Clinical Trial/Experimental Study

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The anti-infective outcomes of the distal femoral replacement coated with antibiotic cement in limb salvage surgery

A randomized clinical trial

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Abstract

Background: The aim of this study was to observe the anti-infective effect of the distal femoral tumor prosthesis coated with antibiotic cement during limb salvage treatment, and evaluate its potential prospect in clinic.

Methods: In this randomized controlled trial, the en bloc resection and reconstruction were performed in 36 patients with distal femoral primary bone tumor. Patients were divided into 2 groups randomly according to the application of antibiotic bone cement coating, which included antibiotic cement coating group (16 cases) and control group (18 cases). There were 10 men and 6 women in anti-infection group, aged from 18 to 54 years (23.47 ± 3.53), and there were 12 men and 6 women in control group, aged from 19 to 56 years (24.16 ± 4.32). The tumor type, age, sex, and Enneking stage were enrolled with well-matched of the 2 groups of patients. There was no difference between bundles and routine standard care for each group. The antibiotic cement was coated on the surface of polyethylene jacket with punched holes during operation. The peri-prosthetic infection, local recurrence and distant metastasis were followed up and limb functions were evaluated by Musculoskeletal Tumor Society 93 (MSTS93) scoring system.

Results: Patients were followed up till 34.7 months (range 18~62 months). There was no periprosthetic infection in anti-infection group. Four cases in control group showed deep infection. Infection rate had significant differences between the 2 groups ($P < .05$). Infection-related prosthesis mortality was 0% (0/16) in anti-infection group and 16.67% (3/18) in control group. Local recurrence and distant metastasis occurred in 7 of 34 patients with primary malignant bone tumor, wherein 2 cases of local recurrence and 1 cases of distant metastasis occurred in anti-infective group; 2 cases of local recurrence and 2 cases of distant metastasis occurred in the control group. During a latest follow-up, MSTS93 function scoring revealed a mean of 25.6 ± 4.2 in anti-infection group and 18.5 ± 3.3 in control group. The survival rate of anti-infective group is 75%, and the survival rate of control group is 61.11%.

Conclusion: The antibiotic cement-coated technique on the surface of the polyethylene jacket of custom-made distal femoral prosthesis is simple and effective in controlling the periprosthetic infection after tumor prosthesis reconstruction.

Abbreviations: MSTS93 = Musculoskeletal Tumor Society 93, NRD = Nationwide Readmissions Database, PJI = periprosthetic joint infection, PMMA = polymethylmethacrylate, SSI = surgical site infection.

Keywords: antibiotic cement, bone tumor, prosthesis, surgical site infection

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1. Introduction

With improvements in the comprehensive treatment of bone tumors and prosthetic techniques, limb salvage treatment of malignant bone tumor has become the mainstream. Local complete resection of bone tumors and prosthetic replacement can effectively preserve limb function and greatly improve postoperative quality of life.[1,2] However, the tumor prosthetic replacement often leads to various complications, such as soft-tissue failures, aseptic loosening, structural failures, infection and tumor progression. Besides tumor progression, the deep infection is the most serious of these complications, and resulting in multi-step operations for recovery, and sometimes failure of limb salvage.[3,4]

Surgical site infection (SSI) or periprosthetic joint infection (PJI) has a significantly higher incidence of bone tumor prosthetic replacement than nontumorous prosthetic replacement. Usually, postoperative infection requires irrigation and debridement, 2-stage revision, or amputation. This will severely increase medicare payments and worsened quality of life in patients. In China, a survey of revision burden due to PJI after total hip or knee arthroplasty showed that 429 (1.77%) of 23,443 knee arthroplasty patients had revision, of which PJI revision burden was 205 (0.85%), and PJI was the most common cause for knee revision.[5] There are also studies using the 2013 Nationwide Readmissions Database (NRD), health care resource utilization was compared between propensity score matched patient groups with and without SSI-related readmissions within the 90-day episode of care following total joint replacement. The results showed that SSIs were associated with significantly longer hospital length of stay and increased costs following hip and knee joint replacement procedures. Among them, SSI related knee arthroplasty extra hospital days ranging from 4.9 to 5.2 days and extra cost ranging from $12,689 to $12,890.[6] Some scholars also followed up SSI cases after knee arthroplasty for 2 years and found that the cost of SSI treatment was 8 times that of uninfected controls.[7] Therefore, it is very important to effectively reduce SSI or PJI.

Some researchers designed bone tumor prosthesis coated with silver to overcome high infection rate of giant bone tumor prosthesis.[8] However, preparation of this prosthesis is very complex and expensive, with unclear antibiotic mechanism, which confines its application. Referring to successful application of gentamicin bead chain and packing with antibiotic cement in revision hip arthroplasty,[3,4] we developed a custom-made bone tumor prosthesis coated with antibiotic cement for distal femoral tumors, and compared with traditional custom-made prosthesis to investigate its effect of infection control.

2. Materials and methods

2.1. General information

A total of 34 patients receiving en bloc resection and reconstruction using the custom-made distal femoral prosthesis for treatment of distal femoral malignant or invasive bone tumors between June 2010 and June 2014 were selected. This study was approved by the ethics committee of the Fourth Military Medical University. Among these, there were 22 men and 12 women, aged from 18 to 56 years (23.59 ± 3.96), and 19 tumors were at the left side and 15 cases at the right side. The bone tumor types included: 19 cases of osteosarcoma, 9 cases of giant cell tumor of bone, 3 cases of chondrosarcoma, 3 cases of Ewing sarcoma. According to the application of antibiotic cement coating, patients were randomized into anti-infective group (16 cases) and control group (18 cases). The antibiotic cement (gentamicin sulfate) was coated on surface of polyethylene jacket with punched holes during operation. The comparison of patient information between the 2 groups is shown in Table 1. There were 81.25% (13/16) patients in anti-infective group and 77.78% (14/18) patients in control group accepting chemotherapy treatment after operation, respectively. The periprosthetic infection, local recurrence, and distant metastasis were followed up and limb functions were evaluated using MSTS93 function scoring.

Table 1

Comparison of basic information and baseline data of patients.

		Anti-infective, n = 16	Control, n = 18	*P*
Sex (n)				.800
	Male	10 (62.5%)	12 (66.7%)	
	Female	6 (37.5%)	6 (33.3%)	
Age, y		23.47 ± 3.53	24.16 ± 4.32	.437
Tumor type (n)				.420
	Osteosarcoma	10 (62.5%)	9 (50%)	
	Giant cell tumor	4 (25%)	5 (27.8%)	
	Chondrosarcoma	1 (6.25%)	2 (11.11%)	
	Ewing sarcoma	1 (6.25%)	2 (11.11%)	
Limb (n)				.515
	Left	8 (50%)	11 (61.11%)	
	Right	8 (50%)	7 (38.89%)	
Enneking stage				.218
	IA	1 (6.25%)	2 (11.11%)	
	IB	1 (6.25%)	1 (5.56%)	
	IIA	2 (12.5%)	5 (27.78%)	
	IIB	12 (75%)	10 (55.56%)	

2.2. Surgical procedure

Preoperative preparation: Preoperative biopsy was performed to confirm tumor features. Patients with primary malignant bone tumors (except for chondrosarcoma) firstly received novel adjuvant chemotherapy for 3 times, and efficacy was assessed. After that x-ray and MRI examinations of the affected limbs were performed again to re-evaluate tumor range and tumor prosthesis was designed according to osteotomy range, and the relevant data were sent to Beijing Chunlizhengda Co,.Ltd. for preparing prosthesis. The prosthesis was a custom-made axial bone tumor prosthesis, with a 2 mm layer of polyethylene jacket. Holes were drilled uniformly on the polyethylene jacket, with the diameter of 2.5 mm, the depth of 2 mm, and the pitch of 1.5 cm (Fig. 1). The antibiotic bone cement was commercialized (Rabin corporation, France). Monomer (40 g) included: polymethylmethacrylate 83.8% (33.52 g), benzoylperoxide 2.8% (1.12 g), barium sulfate 9.6% (3.84 g), and gentamicin sulfate 3.8% (1.52 g). Solvent (16.4 g) included: methacrylate 85.3% (13.99 g), butyl methacrylate 13.2% (2.16 g), N, N-dimethyl-p-toluidine 1.5% (0.24 g), and hydroquinone 20 ppm. The bone cement coated on prosthesis surface was low-viscosity self-curing radiopaque antibiotic cement.

Surgical procedure: Patients received continuous caudal or general anesthesia, incisions were made at lower thigh and medial or lateral knee joints according to the distal femoral tumor

Figure 1. Surgery-related data. (A) Each component of custom-made axial distal femoral tumor prosthesis (perforated polyethylene jacket, metal parts, polyethylene liner). (B) Assembled distal femoral axial tumor prosthesis. (C) Knee extension and flexion at 6 months. (D) Coat antibiotic cement on the surface and holes on polyethylene jacket.

location, then the biopsy channel was removed, layer by layer dissection was performed to reveal distal femoral tumor while retaining a layer of normal soft tissue in the tumor margin. The planned osteotomy segment was revealed and the femur was truncated, and the medullary cavity tissue at the broken end was sent for frozen pathological examination and the results confirmed there was no tumor invasion. All the ligaments of the knee were separated while protecting posterior nerves and blood vessels and other structures, and the distal femur was completely resected. After flushed with saline, the medullary cavity in the large femur was expanded according to the custom-made prosthesis, tibial flateau osteotomy was performed and the tibial bone medullary cavity was expanded. The axial bone tumor prosthesis was assembled to determine the lower extremity force line, length, knee joint range of motion and stability, then the prosthesis was fixed using anti-infective cement. In the anti-infective coating group, the antibiotic bone cement was mixed evenly according to the solid–liquid ratio 2 g:1 mL, stirring the solid-liquid mixture in the same direction for about 3~5 minutes, subsequently, coated the solid–liquid mixture on the surface and holes of the polyethylene jacket slowly and evenly. About 5 to 8 minutes, the bone cement and polyethylene jacket would be firmly bonded together (Fig. 1). The amount of cement on the surface was 10 to 15 g and thickness was 2 to 3 mm. After solidification of the bone cement, it was flushed with saline, and a negative pressure drainage was placed. Then layer by layer suture was performed to close the incision. Postoperative patients received intravenous drip of antibiotics for 3 days, and they began CPM-assisted extension and flexion of knee joints at 2nd day after the surgery. The drainage tube was removed at 3 to 5 days after the surgery, and patients walked with crutches.

MSTS93 scoring system was applied for functional assessment in patients during follow-up. This system includes numerical values from 0 to 5 points assigned to each of the following 6 categories: pain, level of activity and restriction, emotional acceptance, use of orthopedic supports, walking ability, and gait. The final MSTS score is calculated as a percentage of the maximum possible score; the higher the percentage, the better the functional outcome.

2.3. Statistical analysis

Statistical analysis was performed using SPSS22.0 software (SPSS Inc, Chicago, IL). Comparisons between groups were performed using χ^2 test of 4-fold table, *t* test, and rank sum test Kaplan–Meier survival analysis for estimation of implant survival, where $P < .05$ was considered statistically significant.

3. Result

A total of 34 patients received en bloc resection and reconstruction using the custom-made distal femoral prosthesis for treatment of distal femoral malignant or invasive bone tumors. There was no significant difference in the sex ($P = .800$), age ($P = .437$), tumor type ($P = .420$), affected limb ($P = .515$), and Enneking stage ($P = .218$) of patients between the control and anti-infective groups. The mean follow-up of all the patients was 34.7 months (range 18~62 months). The results of x-ray showed that antibiotic cement did not appear ecclasis and shedding during the follow-up period.

The postoperative infection and treatment of the patients are shown in Table 2. Patients 1~4 are the control group. In all infected patients, 3 cases were infected with *Staphylococcus aureus* and 1 case was infected with *Acinetobacter cloacae* (patient 4). All infected patients received chemotherapy treatment after surgery, except patient 3. Four cases had periprosthetic infection in control group. Among these 4 patients, 1 case, infection occurred at 3 months after surgery and controlled after receiving infusion and drainage. Infection occurred in 1 case at 16 months after surgery and was not controlled after receiving infusion and drainage and 2-stage revision, then received amputation. In 1 case, periprosthetic infection occurred within 13 months, and the infection was not controlled after receiving infusion and drainage, then receiving two-stage revision by anti-

Table 2

Postoperative infection and treatment of the patients.

	Control			
Patients	1	2	3	4
Infection time, mo	3	8/15	11	16
Pathogen	*Staphylococcus aureus*	*Staphylococcus aureus*	*Staphylococcus aureus*	*Acinetobacter cloacae*
Chemotherapy	YES	YES	NO	YES
Treatment	Irrigation and debridement	Irrigation and debridement/ 2-stage revision	Irrigation and debridement + 2-stage revision	Irrigation and debridement + 2-stage revision + amputation
Infection rate	22.22%			

Table 3

MSTS93 scores of 2 groups after the follow-up.

Groups	n	Average score ($\overline{X} \pm S$)	Excellent, n (%)	Good, n (%)	Moderate, n (%)	Bad, n (%)	Excellent or good rate, n (%)
Anti-infective	16	25.6 ± 4.2	9 (56.25)	4 (25.00)	2 (12.50)	1 (6.25)	13 (81.25)
Control	18	18.5 ± 3.3	9 (50.00)	5 (27.78)	2 (11.11)	2 (11.11)	14 (77.78)
Statistic		t = 5.512	U = 133.5	χ^2 = 0.062			
P		<.001	.691	.803			

infective coating prosthesis. It is worth mentioning that there was 1 case receiving irrigation and debridement and being controlled; however, the case re-infected at the 15th month and received 2-stage revision by anti-infective coating prosthesis. The infection rate of the anti-infective group (0/16) was significantly lower than that of the control group (22.22%, 4/18), ($\chi^2 = 4.03$, $P = .045$).

In the last follow-up, MSTS93 function scoring (Table 3) showed that the average scores were 25.6 ± 4.2 in the anti-infective group, of which 9 cases were excellent, 4 cases were good, 2 cases were moderate, and 1 case were bad, with an excellent or good rate of 81.25% (13/16). The average score in the control group was 18.5 ± 3.3, of which 9 cases were excellent, 5 cases were good, 2 cases were moderate, and 2 cases were bad, with an excellent or good rate of 77.78% (14/18). There was significant difference in the MSTS93 function average scores of patients between the control and anti-infective groups ($P < .001$).

During the follow-up period, 2 cases of local tumor recurrence in the anti-infective group, both underwent amputation and 1 cases of distant metastasis. There were 2 cases of local recurrence in the control group and underwent amputation, and 2 cases of distant metastasis. There was no significant difference in the incidence of tumor local recurrence and distant metastasis between the two groups ($\chi^2 = 0.062$, $P = .803$). Two patients in the anti-infective group and 2 patients in the control group were received 2-stage revision due to other reasons. The prosthesis survival rate of the 2 groups of patients is shown in Figure 2; the survival rate of anti-infective group is 75% (12/16), and the survival rate of control group is 61.11% (11/18).

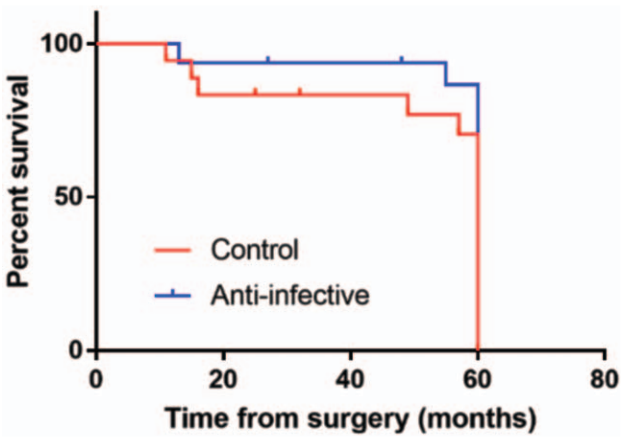

Figure 2. Survival curve of the prostheses. During the follow-up period, we investigated the prosthesis survival rate and found that the survival rate of anti-infective group is 75% (12/16), and the survival rate of control group is 61.11% (11/18).

4. Discussion

Presently, peripheral infection after tumor prosthesis replacement has become the most significant and most troublesome complications for surgeons and patients. This study presents a composite prosthesis, consisting of an antibiotic cement coating on the tumor prosthesis, that could effectively reduce the surgical site infection after distal femoral replacement and improve the patient's limb function.

Reasons for high incidence of infection after tumor prosthesis reconstruction included: a wide range of soft tissue resection, long surgical duration, and immune suppression caused by chemo-radiotherapy.[9] In addition, soft tissue defects after tumor resection was likely to induce dead space which leads to hematocele and dropsy, and the repulsion of prosthesis and lacuna between peripheral soft tissues were also likely to cause postoperative infection. At present, the postoperative infection rate after nontumorous prosthetic replacement has been reduced to 0.7% thanks to the improved preparation technique of prosthesis, standardized surgical operation and rational use of drugs, among others,[10] whereas the infection rate after tumorous prosthetic replacement is still as high as 12.5% to 30%.[11] Postoperative infection after prosthesis reconstruction often exerts great pain and economic burden, severe limitation of articular function to patients, and even leads to amputation when infection is uncontrolled.[12]

To overcome problems of postoperative infection after prosthesis replacement for bone tumor, many scholars committed to developing antibiotic coating for prosthesis surface to control periprosthetic infection. However, the above methods have deficiencies such as fast drug release, tissue toxicity, effects on mechanical bonding strength of prosthesis and bone, among others.[13,14] In recent years, some researchers proposed a biodegradable antibiotic sustained release system[15]; however, its application is still limited due to the deficiencies in material composites and drug- controlled release and other techniques. Arne et al developed silver-coated bone tumor prosthesis[8]; however, it has not been widely used due to the complex preparation, high cost, unclear antibiotic mechanisms, and the risk of toxic and side-effects. Other researchers reported to construct an antibiotic controlled release microsphere system on surface of low-modulus of elasticity β titanium alloy implant, so as to develop new techniques for preparing antibiotic coating for metallic surface,[16] whereas it has not been applied in clinic. Therefore, it is necessary to investigate on the design and preparation of a novel anti-infective bone tumor prosthesis.

In 1970, Buchholz and Engelbrecht for the first time proposed to prevent postoperative infection after joint replacement using antibiotic cement, and reported that the postoperative infection was reduced from 6% to 1.6% after applying antibiotic cement in total hip replacement.[17] The antibiotic cement has been gradually applied in clinic after it has been confirmed to reduce infection after joint replacement. Yoo et al[18] applied the anti-infective cement rods in knee arthroplasty and achieved good results. Wahlig[19] proved that after placing gentamicin cement bead chain in animal osteomyelitis lesions, its local concentration was significantly higher than the concentration using intravenous administration and concentration required for therapy. About 11% of the gentamicin was released in the first 24 hours, and it was retained in an effective bacteriocidal concentration within 15 weeks. Its concentration in the serum and urine were 0.3 μg/mL and 0.1 μg/mL, respectively, which was proved to have no adverse effects on renal cells and was toxicity free by using renal culture. The local antibiotics concentration was elevated after applying antibiotic cement, which not only improved local anti-infective effect after prosthesis replacement, but also prevented toxic and side-effect of systemic administration.

These mature and effective local antibiotic methods inspired that whether the gentamicin bean chain or antibiotic cement techniques can be applied to prevent periprosthetic infection after prosthetic reconstruction for bone tumors? In this study, the punching in the polyethylene jacket was carried out on the surface of custom-made axial bone tumor prosthesis, and uniformly coated gentamicin cement with antibiotic release effect on holes and surface of the polyethylene jacket. Local anti-infective effect was achieved through the release of antibiotics to prevent toxic and side-effects caused by systemic administration.

This design retains the supporting strength of the prosthesis metal structure, and holes on the surface of polyethylene jacket ensure to prevent shedding of the bone cement, which ensures the safety and effectiveness of bone tumor prosthesis. This technique is simple, without prolonging surgical time and without increasing economic burden. Our clinical results showed that during the follow-up and among the 16 patients receiving anti-infective prosthesis, no infection and no shedding of bone cement from polyethylene jacket surface were found. Although among the patients without receiving anti-infective prosthesis, the postoperative infection rate was up to 22.22% (4/18), of these 2 patients underwent the 2-stage revision and 1 patient underwent amputation. The postoperative periprosthetic infection had statistically significant difference between the 2 groups. Thereafter, anti-infective cement coating is able to effectively prevent periprosthetic infection after bone tumor prosthesis, and it is a simple and convenient method.

Of the 34 patients with primary malignant bone tumors, the incidence of postoperative local recurrence and distant metastasis was 20.58% (7/34), of these 2 cases appeared local tumor recurrence and 1 cases appeared distant lung metastasis in the anti-infective coating group, whereas 2 cases and 2 cases in the no anti-infective coating group had local tumor recurrence and distant metastasis, respectively. The incidence of local recurrence and distant metastasis had no statistically significant difference between the two groups ($P = .803$), indicating the anti-infective coating did not have significant effect on the tumor control. Postoperative MSTS93 score showed that the excellent or good rate in the anti-infective coating group was significantly improved compared with the no anti-infective coating group, where their average scores were 25.6 ± 4.2 and 18.5 ± 3.3, respectively, suggesting that the postoperative periprosthetic infection had significant effect on limb functions.

Antibiotics mixed in the antibiotic cement that are widely used mainly include tobramycin, gentamicin and vancomycin.[20,21] The tobramycin and gentamicin have been widely used in antibiotic cements due to broad antibiotic spectrum, good thermal stability and quick absorption. Although all the microbes can cause periprosthetic infection after prosthesis replacement, the most common pathogens are plasma coagulase-negative staphylococci and *Staphylococcus aureus*. Berbari et al[22] cultured periprosthetic infection tissues after receiving early and middle-phase prosthesis replacement, and their results revealed that agglutination-negative staphylococci accounted for 30% to 43% and *Staphylococcus aureus* accounted for 12% to 23%. Our preference for local administration of gentamicin for peripresthetic infection was mainly based on the bacteriological test results.[22] Although it is still controversy on preventing periprosthetic infection with antibiotic cement after receiving prosthesis replacement, the efficacy of bone cement containing antibiotics in preventing and treating infection after prosthesis replacement has been supported via animal experiments and clinical data, and its mechanism has become clearer. However, its effectiveness under specific conditions as well as interactions among organisms, bone cement, and antibiotics need further investigation, and the resistance caused by antibiotic cement has yet to be resolved.

In this study, there are still certain limitations. First of all, the number of cases in this study is only 34, and the cases number is relatively low. Therefore, in the next study, we will expand the number of cases to further prove the anti-infection effect of this prosthesis. Second, this study will further expand the follow-up time to observe the long-term efficacy of the prosthesis.

5. Conclusions

The custom-made punching on polyethylene jacket on surface of distal femoral tumor prosthesis and antibiotic cement coating can effectively control infection after distal femoral resection and prosthesis reconstruction, and enhance the prosthesis effect and limb functions, as well as improve the life quality of the patients. This method is very simple and convenient, and worth clinical promotion, although its long-term efficacy needs further follow-up observation.

Author contributions

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