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Biological basis of distraction osteogenesis – A review

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ABSTRACT

Objective: Slow but sure bone lengthening using distraction osteogenesis principles is the gold standard for the treatment of hypoplastic facial bones, though the time required for the treatment is a major drawback of this procedure. The objective of this study is to review the contemporary literature and recapitulate the cellular and molecular events occurring during membranous craniofacial distraction osteogenesis.

Results: Mechanical encouragement by distraction provokes a biological comeback of skeletal renaissance that is accomplished by a cascade of biological processes which include delineation of pluripotent tissue, angiogenesis, osteogenesis, mineralization, and remodeling. Immediately after the osteotomy, hematoma formation and accumulation of inflammatory infiltrates take place which closely resemble as in any standard osteotomy or in fracture. Most authors observed that the levels of proinflammatory cytokines IL-1 and IL-6 are increased which further induce osteoclastic activity and may verify the 'Coupling Phenomena' between bone development and resorption and also there is marked increase in the level of transforming growth factor-beta 1 (TGF-β1) mRNA. These findings suggest that there is a regulatory mechanism for TGF-β1 in induction of collagen deposition and non-collagenous extracellular matrix proteins involved in mineralization and remodeling of bones. Furthermore, physical factors along with chemical factors also influence the outcome of distraction osteogenesis.

Conclusion: Knowing the molecular mechanism helps in the development of targeted strategies intended to improve distraction osteogenesis and speed up bone renaissance that may lead to shorten the treatment time and helps craniofacial surgeons in understanding about various factors affecting the distraction process at different stages.

Contents

☆ Asian AOMS: Asian Association of Oral and Maxillofacial Surgeons; ASOMP: Asian Society of Oral and Maxillofacial Pathology; JSOP: Japanese Society of Oral Pathology; JSOMS: Japanese Society of Oral and Maxillofacial Surgeons; JSOM: Japanese Society of Oral Medicine; JAMI: Japanese Academy of Maxillofacial Implants.

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1. Introduction

Gradual traction on living tissues creates stress that can stimulate and maintain regeneration and active growth of involved tissues – "Law of Tension Stress" [1,2].

Distraction osteogenesis (DO), also known as callus distraction, callotasis, osteo-distraction, and distraction histogenesis, is a biological process of producing new bone and overlying soft tissue by gradual and controlled traction of the surgically separated bone segments [3]. In other words it can be said that it is a slow and continuous application of a constant force to a created osteotomy gap, resulting in formation of new bone and soft tissues. In distraction as the edges of the osteotomized bones are advanced the overlying soft tissues envelop is also stretched, inducing hyperplasia of the adjacent tissues. According to Karp et al. the gap created by osteotomy is first filled by collagen fibers (type I) which are arranged parallel to the vector of the distraction force [4]. If adequate stability is maintained within the newly formed regenerate there occurs direct ossification of the collage fibers. Another unique feature of distraction osteogenesis (DO) is that the bone and its periosteum act as a guide for new bone formation in a manner that the newly formed bone and soft tissues have the same size and morphology as the native tissues. When adequate bone is formed from the process of distraction, it is held in neutral fixation (i.e. consolidation phase). In this phase of distraction the newly formed regenerate is allowed to ossify completely and during this period patients are encouraged to perform active physical therapy as a result of which newly formed regenerate undergoes functional remodeling process to form a regenerate which resembles native bone and this remodeling is induced by the pull of nearby musculature [5].

Cope and Samchukov in the year 2000 concluded that the increased new bone formation as a result of distraction is because of the stimulatory effect of tension on angiogenesis and on bone forming cells [6]. In addition, distraction osteogenesis is important to scientists as a method to investigate the biologic effects of stress (mechanical stimulation) on tissues in vivo. The importance of mechanical loading in maintaining the bone mass has been long recognized by Amir et al. [7]. When stresses are applied to bone, it will either deposit or resorb in accordance to stresses. This principle is known as "Wolff's Law" [8]. A cascade of biological process is demonstrated to occur in response of mechanical loading during active phase of distraction which includes cellular differentiation, formation of new vascular elements, formation and mineralization of bone matrix and functional bone remodeling [6,9–13].

1.1. *History of distraction osteogenesis*

Codivilla from Italy first reported lengthening procedure by applying skeletal traction following osteotomy of the femur [14]. However, it was a Russian surgeon, Gavriel O. Ilizarov, who pioneered the biological principles of bone and soft tissue regeneration and popularized the technique of distraction osteogenesis, when he discovered that under slow and gradual traction new bone is formed between the osteotomy gaps [1,2]. In 1973, Snyder et al. applied distraction concept to mandible [15]. In 1976, Bell and Epker described the technique of rapid palatal expansion to increase the maxillary width in cases of transverse deficiency [16]. In 1990, Guerrero described an intraoral symphyseal osteotomy for widening of mandible [17]. McCarthy et al. first applied the principle of DO in craniofacial skeleton in lengthening of hypoplastic mandible [18,19]. In 1998, Liou and Huang first reported Periodontal Distraction followed by other authors [20].

1.2. *Review of bone mechanics*

To understand the effects of mechanical loading i.e. stresses on bone, for instance those occurring during distraction osteogenesis (DO), it is important to understand the physiological aspect of bone and the features that allow it to perform in response to mechanical loading. Bone is a complex and extremely specialized supporting structure of the body and it is characterized by its stiffness, rigidity and power of repair and regeneration. According to Taichman bone acts as a pool for calcium homeostasis and growth factors and cytokines and also participates in acid–base regulation [21]. Bone regularly undergoes remodeling throughout the life to overcome the ever-changing biomechanical stresses and to remove old bone and to replace it with new, much stronger bone to preserve the strength. The process of remodeling is affected by several factors like nutrition, disease, and mechanical milieu. These factors can alter the quantity and quality of bone depending upon their severity and duration. For practical purpose, bone can be considered as a hierarchical composite material i.e. bone tissue is composed of inorganic and organic phases and water. Organic material, for example collagen, provides the essential resilience and tensile strength to bone and the inorganic or mineralized matrix provides compressive strength. The inorganic matrix also serves as structural cover for the osteocytes. The osteocytes are most ample bone cells in body and play a role of bone forming osteoblasts before encasing in their own matrix. Osteocytes residing in lenticular cavities are called lacunae. Lacunae are connected to one another by inter-connecting channels called canaliculi. This lacuna–canalicular network is immersed in interstitial fluid and this interstitial fluid provides a medium for exchange of nutrients. This lacuna–canalicular network may also play an important role in transferring mechanical signals [22].

Cowing and Weinbaum believed that osteocytes are able to intensify the mechanosensory response at the cellular level such that minimal loading can maintain bone integrity [23]. Thompson hypothesized that osteocytes could act as a strain gauge and sense mechanical deformity as well as communicate this signal to bone forming osteoblasts, which further synchronize their activity with osteoclasts, possibly by the way of soluble signaling [24]. According to porosity bone can be divided into two types:

1. Cortical (compact) bone: This type of bone has porosity of about 5–10% and surrounds marrow spaces.
2. Cancellous (spongy or trabecular) bone: This type of bone has porosity of about 75–95% and forms bodies of flat and cuboidal bones.

The mechanical performance of bone under stress is governed by its shape, size and material by which it is made of. When bone is subjected to low-velocity trauma, the bone has adequate amount of time to absorb the energy of that trauma ensuing in simple fracture but when bone is subjected to high velocity trauma then there is scarcity of time for bone to absorb the energy of that trauma ensuing in comminuted fracture. So, it is essential to produce a noncomminuted, simple and stable fracture at the site of