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ORIGINAL ARTICLE

New bone formation using antibiotic-loaded calcium sulfate beads in bone transports for the treatment of long-bone osteomyelitis

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Abstract

Purpose Bone transport is one of the most frequently used techniques for critical-sized bone defects due to trauma or infection. To fill the defect area and avoid the collapse of soft tissues during transport, some authors have described the use of polymethylmethacrylate or absorbable antibiotic carriers in the form of cylindrical blocks.

Methods In this article, we present our experience in the treatment of post-traumatic osteomyelitis of the lower and upper limbs, using a bone transport technique with antibiotic-loaded calcium sulfate in the form of beads. Results

With the progressive absorption of calcium sulfate, we observed the formation of a bone-like tissue envelope at the periphery of the defect area. Histological analysis and direct visualization during open revision surgery of the docking site in all patients confirmed the presence of newly formed bone tissue with a high presence of osteoblasts and few osteoclasts; no areas of necrosis or signs of infection were observed. This bone envelope maintained the mechanical protective function of the transport path and docking site, and also provided a biological stimulus to avoid the development of necrotic areas and optimize the consolidation phase. Conclusion

Bone transport with calcium sulfate beads improves biological and mechanical support and reduces the number of surgeries required.

Keywords Distraction osteogenesis · Ilizarov technique · Osteomyelitis · Bone regeneration · Histology

Introduction

Treatment of infected critical-sized bone defects is still a challenge for orthopedic surgeons; two of the most widely used therapeutic strategies currently are the induced-membrane technique (described by Masquelet [1]) and bone transport [2]. The latter is based on distraction osteogenesis according to the Ilizarov technique, and involves the gradual transport of a healthy bone segment, with intact blood supply, to fill the area of bone defect [3, 4]. An important advantage of bone transport, and in general of the Ilizarov technique, is the possibility of simultaneously correcting soft tissues loss, joint contractures, bone deformities and shortening [5].

Some authors have described the placement of antibiotic-impregnated polymethylmethacrylate (PMMA) cement in the area of bone defect, before it is filled by the transported bone segment [6]; in this way, the cement acts both with a gradual release of antibiotic and as a spacer, preserving a tunnel of soft tissues for bone transport. However, the release of antibiotic from the cement is high in the first 48–72 h after implantation, but subsequently decreases to subtherapeutic levels that are maintained for long time [7]. Moreover, the cement is not absorbable, thus subsequent surgical removal is required to clear the way for the transported bone segment.

Ideally, a bone filler for osteomyelitis should be biocompatible, bioabsorbable, osteoconductive, capable of releasing antibiotics at high local concentrations, and characterized by

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mechanical strength [7]. Recently, biodegradable ceramics have been developed that are capable of gradually releasing antibiotics; their composition is mainly based on calcium sulfate or calcium phosphate. The use of those biodegradable carriers is indicated in the treatment and prevention of musculoskeletal infections. In vitro and in vivo studies have demonstrated the excellent dissolution and antibiotic elution profile of the carriers, which are capable of releasing high concentrations of antibiotic while avoiding systemic toxicity [8].

The purpose of this article is to describe the use of absorbable antibiotic carrier beads in bone transport, for the treatment of osteomyelitis of the lower and upper extremities, and to report the clinical, radiological and histological evidence of the peripheral bone neoformation.

Materials and methods

Patient population

This is a retrospective study describing bone transport surgeries performed at our Institution between March 2021 and August 2021, using an absorbable antibiotic carrier.

Participants in this study were selected according to the following inclusion criteria:

- Post-traumatic infection with diffuse osteomyelitis (type IV according to Cierny-Mader classification [9])
- Bone transport surgery with external fixation
- Use of an absorbable calcium sulfate carrier (i.e., Stimulan®, Biocomposites, Keele, UK) mixed with vancomycin and gentamycin, in the form of beads, to fill the area of bone defect
- Completion of the transport phase
- Docking site open revision surgery with autologous bone graft from the iliac crest.

The final sample consisted of five cases. Patient characteristics are described in Table 1. Patient 1 had pre-existing type 2 diabetes mellitus, hypertension and ischemic heart disease. Patient 3 had a history of alcohol and drug abuse. The other patients had no comorbidities.

For the diagnosis and management of fracture-related infections, we relied on the evidence and recommendations of recent literature [10, 11]. All patients presented at least one of the clinical signs among confirmatory criteria: sinus tract, wound breakdown, purulent drainage. Microbiological analyzes confirmed the presence of phenotypically indistinguishable pathogens identified by culture from at least two separate deep tissue specimens in every patient.

All patients were informed about the surgery and provided their consent.

Clinical and radiographic evaluation

All patients underwent outpatient follow-up with X-rays and orthopedic visits 15 and 30 days after surgery, and subsequently at least once every 30 days.

Histological evaluation

During docking site open revision surgery, we sent samples to Pathological Anatomy to perform the histological examination. The material was formalin fixed, decalcified with HNO_3 (nitric acid) and paraffin embedded; bone tissue was cut in 3 µm section and slides were stained in hematoxylin and eosin.

Surgical procedures

Three patients had osteomyelitis that involved the distal third of the tibia, extending from the diaphysis to the whole epiphysis; all these infections had developed following osteosynthesis for tibial pilon fractures, with internal fixation devices. The first signs of osteomyelitis appeared 105, 41 and 249 days after osteosynthesis, respectively, in patient 1, 2 and 3. We decided to perform bone transport and subsequent tibio-astragalic arthrodesis with external fixation. In all three, we performed a first surgery with complete removal of internal fixation devices, minimal debridement, irrigation and multiple tissue biopsies for microbiological culture and histopathological examination. This first surgery was performed 9, 10 and 16 days after the first signs of osteomyelitis, respectively, in patient 1, 2 and 3. A multidisciplinary evaluation with infectious disease specialists was performed once we had the results of the culture tests,

Table 1 patient demographics and osteomyelitis data

Patient #	Sex	Age	Site of osteomyelitis	Infectious agents
1	M	69	tibia (distal third)	Staphylococcus epidermidis + Streptococcus agalactiae
2	M	39	tibia (distal third)	Coagulase-negative Staphylococcus
3	F	40	tibia (distal third)	Staphylococcus aureus
4	M	17	humerus (shaft)	Staphylococcus hominis + Staphylococcus epidermidis
5	M	42	ulna (shaft)	Staphylococcus aureus

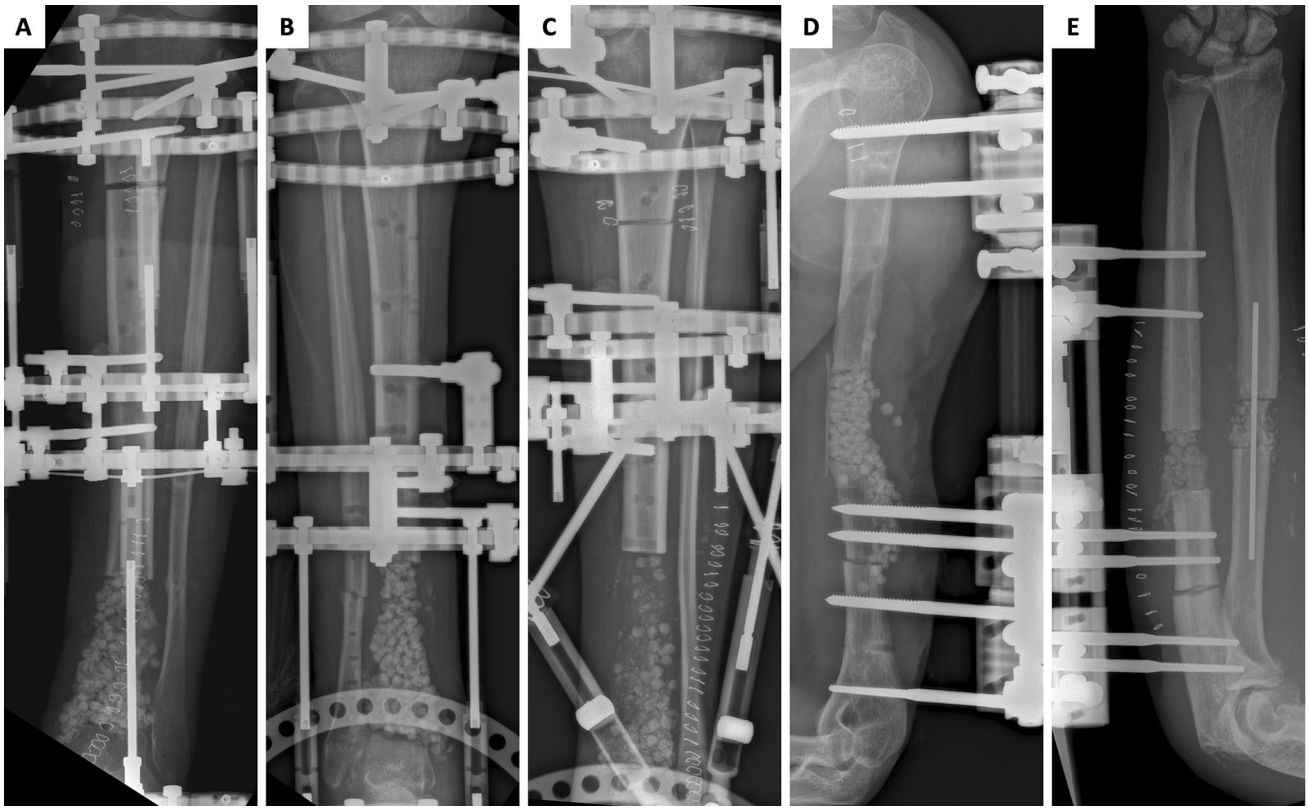

Fig. 1 Postoperative radiographs of the bone segments after debridement and bone transport surgery. **A**: patient 1. **B**: patient 2. **C**: patient 3. **D**: patient 4. **E**: patient 5

to optimize the treatment process. The antibiotic therapy prescribed for patient 1 was dalbavancin and rifampicin for 10 weeks; for patient 2 rifampicin and amoxicillin/clavulanic acid for 10 weeks; for patient 3 oxacillin and doxycycline for 2 weeks, then cefixime for 8 weeks.

The subsequent surgery was what is referred to as one-stage extensive debridement and bone transport [12], which we adapted using antibiotic-loaded calcium sulfate beads. The time between the first debridement and this subsequent surgery was 20 days for patient 1, 25 days for patient 2, and 21 days for patient 3.

Using an anteromedial (for patients 1 and 2) or anterolateral (for patient 3) approach to the distal tibia, we resected the infected area including the articular surface, proceeding proximally until we reached bone tissue that was viable and had no signs of infection; we assembled a circular external fixator extending from the proximal tibia to the foot, and we performed a proximal metaphyseal osteotomy of the tibia with a Gigli saw, according to the Afghan technique [13]. In patients 2 and 3, we subsequently performed a second tibial osteotomy at the diaphyseal level to convert the bone transport from bifocal to trifocal [14]. The resection area was filled with 10 to 20 cc of antibiotic-loaded Stimulan® beads with diameters 4.8 and 6 mm, prepared with a conventional ratio (vancomycin 1000 mg and gentamycin 240 mg for every 10 cc of calcium sulfate), since all previously isolated bacteria were sensitive to these antibiotics. We carefully preserved all viable, uninfected tissue around the resection; in this way, the calcium sulfate beads were contained by the surrounding tissues at the end of the procedure.

The circular external fixator had 1.8 mm Kirschner wires and 6 mm pins (also called Schanz screws) in the tibia, two 6 mm pins in the calcaneus, and two 3.5–4.5 mm pins in the metatarsal bones; all pins had conical thread and hydroxyapatite coating. After 10 days, bone transport was started with a speed of 0.5 mm per day for every osteotomy site. The transport phase lasted 6, 5 and 11 months for patients 1, 2 and 3, respectively. Patient 3 experienced social problems for which she missed numerous follow-up visits and slowed bone transport progression. However, this did not result in early consolidation of the regenerate, so the patient continued her planned treatment without serious adverse events and without the need for further unanticipated surgery.

Two other patients were treated for osteomyelitis of the upper limbs: in the humeral shaft and in the ulnar shaft, respectively. They had both been treated with osteosynthesis in their home states following motorcycle accidents with

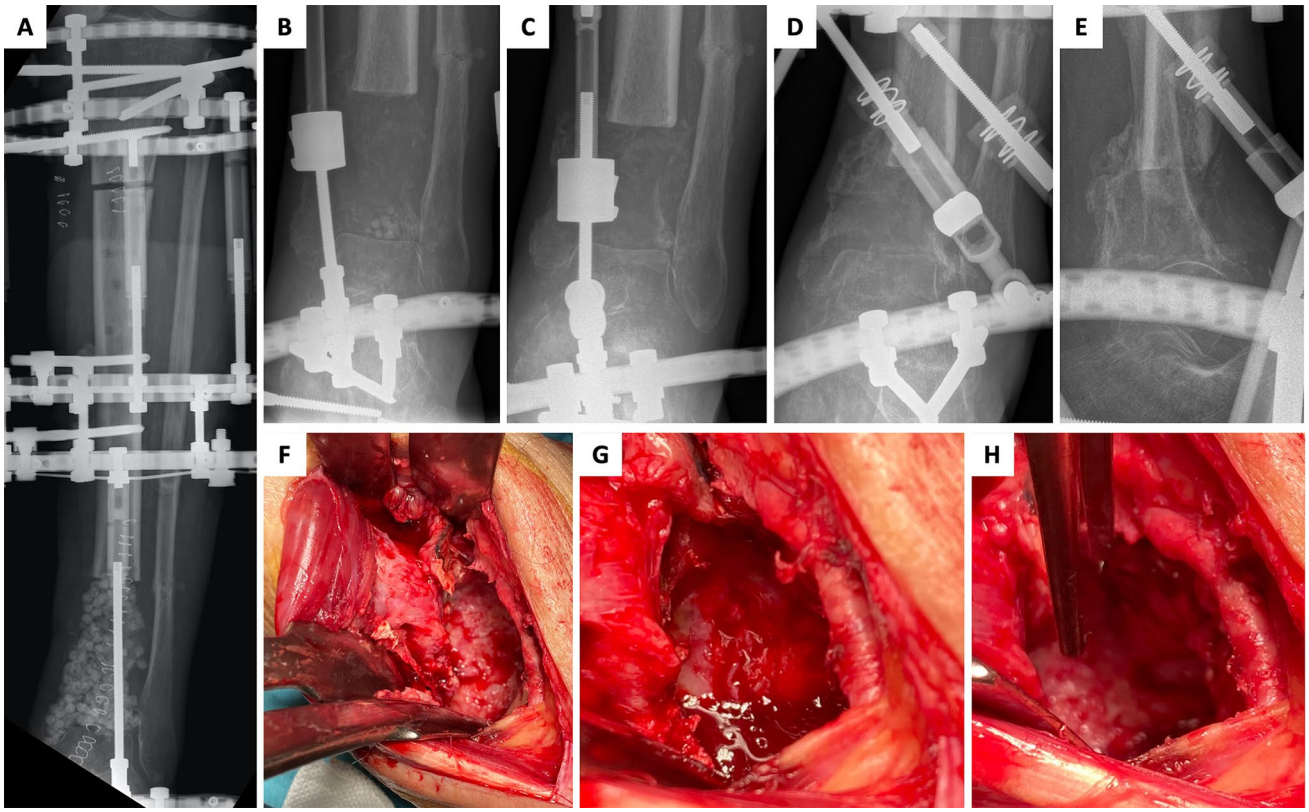

Fig. 2 Distal tibia osteomyelitis in patient 1. **A**–**C**: AP radiographs of the left distal leg after debridement and bone transport surgery **A** and at 1 month **B** and 2 months **C** after the start of bone transport. **D**–**E**: AP and LL radiographs 5 months after the start of bone transport. **F**–**H**: intraoperative photos during the open surgical revision of the docking site, 6 months after the debridement surgery: macroscopic appearance of the outer surface of the bone envelope **F** and its inner surface after opening an anterior window (**G**–**H**)

multiple fractures, and subsequently developed fracture-related infections with severe tissue damage. They came to our attention 70 and 37 days after their osteosynthesis surgery, respectively. In both cases, we performed a first urgent surgery with debridement, removal of internal fixations devices, irrigation and tissue biopsies for culture, followed by a case evaluation with infectious disease specialists and adjustment of intravenous antibiotic therapy: patient 4 was given meropenem and daptomycin for 8 weeks; patient 5 was given oxacillin and rifampicin for 3 weeks, then rifampicin and amoxicillin/clavulanic acid for 9 weeks.

For the subsequent treatment, unlike in cases 1–3, we opted for a two-stage approach: first-stage radical debridement and second-stage bone transport.

To fill the bone defect area after stage 1, we used a combination of an antibiotic-loaded PMMA cylinder and calcium sulfate beads with vancomycin and gentamicin. In the second-stage surgery, we removed the PMMA, added calcium sulfate beads to fill the defect area, performed an osteotomy with a Gigli saw and assembled a monoaxial external fixator for bone transport. The humeral external fixator had 6 mm and 3.5–4.5 mm pins, while the ulnar one had only 3.5–4.5 mm pins; all pins had conical thread and hydroxyapatite coating. In the humerus, the osteotomy was done distal to the resection area, in the ulna it was done proximally. The transport then began after 10 days, with a speed of 0.5 mm per day. The transport phase lasted 2 months and 11 days for patient 4, and 2 months and 24 days for patient 5. In all patients, we performed docking site revision surgery within 10 days of completing the transport phase. Postoperative radiographs for each patient after debridement and bone transport surgery are shown in Fig. 1.

Results

In all patients, we observed the progressive formation of radio-opaque tissue in the periphery of the bone defect area, parallel to the reabsorption of the Stimulan® beads. This newly-formed tissue, with a radiographic appearance similar to immature bone, resembled the anatomy of the removed bone section, avoiding the collapse of the soft tissues and

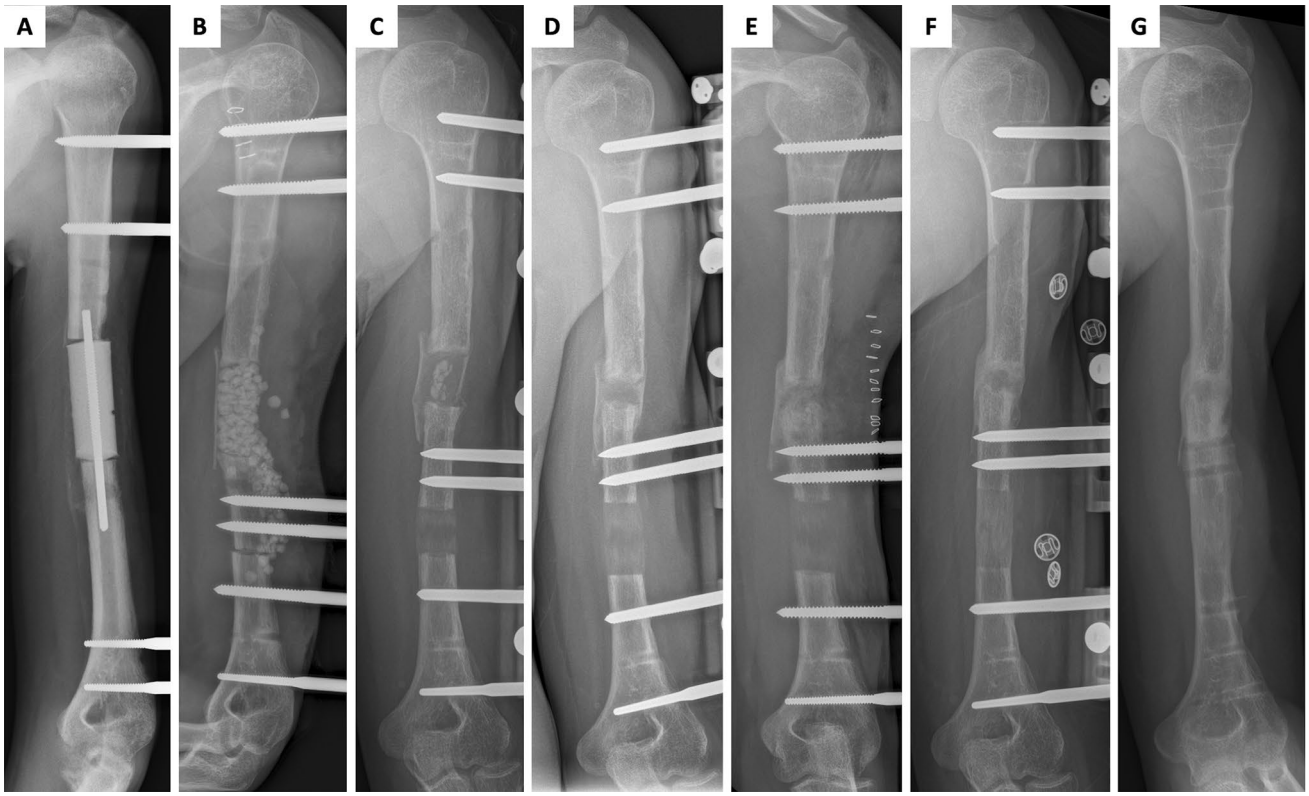

Fig. 3 Humeral shaft osteomyelitis in patient 4. Radiographs of the left humerus after initial debridement (**A**); after bone transport surgery (**B**); at 1 month **C** and 2 months **D** after the start of bone transport; after open revision of the docking site (**E**); at 5 months **F** and 6 months after the start of bone transport

preserving a tunnel for transport (Figs. 2, 3). However, it did not hinder or deflect the advancement of the transported segment.

Similarly in all cases, during the revision surgery of the docking site we directly observed this rigid tissue envelope, abundantly vascularized and macroscopically similar to bone, surrounding an empty chamber (Fig. 2). We preserved as much of the newly formed tissue as possible, removing only the amount necessary to access the docking site. This was done to keep the mechanical and biological support properties as much as possible.

Histological analysis confirmed the presence of newly-formed bone tissue with a high presence of osteoblasts and few osteoclasts (Fig. 4). No necrotic, infected, or poorly viable areas were observed.

As complications, there were minor pin site infections, grade 1 and 2 according to the Checketts-Otterburn classification [15], in the three cases of tibial transport, and one grade-3 infection in the case of humeral transport. In patient 4, a slight aseptic leakage from the wound occurred in the first two weeks after the second-stage surgery, but it subsequently stopped, and the wound closed normally. In the other patients, there were no problems with aseptic leakage or delayed wound healing. No other complications, neither local nor systemic, were found.

Discussion

Previous studies have shown that calcium sulfate antibiotic carriers have similar efficacy to antibiotic-impregnated PMMA cement in the treatment of osteomyelitis and infected nonunions, while being completely biodegradable [16, 17]. In particular, membrane formation was observed in vivo using calcium sulfate instead of PMMA in a modified Masquelet technique [18].

By comparing calcium sulfate and PMMA in the Masquelet technique in a rat model, Ma et al. [19] demonstrated the presence of endochondral ossification in calcium

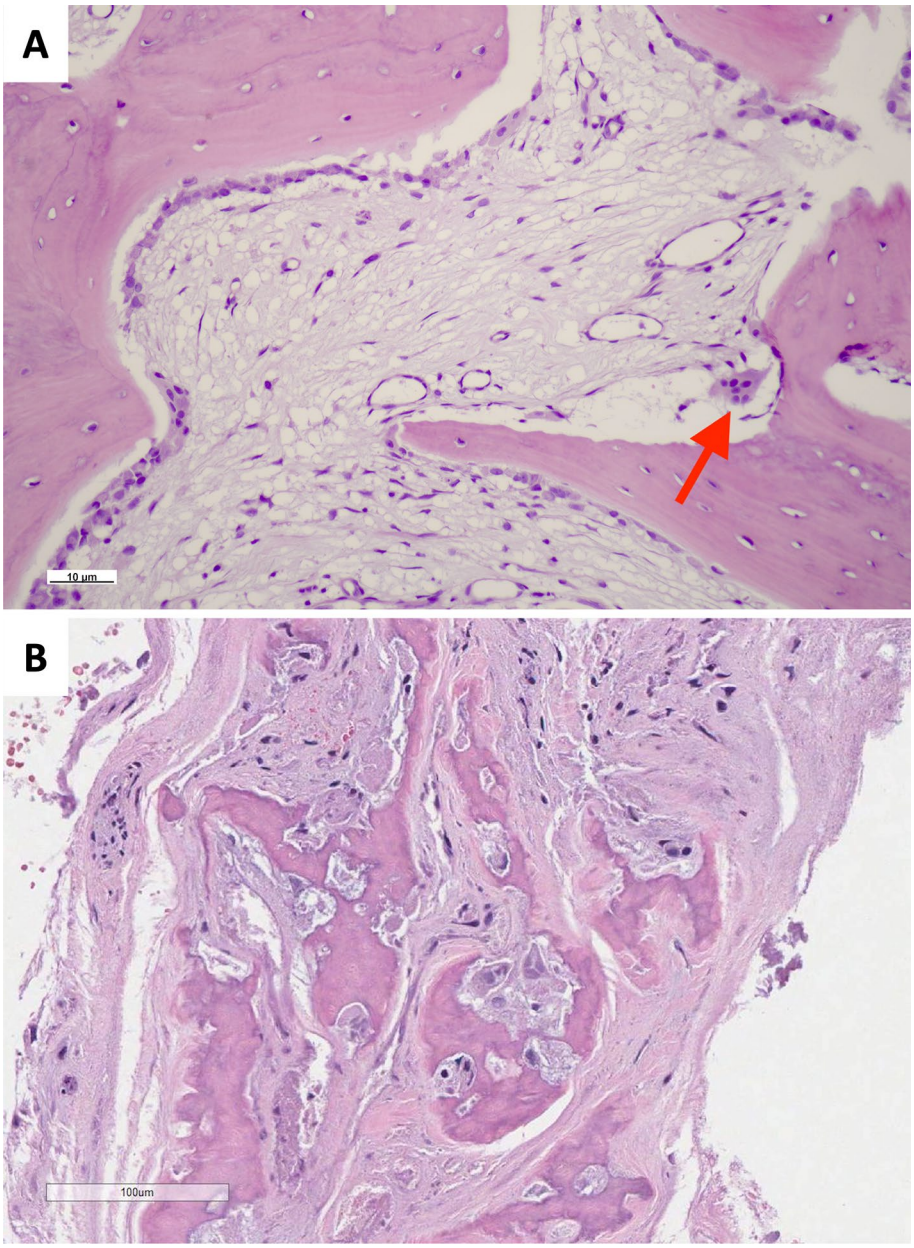

Fig. 4 **A** Histological analysis of newly formed bone tissue harvested from the periphery of the tibial bone defect area in patient 1. Presence of bone trabeculae bordered by osteoblastic rims, a single osteoclast (red arrow). Edematous intertrabecular stroma. No areas of necrosis. Hematoxylin and eosin staining. Bar: 10 µm **B** Histological analysis of tissue harvested from the periphery of the humeral bone defect area in patient 4. Newly formed bone tissue with disorganization of the trabeculae and osteoblastic activation. Osteoclasts are rare (not visible in this image). No areas of necrosis. Hematoxylin and eosin staining. Bar: 100 µm (color figure online)

sulfate-induced membranes, but not in PMMA-induced membranes; in addition, they observed higher levels of VEGF, BMP-2 and TGF-β1 in membranes induced by calcium sulfate.

In the reconstruction of large segmental bone defects in rabbits, a mixture of autologous cancellous bone and calcium sulfate hemihydrate (50%–50% proportion) showed similar bone repair capacities to the use of isolated autologous cancellous bone [20]. More recently, Zhao et al. [21] described the use of a mixture of autogenous iliac bone and vancomycin-impregnated calcium sulfate/calcium phosphate composites, at a ratio of 3:1, for the treatment of large infected bone defects in humans.

Huang et al. [22] reported the use of calcium sulfate cement loaded with antibiotics in tibial defects, together with Ilizarov bone transport over an intramedullary nail or a plate, to treat patients with large tibial defects, and achieved good clinical results. Compared with traditional Ilizarov bone transport, patients treated with this technique had shorter time in external fixator, better limb functions, lower postoperative anxiety score and lower complication incidence [22].

The treatment we used in our patients with tibial osteomyelitis has been described as "one-stage debridement and bone transport"; in a retrospective comparative study focused on 102 patients with tibial or femoral post-traumatic osteomyelitis, this treatment has been shown to be safe and effective, with complication rates comparable to

classic two-stage treatment (first-stage debridement, second-stage osteotomy and bone transport) [12]. However, in all our patients, we used the calcium sulfate carrier in the form of beads, while Zhou et al., along with other articles [12, 22–26], describe its use as a single block or cylinders filling the bone defect area. We preferred to use this form in consideration of the greater surface area, and consequently the higher local release of antibiotic in the initial stages of treatment.

We routinely perform docking site open revision surgery with autologous bone graft from the iliac crest in long bone transports, to favor the consolidation of the docking site and decrease the time of external fixation [27]. Moreover, in the cases described here, this surgery also allowed us to directly visualize the newly formed bone tissue at the periphery of the defect area.

In this article, we report debridement and bone transport surgery with antibiotic-loaded calcium sulfate beads. This technique can be applied both in the lower limbs and in the upper limbs, as shown by our series. In addition, we reported the first described histological analysis of new bone formation in calcium sulfate-induced membranes.

Using our technique, calcium sulfate initially guarantees a local release of high concentrations of antibiotics and acts as a spacer avoiding the collapse of soft tissues; with the progressive absorption of calcium sulfate, the peripheral bone envelope maintains the function of spacer and, thanks to its abundant vascularization, provides a fundamental biological stimulus for the docking site and avoids the development of necrotic areas at risk of infection. We preserved a large portion of the newly formed tissue, to act both as a rigid envelope for mechanical protection and as a source of vascularization for the docking site; this proved to be particularly important in tibio-talar arthrodesis in patients 1 and 2, since the two bone ends had not yet come into full contact.

In this way, therefore, we have obtained all the properties of the ideal bone filler for osteomyelitis [7]: biocompatibility, bioabsorption, osteoconduction, mechanical strength, and release of high concentrations of antibiotics.

In this article, we describe an original technique and we report the clinical, radiological and histological evidence of the peripheral bone neoformation. Our technique can be used in all long bone transport, with significant advantages in terms of biological support and reduction of surgeries required. The main limitation is the absence of clinical follow-up results, which however are not among the purposes of the study; we are planning to perform future studies on the outcomes of patients treated with this method in comparison to traditional techniques.

Author Contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by MD. The first draft of the manuscript was written by MD and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Approval from the ethics committee was not required due to the characteristics of the study and the number of patients.

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