Masquelet Technique Combined with Tissue Flap Transplantation in The Treatment of Infectious Complex Tissue Defect: A Clinical Analysis

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Research

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Abstract

Background: Infectious complex tissue defects have been described as injuries with composite infectious bone defects and extensive soft tissue damage, which are still austere challenges for orthopedists all around the world. The study retrospectively evaluated the Masquelet technique combined with the tissue flap transplantation for the treatment of infectious complex tissue defects and assess key factors of success in this technique.

Methods: From December 2016 to December 2019, 22 patients of infectious complex tissue defects were recruited for the study. All the cases experienced a two-stages treatment. Thorough debridement, stabilization of fracture by external fixation and implantation of a cement spacer mixed with antibiotics in the first stage. Simultaneously, suitable tissue flaps were designed and transplanted for the soft tissue defect. 6-8 weeks later, after the elimination of the infection, the cement spacer was removed carefully from the induced membrane and cancellous bone was grafted into the site of bone defect. The average duration of follow-up was 21 months.

Results: Infection was eliminated after the first stage intervention without recurrence. All the transplanted tissue flaps were survived. Bone union was achieved in all patients in a period of 16-31 weeks following the second stage surgery. According to the Paley fracture healing score, 17 patients showed excellent results and 5 patients displayed good results regarding bone outcomes. When considering functional outcomes, 14 patients exhibited excellent results and 8 patients displayed good results.

Conclusions: This study showed evidences that Masquelet technique combined with tissue flap transplantation was an effective method to repair the infectious complex tissue defects. We also demonstrate that a complete soft-tissue envelope plays an important role in the formation of the induced membrane which promote bone union and in the anti-infection treatment.

Background

Infectious complex tissue defects have been described as injuries with composite infectious bone defects and extensive soft tissue damage which can lead to increased susceptibility to significant long-term morbidity and disabilities such as amputation [1]. The main causes of the infectious complex defects are open fracture such as Gustilo-Anderson type III trauma and infection after internal or external fixation [2]. According to statistics, the incident of infection for all orthopedic subspecialties ranged from 0.1–30% and the costs per patient reached up to \$150,000 [3]. To date, due to the high recurrence rate and high disability rate, the treatment of infectious complex tissue defects is still an austere challenge for orthopedic surgeons.

A wide range of surgical interventions using for treatment of bone defect are reported including free vascularized bone grafting, Papineau bone grafting, Ilizarov technique, massive allograft transplantation and tissue engineering techniques [4]. The Masquelet technique, also known as induced membrane technique, is one of the treatments that has shown satisfactory outcomes in the management of bone defects [5]. Numerous successful cases have been reported when Masquelet technique was applied in the management of bone defect, nonunion and osteomyelitis [6, 7]. The length of the defect repaired by Masquelet technique can reach 25 cm [8]. Application of Masquelet technique in the treatment of infectious complex tissue defect has been sparsely reported. In this study, we applied Masquelet technique combined with the tissue flap transplantation to treat infectious complex tissue defects and encouraging outcomes were achieved.

The purpose of this study was to: i) demonstrate our experience with the united use of tissue flap transplantation and Masquelet technique in the management of infectious complex injuries with composite bone and soft tissue defects; ii) assess the clinical effect of this method;

Methods

This retrospective study was reviewed and approved by the institutional review board, and informed consent was obtained from all patients. 22 patients suffered from infectious complex tissue defect were recruited for the study from December 2016 to December 2019. All patients were managed in the orthopedics department of our hospital. The retrospective study involved 13 males and 9 females with a median age of 47 years (24 - 67 years) at the time of surgery. The sites of bone defects localized on

tibia (17), radius (1), calcaneus (2), metatarsus (2). 11 cases were caused by the open fracture, 10 infectious defect were caused by infection after internal fixation and 1 case was caused by infection after external fixation.

X-ray plain film and computed tomography (CT) were performed to find out the size of the bone defect. All patients accepted positron emission tomography (PET-CT) examination to identify the scale of the infection. Necrotic tissue and secretions were obtained for bacterial culture and drug sensitivity test to select sensitive antibiotics. All the patients accepted blood routine examination, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and procalcitonin (PCT) to detect the condition of the infection.

The whole procedure for the treatment of infectious complex tissue defect is shown in figure1. In the first-stage operation, thorough debridement was performed to remove necrotic and infected tissue until healthy tissue presented. In the cases of infection after internal fixation, the internal fixations were removed. After debridement, external fixators were placed to stabilize the affected bone, the fixation nails should be placed outside the scale of the infection and enough space should be reserved for the tissue flap donor area in this procedure. Deep tissue samples from the debridement were taken for microbiological culture and metagenomic next-generation sequencing (mNGS). A polymethylmethacrylate (PMMA) cement spacer mixed with antibiotics was implanted in the site of the bone defect. We designed tissue flaps to cover the wound according to the location and size of the soft tissue defect. 15 local perforator tissue flaps, 3 free flaps and 1 groin flap, were used in this study. In addition, 3 muscle flaps were combined with the skin graft. The temperature and color of the flaps were monitored in order to judge perfusion and venous conditions. Antispasmodic and anticoagulant medications were administered intravenously for five days post-operatively.

6 to 8 weeks later, PET-CT and blood exams were reexamined. When the white blood cell count, ESR, CRP and PCT was within the normal range, result of PET-CT showed no infection signs and clinical signs of infection were precluded, the second stage operation was performed. The healed wound was carefully incised, and a well-formed induced membrane was split longitudinally to remove the cement spacer. Samples of tissues were taken for intraoperative frozen section diagnosis. If the intraoperative frozen section reported less than 5 neutrophils per high power field, the bone graft could be performed. The anterior superior iliac spine was resected and cut into autologous granular cancellous bone. These cancellous pieces mixed with allogeneic granular cancellous bone were inserted into the site of the bone defect and the induced membrane was preserved and sutured. Internal fixations were applied for the fracture stabilization. External fixation maintained if the bone defect was large.

Post-operatively, we permitted patients to ambulate with protected weight bearing and encourage them to perform joint range of motion exercise. Clinical and radiological follow-up were performed every 4-6 weeks before bone union. Bone growth results, functional results and relative complications were checked every 3 months for the following period. At the final follow-up, the fracture healing index was assessed using the Paley fracture healing score.

Results

22 patients were followed up for an average of 21.3 (12 to 36) months. All patients were diagnosed as infectious complex tissue defects according to the clinical and imaging examinations. The demographic and clinical characteristics are shown in Table 1.

3 cases repeated the first stage operation when the PET-CT results showed sign of infection before the second stage operation. Infection was eliminated without recurrence in all patients. Microbiological cultures from tissue samples tested positive in 13 cases and the results of mNGS showed positive in 19 cases. The bacteria found in the site of infection including *Staphylococcus aureus*, *Enterobacter cloacae*, *Enterococcus faecalis*, *Enterococcus faecium*, *Pseudomonas aeruginosa*, *Streptococcus viridans*, *Clostridium perfringens*, *Actinomyces radingae* and *Anaerococcus hydrogenalis*.

The tissue flap size ranged from 6*3 cm² to 21*10 cm². All the transplanted tissue flaps were survived. Necrosis was occurred on the edge in 3 flaps, but the complete coverage of wound was not affected. All soft tissue defects were successfully repaired after the first stage intervention.

Bone union was achieved in all patients at a mean of 22.2 weeks (12 to 31 weeks). The mean interval between the two stages was 7.7 weeks (range 6 to 11 weeks). The median length of the bone defect was 5.4cm (range 3.0 to 13.6 cm). Redness and swelling appeared around the external nail in 4 patients. These symptoms vanished after the external fixations were removed. At the final follow-up, all patients displayed full weight-bearing capacity with no assistive device. According to the Paley fracture healing score (Table2) [9], 17 patients showed excellent results and 5 patients displayed good results in bone outcomes. When considering functional outcomes, 14 patients exhibited excellent results and 8 patients displayed good results.

Table 1
Demographic and clinical characteristics of the patients.

ID	Gender/Age (years)	Etiology	Site of defect	Bone defect (cm)	Size of flaps (cm ²)	Type of flaps	Microbiological culture	mNGS	Bone union time (weeks)
1	M/37	Infection after external fixation	Tibia	6.6	7*4	muscle flap	<i>Enterobacter cloacae</i>	Mixed infection	20
2	M/67	Infection after internal fixation	Tibia	3.3	12*6	local flap	/	<i>Clostridium perfringens</i>	27
3	F/50	Open fracture	Tibia	2.2	15*9	free flap	<i>Staphylococcus aureus</i>	<i>Staphylococcus aureus</i>	30
4	M/24	Open fracture	Radius	10.3	20*6	groin flap	<i>Pseudomonas aeruginosa</i>	<i>Pseudomonas aeruginosa</i>	31
5	M/34	Infection after internal fixation	Calcaneus	5.2	10*3	local flap	<i>Staphylococcus aureus</i>	<i>Staphylococcus aureus</i>	28
6	F/61	Infection after internal fixation	Tibia	4.9	7*3	local flap	/	<i>Streptococcus viridans</i>	26
7	M/33	Open fracture	Tibia	4.2	9*4	muscle flap	<i>Escherichia coli</i>	<i>Escherichia coli</i>	24
8	F/58	Open fracture	Tibia	6.5	8*4	local flap	/	Mixed infection	27
9	F/42	Infection after internal fixation	Tibia	5.3	23*7	free flap	<i>Enterococcus faecalis</i>	Mixed infection	24
10	F/63	Open fracture	Tibia	7.7	8*5	local flap	<i>Pseudomonas aeruginosa</i>	<i>Pseudomonas aeruginosa</i>	22
11	M/46	Infection after internal fixation	Tibia	6.2	7*4	muscle flap	<i>Enterobacter cloacae</i>	Mixed infection	19
12	M/64	Open fracture	Tibia	8.7	11*5	local flap	/	/	23
13	M/53	Infection after internal fixation	Tibia	7.2	6*3	local flap	/	/	16
14	M/57	Infection after internal fixation	Tibia	3.5	7*4	local flap	<i>Staphylococcus aureus</i>	<i>Staphylococcus aureus</i>	20
15	F/35	Open fracture	Tibia	7.8	12*4	local flap	<i>Enterobacter cloacae</i>	<i>Enterobacter cloacae</i>	25

ID	Gender/Age (years)	Etiology	Site of defect	Bone defect (cm)	Size of flaps (cm ²)	Type of flaps	Microbiological culture	mNGS	Bone union time (weeks)
16	F/38	Open fracture	Tibia	6.7	12*8	local flap	<i>Staphylococcus aureus</i>	Mixed infection	22
17	M/41	Infection after internal fixation	Calcaneus	6.3	12*4	local flap	/	<i>Clostridium perfringens</i>	31
18	F/35	Open fracture	Metatarsus	2.1	21*10	free flap	<i>Enterococcus faecium</i>	Mixed infection	17
19	M/47	Open fracture	Metatarsus	1.7	12*4	local flap	<i>Staphylococcus aureus</i>	<i>Staphylococcus aureus</i>	12
20	M/58	Infection after internal fixation	Tibia	3.2	16*6	local flap	<i>Pseudomonas aeruginosa</i>	<i>Pseudomonas aeruginosa</i>	16
21	M/61	Open fracture	Tibia	4.2	8*4	local flap	/	/	18
22	F/49	Open fracture	Tibia	5.3	17*6	local flap	<i>Staphylococcus aureus</i>	Mixed infection	12

* F: female; M: male; mNGS: microbiological metagenomic next-generation sequencing;

Table 2 Evaluation Criteria of Bone and Functional Results

Bone results	Criteria	Functional results	Criteria
Excellent	Union, no infection, deformity <7°, limb length discrepancy (LLD) <2.5 cm	Excellent	Active, no limp, minimum stiffness (loss of <15° knee extension/<15° ankle dorsiflexion), no reflex sympathetic dystrophy (RSD), insignificant pain.
Good	Union plus any two of the following: absence of infection, deformity <7°, LLD <2.5 cm.	Good	Active, with one or two of the following: limb, stiffness, RSD, significant pain
Fair	Union plus any one of the following: absence of infection, deformity <7°, LLD <2.5 cm	Fair	Active, with three or all of the following: limb, stiffness, RSD, significant pain
Poor	Nonunion/refracture/union plus infection plus deformity >7° plus LLD >2.5 cm	Poor	Inactive (unemployment or inability to return to daily activities because of injury)

Discussion

Because of the the high recurrence rate and high disability rate, the infectious complex tissue defect is still a conundrum for orthopedic surgeons. It also brings heavy burden to the patients. Effective treatments for the disease are rarely reported. In this

study, we applied Masquelet technique combined with tissue flaps transplantation to address the issue and achieved promising results.

For the management of infection, we took a very prudential strategy. The treatment of infection just like a war against bacteria. We need to know where and who are the enemies. PET-CT examination before the first debridement could offer an explicit range of the infection, which was an important reference for the thorough and accurate debridement. Thorough debridement of infectious bone and soft tissue is the most crucial factor to prevention of infection recurrence [9, 10]. Deep tissue from the debridement was taken for both microbiological culture and mNGS to identify the pathogen. These results were going to guide the application of antibiotics. The mNGS had a higher positive rate in the study and identified more mixed infection. mNGS can get the results in 24-36 hours while microbiological culture takes a few days. Although the microbiological culture is still the gold standard of pathogen diagnosis, in our procedure, we combined microbiological culture and mNGS that can improve the speed and accuracy of the diagnosis. During the first stage operation, the antibiotic-impregnated cements were inserted in the site of the bone defect. Local antibiotics usage is characterized by high local concentration and low systemic toxicity which has strong capacity to eradicate infection in the bone defect site. Patients underwent the second PET-CT before the second stage operation. If the reports showed no infection signs, then the second stage operation could be proceeded, else the first stage operation will be repeated. During the second stage operation, intraoperative frozen sections were taken to assure the security of the bone defect reconstruction. The prudential strategy is the key factor for the success of the treatment of infectious complex tissue defect.

The optimal timing for antibiotic-impregnated cements removal was described as 6-8 weeks, according to Masquelet [11]. At this time, the induced membrane is rich in vascularization and high concentration of growth factors, conducive to osteogenesis [12]. Theoretically, the effectiveness of the Masquelet technique depends on the quality of the vascularized membrane. In our study, the interval ranged from 6 to 11 weeks, mainly to eradicate maximum infection. The average time to bone union was 22.2 weeks, which was consistent with the previous studies [9, 13].

According to the basic surgical principles for the management of Gustilo III open fractures, early soft tissue coverage has been proven crucial and effective during the treatment [14, 15]. Tissue flaps transplantation can offer soft tissue coverage for the wound, increase blood supply, defend against infection, and improve bone healing [16]. For Masquelet technique, the complete soft tissue envelope of the site of the bone defect assists the formation of a complete and well vascularized induced membrane which is crucial for the reconstruction of the bone defect [17, 18]. What's more, the closure of the wound in the first stage operation can provide great confidence to the patients. An optimistic attitude is also important for the healing.

The united of Ilizarov technique and tissue transfer has also been reported as an effective method for limb salvage in composite injuries. However, the drawbacks of this technique including long treatment time, joint stiffness, and high technical requirement should not be ignored [19]. Compared the Masquelet technique combined with tissue flap transplantation and other treatments of infectious complex tissue defects such as Ilizarov technique and free vascularized bone grafting. The former had the advantages of simple surgical operation, reliable treatment effect and relatively short treatment cycle.

Although this study demonstrated the reliable results of the Masquelet technique combined with tissue flap transplantation in the treatment of infectious complex tissue defects, there are some limitations. For the long segmental bone defects in the lower extremities, we don't recommend this technique because of the difficulty of fracture stability and the grafted bone resorption. The limitations of our study are the small number of cases, the lack of a direct comparison with a control group. A prospective study with more cases should be performed to get more convincing conclusions.

Conclusion

The Masquelet technique combined with the tissue flap transplantation provides an effective and reliable protocol for the treatment of infectious complex tissue defects, which simplifies surgical procedures and improves the success rate of limb salvage. Moreover, firm fixation is crucial to this technique. While considering the small number of individual cases in this study, a multicenter controlled comparative trial may be necessary to determine the real potential of this technique in the treatment of such complex tissue defects.

Declarations

The study was approved by the Independent Ethics Committee of Shanghai Jiao Tong University Affiliated Sixth People's Hospital. Informed consents were obtained from all participants. The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. The authors declare that they have no competing interests. This work was sponsored by the National Natural Science Foundation of China (No.81974325, No. 81702183) and the Science and Technology Commission of Shanghai Municipality (No.18ZR1428700).

RZ and ZYB analyzed and interpreted the patient data regarding the infectious complex tissue defect and edit the manuscript. CWJ, DJF and CPF collected the follow-up data of the patients. HP and XZY provided technical suggestions and reviewed the manuscript. All authors read and approved the final manuscript.

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Figures

Figure 1

Procedure for the treatment of infectious complex tissue defect.

Figure 2

Case 1 A 37-year-old male was admitted to our hospital due to the infection of new bone after distraction osteogenesis of left tibia, which combined with soft-tissue defect. a) PET-CT showed infection of new bone after after distraction osteogenesis. b), c) and d) defects of bone and soft-tissue after debridement, bone defect was implanted with antibiotic cement and soft tissue defect was repaired with gastrocnemius flap and skin graft. e) and f) autologous bone graft was performed 8 weeks after the

first-stage operation. The grafted bone was fixed by screws and the external fixation was remained. g) and h) wound healing and bone union were achieved.

Figure 3

Case 2 A 24-year-old male suffered from infection by *Pseudomonas aeruginosa* after open fracture in right radius. a) large segmental bone defect (10.3cm) and extensive soft tissue damage were presented after the aggressive debridement. b) and c) antibiotic cement was implanted in the site of bone defect and a groin flap was performed to cover the soft tissue defect. d) autologous bone graft was performed 7 weeks after the first-stage operation. The external fixation was remained. e) and f) wound healing and bone union were achieved.