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Simultaneous reconstruction of tibial osteomyelitis-complicated soft tissue defects using free flap transplantation in conjunction with the masquelet technique: a retrospective study

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Abstract

Objective To investigate the clinical effect of anterolateral femoral free flap combined with Masquelet technique in the treatment of tibial osteomyelitis with wound surface.

Methods A retrospective study was conducted to analyze the clinical data of 25 patients with tibial osteomyelitis combined with defected wounds in Xijing Hospital of Fourth Military Medical University from Jun 2017 to Oct 2021. After one-stage treatment with free flap combined with Masquelet technique, the infection index, lower extremity function score (LEFS), and Mazur ankle function score were compared before bone defect repair and at the last follow-up.

Results The anterolateral femoral free flaps of 25 patients in phase I survived. The healing time of bone fracture after stage II operation was 8–12 months [(7.2 ± 0.9) months]. At the last follow-up, the infection index was significantly lower than that before bone defect repair ($P < 0.01$). The LEFS and Mazur ankle function scores [(56.2 ± 7.9) and (78.2 ± 16.1)] of the affected limb were significantly higher than those before bone defect repair [(26.0 ± 8.6) and (44.7 ± 18.2)] ($P < 0.01$). Wounds of all patients' legs healed well, without complications (foot drop, joint dysfunction, or deformity in the affected limbs).

Conclusion The anterolateral femoral free flap combined with Masquelet technique is an effective treatment strategy for tibial osteomyelitis combined with soft tissue defects. This technology can effectively repair limb trauma, inhibit infection, and improve flexion and extension functions of knee and ankle joint.

Keywords Free flap, Masquelet technique, Debridement, Bone defect, Tibia, Osteomyelitis

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Introduction

Musculoskeletal diseases remain the main chronic disturbs for human beings [1–6]. The treatment of tibial osteomyelitis with concomitant soft tissue defects is challenging, with high demands for the repair of soft tissue wounds and bone defects. It is a current clinical focus and is recognized as a difficult point [7]. Traditional treatment methods require the complete removal of infected bone and soft tissue, often leading to more extensive soft tissue and bone defects. First developed in the late 1970's by AC Masquelet but only recently popularized, the chief advantages of this strategy include control of the local infection with radical debridement, placement of a polymethylmethacrylate (PMMA) cement spacer for maintenance of dead space, and induction of a periosteal membrane that protects against graft resorption. Masquelet technique is length-independent and is therefore a viable option for the treatment of larger osseous defects [8]. The Masquelet technique represents a two-staged reconstructive procedure that overcomes several of the shortcomings in the treatment of osteomyelitis defects, particularly those located to the long bone and associated with infected and/or non-viable soft tissue [9].

Due to the absence of soft tissue coverage, the bone cement failed to form an osteoinductive membrane for osteomyelitis with accompanying wounds. This renderd the subsequent bone defect reconstruction unachievable, resulting in a prolonged overall treatment time, increased surgical complications, difficulties in infection control, and poor limb function recovery [10]. Recently, studies found that simultaneous treatment of bone and soft tissue can be carried out during a single debridement session for osteomyelitis with wounds. The Masquelet technique employed antibiotic bone cement to control bone infection, and flaps were used to repair soft tissue defects. This approach aimed to control infections, shorten treatment cycles, reduced the number of surgeries, and achieved good therapeutic effects [11, 12].

A few studies used the induced membrane technique combined with free flaps to treat lower limb composite tissue defects, with produced favorable results. However, there lacked extensive clinical evidence on the treatment outcomes for tibial osteomyelitis with wound formation [13, 14]. Thereby, we conducted a retrospective case series study analyzing the clinical data of 25 patients with tibial osteomyelitis accompanied by wounds, treated at the Xijing Hospital of the Fourth Military Medical University from Jun 2017 to Oct 2021. The study aimed to explore the therapeutic effects of using the anterolateral thigh-free flap combined with the induced membrane technique to treat tibial osteomyelitis with wound formation.

Clinical data and methods

General information

Inclusion Criteria: (1) A confirmed diagnosis of the chronic tibial osteomyelitis with concomitant soft tissue wounds (more than the range of 14.0 cm x 8.0 cm). (2) There was no significant improvement after conventional anti-infective treatment and multiple debridements; (3) The culture result of purulent secretion of the wound was positive, and SPECT/CT showed that local bone metabolism of the tibia was active, which was consistent with the manifestations of osteomyelitis. (4).$\geq$ 18 years old. Exclusion Criteria: (1) A definitive vascular lesion or a history of high-level vascular trauma in the affected limb. (2) A history of cardio-cerebrovascular events within 3 months. (3) The patient had a history of blood disease, abnormal coagulation function, and hemangioma [15].

Twenty-five patients diagnosed with tibial osteomyelitis accompanied by wounds were included. Among these, 19 were males and 6 were females, ranging from 22 to 65 ($\bar{x} \pm$ SEM: 36.4 ± 6.6) years old. The causes of the injuries: 10 cases from traffic accidents, 8 crushed by heavy objects, 5 from medically-induced infections, and 2 from hematogenous osteomyelitis. Enrolled patients were with soft tissue and bone infection, purulent secretion examination of positive results, and high infection index. Preoperative SPECT/CT showed surrounding soft tissue and bone infection. After thorough debridement of soft tissue defect in the range of 14.0 cm x 8.0 cm ~ 30.0 cm x 16.0 cm, the tibia defect length is 3.0 cm ~ 11.0 cm/ (5.3–1.9) cm. After the first-stage intraoperative debridement, the local soft tissue defect in the calf ranged from 14.0 cm×8.0 cm to 30.0 cm×16.0 cm, and the length of the tibial bone defect reached 3.0 ~ 11.0 cm. All patients were informed about the treatment plan and signed an informed consent form. This study was approved by the Medical Ethics Committee of Xijing Hospital of the Fourth Military Medical University.

Treatment method

First Stage-Masquelet induced membrane technique combined with anterolateral thigh free flap

After thorough debridement of the patient's infected bone and soft tissue, the soft tissue defects was covered with an anterolateral femoral free flap, and the tibial bone defect area was filled with antibiotic bone cement. The surgical process entailed the following: After successful anesthesia, the localized sinus tracts, periosteal scars, poorly vascularized tissue, and necrotic bone tissue in the infection site were completely removed. Tissues for culture were sampled from multiple infection sites during surgery. Postoperatively, bacterial cultures and drug sensitivity tests were conducted. Infected soft tissue and bone samples were sent for pathological examination.

The tibial defect area was completely filled with vancomycin antibiotic bone cement (40 g bone cement containing 3 g vancomycin), and the bone cement covered about 1 cm of the broken end on both sides [14]. The bone defect was fixed with a reconstruction plate (produced by Xiamen Dabo Medical Equipment Co., Ltd.), and external fixation was applied when needed. After thorough debridement, an anterolateral thigh-free flap was designed on the opposite limb, ensuring that the flap size was about 2 cm wider than the soft tissue defect. The smallest flap size harvested during surgery was 16.0 cm×10.0 cm, and the largest was 32.0 cm × 18.0 cm. After harvesting the free flap, it was transplanted to the soft tissue defect site, where the flap's vascular pedicle was anastomosed with the anterior tibial artery and vein. The flap survival was then observed. Among them, 4 patients had vascular crisis after the operation of free flaps. The flap showed bruising and swelling. Surgeons dredged the vessels, extracted thrombus, which relieved the symptoms of 4 patients. Eight patients had a small amount of necrosis at the edge of the flaps, which were sutured and repaired after debridement, and the wounds could still be completely covered. If the donor site wound was large, split-thickness skin grafting was employed; if it was small, direct suturing after tension release was done. Vacuum Sealing Drainage (VSD) negative pressure drainage was employed on the grafted skin. Postoperative standard treatment included anti-infection and antithrombotic therapies, as well as limb function exercises. The anti-infective plan (4 weeks in total i.v.) is that initially empirical anti-infective treatment with third-generation ceftriaxone (ceftriaxone sodium i.v.). Thereafter, it will be replaced with corresponding sensitive antibiotics according to drug susceptibility results.

Second stage-bone defect reconstruction

The skin flap wound was completely healed after 6–8 weeks after the first-stage surgery. The edge of the flap directly heals well, were connected with the surrounding skin and soft tissue closely, without exudation or redness. The tension, color, and the temperature of the flap is normal. The second-stage surgery was performed after the infection indicators returned normal in the re-examination. If the patient still had clinical manifestations of infection, or laboratory tests revealing the possibility of infection, or the deep tissue purulent exudation and poor induced membrane formation in the second stage operation, the first stage operation should be repeated until the infection is completely controlled and the induced membrane formation is satisfactory. In this study, 3 patients underwent secondary debridement, and the remaining patients underwent primary debridement. The broken ends of the bone defects in the second-stage surgery were all subjected to strong internal fixation (Xiamen Dabo Medical Equipment Co., Ltd, China). An incision was made along the edge of the skin flap. The first choice for repairing bone defects is autogenous iliac bone, which is cut into 0.5 cm (Allograft: autogenous bone < 1:2). Early postoperative exercises mainly focused on active plantar flexion, dorsiflexion, and isometric contraction of the quadriceps and functional training of flexion and extension of ankle joint. Weight-bearing started after the callus appears on the X-ray review. The bone grafting area was mineralized and the clinical examination was completed. After there is no slight movement, pain or discomfort in the area and no longitudinal percussion pain, patients fully bear body weight.

Postoperative treatment

The patients were routinely treated with antibiotics, anti-vasospasm, microcirculation improvement, and anti-thrombosis after operation. They were actively given visible light to keep warm, regularly observed and changed dressing, and timely corrected anemia and hypoproteinemia. Early rehabilitation exercise and nutrition were provided. The infection indicators were regularly reviewed, and the general conditions and functional status of the affected limbs were observed, including 1) Swelling levels, color, and temperature of limbs; 2) Tension, temperature, and color of the flap; 3) The healing status of the wound; 4) Joint function and muscle strength; 5) Patient's subject feeling of pain.

Observation indicators

One week after the first-stage surgery, the survival of the free flap and graft was observed. Blood tests were conducted to determine white blood cell counts, procalcitonin, erythrocyte sedimentation rate, and C-reactive protein to monitor infection indicators. After the second surgery, the time taken for bone defect repair was observed. The lower extremity functional scale (LEFS) and the Mazur ankle joint functional score were used to evaluate limb function before bone defect repair and at the last follow-up [16]. Three-dimensional CT scans of the affected area were taken during the final follow-up to assess the status of bone defect repair. The functional outcomes of the patients were evaluated using the Johner-Wruhs score [8, 17]. Clinical diagnosis and treatment process as shown in Fig. 1.

Statistical methods

Statistical Analysis SPSS 20.0 statistical software was employed. Kolmogorov-Smirnov method was used to test the normality of the measurement data. The measurement data in accordance with normal distribution were expressed as Mean ± SD, and paired sample t test

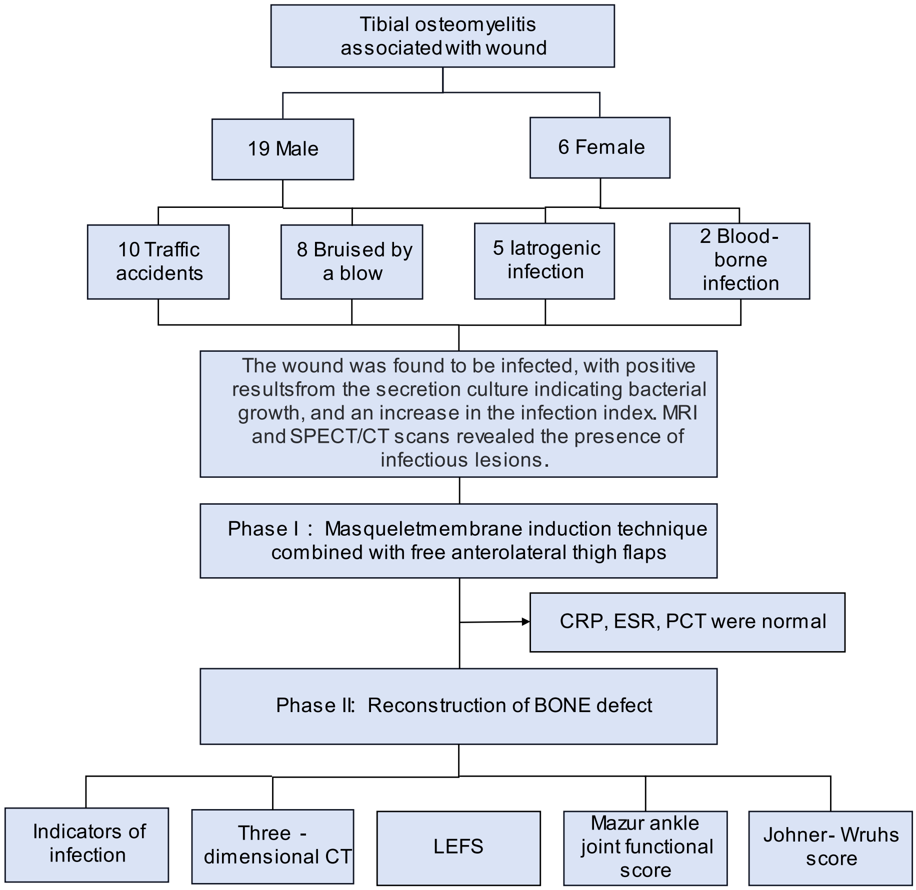

Fig. 1 The flowchart for a retrospective clinical study. Twenty-five patients with tibial osteomyelitis accompanied by soft tissue defects were selected for a clinical retrospective study. The cohort consisted of 19 males and 6 females. Among them, there were 10 cases resulting from traffic injuries, 8 cases caused by heavy object crush injuries, 5 cases due to iatrogenic infections, and 2 cases originating from hematogenous osteomyelitis. All patients presented with concurrent soft tissue and bone infections at the time of enrollment, as confirmed by positive results in purulent secretion cultures. The infection index was elevated. Preoperative MRI and SPECT/CT scans revealed surrounding soft tissue and bone infections. Following one-stage debridement, wound repair was performed using the anterolateral thigh free flap combined with the Masquelet technique to reconstruct the bone defect area. In the second stage, once signs of infection had subsided, bone grafting and internal fixation were conducted in the affected region. Postoperative X-ray imaging along with reexamination of CRP (C-reactive protein), ESR (erythrocyte sedimentation rate), PCT (procalcitonin) levels were carried out to assess limb function

was used for statistical analysis. $P<0.01$ defined as statistical significance.

Results

All patients were followed up with the follow-up period ranging from 10 to 54 months [(28 ± 8.1) months]. After the first-stage surgery, all patients exhibited good survival of the anterolateral thigh free flap, effectively covering the soft tissue wound surface. The donor site wounds either closed naturally or survived through grafting. Inflammatory infection indicators at the last follow-up showed a significant decrease compared to the indicators before the second-stage surgery ($P<0.01$, Table 1).

The lower extremity functional scale (LEFS) scores of the affected limb improved from 26.0 ± 8.6 points before the bone defect repair to 56.2 ± 7.9 points. The Mazur ankle joint functional score increased from 44.7 ± 18.2 points to 78.2 ± 16.1 points ($P<0.01$, Table 2). At the last follow-up, all bone defect areas were repaired well, with the bone ends completely healed. The healing time for the bone defect ends ranged from 8 to 12 months [(7.2 ± 0.9) months]. At the last follow-up, the lower limb's Johner-Wruhs score had a 96% excellent to good rate, with 23 cases rated as excellent, 1 as good, 1 as moderate, and 0 as poor. A typical case is shown in Fig. 2.

Discussion

Interpretation

Tibial osteomyelitis is commonly observed in clinical settings. Due to the thinness of the soft tissue on

Table 1 Comparison of inflammatory infection indicators before the second-stage surgery and at the last follow-up in 25 patients with tibial osteomyelitis combined with wound. (Mean ± SD)

Time	WBC(x10E9/L)	hs-CRP(mg/L)	ESR(mm/hr)	PCT(ng/ml)	IL-6(pg/ml)
Before the second-stage bone repair	6.9 ± 0.9	5.2 ± 0.7	14.75 ± 2.2	0.035 ± 0.003	5.2 ± 0.4
Last follow-up	3.7 ± 0.6	3.1 ± 0.4	9.6 ± 1.8	0.017 ± 0.003	3.2 ± 0.4
t value	16.18	14.31	10.06	25.58	19.82
P value	<0.01	<0.01	<0.01	<0.01	<0.01

Table 2 Comparison of LEFS and Mazur ankle function scores before the second-stage bone tissue repair and at the last follow-up in 25 patients with open tibial fractures complicated by osteomyelitis. (score, mean ± SD)

Time	LEFS	Mazur Ankle Joint Function Score
Before the Second-stage Bone Repair	34.8 ± 6.2	56.7 ± 14.6
Last follow up	53.2 ± 8.1	72.2 ± 11.1
T value	-9.44	-3.84
P value	<0.01	<0.01

the anterior side of the tibia, it is prone to concomitant wound infections. Following surgical debridement, in addition to the bone defect, there was often a significant soft tissue deficit, necessitating flap transplantation for repair [18, 19]. For tibial osteomyelitis with accompanying bone and soft tissue defects post-debridement, the conventional treatment approach entailed staged treatments for soft tissue coverage and bone defect fixation. However, this often resulted in delayed coverage of soft tissue, prolonged exposure of deep tissues, and difficulties in infection control. Due to the extended treatment duration, patient rehabilitation exercises becomed limited, impeding limb functional recovery.

The current treatment methods for postoperative bone defects of chronic tibial osteomyelitis include Ilizarov distraction osteogenesis technology, titanium mesh bone grafting technology, vascularized bone grafting technology, genetic engineering technology, and Masquelet technology. The Ilizarov technique is easy to operate with accurate therapeutic results, which can improve bone defects and soft tissue defects simultaneously. However, its treatment cycle was long and with complications such as nail tract infection, loosening, broken nails, poor fracture alignment, and poor survivability. Titanium mesh bone grafting technology was only applicable to partial soft tissue, especially, free skin flaps are essential in this technology to repair soft tissue defects. Its application value was limited in patients with long bone defect segments.

Recent studies demonstrated that a combination of flap grafts with induced membrane technique for treating bone and soft tissue defects is an effective therapeutic strategy. However, current clinical reports were sparse, and there was a lack of extensive clinical data supporting its efficacy in treating tibial osteomyelitis with wound formation [13, 14]. Our research, based on 54-month follow-up of 25 patients, indicated that the anterolateral thigh free flap, combined with induced membrane technique, provided effective treatment outcomes for tibial osteomyelitis with wound formation and merits broader clinical application. For cases of tibial osteomyelitis that did not involve soft tissue wounds, the induced membrane technique alone can usually suffice for treatment. The technique was widely adopted in the treatment of osteomyelitis, yielding positive outcomes.

Masquelet proposed induced membrane technique for the treatment of long-segment bone defects, which was applied clinically and achieved good therapeutic results. The core of this technology was the induced membrane, which was filled with bone cement in the bone defect area and stimulates the surrounding soft tissue to form a good biofilm in the body. The membrane was rich in mesenchymal cells and fibroblasts and had the ability to promote bone cell differentiation and capillary growth. Cytokines for vascular differentiation not only improved local blood circulation, but also had the ability to form intramembranous bone [10–12]. For patients with chronic tibial osteomyelitis with soft tissue defects, infection still existed after anti-infective treatment and multiple debridements, and the difficulty of treatment was gradually increasing. It was undoubtedly a great challenge to complete the simultaneous repair of soft tissue and bone while treating the infected lesions. For patients with chronic osteomyelitis, after one-stage thorough debridement, the removal of bone infection lesions led to segmental bone defects and large areas of soft tissue loss. For small areas and good surrounding soft tissue conditions, peripheral pedicled flaps and muscle flaps were selected to cover. However, due to trauma, multiple operations, chronic

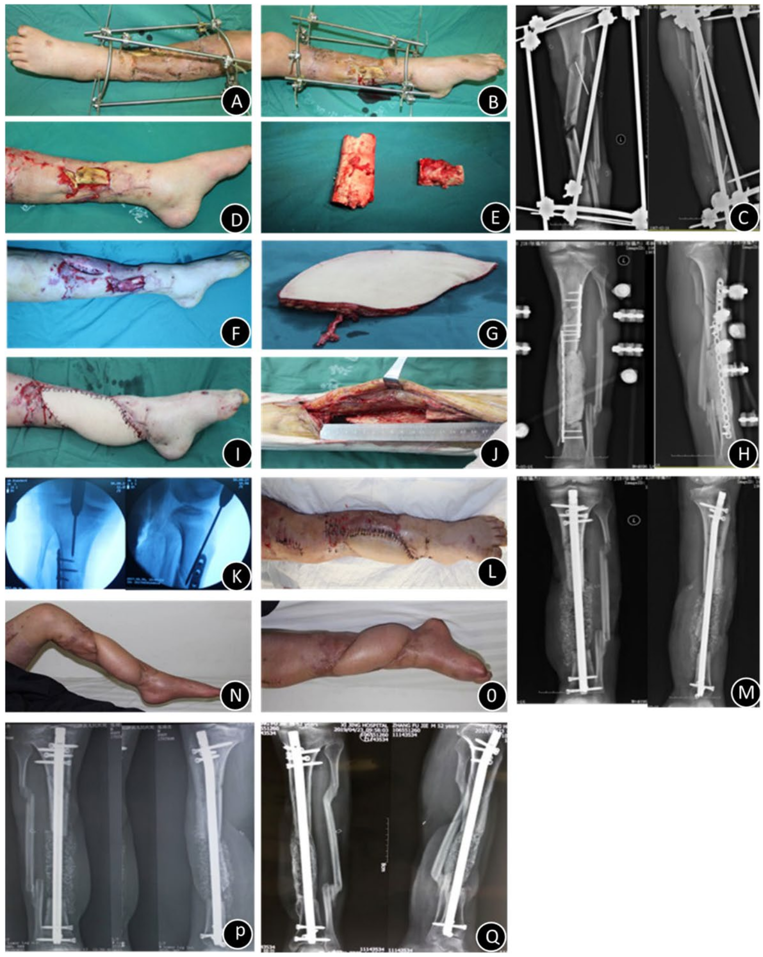

Fig. 2 A case of free flap combined with Masquelet technique for bone and soft tissue defect after debridement. A male patient, 50 years old, suffered from post-operative bone infection, necrosis, and exposure to an open fracture in the left lower leg caused by a traffic accident, with the wound persisting for 3 months. The patient had tibial exposure and proximal tibial fracture caused by trauma, and the anteromedial soft tissue defect of the lower leg was 8cm×12cm. SPECT/CT showed that the length of bone infection was 10cm. The patient's leg exhibited extensive scarring, indicating a severe soft tissue injury with a significant defect area that cannot be effectively addressed through local flap transfer. In the first stage of hospital admission, the patient underwent debridement, lesion removal, internal fixation of the proximal tibial fracture, induced membrane technique in the bone defect area, temporary fixation using a reconstructive steel plate and external fixation frame, and coverage of the wound with an anterolateral thigh free flap. Eight weeks later, a second-stage procedure was performed to graft the iliac bone and replace the internal fixation. **A**, **B**: Preoperative appearance of the patient's lower leg wound, with bone infection, bone exposure, necrosis, and external fixation. **C**: Preoperative X-ray showing post-operative displacement of the proximal tibial fracture, mid-tibial bone defect, and angular deformity. **D**, **E**, **F**: After removal of the external frame and resection of the infected bone segment, the appearance of soft tissue and bone defects post-debridement. **G**, **H**, **I**: Based on the wound defect, an anterolateral thigh-free flap was harvested from the opposite limb, proximal tibial repositioning and fixation were done, and the induced membrane technique was used for the mid and distal bone defect treatment. Post-operative appearance after free flap wound coverage. **J**: Eight weeks postoperatively, the bone defect was reconstructed, measuring a bone defect length of 12cm. **K**: Preoperatively, the patient had partial knee joint stiffness and a drooping deformity of the ankle joint. An intramedullary nail was placed through the patellar approach, with intraoperative fluoroscopy. **L**, **M**: Post-operative appearance after bone grafting, intramedullary nail fixation in the bone defect area, and adequate bone grafting. **N**, **O**, **P**: Four months post-grafting, follow-up appearance and X-rays showing partial mineralization of the grafted area in the lower leg. **Q**: One-year post-grafting follow-up, with a soft flap texture, satisfactory mineralization in the grafted area, and complete healing of the bone ends

infection, scar healing and other reasons, local pedicled flaps, muscle flaps, and myocutaneous flaps failed to be transferred to the patients in this study, thereby free anterolateral thigh flaps can be the first choice. It had the advantages of wide coverage, simple operation, high survival rate and strong anti-infection ability [20, 21].

In the past, patients with tibial osteomyelitis and soft tissue defects were often treated by staged surgery, such as multiple debridements combined with VSD, flap surgery again, and finally bone transplantation. Some patients choose amputation due to the high cost, number of operations, and postoperative limb disability [22, 23]. Addressing these challenges, we proposed a comprehensive debridement in one stage, followed by covering the soft tissue defect with an anterolateral thigh flap and filling the bone defect with bone cement for induced membrane. Leveraging the combined anti-infective properties of the anterolateral thigh flap and antibiotic bone cement yields superior infection control [24]. Once the infection is under control, a secondary grafting procedure for the bone defect was promptly executed. By utilizing the osteoinductive membrane formed on the anterolateral thigh flap during the primary surgery, graft materials were enveloped, accelerating bone defect repair. Follow-up studies of 25 patients revealed that this method delivers excellent therapeutic results, facilitating the repair of both soft tissue and bone defects, significantly reducing infections, and enhancing lower limb functional recovery [25].

Limitations

Though innovations, this study bear limitations. Firstly, this study was a retrospective study with a small sample size, which limited its promotion in most patients with osteomyelitis complicated with wounds. Secondly, post-traumatic tibia osteomyelitis was complicated with soft tissue defect due to its complexity of clinical patients, namely the area of soft tissue defect, species differences, bone exposed parts and area differences, which led to difficulties for feasibility of operation and postoperative rehabilitation. Finally, this surgical protocol had technical difficulties and is not easy to promote. This technology required anastomosis of extremely small blood vessels under a microscope and required extremely high surgical skills. The first-stage debridement needed to be completed by a senior attending physician or associate chief physician to meet the requirements of complete debridement.

Conclusion

Studies have shown that anterolateral thigh free flap combined with Masquelet technique is an effective treatment strategy for tibial osteomyelitis with wound, with low infection rate and satisfactory postoperative function. In the treatment of tibial osteomyelitis patients with soft tissue defect and bone defect, this treatment scheme preserves the function of the affected limb to the greatest extent and reduces the occurrence of complications.

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Authors' contributions
BX and CY- acquisition, analysis, and interpretation of data; and drafted the manuscript. HD- acquisition, analysis, and interpretation of data. JF- design of the work, analysis and interpretation of data. TL - conception and design of the work; interpretation of data; and revised the drafted version. YP and BW participated in revision of the revised manuscript, writing of response letter, and analyzed all data again. DL participated in revision of the revised manuscript and analyzed all data. All authors: approved the submitted version and agreed both to be personally accountable for the author's own contributions.

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Data availability
The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved by the Medical Ethics Committee of Xijing Hospital of the Fourth Military Medical University (KY20220006-E-2). All participants signed informed consent before entering the study. All methods were performed with the relevant guidelines and regulations (Declaration of Helsinki).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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References

1. Wei FL, et al. Decompression alone or decompression and fusion in degenerative lumbar spondylolisthesis. EClinicalMedicine. 2022;51:101559.
2. Gao K, et al. Association between Sarcopenia and depressive symptoms in Chinese older adults: evidence from the China Health and Retirement Longitudinal Study. Front Med (Lausanne). 2021;8:755705.
3. Gao QY, et al. Oblique lateral interbody fusion vs. minimally invasive transforaminal lumbar interbody fusion for lumbar spinal stenosis: a retrospective cohort study. Front Med (Lausanne). 2022;9:829426.
4. Tang Z, et al. Three-dimensionally printed Ti2448 with low stiffness enhanced angiogenesis and Osteogenesis by regulating macrophage polarization via Piezo1/YAP Signaling Axis. Front Cell Dev Biol. 2021;9:750948.
5. Wang Y, et al. LncRNA THUMPD3-AS1 enhances the proliferation and inflammatory response of chondrocytes in osteoarthritis. Int Immunopharmacol. 2021;100:108138.
6. Wei FL, et al. Efficacy and safety of pharmacologic therapies for prevention of osteoporotic vertebral fractures in postmenopausal women. Heliyon. 2023;9(2):e11880.
7. Hohmann E, Glatt V, Tetsworth K. What is the optimal timing for bone grafting during staged management of infected non-unions of the tibia? A systematic review and best evidence synthesis. Injury. 2020;51(12):2793–803.

8. Del Buono A, et al. Pulsed electromagnetic fields after intramedullary nailing of tibial fractures: a case control study. Int Orthop. 2021;45(11):2945–50.
9. Masquelet AC, Begue T. The concept of induced membrane for reconstruction of long bone defects. Orthop Clin North Am. 2010;41(1):27–37. table of contents.
10. Wagner F, et al. Daily subcutaneous teriparatide injection increased bone mineral density of newly formed bone after tibia distraction osteogenesis, a randomized study. Injury. 2019;50(8):1478–82.
11. Andrzejowski P, Masquelet A, Giannoudis PV. Induced membrane technique (Masquelet) for bone defects in the distal tibia, Foot, and ankle: systematic review, Case Presentations, Tips, and techniques. Foot Ankle Clin. 2020;25(4):537–86.
12. Liu HM, et al. [Clinical characteristics of 18 children with chronic nonbacterial osteomyelitis]. Zhonghua Er Ke Za Zhi. 2022;60(12):1271–5.
13. Allesina L, et al. Surgical treatment of critical size bone defects with Masquelet technique versus bone transport: a systematic review and meta-analysis of comparative studies. Arch Orthop Trauma Surg. 2023;143(12):7081–96.
14. Ren C, et al. A meta-analysis of the Masquelet technique and the Ilizarov bone transport method for the treatment of infected bone defects in the lower extremities. J Orthop Surg (Hong Kong). 2022;30(2):10225536221102685.
15. Fung B, et al. The induced membrane technique for the management of long bone defects. Bone Joint J. 2020;102–b(12):p1723–1734.
16. van den Kieboom J, et al. Diagnostic accuracy of serum inflammatory markers in late fracture-related infection: a systematic review and meta-analysis. Bone Joint J. 2018;100–b(12):1542–50.
17. Teimouri M, et al. Intramedullary nail versus minimally invasive plate osteosynthesis for displaced extraarticular proximal tibia fractures: a prospective comparative cohort study. Eur J Orthop Surg Traumatol. 2023;33(7):3067–79.
18. Arshad Z, et al. Management of chronic osteomyelitis of the femur and tibia: a scoping review. EFORT Open Rev. 2021;6(9):704–15.
19. He J, et al. Customized reconstruction of complex soft tissue defects in the upper extremities with variants of double skin paddle anterolateral thigh perforator flap. Injury. 2021;52(7):1771–7.
20. Jitprapaikulsarn S, et al. Utilizing the various forms of the gastrocnemius muscle in fix & flap protocol: a reliable remedy for open proximal tibial fractures with accompanying soft tissue defect. Eur J Orthop Surg Traumatol. 2022;32(3):505–13.
21. Zhang Z, et al. Epidemiology and drug resistance of fracture-related infection of the long bones of the extremities: a retrospective study at the largest trauma center in Southwest China. Front Microbiol. 2022;13:923735.
22. Crunkhorn A, et al. Management of upper limb amputation rehabilitation: synopsis of the 2022 US Department of Veterans Affairs and US Department of Defense Clinical Practice Guideline for Acquired Amputation. Am J Phys Med Rehabil. 2023;102(3):245–53.
23. Paro J, Chiou G, Sen SK. Comparing muscle and fasciocutaneous free flaps in lower extremity reconstruction–does it matter? Ann Plast Surg. 2016;76(Suppl 3):S213-5.
24. Cyphert EL, et al. PMMA bone cement composite functions as an adjuvant chemotherapeutic platform for localized and multi-window release during bone reconstruction. Macromol Biosci. 2022;22(5):e2100415.
25. Mathieu L, et al. The Masquelet technique: can disposable polypropylene syringes be an alternative to standard PMMA spacers? A rat bone defect model. Clin Orthop Relat Res. 2021;479(12):2737–51.