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The potential roles of nanobiomaterials in distraction osteogenesis

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Abstract

Distraction osteogenesis (DO) technique is used worldwide to treat many orthopedic conditions. Although successful, one limitation of this technique is the extended period of fixators until the bone is consolidated. The application of growth factors (GFs) is one promising approach to accelerate bone regeneration during DO. Despite promising in vivo results, its use is still limited in the clinic. This is secondary to inherent limitations of these GFs. Therefore, a development of delivery systems that allow sustained sequential release is necessary. Nanoparticles and nanocomposites have prevailing properties that can overcome the limitations of the current delivery systems. In addition, their use can overcome the current challenges associated with the insufficient mechanical properties of scaffolds and suboptimal osteogenic differentiation of transplanted cells in the distraction gap. We discuss the clinical implications, and potential early applications of the nanoparticles and nanocomposites for developing new treatments to accelerate bone regeneration in DO.

From the Clinical Editor: This comprehensive review discusses the clinical implications, and potential early applications of nanoparticles and nanocomposites in the development of new treatments to accelerate bone regeneration in distraction osteogenesis.

Key words: Nanoparticles; Nanotechnology; Nanobiomaterials; Distraction osteogenesis; Bone regeneration; Bone healing; Delivery system

Nanotechnology implies the science of manipulation of single or groups of atoms at nanometeric scale.[1] The reduction of size in the biomedical materials to a nanometer scale modifies their chemical, physical and biological proprieties, resulting in new wide diversity of applications. In fact, this technology has induced a revolution in several fields of science. Although its use has shown promising results in various bone tissue engineering applications, its potential role in the context of distraction osteogenesis (DO) remains unclear. The aim of this article is to review and discuss the potential applications of nanobiomaterials to address current issues related to DO and to improve the outcome of this procedure.

Distraction osteogenesis

Distraction osteogenesis and its clinical value

Bone possesses an intrinsic capacity to heal spontaneously following injury. Nevertheless, this capacity cannot be achieved beyond a certain critical size defect and therefore an exogenous intervention is required. Several procedures are currently available to manage these large defects including the gold standard autogenous bone grafts, allografts and vascularized fibular bone grafts. In addition to the huge financial cost, these procedures have other limitations in cases of severe bone loss or when large segments of bone need to be lengthened.[2-5] DO is considered a valuable alternative in such instances. DO technique is a controlled surgical procedure that has the ability to achieve spontaneous bone regeneration by means of mechanical forces to stimulate the endogenous biological

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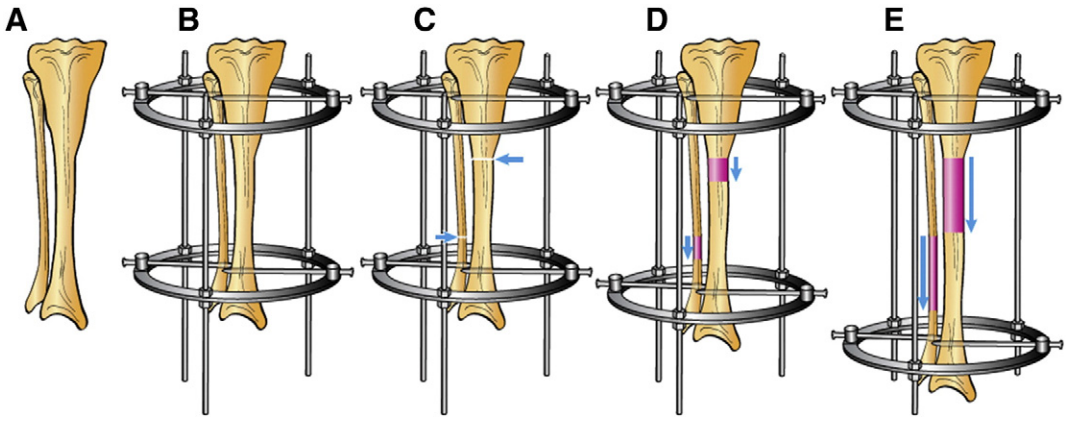

Figure 1. Description of distraction osteogenesis technique. **(A)** Showing the tibial bone that need to be lengthened. **(B)** Application of external fixator at the proximal and distal end. **(C)** Tibial and fibular osteomty. **(D)** Distraction phase. Note the new bone formation in the distraction gap **(E)** consolidation phase.

response.[6] The technique is performed as follows: the proximal and distal ends of the bone are immobilized and typically fixed by using an external fixator device followed by a low energy osteotomy to divide the bone in two segments (proximal and distal). Then, a latency phase of 5-10 days is required to allow for the hematoma formation. Subsequently, the distraction phase is initiated in which the two-bone segments are gradually distracted at specific rhythm and rate until the desired lengthening is obtained. The consolidation phase follows in which the distraction is ceased and the two-bone segments are held in place until the new bone in the distraction gap is completely consolidated. Each one centimeter of lengthening typically requires one month period of consolidation (Figure 1).[7] The external fixator can be removed once sufficient consolidation of bone is obtained.

Three modes of ossifications occur in DO. These include endochondral bone formation which dominates the early stages of DO and typically occurs external to the periosteum, intramembranous ossification which is the predominant mechanism of ossification, mainly in the late stages of DO and occurs internal to the periosteum at the proximal and distal edges of the callus. The third mode is transchondroid bone formation in which chondroid bone is formed directly by chondrocyte like cells, with gradual transition from fibrous tissue to bone.[6]

During the latency phase, immediately after osteotomy, an intense local inflammatory reaction eliciting secretion of cytokines (interleukin-1, interleukin-6), growth factors [transforming growth factor-β (TGF-β), bone morphogenetic proteins (BMPs), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), insulin growth factor (IGF) and vascular endothelial growth factor (VEGF)] and activation of Wnt signaling pathway.[6,8] This enables local deployment, differentiation and proliferation of mesenchymal cells, fibroblasts, and osteoprogenitors as well as fibrin/collagen matrix edification and capillary invasion. The osteogenic potential of these pathways is achieved by inducing the expression of bone-specific genes (e.g. Runx2, Osterix).[9] Differentiation of osteoblast is associated with an increased expression of type 1 collagen and alkaline phosphatase. Osteocalcin is also increased during matrix deposition and mineralization. Once these are achieved, a soft callus between (endosteal) and around the osteotomy bone ends (periosteal) is formed.

During distraction phase, the incipient callus is subjected to tensile stresses meant to facilitate bone regeneration in the distraction gap. The mesenchymal stem cells that migrated and proliferated into the callus differentiate initially into fibroblastlike cells. They adopt a well-defined orientation, parallel with the vector of distraction, as do their secreted collagen fibers[7] (Figure 2). As distraction progresses, the osteoblasts appear along the periosteum and in the gap area. There is increased blood flow, neovascular proliferation and ongoing up-regulation of growth factors pathways, Wnt signaling pathway and matrix proteins.[8,10] The physical forces are converted into biochemical signals which are then integrated into cellular responses via mechanotransduction. This is responsible for maintaining the dynamic balance between bone formation and bone resorption. From a mechano-modulation standpoint, the bone tissue is described as an extensively connected cellular network where the osteocytes constitute the sensory cells and the osteoblasts and the osteoclasts serve as the effector cells. Loads applied to the entire bone are related to the flow past the osteocytic processes in their canaliculi. The osteocytes can sense the flow of fluid and then produce signaling molecules that regulate osteoblast-mediated bone formation and osteoclast-mediated bone resorption. Formation of a good regenerate that is robust enough to sustain physiological loadings requires accuracy in surgical technique, and distraction rate, rhythm and duration.[11,12]

Since its introduction by Ilizarov in early 1950s, DO technique has been utilized worldwide to treat many complex orthopedic and craniofacial conditions with satisfactory outcomes. These conditions include nonunions, congenital and acquired longitudinal bone deficiencies, and severe bone loss secondary to infections and bone tumors.[13] DO can treat large bone defects using the bone transport technique (Figure 3). In fact, the magnitude of this problem is massive as approximately 150,000 large bone defects are sustained in United States annually secondary to trauma.[14] DO is considered the best in vivo tissue engineering techniques as it has the ability to achieve spontaneous formation of de novo native bone without the need for bone grafts. In addition, DO has the unique ability to regenerate both bone and soft tissues (e.g. vessels, nerves and