

Study of the therapy of multiple myeloma monoclonal antibody

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Abstract: This paper aims to discuss the initial clinical effect of treating bone defect of long bone osteomyelitis with Masquelet technology. A retrospective analysis was made among the recruited 25 patients with long bone osteomyelitis patients from April, 2013 to February 2014 from Henan Provincial People's Hospital. Clinical effect of treating long bone osteomyelitis with Masquelet technology and the possible effects of vancomycin in different doses on knitting were also evaluated in follow-up visit lasting for 6~18 months, and 22 cases' bone was healed on imaging at the last follow up. According to Samantha X ray score criteria, Samantha score of regular dose group and high dose group in 4 months after operation was 4.16 and 3.09, respectively. There were 12 cases in regular-dose antibiotic group, among which, 1 case had delayed wound healing, and 3 cases reoccurred; there were 10 cases in high-dose antibiotic group, among which, no cases reoccurred after operation. Masquelet technology is a reliable and easy osteomyelitis treatment. Notably, it shows significant advantages for long bone reconstruction induced by infection and trauma. Bone cement with high dose of vancomycin has better effect on controlling osteomyelitis than bone cement with regular dose of vancomycin.

Keywords: Osteomyelitis; bone defect; Masquelet technology.

INTRODUCTION

Post-traumatic osteomyelitis is a disease faced by clinical orthopedic surgeon for a long time. Infection control and bone reconstruction are two problems that puzzle clinical treatment. Thus the study in this aspect is also a common focus of many experts. In paper from Xiao Jun, *et al*, it analyzed the clinical application of free vascular fibular transplanatation in treating long bone defect and osteomyelitis, and it proved that this transplation was a better method in clinical treatment (Jun *et al*, 2011). In paper from Chen Qiuyue, Shang Peng, it focused on the important regulation effect of RANKL in controlling the product of osteoclast by osteoblast (Qiuyue and Peng, 2013). It illustrated that RANKL played a major role in sustaining the bone reconstruction and it furtehr made some explanation by taking this as a center. Besides, it introduced the function mechanism of RANKL in molecule within bones in detail, which provided a new theoretical reference for bone construction, a complex medical engineering, and directed the road to developing a new medicine for bone diseases. Lizarov technology gives continuous tension on fracture ends relying on external fixator, thus to stimulate tissue regeneration and achieve bone reconstruction. However, the disadvantage of this method includes complex instruments, tedious clinical operation and long treatment cycle. Masquelet technology is a kind of bone reconstruction method invented by Masquelet *et al* (Masquelet *et al*, 2000). Bone of 35 cases treated by this method was healed on imaging in 4 months after operation. At present, there are a few reports on this method around the world, but the amount of cases is small. Meanwhile, careful clinical observation for early-stage bone healing after operation is

lack of. This method has not drawn wide attention at domestic. Our department treated 25 cases of bone defect of long bone osteomyelitis and post-traumatic bone defect with Masquelet technology and obtained satisfactory effect, hoping to provide a basis on promoting Masquelet technology in the treatment of bone defect of long bone osteomyelitis and post-traumatic bone defect in clinic.

MATERIALS AND METHODS

Data instructions

There were 25 patients, ranging in age from 19 to 68 years (mean 39.6 years), including 6 males and 19 females. Of the 22 cases infection cases, 14 cases were infection after internal fixation, accompanied by obvious sinus tract clinical presentation; 3 cases were nonunion after fracture internal fixation, which has intact skin before operation but is proved to be osteomyelitis when a large amount of fester is found; 5 cases had infection history or osteomyelitis debridement therapy history in the past; the remaining 3 cases were post-traumatic bone defect or bone ununion after repeated treatment. Of the 22 cases of osteomyelitis, bacterial culture of 19 cases were positive, including 4 cases of MRSA⁺, 2 cases of *Pseudomonas aeruginosa*, 4 cases of *Staphylococcus aureus*.

1 case of *Serratia marcescens*, 1 case of *Staphylococcus hominis*, 1 case of *Staphylococcus warneri*, 1 case of *Staphylococcus epidermidis*, 5 cases of mixed strain infection.

Monomer and powder was mixed in whole package since it is impossible to properly match bone cement monomer and powder. Finally, the dosage is determined by range of bone defect. Cases can be divided into two groups based

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on the dosage of antibiotic used: regular-dose antibiotic group and high-dose antibiotic group. There were 12 cases in regular-dose antibiotic group with 40g cement mixed with 2g vancomycin. There were 10 cases in high-dose antibiotic group, among which, 2 cases were failed cases in regular-dose antibiotic group, with 40g bone cement mixed with 5g or 10g vancomycin.

Therapeutic method

The operation was performed in two times: first time was to debride wound and implant antibiotic bone cement; second time was to take autogenous bone and implant. Tourniquet was ligatured on end of limbs. Then do regular disinfection and spread drape. Select proper approach after determining lesion by magnetic resonance imaging before operation. Clear sequestrum and necrotic tissue. During the operation, sequestrum was performed bacterial culture and pathological examination. Replace all internal fixation materials and clear surrounding tissue. Hemorrhage syndrome appeared when polishing capitulum. Clear medullary space. Then wound was washed with dilute hydrogen peroxide and normal saline, and cleared by pulse washing system with 2 to 3 bags of washing liquid. Implant bone cement into bone defect part. Polish it that is covered by bone cement into fusiform capitulum exceeding 1~2 cm. The dosage of bone cement should be paid attention, in order to avoid the difficulty of closing incision. Brine ice was slowly poured into the wound to prevent burn on tissue caused by heat dissipation of bone cement. External fixator was suitable for fixation. Patients who was performed fixation should be fully informed the risks. The second stage operation was performed at 6~8 weeks after bone cement implantation. The above procedures could be repeated if inflammation reoccurred during that period. Autogenous bone taken from posterior superior iliac spin was cut into pieces for later use. Expose bone cement along previous incision approach. Hit the place where connected with capitulum and take out bone cement. It can be seen that, there was a layer of white pseudomembrane on the tissue that closely connected to the surface of bone cement. Get through pulp cavity on two ends. Take samples of pulp cavity and pseudomembrane for bacterial culture. Protect the integrity of pseudomembrane with little exposure as possible. Do full bone grafting within pulp cavity, and cancellous bone fully covered up fusiformis capitulum. Indwell drainage and close incision.

Postoperative management

The patients were treated with sensitive antibiotics selected based on susceptibility results for 2 weeks after the first stage operation. Negative pressure drainage ball was indwelled for 5~7 days. Perform X ray examination at first day after operation. Review blood routine and hepatorenal function at 3rd and 7th day after operation. After the second stage operation, vein was processed by antibiotics for 24~28 h for preventing wound infection. At

1st day after operation, perform X-ray examination. As to nonunion patients, length of medial and lateral cortical bone defect was measured on anteroposterior X-ray film, the length of front and back cortical bone defect was measured on lateral X ray film. As to lacuna bone defect patients, their length of cortical bone defect was measured on anteroposterior and lateral film. The loads should be reduced in 1 month after bone grafting. Activities can gradually increase if poroma forms when reviewing X-ray film.

Postoperative follow-up

Follow-up visit was performed in 1st, 2nd, 4th, 6th, 8th, 12th, 18th, 24th month after the operation. Follow-up content is to assess the growth of poroma with Samantha X ray assessment (Salkeld *et al.*, 2001): assess for 1 point if radioactive rays density of bone grafting lightly increases; assess for 2 points if radioactive rays density of bone grafting obviously increases; assess for 3 points if at least one side cortex of osteotomy end connects with uneven sclerotin; assess for 4 points if medial and lateral osteotomy end connects with cortical bone but osteotomy end can also be distinguished; assess for 5 points if there is at least one dim osteotomy besides same presentation of 4 levels; assess for 6 points if bone defect completely connects with newborn bone cortex and bone density is even.

RESULTS

A total of 25 cases were all followed up for 6~18 month. A total of 22 cases were seen knitting on imaging at the last follow-up. According to Samantha X-ray score criteria: 5 cases were assessed for 1 point in 2 months after the operation, 18 cases for 2 points, 2 cases for 3 points; 1 case was assessed for 2 points in 4 months after the operation, 4 cases for 3 points, 15 cases for 4 points, 5 cases for 5 points. Of 18 cases of nonunion (bone defect length in 2~9cm, as shown in table 1 and 2), 4 cases with bone defect ≤ 3 cm obtained the lowest score, 8 cases with bone defect ≥ 5 cm obtained the highest score; 16 cases was seen knitting on imaging at the last follow up.

Of 12 cases of regular-dose antibiotic group, 1 case had delayed incision healing after the operation, 2 cases had infection on posterior superior spine, and 3 cases reoccurred at 41~ 90 days after the first stage operation. Of 10 cases of high-dose antibiotic group, there were no reoccurring cases after the operation, including 2 cases that reoccurred in regular-dose group but turned to high-dose antibiotic after debridement. At follow-up visit in 4 months after the operation, Samantha score was similar in regular-dose group and high-dose group, 4.16 and 3.90, respectively. There was no significant abnormality among two groups while reviewing hepatorenal function.

Table 1: Samantha score of patients with nonunion in different part after the operation

Parts	Case number	Average age (year)	Defect length (internal and external cortex of antero-posterior film, mm)		Defect length (front and back cortex of lateral film, mm)		Samantha score	
			Internal	External	Front	Back	2 month after operation	4 month after the operation
Tibia	10	42	62	52	54	45	1.70	3.70
Thighbone	5	39	41	42	38	47	2.00	4.00
Radius and ulna	2	42	51	52	48	47	2.50	4.00
Fibula	1	38	56	41	45	48	2.00	4.00

Table 2: Samantha score of nonunion patients with different bone defect length after the operation

Length	Case number	Average age (year)	Samantha score	
			2 month after operation	4 month after operation
≤3 cm	4	35	1.50	3.25
>3~<5cm	6	49	1.83	4.00
≥5cm	8	36	2.13	4.13

**Fig. 1:** X-ray film performance of 1 female patient with thighbone post-traumatic osteomyelitis before and after Masquelet bone reconstruction.

A: before the surgery; B: after the first stage surgery; C, D: after the second stage surgery and local zoom; E, F: in 2 months after the surgery and local zoom; G, H: in 4 months after the surgery (anteroposterior position) and local zoom; I, J: the last time follow-up visit (anteroposterior and lateral position in 8 months after the surgery)

**Fig. 2:** X-ray film performance of 1 male patient with 9 cm tibia post-traumatic segmental bone defect before and after Masquelet bone reconstruction

A: before the surgery; B: after the first stage surgery; C, D: after the second stage surgery and local zoom; E, F: in 2 months after surgery and local zoom; G, H: in 4 months after the surgery (anteroposterior position) and local zoom; I, J: the last time follow-up visit (anteroposterior and lateral position in 8 months after the surgery)



Fig. 3: Observation of the female patient before and after granular autologous cancellous bone grafting during the second stage surgery
A: before bone grafting; B: after bone grafting

Typical case 1: female, 28 years old, osteomyelitis in the middle part of left thighbone. Skin of patients has wide scar and contracture due to the trauma. In addition, local sinus tract suppurate and discharge, accompanied by bone exposure. The patient was performed Masquelet bone reconstruction. Capitulum was fusiformis and fully covered by bone cement and cancellous bone. The wounds were healed well after the operation. In 2nd and 4th month, Samantha score was 2 points and 4 points, respectively (fig. 1). Typical case 2: male, 22 years old, left tibia unhealed after left tibia distal fracture surgery. The patient has open fracture history, with fixation of external fixator. Perform Masquelet bone reconstruction, and measure the length of bone defect was 9 cm. The wound healed well after the operation. In 2nd and 4th month, Samantha score was 2 points and 4 points (figs. 2 and 3).

DISCUSSION

Infection control and bone reconstruction are two difficulties in post-traumatic osteomyelitis. Bone reconstruction is the core problem that puzzles osteomyelitis treatment. Due to the lack of relative bone reconstruction means, surgeons usually hesitate during debridement, and even reimplant in situ after the inactivation of sequestrum. Typical bone reconstruction technologies, no matter Ilizaro bone lengthening or vascularized fibula grafts, all exist drawbacks that is hard to overcome by itself. Granular autologous cancellous bone grafting is widely applied since it has good bone conduction and induction characteristics. In segmental bone reconstruction, the length of bone reconstruction generally does not exceed 4-5cm due to the easy occurrence of bone absorption and incomplete corticalization. Scholars are constantly searching for solution for this problem, such as alginate membrane, rhBMP (Giannoudis and Dinopoulos, 2010).

In 2000, Masquelet *et al* (Masquelet *et al.*, 2000) reported a kind of pseudomembrane induced bone reconstruction method, including 35 patients with bone defect length of 2~25 cm. Key of this method is that, use bone cement to fill bone defect to form a visible white pseudomembrane in the first stage; carefully implant fresh autologous cancellous bone into pseudomembrane cyst in the second stage. In the condition of lack of bone source, allogeneic bone and autologous bone can be mixed in ratio of 1:3 or 1:4. What surprise us is that, these bone defects with different length, part and pathogenesis all healed on imaging in 4 months after the operation. Similar research results have been proved by the researches in other countries (Stafford and Norris, 2010; Chong *et al.*, 2011; Chotel *et al.*, 2012). In order to prove the importance of membrane, Klaue *et al* (Kaj *et al.*, 2009) designed a group of animal experiments that took sheep as model: take 3 cm of backbone, and design membrane and autologous bone grafting into two variables. It was found that, only when membrane and autologous bone exist at the same time can bone rapidly heal. Pelissier *et al* (2004) found that, the membrane that forms by bone cement induction can secrete factors such as BMP-2 and VEGF, and plays an important role in bone remodeling.

Masquelet held that, membrane is the key factor that lead to rapid healing of bone defect, thus membrane should be protected. In order to make induced membrane fully cover bone grafting area and capitulum cross-connecting area (1~2cm), capitulum should be fully polished and removed corticalization, finally, in fusiformis form, in the premise of completely clear focus during debridement in first stage. Antibiotic bone cement covered up capitulum and fully full tissue gap, but too much antibiotics should be avoided for preventing difficulty of incision close. What deserves attention is that, bone cement in hip and knee replacement surgery is mainly within pulp cavity, and not connected with soft tissue directly. However, the

antibiotic bone cement used here was connected with soft tissue closely and a large amount of heat would produce during remodeling and burn the tissue, therefore, ice water was needed for cooling. Although there was studies demonstrating increasing the amount of antibiotics can lower the intensity of bone cement, Masquelet bone reconstruction do not shoulder mechanical task. Bone cement with increased amount of antibiotics has more brittleness, therefore, is easy to be removed compared with ordinary bone cement, especially in the condition of using internal fixation. Moreover, the release property of self-control cement is significantly lower than antibiotic bead chain. Shinsako *et al* (2008) made 3 kinds of antibiotic bead chain with different sizes by adding 6 g of vancomycin into 40 g bone cement, and found that, the release of vancomycin briefly rose and then maintained. Release amount of vancomycin bead chain of the smallest volume (0.96g) and of the largest volume were 7.2% and 3.1%, respectively. Therefore, it was speculated that, adding 5 g or 10 g of vancomycin into bone cement was safe. In addition, part of bone cement after mixing was used, and the concrete dosage depends on the length of bone defect. Through the comparison of hepatorenal function before and after the operation and clinical follow-up, it was found that, the hypernormal dosage of vancomycin in bone cement did no harms to the patients. A total of 10 cases local high-dose vancomycin patients successfully completed bone grafting after one time of debridement and non-cases reoccurred infection. Samantha score of two groups of patients after the operation was much similar. High-dose vancomycin did not produce toxic and side effect on local, thus its effect on fracture healing was avoided. In the sampling culture of induced membrane and pulp cavity in the second stage, there were 2 subcultured cases in regular-dose group showing positive, the same in the local high-dose treatment group. At the same time, the kinds of bacteria also changed. ESR and CRP had no increase through detection. These positive cases were performed autologous cancellous bone grafting and healed, and infection did not reoccur among them at the last follow-up visit. Some scholars at domestic (Yan *et al.*, 2014; Gaoling and Changying, 2014) conducted research on adding high-dose vancomycin into bone cement, but its safety and long-term curative effect need to further observed and followed up in clinic.

There are studies suggesting to induce concept of bone cancer into osteomyelitis treatment and directly perform Enbock excision on segmental infection (Sanders and Mauffrey, 2013). Although there is a lot of means that cause segmental bone defect, there is still no unified and reliable solution. For example, vascularized fibula grafts and remodeling is slow. The growth rate in the first and second year after the operation were 31.53% and 26.61%, respectively (Youshui *et al.*, 2012; Yanqin *et al.*, 2014); Ilizarov bone lengthening has long cycle and painful

process with healing index of 35~50 d/cm. In this study, 8 cases with bone defect ≥ 5 cm and 6 cases with bone defect between 3~5 cm all healed rapidly. Their Samantha score difference was small, for example, the scores of case 1 and 2 were both above 4 points.

CONCLUSION

Based on these discussions, a good therapy should intergate several aspects of osteomyelitis. Based on Masquelet technology, implanting antibiotic bone cement to fill dead space can avoid palindromia of inflammation. A local release of antibiotic in high concentration to inhibit the regeneration of bacterial biofilm, and can also lay a basis on the bone reconstruction in later stage. This is the main difference between the antibiotic cement applied in this method and that applied in cement replacement for hip and knee fractures. Of course, there remain a great number of problems without solution in Masquelet technology. Only with a constant study, trial and an active cooperation and contact with the foreign world, can we be available for the therapy of osteomyelitis at home.

To sum up, Masquelet technology is a reliable and simple osteomyelitis treatment method. Notably, it shows significant advantage in segmental bone reconstruction caused by trauma. The osteomyelitis controlling effect of bone cement with high-dose vancomycin is better than bone cement with regular-dose vancomycin.

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