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The induced membrane technique for bone defects: Basic science, clinical evidence, and technical tips

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Abstract

The clinical management of large bone defects continues to be a difficult clinical problem to manage for treating surgeons. The induced membrane technique is a commonly employed strategy to manage these complex injuries and achieve bone union. Basic science and clinical evidence continue to expand to address questions related to the biology of the membrane and how interventions may impact clinical outcomes. In this review, we discuss the basic science and clinical evidence for the induced membrane technique as well as provide indications for the procedure and technical tips for performing the induced membrane technique.

Keywords: bone defects, induced membrane technique, Masquelet technique, orthopaedic trauma, surgical technique

1. Introduction

The clinical management of large bone defects continues to be a difficult clinical problem to manage for treating surgeons and is often complicated by patient factors, soft tissue injury, and the physiology of injury. The induced membrane technique (IMT), also known as the Masquelet Technique, was initially developed in the late 1970s for the management of bone loss resulting from the treatment of septic nonunion of the leg.[1] Over time, this technique has been adopted as a technique to manage segmental bone defects of most long bones, irrespective of the etiology of bone loss.[1,2]

The IMT consists of a planned two-stage procedure with the first stage being debridement, bone stabilization, and placement of a polymethylmethacrylate (PMMA) cement spacer to preserve the potential dead space for later grafting. The PMMA spacer secondarily causes the induction of a membrane that envelops the spacer and contains the space. The induced membrane is biologically active and has been shown to be highly vascularized, secrete osteoinductive and angiogenic growth factors, and contain mesenchymal adult stem cells (MSCs), which are the conditions for eventual tissue regeneration.[3] The planned second stage consists of stable bone fixation with the removal of the cement spacer and insertion of bone graft, usually in the form of autograft.

In this review, we discuss the basic science and clinical evidence for the IMT as well as provide indications for the procedure and technical tips for performing the IMT.

2. Basic science evidence for the induced membrane technique

Here, we review the basic science evidence surrounding the timing of the second stage as well as the impact of defect location and spacer types on the properties of the induced membrane. It should be noted that one of the major shortcomings of the basic science IMT literature is the lack of focus on bone union as an outcome, which is the ultimate goal of the IMT in a clinical setting.

2.1. Timing of the second stage

The basic science evidence regarding the optimal timing of the second stage has been somewhat conflicting and suffers from the main limitation noted above. It is important to recognize there are often competing priorities between optimized biology of the membrane and practical factors such as adequate soft tissue healing, resolution of infection, and optimal handling characteristics of the membrane. Nonetheless, extensive basic science investigation has provided valuable insights into the biological processes that the membrane undergoes and the optimal timing of these.

Following the implantation of the PMMA spacer during the first stage, a cellular reaction occurs with inflammatory cell infiltration and edema, contributing to the formation of the membrane.[4] Neutrophils and eosinophils can be seen concentrated around blood vessels and the PMMA surface, consistent

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with an inflammatory reaction to the PMMA spacer.[5] Animal models demonstrate that this inflammatory reaction completely resolves by 6 to 8 weeks.[6] Similarly, there is a lack of an active inflammatory reaction (by histology as well as immunohistochemical staining for $CD14^+$ cells) by 6 weeks. The clinical implication would be to suggest that based on this evidence, the second phase of grafting should not be undertaken until this inflammatory process is complete.

Vascularity likely has the greatest impact on the induced membrane's ability to promote endogenous growth factors, affect differentiation of the various cellular lineages, and facilitate the incorporation of secondary bone grafting materials. The temporal development of membrane vascularization has implications with regard to the timing of the secondary grafting procedures. The development of neovascularity increases significantly over time following spacer implantation, with the greatest increase occurring between 2 and 4 weeks.[6] As maturation of the membrane continues, by 4 weeks, an increase in larger caliber blood vessels can be seen and appears to plateau.[5,7,8] After 4 to 6 weeks postimplantation, there is a progressive decrease in vascularity, which is demonstrated in both animal and human findings.[6,8,9] Applied clinically, this evidence suggests performing the second stage within a 4 to 6 week window may be preferred to ensure adequate vascularity.[9]

Animal models evaluating segmental defects have identified the presence of mesenchymal stem cells (MSCs) as well as osteoblast presence from harvested membranes in a time-dependent cascade.[3,10–13] MSCs were detected very early after PMMA spacer placement, and appeared to peak after 2 to 3 weeks. Interestingly, the cells slowly dissipated and were undetectable after the 4- to 6-week time period postimplantation.[3,10–13] The exact clinical effect of this decline is as of yet unknown. However, one could postulate that the critical time for secondary bone grafting would be optimized when the largest number of osteogenic cells is located in the surrounding graft envelope.

2.2. Location and muscle coverage

A study by Henrich et al evaluated membrane morphology with regard to the location of the bone defect.[6] Femoral membranes, developed in a circumferential muscular envelope, were found to have a significantly higher cell number, increased growth factors, and vascularity compared to membranes from subcutaneous locations—that is, tibial defects.[6,14] Furthermore, no MSCs were seen at any time point (2, 4, or 6 weeks) in membranes formed in subcutaneous sites.[6,14] Although these findings have yet to be confirmed in human studies, they suggest that bone defects contained in a muscular environment (i.e., femoral, humeral) may induce a more favorable membrane for healing compared to subcutaneous bone defects (i.e., tibial and distal ulnar).[4,6] In contrast, previous studies comparing muscular versus fasciocutaneous flaps for coverage over bony defects have reported no difference in failure rates.[15–18] Regarding their osteogenic properties as related to membrane thickness, further clinical investigations should be conducted to examine the characteristics of induced membranes covered by muscular free flaps versus faciocutaneous flaps.[15–17]

2.3. Spacer type and antibiotic use

Although not originally described as a component of the Masquelet technique, the use of antibiotic-impregnated PMMA spacers is common. Little to no evidence exists on the optimal composition of the PMMA spacer, including the type of cement to be used, the use of noncement alternatives, and the utilization of antibiotics. There has been relatively little investigation of the effects of antibiotic-impregnated cement on the expression of angiogenic and osteogenic factors. However, it is well known that the primary cause of failure of this technique is recalcitrant infection.[19]

In a rat femur defect model, Nau et al[20] evaluated the effects of using different bone cement spacers with or without the addition of antibiotics (gentamicin, vancomycin, and clindamycin) concluding that the type of cement and antibiotic additive influenced the membrane thickness and proportion of elastic fibers within the IM, with clindamycin containing spacers having the thinnest membrane and least vascularity at 6 weeks in comparison to spacers that contained vancomycin or gentamycin alone.

Shah et al studied the effect of clindamycin-impregnated PMMA spacers in rat femoral defects inoculated with *Staphylococcus aureus*.[21] At 4 weeks, only 12% of the animals treated with PMMA spacers supplemented with clindamycin were still infected, however, all animals treated with PMMA spacers without antibiotics remained infected.[21] Furthermore, analysis of the harvested induced membranes found that the clindamycin did not negatively impact gene expression of inflammatory cytokines, growth factors, and stem cell markers.[21] However, there has been relatively little investigation into the effects of antibiotic-impregnated cement on the expression of angiogenic and osteogenic factors of the membrane.

3. Clinical evidence for the induced membrane technique

The majority of clinical evidence for the IMT is based on small case series or cohorts. Morelli et al published a systematic review of the IMT in 2016 that included 17 studies totaling 427 patients.[22] Within this review, the average-sized defect was 5.53 cm (range, 0.6 to 26 cm) with 62% of the cases in the tibia. Additional surgery for infection or nonunion was required in 36.2% of patients, and the complication rate was 49.6%. The union rate was reported as 89.7%, and the infection eradication rate was 91.1%. It was difficult for the authors to make definitive conclusions from the study because of the number of variables—locations, indications, defect sizes, and bone grafting source—but bone infection as an indication did have a higher complication risk and lower odds of achieving union.

The majority of studies using IMT cited iliac crest bone graft as the primary source of bone graft for the second stage.[22–24] In 2010, Stafford and Norris[25] used intramedullary femoral bone graft in 25 segments with an average defect of 5.8 cm. Ninety percent of these defects were healed at 1-year follow-up with a single bone graft procedure. In 2017, Wu et al[26] reported a series of 20 patients using a one-third allograft to autograft ratio and demonstrated no difference in the healing rate when compared to autograft alone.

Outside of this systematic review providing context for the IMT as a whole and analyzing the evidence for graft selection, it is most useful to examine the clinical evidence for the IMT by its use in different anatomic locations.

3.1. Femur

Tong et al. compared the IMT in 7 cases to bone transport in 6 cases.[27] The patient-reported functional scores were better in the IMT group in comparison to the bone transport group. The

study's authors attributed this improved functional score for the IMT groups to the lack of pins and wires for the periarticular defects that normally would affect the range of motion in the knee.[27] In the largest study to date, Morwood et al[28] reported on 65 femoral critical-sized defects treated with IMT and compared plate fixation to intramedullary nail fixation (IMN). Femoral defects treated with IMN united faster and with fewer additional bone grafting procedures when compared to plate fixation, suggesting that outcomes may be improved when the IMT is used with nail fixation versus plate fixation. The authors also evaluated the impact of defect location within the femur and reported inferior outcomes in distal defects versus proximal and middle defects.

3.2. Tibia

The tibia is the most commonly reported segment where the IMT technique is used, with many studies documenting extensive use of flaps for soft-tissue coverage. In a study by Wang et al,[29] all 12 tibial segmental defects were treated with flaps, as well as in the study by Azi et al[30] in which 11 of 19 required flap coverage. Many studies reported multiple required surgeries to achieve infection-free union. In the paper by Taylor et al,[23] 35 patients required 4 surgeries on average to achieve the end result. Morwood et al reported on 56 tibias with critical-sized bone defects treated with IMT and compared plate fixation to intramedullary nailing.[28] The average time to weight bearing was lower in the IMN group when compared to plate fixation. Of the 56 tibias, 23 required flap coverage.

3.3. Humerus

There are very few studies documenting the use of the IMT in the humerus. Only 4 studies have reported more than 2 cases in their series that were located in the humerus, with the union rates reported as 100% with defect sizes ranging from 2.5 to 6 cm.[23,24,31,32]

3.4. Forearm

Allende reported 20 cases with an average-sized defect of 2.5 cm with a 100% healing rate.[33] Luo *et al.* reported 100% healing rate in 7 cases with an average defect size of 5.8 cm and an average number of operations at 3.43.[34]

4. Indications and contraindications for the induced membrane technique

Although it is commonly accepted that the IMT is used to treat critical-sized long bone defects—a term used to describe defects over a certain length that will not heal without additional intervention—there is no clear consensus on the parameters for what ought to be considered critical in size.[35–37] Many have defined critical as missing >50% of the circumference of the tibia for a distance of either 1 or 2 cm,[38–40] despite evidence suggesting nearly 50% of these fractures in the tibia could heal without further intervention.[36] Thus, providing recommendations for a lower limit of defect size that require IMT is challenging, and instead individual cases should be evaluated in the context of additional important factors such as soft tissue injury, nonunion risk factors, and anatomic location.

Success of the IMT is predicated on both an adequate soft-tissue envelope and an adequate biologic environment to induce healing. Residual open wounds, draining wounds, or deep infection will negatively affect the outcome of this technique. In the authors' opinions, the IMT is exceptionally valuable when flap coverage is used in defects that are at least 50% of the circumference of the bone or in situations where coverage may be tenuous and other risk factors for impaired bone healing and non-union are present, such as smoking, devascularized tissue, or poor mechanical stability. Placement of a spacer through the IMT may be less critical in locations where there is sufficient soft tissue coverage, such as posteriorly in the tibia or the femur. Beyond coverage, risk factors for nonunion should be considered. Santolini et al[41] identified and examined 10 risk factors for nonunion, including location, soft tissue damage, vascularization, displacement, type of fracture, method of reduction, mechanical stability, presence of a fracture gap, infection, and smoking. Based on their findings, patients with more than 7 risk factors have very little chance of healing without additional intervention and should be considered for the IMT, whereas those with 4 to 6 risk factors should be evaluated based on the accompanying soft tissue injury.[41]

Similarly, to a lower limit indication for the IMT, debate remains regarding upper limits for bone defects as well. Defects over 20 cm have been successfully treated with grafting following the increased use of the reamer irrigator aspirator (RIA), which has helped overcome the volume limitations of iliac crest bone graft.[32,42] Larger defects are best treated using an intramedullary device in comparison to a plate construct if a 2-stage spacer technique is employed.[28] Likewise, although less effective, allograft bone with osteogenic factors can be used for 2-step grafting. As defects become large enough that sufficient amounts of graft will be difficult to obtain, then bone transport and vascularized grafts become more viable options for definitive treatment. The authors believe that patients with defects larger than 10 cm should be offered transport with either intramedullary devices or external fixation or both.

5. Induced membrane technique: technical tips

5.1. Debridement and infection management

When performing the initial debridement, the indication often dictates how aggressive one should be. In a traumatic setting, initial debridement consideration should be given to using fragments (some with questionable vascularity) that may help obtain length, alignment and rotation while fixation is achieved. These fragments should be re-evaluated following fixation, at the time of cement placement and/or cement removal to determine if they should remain. In the setting of infection, surgical debridement should be aggressive and may require multiple debridements. Additionally, widespread infections involving intramedullary and cortical bone (Cerney-Mader Stage IV) require a thorough debridement and often wide resection in order to assure the eradication of infection. Furthermore, additional debridements/cultures can help with targeted antibiotics both via systemic intravenous antibiotics and/or locally in the cement spacer.

5.2. Cementing techniques

When the wound is ready for placement of a cement spacer, the polymethylmethacrylate (PMMA) cement is mixed with appropriate antibiotics and by hand without a vacuum canister.[20] The increased porosity achieved with mixing without a vacuum will

lend itself to a robust bioactive membrane. The cement is then molded until "doughy" when it can be placed in the defect. Care is taken not to place the cement in close proximity to neurovascular structures as it hardens due to the potential for thermal injury from the exothermic reaction. In some instances, malleable ribbon retractors can be used to protect nearby soft tissues and hold the cement where it belongs. Irrigation with saline should be used sparingly as it will leach out the antibiotic within the cement.

The cement should be placed overlapping the bone ends to provide room within the membrane to place a graft that also overlaps the bone ends. This can help prevent a seam nonunion that can occur with graft "creep" or movement when the patient becomes mobile and gravity might affect the placement of the graft.

The cement spacer can be placed in one block or multiple pieces. In the setting of an intramedullary nail, consideration of the placement of the cement space with 2 half circles or curved pieces, 1 posterior and the other anterior should be given. The 2 pieces facilitate placement and certainly make it easier to remove.

Dye such as methylene blue can be added to the cement to aid in full removal. Some brands of cement look very similar to bone and are easier to discern when the cement is dyed.

5.3. Second stage

The timing of the second stage is variable and is often dependent upon the status of the soft tissue and confirmation that an infection has been eradicated. Basic science evidence, as mentioned above, shows peak membrane biologic activity around the 4 to 6 week window.[7] However, it is not clear that this peak biologic activity is the optimal setting for placement of bone graft. The proinflammatory environment may in some cases lead to resorption of the graft and/or failure to consolidate.[6] In our practice, the timing for the second stage is often much later than this 4 to 6 week timeline, commonly between 8 and 12 weeks. Advantages of this timeline include advanced soft tissue healing, more time to confirm the eradication of infection, and a more robust membrane.[6] However, this thicker membrane does have a less vascular inner layer that may require some attention such as scraping with a cobb elevator or pie-crusting to induce neovascularization.

When returning to the OR for the planned second stage, if there is any concern for persistent infection, we recommend repeating the first stage by taking deep cultures, considering hardware exchange, and placing another spacer. In this event, we then wait for the results of the cultures and return to the OR for bone grafting at a later date based upon the need for repeat antibiotic treatment. We often will order blood levels of CRP and ESR to see if there is an associated elevated inflammatory state.

When opening the membrane, we make one longitudinal incision and elevate it off the proximal and distal bone ends to allow for the bone graft to overlap the outer cortex of the bone. When removing the spacer, it can be removed either en bloc or piecemeal depending on how it was placed and the hardware present. If it must be removed in pieces, we typically use an osteotome ± a drill and place a sponge over the spacer to prevent fragments from becoming airborne and potentially contaminating the surgical field.

After the spacer is removed and the membrane is prepared (i.e., scored or scraped to induce bleeding) it is appropriate to begin graft placement. Autograft is the gold standard either from the iliac crest, or RIA bone graft from the femur. If a femur is not available and a large amount of graft is required, it is possible to use the tibia with the new RIA2. If there are nonmodifiable patient factors (such as advanced age, immunocompromised, prior history of cancer, etc.) adjuvant biologics can be considered (bone marrow aspirates, bone morphogenic proteins, allograft bone with stem cells).[43] When the amount of bone graft required exceeds that typically yielded from RIA (70 cc or greater), we recommend adding cancellous allograft bone. We generally try to keep our ratio of autograft to allograft at least 2:1. In our experience, this strategy both expands graft volume as well as helps counter the fluid effect or settling of the graft that can be seen when patients keep the limb in a dependent fashion (often seen radiographically in larger defects).

Our preferred implant for stability after placement of the graft is an intramedullary nail. Whenever possible and in very distal and proximal bone defects we often consider a nail/plate combination.[28] One benefit of a nail is it aids in intramedullary revascularization and consolidation of the graft. Central graft necrosis is a real clinically observed problem, and the nail obviates this issue. Another method for preventing the central necrosis is using a bioabsorbable spacer such as gel foam centrally when placing the graft in a defect spanned by a plate. This will allow for some intramedullary vascularity to occur as well as decrease the volume of graft needed.

After graft placement, we perform closure of the membrane whenever possible with a monofilament absorbable suture. The graft should not be "overpacked" or too dense as this is thought to inhibit revascularization and can lead to failure to consolidate.

Post operatively for lower extremities after the grafting stage weight bearing is limited based upon fixation achieved and advanced largely by radiologic evidence of graft consolidation and integrity of fixation construct. In patients with intramedullary nailing or nail plate constructs, we encourage early weight bearing as tolerated to help with graft consolidation. Plate constructs will often have to wait 10 to 12 weeks and/or for some consolidation of the graft.

6. Conclusion

The IMT is an effective option for the treatment of segmental bone defects. Basic science and clinical evidence continue to expand to address questions related to the biology of the membrane and how interventions may impact clinical outcomes. When employing the IMT, adequate infection control is paramount to success, and surgeons should consider repeated debridement or additional first stage surgeries in order to improve the chances of success in the setting of infection. Surgeons using this technique must prepare both themselves and their patients for the potential need for multiple procedures to achieve a successful outcome.

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