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Update distraction osteogenesis/histogenesis

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Abstract : Distraction osteogenesis (DO) techniques have been developed in orthopaedics with outstanding clinical outcomes. This review discusses recent advances in understanding the basic biological mechanisms of DO, methods of assessing and promoting bone consolidation in DO and new clinical applications of DO. Mechanical stimulation is known to regulate many genes in skeletal tissues. The changing patterns of BMPs expression, cell proliferation, angiogenesis and apoptosis regulate bone regeneration in DO. High magnitude strain promotes bone remodelling, whereas low magnitude stain stimulates angiogenesis and bone formation. For clinical assessment, plain radiography is the most common imaging technique, followed by ultrasound, mechanical testing, DEXA and QCT. For promoting bone consolidation during DO, minimally invasive interventions are preferable, such as weight-bearing exercise, ultrasound, and electromagnetic stimulation ; whereas systemic administration of anabolic agents and hormones may also be employed and local application of growth factors such as BMPs and other growth factors, peptides remains the last resort. New applications of DO have been extended into treating difficult vascular diseases, cosmetic lengthening, spinal deformities. Through studying DO technique we realise body's self-repair and self-regeneration potentials and its principles and new clinical applications are to be extended to functional tissue engineering in many different systems and disciplines.

Introduction

Distraction osteogenesis (DO) techniques have been developed over the last 50 years and is now widely accepted and practiced in orthopaedics, traumatology, and craniofacial surgery. Using DO methods, many previously untreatable conditions have been successfully managed with outstanding clinical outcomes[1)~8)]. Although the biological mechanisms of DO are still not yet fully defined, it is generally accepted that mechanical stimulation is the key in promoting and maintaining tissues' regenerating capacities. This review discusses recent advances in understanding the basic biological mechanisms of DO, new methods of assessing and promoting bone consolidation during DO treatments and its potential new clinical applications.

Biological mechanisms of DO

Many genes have been found being up- or down-regulated in the bone cells responding to mechanical stimulation[9)]. Mechanical stimulation is the single, most important factor that can

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trigger changes in gene expression and lead to cell proliferation, angiogenesis, cell death and tissue formation and remodelling. For instance, the nuclear proto-oncogene c-fos and c-jun were found to be up-regulated at early stages of DO[10], Fos- and Jun-related genes were related to mechanotransduction and embryonic bone development, their strong expressions during DO provide further evidence to support Ilizarov's hypothesis that DO resembles many aspects of embryonic development. Slow dividing tissues such as Schwann cells retain ability to synthesize myelin during gradual nerve elongation[11], suggesting that DO process is indeed a process of histogenesis, where soft tissues such as muscle, ligament, tendon, blood vessels as well as nerve will regenerate in response to mechanical traction. Mechanical signals play an integral role in bone homeostasis. Low magnitude of tensile stain (2-8% equibiaxial strain) in the tissues has anti-inflammatory effects and inhibits proinflammatory gene expression (such as IL-1β, interleukin 1 beta and COX-2, cyclooxygenase-2), whereas tensile stain of high magnitude (15% equibiaxial strain) induces proinflammatory gene expression, rapidly up-regulated COX-2 mRNA expression and PGE_2 (prostaglandin E2) synthesis[12]. Several studies have suggested that growth factor signalling is also involved in the transduction of mechanical stimuli, for example, epidermal growth factor receptor expression is up-regulated in osteoblastic cells under fluid flow[9]. Taken together, these observations reveal an important mechanism that bone resorption may occur in a field experiencing high magnitudes of strain and bone formation results in fields exposed to physiologic or low magnitude of strain. This may also explain the stimulatory effects on bone regeneration/consolidation by weight bearing exercise, pulsed electromagnetic field stimulation, ultrasound and short-wave treatment.

For bone regeneration during DO, bone morphogenic protein (BMP)-2, 4, 5, 6 and 7 are all expressed continuously from the beginning of DO till 2 weeks after the completion of DO[13] suggesting BMP genes are responsible for controlling the balance of bone formation and remodelling during DO. During DO, new bone forms and undergoes rapid remodelling, the localization of apoptotic cells at the different regions of the regenerate, accompanied by the osteoclast activities, suggest that apoptosis is closely related to bone formation and remodelling during DO[14]. It is well documented that DO is a vascular-dependent process. As to the source of bone-forming progenitors during DO, many believe that the periosteum and bone marrow are the main contributors. Poorly preserved periosteum at surgery may indicate slow bone regeneration or poor regenerate quality[15]. With appropriate soft tissue preservation and mechanical stimulations, good quality of bone regeneration usually occurs, even in the bone following chemotherapy[16]. DO stimulate expression of angiogenic factors, such as VEGF (vascular endothelial growth factor) and bFGF (basic fibroblast growth factor) in the newly formed bones[17]. DO results not only in increased local expression of VEGF and its receptors at the site of distraction gaps, but also leads to increased expressions of VEGF and its receptors levels in distant muscle sides[18], suggesting that DO induces systemic responses, such as releasing of growth factors, cytokines, hormones, stem cells that promote healing[19].

Assess bone quality in DO

DO can be a lengthy procedure and the healing

index, the time needed for each centimetre of new bone to form and mature and to maintain its structure after fixator removal, ranges from 20 days to 4-5 months depending on patient age, bone location, total lengthening and surgical managements[3]. Past research has also suggested that long duration of DO treatment can have negative impact upon the physical and psychological well-being of patients, particularly the young person. Recent study in young people with DO treatment has suggested that with proper support and education, (young) patients can tolerate DO treatment without sustained adverse psychological impact[20].

Non-invasive imaging such as plain radiography remains the most cost effective imaging technique to monitor the regenerate[3], but plain x-ray is not reliable to predict bony union or the quality or quantity of the regenerating bone, since an estimated 40% increase in radio-density is needed to visualize a radiological change, and radiographic changes did not correlate to the changes of mechanical stiffness[21]. Supplemental techniques including mechanical testing for bone strength and stiffness, DEXA (dual-energy x-ray absorptiometry) for bone mineral density, QCT (quantitative computerized tomography) for density and cortical continuity, ultrasound for cyst detection and Doppler or angiography for local blood flow and vascularity have all been used clinically. Among them, ultrasound is a useful and accurate method to evaluate bone cyst in DO[22][23]. Ultrasound examination does not produce metal artefact and radiation exposure and the cost is low, but the facilities for ultrasound follow-up must be developed with an experienced radiologist and it is only recommended where this possibility exists[23]. The mechanical stiffness does not always correlate with the plain radiographic and ultrasound data[21], even when radiographic consolidation of the distraction regenerate is observed, the literature recommends waiting for 2 extra months before removing the external fixation[24], hence the clinical decision of fixator removal has to be made on case by case basis by experienced clinicians.

Promote bone consolidation in DO

Although DO has revolutionized the treatment of many orthopaedic disorders, one of the problems of this technique is the long waiting period for newly formed bone to consolidate, which can cause considerable morbidity to the patients, such as pin-track infection, delayed consolidation and discomfort caused by the bulky frame[24]. Various approaches have been tested to enhance bone formation during DO, these are summarised in Table 1.

Mechanical stimulation by controlled weight-bearing exercises promotes bone consolidation by stimulating angiogenesis, the newly formed vessels in the periosteal region are more sensitive to mechanical stimulation than the endosteal vessels[25]. This again suggests the importance of periosteum preservation and postoperative physiotherapy managements. Pulsed electromagnetic field stimulation may be a safe and cost-effective way of promoting bone consolidation in DO, since electromagnetic field stimulation increases callus formation but does not affect the callus remodelling phase[26], and electromagnetic stimulation can reduce the latency period, from 7-10 days to 1 day, following osteotomy without compromising overall bone regeneration of DO[27].

Some studies suggest that early conversion from external to internal fixation may be an alternative for reducing complications of DO[24] or using lengthening over the nail technique[28].

Table 1. Factors Promote Bone Consolidation in Distraction Osteogenesis

Mechanical
● Weight-bearing (mechanical compression)
● Ultrasound (low velocity)
● Electromagnetic field stimulation
● Electrical currents stimulation
● Short-waves treatment
Biomaterials/Cells
● Calcium sulfate
● Tri-calcium phosphates
● Autologous bone grafts and allografts
● Chitosan and other biopolymers
● Osteoblastic cells
● Bone marrow extracts
● Platelets
Hormones/Anabolic and Antiresorptive Agents
● Growth Hormone
● PTH
● PGE_2 receptor modulator
● Bisphosphonates/Zoledronic acid
Biomolecules/Growth Factors
● BMP-2/BMP-4
● BMP-7/OP-1
● VEGF
● FGF-2
● TGF-β
● Thrombin-related peptide
● Others

After the lengthening is achieved by external fixator, fixator can be removed and the limbs supported with interlocked intramedullary nails, this will reduced the complications of re-fracture and infection following DO treatment.

Systemic administration of anabolic agents and hormones to promote bone regeneration is an appealing strategy. Growth hormone has shown to promote early bone consolidation when given a daily subcutaneous injection of 1 IU/kg in a dog DO model[29], and bone mechanical strength increased 3 times in the growth hormone group than in the control group. Prostaglandins are anabolic agents *in vitro*, but they can not be used *in vivo* due to its gut-intestinal side effects[30]. Recent study into the PGE_2 receptor, such as EP2 receptor-selective agonist, may lead to a new class of anabolic agents that can be administrated locally and systemically to stimulate osteogenesis, fracture healing and DO[31]. Antiresorptive agents such as bisphosphonate have been reported to have positive effect on fracture healing. A recent study showed that in a rabbit model of leg-lengthening, systemic administration of zoledronic acid (0.1 mg/kg) once or twice increased distraction regenerate volume, mineralization and strength[32], suggesting bisphosphonate may have anabolic effect in addition to its antiresorptive effects. However, a dose-related negative effect of zoledronic acid on the longitudinal growth of young rabbits has been noted[32] ; therefore, it may not be safe to give bisphosphonates such as zoledronic acid to children undergoing DO treatment.

Local application of growth factors such as FGF-2, BMP-2 and other biological agents to promote fracture healing and spine fusion has become an accepted clinical alternative. In a rabbit DO model with rapid rate of lengthening (2 mm/day), single application of rhBMP-2 (75 μg) by injection or implantation at the end of distraction period has significantly enhanced bone maturation and bone consolidation[33]. In the similar rabbit model of DO, a single injection of 300 μg thrombin-related peptide (TP508) has also shown to promote bone consolidation and the effects were more potent when the TP508 was delivered in slow-released form[34][35]. Since DO is a vascular-dependent process, the angiogenic factors may also have positive effects on bone regeneration during DO. It has been reported that infusion of FGF-2 into the distraction gap in rabbit has significantly promoted bone consolidation[36]. In summary, additional growth factors may enhance bone regeneration and consolidation in conditions where bone argumen-