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ORIGINAL ARTICLE

Treatment of posttraumatic bone defects by the induced membrane technique

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KEYWORDS
Bone reconstruction;
Bone defect;
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Posttraumatic infected non union

Summary
Introduction: Among bone reconstruction techniques, the induced membrane technique, proposed in 1986 by Masquelet, has rarely been studied or evaluated in the surgical literature until recently. The 2010 French Society of Orthopaedic Surgery and Traumatology (SoFCOT) Annual Convention symposium was the occasion to evaluate a large cases series having used this technique.
Patients and methods: This retrospective study included 84 posttraumatic diaphyseal long bone reconstructions using the induced membrane technique (1988—2009). The series included 79 men and five women (mean age 32-year-old). In 89% of cases, the initial trauma was an open fracture. The leg was involved in 70% of cases. The mean delay between the accident and treatment of bone defects (BD) was 8 months. In 50% of the cases, infection was present. Bone defects were larger than 5 cm in 57% of the cases.
Results: Union was obtained in 90% of cases, a mean 14.4 months after the first stage of the reconstruction. A mean 6.11 interventions were necessary to obtain union. Malalignment was present in 17% of cases. Delayed interventions to correct deformities mostly of the foot were necessary in 16% of the cases. Eight failures (10%) involved severe leg traumas associating extensive bone defects, soft tissue lesions and infection and required amputation in six cases.

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Discussion: This series emphasizes the severity of open fractures of the leg, especially those with primary or secondary infection. The induced membrane technique has been shown to be effective in treating bone defects, regardless of their magnitude. In a two-step procedure, this simple but demanding technique, which may be more complicated when repair of soft tissue is necessary, provides successful treatment in case of initial infection and fulfills the goal of controlling infection before bone reconstruction. Moreover, the induced membrane technique can be integrated in hybrid reconstruction procedures.
Level of evidence: Level IV. Retrospective study.

Introduction

Reconstruction of extensive traumatic bone defects (BD) of the limbs is still a major therapeutic challenge, both for anatomical and functional results. The limits of traditional bone graft techniques are now clear, mainly because of uncontrollable graft resorption, even when the recipient site is well vascularized [1]. Although experimental and clinical reports on grafts wrapped in vascularized periosteal flaps are encouraging [2], the small size of these flaps limits their use to small bone defects. Among the most recent techniques, bone transport distraction osteogenesis and free vascularized bone transfers have provoked the most interest as potential reliable solutions in these difficult cases.

In 1986, one of the authors of this article (A.C. Masquelet) conceived and developed an original reconstruction technique for large diaphyseal bone defects, based on the notion of the induced membrane [3—5]. A retrospective multicenter study was performed for the SoFCOT[2] symposium including 204 files with BD, 84 of these treated by the induced membrane technique. The aim of the present study was to analyze the results of this series and compare them with results obtained using other reconstructive techniques in the symposium series but also with those in the literature.

Patients and methods

All the orthopedic surgery units in France and its overseas territories were asked to forward their files involving traumatic bone defects. A formula for data collection was drafted and the files were entered on line.

Principles of the induced membrane technique

The principle of the induced membrane technique involves provoking a reaction to a foreign body by placing a cement spacer in the bone defect. The membrane induced by this foreign body is in fact a biological chamber which prevents graft resorption by providing vascularization and growth factors, as shown by various clinical, experimental and basic studies [3—12].

The induced membrane technique is a two-step procedure (Fig. 1):

- the first step includes a large excision of infected or nonviable tissue, if necessary a cover flap is created and the cement spacer is placed in the bone defect following debridement, after careful stabilization of the bone;
- the second step, performed at least 6 to 8 weeks after the first includes removing the spacer and filling the biological space which has been created with small morsels of cancellous graft, 1—2 mm^3, which may be associated with bone substitutes. This step is performed after any remaining infection has healed.

There are certain essential technical details:

- the cement spacer should surround the extremities of the bone defect to prepare a graft which ''wraps'' around these extremities;
- when grafts are transferred, the medullary cavity should be debrided and permeable and the bone extremities should be decorticated. Closure of soft tissue, including the neo-formed membrane creates a closed biological chamber, containing the graft;
- for tibial reconstructions, the cement spacer is placed in contact with the fibula to plan a very strong segmental reconstruction. Moreover, a future proximal and distal intertibiofibular graft is planned at the extremities of the tibial defect;
- weight-bearing is usually delayed until union is obtained.

The series

Between 1988 and 2009, 84 patients underwent bone reconstruction by the induced membrane technique for traumatic diaphyseal (BD). The series included 79 men and five women, mean age 32 (4—77). The source of the initial trauma was a road accident in 63 patients, sports accidents in six, firearm accidents in four. The bone segments included the tibia in 61 cases, (including 54 with the fibula), the femur in 13 cases, the humerus in six cases and the forearm in four cases. Seventy-five fractures (89%) were open, (38 stage 3a or 3b on the Gustilo classification). Eight patients initially presented with an ischemic syndrome.

Primary stabilization of the fracture was ensured by external fixation in 46 cases, intramedullary nail in 19 cases, plate or pins in other cases. The delay between the initial trauma and treatment of BD was a mean 8 months and a mean 4.5 between prior interventions and reconstruction. Forty-one patients had infections when treatment of BD began. Forty-six flap covers were performed before actual bone reconstruction.

[2] Work presented at the symposium: ''Treatment of posttraumatic diaphyseal bone defects'' 85th Annual SoFCOT Meeting, Paris, November 2010.

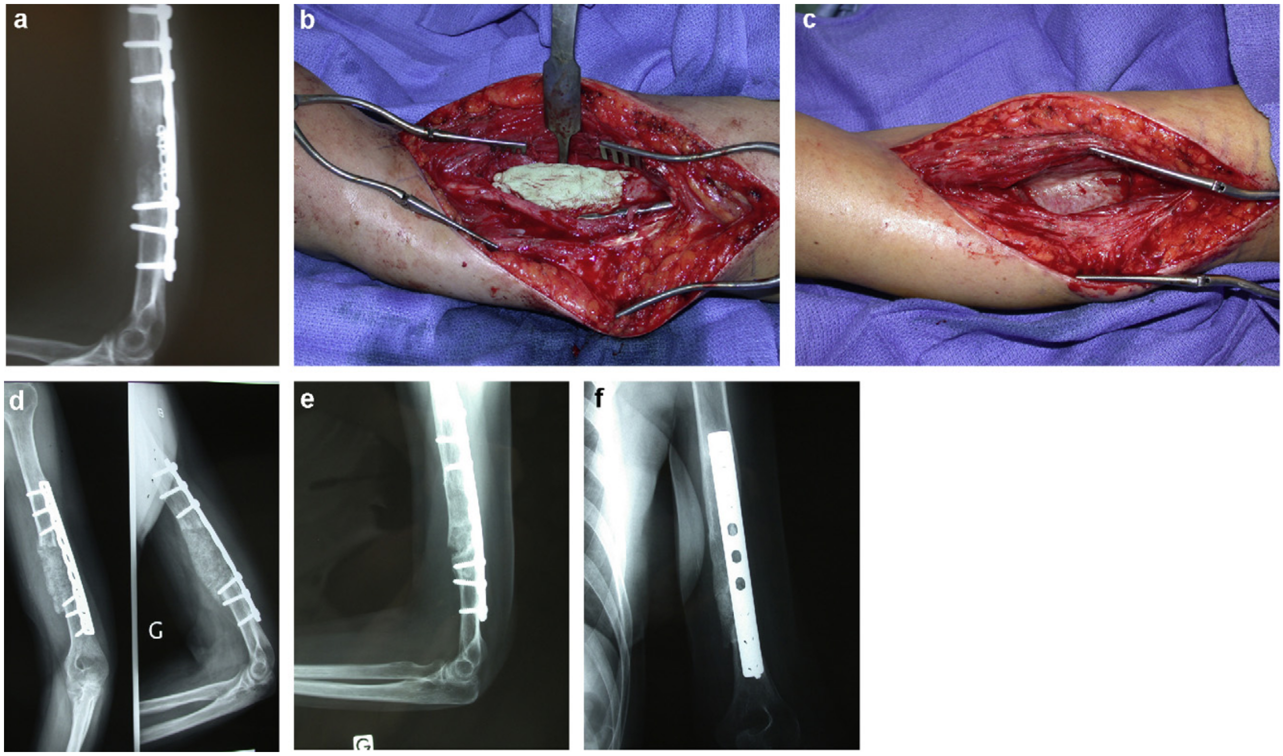

Figure 1 a: bone defect of the humeral diaphysis, in which filling with an iliac autograft was attempted; graft resorption; b and c: revision by external approach, debridement of the bone ends to reach healthy tissue and insertion of a cement spacer for 2 months (b). The induced membrane appears pearly when the cement is removed (c); d: radiological view of a massive cancellous autograft 4 months after the biological chamber was created. Note the ''wrapping'' of the ends by the graft; e and f: radiological view at 1 year. Courtesy A.C. Masquelet.

Evaluation of the size of BD was based on four radiographic parameters: length of the defect on an AP view of the lateral and medial cortices and lateral views of anterior and posterior cortices. The mean values of these measurements were:

- 68 mm AP view lateral cortex;
- 71 mm AP view medial cortex;
- 70 mm lateral view anterior cortex;
- 64 mm lateral view posterior cortex.

The largest BD in the series was 230 mm in a tibia.

The bone defects in the series were classified into four types according to the size of the defect (type I = less than 20 mm, type II = between 20 and 50 mm, type III = 50—100 mm, type IV = more than 100 mm) and the type of defect, segmented (S) or bevelled (B).

The series was grouped as follows:

- type I = 6 patients = 7% (all S);
- type II = 29 patients = 34% (23 S and 6 B);
- type III = 26 patients = 30% (20 S and 6 B);
- type IV = 23 patients = 27% (all S).

During the first step of debridement and placement of the spacer, primary fixation was preserved in 32 cases, modified in 47 cases (30 changes of the external fixator, eight nails, eight plates, one elastic nails). The reconstruction graft was usually cancellous or corticocancellous bone, alone or associated with bone substitutes. In seven cases, this was associated with a vascularized graft (four iliac crests, two fibulas, one rib). Fifteen intertibiofibular grafts were performed in the 61 tibial BD. Growth factors were added in 25 patients.

The statistical study, performed with Stata software was performed by the ''*UF de méthodologie en recherche clinique*'' of the University of Toulouse, France. $P < 0.05$ was considered to be significant. Study of the relationships among the variables was performed with the Khi^2 or Fisher exact test to compare qualitative variables, the Student *t*-test or Mann-Whitney test to compare quantitative and qualitative variables for two groups and the Anova or Kruskall Wallis test to compare quantitative and qualitative variables for more than two groups.

Results

Anatomical results

Union was obtained in 76 of the 84 patients (90%), a mean 14.4 months after the first step of surgical repair. Union was obtained within a mean 14.9 months with the other techniques in the series ($P = 0.90$).

The time until union was not influenced by the size of the bone defect (Table 1), or by the bone segment involved

Table 1 Delay to union (months) after the beginning of treatment of bone defects (BD), number of interventions before union, rate of union, according to the size of the BD. Union obtained in 76 cases.

Size of BD	Type I $n=5$	Type II $n=26$	Type III $n=23$	Type IV $n=22$
Time to union	10	10	10	9
Number of interventions	7.8	7.3	5	5.5
Rate of union (%)	88	88	90	95

Type I: < 20 mm; type II: 20—50 mm; type III: 50—100 mm; type IV: > 100 mm.

(Table 2). Nevertheless, union was obtained more rapidly in upper limbs, in particular in the forearm, however the few number of cases makes it impossible to draw definite conclusions (Fig. 1). All malunions involved the tibial segment. Although it is highly recommended for tibial BD, the addition of an intertibiofibular graft did not significantly influence time until union.

A mean 6.11 interventions were necessary to obtain union. Malalignment was observed in 15 patients requiring surgical correction in three cases after union. A mean length discrepancy of 35 mm was observed.

Functional results

Full weight-bearing was possible in legs a mean 17.4 months after treatment of BD and 23.7 months after the initial trauma.

At the final follow-up, one out of two patients was walking without canes, eight were using support devices, 13 had resumed sports and seven could run.

Range of motion was limited in 11 cases, and there were eight cases of fixed ankle equinus. Fourteen additional procedures were performed on the ankle and foot: 15 lengthening of the Achilles tendon, four arthrolyses, two arthrodeses of the hind foot, one partial amputation and two procedures on the forefoot.

Patients returned to work a mean 32.8 months after the initial trauma and 25.3 months after treatment of BD. Thirty patients returned to the same job, four were reclassified and 13 were considered disabled.

Failures

Eight failures (9.5%) were observed which were all open tibial fractures including two with ischemia. The extent of BD did not influence failure, because these eight cases included two type I BD, three type II, two type III and one type IV. Failure was associated with severe functional sequella in two patients, although union of the reconstructed bone was successful.

There were no failures in the 15 patients who received an associated intertibiofibular graft.

Six of the eight failures required amputation of the leg:

- four for non union;
- two for functional sequella, making normal walking impossible.

Discussion

Procedures to treat extensive BD are still the subject of debate. In a series of 204 files studied for the symposium, the 96 cases of bone defects larger than 5 cm (types III and IV) were treated as follows:

- segmental bone transport: 19;
- vascularized transfer: 19;
- induced membrane: 49;
- isolated autograft: 10.

Thus, the induced membrane technique was the most frequently used procedure in this series. It has the advantage of being simple, although technical execution must be carefully performed. The two-stage procedure is an advantage in case of infection because the aim of the first step is to cure infection and restore the envelope of soft tissue. Repeated debridement may be necessary, which makes the choice of instrumental stabilization difficult. Rigid external fixation makes revision surgery possible. If there is no infection, intramedullary nailing preserves limb length and especially alignment; however this type of fixation is not optimal for extensive bone defects and fragile limbs.

The optimal conditions for secondary graft union are based on empirical rules that are difficult to quantify: in our opinion, the gold standard technique is the morselized cancellous autograft. Bone harvested from four iliac crests can be used for tibial reconstructions of 15—20 cm. There was no morbidity in the donor site because the cancellous bone was

Table 2 Delay to union (months) after the beginning of treatment of bone defects (BD), number of interventions, rate of union according to the bone segment (84 files).

Location	Tibia $n=61$	Femur $n=13$	Humerus $n=6$	Forearm $n=4$
Delay to union	14.6	17.7	12.5	3.8
Number of interventions	11.5	2	5.4	7.6
Rate of union (%)	86	100	100	100

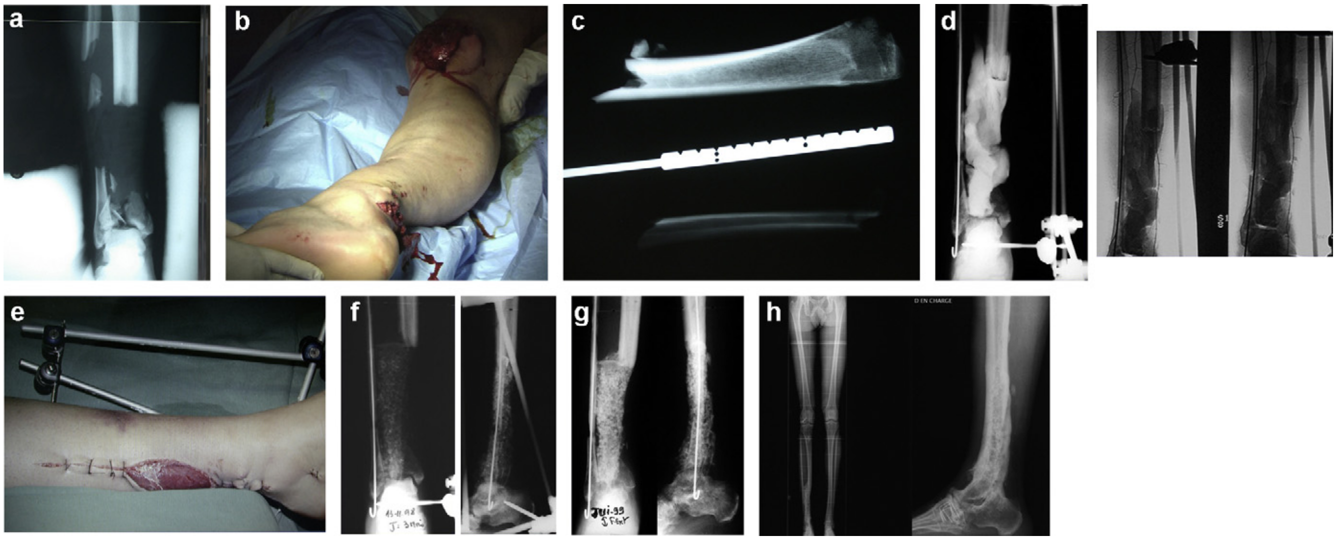

Figure 2 a and b: Gustilo stage IIIa open fracture of the leg from a motorcycle accident with 15 cm diaphyseal bone defect of both leg bones; c: the two missing segments, which were literally ejected from the limb from a skin wound were recovered at the site of the accident. The decision was made to only implant the fibular segment; d: tibial bone defect is filled during an emergency procedure with surgical cement after excision of the wound. The limb is stabilized with an external fixator; e: the skin wound is filled with a muscle flap cover; f: filling with bone autograft and allograft (50%-50%) was performed 2 ½ months after the accident. Postoperative view of arthrodesis-reconstruction. A cortical graft was placed between the tibia and the fibula in the proximal area of the bone defect; g: removal of the external fixator after 10 months and gradual weight-bearing; h: at the 7 year follow-up. Note the radiological image of progressive tubules in the graft which appears lighter in the center of the reconstruction. Courtesy H. Mathevon et A.C. Masquelet.

harvested with an appropriate technique without removal of the cortex. The significant difference in the time until union between the symposium series and Masquelet et al. [3—5], in particular for tibial reconstructions, is because Masquelet evaluated the time until union from the moment the bone graft was performed and not from the moment general management of BD began, as in our series. Moreover, Masquelet systematically performed tibial reconstructions that pressed upon the fibula and were reinforced by intertibiofibular grafts at both ends of the reconstruction, an important technical detail which could reduce the time until union.

Addition of an allograft or xenograft does not affect the delay to or the mechanical quality of union, as long as the ratio is not greater than one-third: however this notion is purely empirical because rapid, good quality union has been obtained with an autograft-allograft ratio of 1 (Fig. 2). The systematic use of growth factors does not seem to significantly affect the result: the use of BMP could not be codified in this retrospective series. Nevertheless, it should be noted that Masquelet and Bégué [5], reported certain difficulties with bone union that might be explained by the uncontrolled use of growth factors. Several hypotheses have been suggested for this: dose effect (insufficient or excessive), irregular distribution of the product in the reconstructed bone, or the effect of postoperative drainage. The presence of the membrane which prevents dispersion of the product into surrounding soft tissue should concentrate BMP inside the graft. There may also be antagonistic reactions between the added product and the growth factors secreted by the membrane. This type of reaction has been reported experimentally between TGF beta 1 and BMP-2 [13]. Moreover, although BMP-7 is known to stimulate differentiation of bone cells in vitro, if the concentration is too high, BMP-7 inhibits alkaline phosphatase activity in the presence of vitamin D [14]. In fact, little is known about the effect of growth factors on massive intramembrane grafts, although their benefits are well known in the treatment of pseudarthrosis without bone defects.

Finally, even if numerous questions remain unanswered, the notion of the induced membrane opens new perspectives:

- the first question is identifying the foreign body which will induce the best ''membrane effect''. Until now, we have been using acrylic cement. Other substances such as metal or polymers could induce membranes with different properties;
- the second question concerns the osteoinductive factors secreted by the membrane. In the study by Pélissier [8], only BMP-2 was isolated by a specific method. Other factors which have not yet been searched for, probably also play a role;
- the third question concerns the type of fixation: most cases refer to septic pseudarthroses, in which the preferred type of fixation is external fixation. However, this type of external fixation does not provide stabilization that is rigid enough to preserve alignment of the reconstruction throughout the entire process of healing, in particular in case of very extensive segmental bone defects. Nailing does not resolve all of the problems of stabilization and includes the risk of recurrent infection [15]. Experience now suggests that circular or hybrid types of fixation should be used;

- finally, what graft material is most likely to result in rapid union and provide the best mechanical results? All osteoconductive and osteoinductive combinations can be experimentally tested with the induced membrane. The recent clinical insertion of a graft harvested from the medullary cavity of a long bone by the RIA (reaming, irrigating, aspirating) procedure increases the capacity of bone reconstruction [16]. However, the use of this graft alone, which is very dense, seems to result in irregular union which may be due to insufficient revascularization of the central part of the graft [5,16]. Based on existing knowledge, the gold standard graft material is the cancellous autograft in small chips of no more than 1—2 mm^3.

In conclusion, successful reconstruction of extensive bone defects is possible with the induced membrane technique; at present it is widely used [16—19] and its indications include non-traumatic bone defects. The technique is simple if the sometimes complex procedures to repair of soft tissue are excluded. The two-step surgical procedure is an advantage in case of primary infection and if repeated, debridement is necessary. The notion of a biological chamber which is involved in this method, provides a vast experimental field that must still be explored.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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