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Distraction Osteogenesis: clinical applications and biologic principles for Orthodontics and Dentofacial Orthopaedics

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Abstract
Dentofacial Distraction Osteogenesis is the gradual and incremental traction force/ tension to surgically separated bony segments of the stomatognathic system to produce additional bone with regeneration of attendant soft tissue. Distraction Osteogenesis/Histogenesis is a primary example of surgically induced tissue engineering. The distraction causes a cascade of biological factors to generate tissue(bone and soft tissue). It has become a substitute for current techniques of bone grafting and alloplastic materials in Dentofacial surgery. The principles of distraction osteogenesis can be simplified into 4 periods: 1. Creation of a distraction zone;2. Latency period;3. Activation period; 4. Consolidation period. The primary purpose of these principles is to shift the bony segment into the defect with regeneration of hard and soft tissues around the space of transported segment. There are 3 common types of distraction osteogenesis: unifocal, bifocal and trifocal depending upon number and direction of distraction devices employed and number of transport segments created. The process by which mechanical forces are converted to cellular signals is termed mechanical transduction. Through the conversion of mechanical (tension stress) signals to biological cascades, the DH method can activate a number of regulatory processes and restart the vigorous regenerating capacity of musculoskeletal tissues. The molecular mechanisms of DH are still expanding as a result of new technologies like next-generation sequencing, proteomics, and metabolomics, despite the fact that, any research have concentrated on them and the surgical concepts of DH have been better defined and perfected. This article explores types, histological stages, cellular and molecular mechanisms & indications.

Keywords: Distraction osteogenesis, dentofacial orthopaedics, orthodontics, tissue engineering, bone regenerate, mechanotransduction, cellular mechanisms

Introduction
Intraoral Distraction Osteogenesis (DO) Callus Distraction/Distraction Histogenesis (DH) is an orthopaedic/surgical procedure used to lengthen or reshape bones and consequently adjacent soft tissues of the stomatognathic system, through controlled traction of separated bone segments with generation of new bone and adjacent soft tissue. The primary biologic concepts of osteogenesis and histogenesis are at the core of these procedures. It is often used to correct abnormalities or defects in the jaw or other facial bones that may affect the function or appearance of the face [1, 2].

Distraction Osteogenesis has a history dating back to Hippocrates, Codivilla (1905) and Gravril A Illizorov (limb lengthening) [3, 4]. Distraction osteogenesis was first applied to the human mandible in 1992 by McCarthy *et al.* [1, 5] In 2001, Liou and Huang [6, 7] first applied DO to orthodontic treatment in 1998 using a technique called " Dental distraction" to rapidly retract canines. Iseri *et al*. and kisnisci *et al*. later developed a different technique called "dentoalveolar distraction" for rapid canine distalization using osteotomies [8, 9]. Intraoral DO can be an effective treatment for a variety of conditions, including both congenital and acquired abnormalities of jaw, midface, zygomatic bones and calvarium, condylar reconstruction in temporomandibular joint ankylosis, facial injuries including non-healing fractures, Cystic and oncologist jaw deformities and issues resulting from previous surgery.

Cases of syndromic (Pierre-Robin, Godenhar, Treacher Collins, Facial Clefts, alveolar clefts, cranial microsomia**)** or calvarial, fronto-orbital complex hypoplasias and non-syndromic bimaxillary shortening e.g. retrognathic mandible in Obstructive Sleep Apnea (OSA) where orthognathic surgery is not the first choice, are indicated for DO. It can also be used to correct problems with the bite or teeth, such as an overbite or underbite, movement of a tooth e.g. canine, impacted tooth or a group of teeth e.g. anterior teeth retraction and expansion of palate. Correction of alveolar atrophies, cross bites and canting of occlusal planes are indicated for DO. DO has been shown to be effective in speeding up orthodontic treatment time [10].

DO/DH procedures have an advantage over routine orthodontic and orthognathic procedures in that there is absence of relapse due to histogenesis and growth of soft tissues [11, 12]. DO/DH procedures in newborns for mandibular advancement for airway enlargement due to growth problems can avoid tracheostomy [13, 14]. DO can reduce treatment time and complications of future orthodontic and orthognathic procedures [15, 16]. Some of the disadvantages of DO include inaccurate vector orientation leading to unfavourable loading of joints and tissues, scaring, pain, oral hygiene maintenance, daily visits for activation. Such disadvantages are reduced with improvements in three dimensional control device designs resulting in accuracy and less negative impact on adjacent tissue [17, 18].

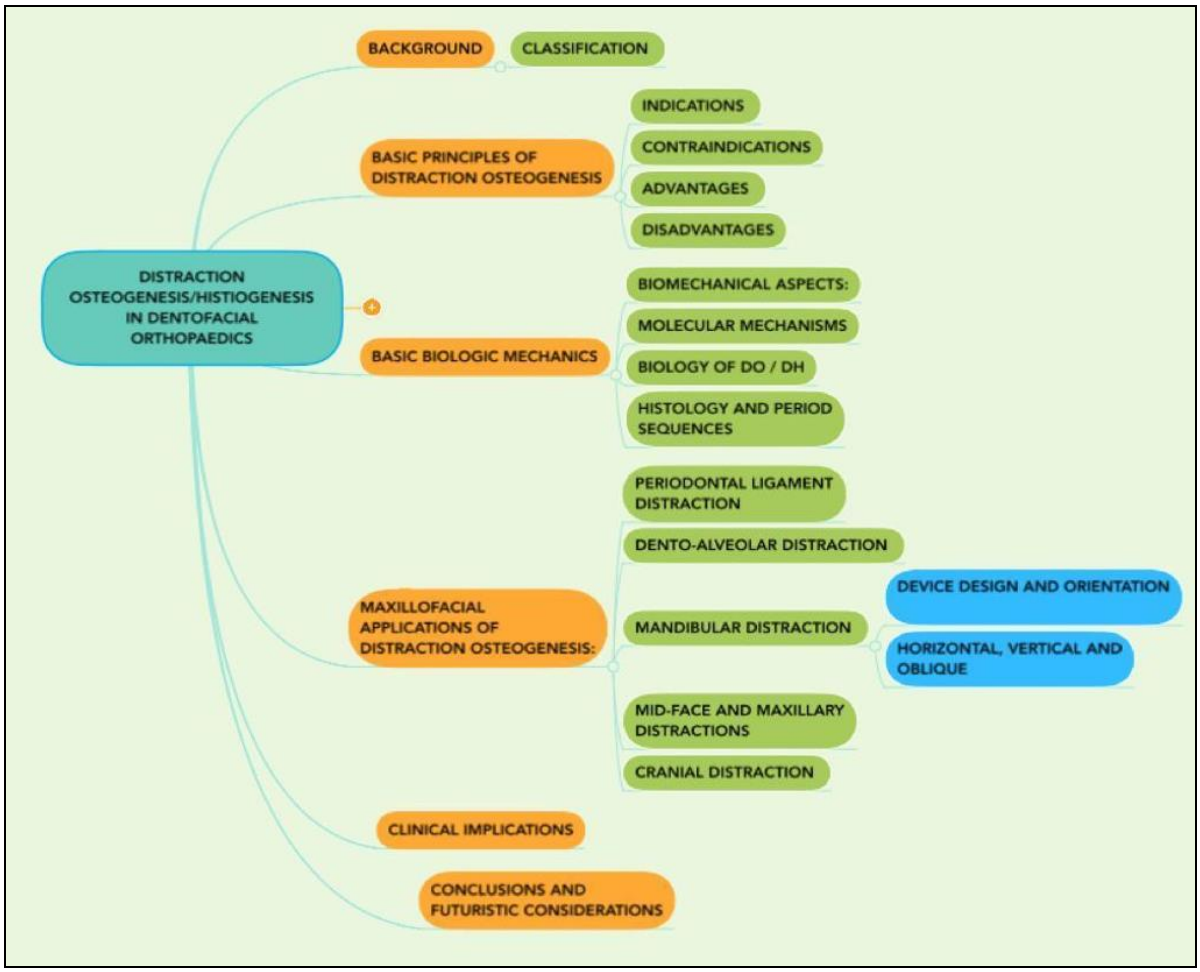

Fig 1: Brief Outline of Distraction Osteogenesis.

Device

A distractor is a device that comprises of two halves connected by screw, secured to the bones/teeth to be distracted and distraction of segments is achieved over a period of several weeks with activation of screw. Classification of distractor devices used in the maxillofacial region can be based on the site, such as the mandibular, midface or maxillary, alveolar, transport (reconstruction of neo-mandible/ neocondyle). Devices can also be classified based on their use, such as (RED) Rigid External Distractors secured to the bone using percutaneous pins, fixation clamps, and distraction rods and Internal Distractors which can be inserted either under or above the oral mucosa. External distractors can further be divided into unidirectional, bidirectional and multiplanner, whereas internal distractors can be mandibular intraoral distractors, modular internal distractors (MID) and tooth borne distractors. Devices can also be classified as tooth borne, bone borne, or a hybrid type [19]. The material of the distraction device can also be a basis for classification, with bioresorbable devices used in infants with congenital disorders and non-resorbable, metallic devices. Distraction techniques can also be divided into two categories such as callotasis and distraction of the bone growth plate resulting in distraction epiphysiolysis and chondrodiatasis. Distraction methods can be further divided into three categories, such as Monofocal, Bifocal, and Trifocal. They are differentiated on the basis of number of osteodistraction gaps and calluses produced by surgical fracture with monofocal used for minor adjustments and trifocals used for major surgical realignments [20, 21].

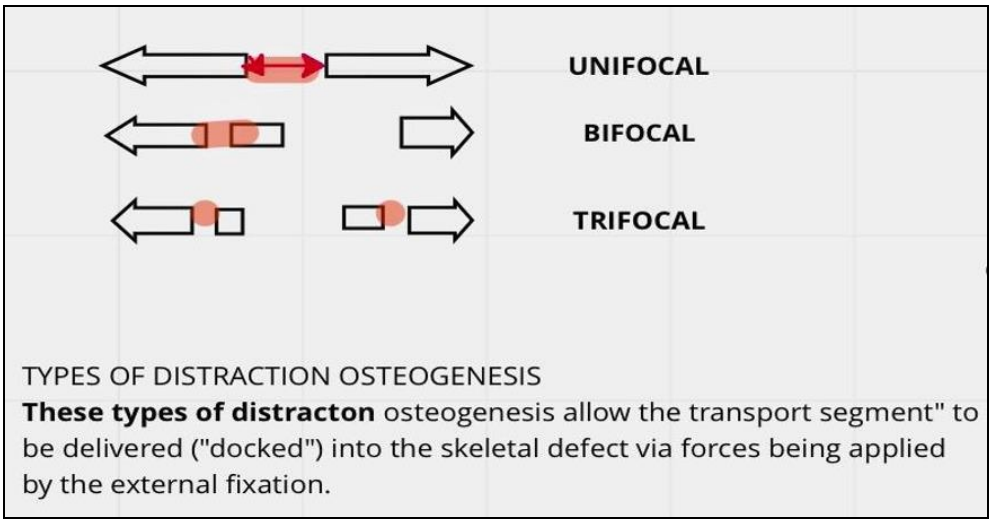

Fig 2: Types of Distraction Osteogenesis.

Basic Principles

The selection and placement of the distraction device on the mandible/maxilla is determined by a combination of factors. The biological and mechanical forces that shape the regenerate (newly formed bone during active period of distraction osteogenesis) are essential in determining the appliance position. The desired change in shape and function can be achieved by selecting and controlling the force vectors that operate during active distraction [1, 22]. The clinical extension of functional matrix concept is demonstrated by the quality, quantity and morphometrics of regenerated bone being dependent on the biologic forces of soft tissue neuromuscular envelope. Mechanical forces generated by occlusion, force vector generated by design and activation of distraction device and orthodontic auxillary, use during the different phases of distraction, determines the regenerated tissue morphometrics. Both these biologic and mechanical forces must satisfy the orthodontic treatment objectives of structural integrity, functional optimisation and aesthetics. Force transduction via adjacent structures influences the regeneration of the tissue between the bone fragments by modulating the stress produced within the callus [22, 23]. Stable fixation of the osteomised bone segments is critical for successful distraction and the distraction axis must be parallel to the anatomic axis of the bone and not to the biomechanical axis of loading to avoid unfavourable loading of the joint. Clinical studies have verified that the alteration in skeletal morphology is directly influenced by the device's orientation to the mandible and the best way to characterise the device's position is in reference to the mandibular body's long axis. There are three types of device placement: vertical, horizontal, and oblique. During planning distraction, the powerful impact of both biological and mechanical force systems must be considered in order to anticipate their resultant effects. The velocity and rhythm of the separating pressures affect how successfully new bone is formed during this process of distraction [24, 25].

The following is the order of the stages in distraction osteogenesis:

Osteotomy

To start and maintain the distraction osteogenesis, each bone segment that has undergone an osteotomy must have an enough number of live osteocytes. Because the periosteum in the well-vascularized craniofacial region affords significant osteoblastic activity, complete osteotomy is not preferable over corticotomy [26].

Latency

The production of soft calluses occurs during the latency phase of distraction osteogenesis, which has a similar histological sequence to the mending of broken bones. The suggested initial delay duration ranges from 5 to 10 days [27].

Distraction

The application of progressive traction to the soft callus interrupts the natural healing process of the fracture during this period. The tension brought on by this traction force produces a dynamic microenvironment that promotes the growth of new tissue in a direction perpendicular to the traction vector. Afibrous, less vascular centre with collagen fibres parallel to the distraction vector, a transition zone of early bone formation, a bone remodelling zone, and mature bone at the ends are the four zones that emerge during distraction. The distraction process typically progresses between 0.5 and 1 mm every day [1, 28].

Remodeling and consolidation

Before the shape of the newly created bony tissue is comparable to that of preexisting bone and in which soft tissue adaptation also takes place, bone maturation begins and continues over a period of a year or more. When the distraction stops, this soft callus hardens and, mostly through intramembranous ossification, an unique zone of woven bone entirely fills the gap. For craniofacial bones, it is recommended that Pediatric patients undergo a 3-5 week phase and adults undergo a 6-12 week phase [29].

Distraction Osteogenesis involves a four stage process comprising of a fibrous central zone, transition zone, remodelling zone and mature zone. During the fibrous central zone, mesenchymal proliferation occurs and collagen bundles are longitudinally oriented. In the transition zone, osteoids begin to form along the collagen bundles. In the remodelling zone, osteoclast formation and remodelling of the newly formed bone occur. The last stage is the mature zone. The process by which mechanical forces are converted to cellular signals is termed mechanical transduction [30].

Two important factors set the healing process in DO apart from a fracture repair: 1) regulated microtrauma; and 2) an intramembranous rather than an endochondric ossification mechanism [1, 26].

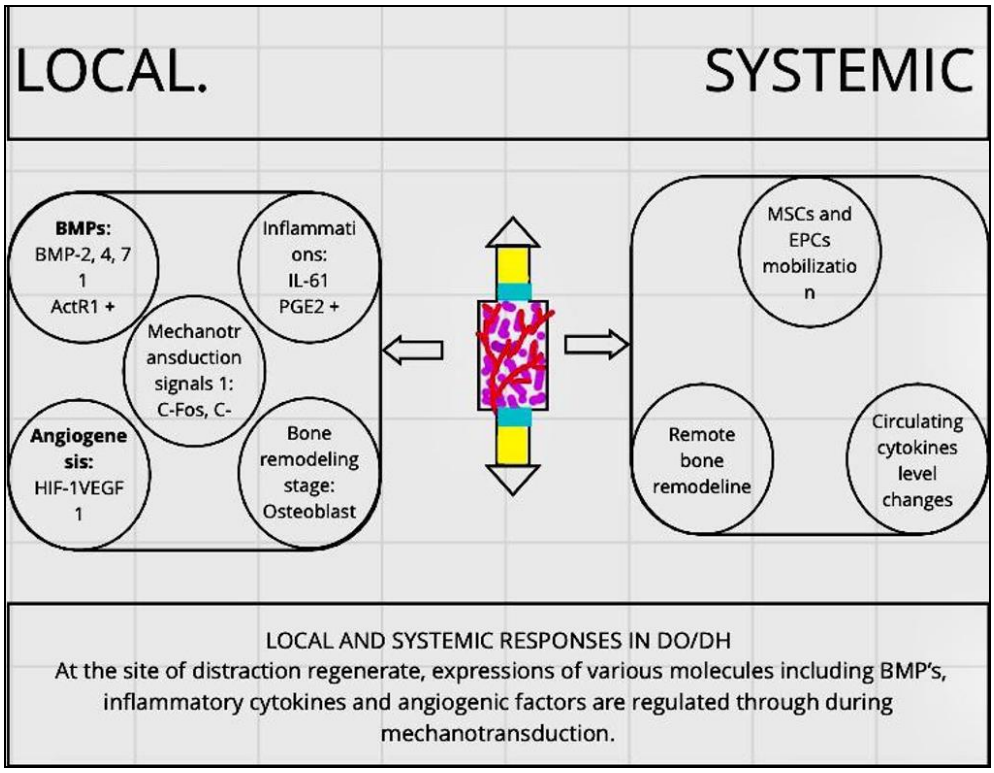

Fig 3: Local and Systemic Responses in DO/DH.

Molecular Mechanisms

The Distraction Osteogenesis/Distraction Histogenesis (DO/DH) technique can stimulate the robust potential of musculoskeletal tissues for regeneration and resume a number of regulatory processes. Through next-generation sequencing, proteomics, and metabolomics, research is uncovering the molecular pathways underlying DO/DH. Tension stress during DO/DH affects signal transduction molecules, BMPs, inflammatory and vascular proteins, as well as epigenetic factors [31, 32]. The biological pathways of DO/DH are being explored to improve clinical applications. During DH, inflammatory and immunomodulatory reactions are necessary for bone homeostasis and high levels of tensile strain induce the expression of pro-inflammatory genes (Prostaglandins, COX2) [33, 34]. Research is still uncovering how tensile stress affects systemic immune responses. Bone remodelling is necessary for medullary cavity recanalization during the late consolidation phase of DO, which can be regulated by PEMF, ultrasound and shock wave. Interleukin-6 and Tumour Necrosis factor are increased during consolidation and reduced bone formation, respectively [35, 36]. Tensile stresses have also been reported to modulate immune response. Mechanotranduction signalling mechanisms (YAP, TAZ, ERK-1/2) stimulate genes responsible for bone homeostasis and regeneration of Schwan cell derived myelin sheath during nerve cell lengthening. Elevated levels of Hippo signalling pathways, nuclear proto-oncogene proteins, C-fos and C-jun, BMP-2,4,6,7 during bone length increase and consolidation phase of bone remodelling have been identified establishing the interconnectedness of mechanical stimuli, gene activation and chemical response at molecular and cellular levels [19, 62].

The Distraction Histogenesis (DH) process is reliant on the production of Endothelial Progenitor Cells (EPCs) and their homing to the site of new bone production. The activation of VEGF receptors 1 (VEGFR1) and 2 is essential for neovascularization and bone production during DO [37, 38]. Hypoxia-induced factor 1 (HIF-1) and mechanical manipulation of the consolidation period through the accordion technique also influence the paracrine loop of VEGF and BMP-2, to maintain the coupling of angiogenesis and osteogenesis. Blocking either VEGFR1 or VEGFR2 has been found to decrease bone mineral density in the lengthening gap.

Bone marrow and adipose-derived MSC transportation has been shown to reduce the time required for bone consolidation in DO and DH models of limb or mandibular lengthening [39, 40]. The paracrine actions of the transferred cells are essential for bone healing. Growth hormones and EP2-specific agonists have been investigated to improve bone regeneration by delivering hormones, polypeptides, and anabolic agents throughout the body. In a rabbit DO model, single injection of 300mg of thrombin peptide 508 (TP 508) in propylene fumarate (PLGA) microparticles significantly facilitated bone consolidation. Post-transcriptional regulation of DO/DH-related genes is heavily depended on small non-coding RNAs (miRNAs). Bone production in DO models was increased by MSCs modified with basic fibroblast growth factor (Bfgf) and dental pulp stem cells (Runx2). Scaffolding materials such as lithium carbonate and magnesium have been investigated to promote bone development and consolidation [41, 42].

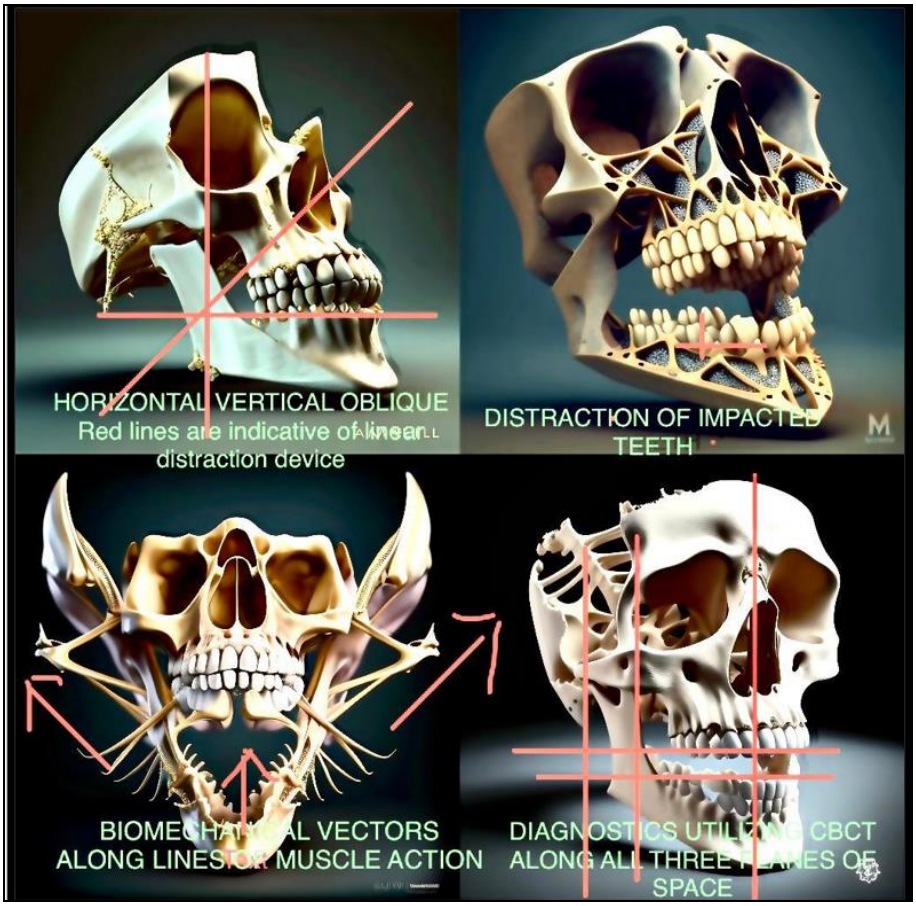

Fig 4: Clinical Applications.

Clinical implications for maxillofacial applications for distraction osteogenesis:

Device design, configuration, sturdiness and attachment stability impact the clinical success of the distraction osteogenesis procedure. Distraction device's orientation and the operational vector in relation to the anatomical axes of the bony segments involved are other device related factors that impact the success of the procedure. The bone geometric morphometrics, the cross-sectional area of bones involved, the bone density, the length of the transport-gap, and the tension of the soft envelope of muscles and nerves are tissue-related factors that influence the quality of the hard and soft tissue generated by osteodistraction. Use of an external or an internal device is one of the main planning factors in dento-maxillofacial distraction procedures. The external devices include three dimensional transportation capability and have an inherent capability to generate clinically optimal vector for bone transport. Internal devices usually have smaller, 25mm or less, range of distraction. Facial scarring and increased perpendicular distance from force generating point on distractor to the point of force application on bone, are some of the disadvantages of external distractor devices. The other disadvantage is inability to change force direction once inserted. External frame distraction is not used in Pediatric patients unless the airway is compromised [1, 43]. Internal distraction devices overcome most of the disadvantages of external frame devices because of their small size and ease of application enabling occlusal relations to be changed before the patient enters the consolidation phase of bone healing and allows for micro management of the process to be done while the distraction is happening. In patients with active growth when bone is more elastic distraction procedures are avoided until growth maturity. Osseodistraction with corticotomy of the external cortex is advised in younger individuals [26]. Adults internal cortex has higher fracture resistance reducing the chances of failure. A waiting period of 4–7 days after osteotomy is advised before starting the distraction procedure, based on the findings with long bone distractions. Premature bone union is significantly more likely if distraction is delayed (beyond 10 to 14 days). The latency appears to be between 5 and 7 days with a distraction rate of 1mm/day [44]. The gold standards in the field of craniofacial distraction osteogenesis appear to be a distraction rate of 1mm/day and a delay of 5 to 7 days [1, 26, 43]. The following are some of DO/DH maxillofacial procedures that have been accomplished in collaboration with orthodontists in the recent past:-

Dento-alveolar distraction. In 1996, Chin and Toth[45] reported the first clinical application of vertical mandibular alveolar distraction osteogenesis. Block and co-workers established the validity of distraction osteogenesis for alveolar ridge augmentation in mandibular canine. Osteodistraction of the alveolar process provides superior three dimensional reconstruction as compared to other procedures like grafting and tissue regeneration. To increase alveolar ridge bone volume for the placement of implants or for orthodontic tooth movements, alveolar ridge distraction is recommended.

Mandibular distraction: Clinical application of Illizarov's bone lengthening concepts were verified for face and jaws by Snyder *et al*. (external distractor for canine distraction), McCarthy *et al*. (external distractors for congenital facial defects) and Guerrero (mid symphyseal widening with hyrax type screw) [46, 47, 48]. Patients with facial dysmorphism, respiratory functioning issues, and disorders such Pierre

Robin, Treacher Collins syndrome, developmental micrognathia, and craniofacial microsomia. Ankylosis of the temporomandibular joint and post-ablative mandibular problems. Infant or Pediatric patient with sleep apnea and/or with swallowing difficulties. Trans-cutaneous (submandibular) or intraoral incisions are employed for intraoral or external device placement. Comparing distraction-based osteotomies to conventional osteotomies: earlier surgery, shorter procedure, less postoperative problems (including transfusions), and reduced need for additional surgery (grafts); a corresponding lengthening or expansion of the muscles and soft tissue envelop above (distraction histogenesis) results in over time the relapse rate being decreased [49].

Periodontal ligament distraction. Liou and Huang in 1998 introduced the concept of osteogenesis in the periodontal ligament during rapid orthodontic tooth movement that is comparable to the osteogenesis in the mid palatal suture during rapid palatal expansion. Distractor activation of 1mm/day combined with interseptal bone fracture of the extraction socket has been reported to reduce orthodontic treatment time by 3 to 4 months [50, 51].

Maxillofacial and mid face applications:

Polley *et al*. in one of the earliest clinical attempts used an fixed cranial halo to distract the midface. The advantages and disadvantages of Rigid External Distraction (RED) are the same as discussed above in other distraction procedures. Complete clinical regeneration of hard and soft tissues of mid-face with distraction was demonstrated by Figueroa *et al*. Maxillary Le Fort I distraction is indicated for the retrusion/protrusion in patients with Cleft Lip and Palate with attendant dental and soft tissue problems. Other indications for Midfacial Distraction with Maxillary Le Fort III distraction for midface retrusion, include respiratory issues, malocclusion and severe dysphmorphism especially in the syndromic craniofacial synostosis with Exorbitism and Craniofacial Microsomia (can be treated with combined maxilla-mandibular distraction) [52].

Cranial distraction:

Polezhaev [1, 19] demonstrated the first clinico-experimental study on cranial osteodistraction for bone transport to a calvarial defect. Cranial distraction procedure is performed with both external frame and internal miniature devices for simultaneous midface and forehead distraction after a Lefort IV osteotomy [53, 54]. Indications for cranial distraction procedures include a wide spectrum of craniofacial deformities, such as crouzon's syndrome, Aperts syndrome, Pfeiffer's syndrome and mid face abnormalities owing to craniofacial anomalies.

Orthodontic Treatment Protocol

- Predistraction orthodontics includes leveling, alignment, maxillary and mandibular arch co-ordination, decompensation with teeth placed over basal arch, root divergence at osteotomy site for its facilitation.
- Orthodontics during distraction and consolidation phase includes the use of intramaxillary and/or intermaxillary elastics, mini implants, headgear to initiate movement towards post distraction position and control clockwise or counterclockwise rotation of distracted segments according to developing clinical situations. Orthodontic treatment in this phase exerts a three dimensional control in horizontal, vertical and transverse dimensions to effect a favourable biomechanical system for correction of distracted segments.
- Post distraction orthodontics includes completion of residual dentoalveolar movements, finishing and detailing of occlusion, root paralleling and artistic positioning of teeth for functional occlusion and facial esthetics.
- Retention of achieved dentoalveolar and bone shape and position is accomplished with fixed or removable retainers [55].

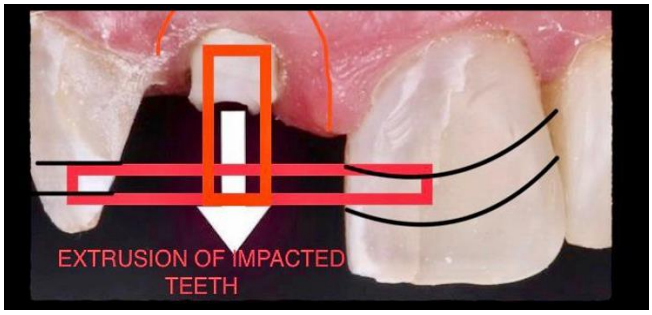

Fig 5: Extrusion of Impacted Teeth.

Experiment studies have demonstrated that after four days of consolidation, the load-bearing group displayed a larger percentage of regenerated bone as well as higher levels of osteocalcin, type I collagen, morphogenetic proteins 2 and 4 (BMP-2 and BMP-4), and BMP-2. Extracellular matrix (ECM) proteins, cytokines, and growth factors are all involved in the processes of bone formation at the distraction gap. Recombinant human fibroblast growth factor (FGF) was used, according to Okazaki *et al*., towards the conclusion of the diversion period [56]. The efficacy of DO was demonstrated by ECM proteins like osteocalcin, whose mRNA and protein expressions fluctuate across the various stages of distraction. Osteocalcin and other ECM proteins have successfully been used in DO. These regulatory factors mRNA and protein expressions change during the various stages of distraction, so using the right protein at the right time should maximise the result. The main sources of osteoblast precursors, the periosteum and endosteum, should be protected from heat or mechanical damage during surgery. Osteogenesis depends on a healthy blood supply to the distraction site. The doctor must make sure the soft tissues close to the potential distraction site are properly vascularized. In the regeneration, arterial insufficiency may cause ischemic fibrogenesis, which results in a loose, asymmetrical collagen network rather than the desired dense, regular collagen pattern. Cystic degeneration of the regeneration has been linked to restriction of the venous outflow. A corticotomy should only be conducted through a small periosteal aperture since early investigations in long bones found that an undamaged periosteum and endosteum were essential for effective osteogenesis [57, 58].

Conclusions and Futuristic Considerations

Due to their expertise in biomechanics and long-term patient care, orthodontists are well-suited to administer and utilise this novel therapeutic treatment. It will be crucial for orthodontists to comprehend the next generation of internal distraction devices and learn how to include distraction osteogenesis into their treatment plan as distraction osteogenesis obtains more clinical recognition. Finally, just like other types of orthognathic surgery, distraction

osteogenesis relies on the cooperation and preparation of the surgeon and orthodontist. For the purpose of lengthening mandibles and other craniofacial bones, distraction osteogenesis is a crucial clinical process; nonetheless, it necessitates interdisciplinary and coordinated care to guarantee a positive clinical outcome for the patient.

The DO/DH technique has a future in the management of osteoarthritis (OA) by unloading the joint cartilage and subsequent reduced inflammatory infiltrates and pain, increased angiogenesis and function, with internal distractors offsetting the disadvantage of prolonged wear of external distractors (Wiegant *et al*.) [59]. Disorders related to vascularity and circulation as in diabetic ulcers are other pathologies amenable for correction with DO/DH in future as demonstrated by Qu *et al*. in the treatment of thromboangitis obliterans [60, 61] Kong *et al*. [62, 63] stated that researches in DO/DH will extend our knowledge of tissue regeneration including neural regeneration in vascular and neurological disorders.

DH has traditionally employed least invasive approaches like ultrasound and electromagnetic stimulation but current methods of enhancing bone growth by transport of undifferentiated cells locally and mechanotransduction induced molecules and injection of hormones will in the near future favour distraction procedures for improved clinical outcomes. To extend our understanding of the basic biological processes research in these areas is an ongoing processes. Enhanced therapeutic applications of the DH approach will be made possible by knowing these basic pathways.

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