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Review

Induced membrane technique: Advances in the management of bone defects

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HIGHLIGHTS

- Induced membrane technique has initiated the new era for management of bone defects.
- Remarkable advances have been made in radical debridement, placement of cement spacer, limb stabilization, and bone grafting.
- Seeking ideal spacer material and graft substitutes, and improvement of fixation method will be the focus of future research.

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ABSTRACT

Management of bone defects caused by trauma, osteomyelitis, and tumors is challenging, with many controversies over the optimal reconstruction method. Masquelet discovered induced membrane in management of large diaphyseal defects accidentally, and developed this technique with a concept of induced membrane. Induced membrane technique holds great potential for the reconstruction of bone defects, alternatively to manage this clinical challenge quiet easily. Induced membrane has unique structural characteristics and biological properties, which render this technique has an advantage of the time to bone healing is relatively independent of the length of bone defect. Herein, we reviewed the latest advances made in induced membrane technique and highlighted the concept of induced membrane in the management of bone defects.

1. Introduction

The induced membrane was accidentally discovered in 1986 by Masquelet [1], in a study of series of 35 cases of large diaphyseal defects which were treated with a two-stage technique [2]. Cement spacers were used to fill bone defect, and the induced biologic membrane around the cement spacer was initially maintained only to avoid excessive bleeding [3]. However, subsequently it was found that the pseudosynovial membrane induced by the cement spacer help avoiding the resorption of the graft while promoting its vascularity and corticalisation simultaneously [2]. With the discovery of structural characteristics along with biological properties of induced membrane [3,4], the role of membrane was gradually studied in animal models [5–7]. In 2010, Masquelet firstly developed the concept of induced membrane and asserted that induced membrane acts as a biological chamber opening new perspectives [3].

2. The characteristics of induced membrane

2.1. Structural characteristics

The membrane consisted of epithelial-like cells, fibroblasts, myofibroblasts, and type I collagen [4,8] as confirmed by histologic and immunochemical analyses. It is richly vascularized in all its layers, and blood vessels are pointing to the orientation of bone defect [5,7]. The inner part of the membrane is epithelial-like cell, the outer part is made of fibroblasts, myofibroblasts, and collagen

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bundles [3,4]. Induced membrane has certain mechanical strength, and form a closed biological chamber after cement removed, which maintained the volume of bone graft, decrease resorption of the cancellous and prevent ingrowth of soft-tissue [3,5,6,8]. Different cement and various supplemental antibiotics had a significant effect on assembly of induced membrane [9].

2.2. Biological properties

Analysis of membrane proteins suggested that the membrane contains vascular endothelial growth factor (VEGF) [3,4,10–12], transforming growth factor-β1(TGF-β1) [4,12], and BMP-2 [4,10–12]. However, expression of VEGF [4,10] and BMP-2 [4,10,12] decreased in membranes after one month post-implantation of the cement spacer [10]. Co-existence of VEGF and BMP-2 can affect osteogenesis [13,14] by promoting bone marrow stem cell homing and differentiation [15]. TGF-β1 can mediate the expression of VEGF [16], and these two growth factors together play a significant role in angiogenesis [17].

Pelissier's study showed that induced membranes facilitated human bone marrow stromal cell differentiation to the osteoblastic lineage [4]. Molecular analyses of expanded cells from induced membrane has revealed a broadly but similar RNA profile to BM-MSCs with respect to osteoprogenitor and chondroprogenitor transcripts [11]. Furthermore, core-binding factor α-1 (Cbfα1), a critical transcription factor that favors the osteoblast differentiation of MSCs [18], have been found in the fibroblast within the membrane [5,19]. It demonstrated that the induced membrane might have the characteristics of inherent osteogenesis.

In some animal models, the bone defect was not filled with bone graft after removal of spacer, additional bone formation was found on the inner side surface of the membrane [7,8]. Aho et al. found new osteogenesis calcification area within histological sections of induced membranes [10], and these more confirmed that the induced membrane might have in situ osteogenic properties.

2.3. Induced-periosteum and biomimetic induced membrane

There are certain similarities between the induced membrane and periosteum in terms of biological properties [20]. Recently studies has revealed that induced membrane is a thick, vascularized structure that resembles periosteum with a cellular composition and molecular profile which facilitating large defect repair and therefore may be described as an “induced-periosteum” [11]. A synthetic biomimetic induced membrane, consists of an outer osteogenic layer and an inner pre-vascularized layer, had been developed using cell sheet engineering [21]. In the absence of infection, it has the potential for treatment of bone defects [21]. In addition, Gouron et al. found that osteoclasts and their precursors were also present in the induced membrane [22]. Osteoclasts may take part in bone reconstruction. As a specialized tissue, induced membrane provides favorable local environment for bone graft osteointegration, and have implications for the tissue engineering [6,8].

3. Management of bone defects with induced membrane technique

3.1. Radical debridement

Radical debridement is critical in the first stage, especially for infected bone defect, such as septic nonunion, osteomyelitis. Osteomyelitis is a biofilm inflammation [23,24], and the mature bacterial biofilm can resist host immunity [23] and antibiotics [25,26]. Other factors, such as bacterial internalization [23,27], small clony variants [28,29], local existence of sequestrum and foreign body, all possibly cause the debridement failure. Conservative debridement [30,31] and repeated usage of negative pressure drainage [24] are major reasons for high recurrence rates. Only radical debridement and removing all lesions, which save the bacterial biofilm, such as implants, sequestrum, scars, granulation, and non-vital tissues, can heal wounds. Similarly it was advocated aggressive surgical debridement and suggested that infected bone should be surgically treated as a malignancy [32] (Fig. 1). In case of intramedullary infection, the canal should be reamed and irrigated [33].

3.2. Placement of cement spacer

Bone defect must be managed following radical debridement. Masquelet [2] inserted cement spacer into the defect just to avoid the collapse of the soft tissue into the bone defect [3]. But they subsequently found that the cement played mainly biological role, by inducing a foreign body surrounding the membrane [3]. Most researchers suggested that the cement should be placed over the edges of the bone and avoid nonunion of docking site [1,3,33–36].

Initially, no antibiotics added to the cement to avoid masking inadequate debridement [2]. Schottle et al. firstly filled the bone defect (biological chamber) with a gentamycin-impregnated cement spacer for local depot delivery in the management of infected nonunion [37]. Local depot delivery of antibiotics raised the level of antibiotic concentration multi-fold than the bacterial minimal inhibition concentration. At the same time, does not led to any increase in the level of antibiotic concentration in the blood, and significantly reduce the systemic side effects [38]. With the increase of the concentration of antibiotics in bone cement, the elution mass and rate of antibiotics are associated with increment over time [39]. Hsieh et al. recommended that the quantity of antibiotics is less than a threshold of 8 g per 40 g of cement [40], or otherwise, the cement mechanical characteristics would be altered. The elution rate of the antibiotics are not significantly influenced by surface area and volume of cement [39]. For this purpose commonly used antibiotics include gentamycin, tobramycin, and vancomycin. Recently it was reported that different cement and various supplemental antibiotics had a significant effect on assembly of induced membrane [9].

Not only the concentration of antibiotics, but also mixing method and the type of bone cement all may affect the elution of antibiotic-impregnated cement. Meyer and co-workers found that vacuum-mixing had significantly product-specific effect on antibiotic elution features of bone cements [41]. Traditionally, cement and antibiotics are mixed by hand in surgical procedure, and then liquid monomer is added. Amin along with his colleagues reported a new method, where they used mixture of cement and liquid monomer with delayed antibiotic addition, which can increase antibiotic elution compared with the traditional method [42]. Although improving the plasticity of antibiotic-impregnated cement, increase the amount of liquid monomer in the mixture could lessen antibiotic elution from bone cement [42].

After the bone canal was reamed and irrigated, placement of antibiotic-impregnated cement rods/nails is a useful method to the antibiotic treatment for some patients suffering intramedullary infection (Fig. 2). Chest tube is the common mould for fabricating antibiotic rods/nails intraoperation [43–45]. However, it is very difficult to remove the chest tube from antibiotic rod/nail. Cooling the antibiotic-impregnated cement rod/nail in cold water and prelubrication of the chest tube with mineral oil would make the fabrication of antibiotic-impregnated cement rod/nail as convenient and practical [46,47].