Why high frequency of distraction improved the bone formation in distraction osteogenesis?

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SUMMARY

Distraction osteogenesis, currently a standard method of bone lengthening, is based upon the “tension–stress principle”, as proposed by G.A. Ilizarov. Mechanical stimulation by distraction induces biological responses of skeletal regeneration that is accomplished by a cascade of biologic processes including differentiation of pluripotential tissue, angiogenesis, mineralization, and remodeling. The exact mechanism by which strain stimulates bone formation remains unclear. Distraction rate and rhythm must have great influence on the quality of the newly formed bone generated by mechanical traction. The preliminary results demonstrated that for a given rate higher frequency of distraction improved the bone formation, but the mechanism remains unclear. In this article we present a hypothesis that the reason why higher frequency of distraction improved the bone formation for a given rate is that higher frequency of distraction provides smaller microtrauma to tissues within the gap and longer existence time of the microenvironment stimulating tissues within the gap than low frequency distraction. This hypothesis, if proven to be valid, will not only represent a breakthrough in research of mechanism of distraction osteogenesis, but also will open a new door to the bone regeneration.

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Introduction

Distraction osteogenesis (DO) is a well established technique of endogenous tissue engineering. This surgical method was initially developed for long bone lengthening in orthopaedic surgery. However, it did not gain wide acceptance until Ilizarov identified the physiological and biomechanical factors governing successful endochondral distraction [1–4]. The essence of this technique is the gradual distraction of a fracture callus after low-energy “corticotomy” of the long bone with careful preservation of the soft tissue envelope surrounding the bone. It is Snyder’s research [5] that ignited the field of craniofacial DO and created the momentum for numerous experimental surgical models [6–9]. Distraction osteogenesis can be divided into three temporal and dynamic phases: latency, distraction, and consolidation. The latency phase, which starts immediately following creation of the osteotomy and extends until the onset of active distraction, allows for the initial trauma response to take place. What take place during this phase are basically the same as those in the early stages of fracture repair. During the distraction phase, bone regeneration happens. Mechanical stimulation by distraction induces biological responses of skeletal regeneration that is accomplished by a cascade of biologic processes including differentiation of pluripotential tissue, angiogenesis, mineralization, and remodeling. Several growth factors, such as BMPs, TGF-β, IGF-1, bFGF, and VEGF express during the latency and distraction period [9–17], making distraction osteogenesis much more effective than fracture healing. Once the desired bone length is achieved, distraction ceases, and the consolidation phase begins, where bone and extensive amounts of osteoid undergo mineralization and eventual remodeling.

Bone regeneration during distraction osteogenesis is believed to occur in response to the longitudinal mechanical strain applied to the callus during healing. The exact mechanism by which strain stimulates bone formation remains unclear. It has been suggested that living tissues become metabolically activated by slow, steady traction, a phenomenon called mechano-transduction, characterized by the stimulation of proliferative and biosynthetic cellular functions [2]. The mechanical stimulation generated by gradual traction induces the biological response of skeletal regeneration in a cascade of bone induction and formation processes, and the molecular signaling during distraction osteogenesis is amplified and prolonged as long as the mechanical traction is in progress [14]. Therefore, the distraction rate and rhythm must have great influence on the quality of the newly formed bone generated by mechanical traction [3,18–24]. The preliminary results demonstrated that for a given rate higher frequency of distraction improved the bone formation [3,23,24], but the mechanism remains
unclear. In this article we present a hypothesis that explains these unexpected results.

Hypotheses

From a macro perspective, bone regeneration in the osteotomy gap is a consequence of distraction of the tissue in the gap. While from a micro perspective, it is the mechanical microenvironment around the tissue activates the proliferative and biosynthetic cellular functions. We would like to explain the results that for a given rate high frequency of distraction improved the bone formation from two aspects. From a macro perspective, the microtrauma in the distraction zone from abrupt activation of the distractor may be missing, at least will be much smaller, when activation frequency is higher. Form a micro perspective, high frequency of distraction let the mechanical microenvironment around the tissue persist for longer than low activation frequency. Cells involved in the bone formation and vessel formation have more opportunity to be simulated by surrounding mechanical microenvironment. As a result, more cells could be activated and could become deeply activated.

Evaluation of the hypotheses

The distraction rate is the product of the distraction distance per time and the distraction rhythm per day. For a given distraction rate, there are three different points when high frequency distraction compares with low frequency distraction. First, the distraction distance per time is shorter. Second, the mechanical force applied to the gap per time is smaller as a result of shorter distraction distance. Third, the frequency when the gap is distracted is higher. Ilizarov [2–3] claimed that the shape and size of the bone are influenced by the amount of load applied on the bone and its blood supply. From a macro perspective, low frequency distraction results in microtrauma in the distraction zone due to relative large movement and higher distraction force, and finally leads to the delayed bone healing compared with high frequency distraction osteogenesis, in which the mechanical force applied to the gap is smaller as a result of shorter distraction distance [24,25]. During the deposition of osteoid, collagen fibers serve as bracket. Tensile forces are applied to the callus with a specific rate (distance distracted per day) and rhythm (number of distractions per day), consequently forming a central fibrous zone, called the fibrous interzone (FIZ), which is rich in chondrocyte-like cells, fibroblasts, and oval cells, which are morphologically intermediate between fibroblasts and chondrocytes [10–12]. The differentiating osteoblasts at the fibrous interzone deposit osteoid along collagen bundles. They subsequently undergo mineral crystallization parallel to the collagen bundles, forming a zone called the ‘zone of micocolumn formation’ (MCF) [13]. Fratzl et al. [26] have shown that low strains lead to a straightening of collagen fibers, whereas higher strains induce a molecular gliding within the fibrils, resulting ultimately in the disruption of the fibrillar organization. Bone formation may be delayed resulting from the injury of the collagen fibers. Ample evidence has emphasized the contribution of local neovascularity on bone formation during distraction [14,18,27]. When distraction force is hyperphysiological, vessels are disrupted and micro-hematomas are formed. The healing process is interrupted and has to re-start after each activation of the distractor. The trauma from abrupt activation of the distractor in low frequency distraction may be missing when distraction frequency is high. Meyer et al. reported that in contrast to mandibles distracted at low strain magnitudes, in which only minimal evidence of apoptotic cell death was detected, the application of hyperphysiological strain magnitudes resulted in an increased apoptosis rate of osteoblasts [28].

When the distractor is activated each time, tension forces are applied to bone-forming osteoblasts and other cells present within the bone microenvironment. During the time between two activations, active cellular events take place within the distraction gap, resulting in the growth of the tissue within and surrounding the gap. With the growth of tissue, mechanical microenvironment generated by distraction will change. Mechanical stimulation by distraction will diminish or even disappear. High frequency distraction makes mechanical microenvironment around the tissue persist for longer than low distraction frequency. Bone-forming osteoblasts and other cells present within the bone microenvironment could be stimulated by the distraction force for longer than low activation frequency. Consequently, cells could become a high grade of activation, characterized by more active cellular functions of proliferative and biosynthetic. In addition, more cells could be activated when distraction frequency is high, which results in longer existence of the mechanical microenvironment. Thus, the quality of new bone and the speed of bone formation are better under frequency distraction. There is a positive correlation of high mechanical traction frequency and up-regulation of gene expression of the osteogenic factors contributing to the accelerated bone formation [29]. High frequency of distraction also can up-regulate gene expression of the angiogenic mediators resulting in an increase of new vessel formation [30]. It appears to be the high frequency that results in accelerated bone regeneration. In our opinion, it is the longer existence of the mechanical microenvironment that improves the bone formation.

Conclusion

The biomechanical impact of distraction osteogenesis on regenerating bone tissue is a highly complex and dynamic process. The distraction rate and rhythm have great influence on the quality of the newly formed bone generated by mechanical traction. Based on reported studies, we present a hypothesis that the reason why higher frequency of distraction improved the bone formation for a given rate is that higher frequency of distraction provides smaller microtrauma to tissues within the gap and longer existence time of the mechanical microenvironment stimulating tissues within the gap than low frequency distraction. This hypothesis, if proven to be valid, will not only represent a breakthrough in research of mechanism of distraction osteogenesis, but also will open a new door to the bone regeneration.

Conflicts of interest statement

The authors indicate no potential conflicts of interest.

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