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Enamel Matrix Derivative In Pulpal Regeneration And Repair

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Abstract:

"Enamel matrix proteins" has role in development of dentin, acellular cementum and alveolar bone during tooth formation. is produced from porcine Hertwig's epithelial root sheath at the time of development of tooth. EMD has BMP like molecules and BMP expressing cells. Among them, BMP like molecules induce differentiation of odntoblasts and form the reparative dentin. Reports state that EMD consists of TGF-β like molecules. Also, EMD is capable of suppressing inflammatory cytokine production by immunocytes. This provides a constructive environment which promote healing of the wounded pulp tissues.EMD comprise of proteins which belong to the family of amelogenin which takes part in final odontoblastic differentiation and simultaneous dentin production. A formulation of EMD has its availability in the market with the brand name of Emdogain®. It has shown success in induction of hard tissue bridge production. Teeth having undergone vital pulp therapy with EMD displayed signs of classical wound healing. Study conducted recently stated that the combination of MTA and EMD leads the human dental pulpal cells to differentiate faster in comparison to the situation where MTA is used alone. This suggests that a hybrid approach is beneficial in keeping EMD in a stable position over the pulpal exposure site by a hard-setting pulp-capping material. In spite of the potential of

EMD to induce the mesenchymal stem cells to differentiate into odontoblasts, the reparative hard tissues assessed in current studies had resemblances with "atubular osteodentin" instead of "tubular dentin".

Keywords: "Enamel matrix proteins", "Emdogain", Direct Pulp Capping,

1. INTRODUCTION

Direct pulp capping (DPC)- a common method for treating small accidental pulpal exposure in permanent dentition. A variety of materials have been put to application formerly in capping exposed pulp and pulpotomy procedures. Out of these, calcium hydroxide has been conventionally put to use in clinical practice[1]. Nevertheless, reports have shown that the pulp tissue gets intensely irritated, and formation of a layer of necrosis is seen due to the alkaline action of calcium hydrate. $Ca(OH)_2$ produce a fresh layer of reparative dentin which has a porous structure leading to its poor sealing ability[2]. Pores thus formed increases the risk of microbial infection. Study conducted by Olsson et al stated that pulp capping undertaken using $Ca(OH)_2$ didn't give satisfactory results[3]. Thus, efficacy of $Ca(OH)_2$ in DPC has been compromised because of its inferior quality of seal, its degradation over the period of time & the occurrence of tunnel defects in dentine bridges. These challenges of $Ca(OH)_2$ gave way for the development of novel pulp-capping agents which can induce the dentin/pulp complex. In recent times, a lot of studies have shown that newer biocompatible agents like "bone morphogenetic proteins" (BMPs), "osteogenic protein–1" (OP-1), demineralized dentin, and "mineral trioxide aggregate" (MTA) can induce the formation of reparative dentin. Current research has suggested that Emdogain gel (EMD) (BIORA AB, Malmö, Sweden), which has its application majorly in "periodontal regenerative therapy", also has the capacity to induce rapid reparative dentin formation in a teeth that has undergone pulp capping[2].

"Enamel matrix proteins" has role in development of dentin, acellular cementum and alveolar bone during tooth formation. The prime non-collagenous protein expressed in bone and dentine are bone sialoprotein and osteopontin. "Enamel matrix proteins" have shown to accelerate the levels of mineralization markers (like bone sialoprotein and osteopontin) in odontoblasts. Using this idea, formulation of "enamel matrix derivative" (EMD) was done. Method of regeneration by EMD comprise of odontoblastic differentiation simultaneously with the development of the dentin bridge and the wound healing of the pulp tissue without having an impact on the vitality of the rest of the pulp. This simulates the normal process of dentinogenesis. The main component of EMD is Amelogenin and Amelin which plays a major part in the formation of dentin bridge during dentinogenesis. EMD also has certain growth factors like "transforming growth factor-beta 1" and small amelogenin peptides. They take part in cell signalling during stimulation of matrix formation and mineralization. These growth factors mediate tissue homeostasis, inflammatory processes, healing and neogenesis.

2. HISTORY

L hammarstrom concluded that in humans, the expression of amelogenin occurs at the apical end of a developing root of teeth. He supported the idea that "enamel matrix protein(s)" takes part in formation of cementum and such proteins can be put to use as a resource in regeneration of acellular extrinsic fiber cementum[4].

After the initial confirmation that a major portion of amelogenin is present in enamel matrix

derivatives, the first human trial on EMD was conducted by Heijl in 1997. He undertook a trial on a single experimental defect . He suggested that enamel matrix derivative could be used as an adjunctive to the regeneration of true peridontium[5].

In another clinical trial Heijl et al researched the long term impact of EMD on regeneration of infrabony defects. This evaluation was found to be promising. The trial demonstrated that topical application of EMDOGAIN resulted in an enhanced gain of bone as seen radiographically and also a gain in clinical attachment was observed[6].

Hence a series of clinical trials and studies were conducted which confirmed the efficacy of EMD and its therapeutic effect on regeneration of periodontal tissues[7]. Also a total of 173 of furcation defects were treated using EMD as an adjunct and have have confirmed the clinical effect of EMD in five year of observation[8].

EMD comprise of proteins which belong to the family of amelogenin. This is the hydrophobic part of the "enamel matrix proteins" (Fisher & Termine, 1985).

3. MECHANISM OF ACTION

EMD is produced from porcine Hertwig's epithelial root sheath at the time of development of tooth. It regulates enamel mineralization and has a major part in forming periodontal tissue by stimulating the acellular cementum, PDL, and alveolar bone to regenerate. EMD has BMP like molecules and BMP expressing cells. Among them, BMP like molecules induce differentiation of odntoblasts and form the reparative dentin. Reports state that EMD consists of TGF-β like molecules. Also, EMD is capable of suppressing inflammatory cytokine production by immunocytes. This provides a constructive environment which promote healing of the wounded pulp tissues. BMP is from the super family of transforming growth factor beta (TGF-b). TGF b has the potency to modulate repairing of tissue in various conditions. BMP-2, 4 & 7 has major part to differentiate adult pulpal cells into odontoblasts at the time of pulpal healing[9].

Lianjia et al., discovered that BMPs play an important role in dentinogenesis, induce undifferentiated mesenchymal cells of pulpal chamber to form "odontoblast-like cells", thus leading to osteodentin and tubular dentin deposition. This takes place whenever BMP are applied as pulp protectors directly. Hu et al., assessed the different growth factors such as "epidermal growth factor", basic "fibroblast growth factor", "insulin-like growth factor II", "platelet-derived growth factor-BB", "TGF-b 1" in rat molars and came to a conclusion that only TGF-b 1-improves and increases reparative dentin deposition[10].

A freshly exposed vital pulp will undergo repair by hard tissue bridge formation subjacent to the exposed sites. Clinically, we simulate the process that occur at the time of odontogenesis by evaluating the influencing factors and substances linked to the initial stages of dentin production. An example of such factor is "Amelogenin". According to Inai *et al,* 1991and Hammarstrom, 1997, during crown development, amelogenin translocate to the odontoblasts undergoing differentiation just before the production and deposition of circumpulpal dentin. Inferring from this, it is said that amelogenin takes part in final odontoblastic differentiation and simultaneous dentin production. A formulation of EMD has its availability in the market with the brand name of Emdogain®. It has shown success in induction of hard tissue bridge production[11].

Teeth having undergone vital pulp therapy with EMD displayed signs of classical wound healing - a surface layer or scabs, comprising extracellular matrix proteins & necrotic cell remnants. Subjacent to it is a zone showing infiltration of chronic inflammatory cell. Beneath this site of wound healing, formation of a bridge of novel hard tissue can be seen. This seals off the wound from the vital pulpal tissue. Pulpal tissue beneath the layer of the new hard tissue does not have any signs of inflammation. Also, formation of a layer of "odontoblast-like cells" can be observed, bordering the new mineralized tissue thus formed. This implies that EMD have the ability to induce production of a dentin-like hard tissue on its application on the wound of coronal pulp. The novel hard tissue formed has resemblances to tubular dentin which is outlined by odontoblast-like cells. Laboratory findings state that in exposed pulpal cells, EMD leads to induction of an intracellular cyclic-AMP signal. According to Lyngstadaas *et al.*, 2001, in mesenchymal cells, this intracellular signal leads to release of "autocrine growth factor" in a well-arranged cascade. This is followed by secretion of growth factors like PDGF and TGF-pi. This leads to proliferation of EMD-exposed cells and its maturation into "extracellular-matrix-secreting cells". This kind of mechanism is seen during the pulpal wound healing in the presence of EMD[9]. DPC using EMD should always be carried out under local anesthesia to lessen the uncomfortable post operative signs and symptoms[12,13].

4. ADVANTAGES-

- Induces differentiation of odontoblast and helps in forming reparative dentin.
- Inflammatory cytokine production gets suppressed and this leads to creation of a good environment which promote wound healing in the site of pulpal tissue injury[1].
- Quantity of hard tissue formation in teeth post EMD treatment is double than that of $Ca(OH)_2$.
- Symptoms that arise post treatment are much reduced.
- MTA when placed in adjunct with Emdogain produced an enhanced type of reparative hard tissue reaction than in comparison to that of $Ca(OH)_2$.

5. DISADVANTAGES-

- EMD gel (gel of propylene glycol alginate containing EMD)when used without any adjunctive pulp capping material, upon its application onto freshly exposed pulp tissue resulted in a poor seal. The hard tissue barrier thus produced is of inferior quality.
- Benefits of using EMD in clinical practice are still to be verified[1].

6. RECENT ADVANCES-

Studies showed that EMD gel (gel of propylene glycol alginate containing EMD) was inefficient in forming a barrier of hard tissue as the seal formed by it is of inferior quality. A study was conducted in human primary canines where pulpotomy was done using EMD gel. Results showed unconvincing evidence of the benefits of hard tissue barrier thus formed by EMD gel[14]. Recently 2 different randomized controlled clinical trials was conducted- in primary molars using EMD gel for DPC procedures[15] or partial pulpotomy[16] in permanent premolars. They did not see any enhancement in the quality of the formed hard tissue barrier as compared to the ones produced by the conventional pulp capping agents. Former studies have shown direct application of EMD on exposed pulp tissue without any usage of adjunct

pulp-capping material. One of the cell culture study conducted recently stated that the combination of MTA and EMD leads the human dental pulpal cells to differentiate faster in comparison to the situation where MTA is used alone[17]. This suggests that a hybrid approach is beneficial in keeping EMD in a stable position over the pulpal exposure site by a hard-setting pulp-capping material. Although calcium hydroxide is popularly used as a DPC agent yet it is known for its certain disadvantages like the occurrence of tunnel defects in the structure of the dentinal bridge itself, its slow but steady dissolution and its inferior sealing properties. MTA provides a better seal and has an excellent tissue responses[18]. It has shown success in DPC and pulpotomy procedures[19]. Portland cement which has a somewhat similar composition like MTA shows good biocompatibility with pulpal tissue. $Ca(OH)_2$ and MTA displays good dissolution in ‘‘fossilized’’ bioactive matrix components like transforming growth factor-b1 from mineralized dentin.

7. CONCLUSION-

EMD leads to induction or promotion of intrinsic reparative activities in the dental pulp. Nevertheless, we are yet to explore a lot more in this field in order to address the accurate and distinct mode of action and characteristic properties of EMD-induced reparative hard tissue production in a dental pulp wound[11]. In spite of the potential of EMD to induce the mesenchymal stem cells to differentiate into odontoblasts, the reparative hard tissues assessed in current studies had resemblances with "atubular osteodentin" instead of "tubular dentin". Even though it is a matter of controversy that EMD is advantageous in giving us a more efficient barrier to check the progress of bacteria in times of carious processes, the inability to produce tubular dentin highlights the challenges of EMD alone in organising & promoting a well-designed and efficient dentin matrix in the absence of the help from additional morphogens & nearby pulpal cells. Even the long term evaluation of the regenerative dentin bridge formation is insufficient and needs validation from long term prospective studies and clinical trials. The inefficacy to maintain the viability of EMD through adjunctive use of a feasible carrier for the same need to be introspected. For all the above reasons studies following the already proven facts is the need of the hour in the regenerative area of research.

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