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Comparing the outcomes of the induced membrane technique between the tibia and femur: Retrospective single-center study of 33 patients

Alexandre Baud*, Xavier Flecher, Richard Alexandre Rochwerger, Jean-Camille Mattei, Jean Noël Argenson

A B S T R A C T

Introduction: Bone defects are challenging to treat surgically. The primary objective of our study was to compare the union rate and time to union between the tibia and femur when using the induced membrane technique. The secondary objective was to document how failures were managed.

Material and Methods: This retrospective, single-center study involved 33 patients (23 men, 10 women) who were older than 18 years of age. They were treated surgically for a leg fracture or long bone nonunion (22 tibia, 11 femur) using the induced membrane technique between January 2011 and December 2016 and had a complete follow-up. The minimum follow-up was 1 year for fractures and 2 years for non-union cases. Bone union was defined as the presence of at least two cortices with bridging on two radiographic views and return to full weight bearing.

Results: The mean patient age was 38.3 ± 15.5 years (18–72). The mean bone defect size was 7.9 ± 5.0 cm (2.3–18.0). The mean follow-up was 3.3 ± 1.8 years (1–7.2). The union rate was 61% (20 patients). The mean time to union was 10 ± 6.4 months (3–23). The time to union was significantly longer in the tibia (11.6 ± 6.9 months [3–23]) than in the femur (6.3 ± 2.9 months [3.4–10.3]) ($p = 0.025$). The failure rate did not differ between the tibia and femur. Nine of the 13 patients (69%) in which the treatment failed were reoperated; 7 of them underwent nonunion treatment (78%) and 2 underwent amputation (22%). The other 4 patients were waiting for an infection to resolve before being reoperated.

Conclusion: The induced membrane technique is an effective surgical procedure for large bone defects in both the tibia and femur. However, the time to union was shorter in the femur than the tibia in our cohort.

Level of evidence: IV, retrospective study.

Keywords:
Masquelet
Induced Membrane
Bone defect
Bone graft
Nonunion
Bone infection
Tibia
Femur

1. Introduction

Limb preservation in the context of large bone defects has always been a priority for surgeons, although it may be controversial. Nevertheless, the long-term outcomes are very encouraging [1]. Reconstruction is a challenging surgery [2,3] and requires multidisciplinary [4], early and effective treatment of infections [5–7] and tissue lesions [8]. However, there is no consensus on the management of large bone defects [9,10]. Several surgical techniques have been described in the literature, such as Ilizarov distraction-osteogenesis [11], bone transport [12], transfer of vascularized

bone (with the fibula being the most used graft) [13], and segmental banked bone allograft [14].

In the 1980s, Masquelet described a novel bone reconstruction techniques in which polymethylmethacrylate (PMMA) was placed in the defect to induce a foreign body reaction and formation of an induced membrane [8,15,16] having osteogenic properties: secretion of growth factors, recruitment and osteogenic differentiation of stem cells, and production of angiogenic factors contributing to vascularization and corticalization of the bone graft [17–20]. The surgical induced membrane technique is one of the most effective strategies for filling segmental bone defects with reported union rates of 82% to 100% [21–23].

Recent publications have focused on the biological and mechanical mechanisms that contribute to bone regeneration. Based on the work of Giannoudis et al. and the “diamond concept”, five essential

Table 1
Study population.

	Number of patients	%	Mean	Median	Standard Deviation	Min	Max
Sex							
Male	23	69.7					
Female	10	30.3					
Age at time of accident (years)			38.3	37	15.5	18	72
Cardiovascular risk factors							
Smoking	20	60.6					
Body mass index (kg/m ²)			25.8	25	6.07	12.5	36.8
Bone							
Tibia	22	66.7					
Femur	11	33.3					
Reason for procedure							
Nonunion	15	45.5					
Fracture	18	54.5					
Size of bone defect (cm)			7.9	6.2	5	2.3	18
Classification of bone defect							
Karger 1 (<2 cm)	0	0.0					
Karger 2 (2–5 cm)	12	36.4					
Karger 3 (5–10 cm)	11	33.3					
Karger 4 (> 10 cm)	10	30.3					
Number of open fractures	28	84.8					
Open fracture classification system							
Gustillo 1	2	6.1					
Gustillo 2	11	33.3					
Gustillo 3a	7	21.2					
Gustillo 3b	8	24.2					
Preoperative infection rate	16	48.5					
Non-Union Scoring System (NUSS)			38.7	36	13.24	20	68
Time interval: Fracture–1st stage of surgery (months)			9.4	1.8	13.90	0	65.6
Type of fixation							
External fixator	25	75.8					
Plate	4	12.1					
Rigid splint	4	12.1					
Additional surgical procedures	16	48.5					
Type of plastic surgery							
Gastrocnemius flap	7	21.2					
Latissimus dorsi flap	4	12.1					
Free thigh flap	3	9.1					
Skin graft	2	6.1					
Postoperative infection rate	15	45.5					
Length of hospital stay (days)			25.2	13.5	29.4	3	107
Time interval between two stages of surgery (months)			4.1	3.2	3.2	1.3	18.8
Type of fixation							
Intramedullary nailing	10	30.3					
Plate	22	66.7					
External fixator	5	15.2					
Rigid splint	2	6.1					
Bone graft							
RIA	20	60.6					
Iliac crest	18	54.5					
Allograft	8	24.2					
Postoperative infection rate	9	27.3					
Length of hospital stay (days)			8.2	8	3.1	4	15
Union rate							
Without surgical revision	20	60.6					
After surgical revision	25	75.7					
Time interval 2 nd stage–Union (months)							
Without surgical revision			10	8.9	6.4	3	23
After surgical revision			13.6	10.3	9.6	3	35
Follow-up (years)			3.3	2.6	1.8	1.00	7.2

factors have been identified: osteogenic stem cells, osteoconductive scaffold, growth factors, stable mechanical environment and good vascularization [24,25]. Bone reconstruction using the induced membrane technique that also complies with the diamond concept will optimize the bone regeneration opportunity [26,27].

Some authors have pointed out that the outcomes differ depending on where the defect is located on a given bone [27]. To our knowledge, no published study has documented how the outcomes of this surgical technique differ between two different bones. We hypothesized that the effectiveness of the induced membrane technique (time to union and union rate) will vary depending on the location of the bone defect. The aim of this study was to compare

the time to union and union rate between tibia and femur locations and to describe how failures are managed.

2. Materials and methods

2.1. Cohort description

We carried out a retrospective study of all the patients with extensive posttraumatic bone loss due to fracture or non-union who were seen at the assistance publique hôpitaux de Marseille (AP–HM) between January 2011 and December 2016. Two groups were compared: tibia versus femur. All the patients had undergone

Table 2
Preoperative data for the femur and tibia groups.

	FEMUR (n = 11)						TIBIA (n = 22)						p	
	Number of patients	%	Mean	Median	Standard deviation	Min	Max	Number of patients	%	Mean	Median	Standard deviation		Min
Sex														
Male	4	36.4						19	86.4					0.006
Female	7	63.6						3	14					0.006
Age at time of accident (years)			37.2	36	17.6	18	72			39.0	39	14.81	19	67
Cardiovascular risk factors														
Smoking	8	72.7						12	54.5					
Body mass index (kg/m ²)			26.3	26	8.4	13	36.8			25.4	24.9	4.03	18	33.5
Reason for procedure														
Nonunion	6	54.5						9	40.9					
Fracture	5	45.5						13	59					
Size of bone defect (cm)			9.9	8	5.1	4.3	18			6.9	5.1	4.80	2.3	18
Classification of bone defect														
Karger 1 (<2 cm)	0	0.0						0	0.0					
Karger 2 (2–5 cm)	2	18.2						10	45.5					
Karger 3 (5–10 cm)	4	36.4						7	31.8					
Karger 4 (>10 cm)	5	45.5						5	22.7					
Number of open fractures	8	72.7						20	90.9					
Open fracture classification system														
Gustillo 1	1	9.1						1	4.5					
Gustillo 2	4	36.4						7	31.8					
Gustillo 3a	3	27.3						4	18.2					
Gustillo 3b	0	0.0						8	36.4					0.03
Preoperative infection rate	6	54.5						10	45.5					
Non-Union Scoring System (NUSS)			37.8	38	12.70	20	60			39.1	36	13.80	20	68

Table 3
Intraoperative data for the femur and tibia groups.

	FEMUR (n = 11)						TIBIA (n = 22)						p	
	Number of patients	%	Mean	Median	Standard deviation	Min	Max	Number of patients	%	Mean	Median	Standard deviation		Min
Time interval: Fracture–1st stage of surgery (months)			15.5	12.6	19.7	0	65.7			6.3	1.7	8.90	0	30.2
Type of fixation														
External fixator	7	63.6						18	81.8					
Plate	4	36.4						0	0.0					0.008
Rigid splint	0	0.0						4	18.2					
Additional surgical procedures	3	27.3						13	59.1					
Type of plastic surgery														
Gastrocnemius flap	0	0.0						7	31.8					
Latissimus dorsi flap	1	9.1						3	13.6					
Free thigh flap	0	0.0						3	13.6					
Skin graft	2	18.2						0	0.0					
Postoperative infection rate	2	18.2						13	59.1					0.03
Length of hospital stay (days)			19.8	15	16.3	4	59			28	12	34	3	107
Time interval between two stages of surgery (months)			3.4	3.3	1.5	1.5	6.7			4.5	3.2	3.7	1.3	18.8
Type of fixation														
Intramedullary nailing	2	18.2						8	36.4					
Plate	10	90.9						12	54.5					
External fixator	0	0.0						5	22.7					
Rigid splint	0	0.0						2	9.1					
Bone graft														
RIA	8	72.7						12	54.5					
Iliac crest	4	36.4						14	63.6					
Allograft	3	27.3						5	22.7					
Postoperative infection rate	2	18.2						7	31.8					
Length of hospital stay (days)			8.3	9	2.7	4	13			8.2	8.0	3.4	4.0	15.0

surgical treatment using the induced membrane technique [15]. The minimum patient age was 18 years. A comprehensive follow-up was done throughout the treatment period. The minimum follow-up was 1 year for fracture cases and 2 years for non-union cases. Exclusion criteria were the use of a vascularized fibular graft during the second surgical phase, pathological fractures and bone defects related to gunshot wounds. The primary outcome measures were the time to union and union rate; the secondary outcome measure was an analysis of the management of failed bone grafts in these two locations.

2.2. Induced membrane surgical technique

The 1st stage consisted of wide excision of damaged or infected tissues, with addition of a musculocutaneous coverage flap in some cases. Next, the fracture site was stabilized with an external fixator or internal fixation. The bone defect was filled with a Gentamycin-loaded PMMA cement spacer (Palacos® R+G, Zimmer-Biomet, Warsaw, USA). Several microbiological samples were harvested to determine which bacteria were present in view of treating surgical site infections.

Table 4

Union rate and time to union after the 2nd phase of surgery in the patients with successful and failed induced membrane treatment.

	FEMUR (n = 11)						TIBIA (n = 22)						p	
	Number of patients	%	Mean	Median	Standard deviation	Min	Max	Number of patients	%	Mean	Median	Standard deviation		Min
Union rate														
Without surgical revision	6	54.5					14	63.6						
After surgical revision	7	63.6					18	84						
Time interval: 2 nd stage–Union (months)														
Without surgical revision			6.3	5.3	2.9	3.4	10.3		11.6	10.3	6.9	3	23	0.025
After surgical revision			7.4	6.4	4.9	3.4	17		15.8	16	10.2	3	35	0.015
Follow-up (years)			2.7	2.6	0.6	2	3.3		3.5	3.3	2.1	1	7.25	

Table 5

Outcomes of failed cases of induced membrane treatment.

	Population (n = 33)		Femur (n = 11)		Tibia (n = 22)		P
	Number of patients	%	Number of patients	%	Number of patients	%	
Nonunion rate	13	39.4	5	45.5	8	36.4	
Number of reoperations	9	27.3	2	40	7	87.5	
Nonunion treatment	7	77.8	2	100	5	71.4	
Amputation	2	22.2	0		2	28.6	
Union rate after revision	5	55.5	1	50	4	57.1	
Patients waiting for revision surgery	4	12.1	3	60	1	12.5	

The 2nd phase was performed after infections were resolved and the soft tissues had healed completely, approximately 6–8 weeks later. This procedure consisted of removing the cement spacer and filling the gap with bone graft and in some cases, additional bone substitutes. New bone fixation was performed at this point. The options for fixation consisted of an external fixator, internal fixation using a screw plate or intramedullary locked nail, and Sarmiento[®] type rigid splints.

Two types of bone grafts were used in our cases: bone allograft from a tissue bank and autograft obtained by either reaming cancellous bone (RIA[®], DePuy-Synthes, Switzerland) in the ipsilateral or contralateral limb, or by harvesting corticocancellous bone from the iliac crest.

2.3. Data collection

After obtaining the patients' consent, information to support our data analysis was collected (Table 1). The patients were reviewed in person at last 1 year after fracture treatment and at least 2 years after nonunion treatment. All the data were stored in a computerized medical records system (Axigate[®]) at the AP-HM, namely the information collected during the postoperative follow-up visits at 6 weeks, 3 months, 6 months and then every year. This study was approved by our hospital's research ethics board and data processing was approved by the hospitals' data privacy officer. The data collected were compared between the tibia and femur groups (Tables 2 and 3).

2.3.1. Study population

The data collected consisted of age at the time of the accident, sex, smoking habits, body mass index (BMI), bone involved (tibia or femur), surgical indication (fracture, nonunion), size of bone defect using the Karger classification [28] – group 1 (> 2 cm), group 2 (2–5 cm), group 3 (5–10 cm) and group 4 (> 10 cm) – determined using Centricity[®] software, whether or not the fracture site was open using the Gustilo and Anderson classification [29], risk factors for nonunion using the Non-Union Scoring System (NUSS) [30,31], and the preoperative infection rate based on the presence of at least one bacterium at the surgical site identified by microbiology and treated with antibiotics before the surgical procedure.

2.3.2. Follow-up period

During the follow-up period, we recorded the time elapsed between the 1st stage and the fracture, time elapsed between the cement spacer implantation and bone grafting, type of fixation (external fixator, internal fixation or rigid splint) used during each stage, whether a coverage flap was needed at any stage, post-operative infection rate defined by the presence of at least one microorganism found at the surgical site during microbiology sampling and treated by postoperative antibiotics, type of bone graft used during the second surgical stage (RIA[®], iliac crest, allograft) and lastly, the length of hospital stay.

2.3.3. Primary endpoint

Bone union was defined using radiological and clinical criteria: presence of at least two continuous bone bridges on two radiographic views or CT scan and return to full weight bearing. The time to union was defined as the time elapsed between the application of the bone graft and the date bone union was achieved. The union rate was documented in cases that required reoperation after the second stage of surgery along with the time to union and was compared to cases that did not require reoperation.

2.3.4. Secondary endpoint

The main complication of the induced membrane technique is nonunion, which is defined as lack of bone healing on radiographs and the patient being unable to resume walking with full weight bearing at least 1 year after the bone graft was introduced. Among these patients, we determined the reoperation rate: new treatment of nonunion with bone graft or amputation; union rate after revision surgery; number of patients still waiting for treatment because of an ongoing infection (which makes it impossible to perform surgery).

2.3.5. Statistical methods

A univariate analysis was carried out using Fisher's exact test for qualitative variables and Student's *t*-test with Welch's correction for quantitative variables using GraphPad Prism[®] software. The significance threshold was set at $p < 0.05$.

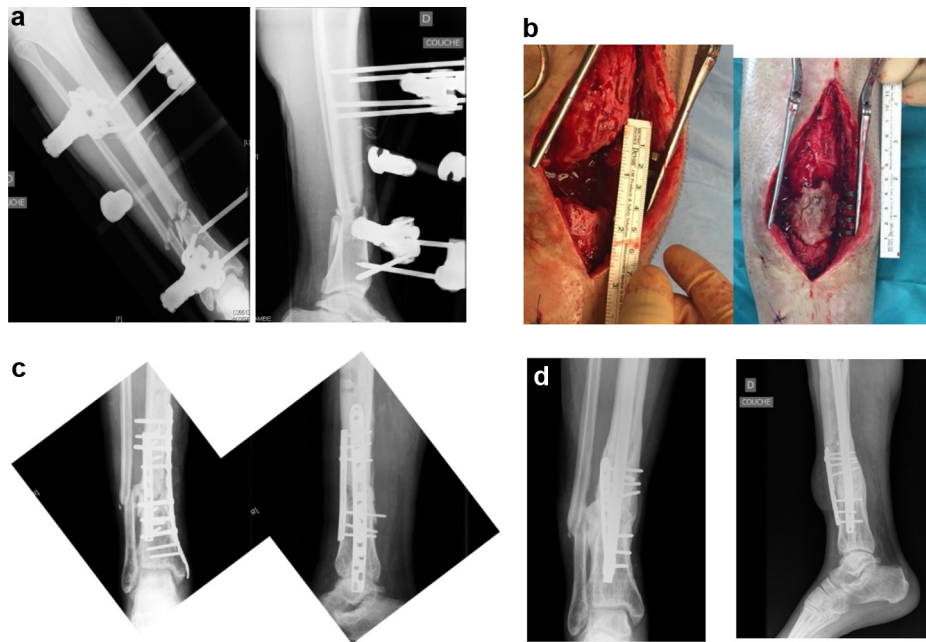


Fig. 1. Male patient, 55 years old, who was treated for infected nonunion of the tibia. a: AP and lateral radiographs of the tibia after application of external fixator in the emergency room for an open (Gustilo 3a) fracture of the distal end of the tibia; progression to infected nonunion; b: photograph of the 1st stage of the Masquelet technique after resection of margins (left) and after implanting the cement spacer (right) 1 year after the fracture event. Bone defect was 4.5 cm long and 2 cm wide; c: AP and lateral radiographs after the 1st stage of surgery with plate fixation and cement spacer; d: Radiographs made 16 months after the second phase (ORIF: plate and intramedullary nailing; bone graft: RIA®) showed bone union.

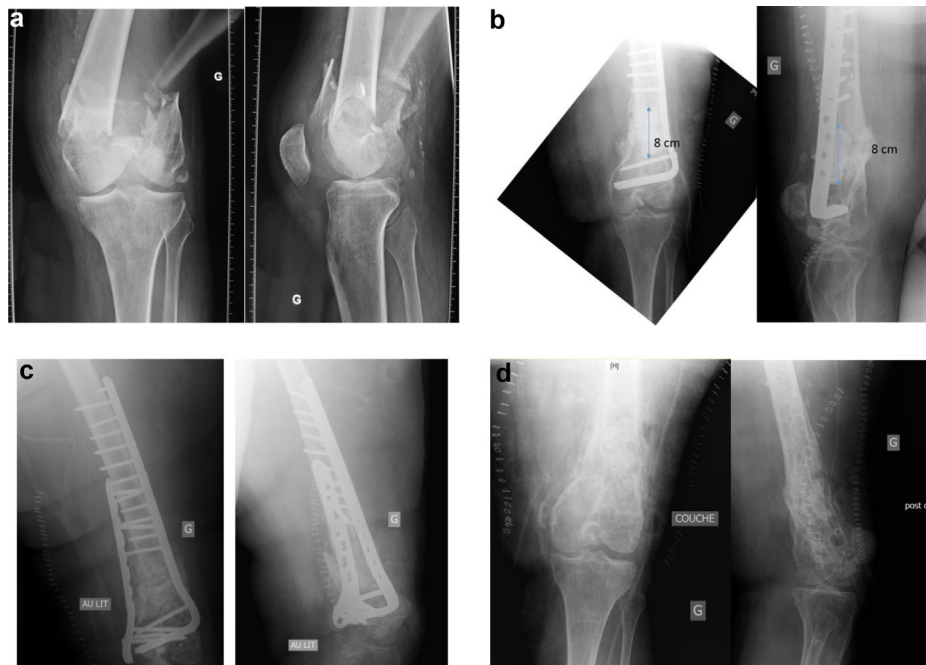


Fig. 2. Female patient, 42 years old, who was treated because of an infected nonunion of a prior femur fracture. a: preoperative AP and lateral radiographs of the knee after motor vehicle accident showing an open distal femur fracture (AO type C3) (Gustilo 2) that was treated at another hospital. External fixator applied, then plate fixation + bone graft (iliac crest). After 2 years: infected nonunion with *Enterococcus faecalis* identified. Patient transferred to our hospital for continuation of care; b: AP and lateral view of the knee after the 1st stage of the Masquelet procedure showing an approximately 8 cm defect which was filled with a cement spacer and stabilized with a blade-plate; c: AP and lateral views of the femur after the second stage (6 week interval) with minimal bone margin resection (especially anterior cortex) followed by plate fixation and cancellous bone grafting (RIA® contralateral); d: AP and lateral views of the knee after hardware removed 1½ years after grafting. Bone union was achieved 3½ months after grafting.

3. Results

3.1. Study cohort

The study cohort consisted of 33 patients (23 men, 10 women) who were treated with the induced membrane technique

(Tables 2 and 3). The procedure was performed at the tibia in 22 cases and the femur in 11 cases. There were more men in the tibia group than the femur group: 19 patients (86.4%) versus 4 patients (36.4%), $p=0.006$. The mean age at the time of the accident was 38.3 ± 15.5 years (18–72). The reason for the surgical treatment was non-union in 15 patients and fracture in 18 patients. The mean

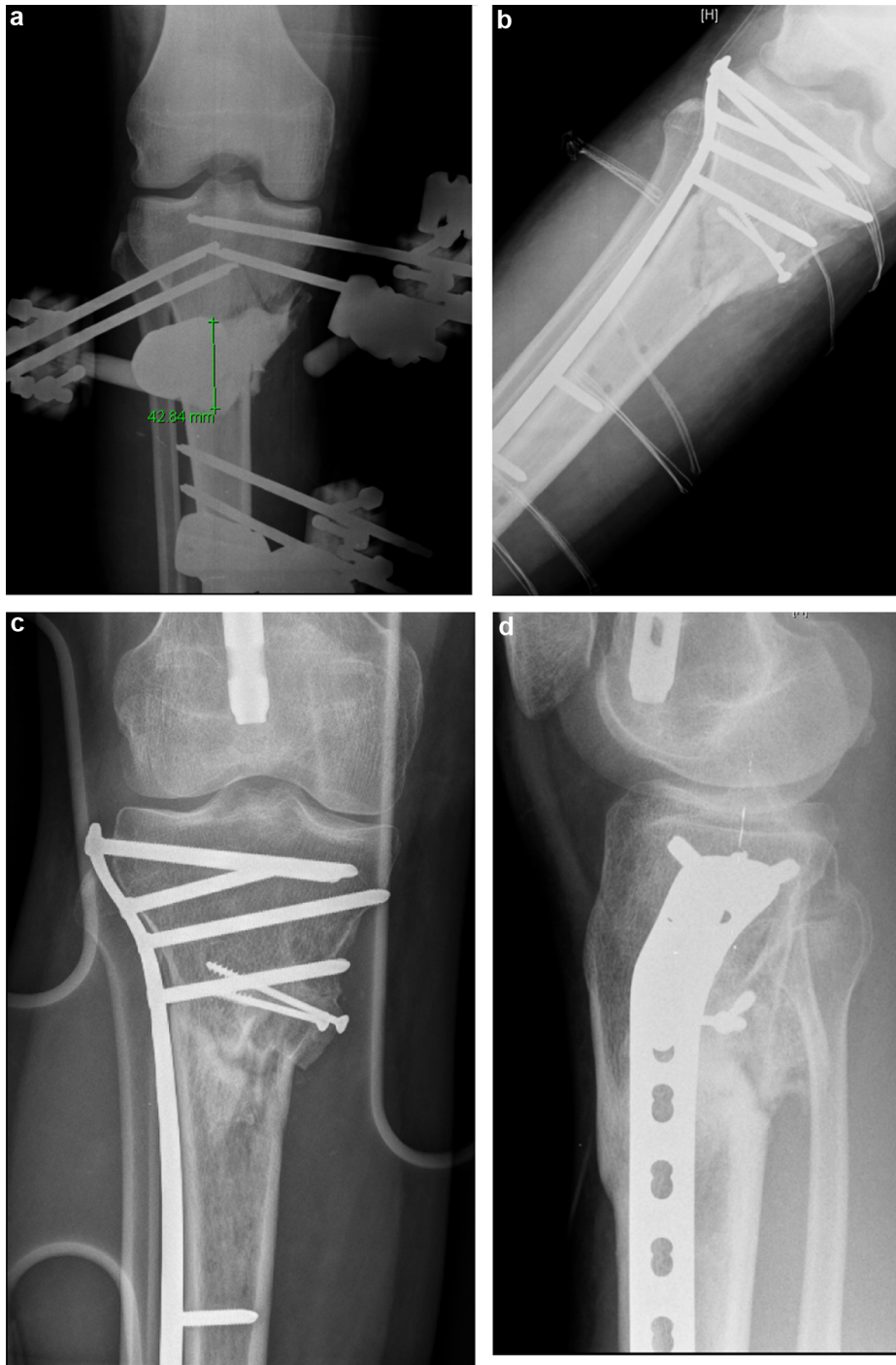


Fig. 3. Male patient, 20 years old, who was treated for a tibial metaphysis fracture. a: postoperative AP radiograph taken after motor vehicle accident showing an open (Gustilo 2) proximal tibial shaft fracture with an approximate 40 mm bone defect. First stage of the induced membrane procedure done in the emergency room: implantation of cement spacer and stabilization with external fixator; b: AP radiograph of the proximal tibia after the 2nd stage of surgery showing the corticocancellous graft from the iliac crest and cancellous graft harvested with RIA[®] along with locking plate fixation 3 months after the injury event; c, d: AP and lateral views of the tibia showing bone union. The patient could walk without pain or crutches and had full weightbearing 12 months after the accident.

defect size was $7.9 \text{ cm} \pm 5.0 \text{ cm}$ (2.3–18.0). An open fracture was present in 28 patients (84.8%).

Before the first surgical stage, the tibia and femur groups were comparable in terms of age at the time of the accident, cardiovascular risk factors, reason for the surgery (fracture or nonunion), size of bone defect, percentage of open fractures, preoperative infection rate. The NUSS did not differ between groups: 37.8 ± 12.7 (20–60) for the tibia versus 39.1 ± 13.8 (20–68) for the femur, $p = 0.7$. However, there were more open Gustilo 3b fractures in the

tibia group than in the femur group: 0 patients versus 8 patients, $p = 0.03$.

The mean follow-up was 3.3 ± 1.8 years (1–7.2) (Table 1). It was 2.7 ± 0.6 years (2–3.3) in the femur group and 3.5 ± 2.1 years (1–7.25) in the tibia group. This difference between groups was not significant.

The tibia and femur groups were comparable in terms of the surgery characteristics except for plate fixation being used more often during the 1st stage in the femur group than the tibia group:

4 patients versus 0 patients, $p=0.008$. The infection rate after the 1st surgical stage was significantly higher in the tibia group than in the femur group: 13 patients (59%) versus 2 patients (18%), $p=0.03$. The infection rate after the 2nd surgical stage did not differ between groups.

3.2. Primary endpoint

The initial union rate was 61% (20 of 33 patients) (Table 4). The union rate was similar between the tibia and femur: 14 patients (64%) versus 6 patients (54%).

The mean time to union was 10.0 ± 6.4 months (3–23) (Table 1). The time to union was significantly higher in the tibia group than in the femur: 11.6 ± 6.9 months (3–23) versus 6.3 ± 2.9 months (3.4–10.3), $p=0.025$.

3.3. Secondary endpoint

The union rate after surgical revision for nonunion was 76% (25 of 33 patients). The union rate was similar between the tibia and the femur: 18 patients (84%) versus 7 patients (64%). The mean time to union after surgical revision for nonunion was 13.6 ± 9.6 months (3–35) (Table 1). The time to union was significantly higher in the tibia group than in the femur: 15.8 ± 10.2 months (3–35) versus 7.4 ± 4.9 months (3.4–17), $p=0.015$ (Table 4).

The non-union rate after the induced membrane treatment was 39% (13 patients). The non-union rate did not differ between the tibia and femur sites. Among the patients who had a non-union, 9 patients (69.2%) were reoperated: 7 underwent another non-union treatment (77.8%) and 2 underwent amputation (22.2%). Of the 7 patients who were reoperated with a new bone graft, 5 achieved bone union. Four patients (31%) were still waiting for an infection to resolve as of our last review point. There was no difference in the management of failures between the tibia and femur locations (Table 5) (Figs. 1–3).

4. Discussion

The induced membrane technique pioneered by Masquelet has been successfully used for many years for bone reconstruction when a single-stage procedure is not feasible [1,26,28]. The primary aim of our study was to compare the outcomes of this technique in two different bones: tibia and femur. There was no difference in the union rate between the two sites. However, the time to union was significantly longer in the tibia than the femur.

The focus of our study was on the union rate, which was 61% (20 of 33 patients) (Tables 4 and 5). Our results are consistent with published studies on this topic reporting union rates from 41.6% to 100% [32]. Karger et al. [28] reported a 90% union rate in 84 patients with a mean union time of 13.2 months (57 weeks). Giannoudis et al. [33] found a 98% union rate in a 42-patient cohort with a mean time of 5.3 months (23 weeks). However, other teams have reported lower union rates. In a recent study of 12 patients, Morris et al. [34] reported a 42% union rate. The failures were due to the high number of preoperative infections (11 of 12 patients). In our study, there was no difference in the preoperative infection rate between the tibia and femur: 45% (10 patients) versus 54% (6 patients), $p=0.72$.

The non-union rate after the induced membrane technique was 39% (13 patients) in our study. Masquelet and his team were the first to describe the complications related to his surgical technique: 5 cases of infected non-union after the second stage among 35 patients [15]. Azi et al. confirmed that infection was the main reason for failure of this surgical technique, as they found a 20% delayed infection rate (7 of 34 patients) [35]. Aparad et al. reported a 42% infection rate after the second phase [36]. El-Alfy et al. reported a 30% non-union rate [37], while it was 17% in a study by Taylor

et al. [31]. The latter identified three risk factors for non-union: post-graft infection (relative risk = 11.8, 95% [4.4–31.9]), wound dehiscence (relative risk = 9.7, 95% [4.3–22.1]) and presence of an infection before the first surgical phase (relative risk = 2.9, 95% [1.1–7.9]). We could not determine which factors contributed to the non-healing in our study since the small sample size precluded a multivariate analysis. However, there was a significant difference between the tibia and femur groups in terms of the number of open fractures and infection rate after the first surgery phase. There were more Gustilo 3b open fractures in the tibia group than in the femur group (8 patients versus 0 patients, $p=0.03$) while the infection rate after the 1st phase was higher in the tibia group than in the femur group (59% versus 18%, $p=0.03$).

Among the 13 patients whose bone defect did not heal after the procedure, 2 underwent an amputation due to chronic osteomyelitis despite antibiotic therapy and several surgical revision procedures. In their study, Karger et al. [28] reported 6 amputations out of the 8 patients who failed treatment. In their meta-analysis, Morelli et al. [32] found that at least 1 amputation was reported in 11 of 17 publications about the Masquelet procedure. Our study confirms that the amputation rate is not insignificant after failed treatment with the induced membrane technique.

5. Conclusion

In summary, the induced membrane technique described by Masquelet is an effective treatment solution for managing large bone defects in the lower limbs of adults, with a satisfactory union rate, despite several postoperative complications, especially infections. We found that this technique can be used effectively to treat both fractures and midshaft non-union of the tibia and femur. The time to union appeared to be less in the femur than the tibia.

This new information gives surgeons a better idea of the time to union for different bone locations, which they can communicate to their patients to prepare them for the long treatment course.

But we have asked ourselves whether a different surgical technique would be more effective than the induced membrane technique? In our study, this procedure was less effective at the tibia because the time to union was longer than in the femur. In these cases, what is the role of other surgical techniques such as the Ilizarov, bone transport or vascularized bone graft? These questions are good avenues for future research into optimizing treatment of large bone defects.

Disclosure of interest

The authors declare that they have no competing interest.

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None.

Author contributions

A. Baud: data collection, writing of article.
X. Flecher: study coordinator; helped to write article.
R.A. Rochwerger: critical review of article.
J.C. Mattéi: final critical review of article.
J.N. Argenson: final approval of article.

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