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Direct pulp capping in permanent teeth in children – tertiary dentin formation, materials used. Part II

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Summary

Direct pulp capping involves placing therapeutic material on mechanically or traumatically exposed pulp. The most essential requirement of therapeutic success is clinical state of the pulp which should be healthy or in reversible pulpitis. The method is particularly recommended for young permanent teeth due to the high regenerative potential of dental pulp. The mechanisms underlying these repair processes involve the ability of odontoblasts to form dentin bridges via tertiary dentin deposition. If pulp exposure occurs, a layer of odontoblasts is killed and must be replaced with a new odontoblastic population, which differentiates from pulpal stem cells under the influence of a therapeutic agent applied on the pulp. In addition to odontotropic properties and the ability to stimulate production of qualitatively satisfying dentinal bridge, the substance used for pulp capping should be biocompatible, not stain dental tissues, exhibit good adhesion to them, and insolubility in dentin tubule fluid or water. So far an agent which meets all the requirements mentioned above has not been invented. It is crucial to continue research to develop a substance that will yield the best effects in direct pulp capping.

Introduction

Biological pulp treatment plays a particularly important role in the exposure of pulp in young permanent teeth. Direct pulp capping in teeth with incomplete root development is characterised by high success rates and allows for the continuation of apexogenesis. Direct pulp capping is used only in certain clinical situations, which are indications for the procedure. Pulp exposure should have traumatic or mechanical aetiology, and the dental pulp should be either healthy or reversibly inflamed. If the above-mentioned criteria are met, no pathological clinical symptoms or lesions are revealed by the X-ray and tooth separation from the oral environment is possible, there is a good chance of therapeutic success of direct pulp capping.

Tertiary dentin formation

In order to fully understand the mechanisms of pulp treatment using biological methods, it is necessary to analyse the processes leading to the formation of tertiary dentin, a tissue that underlies the success of the discussed therapy.

Tertiary dentin is a type of dentin that forms in response to pathological external stimuli. Its role is to protect the pulp. Lesot et al. (1) were the first to postulate that two types of tertiary dentin need to be distinguished. According to the author, tertiary dentin formed by primary osteoblasts should be referred to as reactive dentin, while dentin produced by newly differentiated odontoblasts or odontoblast-like cells should be referred to as reparative

dentin. The classification was widely accepted due to its possible use in the histological context (2). Since the mechanisms underlying the formation of these two types of tertiary dentin vary, it is necessary to use different treatment strategies. These strategies will depend on the degree of pulp destruction as well as on whether the layer of primary osteoblasts was destroyed.

Reactive dentin forms in pulpal response to an early or slowly progressing stimulus, such as caries, non-cariogenic lesions or dental materials/medications. This type of dentin is formed by healthy odontoblasts at the site of the stimulus action between the pulp and the physiological dentin. If pulp irritation by the stimulus is only minor, as in the case of physiological tooth wear, reactive dentin grows slowly and its structure may not differ significantly from secondary dentin. In the case of stronger stimuli, the structure of dentin is more irregular; however, it is always more or less tubular (2). Indirect capping is a treatment method that affects the formation of reactive dentin.

In the case of major damage or severe pulp irritation, the superficial layer of primary odontoblasts is killed. Undifferentiated mesenchymal cells or dental pulp stem cells are transferred into newly-differentiated generation of odontoblasts, which, along with odontoblast-like cells, form a non-tubular structure, i.e. reparative dentin (2, 3). This mechanism underlies pulp treatment by means of direct capping. Therefore, dental material used for this purpose should be able to stimulate pulp stem cells to differentiate into a new population of odontoblasts.

Materials currently used for direct pulp capping

Perfect material for direct pulp capping should stimulate reparative processes within the pulp, tightly adhere to dental tissues, as well as be biocompatible, cause no dental tissue discolouration and be insoluble in water and dentin tubule fluid. So far, no material has been developed that would meet all these criteria.

Calcium hydroxide

The history of introducing calcium hydroxide as an agent used for direct pulp capping dates back to the early 1930s. The material was introduced into medical practice by Herrmann and for many decades it was considered to be the gold standard in direct pulp capping (4). Calcium hydroxide is used in dentistry in a setting or a non-setting form, with the latter one used in direct pulp capping.

The action of calcium hydroxide involves the release of hydroxyl ions, which alkalise the environment and have antibacterial effects. The development of superficial necrosis is the initial result of its direct contact with the pulp. Minor inflammation develops under the necrotic layer, which stimulates the pulp to defence, i.e. odontoblast differentiation and the formation of dentin bridge (5-7).

Disadvantages of calcium hydroxide include its poor mechanical and physical properties, formation of irregular and porous dentin bridge with evident defects as well as its solubility in dentinal fluid and acids. Also, calcium hydroxide does adhere to hard tissues. The above listed factors contribute to bacterial microleakage, which is one of the main causes of direct pulp capping failure. Calcium hydroxide initiates calcifying processes in the pulp, leading to pulp chamber mineralization, which may hinder the potential future endodontic treatment. Long-term success rates for direct pulp capping with the use of $Ca(OH)_2$ range between 13% and 96%, depending on the author (8). The long-term use of calcium hydroxide as the only agent for biological dental procedures revealed its many advantages, but also many drawbacks, which motivated the search for alternative products described below.

MTA

Mineral trioxide aggregate (MTA) is a material with significantly improved physical properties and lower complication rates compared to calcium hydroxide, which has recently gained popularity. Calcium hydroxide is the main reaction product of MTA and water.

MTA shows good mechanical strength as well as odontotropic, antibacterial and antifungal properties. Due to its limited solubility in tissue fluids, MTA does not undergo resorption as opposed to $Ca(OH)_2$, which improves its sealing efficacy and reduces the risk of microleakage. Furthermore, it is non-toxic towards pulp cells and produces X-ray contrast owing to the addition of bismuth oxide. There are two types of MTA: Grey Mineral Trioxide Aggregate (GMTA) and White Mineral Trioxide Aggregate (WMTA), which was developed to avoid dental discolouration, which occurs after GMTA. WMTA presents longer setting time and, according to some authors, worse physical properties of the formed bridge than GMTA. Other researchers found no statistically significant differences in the thickness of GMTA and WMTA-induced dentin bridge (9).

A more rapid formation of a thicker and more homogeneous dentin bridge is an advantage of MTA over $Ca(OH)_2$ (9, 10). Furthermore, MTA-induced inflammation is milder and short-lasting compared to $Ca(OH)_2$ (9-11). In most studies, long-term success rates for MTA are higher compared to $Ca(OH)_2$ (10, 12).

Biodentine

Biodentine is one of promising alternatives for the commonly used direct pulp capping agents. It is marketed in the form of ready-to-use capsules containing powder and ampoules containing calcium chloride solution, which requires agitation in a vortex mixer. The reaction produces hydrated calcium silicate and calcium hydroxide. Addition of calcium chloride in Biodentine reduces the setting time. Like $Ca(OH)_2$ and MTA, Biodentine has odontotropic activity, stimulating the formation of reactive and reparative

dentin. This was confirmed in *in vitro* studies, which demonstrated that Biodentine stimulates pulpal cells to release TGF-β1, which promotes the differentiation of pulpal stem cells into odontoblasts (13). *In vivo* studies demonstrated the ability of Biodentine to produce dentin bridge of satisfactory quality and thickness (14). Long-term marginal tightness preventing bacterial microleakage is an important advantage of this material. Furthermore, Biodentine may be used not only as an odontotropic agent, but also as dentin substitute to reconstruct the missing crown portion without the need for conditioning (13).

Attempts to use other direct pulp capping preparations

BioAggregate

BioAggregate (likewise MTA and Biodentine) belongs to the group of bioceramic calcium silicate-based cements. The material is available in the form of white powder consisting mainly of calcium silicate, calcium phosphate and hydroxyapatite. As opposed to MTA, BioAggregate releases no toxic substances, such as aluminium. Tantalum (V) oxide instead of bismuth oxide is used in the material as a contrast agent (15).

The biocompatibility of BioAggregate with human pulp stem cells (15, 16) and its mineralisation potential (17) are similar to those of MTA. Furthermore, the BioAggregate-induced stimulation of the differentiation of pulp stem cells into odontoblasts is similar to that of MTA, as demonstrated by monitoring the activity of alkaline phosphatase in *in vitro* studies conducted by Chang et al. (15). Other *in vitro* studies (18) showed beneficial effects of MTA, Biodentine and BioAggregate on odontoblastic differentiation and mineralised foci formation. The biocompatibility of Biodentine and BioAggregate was similar to that of MTA. The study demonstrated that the material can be used in direct pulp capping.

Calcium-enriched mixture

Calcium-enriched mixture (CEM) is a bioactive material that stimulates tissue regeneration, which was invented and patented by Asgary (19). It is also known as new endodontic cement (NEC). CEM is primarily composed of calcium salt, calcium oxide, calcium silicate and calcium phosphate, which are mixed with water-based solution. The preparation shows multiple benefits, such as antibacterial properties, biological activity, ability to form dental bridges and biocompatibility similar to that of MTA (20, 21). In some aspects, CEM is superior to MTA. These include easier application, shorter setting time, and greater thickness of dentin bridges observed in the samples using CEM vs. MTA (22). Furthermore, the composition of CEM is similar to that of dentin hydroxyapatite, which may be a factor facilitating the production of new tissue around the material (23).

Vitamin D_3

1α,25-dihydroxycholecalciferol (1α,25$(OH)_2D_3$) is considered to be the most active vitamin D_3 metabolite. The vitamin is known to play an important role in bone mineralisation and homeostasis. The effects of vitamin D_3 on dental mineralisation are also known. Vitamin D deficiency leads to impaired dentin mineralisation and delayed tooth eruption (24).

Woo et al. (24) showed in their *in vitro* studies that 1α,25$(OH)_2D_3$ stimulates the expression of dentin markers, such as dentin sialophosphoprotein (DSPP) and dentin matrix acidic phosphoprotein 1 (DMP-1). This indicates that 1α,25-dihydroxyvitamin D_3 may be useful in stimulating reparative dentin formation.

Another study verified the expression of dentin sialophosphoprotein (DSPP) and matrix extracellular phosphoglycoprotein (MEPE) following canine dental pulp capping with different combinations of dexamethasone, vitamin D and chitosan added to MTA. The experiment demonstrated that all these agents stimulate the dentinogenic potential of pulp stem cells (25). 1α,25-dihydroxyvitamin D_3 combined with dexamethasone and β-glycerophosphate (named ODM – odontoblastic differentiation material by the authors) was compared with MTA in *in vitro* studies in rats (26). Samples were assessed for inflammation, stem cell differentiation into odontoblasts and reparative dentin formation. More severe inflammation in the teeth treated with direct pulp capping was observed for ODM vs. MTA. Formation of odontoblasts and dentin bridges was observed in both groups, with no statistical differences in the thickness of dentin bridges between samples.

Hydrogel

Hydrogel is a compound composed of bovine serum albumin and glutaraldehyde as a cross-linker. It was patented in 2014 (27).

Studies were conducted to compare the homogeneity of dentin bridges formed by $Ca(OH)_2$ and Hydrogel following dental pulp capping in rat pulp exposure, as well as to assess the related inflammation (28). It was demonstrated that both preparations induce the formation of dentin bridges, which are more homogeneous after the use of Hydrogel. Furthermore, more severe inflammation was observed after pulp capping with $Ca(OH)_2$. So far, these are the only studies using Hydrogel for direct pulp capping, however, the promising results indicate that Hydrogel is likely to be considered as a material for further investigations.

Growth factors

Growth factors are responsible for modulating tissue development and growth as well as stimulating tissue regeneration and wound healing. Therefore, it seems reasonable to use these agents for direct pulp capping. *In vitro*

studies investigating the effects of, among other things, basic fibroblast growth factor (bFGF) (29), bone morphogenetic protein (BMP) (30), and recombinant human insulin-like growth factor-1 (rhIGF-1) (31) showed that these agents stimulate odontoblast formation.

Adhesive systems

The lack of material adhesion to dental tissues, and thus the occurrence of microleakage, is one of the main reasons for failures after direct pulp capping. Therefore, a substance that will ensure adhesion to dentin and, as the same time, meet the requirements for direct capping materials, is sought. For this reason, adhesive systems arouse interest among researchers.

Nowicka et al. (32) compared such parameters as dentin bridge quality, inflammatory infiltration and self-reported subjective symptoms of patients treated with direct capping using calcium hydroxide and self-etching adhesive system. Patients with self-etching adhesive system did not report pain as opposed to the group with calcium hydroxide, where some of patients reported minor symptoms. However, significantly thinner dentin bridges and slightly more severe pulp inflammation were observed in the teeth treated with adhesive system compared to calcium hydroxide. The same authors obtained similar results in their previous *in vitro* studies (33). A number of studies produced similar results – increased inflammation and the lack or poor quality of dentin bridges or complete treatment failure for adhesive systems (14, 34, 35). Another study showed that although pulp inflammation was less severe after adhesive systems than $Ca(OH)_2$, dentin bridge was thinner compared to $Ca(OH)_2$ (36, 37). Furthermore, immunohistochemistry showed no expression of proteins (fibronectin and type 3 collagen) important for reparative dentin formation by the pulp capped with adhesive system (38).

Enamel matrix derivative

EMD in the form of Emdogain preparation is widely used in the regeneration of periodontal tissues. Emdogain is composed of amelogenin proteins and other enamel matrix proteins as well as a carrier - propylene glycol. Amelogenin is involved in odontoblastic differentiation and dentin formation in the process of dentinogenesis (39).

In vivo studies comparing treatment outcomes after direct pulp capping using EMD and $Ca(OH)_2$ showed similar results. Olsson et al. (39) showed in their study that although less severe pain was reported for patients treated with Emdogain, pulp inflammation was increased compared to $Ca(OH)_2$. Although the amount of formed hard tissue was higher in the EMD group than in the $Ca(OH)_2$ group, it did not resemble dentin bridge. The authors suggest that similar research using the same carrier, i.e. propylene glycol, as a negative control is needed to demonstrate that enamel matrix proteins stimulate hard tissue formation. They also postulate that solid material should be used as a carrier as it is more appropriate for hard tissue formation.

A similar study was conducted several years later by Kiatwateeratana et al. (40), who obtained comparable results. The amount of hard tissue obtained in the EMD group was lower compared to the $Ca(OH)_2$ group, whereas inflammation was more severe after EMD vs. $Ca(OH)_2$.

The aim of another study was to characterise the newly formed tissue after the use of EMD by determining markers typical of dentin, i.e. dentin sialoprotein (DSP) and type 1 collagen. The newly formed tissue after direct capping with EMD and $Ca(OH)_2$ contained both markers, indicating that it was dentin. However, the newly formed tissue did not cover completely the site of exposure, raising doubts about its protective potential (41).

The expression of markers typical for dentinogenesis (amelogenin, DMP-1, OC, type 1 collagen) was also evaluated *in vitro* by incubating stem cells derived from human pulp in the presence of Emdogain (42). The results confirmed the hypothesis that EMD stimulates the differentiation of stem cells into odontoblast-like cells. Despite promising *in vitro* findings, the quality of EMD-formed hard tissue seems insufficient to use this agent for direct capping (43).

Conclusions

Direct pulp capping is a method that allows the preservation of pulp vitality, which is a key parameter for long-time tooth maintenance in the oral cavity. It is important to know the therapeutic indications for this method as well as agents that ensure the highest probability of positive outcomes. Therefore, studies to develop dental material ensuring the best possible long-term treatment outcomes are needed.

Conflict of interest

None

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