Clinical and radiological assessment of the induced membrane technique using beta-tricalcium phosphate in reconstructive surgery for lower extremity long bone defects

Aims

To clarify the effectiveness of the induced membrane technique (IMT) using beta-tricalcium phosphate (β-TCP) for reconstruction of segmental bone defects by evaluating clinical and radiological outcomes, and the effect of defect size and operated part on surgical outcomes.

Patients and Methods

A chart review was conducted of consecutive 35 lower extremities treated with IMT using β-TCP between 2014 and 2018. Lower Extremity Functional Score (LEFS) was examined preoperatively and at final follow-up to clarify patient-centered outcomes. Bone healing was assessed radiographically, and time from the second stage to bone healing was also evaluated. Patients were divided into $\geq$ 50 mm and $<$ 50 mm defect groups and into femoral reconstruction, tibial reconstruction, and ankle arthrodesis groups.

Results

There were 10 and 25 defects in the femur and tibia, respectively. Median LEFS improved significantly from 8 (interquartile range (IQR) 1.5 to 19.3) preoperatively to 63.5 (IQR 57 to 73.3) at final follow-up ($p < 0.0001$). Bone healing was achieved in all extremities, and median time from the second stage to bone healing was 6 (IQR 5 to 10) months. Median time to bone healing, preoperative LEFS, or postoperative

LEFS did not differ between the defect size groups or among the treatment groups.

Conclusion

IMT using β-TCP provided satisfactory clinical and radiological outcomes for segmental bone defects in the lower extremities; surgical outcomes were not influenced by bone defect size or operated part.

Take Home Message

- IMT using β-TCP provided satisfactory clinical and radiological outcomes for segmental defects in the long bones of the lower extremities.
- There were no differences in clinical and radiological outcomes between bone defect size ≥ 50 mm and < 50 mm or among femoral reconstruction, tibial reconstruction, and ankle arthrodesis.

Introduction

Large bone defects are caused by trauma, infection, and tumor. Historically, autologous bone graft has been used for bone defects, but, patients with large bone defects > 50 mm often results in poor outcomes.[1] Bone transport distraction osteogenesis using the Ilizarov technique or a free vascularized bone graft has been conventionally used for such large segmental bone defects. However, these procedures are accompanied by protracted healing and a relatively high rate of complications.[2]

Masquelet et al developed induced membrane technique (IMT) as an alternative procedure for reconstruction of segmental bone defects.[3] This technique is a 2-stage procedure, the first stage involves aggressive debridement and placement of a temporary polymethylmethacrylate (PMMA) spacer, which induces formation of a bioactive membrane. The second stage is removal of the PMMA spacer and autologous cancellous bone grafting. Recently, previous reports have demonstrated the effectiveness of IMT for segmental bone defects based on radiological assessments such as bone healing rate and time to bone healing.[3] Despite this, the functional outcomes after IMT are still not known as only a few studies have clarified clinical patient-centered outcomes.[4,5] Other concerns with IMT include the relatively limited surgical indications to obtain satisfactory radiological outcomes. The amount of autologous graft that can be harvested is limited. This restricts the indication of IMT for the patients with large segmental bone defects. To solve this problem, extenders such as cancellous allograft and demineralized bone matrix (DBM) have been applied.[3] Since 2014, grafting of beta-tricalcium phosphate (β-TCP) mixed with autologous cancellous bone from the iliac crest have been used for IMT in our institution to treat cases with large bone defect in the lower extremities (Figure 1). Also, previous studies have proposed that the operated part is a concern as it may affect surgical outcomes following IMT.[6]

This study had two purposes. One was to clarify the effectiveness of IMT using β-TCP for segmental bone defects by evaluating clinical patient-centered and radiological outcomes. The other was to clarify the effect of defect size (≥ 50 mm or < 50 mm) and operated part (femoral reconstruction, tibial reconstruction, or ankle arthrodesis) on surgical outcomes by comparison among these groups. Our hypothesis was that IMT using β-TCP would provide good clinical and radiological outcomes for segmental long bone defects in the lower extremities, with no differences in clinical and radiological outcomes between defect sizes ≥ 50 and < 50 mm or among femoral reconstruction, tibial reconstruction, and ankle arthrodesis.

Patients and Methods

This retrospective study was approved by the review board of the authors' institution. All participants included in this study provided written informed consent.

A chart review was conducted of 36 consecutive lower extremities of 35 patients for infected nonunion, fresh open fracture, osteomyelitis, or congenital pseudoarthrosis in the femur or tibia at our institute between 2014 and 2018. A single surgeon performed all surgical procedures and decided pre- and post-operative care. A diagnosis of nonunion was made based on findings of no healing of the fracture on radiological assessment at 6 months after initial surgery for fracture and instability at the fracture site on stress radiography. Infection was diagnosed based on local physical findings suspicious for infection such as swelling, local heat, redness, or purulent discharge through a skin incision or fistula near the fracture site, identification of a causative organism by culture of preoperative or intraoperative specimen, or elevated C-reactive protein, white blood cell count, and erythrocyte sedimentation rate on blood examination.

Patients for whom the postoperative follow-up period was less than 24 months were excluded. Of the 36 lower extremities in 35 patients, 1 patient with infected nonunion of the tibia was lost to follow-up because of relocation. Thus, 35 lower extremities of 34 patients (30 male, 5 female; median age 46 [IQR 40 to 61] years) were included in this study.

Surgical procedure

First stage

Aggressive debridement of necrotic and infected tissue was performed and a positive paprika sign was used to confirm complete debridement. Then, the fracture site was stabilized according to skin condition in each patient. Intramedullary nailing was performed for the femur shaft, and locking plate fixation was applied to stabilize fractures of the distal femur and proximal tibia. After single plating, second plate fixation was added if a manual stress test showed instability at the fixed part. For the patients with an insufficient condition of skin, temporary fixation using a 3.0-mm diameter Kirschner wire was indicated; this temporary fixation was reinforced by postoperative below-knee cast immobilization. Ankle arthrodesis was selected for extremities in which the talocrural joint could not be saved due to a defect in the tibial plafond after debridement, and temporary fixation using Kirschner wire was also applied for such extremities.

After fixation, an antibiotic-impregnated PMMA spacer was inserted into the bone defect. The PMMA spacer was placed and shaped to match the defect in situ and allowed to cure while in position. For patients with methicillin-resistant Staphylococcus aureus (MRSA) that was confirmed preoperatively, 2.0 g of vancomycin powder combined with 40 g of PMMA (Cemex® RX; Tecres Corp., Verona, Italy) was used. For patients in whom the causative organism was not MRSA or unidentifiable preoperatively, PMMA containing gentamycin (Cobalt™ HV Bone Cement with Gentamicin [G-HV]; Zimmer Biomet Japan, Tokyo, Japan) was inserted. An additional local or free flap was applied if complete coverage of soft tissue over the implanted region of the bone defect was not possible.

Postoperatively, all patients received the following protocol of intravenous antibiotic treatment. Linezolid 600 mg twice daily for 3 days, followed by daptomycin 8 mg/kg once daily, was administered intravenously until routine blood examination indicated normal C-reactive protein, white blood cell count, and erythrocyte sedimentation rate.

Second stage

After confirmed normalization of laboratory values, the second stage of IMT was performed; however, if any laboratory value was subsequently elevated, additional debridement was considered before the second stage procedure.

The induced membrane was identified through the same incision made in the first stage and was incised longitudinally to remove the PMMA spacer. Then, internal fixation was performed for bone defects in the tibial shaft and distal tibia if it had not been performed in the first stage. Antegrade intramedullary nailing was used for the tibial shaft and distal tibia, while locking plate fixation was applied for the patients with a small distal tibial fragment that did not have enough space for insertion of at least 2 interlocking screws. Also, antegrade intramedullary nailing was performed for talocrural arthrodesis in which 2 distal interlocking screws were inserted into the talus. Subsequently, grafting was performed by filling the bone defect with a combination of autologous cancellous bone harvested from the iliac crest and β-TCP which were mixed in approximately equal proportions (Figure 2), using the technique reported by Sasaki et al.[7]

Postoperatively, the same intravenous antibiotic treatment protocol as after the first stage was used in all patients. Active range of motion exercises for the ipsilateral knee and ankle joint were allowed a few days after surgery for patients who underwent reconstruction of the femur and tibia. Next, 1/4 partial weight bearing was allowed at 4 weeks after surgery, and then full weight bearing was permitted at 12 weeks after surgery if pain was absent on partial weight bearing and progression of consolidation was confirmed. For patients who underwent ankle arthrodesis, 1/4 partial weight bearing was allowed 6 weeks after surgery and full weight bearing was permitted at 14 weeks after surgery.

Evaluation criteria

For clinical evaluation, Lower Extremity Functional Score (LEFS)[8] was examined preoperatively and at final follow-up to clarify patient-centered outcomes. The LEFS is a well-known and validated patient-rated outcome measure (PROM) that can be used to measure lower extremity function.[8] The maximum score is 80 which means complete function and the lowest score is 0 which means significant dysfunction. Radiographic assessment was performed to determine whether bone healing was achieved. Bone healing was defined as evidence of callus formation in 2 of 4 cortices as assessed on anteroposterior and lateral plain radiographs.[5]

The time from the second stage of the procedure to bone healing was evaluated by a board-certified orthopaedic surgeon who did not perform the surgery.

Extremities were divided into 2 groups according to the maximum length of the bone defect on radiographic assessment (≥ 50 mm group and < 50 mm group), and radiological and clinical evaluations were compared between the groups. Extremities were also divided into 3 groups according to the operated part and procedure (femoral reconstruction group, tibial reconstruction group, and ankle arthrodesis group), and radiological and clinical evaluations were compared among the groups.

Statistical analysis

Data were analyzed using StatView version 5.0 software (SAS Institute, Cary, NC). The Wilcoxon signed-rank test was used to compare median LEFS at preoperative assessment and LEFS at the final follow-up between the defect size groups and among the treatment groups. The Mann–Whitney *U* test was used to compare median age, time to bone healing after the second stage, time from onset of symptoms or injury to the first stage, and time from the first stage to the second stage between the ≥ 50 mm and < 50 mm groups. The Kruskal-Wallis test was used to compare median age, time to bone healing after the second stage, time from the onset of symptoms or injury to the first stage, and time from the first stage to the second stage among the femoral reconstruction, tibial reconstruction, and ankle arthrodesis groups. A p-value of < 0.05 was considered statistically significant.

Results

Clinical and radiological outcomes are shown in Table I. Overall, median LEFS improved significantly from 8 (IQR 1.5 to 19.3) preoperatively to 63.5 (IQR 57 to 73.5) at final follow-up (p < 0.0001). Bone healing was achieved in all extremities, and the median time to bone healing after the second stage was 6

(IQR 5 to 10) months (Figure 3). Also, 31 / 35 lower extremities (88.6%) obtained the evidence of callus formation in 4 of 4 cortices as assessed on anteroposterior and lateral plain radiographs, 3 (8.6%) had callus formation in the 3 of 4 cortics. In detail, 2 extremities with open tibial fracture required a free flap and 2 extremities with infected nonunion needed a local flap for soft tissue defect in the first-stage procedure. The first-stage procedure was repeated to manage infection 2 times in 2 extremities, 3 times in 1 extremity, and 4 times in 2 extremities.

There were no differences between the ≥ 50 mm and < 50 mm groups in median age, time from occurrence of symptoms or injury to the first stage, time from the first stage to the second stage, time to bone healing after the second stage, preoperative LEFS, or postoperative LEFS (Table II). Furthermore, there were no differences among the femoral reconstruction, tibial reconstruction, and ankle arthrodesis groups in each investigated outcomes (Table III).

Discussion

Giannoudis et al defined four important factors in fracture healing, namely, osteogenesis, osteoconduction, osteoinduction, and mechanical environment, and termed this the diamond concept.[9] Among these factors, autologous cancellous bone has osteogenic, osteoconductive, and osteoinductive ability.[10] However, it is sometimes difficult to perform IMT using only autologous cancellous bone grafting for patients with large bone defects because the amount of autograft harvested from the iliac crest is not enough to fill the bone defects in the second stage. Recently, the Reamer Irrigator Aspirator (RIA) system has been used to harvest a large amount of femoral cancellous bone,[3] but fracture of the femur has been reported to be a major complication associated with this harvesting system.[11] Extenders such as cancellous allograft, DBM, and ceramics have been described as the other solution for patients with large bone defects.[12] Cancellous allograft and DBM have similar osteoconductive ability, but they have no osteogenic and less osteoinductive ability, unlike cancellous autograft. Furthermore, these materials carry a risk, albeit low, of complications such as transmission of pathogens, infection, immune rejection, and incomplete incorporation.[12] In the present study, β-TCP was used as an extender in IMT. This material has some useful characteristics including easy resorption and high osteoconductive and replanting ability.[12] In 2018, Sasaki et al reported surgical outcomes of IMT using β-TCP for femoral or tibial segmental bone loss due to infection in a preliminary report of 7 cases.[7] They stated that in IMT, the defect was filled with a combination of cancellous autograft from the iliac crest and β-TCP, which were mixed in approximately equal proportions, and healing was achieved in all 7 patients at a median of 6 months after the second procedure, although they did not report clinical outcomes after surgery. The same technique was applied in the present study and bone healing in all 35 extremities at a median of 6 months after the second procedure. The larger number of cases in our study (7 vs 35 extremities) provides further evidence of the utility of β-TCP as an extender in IMT for treatment of nonunion and osteomyelitis in the lower extremity.

Despite satisfactory radiological outcomes, some caution should be exercised in interpreting the outcomes from this study. Of our cases, 3 with femoral osteomyelitis and a maximum bone defect size of >180 mm did not ultimately achieve circumferential healing (healing of 4 bone cortices on radiographic assessment) (Figure 4). Further improvement of the procedure may be needed to achieve complete circumferential healing in extremities with large bone defects. Also, complete circumferential healing was not achieved in a case of congenital pseudoarthrosis of the tibia. In the literature, the utility of IMT using corticocancellous autograft from the posterior iliac crest has been reported.[13] This conflict suggests the possibility that corticocancellous autograft may be suitable for congenital pseudoarthrosis instead of a combination of cancellous autograft and β-TCP because of the lower bone regeneration in congenital pseudoarthrosis.

In this study, the autologous cancellous bone was harvested from the anterior iliac crest. It has been well known that the available amount of cancellous bone is more form the posterior iliac crest than from the anterior iliac crest. Burk et al evaluated the available amount of corticocancellous from anterior and posterior iliac crest using 44 cadavers. They reported that the average uncompressed and compressed amount from the anterior iliac crest were 26.29 mL and 20.58 mL, respectively, and those from the posterior iliac crest were 33.82 mL and 24.11 mL, respectively.[14] Furthermore, donor site pain at the posterior iliac crest seems to be less than at the anterior iliac crest. However, the supine position was suitable for the present complicated procedure, and this position did not permit harvest from the posterior iliac crest. To our knowledge, only 2 studies have used a validated questionnaire to assess clinical outcomes after IMT. Zoller et al were the first to evaluate postoperative clinical outcomes of IMT for diaphyseal fractures with segmental defects using the LEFS questionnaire; in 8 patients, the average score was 53.1 (corresponding to 66% of full functionality) at average of 32 months after surgery.[4] Zhang et al evaluated surgical outcomes in 41 patients with infected bone defects treated with 3-stage IMT and showed that mean LEFS at final follow-up was 68.4 corresponding to 85.5% of maximal function.[5] In our study, median LEFS at final follow-up was 63.5 corresponding to 79.3% of maximal function, which was consistent with these 2 previous studies. The results from this study suggest the effectiveness of IMT using β-TCP for reconstruction of segmental bone defects

Our study compared clinical and radiological outcomes between bone defect sizes of ≥ 50 mm and < 50 mm. This cutoff was based on past reviews that defined 50 mm as an indication for autologous cancellous bone graft.[1] In contrast to previous studies, our results showed that bone defect size did not influence clinical and radiological outcomes. This is presumably attributable to an initial bridging callus that formed around the grafted material like a bony collar at approximately 10 weeks after the second procedure and thus allowed ossification to advance toward the center of the defect. This hypothesis needs to be verified through animal studies in the future. Furthermore, surgical results were compared between reconstruction of the femur, reconstruction of the tibia, and ankle arthrodesis; there were also no differences in clinical and radiological outcomes among the 3 groups. Baud et al compared radiological outcomes between reconstruction of the femur and tibia using IMT in a total of 33 patients and found that the time to union was significantly longer in the tibia than in the femur with no between-group difference in union rate.[6] This result was different from our results in this study, which showed no difference in the time to bone healing. This discrepancy may be due to the difference in the total union rate between the 2 studies (Baud et al: 61%; our study: 100%). The union rate of 61% is clearly lower than the rate of 89.7 reported in the only systematic review of IMT, published by Morelli et al in 2016.[15] Although only 1 case report showed successful outcomes of IMT for ankle arthrodesis,[16] no study has shown the effectiveness of IMT for ankle arthrodesis by comparing its surgical outcomes with those of IMT for reconstruction of long bones. Our study revealed that IMT for ankle arthrodesis could achieve good surgical outcomes similar to those of IMT for reconstruction of the femur and tibia.

This study has several limitations. First, this was a retrospective study with a limited number of patients and a short follow-up period. Although clinical and radiological outcomes with long-term follow-up are necessary to clarify the effectiveness of IMT using β-TCP, the minimum follow period in this study was only 24 months. Second, this study had no control group for comparing IMT using β-TCP with a conventional technique such as autograft from the iliac crest, RIA autograft, or allograft. If a large randomized controlled trial that compares the present procedure with other methods through long-term follow-up examinations and accurate objective postoperative evaluation, including radiological examination, is performed in the future, the effectiveness of this procedure is confirmed. However, it may be difficult because the occurrence of nonunion or osteomyelitis of the long bones in the lower extremities seems to be less frequent with the present technique. Third, approximately equal proportions of β-TCP and autograft were used in this study. It is important to identify the optimal ratio of the autograft and β-TCP that would provide reliable bone healing with reduced volume of harvested autograft as compared with conventional techniques. Although the data in this study were limited, further evaluations in larger series may further clarify the utility of β-TCP as a bone substitute in IMT.

In conclusion, IMT using β-TCP provided satisfactory clinical and radiological outcomes for segmental bone defects of the long bones in the lower extremities. There were no differences in surgical outcomes between bone defect sizes of ≥ 50 mm and < 50 mm or among femoral reconstruction, tibial reconstruction, and ankle arthrodesis.

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Figure Legends

Fig. 1 Schematic illustration of the surgical technique. PMMA, polymethylmethacrylate; β-TCP, beta-tricalcium phosphate.

Fig. 2 Intraoperative photographs in second stage procedure. A: induced membrane over the PMMA, B: 90mm bone defect after removal of PMMA, C: grafting of autologous cancellous bone mixed with β-TCP

Fig. 3 Postoperative radiographs for infectious nonunion of tibia. A: just after the first stage, B: after the second stage, C: 6 months after the second stage

Fig. 4 Postoperative radiographs and computed tomography for osteomyelitis of femur. A: just after the second stage, B and C: 12 months after the second stage

Table I. Patient characteristics and clinical and radiological outcomes.

N = 35	Data
Median patient age, years (IQR)	46 (40 to 61)
Male:female patients, n (%)	30:5(85.7:14.3)
Median maximum bone defect size, mm (IQR)	48 (34.5 to 72.5)
Part of bone defect, femur:tibia, n (%)	10:25 (28.6:71.4)
Size of bone defect, ≥ 50 mm:< 50 mm group, n (%)	16:19 (45.7:54.3)
Median time from onset to the first stage, months (IQR)	11 (3.5 to 25.5)
Median time from the first stage to the second stage, days (IQR)	49 (42 to 60.5)
Median time to bone healing after second stage, months (IQR)	6 (5 to 10)
Median postoperative follow-up duration, months (IQR)	36 (29.5 to 44)
Rate of bone healing, %	100
Preoperative median LEFS (IQR)	8 (1.5 to 19.3)
Postoperative median LEFS (IQR)	63.5 (57 to 73.3)

LEFS, Lower Extremity Functional Score.

Table II. Comparisons between the ≥ 50 mm and < 50 mm groups.

	≥ 50 mm group	< 50 mm group	p-value
Median patient age, years (IQR)	43.5 (38.5 to 51.3)	49 (43 to 62.5)	0.21
Median time from onset to first stage, months (IQR)	12 (6.3 to 49.5)	6 (2.5 to 17.5)	0.17
Median time from first stage to second stage, days (IQR)	49 (42 to 58)	49 (41.5 to 74.5)	0.94
Median time to bone healing after second stage, months (IQR)	7 (5 to 10)	6 (5.5 to 9.5)	0.80
Preoperative median LEFS (IQR)	8.5 (2.3 to 14)	8 (1.5 to 19.3)	0.84
Postoperative median LEFS (IQR)	66.5 (61 to 76.3)	59 (48.5 to 68)	0.08

Data are shown as the median (IQR).

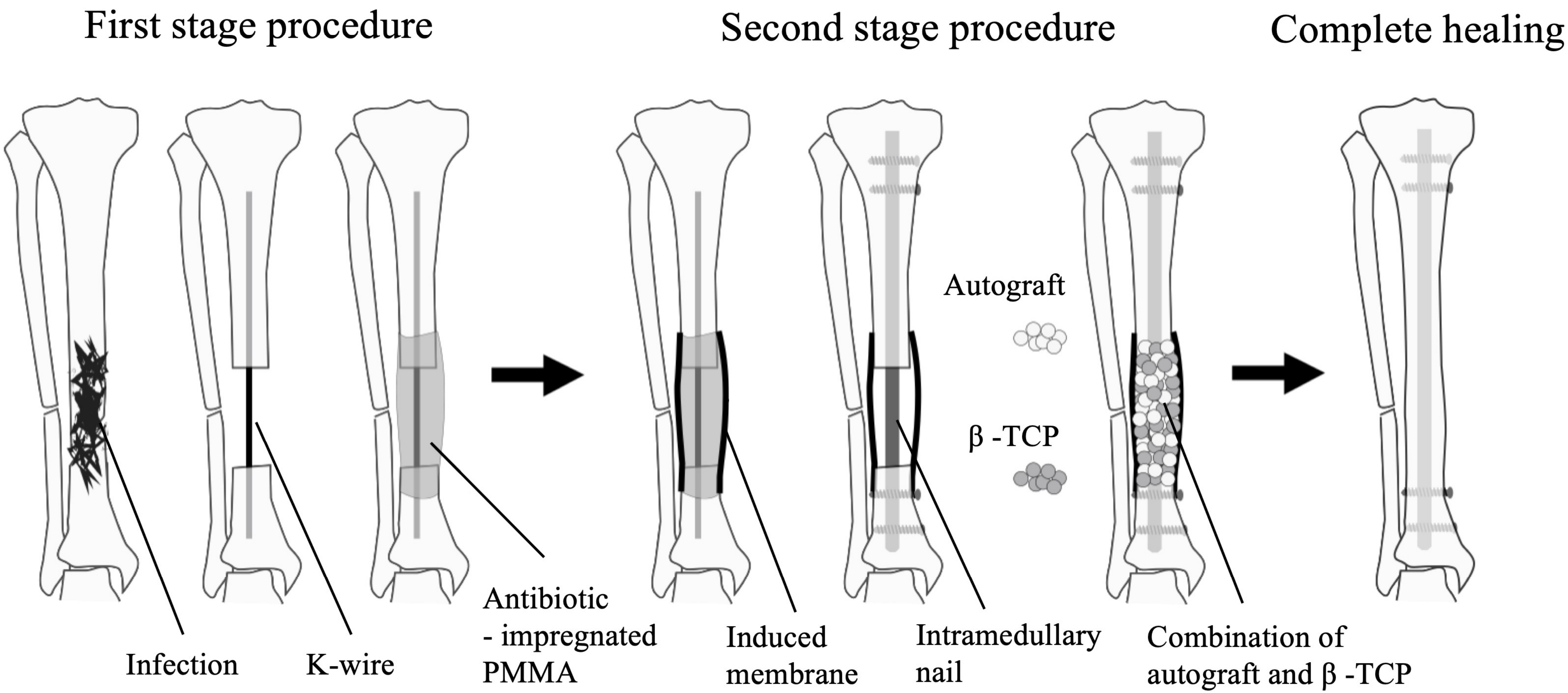
IQR, interquartile range; LEFS, Lower Extremity Functional Score.

Table III. Comparison between the femoral reconstruction, tibial reconstruction, and ankle arthrodesis groups.

	Femoral reconstruction	Tibial reconstruction	Ankle arthrodesis	p-value
Median patient age, years (IQR)	48.5 (39.3 to 60.3)	47.5 (40 to 61.3)	43 (40 to 48)	0.64
Median time from onset to first stage, months (IQR)	20 (3 to 303)	10.5 (3.8 to 22.3)	7 (5 to 11)	0.58
Median time from first stage to second stage, days (IQR)	47.5 (44.5 to 54.3)	49 (40.8 to 66.5)	58 (49 to 72)	0.45
Median time to bone healing after second stage, months (IQR)	9.5 (7.3 to 10.8)	6 (5 to 8.3)	8 (5 to 9)	0.12
Preoperative median LEFS (IQR)	8 (1.5 to 31.3)	9 (5 to 13.5)	0 (0 to 10)	0.84
Postoperative median LEFS (IQR)	62.5 (59.5 to 70.5)	65 (55.5 to 75)	61 (44 to 65)	0.50

Data are shown as the median (IQR).

IQR, interquartile range; LEFS, Lower Extremity Functional Score.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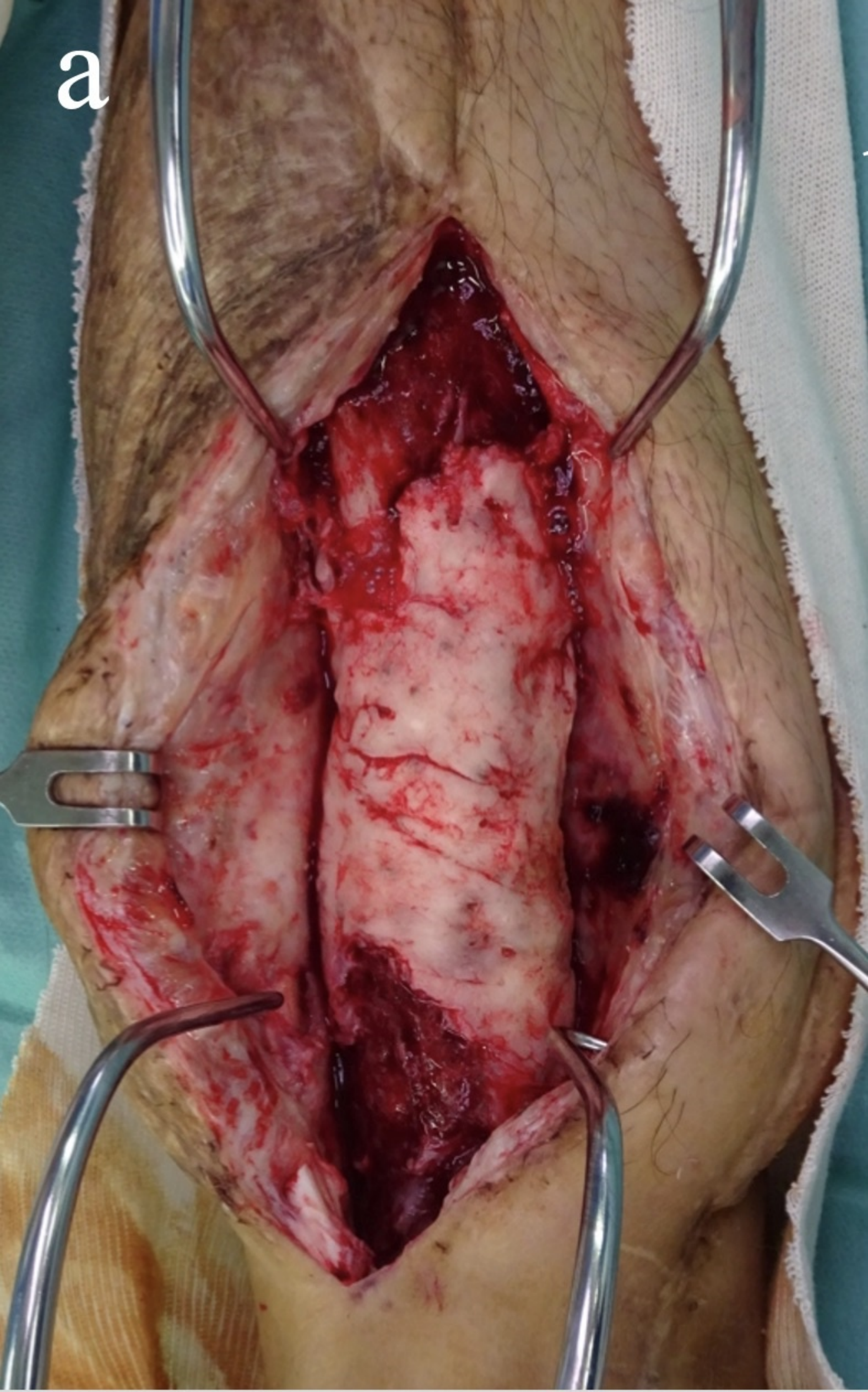
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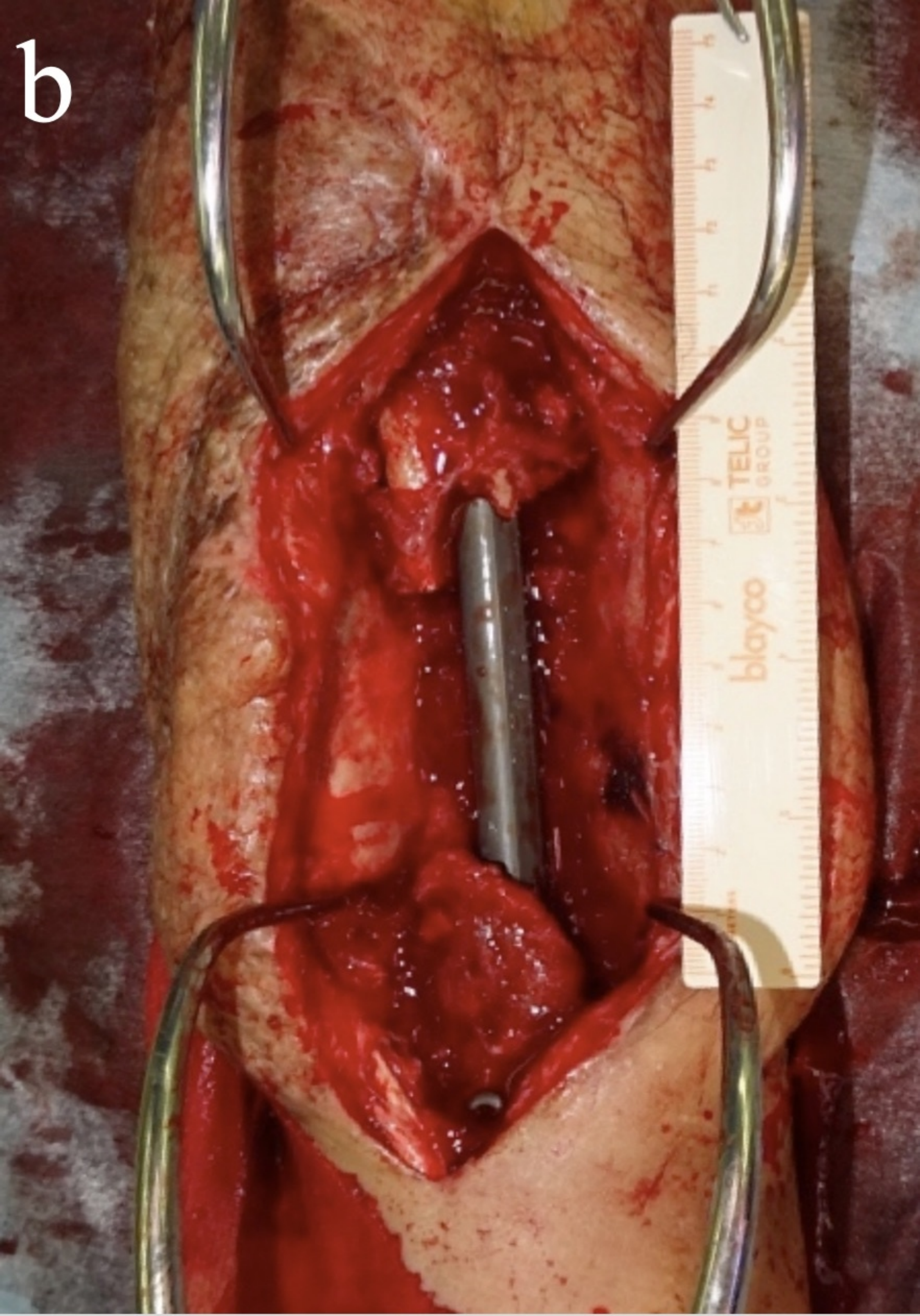
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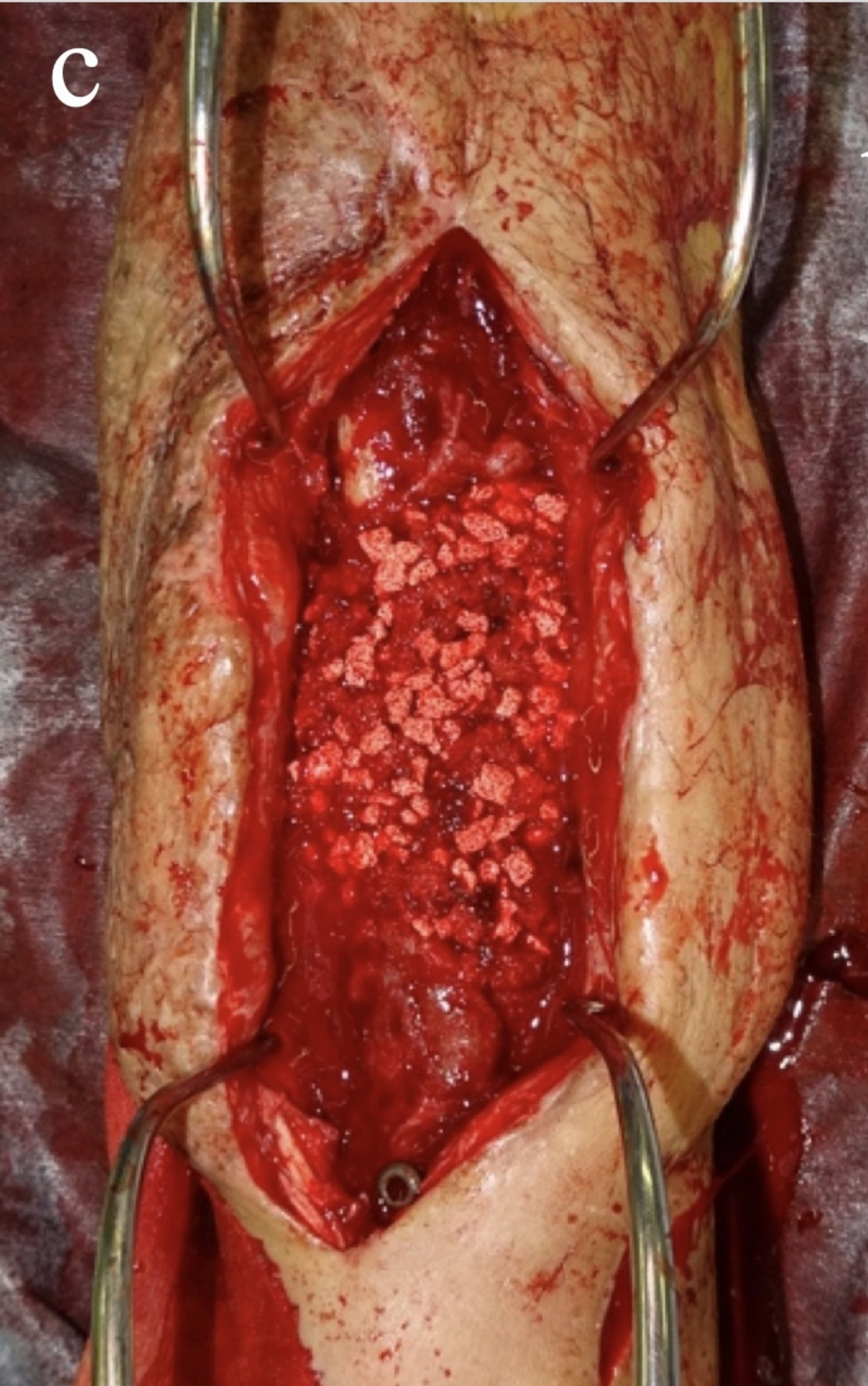
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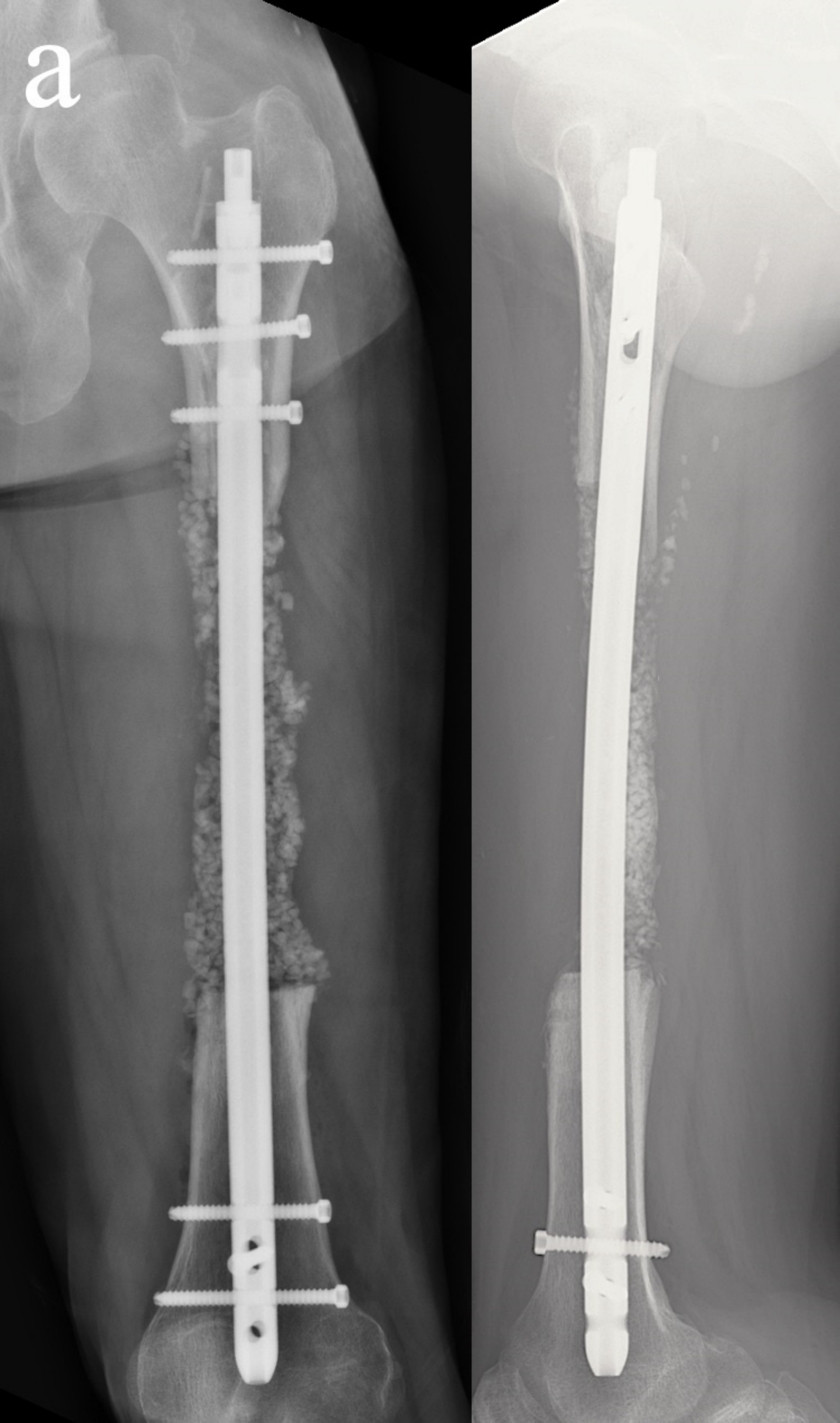
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