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Review

Biomolecular phases in transverse palatal distraction: A review

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ABSTRACT

Transverse palatal distraction is a biological process of regenerating new bone and enveloping soft tissues in the maxillary palate region. This technique is similar to Osteo-distraction (OD) procedure for bone lengthening in which gradual and controlled traction forces are applied on the osteotomy gaps to produce new bone in between the surgically separated bone segments. This review describes the different phases after osteotomy and the biological process involved during the new bone and soft tissue formation. The mechanical environment formed in the distraction area is due to the traction forces by the distractor appliance. This environment stimulates differentiation of pluripotent cells, neovascularization, osteogenesis and remodeling of newly formed bone. The role of different pro-inflammatory cytokines, interleukins, bone morphogenic proteins, transforming growth factors, fibroblast growth factors-2) and extracellular matrix proteins (osteonectin, osteopontin) during the distraction phases has been described in detail. Also, an important note on the nutritional aspect during Osteo-distraction will benefit the clinicians to guide their patients after osteotomy throughout the distraction process.
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Contents

1. Introduction

Transverse palatal distraction is a technique of rapid maxillary expansion to increase the maxillary width in case of transverse palatal deficiency. This is achieved by osteo-distraction technique (OD) which is routinely used for new bone formation by stimulatory effect of tension and stress on bone forming cells (Cope et al., 1999).

Osteo-distraction is a surgical method for regenerating bony deficiencies. The traditional method which involves osteotomies and replacing the osteotomy gaps with bone grafts have resulted in intraoperative morbidity and postoperative regression. These disadvantages have been overcome by Osteo-distraction which does not require bone harvesting from other sites (Marchac and Arnaud, 2012; Perez et al., 2011). Osteo-distraction, also known as distraction osteogenesis, callotasis, and distraction histogenesis, is a process of regenerating new bone and overlying tissue by slow, continuous and controlled application of traction force on a

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surgically fractured bone (Osteotomy). The main advantage of this process is that the newly formed bone and soft tissue is similar to the native tissues. The consolidation phase in this process plays a major role for functional remodeling of the new bone and soft tissues which resembles the native bone and overlying soft tissue (Cope and Samchukov, 2000; Rowe et al., 1999; Choi et al., 2000)

Osteo-distraction is based on two principle laws i.e.; "Wolff's Law" and "Law of Tension Stress". According to Wolff's law, when stresses are applied on bone, it will remodel in accordance to the stresses, whereas, Law of Tension Stress suggests that gradual and constant force application on living tissues creates stress that can regenerate new tissues similar to the native tissues (Amir et al., 2009; Frost, 2004; Li et al., 1997). Snyder et al. (1973), applied the concept of osteo-distraction in mandible. In 1976, Bell and Epker used osteo-distraction technique for transverse palatal distraction in cases of transverse deficiency of maxilla.

The indications of transverse palatal distraction include maxillary deficiency in facial clefts, severe obstructive sleep apnea, hypoplastic maxilla and complex trauma. There is no relative contraindication for distraction as far as adequate bone is present where the distraction device is placed. However, patient compliance is pivotal for success of distraction procedures (Rachmiel et al., 2005, 2006, 2012; Polley and Figueroa, 1999).

A retrospective study by Ernst and Adolphs (2016), has discussed the clinical application of TPD for the correction of transverse maxillary deficiency in 109 cases, out of which 94 were predominantly bone-borne and other (n = 15) cases consisted of tooth-borne orthodontic expansion appliances (Hyrax screws). In the TPD group, failure of the procedure was observed in only one mentally retarded patient with relevant infection of the alveolar crest. Adolphs et al. (2015) have also demonstrated clinically successful application of TPD in a group of pediatric patients (n = 8) resulting in correction of transverse maxillary deficiency before skeletal maturity.

The distraction procedure includes several days of latency period followed by several weeks for active lengthening, and several months of consolidation phase till mature lamellar bone is formed for good prognosis (Aizenbud et al., 2008; Forriol et al., 1999). This gradual distraction by mechanical stimulation initiates biological responses for skeletal remodeling that includes differentiation of pluripotent tissue, angiogenesis, osteogenesis, mineralization and regeneration (Rachmiel and Leiser, 2014). The purpose of this review is to summarize the cascade of biological processes during the different phases of OD. The knowledge of this biomolecular mechanism helps the practitioners to improve the clinical results with bone quality and quantity. Understanding the biological aspect during different phases of OD may guide the development of new techniques to shorten the consolidation time with limited relapse.

1.1. Bio-mechanical aspect of TPD

According to Karp et al., (1992), the healing after distraction differs from normal fracture healing in two ways;

a. In OD membranous ossification occurs compared to endochondral ossification seen in regular fracture healing
b. In OD controlled micro trauma is done to create osteotomy gaps

There are five cascades of events that occur in OD, with differing biological processes in each phase:

a. Osteotomy
b. Latency phase
c. Distraction Phase
d. Consolidation phase
e. Remodeling phase (Singh et al., 2016)

1.2. Osteotomy phase

During this phase controlled micro trauma is done without damaging the enveloping soft tissues, followed by fixation of distractor device which will produce tension and stress on the bone resulting in new bone formation.

1.3. Latency phase

This phase lasts from 1 to 7 days depending on the severity of trauma on bone, during which the initial inflammatory response can be observed. There is formation of periosteal and endosteal callus, which consists of inflammatory cells, fibroblasts, fibrin matrix, and collagen. The lack of oxygen (hypoxia) in the zone of injury stimulates an angiogenic response which result in migration of undifferentiated mesenchymal cells and synthesis of collagen type I matrix (McCarthy, 2007). The mechanical environment created by distraction forces leads to a marked raise in the levels of cytokines interleukin (IL)–1 and IL–6, BMP-2, 4, 6 which leads to inflammation followed by ossification (Waanders et al., 1998; Jazrawi et al., 1998; Sato et al., 1998; Rachmiel et al., 2004).

1.4. Distraction period

During this phase the tension is applied on the osteotomy gap in the bone, resulting in new immature woven bone and consists of fibro-vascular matrix in which fibers are aligned parallel to the force of distraction. Histologic studies on these distraction area of bone shows five zones (Rachmiel et al., 2002).

- Zone of mesenchymal proliferation.
- Two transitional zones – consists of osteoid formation with collagen bundles.
- Two remodeling zones – consists of osteoclasts with remodeling.

Also recently it has been established that four transitional areas are present between these zones. However, it is still not clear that which of these five zones or four areas undergo tensile strain in response to distraction forces (Yu et al., 2004).

The first evidence of active calcifications starts after three weeks leading to formation of bony spicules that extends from the edges of osteotomy gaps towards the central distraction zone. The collagen bundle present in the distraction gap mainly consists type I fibers which supports the theory that tension and stress induces intra-membranous ossification (McCarthy, 2007). According to Fang et al. (2005), there is 10 times increase in angiogenesis compared to normal healing of bone. This increase in blood supply leads to differentiation of chondroblasts and osteoblasts resulting in new bone formation. The results of this study concluded that mechanical environment due to distraction forces creates an environment favorable for angiogenesis by triggering a stress sensitive gene. Immobilization of the bone fragments during the activation and consolidation phase is mandatory for new bone formation (Illizarov, 1989a, 1989b).

The up-regulation of IL-6 during this phase promotes intramembranous ossification and the cartilaginous bone formed during Latency phase is resorbed due to the high ratio of RANK ligand/OPG (osteoprotegerin). Angiogenesis in this phase is increased by the induction of VEGF and angiopoietin (Cho et al., 2007; Wang et al., 2005).

Hypoxic environment as discussed earlier in latency period creates challenges for the survival of bone forming cells during dis-

traction phase; also leading to a complex mechanism of angiogenesis and bone remodeling. According to Blengio et al. (2013), due to hypoxic microenvironment in the distraction site there is inflammation followed by up-regulation of osteopontin, vascular endothelial growth factor (VEGF), and IL-1. This microenvironment promotes cell differentiation, angiogenesis and osteogenesis.

BMPs (Bone Morphogenic Protein) play an important role in regeneration of new bone and maintenance. BMPs have been isolated from demineralized bone matrix in different mammalian species. 42–45 BMPs act on the pluripotent mesenchymal cells at the distraction site and have an important role in recruitment, proliferation and differentiation. BMPs also stimulate the production of other growth factors like TGF-β, FGFs, and IGFs. During the distraction phase, the tension produced by distraction appliance leads to expression of BMP-2 and BMP-4. This has been proved by different studies which concluded that the expression of BMP-2 and BMP-4 gradually decreased after the distraction was terminated (Marukawa et al., 2006; Rauch et al., 2000; Yazawa et al., 2003). TGF-β expression decreases in distraction phase as compared to latency phase. TGF-β was described to be a suppressor of osteoblast maturation by delaying mesenchymal differentiation during distraction stage. Other morphogens and growth factors such as IGF-1 and basic FGF (bFGF) are up-regulated during distraction phase (Lammens et al., 1998; Wang et al., 2009; Liu et al., 2008).

The role of angiogenic factors during distraction forces should not be undermined due to the increased blood flow at the osteotomy site. The expression of VEGF-A, neuropilin-1 and angiopoietin-2 induces neovascularization to the osteoblasts at the mineralizing front and also supply the osteoclasts. It has been demonstrated that increase in VEGF-A and angiopoietin-1 expression is directly related to up-regulation of factor-1α at the distraction site. An optimal neovascularization at the distraction site is directly related to rate of new bone formation at the osteotomy site (Aronson et al., 1994; Carvalho et al., 2004; Pacicca, et al., 2003; He et al., 2008; Meyers et al., 2001).

1.5. Consolidation period (neutron-fixation)

This period in craniofacial distraction starts after 6 weeks and lasts for 12 weeks. During this period, mineralization of newly formed regenerate occurs. There are various factors such as BMP, platelet-rich plasma that help in new bone formation during this final stage (Singh et al., 2016).

BMPs role in new bone formation has been discussed in distraction phase, based on these findings exogenous BMP-2 has been used successfully to shorten time for new bone regeneration in osteo-distraction (Yonezawa et al., 2006; Rachmiel et al., 2004).

Platelet-rich plasma (PRP) consists of growth factors and antimicrobial properties which promote new bone regeneration during consolidation phase. Due to these properties of PRP it has been demonstrated that injection of a combination of PRP with either bone marrow cells or mesenchymal cells into the osteotomy site enhances bone healing and shortens the consolidation phase (Griffin et al., 2009; Kanthan et al., 2011; Tsay et al., 2005; Drago et al., 2013).

1.6. Role of nutrition in Osteo-distraction of palate

The regeneration of new bone and soft tissues requires increased nutritional needs and a lot of energy, similar to any fracture healing process, which is delivered by nutritional food intake. The osteo-distraction process mainly depends on amino acids intake and relative blood supply to the distraction site. The reduced blood flow due to reasons like smoking, sedentary lifestyle will delay the process of healing. The oxidative stress created by biochemical eruption of pro-oxidants results in increased demand for anti-oxidants. Oxidative stress can occur due to imbalance between free radicals and antioxidants mechanism resulting in negative effect on macromolecules and cellular functions (Byun et al., 2005). This oxidative stress can be reduced by dietary intake of antioxidants. Dietary anitoxidants like polyphenols, lycopene and carotenoids, are important in bone remodeling, reduce the risk of fracture and increase bone formation (Tanumihardjo, 2013). The dietary supplements of Vitamin C have been shown to accelerate fracture healing in an animal model. Essential trace elements such as zinc play an important role in differentiation of osteoblastic and osteoclastic cells (Hsieh and Navia, 1980). Zinc supplementation is absolutely necessary during bone healing because it increases alkaline phosphatase activity and increases osteocalcin production. Calcium is an integral component in the bone remodeling, growth and bone mineral density maintenance (Sheweita and Koshhal, 2007). Therefore, dietary calcium supply should be enhanced during bone healing and dairy products are the best source of calcium. Intake of most of the dietary items like vegetables, meat, fruits has a considerable impact on bone metabolism, promote osteoblastogenesis, inhibit osteoclastogenesis and inhibit inflammatory condition. A personalized nutritional program could accelerate the distraction phase in OD, resulting in good prognosis and a successful treatment (Giganti et al., 2014).

2. Conclusion

Distraction osteogenesis is an effective method that has replaced conventional surgical procedures, which provides an excellent method of new bone formation. Understanding the biological aspect of distraction motivates the clinicians to develop methods to shorten the distraction and consolidation phase during the period when distraction forces are applied. The nutritional aspect during bone healing process should not be underestimated; and advising the patients about the importance of nutrition during healing process will result in good prognosis of patients undergoing osteo-distraction.

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