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Masquelet technique and osteomyelitis: innovations and literature review

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Abstract. – OBJECTIVE: Wide diaphyseal bone defects, above all those infected, encounter into Masquelet technique a suitable treatment. The two-step procedure allows the surgeon to eliminate the infected tissues and then to promote new bone formation. We analyzed the literature about the use of the induced membrane technique in osteomyelitis and the innovations recently suggested.

MATERIALS AND METHODS: We reviewed some of the most common web databases using the key-words: Masquelet technique, induced membrane, and osteomyelitis. 66 studies were analyzed.

RESULTS: Comparing the Masquelet technique to other surgical procedures it shows better functional results in large bone defects due to infection. The induced membrane is like a biological chamber that protects the autograft and induces new bone formation promoting growth factors secretion. Different authors tried to improve one or more steps of the surgical procedure.

Some studies focused on polymethyl methacrylate role and the possibility to use different materials instead of cement to induce the membrane. Others analyzed the autograft harvesting and placing techniques trying to reduce the amount of bone essential to fill the gap, like the RIA technique. Moreover, bone substitutes have been used, as beta-tricalcium phosphate, that showed an osteoconductive ability.

CONCLUSIONS: The survey is not a systematic review. Nevertheless, new concepts are introduced and analyzed identifying 6 areas of interest and induced membrane technique development.

Key Words
Masquelet technique, Osteomyelitis, Bone, Infection, Autograft.

Introduction

Osteomyelitis is one of the worst complications in orthopedic surgery. *Staphylococcus aureus* is responsible for 44% of cases, followed by *Staphylococcus epidermidis* (17%) and *Streptococcus* family (16%)[1]. The most common affected sites are forefoot[2], toes (43%) and lower extremities (20%). Like traumas and tumors, bone infections can cause extensive diaphyseal bone defects.

The treatment of broad bone gaps is still a surgical challenge and there is not a consensus about the best reconstruction methods. In 1986 Masquelet developed a two-stage technique to restore wide bone loss and in 2000 introduced the induced membrane concept in an article based on his cases results[3]. The unique biological and structural properties of the induced membrane allow bone healing almost independently of the extent of the bone defect[4].

Based on a new concept, Masquelet et al[3] described a surgical technique combining induced membranes and subsequent autografts. This procedure allows handling diaphyseal defects, long more than 5 cm, in infected, poorly vascularized and irradiated sites. The induced membrane provides an envelope that protects and revascularize the bone graft[5]. Bone defects of both lower and upper limb long bones, mandible[6], hands, and fingers can be treated with success[7,5]. This technique has indications in adults, children[8,9], and also diabetic patients[10].

Standard technique

The Masquelet technique (MT) is a two-stage process. The first stage involves an accurate debridement of all septic and devitalized tissues and an internal fixation of the bone gap. The residual void is then filled with a polymethyl metacrilate (PMMA) spacer. Bone margins must be completely vital and the canal reamed and irrigated to physically eliminate most of bacteria and allow a complete vascularization. Temporary stabilization can be achieved with both external fixator, intramedullary nail or plate (Figure 1). If a nail is used, we recommend metal to be completely covered by PMMA (Figure 2). The cement spacer

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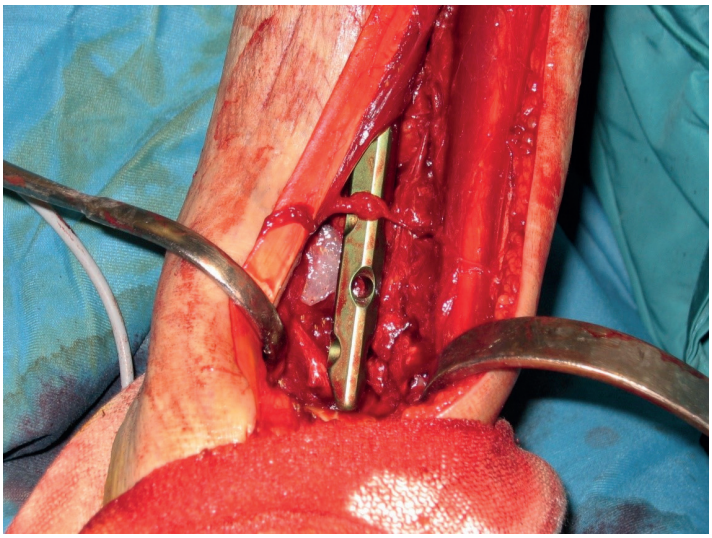

Figure 1. Intramedullary nail positioning after a wide curettage and infected bone removal in a distal tibia osteomyelitis.

prevents soft tissue invasion of the bone defect. In septic conditions, an antibiotic is added to PMMA because cement releases antibiotics locally. As reported by Gasparini in 2014[11], high-dose antibiotic-loaded acrylic cement allows a massive antibiotic release in the first hour, that gradually drops over time. The features of this decrease follow a specific antibiotic connected elution curves formula. Different antibiotics can be used to treat osteomyelitis and have to be chosen looking for the pathogen, the patient general conditions, and the antibiotic elution characteristics.

The presence of cement as a foreign body results in the formation of a pseudosynovial membrane all around the spacer, moreover preventing fibrous tissue to invade the prepared site. Furthermore, it allows a local control of the possible residual bacteria realizing a sterile recipient site. During the second

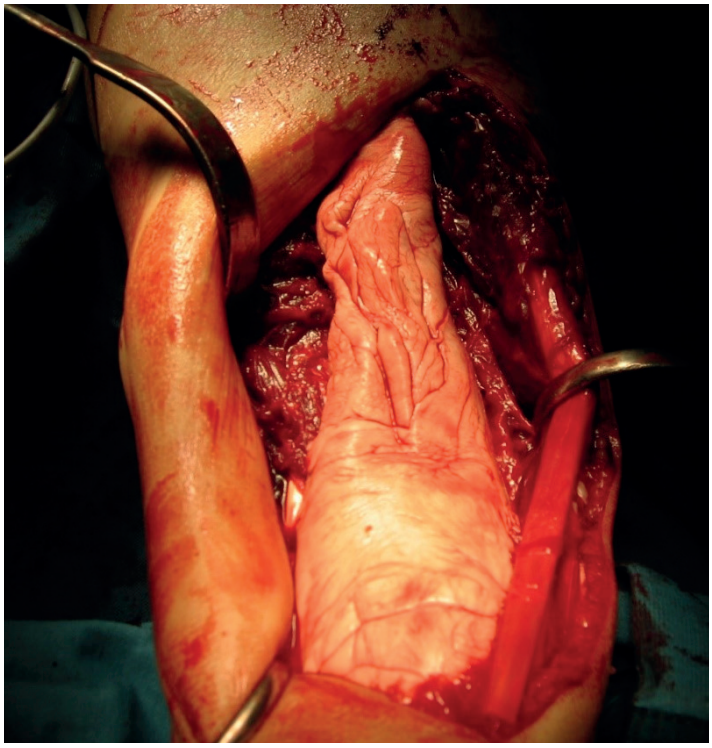

Figure 2. Cement spacer, shaped like the removed bone, fills the void.

stage, performed at least 6-8 weeks after the former, cement is removed and replaced with a huge fresh autologous cancellous bone graft. The membrane must be maintained intact to cover the autograft completely. Spongy bone grafts need coverage of healthy tissues to be revascularized. At the same time, a cancellous autograft placed in soft tissues acts as a foreign body and it will be eliminated by the immune system[12]. The induced membrane elicits new bone vascularization and corticalization, and prevents graft resorption[13,5].

The induced membrane creates a biological chamber that achieves two different tasks. First, when adequately maintained and closed around the autograft, it prevents bone resorption acting as a physical barrier. In addition, it promotes revascularization and, acting as a bioreactor, it allows growth factors secretion (like transforming growth factor β1, vascular endothelial growth factor and bone morphogenetic proteins). The membrane also gathers mesenchymal stem cells with osteogenic potential. It's important to notice that there wasn't bone union in cases with spacer but induced membrane removal compared to cases with still the membrane in place[14,15]. The MT requires to follow each step of the procedure precisely[16].

In the past, when a bone defect exceeded 5-6 cm in long bones, fibula transfer was the treatment of choice and Ilizarov intercalary bone transport (IIBT) was an alternative. Nevertheless, in bone defects due to infections, pathological condition of local soft tissues contraindicates these techniques. Moreover, donor site morbidity and demanding microsurgical technique must be considered in case of fibula transfer. Recently Tong compared MT and IIBT in the treatment of segmental bone defects due to post-tramatic osteomyelitis. He concludes that MT has better functional results and IIBT should be preferred only if present a limb deformity[17].

During the last years, various efforts have been made to improve one or more phases of the MT process, modifying the materials or the surgical technique of the first or of the second stage. Our review aims at examine and summarize the current knowledge and proposed innovations about the MT. It also focuses on MT feasibility for long bones osteomyelitis treatment.

Materials and methods

Our search was performed on the PubMed and Cochrane databases using various combinations of the key-words: Masquelet technique, induced membrane, and osteomyelitis. Only article in English and Italian were considered. The examined range of time was between the years 1996 and January 2018. Both animals and human studies were evaluated.

Results

Spacer

In 2016 Nau[18] analyzed various induced membranes in rats femur defects temporary filled with PMMA added to different antibiotics. The histological analysis showed a significant increase of 221 μm in membrane thickness from 2 weeks to 6 weeks into the group treated with Palacos and Gentamycin. In groups treated with Copal+Gentamycin+Clindamycin and Copal Spacer thickness decreased while elastic fibers fraction arose more than the first group. Those interesting and promising results need to be confirmed with more *in vitro* and *in vivo* studies.

Chadayammury et al[19] underline the importance to use a cement spacer instead of cement beads which promote a too much irregular membrane evolvement. Other authors[20] confirmed, in a 40-patients study, that spacers and beads allow the same rate of infection control but, whereas cement spacer is suitable for large and small bone defects, PMMA beads were not useful to fill large/segmental voids.

The effect on the induced membrane biology of PMMA substitutes has been recently investigated by Ma et al[21] on a rat model. After 6 weeks the osteogenic and neovascular activities of the calcium sulfate (CS) induced membrane were higher than in PMMA group. CS spacer seems to induce a membrane thicker than PMMA, with a similar production of growth factors such as TGF-β1, VEGF and BMP-2 but better osteoinductivity. Moreover, some endochondral ossifications have been observed in the CS group.

Membrane Modifications to Improve New Bone Formation

A recent animal study on 32 goats suggests that scraping the thin innermost layer of the induced membrane increases new bone formation. The layer of foreign body reaction around the spacer was removed with a curette, displaying a surface of fibrous tissue. The hypothesis underlying those results is that raised bleeding could promote bone healing. At the same time, the attempt on another group of animals to use

a textured spacer to enlarge the membrane area showed no effect on the final bone regeneration[22].

It's interesting that, if the induced membrane is placed into subcutaneous tissue it provides a high level of new blood vessels and bone morphogenetic proteins but it doesn't show osteoinductive properties on a macroporous graft beta-tricalcium phosphate (β-TCP) added with hydroxyapatite or bone mesenchymal stem cells. Those results were obtained analyzing subcutaneous-induced membranes on animals models[23,24].

It's fundamental to underline that, in case of infection, two stages are essential to remove all the contaminated tissues and a one stage procedure should jeopardize the infection healing[13]. Despite this, different interesting attempts have been made to reduce the MT into a single procedure, avoiding the time for the membrane to form and the necessity of another surgery[25].

Gindraux et al[14] proposed some similarities between the foreign body induced membrane and the human amniotic membrane, explaining the common structural and biological properties. In 1996 Meining[26] proposed a single-step surgery using a resorbable polymeric porous membrane of polylactide together with autograft, in order to protect it from resorption. Recently Tarchala et al[27] examined the use of a synthetic non-biological membrane of polytetrafluoroethylene in a rabbit model. It seems to act as a functional barrier and shows osteointegrative properties comparable to the induced membrane.

Graft Gathering and Placement Procedures

The bone defect extent influences the graft donor site. Greater voids require more bones and sometimes additional augmentation in order to obtain an acceptable graft strength and dimension[19]. Recently multiple authors have investigated different possibilities to reduce the amount of bone graft necessary to fill the gap. The purposes of those searches are to limit the donor site morbidity, to obtain enough graft for wide defects and, eventually, to find an artificial bone substitute with adequate healing capability. In 2017 Cho[28] proposed the use of bone graft modeled like a circumference around an absorbable gelatin sponge core that allows a correct and durable graft shape and position. An average 21.4% of the defect volume was filled by the gelatin sponge. The 86% of long bones so treated healed on X-rays at 9.1 months.

Many authors[29,30] prefer to use the Reamer-Irrigator-Aspirator (RIA) technique, that demonstrated adequate clinical results on the outcome. The RIA system was developed to overcome intramedullary increase of heat and pressure during reaming procedures and to evacuate and collect debris from the intramedullary canal easily. This is obtained cooling the RIA cutting head with Ringer's solution or NaCl[30].

Stafford e al[31] used femur RIA bone grafts in 27 segmental bone non-unions (7 cases due to infection/osteomyelitis) with a mean deficit size of 5.8 cm. They obtained a 90% non-union healings at 1 year postoperative and no RIA related complications.

Different authors[30,32] compared the concentration of growth-factors and osteogenetic elements between reaming aspirate, obtained through RIA, and iliac crest bone grafts. TGF-β1, BMP-2, PDGFbb, FGFa, and IGF-I resulted, with and without statistically significant differences, higher in the RIA debris than the iliac crest ones. On the contrary, the quantity of FGFb and VEGF was significantly higher into the iliac crest compared to the reaming debris. Some key points of the procedure could help to avoid complications: first of all the reamer head should be smaller (of at least 2 mm) than the narrowest section of the long bone diaphysis. An appropriate irrigation and aspiration can be obtained moving slowly forward and backward in the medullary canal. In addition, it's important to limit blood loss switching off the aspiration when the reaming has been enough[33].

Another procedure that could help bone union during the MT second stage is the application of Low-Intensity Pulsed Ultrasound (LIPUS), but scientific literature provides only case reports. Niikura et al[34] in 2016 treated a patient with an infected tibial pseudoarthrosis using the MT. LIPUS was used after the second stage to help the bone graft union. Low intensity pulsed ultrasound consists of an ultrasound application with an intensity lower than the upper limit of diagnostic intensities. It is usually used to accelerate fracture healing and enhance osteogenesis. It seems to increase blood vessels size and it helps to deliver bioactive molecules[35,36] stimulating osteoblasts proliferation[37]. Despite the interesting *in vivo* and *in vitro* results of this procedure, more studies are indispensable to truly understand its effective potential on autograft integration. Some preclinical studies suggested that also low-level laser irradiation could promote osteogenesis and inhibit adipocytes formation, thus attenuating bone resorption of osteoclasts[38].

Bone Substitutes

Morcellized cancellous bone autograft has always been used as gold standard for bone filling[13]. Different authors investigated the possibility to reduce the amount of autologous bone requested and/or increase new bone formation looking for an adequate bone replacement. Some studies report preliminary results about beta-tricalcium phosphate as bone substitute. Sasaki at al[39] combined β-TCP with a 75% porosity and an equal proportion of autologous bone chips from the iliac crest. They used it to reconstruct lower limb diaphyseal bone defects due to infection in 7 patients. The mean estimated defect volume was 13.6 cm^3 and the mean follow-up was 14 months. Good clinical and radiographic results were obtained, showing a satisfying osteoconductive ability of β-TCP[40]. Beta-tricalcium phosphate was also evaluated by Rousset et al[41] in the treatment of chronic bone infections and infected non-union of long bones of 8 children. The time between the first and second surgical step of MT resulted significantly shorter in cases with BTP used as bone filler compared with bone grafts. In the treatment of large bone defects due to tumor excision, BTP shows a faster integration, compared with ceramics and hydroxyapatite. That is related to a greater material osteoconductivity compared to the others[42]. Synthetic scaffolds (tricalcium phosphate hydroxyapatite scaffold, HA-TCP scaffold) were also evaluated in addition with BMP-7 and systemic bisphosphonate to repair rat femoral defects. Radiographic, micro-CT and histologic bone callus properties improved in cases treated with the association of scaffold, BMP-7 and bisphosphonate compared to BMP-7 and scaffold alone or combined[43]. Masquelet[44] himself used recombinant BMP-7 into the autologous bone graft, but he observed an increased autograft resorption. Another interesting material to improve bone formation, currently studied *in vitro*, is an absorbable bioactive glass-calciumphosphate cement. It increases bone morphogenetic protein and TGF-β expression so promoting osteoblasts adhesion and proliferation[45]

Different authors proposed the use of non-vascularised bone grafts and bone transport to fill the bone defect, associated or not with morcellised autograft. El-Alfy[46] obtained satisfying results in 15 young adults bone loss treated with a free non-vascularized fibula graft. The average time to bone union was 7 months. Two cases showed graft non-union. The study was conducted on only post-traumatic defects. Marais[47] proposed bone transport in 7 tibial bone defects due to osteomyelitis. During the second stage a metaphyseal osteotomy was performed and the Ilizarov external fixator arranged. All patients (excepted one) achieved infection resolution and bone union but there was a high rate of major and minor complications.

Masquelet Technique's Drawbacks

Despite the notable benefits of the MT procedure some downsides must be kept in mind. The sine qua non condition to obtain bone union is the infection resolution. In a recent systematic review, Aurégan et al[48] reassumed the rate of different complications in a pediatric population treated with MT. Bone union occurred in 40 patients on a total of 69, with improvement after revision surgeries. Non-union, fracture, and lysis of the graft were observed as the most frequent problems. Only 1 patient suffered of deep infection. The analysis of risk factors showed an interesting role of the bone defect site (femur locations) and dimension (wide voids), a long pause among first and second stage, a not stable synthesis and the association of the autograft and other bone substitutes.

Morelli et al[49], in a recent review, demonstrated that, on 237 patients affected by infected bone defects, MT achieves infection healing in 91.1% of cases. Among all the 427 cases cited (infected and not infected) the bone union rate was 89.7%, 16 patients underwent amputation and 25 suffered of bone non-union. Patients with bone defects due to infection were subjected to a higher risk of surgical complications.

Graft harvesting could cause direct complications on donor site that should have been included in induced membrane technique pitfalls[49]. Iliac crest bone harvesting complications include: iliac wing or superior iliac spine fractures and hematoma (higher if the harvesting is on the anterior iliac crest) and infection. It can also cause long-lasting donor site pain, vessels and nerves injuries and a cosmetically unaccepted scar[50]. RIA technique carried out in lower limb long bones of 233 patients, shows a 6% complications rate while, on 6449 patients with iliac crest harvesting, the complications rate was 19.37%[51]. Donor site complications of RIA procedure include complete fractures or anterior cortex lesions, adjacent joint injuries, heterotopic ossifications, and hypertrophic scars. Moreover, it should be avoided to pack tightly the harvested bone filling the bone defect because it could promote graft necrosis[19].

Conclusions

The induced membrane technique offers a successful possibility to solve long bones infected defects[49]. Although some technical and biological features of the induced membrane concept remain fundamental, a wide spectrum of possibilities to modify and improve the single steps of the procedure is ongoing. Our survey identified 4 areas of investigation and trial: the mechanical possibilities to increase new bone formation modifying the surgical technique, the various surgical methods to harvest and shape the autograft, the role of the spacer and its composition options and the different available bone substitutes.

The study results are limited by the not systematic nature of the review analysis.

Conflict of Interests

The Authors declare that they have no conflict of interest.

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