International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2020): 7.803

Biological Aids for Orthodontic Retention- A Review

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Abstract: ***In orthodontics, post-treatment retention remains one of the greatest challenges. Orthodontic tooth movement involves mechanical stimulation and biological response. So, in addition to conventional mechanical retention, biological intervention also makes it possible to hold teeth in their newly moved position. Biological intervention makes it possible to accelerate tissue recovery post-treatment and reduce or eliminate the need for mechanical retention. This review article was aimed to discuss the effect of various biological agents on post-orthodontic stability and retention.***

Keywords: Orthodontics, Retention, Osteoprotegerin (OPG), Bone Morphogenic proteins (BMPs), extracellular vesicles (EVs)

1. Introduction

Prevention of undesirable post-treatment changes remains one of the major challenges in orthodontics. Retention is an integral part of orthodontic treatment to prevent relapse of the final occlusal outcome. Both gingival and periodontal tissues are affected by orthodontic tooth movement and require time for reorganization when the appliances are removed.

In recent years, the retention protocols and appliances used in orthodontics have witnessed major changes. This includes mainly the inclusion of biological agents and adjunctive procedures, along with conventional approaches [1]. The biological and pharmacological agents that have been investigated in orthodontics usually target factors that control bone metabolism. Also, the ability of various hormones, cytokines, growth factors, and therapeutic agents to inhibit tooth movements has been well studied.

Thus, the aim of this review article is to discuss the biological mechanisms of action of various biomedical agents, focusing on their potential orthodontic applicability and suitability for further investigation.

2. Biological Approaches to Improve Retention – A New Horizon

It possible to enhance tissue recovery after treatment by means of biological intervention. These agents eliminate the need for conventional mechanical retention and they typically target factors that control bone metabolism. Orthodontic tooth movement occurs by alveolar bone remodelling. So, the challenge for the orthodontist is to establish conditions where the periodontal ligament (PDL) and bone alveolar bone are promptly remodelled, preserving the new position of the tooth [2]. Understanding the biological factors affecting relapse and by focusing on their potential to improve post-treatment outcome will help to establish a stable post-treatment occlusion and minimizes relapse.

Osteoprotegerin (OPG)

Osteoprotegerin (OPG) is a naturally occurring endogenous competitor protein with homology to members of the TNF receptor family. It is a cytokine that controls differentiation and activation of osteoclasts [3]. It counteracts the resorptive action of RANKL (receptor activator of nuclear factor kappa-b ligand) by blocking it from binding to RANK [4]. RANKL is essential for osteoclast differentiation, function, and survival [5]. RANK is another (TNF) family receptor that is present on osteoclast cells and their precursors. By binding of RANKL to RANK, bone resorption is activated. In bone metabolism, the RANKL: OPG ratio is a major factor. An increase and decrease of this ratio are often associated with bone resorption and formation, respectively. Increased OPG levels result in a significant increase in bone mineral density and bone strength due to its anti-resorptive effect.

The role of OPG to prevent relapse and enhance anchorage has been investigated in orthodontics. Several experimental studies have shown that local or systemic injections of OPG inhibit orthodontic tooth movements and reduce relapse [4], [5]. OPG has a major role in blocking RANK-RANKL binding, as well as differentiation of pre-osteoclasts to osteoclasts. OPG also inhibits osteoclast formation, function, and survival [6].

Dunn et al [7] and Schneider et al [8] done several experiments and concluded that OPG can affect the amount of incisor retraction to molar anchorage loss. There is greater inhibition of molar movement than incisor movement with high dose of OPG. Recombinant OPG protein (OPG-FC) maintains orthodontic tooth movement and prevents relapse and it is a safe and effective biological means to control osteoclasts locally [8]. With rapid maturation of PDL and inhibition of bone resorption OPG exhibits desirable effects affect orthodontic treatment and prevents relapse [9]. The potential side effects include development of anti-OPG antibodies that could neutralize endogenous OPG. Sometimes OPG block TNF – related apoptosis –inducing ligand protein and interfere with normal immune mechanism [10].

Denosumab

Denosumab is a monoclonal antibody against human RANKL. It is structurally different from OPG and has same effect on bone as OPG but does not have the side effects of OPG [11]. It increases the duration of inhibition of RANKL and also patient's compliance. Denosumab is applied every 6 months. A single dose of Denosumab is a potent, long acting, well tolerated, safe anti-resorptive agent and has sustainable effect on RANKL inhibition [12]. This property of Denosumab can be used for orthodontic retention purposes. Denosumab has been approved by the Food and Drug Administration for use in adults and skeletally mature individuals [13]. Romosumab is another humanized monoclonal antibody which when injected locally on to the tension side of the tooth can stimulate bone formation by inhibiting sclerostin activity and reduces relapse [14].

Bisphosphonates

Bisphosphonates are primary agents in the current pharmacological arsenal against osteoclast-mediated bone loss due to osteoporosis, Paget disease of bone, malignancies metastatic to bone, multiple myeloma, and hypercalcemia of malignancy [15]. Among different agents, most commonly tested in orthodontics are Pamidronate and Zoledronate [4], [16]. Their mechanism of action is by inhibiting osteoclastic activity [18] and thereby decreases bone resorption. Several studies have been done to evaluate the effect of BPs on tooth movement [4], [16], [17]. With single dose applications, BPs may provide an adjunctive retention therapy in orthodontics. The potential side effects include increased risk of osteonecrosis of jaw. However, single doses of BP in orthodontic experimental models have shown no signs of BP-related osteonecrosis of the jaw [16]. However, further orthodontic investigations are required to consider their efficacy and long-term safety.

Bone morphogenic proteins

BMPs are multi-functional growth factors that induce bone, cartilage and pdl formation. The effects of BMPs on the bone and surrounding tissues are only temporary [18]. Hassan et al evaluated the role of BMPs on post orthodontic stability and concluded that BMPs have favourable effect on incisor stability and regeneration of surrounding tissues [19]. Further research is necessary to rule out the risk of ankylosis, root resorption and stability.

Relaxin

Relaxin is a hormone which has stimulatory effects on PDL collagen metabolism by increasing the expression of MMP-1 and MMP-8 in the PDL [20]. Experimental studies by Hirate et al showed that Relaxin injections reduced the percentage of relapse in orthodontically moved teeth [20]. Stewart et al (2005) investigated the effect of Relaxin on reducing or preventing relapse and found that gingival administration of Relaxin produced an effect similar to that of a surgical gingival fiberotomy in most animals [21]. The Relaxin is an unfavourable agent for clinical application as it requires frequent applications which make it inconvenient for the patient and the orthodontist.

Simvastatin

It is a member of statin family which reduces cholesterol levels and thought to prevent cardiovascular diseases. The effects of statins on bone anabolism involve the promotion of osteoblast differentiation, the suppression of osteoblast apoptosis and the blocking of osteoclastogenesis through RANK-RANKL-OPG pathway [22]. Simvastatin has been experimentally evaluated in orthodontics for its effect on post-orthodontic stability [23] and found that Simvastatin decreased the extent of relapse via regulating OPG and RANKL expression to control osteoclastic resorption activity and then stimulating bone formation. Further investigations are needed to confirm the effect of Simvastatin on post orthodontic retention.

Strontium

Strontium renalate (proteolos) is a newly developed antiosteoporotic drug that acts by reducing bone resorption and promoting bone formation thereby inducing a positive bone balance [24]. It is used to treat osteoporosis and other bone-related disorders. It acts mainly by significantly down regulating both mRNA and protein levels of the osteoblast induced signals for osteoclastogenesis through the CaSR and has positive effects on osteoblastic replication, differentiation and lifespan [25].

In orthodontics, Duliamy et al have done an experimental study to demonstrate effects of strontium chloride on orthodontic relapse [26]. They reported that local injection of strontium is a promising approach to enhance both orthodontic retention and anchorage. However further orthodontic investigations are restricted because of the risk of adverse cardiovascular events [27].

Role of extracellular vesicles/ exosomes

For osteoclast formation and bone resorption, it is essential to stimulate the RANK-RANKL binding. RANK is also packaged into extracellular vesicles (EVs) and released by osteoclasts [17]. EVs that contain the protein receptor activator of nuclear factor kappa B (RANK) are released by osteoclasts and both inhibit bone resorption and stimulate bone formation [28]. Direct application of RANK-containing EVs could enhance bone formation of the tension side [29]. They would be expected to stimulate tension-side bone formation and to speed the maturation of the post-orthodontic alveolar bone remodelling.

3. Conclusion

Conventional approaches to retention have revolved around provision of fixed or removable retainers. Biological intervention makes it possible to accelerate tissue recovery after treatment and reduce or eliminate the need for mechanical retention. Biological agents do not rely on patient compliance and limit the complications associated with traditional retainers. Several biomedical agents, such as OPG, BPs, and BMPs, exhibit favourable effects on bone metabolism that could help hasten the tissue-recovery process after orthodontic treatments. Further research is necessary to determine the clinical applicability of these agents for orthodontic retention.

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