Alternative Interventions to Formocresol as a Pulpotomy Medicament in Primary Dentition: A Review of the Literature

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Dental caries continues to be a major problem in pediatric dentistry and should receive significant attention in everyday practice, not only from the standpoint of restorative procedures but also in terms of preventive practices designed to reduce the problem[1].

Despite modern advances in the prevention of dental caries and the increased understanding of the importance of maintaining the natural primary dentition, many teeth are still lost prematurely. This can lead to malocclusion with aesthetic, phonetic and functional problems that may be transient or permanent. Therefore, maintaining the integrity and health of the oral tissues is the primary objective of pulp treatment. It is desirable to maintain pulp vitality whenever possible. Pulp autolysis, however, can be stabilized, or pulp can be eliminated without significantly compromising the function of the tooth[2].

The treatment of the dental pulp exposed by the caries process, by accident during cavity preparation, or even as a result of injury and fracture of the tooth has long presented a challenge in treatment. Pfaff, as early as, (1756) reported placing a small piece of gold over a vital exposure in an attempt to promote healing[3].

Different types of pulp treatment procedures have been recommended for primary teeth. They can be classified into two categories:

Conservative Treatment

Aims to maintain pulp vitality, such as, **Indirect Pulp Treatment**, in which the deepest layer of the remaining dentin is covered with a biocompatible material to prevent pulp exposure, and **Pulpotomy**, where pulp tissue is capable of healing after amputation and dressing of the affected or infected coronal pulp[2].

Radicular Treatment

Consisting of **Pulpectomy** and **Root Filling**. Those procedures are indicated in teeth that show evidence of chronic inflammation or necrosis in radicular pulp[2].

Successful pulpal therapy in primary dentition requires a comprehensive understanding of tooth development, etiology and pathogenesis of the pulp and the periradicular tissues. Although it has been established that the pulp is capable of healing, there is still much to learn regarding the control of infection and inflammation in vital pulp.

More effective methods of pulp therapy are still needed, innovative products are continually introduced and researchers are always working and striving to create the ideal pulp treatment[4].

Preservation of the remaining vital portion of cariously exposed pulpal tissue in primary teeth, where the demand is to keep a functioning tooth in site, was one of the most frequent problems in pediatric dentistry. To solve this problem pulpotomy therapy was introduced, developed and classified according to treatment objectives.

Pulpotomy

Involves amputation of the coronal portion of affected or infected dental pulp. Treatment of the remaining vital radicular pulp tissue surface should preserve the vitality and function of all or part of the remaining radicular portion of the pulp[5]. Furthermore, it is an accepted procedure for treating both primary and permanent teeth with carious pulp exposures[3].

Pulpotomy has become the dominating pulp therapy for the deciduous dentition, because of the complicated anatomy of the root canals in primary teeth, the proximity of the permanent tooth germ and the difficulties in finding a root-canal

filling material compatible with physiological root resorption[6].

Objectives of Pulpotomy

There should be no adverse clinical signs or symptoms such as prolonged sensitivity, pain, or swelling. The majority of the radicular pulp should remain vital. No internal resorption, abnormal canal calcification, or breakdown of periradicular supporting tissue should be evident[5].

Pulpotomy therapy for the primary dentition has developed along three lines: **Devitalization**, **Preservation**, and **Regeneration**[7].

Devitalization

The first approach to pulpotomy treatment of primary teeth was devitalization, where the intent is to destroy vital tissue. It is typified by **Formocresol**, **Electrosurgery** and **Laser**.

Formocresol Pulpotomy

Sweet (1930)[8], introduced the multiple -visit formocresol technique. Sweet's original methodology called for the procedure to be accomplished over multiple appointments, where the formocresol was left in contact with the radicular tissue for long periods of time (2-3 days)[9]. This procedure was designed to mummify the tissue completely. When completely fixed, the radicular pulp was theoretically sterilized and devitalized, thereby avoiding infection and internal resorption[10].
However, Sweet reduced the number of visits over the years, presumably because of economic and behavior management considerations.

Nacht (1956)[11], proposed modified devitalization technique, in which pulpotomy procedure was done in one or two appointments.

Doyle *et al.* (1962)[12], used a two-visit procedure in their comparative study of formocresol and calcium hydroxide. The two-visit procedure was actually a two-appointment procedure in which formocresol was applied to the tooth at the first appointment. The base (zinc oxide- eugenol) mixed with paraformaldehyde, was placed in the same tooth at the next visit[9].

Redig (1968)[13], reported the results of a five-minutes formocresol protocol, and since that time mummification has been abandoned by the profession.

Berger (1972)[14], reported the histological picture of pulpal tissue after formocresol pulpotomy. Fixation of the pulp tissue appeared adjacent to formocresol application sight, the middle third showed loss of cellular integrity which, alters the blood flow resulting in areas of ischemia. Middle to apical third showed an ingrowth of granulation tissue.

Hicks *et al.* (1986)[15], led a retrospective radiographic study on formocresol pulpotomies in primary molars. The results showed acceleration of root resorption, calcific metamorphosis and cases of furcation radiolucencies.

Roberts (1996)[16], reported prospectively the clinical success and effect upon the age at which primary molars that had received formoceresol pulpotomies exfoliated. High clinical success rate among vital teeth was reported. There was no significant effect on primary teeth exfoliation after pulpal treatment.

Farooq *et al.* (2000)[17], performed a study to retrospectively evaluate treatment of deep caries in primary molars with formocresol pulpotomy and indirect pulp therapy. Indirect pulp therapy success was significantly higher than formocresol pulpotomy. The exfoliation of primary molars was significantly hastened by formocresol pulpotomy.

Salako *et al.* (2003)[18], in their comparative study between bioactive glass, mineral trioxide aggregate, ferric sulfate and formocresol as pulpotomy agents in rat molar, reported that formocresol histologically showed zones of atrophy, inflammation and fibrosis. Fibrosis was more extensive at 4 weeks with evidence of calcification in certain samples.

Causes of Failure of Formocresol Pulptomy

Following the initial clinical trial by Redig (1968)[13], the five-minutes-treatment with formocresol became and has remained the standard against which all new modalities are compared. However, the original advantage of complete mummification, sterilization and metabolic suppression was lost. Instead the short treatment leaves the pulp only partially devitalized[7]. Commonly, the pulp remains half dead, half vital and chronically inflamed. In this state, the pulp is susceptible to abscess formation, and the root to internal resorption[14].

For many years, there has been controversy over the value of antimicrobial drugs for dressings in pulpotomies. Many investigations have been conducted to measure the risk of exposure to formocresol. It was clear that it posses a known toxic mutagenic and carcinogenic potential risk in humans[19].
The International Agency for Research on Cancer (IARC) classified formaldehyde as carcinogenic to humans in June (2004). There is now sufficient evidence that it causes nasopharyngeal cancers in humans, limited evidence of nasal & paranasal sinuses cancers, and strong but not sufficient evidence for Leukemia[20].

Other concerns have been raised regarding a valid evidence that formocresol is systemically absorbed, distributed and will initiate a specific humoral response as well as its effect on the succedaneous teeth. In particular, a correlation has been established between enamel defects in succedaneous teeth and formocresol pulpotomies performed on the primary dentition, such as, an increase in the prevalence of hypoplastic and/or hypomineralization defects.

Furthermore, an increased prevalence in positional alteration of the succedaneous teeth was reported[21]. Finally, there are indications that if formocresol touches the gingiva, it will cause necrosis and sloughing of the tissue[22].

This makes it very important for the profession to look for viable alternatives to Formocresol.

Electrosurgical Pulpotomy

Another form of non-chemical devitalization that emerged during the last decade, seeking to avoid medicaments was electrosurgical pulpotomy.

It is described as a technique in which the cutting effect of an electrosection is performed without manual pressure or crushing of the tissue cells. It results from heat generated by the resistance of the tissues offering passage to a radiofrequency current applied with a fine antenna called a surgical electrode. Unlike cautery, this technique allows more precise control of heat at the surgical site and hence minimal tissue destruction[23].

Therefore, the rationale for electrosurgical pulpotomy is that after the removal of affected coronal pulp tissue, a layer of coagulation necrosis caused by electrosurgery application provides a barrier between healthy radicular tissue and the base material placed in the pulp chamber[24].

Shulman *et al.* (1987)[25], led a histological study that compared the electrosurgery and formocresol pulpotomy techniques in monkey primary teeth. They reported that electrosurgically treated teeth showed pathological root resorption, periapical pathology and a spectrum of pulpal effects including acute and chronic inflammation, edema, fibrosis and diffuse necrosis.

Mack and Dean (1993)[26], in their clinical and radiographic retrospective human study, reported a success rate in electrosurgical pulpotomy procedure after two years. This study was compared to a previous formocresol pulpotomy study of similar design, which showed a significantly higher success rate for the electrosurgical pulpotomy procedure.
Dean *et al.* (2002)[27], prospectively compared electrosurgical pulpotomies versus formocresol pulpotomies in human vital primary teeth. This study failed to demonstrate clinical and radiographical differences in the success rate between the electrosurgical and formocresol techniques.

However, the electrosurgical procedure does have two distinct advantages in that it can be performed more quickly and there are no drugs involved that may produce undesirable systemic effects[23].

Laser Pulpotomy

Different studies were led on laser energy to overcome the histological deficits of electrosurgery. Ideally, **laser** irradiation creates a superficial zone of coagulation necrosis that remains compatible with the underlying tissue[7].

Shoji *et al.* (1985)[28], used CO_2 laser on exposed pulps in dogs and reported no histological damage to radicular pulp tissue.

Wilkerson *et al.* (1996)[29], studied the effects of argon laser on primary tooth pulpotomies in swine. They reported that after sixty days, pulps appeared to retain their vitality and capability of normal pulp healing. They also concluded that the use of argon laser pulpotomy did not appear to be detrimental to pulp tissues.

Moritz *et al.* (1998)[30], used CO_2 laser in direct pulp capping. Thermal tests were used for vitality assessment and laser Doppler flowmetry for direct measurement of pulpal blood. The last recall examination at 12 months demonstrated that 89 teeth remained vital, corresponding to a success rate of 89%. They concluded that CO_2 laser seems to be a valuable aid in direct pulp capping.

This study and others led to the use of laser for pulpotomy in primary teeth for better clinical, radiographic, and histological results, although much research is still needed to investigate this technique taking into consideration the high cost[31].

Preservation

This category is intended to only minimally insult the pulpal tissue, while not being capable of initiating an inductive process. Preservation of the pulpal tissue is exemplified by **Glutaraldehyde** and **Ferric Sulfate** treatment, in which there is retention of maximum vital tissue and virtual conservation of the radicular pulp without induction of reparative dentin[7].

Glutaraldehyde, has been suggested as an alternative to formocresol as pulpotomy agent, based on its superior fixative properties, low antigenicity, and low toxicity.

Dankert *et al.* (1976)[32], proposed glutaraldehyde as a prospective substitute for formocresol as pulpotomy agent.

Gracia-Godoy (1983)[33], found glutaraldehyde to be more acceptable biologically because of its high molecular weight that limits its tissue penetration.

Fuks *et al.* (1987)[34], reported that glutaraldehyde has a self-limiting penetration, hence, reduces the extent of inflammatory response.

Rusmah (1992)[35], in his study on pulpal tissue reaction to buffered glutaraldehyde, reported that the histological picture of treated pulp shows a zone of superficial fixation with very little underlying inflammation.

The clinical success rates with glutaraldehyde have ranged widely, due to superficial fixation that may result in insufficient depth of antibacterial action causing a deep zone of chronic cell injury. Systemic distribution may also be increased as a result of application of greater quantity of the agent[36]. It has also been observed that inadequate fixation leaves a deficient barrier to sub-base irritation, resulting in internal resorption[37].

Ferric Sulfate, a nonaldehyde agent that produces hemostasis at pulp stumps by chemically sealing cut blood vessels[38].

Landau and Johnsen (1988)[39], who proposed ferric sulfate as a pulpotomy medicament for vital primary teeth, have also found favorable histological results in the form of secondary dentin and bridging.

Furthermore, ferric sulfate acts as hemostatic agent by agglutination of blood protein, without the presence of a blood clot, which suggested that preventing clot formation might minimize the chances for chronic inflammation[40].

Fei *et al.* (1991)[41], led a study that demonstrated greater clinical and radiographic success rate of ferric sulfate pulpotomy over formocresol pulpotomy at one-year recall, and concluded that ferric sulfate was successful as a pulpotomy medicament in primary teeth.

Fuks *et al.* (1997)[42], investigated the pulp response to ferric sulfate solution and diluted formocresol in pulpotomized primary teeth of baboons. Ferric sulfate produced pulp responses that compared favorably to those of diluted formocresol.

Casas *et al.* (2004)[43], studied the long-term outcomes of primary molar ferric sulfate pulpotomy and conventional root canal therapy. Root canal treated molars demonstrated significantly greater survival than ferric sulfate treated molars three years after treatment.
Earlier clinical evaluation of ferric sulfate pulpotomies showed an excellent success rate. Recently the results reported from long-term studies were considerably less favorable, which opens an era for more investigations[42].

Regeneration

Unlike the other two categories of pulp treatment, the rationale for regeneration is the induction of reparative dentin formation by the pulpotomy agent. Ideally, it should leave the radicular pulp vital, healthy and completely enclosed within an odontoblast-lined dentin chamber. In this situation, the tissue would be isolated from noxious restorative materials, thereby diminishing the chances of internal resorption. Additionally, the odontoclasts of an uninflamed pulp could enter into the exfoliative process at appropriate time and sustain it in a physiologic manner[7].

The dental pulp is a highly vascular and innervated connective tissue, which is capable of healing by producing reparative dentin and/or dentin bridges in response to various stimuli and surgical exposure[44].

Calcium Hydroxide was the first agent used in pulpotomies that demonstrated any capacity to induce regeneration of dentin. However, because of its extreme alkalinity (pH of 12), that frequently causes necrosis, acute or chronic inflammation and dystrophic calcification in the pulp tissue, it is not recommended for pulpotomies in primary dentition[45].

Adhesive Liners were suggested as pulpotomy agents with the introduction of adhesive dentistry. Materials tested in permanent teeth are now being used in both primary and permanent dentition. Many studies have indicated that composite materials are compatible with pulp tissue. The success of adhesive dentistry is dependent on etching the enamel and dentin of the tooth requiring a restoration. When phosphoric acid was used as an etching agent, in teeth with pulp exposures, it did not produce inflammation and/or necrosis[46,47].

Usami *et al.* (1993)[46], tested the pulpal response of a light-activated fluoride releasing adhesive liner in dogs. All cavity preparations were 1mm of the pulp. There was none to slight inflammatory response, and no bacterial penetration found on either the dentin or the dentinal tubules.

Tsuneda *et al.* (1995)[47], tested four adhesive liners placed directly on exposed pulp tissue in rat molars. The best histological results obtained with the

use of the highest adhesive material, which forms a complete marginal seal, prevents microleakage and prevents bacterial intrusion. Presence of secondary dentin was also noted.

Kopel (1997)[48], in his review on adhesive liners as pulp capping material, advocated the use of adhesive liners for pulp capping procedures in primary teeth.

Tarim *et al.* (1998)[49], evaluated the biocompatibility of a resin-modified glass-ionomer on monkeys' pulps. It exhibited acceptable biologic compatibility and some teeth showed deposition of secondary dentin.

Hebling *et al.* (1999)[50], reported in their study on the biocompatibility of an adhesive system applied to exposed human pulps that the (all bond 2) adhesive system did not appear to allow any pulp repair and does not appear to be indicated for pulp capping of human teeth.

Costa *et al.* (2000)[51], evaluated the pulp response following direct pulp capping with (Prime & bond 2.0) adhesive system on pulp exposures in rat molar teeth. This adhesive system allowed pulp repair, characterized by recognition of a new odontoblast cell layer underlying the dentin bridge formation.

Costa *et al.* (2003)[52], evaluated and compared the response of pulps of rats capped with resin-modified glass-ionomer cement or self-etching adhesive system. Despite some inflammatory pulpal response, both experimental pulp-capping agents allowed pulpal healing characterized by cell-rich fibro dentin and tertiary dentin deposition.

The results of the studies cited above indicated debates on the ability of the adhesive liners to ensure pulpal healing. However, there have been no scientific human study to date that support this procedure[53].

Fortunately, the era of chemicals like calcium hydroxide and adhesive liners may be coming to an end. Recent advances in the field of bone and dentin formation have opened exciting new vistas for pulp therapy, and are fast approaching a rational period in treatment of pulp tissue. The prospect of being able to induce reparative dentin with recombinant dentinogenic proteins similar to the native proteins of the body is now present[7].

Biological Modulators

Innovative therapies apply biological modulators that have been identified during tooth and bone embryogenesis and later became cloned for experimental and clinical application. These modulators are intended to improve treatment modalities and ultimately induce tissue regeneration. It is hoped that the biological modulators will be the promising materials that will bear a potential of success, that will revive the expectations for regeneration of the exposed pulp tissue, rather than, devitalization of the pulp tissue that presumably replaces an acute inflammation with a chronic one, although it is the most beneficially used therapy from a long time ago and is still the most popular one[4].

Growth factors are biological modulators that are able to promote cell proliferation and differentiation. Naturally occurring osteogenic proteins, such as bone morphogenetic proteins (BMPs), are members of the transforming growth factor super family of bone-matrix polypeptides[4].

These bioactive molecules appear to modulate cartilage and bone deposition and/or resorption. The osteogenic properties of BMPs were initially demonstrated using demineralized bone matrix or reconstituted extracts of purified solubilized bone matrix[54]. This was followed by molecular cloning and expression of several recombinant human proteins BMPs (osteogenic proteins-1 [OP-1] and osteogenic proteins-2 [OP-2])[55].

Recombinant human BMP-2, BMP-4 and OP-1 (BMP-7) initiate endochondral bone formation when simply implanted subcutaneously or intramuscularly and when combined with insoluble collagenous bone matrix[56].

Other osteogenically active growth factors that have been identified are PDGF (platelet-derived growth factor[57], IGF (insulin-like growth factor) and FGF (fibroblast growth factor)[58].

Rutherford *et al.* (1993)[55], pioneered the use of human cloned bioactive osteogenic protein-1 (hOP-1) with a carrier matrix of purified bovine type-1 collagen powder (CM), moistened with sterile saline, for inducing reparative dentin formation in monkeys. They reported that substantially more new dentin was present in teeth treated with a contrast of recombinant hOP-1/CM. It was replaced initially by pulp like connective tissue that subsequently mineralized to form dentin.

Nakashima (1994)[59], found that bone morphogenic proteins BMP-2 and BMP-4 were capable of inducing dentin formation in amputated canine pulp. At two months the pulps were covered with tubular dentin at the pulp tissue side. The authors noted that BMP-2 and BMP-4 induce differentiation of adult pulp cells into odontoblasts, and concluded that BMPs may have role in dentistry as bioactive pulp treating agents for dentin formation.

Jepsen *et al.* (1997)[60], placed recombinant human

osteogenic protein-1 (hOP-1) in miniature swine of experimentally exposed dental pulps. Authors concluded that hOP-1 in collagen barrier appeared to be suitable as a bioactive pulp therapy agent.

Hu *et al.* (1998)[61], applied several growth factors (i.e. epidermal growth factor, basic fibroblast growth factor, insulin-like growth factor II, platelet derived growth factor –BB, and transforming growth factor-beta1) onto synthetic collagen barrier. These growth factors with collagen barriers were used separately as pulpal medicaments in rat molars. Pulps treated with TGF-beta-1 showed significantly improved soft and hard tissue healing at week three and enhance reparative dentin formation in rat molars, when used as medication.

Six *et al.* (2002)[62], assessed the effect of bone morphogenic protein-7 (BMP-7) in inducing reparative dentinogenesis in the exposed pulps of rat molars. In most BMP-7 treated specimens, heterogeneous mineralization or osteodentine filled the mesial coronal pulp. However, the complete filling of the root pulp with calcified tissue is not a reparative response, but is rather considered as pulp calcific degeneration since the entire root canal is replaced by mineralized tissue.

Goldberg *et al.* (2002)[63], evaluated bone sialoprotein (BSP), bone morphogenic protein-7 and chondrogenic inducing agents (CIA) implanted in amputated coronal pulp. Pulp tissue was evaluated for different levels of mineralization. They reported that these agents caused the formation of reparative dentin closing the pulpal wound (CIA), or filled the mesial part of the coronal pulp (BSP), or filled totally the pulp located in the root canal (BMP-7), and concluded that these molecules have great potential for clinical application in the near future.

The involvement of growth factors and extracellular matrix molecules in signaling and regulating dentinogenic events during tooth development, recommended the application of exogenous signaling factors for regenerative therapies. A number of delivery considerations must be addressed before these can be introduced into clinical practice[44].

However, none of these growth factors was highly effective for inducing dentine bridge formation in amputated pulp and further research is desired to provide continuance towards biological modulators and its clinical applicability[4].

Mineral Trioxide Aggregate (MTA)

A new material currently being used in pulp therapy, has been demonstrated to provide an enhanced seal over the vital pulp. It is a non-resorbable material that has been used experimentally for a number of years and was approved for human usage by the FDA[64]. Several in vitro and in vivo studies have shown that MTA prevents microleakage, is biocompatible and promotes regeneration of the original tissues when it is placed in contact with the dental pulp or periradicular tissues[65].

MTA is an ash-colored powder made primarily of fine hydrophilic particles of tricalcium aluminate, tricalcium silicate, silicate oxide, and tricalcium oxide. When the material is hydrated it becomes a colloid gel, it sets in approximately 3-4 hours, and bismuth oxide has been added for radiopacity[66].

Many investigators indicated that the healing of dental pulp exposures is not dependent on the pulp-capping material, but is related to the capacity of these materials to prevent bacterial leakage. MTA has been investigated as a potential compound to seal off the pathways of communication between the root canal system and the external surface of the tooth, which prevents the bacterial leakage and has a high level of biocompatibility[65].

Koh *et al.* (1998)[67], demonstrated that MTA has the ability to stimulate cytokine release from bone cells indicating that it actively promotes hard tissue formation. MTA has also been proposed as a potential medicament for pulpotomy procedures, pulp capping, apexification, and repair of root perforation.

Eidelman *et al.* (2001)[68], in their comparative study between MTA and formocresol in pulpotomized primary molars, reported clinical and radiographic success rates of pulpotomies with MTA and presence of dentin bridge.

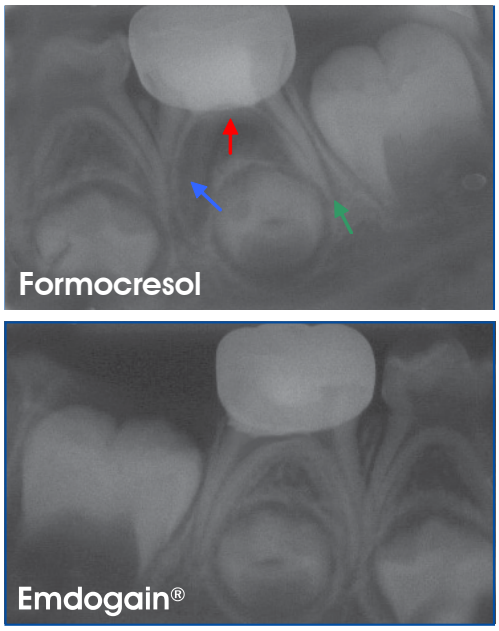
Salako *et al.* (2003)[18], in their histologic comparison of bioactive glass, mineral trioxide aggregate, ferric sulfate, and formocresol as pulpotomy agents in rat molars, concluded that MTA performed ideally as a pulpotomy agent causing dentine bridge formation while simultaneously maintaining normal pulpal histology.

MTA showed clinical, radiographic and histologic success as a dressing material following pulpotomy in primary teeth. After a short term evaluation period, it seems to have a promising potential. Despite the high success rate observed, it is still premature to draw definitive conclusions as the follow up periods are still short, and further investigation is needed[68].

Enamel Matrix Derivative

(Enamel matrix proteins) like amelogenins from the pre-ameloblasts, are translocated during odontogenesis to differentiating odontoblasts in dental papilla,

Periapical radiographs showing lower 2nd primary molars of the same patient treated with formocresol (on the left side) and Emdogain® (on the right side)



(Figure 1) At 6 months furcation radiolucency (↑) periapical radiolucency (↑) internal resorption (↑)

(Figure 2) At 6 months no radiographic changes

suggesting that amelogenins may be associated with odontoblast changes during development[69]. Enamel matrix derivative (EMD), obtained from embryonic enamel of amelogenin, was demonstrated in vitro, using a wound healing model, to be capable of stimulating periodontal ligament cell proliferation at earlier times (i.e., days one to three) compared to gingival fibroblasts and bone cells[70].

Heijl *et al.* (1997)[71], led a clinical trial on enamel extracellular matrix proteins in form of the enamel matrix derivative, EMD commercially presented as EMDOGAIN® which has been successfully employed to incite natural cementogenesis to restore a fully functional periodontal ligament, cementum and alveolar bone in patients with advanced peridontitis.

The ability of EMD to facilitate regenerative processes in mesenchymal tissues is well established. The EMD-induced processes actually mimics parts of normal odontogensis, and it is believed that the EMD proteins participate in the reciprocal ectodermal-mesenchymal signaling that control and pattern these processes[72]. Based on these observations, it has been suggested that amelogenin participates in the differentiation of odontoblasts and the subsequent predentin formation[18].
Nakamura *et al.* (2001)[73], demonstrated that EMD quickly induced a large amount of new dentin-like tissue when applied as a direct-capping material onto the exposed pulp tissue of permanent molar teeth in adult miniature swine. The pulp wound showed features of classic wound healing. Subjacent to the healing wound, a bridge of new hard tissue was formed, sealing off the wound from the healthy pulp tissue. The pulp tissue subjacent to this new hard tissue was invariably free of all signs of inflammation. Moreover, a layer of odontoblast-like cells had formed, abutting the newly formed mineralized tissue.

Nakamura *et al.* (2002)[74], in another study designed to examine if EMD could induce reparative dentin formation without eliciting adverse side effects in pulpotomized teeth in miniature swine. The results demonstrated the potential of EMD as a biologically active pulp dressing agent that specifically induces pulpal wound healing and dentin formation in the pulpotomized teeth without affecting the normal function of the remaining pulp. Furthermore, it was also reported that growth of some bacteria including Streptococcus mutans, is inhibited by the presence of EMD.

Ishizaki *et al.* (2003)[75], examined the histopathological response of dental pulp tissue to EMD used in pulpotomized teeth of mongrel dogs. Histologically, the treated teeth demonstrated an increase in tertiary dentin, suggesting that EMD exerts a considerable influence on odontoblasts and endothelial cells of capillaries in dental pulp tissue. These results imply that EMD use as a pulp treatment material plays a role in the calcification of dental pulp tissue.

Olsson *et al.* (2003)[76], led a study on the effect of EMD gel on experimentally exposed human pulps and registered postoperative symptoms. After twelve weeks, EMD gel demonstrated extensive amounts of hard tissue that was formed alongside the exposed dentin surfaces and in patches in adjacent pulp tissue. Moreover, postoperative symptoms were less frequent.

Sabbarini *et al.* (2008)[77], led a study to compare the clinical and radiographic success rates of enamel matrix derivative (EMD) versus formocresol (FC) as pulpotomy agents in the Primary Dentition. After 6 months, the clinical success rates for the FC and EMD groups was not statistically significan. However, the radiographic success rates for the FC and EMD groups showed a statistical significance between the two groups at 6 months **(figure1)** and **(Figure2)**.

The clinical and radiographic assessment of EMD pulpotomized teeth in that study offers preliminary evidence that EMD is a promising material which may be as successful, or more so, than other pulpotomy agents.

Based on these experiments, Emdogain® gel has several potential clinical applications and shows promising results as a valuable material for use in pulpotomy procedures especially in primary dentition. However, more experimental data and further human research

is needed, before Emdogain® gel can be developed as a material for predictable induction of dentin formation, which seems a reasonable challenge that is worthy of investigation.

Conclusion

From the published data available, it is concluded that Ferric sulphate, MTA and Indirect pulp capping appear to be promising alternatives to formocresol pulpotomy for cariously exposed vital primary molars [78].

However, further research is required to increase our knowledge of the clinical efficacy, histological effects and systemic impact of all the possible alternatives reviewed here. Therefore, long term studies with highest level of evidence are required to enable us to identify acceptable alternatives which can replace formocresol.

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