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Masquelet technique for the treatment of bone defects: Tips-tricks and future directions

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ABSTRACT

Reconstruction of diaphyseal bone defects still represents a major clinical challenge. Several approaches are used with the common objective to regenerate bone loss and restore function. The methods most commonly used are the vascularised fibula autograft and the Ilizarov bone transfer technique. Recently, Masquelet proposed a procedure combining induced membranes and cancellous autografts. The aim of this article was to briefly describe the technique, to review the current evidence and to discuss the tips and tricks that could help the surgeons to improve outcome. Future directions to increase its effectiveness and expand its application are also being discussed. However, predicting the outcome of reconstruction of bone defects remains difficult; and the patient should always be informed that, although potential complications are mostly predictable, in most of the cases the reconstruction process is long and difficult.

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Introduction

Reconstruction of diaphyseal bone defects still represents a major challenge. Several approaches are used in bone reconstruction with the common objective to regenerate bone loss and restore function. However, it is difficult to achieve these objectives in some pathological situations, such as when a large bone defect is associated with loss or infection of the surrounding soft tissues. This may occur after large bone resection following tumours or infected tissue removal or as a consequence of severe traumatic injuries.[1] The most commonly used methods for reconstruction of large bone defects are the vascularised fibula autograft and the Ilizarov bone transfer technique.[2,3] Autologous bone grafting alone is not recommended if the defect exceeds 5 cm because of the risk of resorption despite good soft tissue coverage.[4]

Recently, Masquelet proposed a procedure combining induced membranes and cancellous autografts.[5] He first described this techniques back in 1986 for the reconstruction of extensive diaphyseal bone loss up to 25 cm in length, without the need for vascularised autograft.[6] Overall, this technique allows the reconstruction of wide diaphyseal defects even if the recipient site has been irradiated or infected, provided that an envelope is previously created to protect and revascularise the bone graft.[6,7]

The purpose of this paper is to succinctly describe the Masquelet technique, to evaluate the current evidence by reviewing the relevant animal and clinical studies, and to discuss useful tips and tricks from our own clinical experience. Future directions for the use of this technique for the treatment of bone defects are also being discussed.

The Masquelet technique

The reconstruction requires a two-staged approach. At the first operation, radical soft tissue and bone debridement is undertaken. A polymethyl methacrylate (PMMA) cement spacer is implanted at the site of the bone defect and the limb is stabilised with an external fixator. The cement spacer has two roles.[8] The first one is mechanical as it obviates fibrous tissue invasion of the recipient site. Moreover, as the spacer behaves as a foreign body, absence of infection after two months is an excellent witness of adequate local conditions for bone grafting. The second role is biological by the induction of the surrounding membrane that will revascularise the bone graft and prevent its resorption. Finally, in the first stage of the Masquelet technique, the soft tissue envelope is repaired (with vascularised flap transfer if required). At the second stage, approximately 6–8 weeks later, the cement spacer is carefully removed ensuring that the formed "induced membrane" is minimally disturbed; and the defect is filled with morcellised cancellous autotlogous bone graft (with additional bone graft

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substitute if the graft is insufficient, not exceeding a 1–3 ratio) and the bone is usually stabilised with a plate or other means of fixation.[6]

The histological and biochemical characteristics of the induced membrane have also been evaluated. It has been shown that the induced membrane becomes highly vascularised and secretes a combination of important growth factors, such as VEGF,TGF-beta 1 and BMP-2.[8] Additionally, it has been demonstrated that the induced membrane formed around the foreign body (cement spacer) during the interval between surgeries prevented resorption of cancellous bone graft and also had a positive effect on consolidation of the defect.[9]

Current evidence

Overall, 4 animal studies[10–13] and 16 studies in humans[6,12,14–27] were identified reporting on the Masquelet technique. These are summarised in Tables 1 and 2.

Animal studies showed better results with the use of both, graft and induced membrane, than with bone graft only or induced membrane only, for the reconstruction of large diaphyseal bone defects.[10] The rate of healing in bone defects in an experimental bovine model was higher when morcellized autologous corticocancellous graft was used;[13] and the use of bone graft substitutes during the second stage of the technique was found to hinder bone formation and the continuity of new cortical bone.[12] Bone formation has been observed even in heterotopic sites in a previously induced membrane with or without the additional loading of growth factors.[11] Additionally, microscopic and immunochemical analysis of the biological membranes formed by foreign body reaction showed that they are very rich of capillary vessels and contain growth factors, which stimulate angiogenesis and bone formation.[12,13]

The "induced membrane" technique, as described by Masquelet or modified, has been used in a variety of clinical cases requiring bone reconstruction. Flamans et al.[15] evaluated the technique for the treatment of bone defects in the hand or wrist, and observed a union rate of 82% within 4 months, without major complications. The modification of the technique to reconstruct the defect with an intramedullary locking nail in the first stage and place the cement around the nail has also been evaluated with satisfactory results.[14,18,19] For example, in segmental tibia bone loss of an average of 8.7 cm, resulting from trauma, infection or aseptic necrosis, a 91.6% union rate has been reported, but with a 41.6% infection rate.[14] The technique has also been used for the treatment of segmental tibial bone loss by Ilizarov bone transport in an induced membrane, with union at 7 months and no further functional sequelae.[17] Bone defects secondary to deep infection, including infected non-unions or severe osteitis, as well as a case of Ewing sarcoma in the femur have been successfully treated with the Masquelet technique.[14,15,18,19,21,23,24] A recent study reported on four cases of mandibular reconstruction due to osteoradionecrosis using this method.[12]

Finally, modifications of the Masquelet technique and the use of bone graft substitutes additionally to autologous bone graft during the second stage have been evaluated.[12,14,22] Hydroxyapatite and tricalcium phosphate substitutes as well as bone morphogenetic proteins (BMP-7) have been used to augment the volume and osteoinductivity of the graft. For additional structural support, a non-vascularised fibular graft to fill the defect has been used in combination with autologous iliac crest bone graft in an 11 cm humeral defect. [23]

Tips and tricks for the Masquelet technique

In general, the key for a good outcome is to understand the overall concept of the induced membrane technique: The pseudosynovial membrane formed around the cement spacer (as a foreign bogy reaction- first stage) acts as a chamber around the bony defect to contain the bone graft and stimulate bone regeneration (second stage).

Tips and tricks for the first stage

- Thorough debridement and irrigation are critical, especially if infection is the cause of the defect. In patients with infected non-union (Fig. 1) or osteomyelitis, this two-stage technique ensures that adequate debridement has been undertaken at the first operation with no evidence of recurrence. Bone edges of the bone fragments should be healthy with a viable bleeding bed (Fig. 2).

Table 1
A summary of the animal studies evaluating bone formation with the induced membrane technique.

Author/year	Animal model	Study design	Assessment	Outcome
Klaue[10] 2009	Sheep	Mid-diaphyseal femoral defects (3 cm) Locking plate and PMMA. Group A: graft + induced membrane Group B graft only Group C: induced membrane only Group D: no graft, no induced membrane	At 16 weeks Histological and radiographic assessment of union	Groups A: full-width bone formation. Group B: loose radiodense bodies at the site of the plate Group C: nearly no resorption Group D: clear resorption with fixation failure
Pélissier[11] 2009	Rabbits	Implantation of cylindrical-shaped ceramic implants ± loaded with OP-1 in heterotopic sites: - in a subcutaneous tunnel - in a previously induced membrane subcutaneously	At 4 and 16 weeks Assessment of bone formation in the implants at three different levels (extremities and middle)	Untreated implants: no bone formation Implants inserted in an induced membrane: less resorption and bone formation (80%) at 4 months
Zwetyenga[12] 2009	Rabbits	Segmental osteotomy of mandible Miniplate and PMMA Second stage: cancellous autograft ± hydroxyapatite and triphasic calcium phosphate	At 1,3, and 6 months Microscopic and immunochemical analysis	Induced membranes: positive for VEGF and a high number of capillaries The new cortical bone was similar in both groups. Slow resorption of bone substitutes hindered formation and continuity of new cortical bone.
Viateau[13] 2006	Sheep	Mid-diaphyseal metatarsal bone defects (2.5 cm) Dynamic compression plate and PMMA Second stage: Group 1: defect unfilled Group 2: morcellized autologous corticocancellous graft + external coaptation for 6 months	At 6 months Radiographic, CT and histologic Assessment of bone formation	Group 1: Non-union Group 2: Bone formation Induced membranes: blood vessels, CBFA1 and cells, and very few macrophages entrapped in a collagenous tissue positive for type I collagen

Table 2
A summary of the clinical studies using the Masquelet technique for reconstruction of bone defects.

Author/year	Type of study	Number of patients	Location (size) and cause of bone defect	Surgical technique	Outcome	Complications
Apard [14] 2010	Case series	12	Tibia (8.7 cm; range: 6–15 cm) Trauma, aseptic necrosis and infection	Modified Masquelet technique First stage: static IM nailing and cement around the nail + free muscle flap or a pediculated fasciocutaneous flap Second stage: at 4 months (range: 2–6 months) with cancellous bone grafting (+ tricalcium phosphate substitute in 4 cases)	Mean FU: 39.5 months (range: 12–94 months) Complete weight-bearing at 4 months (range: 3–7 months)	5 deep infections (1 fixation failure, 2 exchange nailing, 2 prolonged antibiotic therapy)
Flamans[15] 2010	Case series	11	Hand and wrist Trauma (but intact pulp) and infection	First stage: stable fixation, flap if necessary, and PMMA spacer Second stage at 2 months with cancellous bone	9 cases with union within 4 months (3–12 months)	2 non-unions
Stafford[16] 2010	Case series	25[a]	Tibia and femur (range: 1–25 cm) Trauma and infection	First stage: debridement, stable fixation (nail and/or plate, or extrernal fixation) and antibiotic-loaded PMMA spacer Second stage at 6–8 weeks with RIA bone graft	24 cases with union at 12-month FU (1 patient lost to FU)	1 non-union 1 deep infection requiring BKA
Uzel[17] 2010	Case report	1	Tibia (10 cm) Trauma	Modified Masquelet technique (with Ilizarov frame) First stage: Antibiotic loaded spacer with external fixation Second stage at 4 months with removal of cement and change to Ilizarov frame and bone transport (without bone graft)	Union at 7 months Frame kept for 9 months	No
Woon[18] 2010	Case series	2	Tibia (4 and 6 cm) Infected non-unions	Case 1 – First stage: IM nailing and antibiotic cement spacer Second stage at 2 months: with autologous iliac bone graft Case 2 – First stage: external fixation and cement Second stage at 11 weeks: ankle fusion with corticocancellous graft	Union at 9 months (case 1) and at 18 months (case 2)	Ankle stiffness and a claw-toe deformity (case 1) Case 2 required a second bone grafting procedure at 7 months
Biau[19] 2009	Case report	1[b]	Femur (16 cm) Ewing sarcoma	Modified Masquelet technique with IM nail First stage: resection, reconstruction with a locked IM nail and a PMMA spacer Second stage at 7 months with cancellous and cortical bone autograft	Union at 1 year Asymptomatic and tumour free 1 cm leg length discrepancy	No
Largey[20] 2009	Case report	1	Foot (90% loss of the medial cuneiform) Trauma	First stage: saphenous cross-leg flap and interposition of a cement spacer Second stage at 2 months with corticocancellous iliac bone graft	Union at 12 months	No
Powerski[21] 2009	Case report	1[b]	Radius Osteomyelitis post elastic intramedullary nailing	First stage: debridement, plate fixation and antibiotic-loaded cement spacer Second stage at 4 months with cancellous bone graft	Union at 3 months	No
Zwetyenga[12] 2009	Case series	4	Mandible (11.2 cm; range: 9–14 cm) Osteoradionecrosis	First stage: Resection and segmental mandibulectomy with 1 cm safe margins and PMMA Second stage at 8 weeks with 50% cancellous bone graft and 50% bone graft substitutes	Union in 2 cases at 6 months	2 deep infections and failure at 8 and 18 days
Masquelet[22] 2008	Case series	11	Tibia, femur, humerus (10.5 cm; range 5–18 cm) Infected non-unions	First stage: external fixation and cement spacer and muscle flaps Second stage at 6–8 weeks with cancellous autograft augmented with BMP-7	10 cases of union at 11.5 months (6–18 months)	1 BKA for dystrophy of the foot and non-union
Gunepin[23] 2008	Case report	1[b]	Humerus (11 cm) osteomyelitis	First stage: debridement, external fixation, and cement spacer Second stage at day 45 with non-vascularized fibular graft and autologous iliac crest bone graft	Union at 20 weeks No recurrence of infection No functional complaint	Decreased shoulder ROM Elbow stiffness
Roche[24] 2005	Case series	11	Humerus, femur, tibia (5.5 cm; range: 1.5–10 cm) Infected non-unions	First stage: debridement, fixation and antibiotic-loaded cement Second stage at two months and autologous bone graft	Mean FU: 3 years (range:1–5) Union in all cases within 4.5 months (3–6 months)	No
Schöttle[25] 2005	Case series	6	Tibia (6.5 cm; range: 5–8 cm) Infected non-unions	First stage: debridement, external fixation antibiotic-loaded cement, and free microsurgical tissue transfer Second stage at 105 days (91–119) with autologous bone graft (± allograft)	Mean FU: 3 years (range: 1.5–5) Union in 5 patients at 7 months (6–8 months)	2 superficial pin site infections 3 flap haematomas 1 refracture after fixator removal at 10 months
Pelissier[26] 2003	Case series	3	Tibia, calcaneus (7.6 cm) Trauma Osteomyelitis	First stage: cement spacer and external fixation Second stage with cancellous bone graft	Union at 8 months (range, 5–10 months)	1 BKA for dystrophy of the foot and fixed ankle flexion
Pelissier[27] 2002	Case report	1	Foot Trauma	First stage: cement spacer Second stage with cancellous bone graft and hydroxyapatite	Union at 9 months	No
Masquelet[6] 2000	Case series	35	Upper and lower limbs (range: 5–25 cm) Trauma, infection	First stage: debridment, external fixation, and cement spacer Second stage at 6–8 weeks with autologous cancellous bone graft + - allograft when required (to a maximum ratio of 1/3)	Average time to union 8.5 months (6–17 months) No recurrence of infection	4 stress fractures (2 early, 2 late)

FU, follow-up; PMMA, polymethylmethacrylate; RIA, Reamer/Irrigator/Aspirator; BMP, bone morphogenetic protein; BKA, below-knee amputation; ROM, range of motion.
[a] 25 patients with 27 non-unions.
[b] Child or adolescent.

Fig. 1. (a) A case of an infected non-union in a 49-year old female diabetic patient with previous ORIF of a distal tibial fracture (AP radiograph shown). (b) The plate is exposed over the medial malleolus with an associated skin defect.

In case of infection (osteitis and/or presence of an IM nail), the canal should be reamed for debridement and irrigated.
- Appropriate fixation of the bone defect is desirable. With the traditional technique, a temporary external fixator is used to provide mechanical stability (Fig. 3). The placement of the pins is essential in order to optimise stability, but not to interfere with next incision or future plate position if possible. The length, mechanical axis and the rotation of the extremity should also be maintained.
- Meticulous pin site care is crucial to minimise the risk of infection.
- In case of other fixation methods (IM nailing or plating), the provided stability should be adequate as it may not be revised at the second stage.
- For optimum membrane induction and better stability of the construct, the cement should be placed inside the canal and over the edges of the bone and should maintain the space of reconstruction (Fig. 4a and b). The surrounding soft tissue envelope should have adequate blood supply.

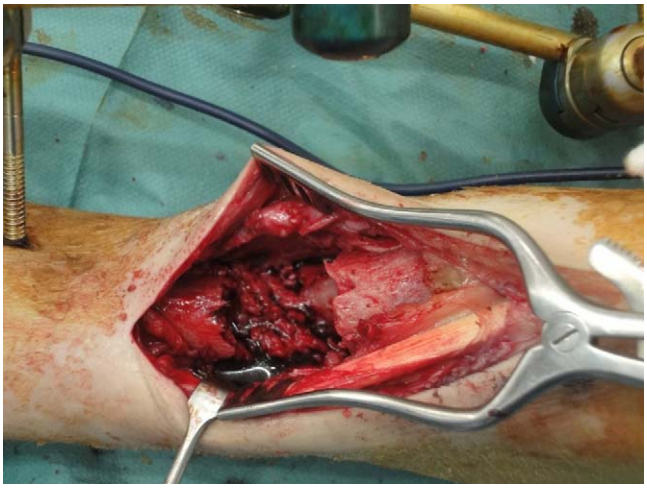

Fig. 2. During the first stage of the Masquelet technique and after thorough debridement, the edges of the bone fragments are healthy with a viable bleeding bed.

- Insertion of cement spacer loaded with antibiotics in case of infected non-union.
- Good soft tissue coverage is essential and free tissue transfer may be required.
- Wound closure must not be under tension.

Tips and tricks for the second stage

- Samples for culture must be obtained to exclude persistence of infection in previously infected cases prior to administration of antibiotics intra-operatively.
- The membrane must be incised with caution (Figs. 5 and 6).
- The cement spacer is removed with a saw or an osteotome with caution not to break the bony edges or to damage the membrane.
- The IM canal is carefully prepared with hand reamers or a curette and debrided if needed.
- All non-vital tissues must be removed (Fig. 7a).
- Depending on the size of the defect, adequate volume of graft material should be available. Autologous bone graft can be obtained from the iliac crest or from the intramedullary canal of the femur (or tibia) using the novel Reamer/Irrigator/Aspirator (RIA) system.[16,28,29] For large defects, autologous bone graft can be augmented with allograft or bone substitutes (Fig. 7b).

Fig. 3. Adequate mechanical stability is provided using a temporary external fixator.

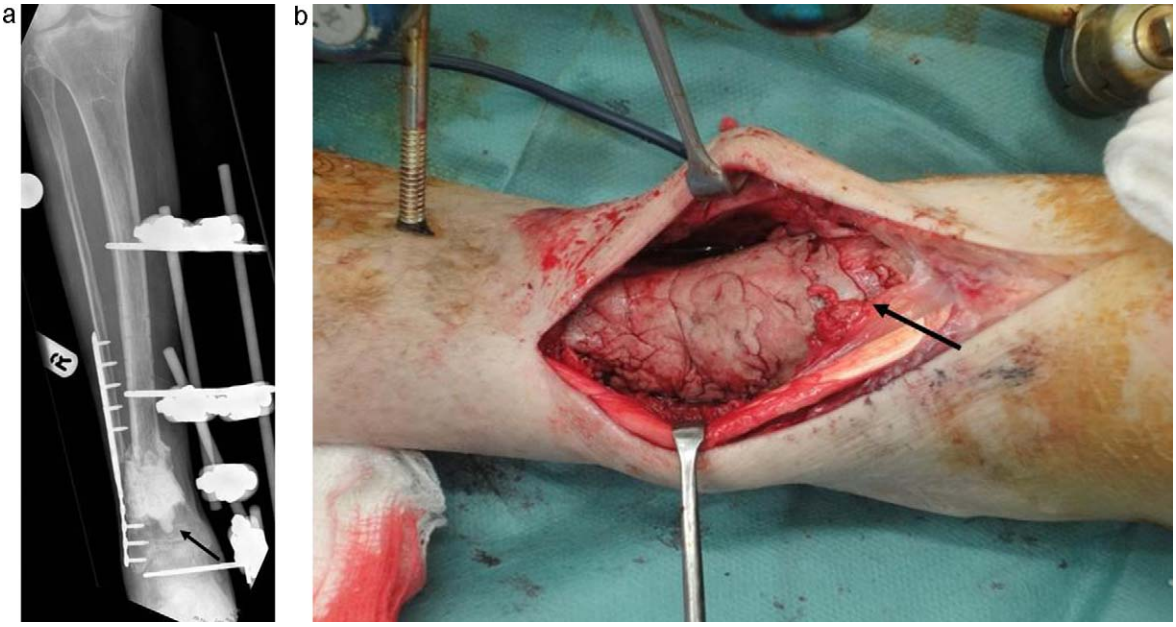

Fig. 4. For optimum membrane induction and better stability of the construct, the cement should be placed (a) inside the canal (black arrow), and (b) over the edges of the bone (black arrow) and should maintain the space of reconstruction.

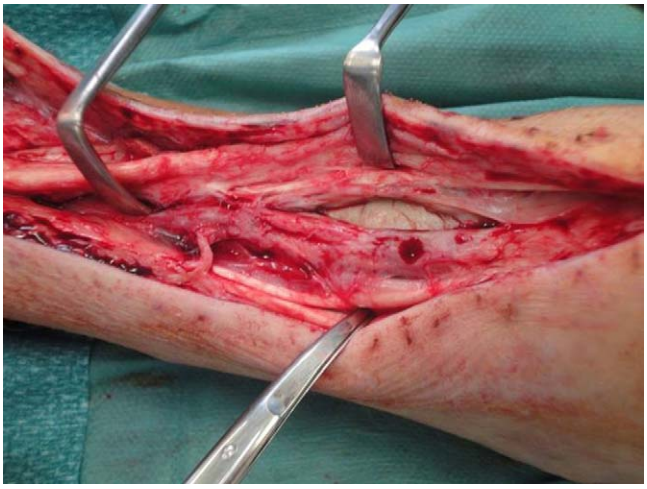

Fig. 5. During the second stage, the membrane is incised with caution.

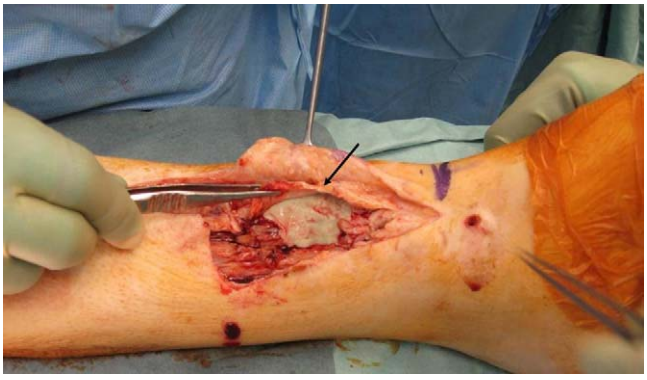

Fig. 6. An intra-operative picture from another case showing the thickness of the membrane formed over the cement spacer (black arrow).

- Bone graft material can be enhanced with osteoprogenitor cells (from bone marrow aspirate) or with osteoinductive growth factors (commercially available BMPs), (Fig. 7b).[30,31] These can be mixed with the autograft prior to filling the defect or they can be placed inside the medullary canal and in the bed of the defect, whilst the autograft can be inserted next for better containment.

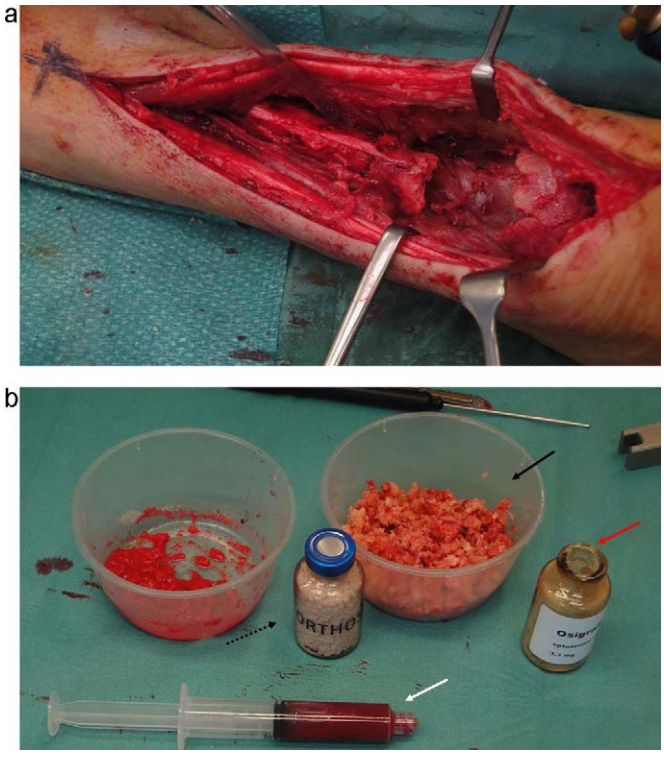

Fig. 7. (a) All non-vital tissues are removed prior to 2nd stage reconstruction, and (b) adequate volume of bone graft is obtained to fill the defect (black arrow: cancellous autograft mixed with allograft, dotted arrow: bone substitute, red arrow: BMP-7, white arrow: bone marrow aspirate).

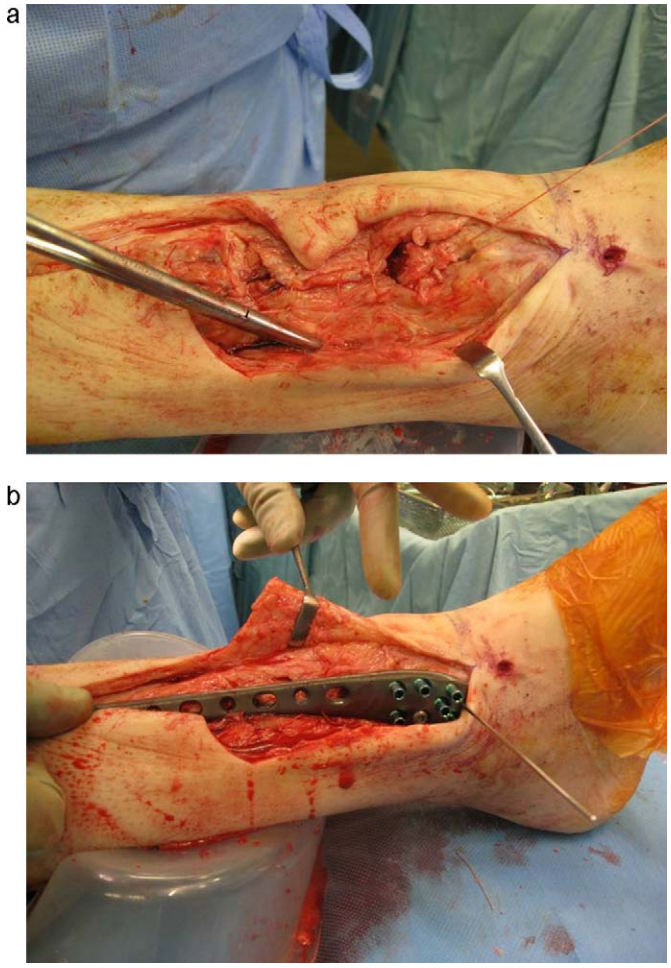

Fig. 8. (a) The membrane is closed to ensure that bone graft is contained into the chamber, and (b) adequate mechanical stability is provided with plate fixation; which in this case is placed epiperiosteally.

- The membrane must be closed to ensure that the graft material is contained into the chamber (Fig. 8a).
- Adequate mechanical stability must be provided, usually with plate fixation. The plate can be placed either under the membrane or epiperiosteally (Fig. 8b), in an effort to minimally disturb the periosteal blood supply and to assure firm closure of the membrane under the plate.
- Soft tissue coverage should be adequate and wound closure should be performed without tension.

Discussion

The concept of the induced membrane is a well established method for reconstruction of bone defects secondary to chronic osteomyelitis, tumour excision, traumatic bone loss and post-traumatic septic or aseptic non-unions.[32] Successful regeneration of bone defects up to 25 cm in length has been reported;[6] and overall there are numerous studies reporting on satisfactory outcome regarding bone healing and limb function (Table 2). Knowledge of the basic concept of the technique and its tips and tricks is important in order to reduce associated complications and increase its efficacy. The advantages of this method are that the induced membrane not only contains the bone graft and prevents its resorption at the early stages; but it also plays an important role in revascularisation and bone formation and consolidation throughout the regeneration process. Cancellous bone graft can be used even if the recipient site has initially been irradiated or infected or in cases of malignancy, as long as thorough debridement has been performed. The graft can be augment with cells, growth factors, allograft or other bone substitutes depending on local requirements. With this technique, the length of the defect is being mainly preserved and the soft tissue coverage is either adequate or is restored with soft tissue transfer.

The induced membrane technique constitutes a staged procedure, requiring two different interventions and in this respect this can be considered as drawback. But it should be kept in mind that for the management of cases requiring extensive bone reconstruction, especially in the presence of infection, two surgical steps are unavoidable in any case to remove infected and necrotic tissues initially and minimise the risk of recurrence of the infection. Also, the availability of the autograft is limited and the associated donor site morbidity should be considered. In addition, as there is no simultaneous histogenesis as seen in distraction osteogenesis,[3] the need for supplementary procedures for soft tissue transfer may be required, increasing further the surgical demands upon the patient.

In general terms, the vascularised fibular autograft and the Ilizarov bone transfer technique are still the most commonly used methods for reconstruction of large bone defects.[2,3] Despite their advantages as bone regeneration methods, they are also associated with complications and significant drawbacks. Such disadvantages include the considerable donor site morbidity, the demanding microsurgical technique and prolonged operative time, as well as risk of the fracture or inadequate hypertrophy of the graft for the use of vascularised fibula autografts. For distraction osteogenesis, the risk of infection and especially of septic arthritis when used closed to a joint, and the prolonged time required for distraction and consolidation of the regenerate, often dictate the need for an alternative method of bone reconstruction. Therefore, the Masquelet technique as well as other techniques for restoration of large bone defects, such as intramedullary lengthening devices,[33] the use of cylindrical metallic or titanium mesh cages,[34,35] and the monorail method for segment bone transport,[36] can be used as alternative methods for certain cases.

Whether the Masquelet technique is used, or any other aforementioned method of reconstruction of bone defects, it remains difficult to predict the final functional outcome. Patient should always be informed that, although potential complications can be predictable; in most of the cases, the reconstruction process is long and difficult, requiring further procedures if necessary. Particularly in emergencies, the decision between an attempt for limb salvage versus early amputation is never easy; with the literature being controversial on the long-term functional outcomes of salvage procedures.[26] The selection of patients for reconstruction of bone defects with any method including the Masquelet technique is important for the final outcome. Key factors predicting the outcome of reconstruction are the presence of infection or vascular deficiency of the extremity, as they are associated with high complication rate (delayed union, non-union, or vascular thrombosis) and a poor functional result.[26]

Overall, the Masquelet technique has been used in the clinical setting for more than 2 decades as a method for reconstruction of bone defects with good results. Its concept open new perspectives, especially for the management of large bone defects, by enhancing the biology of bone regeneration; since the induced membrane promotes the vascularisation and the corticalisation of the cancellous bone, and it delivers growth and osteoinductive factors.

Future directions

Despite the current evidence, further research is required to clarify issues regarding the use of the induced membrane

technique in order to improve the clinical outcome. A crucial question is about the actual biological properties of the membrane. Regarding its osteoinductivity, although immunochemical analysis has confirmed the production of BMP-2,[8] a recent *in vivo* study has shown that induced membranes placed in a non-osseous subcutaneous site have no osteoinductive properties on a calcium phosphate biomaterial.[37] Therefore, further research is needed to elucidate other osteoinductive factors that may be secreted by the membrane and to evaluate its osteoinductivity *in vivo*. Other growth factors, additionally to BMP-2, VEGF and TGF-beta 1,[8] may also be secreted by the membrane. Finally, the cellular component and the vascularity of the membrane and their role in bone formation need to be further clarified.[8,13]

A second issue is the selection of the optimal type of spacer in an effort to induce a biologically active membrane. Currently, PMMA cement is used; but potentially another spacer may induce a more appropriate type of membrane in terms of synovial like metaplasia and villous hyperplasia.

Thirdly, the issue of the optimal type of material for filling of the defect at the second stage also remains to be solved regarding better mechanical and biological properties. Morcellised cancellous autologous bone graft remains the "gold standard"; but, especially for reconstruction of large bone defects, additional grafting material is required. When an allograft or a synthetic bone substitute are added, the ideal ratio of bone substitute and autograft needs to be determined not to compromise bone healing and mechanical strength. Furthermore, questions that need to be answered in the future include the best bone graft substitute in terms of osteoconductive, osteoinductive and osteogenetic properties. As the osteoinductivity of the membrane may not be sufficient, the graft may be augmented with osteoinductive factors or osteoprogenitor cells to enhance bone formation. Masquelet et al.[22] evaluated the addition of recombinant BMP-7 to autologous bone graft in a prospective clinical study; but the results were not encouraging. Nevertheless, future research is needed to determine the efficacy of additional "biological stimulus" for the second stage of this technique. Issues that need to be addressed include the optimum dose and growth factor-release method to ensure prolonged delivery, as well as the use of a combination of growth factors. Also, the use of additional osteoprogenitor cells from bone marrow concentrate may add to the bone formation process within the defect.

These issues are under research and the use of tissue-engineered grafts is also a promising strategy for bone reconstruction.[38] With this approach, improved scaffolds and composite grafts, that provide growth and osteoinductive factors and cells, may be used in the future to accelerate bone formation at the reconstruction stage of the Masquelet technique. Finally, tissue-engineered bone membrane composites constructed *in vitro* may be used in the future as a "biomimetic periosteum" to reconstruct critical bone defects, as shown in a recent animal study.[39] This could be of great clinical importance; as in non-infected cases or acute traumatic bone loss, the traditional two-staged procedure may be replaced by a single procedure. However, the clinical applications of bone tissue engineering approaches have not still been well developed in the clinical setting.

The induced membrane technique represents an established bone reconstruction procedure for the management of complex cases requiring bone regeneration. Overall, the main questions to be answered in order to improve the clinical outcomes include the identification of what is the best approach to optimise the biological activity of the membrane promoting the bone repair processes.[32]

Conflict of interest

All the authors declare that there is no conflict of interest.

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