ANALYSIS OF THE APPLICATION VALUE OF VANCOMYCIN DRUG DELIVERY SYSTEM IN THE TREATMENT OF PATIENTS WITH RELATED BONE INFECTION AFTER INTERNAL FIXATION OF FEMORAL FRACTURE

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ABSTRACT

Objective: *To investigate the application value of vancomycin drug delivery system in the treatment of patients with related bone infection after internal fixation of femoral fracture.*

Material and Methods: *37 patients admitted to our hospital from April 2017 to April 2019 who received vancomycin drug delivery system were selected as the research group (RG). 39 patients only received routine antibiotic therapy as control group (CG). The recovery of bone infection and skeleton of patients were compared between the two groups.*

Results: *The clearance rate of bone infection, reoperation rate and fracture rehabilitation time in the RG were lower than those in the CG ($p<0.050$), while hip joint function, rehabilitation and bone mineral density (BMD) were higher than those in the CG ($p<0.050$). Multivariate results showed that age, both fracture, non-first injury and reoperation were independent risk factors affecting the rehabilitation of patients. Vancomycin slow-release drug therapy was independent protective factor affecting the rehabilitation of patients ($p<0.050$).*

Conclusions: *Vancomycin drug delivery system can effectively improve the clearance rate of bone infection, accelerate the recovery of fracture and improve the bone health of patients to a certain extent for the treatment of bone infection after internal fixation of femoral fracture. It has great application prospect in clinic in the future.*

Keywords: *Vancomycin, drug delivery system, femoral fracture, bone infection, bone mineral density.*

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Introduction

Femoral fractures are mostly caused by external violence, such as car impact, heavy weight crushing, rolling. Fractures are mostly crushed, dished or similar transverse[(1)]. The displacement of fracture end of femur is obvious, soft tissue injury is usually more serious, and the probability of internal hemorrhage is significant[(2)]. Femoral fractures are common in middle-aged and elderly people, especially in patients with osteoporosis[(3)].

The rapid increase in population aging in recent years is also one of the reasons for the increasing incidence of femoral fractures[(4)]. Femoral fracture is easy to cause a series of complications, such as pelvic fracture, joint dislocation, visceral injury. In more serious cases, avascular necrosis of femoral head and nonunion may occur, posing a threat to patients' daily activities and even life and health[(5, 6)].

At present, the most effective way to treat femoral fractures is surgical treatment, including intramedullary nailing fixation, bone plate screw

fixation and open surgical reduction[7]. However, in the course of surgery, the risk of postoperative bone infection is higher due to the pathological reasons of femoral fracture and the fact that patients are usually middle-aged and elderly patients with poor immune and metabolic abilities[8]. In the face of the increasingly high incidence of femoral fractures, finding a method with remarkable curative effect and extremely low postoperative infection rate is a major research hotspot and difficulty in clinical practice[9]. Jennings et al[10] pointed out that phosphatidylcholine loaded with antibiotics can effectively treat bone infection.

However, Dehnad et al[11] indicated that bone implant can be used to treat bone infection. For bone infection related to internal fixation of bone trauma, the clinical opinion is debridement of wound infection site and treatment with high concentration of sensitive antibacterial drugs[12].

However, long-term and large-dose use of antibacterial drugs can cause systemic adverse reactions of patients, which is not conducive to the rehabilitation of patients[13].

With the deepening of research, sustained release drug delivery of antibiotics has been proved to have significant effects on reducing systemic adverse reactions of patients with bone infection and improving drug efficacy for a long time[14]. Vancomycin, as a common drug for the treatment of infectious diseases, has been proved to have good effect in tibial fracture through the application of drug delivery system[15].

However, there is still little research on vancomycin slow-release drug therapy for femoral fracture after internal fixation. In order to further determine the application value of vancomycin drug delivery system for bone injury, this study provides reference and guidance for future clinical practice by observing the effect of vancomycin drug delivery system on bone infection after internal fixation of femoral fracture.

Materials and methods

Baseline data

76 patients with femoral fracture admitted to our hospital from April 2017 to April 2019 were selected as the research object.

Among them, 37 patients received vancomycin drug delivery system therapy during their visit as the RG. Another 39 patients only received routine antibiotic therapy as CG.

This study was approved by our hospital ethics committees. All subjects have signed the informed consent.

Inclusion and exclusion criteria

Inclusion criteria

- Patients with recent fresh femoral fracture;
- Symptoms such as local redness and pain, significant increase of body temperature, and patients identified with bone infection;
- Age of 20~70 years old;
- Complete case data;
- Agreed to cooperate with investigation arrangements by our hospital medical staff.

Exclusion criteria

- Patients with known severe bone defects;
- Patients with nonunion;
- Patients with blood-derived myeloma;
- Patients with other cardiovascular and cerebrovascular diseases, tumor diseases, digestive tract, respiratory tract, autoimmune defects and mental disorders;
- Patients with organ dysfunction;
- Patients with drug allergy;
- Patients who received other antibiotics within 3 months before admission;
- Patients transferred to another hospital.

Methods

The treatment plan of the CG: the antibiotic drug delivery system was configured according to 0.5 g imipenem and 0.5 mL Wright calcium sulfate, which was embedded in the peripheral area of fracture internal fixation of the patient, and the internal fixation device was removed after fracture healing.

If the patient was in the advanced stage of bone infection, the internal fixation device was removed after the fracture prognosis, and the intramedullary and external necrotic tissues and granulation tissues of the bone were removed, and then the drug delivery system was refilled in the bone cavity.

The treatment plan of the RG: the antibiotic drug delivery system was configured according to 0.5 vancomycin and 0.5 mL Wright calcium sulfate. The operation plan was the same as above.

Observation indexes

Main outcome measures

Clearance rate of bone infection, reoperation rate, fracture and bone cavity healing time of patients in the two groups.

Secondary indexes

Hemodynamics of the two groups before and after operation, including heart rate (HR), systolic blood pressure (SBP) and diastolic blood pressure (DBP). The hip joint function score was investigated by Harris score before surgery (T0), 2 weeks after surgery (T1), 4 weeks after surgery (T2) and 6 weeks after surgery (T3), with a full score of 100. The higher the score, the better the hip joint function. Rehabilitation, joint activity returned to normal and no obvious pain was assessed as excellent. Joint activity returned to normal but occasional pain was evaluated as good. Joint activity was normal, but the pain was obvious and the pain can affect the self-activity evaluation as fair.

No improvement in joint activity and significant pain was evaluated as poor. The rehabilitation rate was calculated. The rehabilitation rate = (excellent+good)/total ×100%.

The prognosis of the patients was followed up for half a year. The density of femoral head including femoral neck, Word triangle and greater trochanter of femur was measured by X-ray BMD tester before and after operation for 6 months.

Statistical methods

SPSS24.0 (Shanghai Yuchuang Network Technology Co., Ltd.) was used for statistical analysis of the experimental results. All the graphs results were drawn by using Graphpad8 (Shenzhen Tianruiqi Software Technology Co., Ltd.). Counting data was expressed in the form of (rate). Chi-square test was used for comparison between groups.

The measurement data were expressed in the form of (mean number ± standard deviation).

T test was used for inter-group comparison. Repetitive measurement and analysis of variance and bonferroni back-test were used for comparison among multiple time points.

Logistic regression analysis was used to analyze the relevant factors. The difference was statistically significant with $p<0.050$.

Results

Comparison of the baseline data

There was no difference in age, BMI, gender, fracture site, cause of fracturee, residential environment, education level, nation, whether the patient was injured for the first time, and smoking of patients between the two groups ($p>0.050$). More details are shown in Table 1.

	RG (n=37)	CG (n=39)	χ^2 or t	*p*
Age/years old			0.594	0.554
	52.6±10.8	54.1±11.2		
BMI (KG/cm^2)			0.214	0.831
	21.62±3.08	21.46±3.41		
Gender				
Male	21 (56.76)	20 (51.28)	0.229	0.632
Female	16 (43.24)	19 (48.72)		
Fracture site			0.091	0.956
Left	15 (40.54)	16 (41.03)		
Right	18 (48.65)	18 (46.15)		
Both sides	4 (10.81)	5 (12.82)		
Cause of fracture			0.448	0.503
Impact	34 (91.89)	34 (87.18)		
Others	3 (8.11)	5 (12.82)		
Residential environment			0.394	0.530
Town	28 (75.68)	27 (69.23)		
Rural	9 (24.32)	12 (30.77)		
Education level			0.053	0.819
>high school	18 (48.65)	20 (51.28)		
≤ high school	19 (51.35)	19 (48.72)		
Nation			0.948	0.330
Han nationality	36 (97.30)	36 (92.31)		
Minority nationality	1 (2.70)	3 (7.69)		
Injury for the first time			0.531	0.466
Yes	30 (81.08)	34 (87.18)		
No	7 (18.92)	5 (12.82)		
Smoking			0.514	0.474
Yes	22 (59.46)	20 (51.28)		
No	15 (40.54)	19 (48.72)		

Table 1: Comparison of the baseline data of patients between the two groups.

Comparison of clearance rate of bone infection and reoperation rate

The clearance rate of bone infection in the RG was higher than that in the CG, while the reoperation rate was lower than that in the CG ($p<0.050$). More details are shown in Table 2.

	RG (n=37)	CG (n=39)	χ^2	*p*
Clearance rate of bone infection			4.116	0.043
	34 (91.89)	29 (74.36)		
Reoperation rate			4.699	0.030
	6 (16.22)	15 (38.46)		

Table 2: Comparison of clearance rate of bone infection and reoperation rate in the two groups.

Comparison of fracture rehabilitation time

The fracture healing time and bone cavity healing time in the RG were shorter than those in the CG (p<0.050). More details are shown in Figure 1.

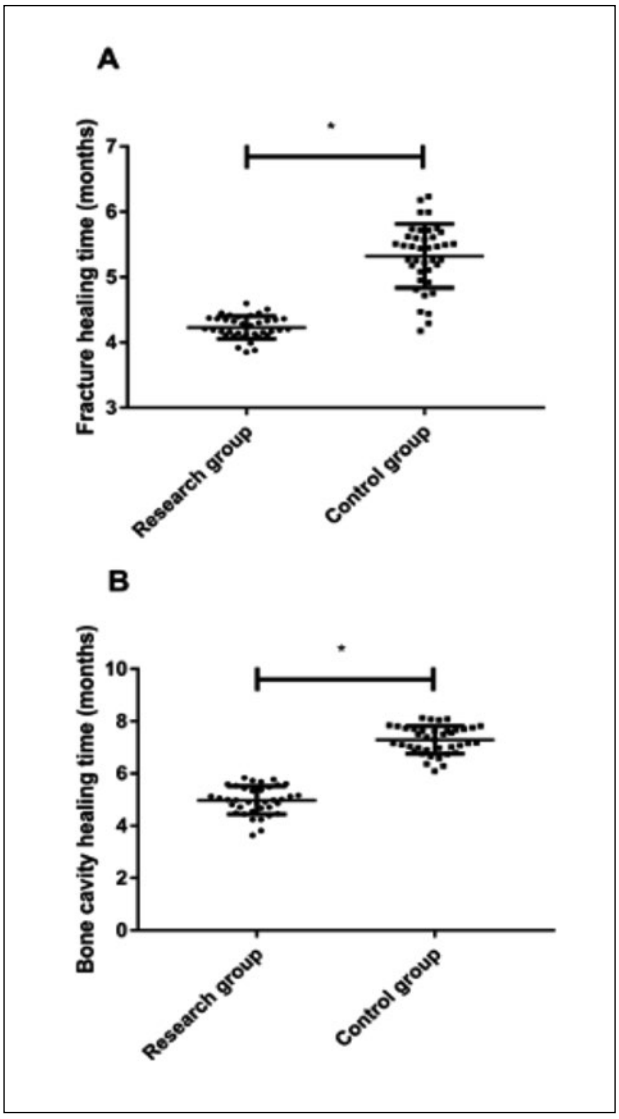

Figure 1: Comparison of fracture rehabilitation time in the two groups.

*A) Comparison of the fracture healing time in the two groups. The RG was shorter than the CG, *p<0.050. B) Comparison of the bone cavity healing time in the two groups. The RG was shorter than the CG, *p<0.050.*

Comparison of hemodynamics

There was no difference in HR, DBP and SBP between the two groups before operation (p > 0.050), while HR, DBP and SBP in the RG after operation were lower than those in the CG (p<0.050).

After operation, HR in the RG was significantly lower than that before operation (p<0.050), while DBP and SBP in the CG were significantly higher than that before operation (p<0.050). More details are shown in Figure 2.

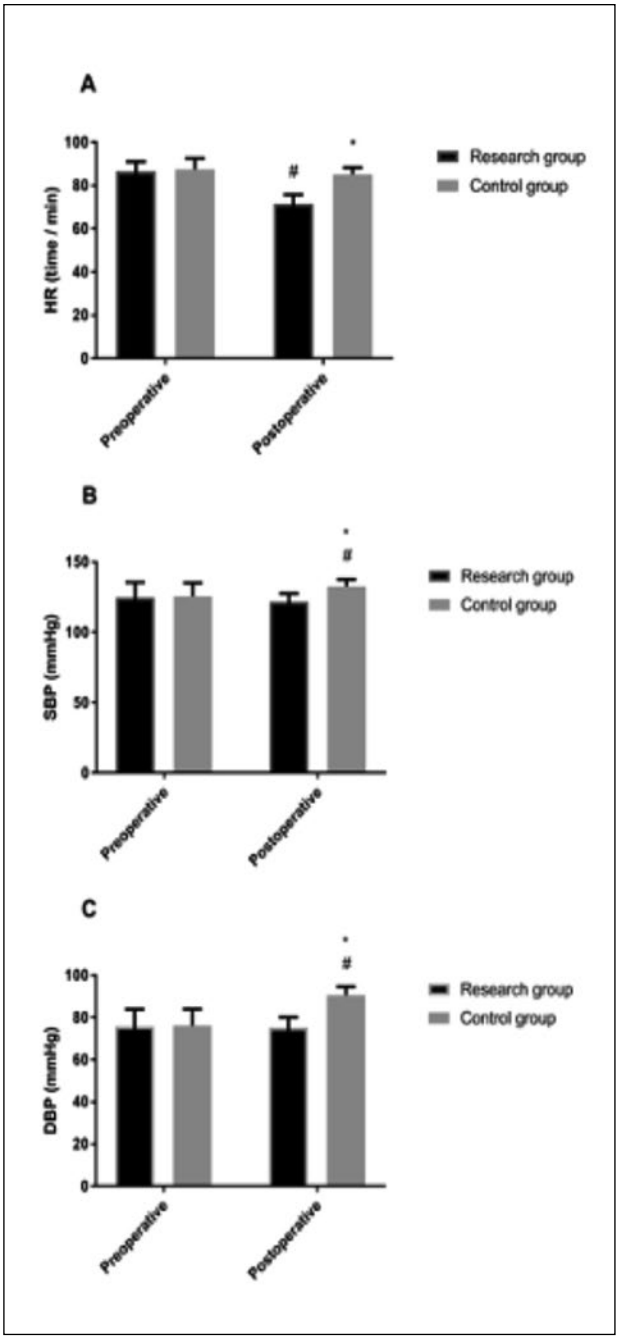

Figure 2: Comparison of hemodynamics in the two groups.

*A) Comparison of HR in the two groups; B) Comparison of SBP in the two groups; C) Comparison of DBP in the two groups. *represents the comparison with the RG after operation, p<0.050; #represents the comparison with the same group before operation, p<0.050.*

Comparison of hip joint function

There was no difference in Harris score in the two groups at T0 and T1 (p>0.050). Harris score in the RG was higher than that in the CG at T2 and T3 (p<0.050). Harris scores in both groups increased at T1, and reached the highest at T3 (p<0.050). More details are shown in Figure 3.

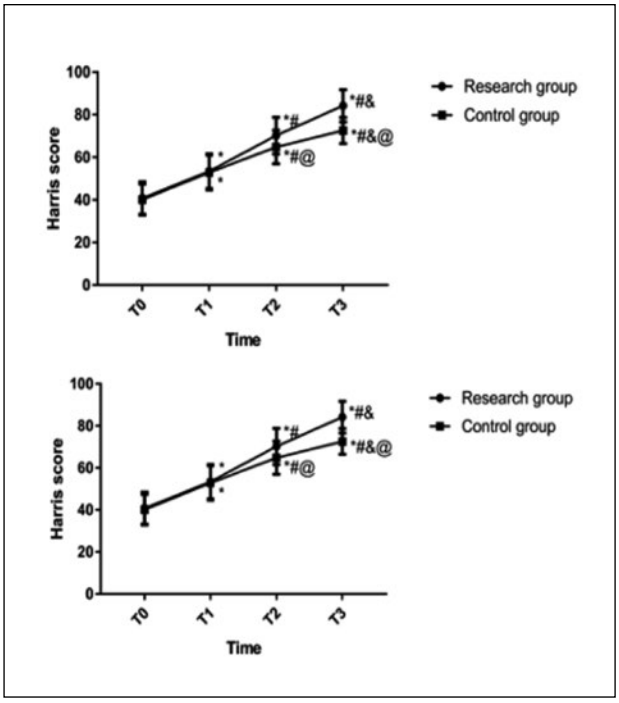

Figure 3: Comparison of Harris score in the two groups. **represents the comparison with the same group at T0, p<0.050; #represents the comparison with the same group at T1, p<0.050; &represents the comparison with the same group at T2, p<0.050; @ represents the comparison with the CG at the same time, p<0.050.*

Comparison of rehabilitation

The rehabilitation rate of the RG was 86.49%, which was higher than that of the CG (61.54%) (p<0.050). More details are shown in Table 3.

	RG (n=37)	CG (n=39)	χ^2	*p*
Excellent				
	15 (40.54)	11 (28.21)		
Good				
	17 (45.95)	13 (33.33)		
Fair				
	3 (8.11)	10 (25.64)		
Poor				
	2 (5.41)	5 (12.82)		
Rehabilitation rate (%)			6.094	0.014
	86.49	61.54		

Table 3: Comparison of rehabilitation in the two groups.

Comparison of BMD

There was no difference in BMD of femoral neck, Ward triangle and greater trochanter of femur in the two groups before treatment (p>0.050). BMD of femoral neck, Ward triangle and greater trochanter of femur in the RG was higher than that in the CG after treatment (p<0.050). BMD in the RG was significantly higher than that before treatment (p<0.050). More details are shown in Figure 4.

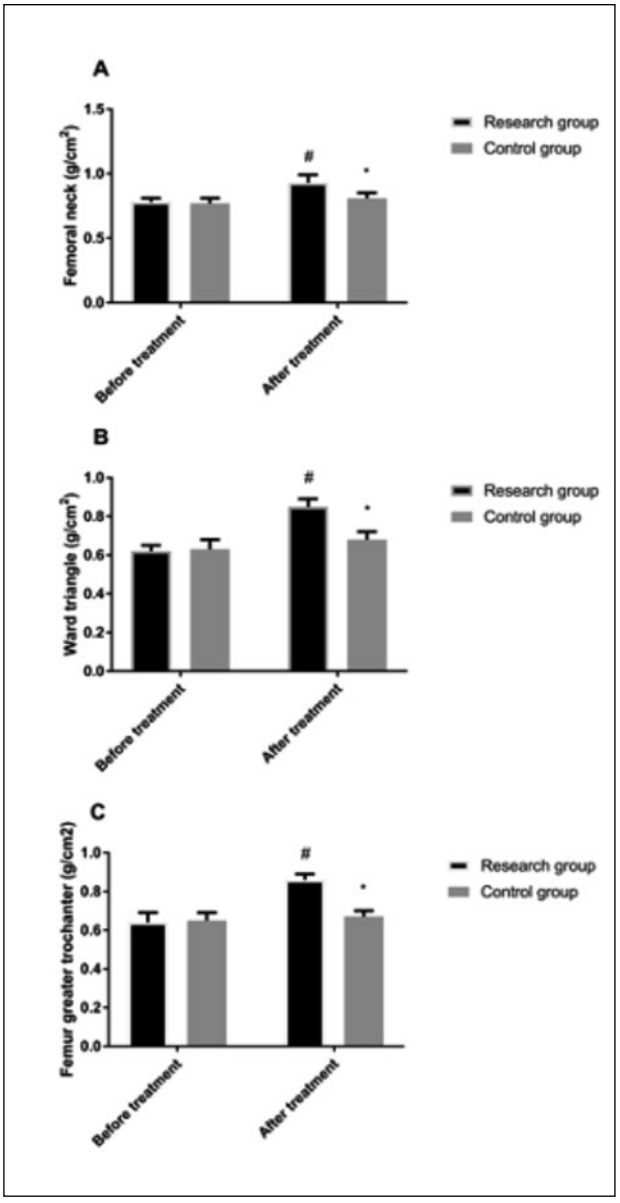

Figure 4: Comparison of BMD in the two groups. *A) Comparison of BMD of femoral neck in the two groups; B) Comparison of BMD of Ward triangle in the two groups; C) Comparison of BMD of greater trochanter of femur in the two groups. *represents the comparison with the RG after treatment, p<0.050; #represents the comparison with the same group before treatment, p<0.050.*

Univariate analysis of affecting rehabilitation of patients

All 76 patients with excellent and good recovery were divided into group A (n=51), and patients with fair and poor recovery were divided into group B (n=25). Univariate analysis was carried out on the two groups. The results showed that age, fracture site, whether the patient was injured for the first time, whether it was reoperation and treatment method were the single factors affecting the recovery of patients (p<0.050). More details are shown in Table 4.

	Group A (n=51)	Group B (n=25)	χ^2 or t	*p*
Age			9.045	<0.001
	42.21±8.26	62.12±4.23		
BMI (KG/cm^2)			0.104	0.917
	21.18±3.48	21.09±3.64		
Gender			0.057	0.812
Male	28 (54.90)	13 (52.00)		
Female	23 (45.10)	12 (48.00)		
Fracture site			14.510	<0.001
Left	23 (45.10)	8 (32.00)		
Right	27 (52.94)	9 (36.00)		
Both sides	1 (1.96)	8 (32.00)		
Cause of fracture			0.253	0.615
Impact	45 (88.24)	23 (92.00)		
Others	6 (11.76)	2 (8.00)		
Residential environment			0.003	0.960
Town	37 (72.55)	18 (72.00)		
Rural	14 (27.45)	7 (28.00)		
Education level			0.060	0.807
> High school	26 (50.98)	12 (48.00)		
≤ High school	25 (49.02)	13 (52.00)		
Nation			0.119	0.730
Han nationality	48 (94.12)	24 (96.00)		
Minority nationality	3 (5.88)	1 (4.00)		
Injury for the first time			22.300	<0.001
Yes	50 (98.04)	14 (56.00)		
No	1 (1.96)	11 (44.00)		
Smoking			0.008	0.928
Yes	28 (54.90)	14 (56.00)		
No	23 (45.10)	11 (44.00)		
Reoperation			33.680	<0.001
Yes	3 (5.88)	18 (72.00)		
No	48 (94.12)	7 (28.00)		
Methods of treatment			9.086	0.003
Vancomycin	31 (60.78)	6 (24.00)		
Imipenem	20 (39.22)	19 (76.00)		

Table 4: Single factors of affecting rehabilitation of patients.

Multiple factors of affecting rehabilitation of patients

Indicators with differences in univariate analysis results were included in assignment (shown in Table 5). Then LR was selected for Logistic regression analysis. The results showed that age, both fracture, non-first injury and reoperation were independent risk factors affecting the rehabilitation of patients (p<0.050), while vancomycin slow-release drug therapy was independent protective factor affecting the rehabilitation of patients (p<0.050). More details are shown in Table 6.

Factors	Assignment
Age	The data conformed to continuous variables and were analyzed by using original data.
Fracture site	Left=0, Right=1, Both sides=2
Injury for the first time	Yes=0; No=1
Reoperation	No=0; Yes=1
Methods of treatment	Imipenem=0; Vancomycin=1

Table 5: Assignment.

Factors	B	S.E.	Wald χ^2	*p*	OR	95%CI
Age	0.715	0.324	5.165	0.018	2.142	1.132~4.062
Fracture site	1.231	0.394	9.216	0.001	3.142	1.568~7.624
Injury for the first time	0.942	0.421	5.085	0.021	2.542	1.154~5.161
Reoperation	0.813	0.348	6.162	0.012	2.258	1.187~4.162
Methods of treatment	-0.162	0.215	3.687	0.004	0.716	0.547~1.386

Table 6: Results of multivariate analysis.

Discussion

With the development of society, frequent traffic accidents caused by the increase of motor vehicles are the key reasons for greatly increasing the incidence of femoral fractures[16], while bone infection in the process of fracture healing is the main factor threatening the recovery of patients, and its severity can greatly affect the life safety of patients[17]. Antibiotic drug delivery system is a new scheme to deal with infectious diseases in clinical practice in recent years. At present, remarkable results have been achieved in the treatment of many diseases[18, 19]. Previous studies have pointed out that the treatment of bone infection through antibiotic drug delivery system can not only increase the drug concentration of internal fixation, but also reduce the incidence of adverse reactions caused by antibiotic therapy[20].

In this study, the efficacy of vancomycin slow-release drug therapy for bone infection with femoral fracture was compared, which has important reference significance for future clinical treatment for such patients. The results of this experiment showed that the bone infection clearance rate and reoperation rate of the patients treated with vancomycin drug delivery system in the RG were significantly lower than those of patients treated with imipenem drug delivery system in the CG.

This also confirmed the important role of vancomycin drug delivery system in the treatment of femoral fractures. This is similar to the results of Ueng et al[21]. This can be taken as evidence of this study. Vancomycin has good stability in the treatment of infectious diseases, and can block pepti-

doglycan synthesis in cell walls by combining with target sites on the bacterial cell walls, thus achieving the purpose of promoting cell death[22]. Vancomycin has a wide antibacterial spectrum, has little damage to osteoblasts and has no negative effect on bone healing, so it is extremely suitable for the treatment of bone infection in the process of fracture[23].

In previous studies, as low-dose vancomycin bioavailability disorder is a major clinical research difficulty, large hydrophilic molecules were ineffective to penetrate lipophilic gastrointestinal mucosa through oral administration of vancomycin, while renal toxicity, allergy and gastrointestinal tract rejection were easy to occur through intravenous administration[24].

The drug delivery system can effectively solve this problem by increasing the local drug concentration while reducing the blood drug concentration, and can avoid rejection adverse reactions in other tissue environments in the body due to direct action on the infected site.

The comparison of fracture rehabilitation time of patients in the two groups also showed that the RG was significantly shorter than the CG, which further illustrated the effectiveness of vancomycin drug delivery system in treating bone infection. However, we observed the hemodynamic changes of patients in the two groups before and after operation and found that the heart rate of the patients in the RG decreased after operation, and the blood pressure changes were more stable, which also suggested that vancomycin drug delivery system had less influence on the hemodynamics of patients with bone infection. Buness et al[25] proposed that vancomycin has potential immunoregulation effect.

We suspected that vancomycin can also play its role in the treatment of bone infection, but the exact mechanism needs further experimental confirmation. Further comparison of Harris score, rehabilitation and BMD changes of hip joints in the two groups showed that the RG was better than the CG, in which the BMD of the patients in the RG after treatment was significantly higher than before treatment, while the CG has no change.

It further indicated that vancomycin has certain effect on improving the bone health of patients. Previous studies have confirmed that vancomycin can improve BMD of rats during fracture healing process[26], which may be due to the influence of vancomycin on intestinal flora[27].

Intestinal bacteria may cause changes in some bone minerals to improve BMD[28].

Through the comparison of the above results, we believed that vancomycin drug delivery system has the following advantages in treating patients with bone infection after internal fixation of femoral fracture:

• It has high biocompatibility and can effectively fill the necrotic tissue due to fracture.

• Vancomycin has a wide antibacterial spectrum, and can kill pathogenic bacteria of bone infection more effectively through local release to achieve the aim of curing.

• It has high stability and low adverse reactions to wound healing at fracture site. It can effectively shorten the rehabilitation process of patients.

• The damage to osteoblasts is small, and it may be more conducive to the prognosis and rehabilitation of patients and improve the bone health of patients by acting on intestinal flora.

Further analysis of the relevant factors affecting the rehabilitation of patients showed that vancomycin slow-release drug therapy was an independent protective factor affecting the rehabilitation of patients, which is also consistent with our above results and analysis. However, age, both fracture, non-first injury and reoperation are independent risk factors that affect the rehabilitation of patients. The causes may be related to the decline of immune ability, metabolic ability and rehabilitation ability of elderly patients. Both fracture is more serious than unilateral fracture and rehabilitation is naturally more difficult. However, in patients with first injury and reoperation, the stability and integrity of bone tissue will be greatly reduced due to secondary injury, which is more adverse to recovery.

In this study, vancomycin drug delivery system was explored to treat patients with bone infection after internal fixation of femoral fracture. However, there are still deficiencies due to limited experimental conditions. For example, the long-term prognosis of patients cannot be determined due to the short study period. We will conduct a longer follow-up investigation on the subjects in this study to obtain more comprehensive results. However, due to the small number of cases, it is not excluded that some of the results are accidental. We will conduct statistical analysis of multiple-case data with several hospitals as soon as possible to obtain more representative results. However, there are still some limitations in the application of vancomycin slow-release drug therapy to patients with bone infection of femoral fracture at present. For example, lesions need to be removed as much as possible during the operation to

minimize residual infection. However, for patients with large-area fractures and complex fractures, there may be accumulation of other surrounding related bone joints. At this time, the use of vancomycin may damage the stability of bone structure and further worsen the patient's condition. Therefore, the application of vancomycin drug delivery system needs to be selected according to the actual clinical situation and we will also conduct a more in-depth analysis on the above to find the best solution.

To sum up, vancomycin drug delivery system can effectively improve the clearance rate of bone infection, accelerate the recovery of fracture and improve the bone health of patients to a certain extent for the treatment of bone infection after internal fixation of femoral fracture. It has great application prospect in clinic in the future.

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