement and plates was carried out in one.

Seven patients had one of the following risk factors: diabetes, obesity, pathological fracture, direct trauma after surgery, curettage before resection, patellar tendon reinsertion and osteosynthesis with a plate for fracture around the prosthesis. There were postoperative complications in three patients, with fever immediately after surgery in two and thrombophlebitis in one.

Infection developed in five patients within three months, in one immediately after surgery. In the remaining five it was evident after a mean of ten months (3 to 59). A draining sinus was detectable in seven patients, in one associated with fever, in two with local swelling and inflammation and in one with wound slough. Culture samples grew coagulase-negative *Staphylococcus* in six patients, in one associated with other bacteria. In three *Staphylococcus aureus* was grown, in one associated with other organisms. In one patient *Escherichia coli* was cultured in association with *Bacteroides fragilis*.

In three patients a spacer was implanted after persistent infection previously treated by local irrigation. In uncemented reconstructions partial or total removal of the implant was always carried out: in two cases only the stems were removed.

As much cement was used as was necessary to fill the whole space left by the retrieved implant. In seven patients the cement was reinforced by a Küntscher nail. Vancomycin was the antibiotic of choice in seven patients, mixed with cement in quantities varying between 3 and 9 g per cement pack. Cefamandole (2 g) was used in two and gentamicin (30 mg) in one.

All the patients were followed clinically and radiologically. Laboratory tests included measurement of the ESR, C-reactive protein, WBC, fibrinogen and gamma proteins. We performed functional evaluation according to the MSTs system.²⁴

Results

Group 1. Details are given in Table II. Surgical debridement and bead insertion were the primary treatment in 16 patients, while in nine the initial debridement was followed by continuous lavage. Partial removal of the reconstruction was performed in three patients with autografts. The infection healed in all three, with satisfactory results in two. Because the signs of infection were mild in three patients treatment was performed without removing the implant with bead chains applied around the body of the prosthesis. However, in two, amputation was necessary and the third patient still has a draining sinus and an unsatisfactory functional result.

In 19 patients in whom the implant was removed, six had the same type of prosthesis reinserted. This was successful in three. Two patients still have infection and one has been lost to follow-up. In five other patients a different reconstruction was performed as a salvage procedure. In four this was successful and one still has infection. Of the remaining patients, four have a flail limb, with one still infected, and four required amputation.

The most constant and significant indicator of infection was the ESR. This returned close to the normal level in most cases after treatment. After a mean interval of 31 months (3 to 83) and between two and eight operative procedures (mean 4.7), the infection settled in 19 patients (76%), although six required amputation (24%) and three have a flail limb. In those treated with postoperative chemotherapy the only notable feature was a higher rate of

amputation (31%). Functional activity recovered at a mean of 25 months (3 to 92) and in patients in whom the lower limb was affected weight-bearing was achieved at a mean of 38 months (6 to 104). Satisfactory functional results were obtained in five patients (20%). The mean follow-up was 96 months (24 to 169).

Group 2. Details are given in Table III. Evidence of infection in most cases was a draining sinus. Removal of the implant was performed in five: two had an allograft, one temporary cement reconstruction and two an HMRS prosthesis. In the remaining patients in whom uncemented components had been used, only the body of the prosthesis could be retrieved. In the composite prosthesis (case 7, Table III) only the allograft was excised and the prosthesis was completely covered by antibiotic-impregnated cement. Three patients required further revision of the prosthesis, in two once, and in

Table II. Results in patients in group 1 (bead chains)

Case	Age (yr)	Type of reconstruction	Site*	Time to infection (mth)	Time to surgery (mth)	Time to heal (mth)	Number of operations	Outcome	Functional result
1	21	KRA†/autog	PT	2	0	76	8	Partial retrieve	Good
2	17	Prosthesis	PH	8	0	3	4	Loosening	Good
3	11	Cement spacer	DF	0	17	13	4	Amputation	Poor
4	13	Prosthesis	PT	0	1	7	5	Prosthesis	Fair
5	13	Cement spacer	DF	1	8	49	4	Prosthesis	Good
6	15	Prosthesis	PT	0	0	28	4	Amputation	Poor
7	12	Prosthesis	PT	0	0	61	8	Flail	Poor
8	13	Prosthesis	DF	1	0	5	8	Prosthesis	Lost to follow-up
9	13	Prosthesis	PH	18	2	30	5	Flail	Poor
10	53	Prosthesis	DF	12	0	/	4	Prosthesis/sinus	Fair
11	13	Prosthesis	DF	0	0	21	5	Prosthesis	Good
12	30	Prosthesis	PH	0	1	5	4	Flail	Poor
13	16	Prosthesis	PT	0	3	1	3	Amputation	Poor
14	28	Cement spacer	PT	1	3	/	2	Autograft/nonunion	Poor
15	20	Cement spacer	DF	3	29	/	2	Prosthesis/sinus	Good
16	13	Autograft	SF	26	5	11	4	Vascular fibula	Poor
17	17	Autograft	ST	7	0	14	4	Partial retrieve	Good
18	11	Cement spacer	DF	2	1	4	3	Amputation	Poor
19	12	Prosthesis	DF	11	3	/	6	Prosthesis/sinus	Fair
20	27	Prosthesis	DF	1	0	83	6	Amputation	Poor
21	15	Prosthesis	DF	61	0	25	5	Amputation	Poor
22	30	Prosthesis	PH	20	0	/	2	Flail limb/sinus	Poor
23	35	Prosthesis	PF	43	5	81	6	Allograft/nonunion	Fair
24	15	Prosthesis	PF	2	1	/	6	Prosthesis/sinus	Fair
25	31	Prosthesis	DF	9	1	13	6	Vascular fibula	Fair

* P, proximal; D, distal; S, diaphysis; T, tibia; F, femur; H, humerus

† Knee resection arthrodesis

Table III. Results in patients in group 2 (spacers)

Case	Age (yr)	Type of reconstr	Site*	Time to infection (mth)	Time to surgery (mth)	Antibiotics x cem pack†	Time to heal (mth)	Number of operations	Outcome	Functional result
1	13	Allograft	PH	3	1	Cef 2 g	2	2	Cement spacer	Good
2	15	Prosthesis	DF	2	0	Vanc 5 g/vanc 5 g	5	4	Prosthesis	Excellent
3	4	Allograft	SF	0	0	Gent 30 mg	4	4	Amputation	Poor
4	33	Prosthesis	DF	59	10	Vanc 9 g	7	3	Prosthesis	Good
5	53	Prosthesis	PT	4	0	Cef 2 g	16	3	Amputation	Poor
6	70	Prosthesis	DF	0	0	Vanc 5 g	/	3	Prosthesis/sinus	Fair
7	11	Allo+ Prost	PF	1	0	Vanc 3 g	6	3	Cement + prosth	Good
8	24	Prosthesis	PT	8	7	Vanc 4 g/vanc 4 g	14	3	Prosthesis	Fair
9	13	Cem spacer	ST	6	2	Vanc 5 g	2	1	Prosthesis	Fair
10	34	Prosthesis	DF	22	0	Vanc 4 g/cef 4 g Cef 4 g/cef 4 g	10	7	Prosthesis	Good

* P, proximal; D, distal; S, diaphysis; T, tibia; F, femur; H, humerus

† Cef, cefamandole; Vanc, vancomycin; Gent, gentamicin

Table IV. Comparison of results with gentamicin beads and cement spacers

	Gentamicin beads	Cement spacer
Follow-up time (mth; range)	96 (24 to 169)	40 (22 to 84)
Number of operations (range)	4 (2 to 8)	3.3 (1 to 7)
Healed cases (%)	19 (76)	9 (90)
Time to heal (mth; range)	31 (3 to 86)	10 (3 to 21)
Recovery of functional activity (mth; range)	25 (3 to 92)	9 (4 to 22)
Weight-bearing (mth; range)	38 (6 to 104)	13 (5 to 26)
Amputation (%)	6 (24)	2 (20)
Flail limb (%)	4 (16)	0 (0)
Satisfactory functional results (%)	6 (24)	5 (50)

one, three times because of persistent clinical signs of infection. The last patient (case 10) suffered an allergic reaction to vancomycin after insertion of the first spacer.

When the infection seemed to have been overcome, a similar reconstruction was performed in six patients. In two a different procedure was carried out and two required amputation.

After a mean of ten months (3 to 21) and between two and seven operations (mean 3.3) infection was overcome in nine patients although two had required amputation. Of those who did not have amputation, vancomycin was used in seven. Satisfactory function was achieved in five patients after a mean interval of nine months (4 to 22) and weight-bearing was possible at a mean of 13 months (5 to 26). The mean follow-up was 40 months (22 to 84). Table IV gives a comparison of the results in both groups.

Discussion

About 10% of prostheses which have been implanted after resection of bone tumours become infected. We have improved our results in the management of this problem by early aggressive surgery, with removal of the implant when indicated, and the use of antibiotic-loaded cement spacers.

There is still controversy as to the treatment of suspected deep infection. When the physical signs suggest the presence of pus surgical debridement should be performed immediately, and in 50% of the cases reported in our previous study¹⁶ healing occurred after continuous irrigation. When the signs of infection are less clear treatment with antibiotics may be started by an inexperienced physician. This may lead to early suppression of the infection which may later become chronic. Definitive treatment will be delayed and may then be less effective (Table II).

Postoperative chemotherapy is not associated with a higher rate of infection, but a leucopenia may weaken the defence of the body against infection when present. A mild infection may progress rapidly in the presence of cytotoxic agents.

Attempts have been made to grade an infection in order to influence decisions about surgery. The most valuable blood test is the ESR and we have found that the clinical signs are the most reliable. We usually wait for six months after infection has subsided before attempting further reconstructions. Attempts at a one-stage procedure have resulted in a rate of reinfection of up to 30%.^{10,21,23,25}

Cement loaded with antibiotic has proved effective but the choice of antibiotic is uncertain. More than 70% of the infections are due to either coagulase-negative cocci or *Staphylococcus aureus* and half are methicillin-resistant.^{26,27} Glycopeptides such as vancomycin and teicoplanin have been shown to be effective against these bacteria. Vancomycin combined with tobramycin is recommended as having a broader action on the CNS compared with gentamicin, and it is less nephrotoxic.^{28,29} Moreover, tobramycin has a better elution characteristic than vancomycin,²⁷ and the combination seems to give enhanced elution with more accurate control of infection.²⁸ There is evidence, however, that other materials such as biodegradable cement and collagen sponges give more complete and faster delivery of antibiotic.^{30,31}

Conclusion. Antibiotic-impregnated cement spacers have been shown to be more effective in the rate and time of healing, frequency of repeated surgery and functional results, as compared with PMMA beads. The treatment of deep infection of large prostheses after resection of bone tumours remains controversial.

In early infection several methods can achieve success in 50% to 70% of the cases, while for the remainder or in late infection, the removal of the implant and a high local concentration of antibiotic are needed. The combination of antibiotics and an improved cement or other material is advisable for a better elution and higher and faster concentration of local antibiotics. Reliable and reproducible laboratory and image-based tests are needed to diagnose more accurately the early onset of the infection and to monitor the outcome.

This study was partially supported by grants from the Research Project of CNR, Italy and the Current Research Project IOR, Bologna.

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.

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