Overview of Different Options for Dental Pulp Therapy: A Systematic Review

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Abstract

The dental pulp has many functions that include nutritive, protective, initiative, and reparative ones. Nevertheless, it has a low threshold of damage, for being enclosed in hard tissue. This could, by time, lead to a loss of the pulp and fragile teeth with low quality of life. To avoid tooth extraction and all of the root canal treatment, the proper pulp capping or regeneration therapy of the pulp should be directly carried out. For that, this systematic review will focus on the different options of dental pulp therapy. A systematic electronic database search was conducted for relevant studies published from inception and till 13th May 2020 in seven databases. We included the most appropriate published studies that reported different techniques of dental pulp therapy, after excluding irrelevant ones and those with poor quality. Therapies for dental pulp include two main categories: direct pulp capping and vital pulp amputation. In this study, we have reviewed current and future dental pulp therapies. Most of the current procedures cause an irreversible sacrifice of tissues, leaving vulnerable teeth. Shortly, new regenerative therapies and DCP agents, thanks to the great ongoing studies, are expected to re-shape the current practice and improve patients' quality of life.

Keywords: Dental Pulp Therapy; Endodontics; Pulpotomy

Introduction

The dental pulp, which is surrounded by dentin, plays an important role in preserving the tooth and supports the vitality of the tooth by supplying it with essential factors through the apical foramen [1]. Blood vessels, providing nutrients and removing waste products, and the neural network, indicating the presence of harmful stimuli through pain, are passing through the apical foramen [2]. The colonization of microorganisms and other foreign antigens in the pulp is prevented by multiple immune cells, such as T lymphocytes, macrophages, and dendritic cells [2]. If the sound dentine has been damaged as a result of tooth damage, fracturing, or caries, the tooth will be repaired.
by odontoblasts or odontoblast-like cells [2]. These cells deposit tertiary dentin that is reactive and reparative dentine on the chamber surface of the pulp [2].

Bacterial infection and inflammation of the pulp, occurring after the development of dental caries or tooth fractures in the tooth crown, and the internal pressure in the pulp chamber increases significantly; leading to pulp ischemia which manifests with severe pain [2]. Eventually, Dentists perform pulpectomy and remove the dental pulp to relieve patients from pain and prevent further dental pulp infection [3]. If there is any delay in performing pulpectomy or it isn't performed, Ischemia progresses as the blood circulation is impaired, accompanied by pulp necrosis and periapical disease [4].

Due to complete perception loss and immune function losses in the non-vital tooth, resistance to external stimuli will be diminished and teeth will become fragile due to the loss of their metabolic capacity [3]. Furthermore, the immune response is impaired in non-vital tooth and this tooth would be usually reinfected. Sensation loss due to reinfecition enables dental caries progression. In this case, the treatment of the root canal does not have a high success rate and root canal retreatment still has to be repeated [5]. Repetition of root canal processing increases the fragility of the teeth and contributes to cracking and/or root fractures. The tooth must then be removed and this leads to quality of life deterioration. To avoid tooth extraction and all of the root canal treatment, the proper pulp capping or regeneration therapy of the pulp should be directly carried out. This systematic review will focus on the different options of dental pulp therapy.

**Methods**

**Search strategy and study selection**

The study process was conducted following the accepted methodology recommendations of the PRISMA checklist for systematic review. A systematic electronic database search was conducted for relevant studies published from inception and till 13\textsuperscript{th} May 2020 in seven databases including Google Scholar, Scopus, Web of Science (ISI), PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), Embase and CINAHL using keywords, medical subject (MeSH) terms. In databases not supporting MeSH terms, combinations of all possible terms were used. Moreover, we conducted a manual search of references from the included articles by searching the primary studies that had cited our included papers and scanning references of the relevant papers in PubMed and Google Scholar to avoid missing any relevant publications.

We included the most appropriate published studies that reported different techniques of dental pulp therapy. Papers were excluded if there were one of the following exclusion criteria: non-original studies, duplicate records, data could not be reliably extracted or incomplete reports, abstract only articles, thesis, books, conference papers. The title and abstract screening were done independently by four reviewers. Then, three independent reviewers performed a full-text screening to ensure the inclusion of relevant papers in our systematic review. Any disagreement was resolved by discussion and referring to the senior author when necessary.

**Data extraction**

Two authors developed the data extraction sheet using the Microsoft Excel software. Data extraction was performed by three independent reviewers using the excel sheet. The fourth independent reviewer performed data checking to ensure the extracted data accuracy. All the disagreements and discrepancies were resolved by discussion and consultation with the senior author when necessary.

**Quality assessment**

Three independent reviewers evaluated the risk of bias in the included studies. The National Institutes of Health (NIH) quality assessment tools were used to determine the quality of included studies, according to their study design [6]. Any discrepancy between the
reviewers was solved through discussion. This step was done only to assess the quality of the evidence to include only studies with fair to good quality (and exclude studies with poor quality), that is why no reporting of individual studies was provided.

Results and Discussion

Search results

We identified 47,477 records after excluding of 5,861 duplicates using the Endnote X9 software. Title and abstract screening resulted in 246 records for further full-text screening. Five papers were added after performing manual search trials. Finally, we included 55 of the different study designs for this systematic review (Figure 1).

Direct pulp capping

Pulpitis and pulp necrosis can result from untreated pulp exposure to the oral cavity; however, pulpotomy and/or direct pulp capping (DPC) can be performed to prevent pulp death [7]. The general concept of DPC is treating the vital pulp, using dental materials, to facilitate reparative dentin formation [8]. The most commonly used DPC materials are calcium hydroxide and mineral trioxide aggregate (MTA) [8]. The current and emerging DPC agents are summarized in figure 2.
Calcium hydroxide

Having excellent antibacterial properties (for having a pH around 12), calcium hydroxide has been considered as the “gold standard” of DPC materials for decades [9]. However, this high pH has shown to cause necrosis and mineralization in the area under the material [10]. An overview of the previous studies comparing the outcome of DPC with calcium hydroxide and adhesive systems is provided in table 1.

<table>
<thead>
<tr>
<th>Study</th>
<th>Teeth No.</th>
<th>Type of exposure</th>
<th>Restoration</th>
<th>Duration</th>
<th>Histological analysis</th>
<th>Pulp capping material*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accorinte., et al. 2006 [13]</td>
<td>40</td>
<td>Mechanical</td>
<td>Total-etch/composite</td>
<td>2 months</td>
<td>Yes</td>
<td>Calcium hydroxide</td>
</tr>
<tr>
<td>De Souza Costa, et al. 2001 [14]</td>
<td>33</td>
<td>Mechanical</td>
<td>Self-etch/composite</td>
<td>10 months</td>
<td>Yes</td>
<td>Calcium hydroxide</td>
</tr>
<tr>
<td>Accorinte., et al. 2008 [15]</td>
<td>34</td>
<td>Mechanical</td>
<td>Self-etch/composite</td>
<td>3 months</td>
<td>Yes</td>
<td>Calcium hydroxide</td>
</tr>
<tr>
<td>Subay and Demirci 2005 [16]</td>
<td>16</td>
<td>Mechanical</td>
<td>Total-etch/composite</td>
<td>1 month</td>
<td>Yes</td>
<td>Calcium hydroxide</td>
</tr>
<tr>
<td>Accorinte., et al. 2005 [17]</td>
<td>25</td>
<td>Mechanical</td>
<td>Total-etch/composite</td>
<td>2 months</td>
<td>Yes</td>
<td>Calcium hydroxide</td>
</tr>
<tr>
<td>Fernandes., et al. 2008 [18]</td>
<td>46</td>
<td>Mechanical</td>
<td>Total-etch/composite</td>
<td>1 month</td>
<td>Yes</td>
<td>Calcium hydroxide</td>
</tr>
<tr>
<td>Hörsted-Bindslev., et al. 2006 [19]</td>
<td>34</td>
<td>Mechanical</td>
<td>Total-etch/composite</td>
<td>2 months</td>
<td>Yes</td>
<td>Calcium hydroxide</td>
</tr>
</tbody>
</table>

*Material with the best performance.

There are two types of calcium hydroxide materials: one-paste non-setting type and two-paste self-setting type [7]. The one-paste non-setting type of calcium hydroxide materials has some major disadvantages; including the lack of setting, bad physical properties, and dissolution gradually [7]. Moreover, the additional components of the two-paste calcium hydroxide material have shown more cytotoxic effects than the one-paste systems [11]. Noteworthy, both of calcium hydroxide material types cause a heterogeneous formation of dentin bridge with tunnel defects, which in turn, lead to failure in providing barriers acting as biological sealants to bacterial infections [12].

Mineral trioxide aggregate (MTA)

The MTA, endodontic’s bioactive material, has been recently used as a DPC agent [20]. It has a Portland cement component and exhibits antibacterial activity, mainly mediated through the release of calcium hydroxide [21]. On one hand, many clinical trials have shown higher success rates of DPC using MTA compared to calcium hydroxide [22-25]. The results of some selected studies are summarized in table 2. On the other hand, several disadvantages of MTA have been reported; including increased setting time [26], toxic elements are present (e.g. arsenic) [27], discoloration [22], freshly mixed state has increased cytotoxicity [8], pH is high [28] and require enough moisture through the process of hardening [8].

In a trial to overcome the flaws of MTA materials in DPC, any MTA-derived agents were tested [26]. For example, replacing the Portland cement part of MTA with pure tricalcium silicate produced an enhanced biomaterial with better physicomechanical characteristics [38]. Moreover, calcium chloride was added to MTA to shorten the setting time and improve biocompatibility [39].

In the same context, a light-curable resin-modified calcium-silicate (L-C.R-M.C-S) based cement has been produced, which outweighs conventional MTA materials by preventing washing out of materials, immediately light-polymerized and better physical properties [40]. Nevertheless, the L-C.R-M.C-S MTA showed higher cytotoxic effects compared to resin-free calcium-silicate or MTA [11]. For that, further research is needed to give more data and appropriate evaluation of these modified materials before using them on a wide range in DPC.

**Table 2: Comparison of direct pulp capping with calcium hydroxide and mineral trioxide aggregate (MTA).**

<table>
<thead>
<tr>
<th>Study</th>
<th>Teeth No.</th>
<th>Type of exposure</th>
<th>Restoration</th>
<th>Follow up</th>
<th>Histological analysis</th>
<th>Pulp capping material*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mente., et al. 2014 [23]</td>
<td>229</td>
<td>Caries/Mechanical</td>
<td>Permanent</td>
<td>123 months</td>
<td>No</td>
<td>MTA</td>
</tr>
<tr>
<td>Hilton., et al. 2013 [24]</td>
<td>376</td>
<td>Caries/Mechanical</td>
<td>Permanent/Temporary</td>
<td>2 years</td>
<td>No</td>
<td>MTA</td>
</tr>
<tr>
<td>Bogen., et al. 2008 [22]</td>
<td>49</td>
<td>Caries</td>
<td>Composite</td>
<td>Up to 9 years</td>
<td>Yes</td>
<td>MTA</td>
</tr>
<tr>
<td>Accorinte., et al. 2008 [29]</td>
<td>40</td>
<td>Mechanical</td>
<td>RMGI/Composite</td>
<td>2 months</td>
<td>Yes</td>
<td>Equal</td>
</tr>
<tr>
<td>Tuna and Olmez 2008 [30]</td>
<td>50</td>
<td>Caries</td>
<td>ZOE/Amalgam</td>
<td>2 years</td>
<td>No</td>
<td>Equal</td>
</tr>
<tr>
<td>Aenichi., et al. 2002 [31]</td>
<td>14</td>
<td>Mechanical</td>
<td>ZOE/Amalgam</td>
<td>6 months</td>
<td>Yes</td>
<td>No Stats</td>
</tr>
<tr>
<td>Iwamoto., et al. 2006 [32]</td>
<td>48</td>
<td>Mechanical</td>
<td>Flowable/Composite</td>
<td>4 months</td>
<td>Yes</td>
<td>Equal</td>
</tr>
<tr>
<td>Min., et al. 2008 [33]</td>
<td>20</td>
<td>Mechanical</td>
<td>RMGI/Composite</td>
<td>2 months</td>
<td>Yes</td>
<td>Mixed</td>
</tr>
<tr>
<td>Qudeimat., et al. 2007 [34]</td>
<td>64</td>
<td>Caries</td>
<td>RMGI/Amalgam/SSC</td>
<td>3 years</td>
<td>No</td>
<td>Equal</td>
</tr>
<tr>
<td>Al-Hiyasat., et al. 2006 [25]</td>
<td>204</td>
<td>Caries/Mechanical</td>
<td>ZOE/Composite</td>
<td>3-10 Years</td>
<td>No</td>
<td>MTA (no direct comparison)</td>
</tr>
<tr>
<td>Percinato., et al. 2006 [35]</td>
<td>90</td>
<td>Caries</td>
<td>RMGI/Composite</td>
<td>1 year</td>
<td>No</td>
<td>Equal</td>
</tr>
<tr>
<td>Nair., et al. 2008 [36]</td>
<td>30</td>
<td>Mechanical</td>
<td>ZOE</td>
<td>3 months</td>
<td>Yes</td>
<td>MTA</td>
</tr>
<tr>
<td>Chacko and Kurikose 2006 [37]</td>
<td>31</td>
<td>Mechanical</td>
<td>ZOE</td>
<td>2 months</td>
<td>Yes</td>
<td>MTA</td>
</tr>
</tbody>
</table>


**Improved MTA/calcium silicates**

In a trial to overcome the flaws of MTA materials in DPC, any MTA-derived agents were tested [26]. For example, replacing the Portland cement part of MTA with pure tricalcium silicate produced an enhanced biomaterial with better physicomechanical characteristics [38]. Moreover, calcium chloride was added to MTA to shorten the setting time and improve biocompatibility [39].

In the same context, a light-curable resin-modified calcium-silicate (L-C.R-M.C-S) based cement has been produced, which outweighs conventional MTA materials by preventing washing out of materials, immediately light-polymerized and better physical properties [40]. Nevertheless, the L-C.R-M.C-S MTA showed higher cytotoxic effects compared to resin-free calcium-silicate or MTA [11]. For that, further research is needed to give more data and appropriate evaluation of these modified materials before using them on a wide range in DPC.
Bioactive glass-based cement

Trace amounts of arsenic and heavy metals [27] have been detected in calcium silicates-based agents (MTA included). Bioactive glass material, a member of bioceramics, can bond to bone through a formed layer of hydroxyapatite [41], which makes it suitable for usage in bone engineering purposes, like in orthopedic surgery discipline [42]. For that, bioactive glass-based cement was recently developed, which shows pH level stability, the formation of a hydroxyapatite-like layer on the hardened cement surface, considerable biocompatibility, and much less/no cytotoxic effects [43]. As a DPC agent, bioactive glass-based cement showed the ability to stimulate the formation of reparative dentin on the exposed pulp surface [44]. Further improvement of this material as a DPC material is still under trials.

Future Perspectives

As mentioned before, regardless of the material, the formation of reparative dentin is mainly induced by the chemical stimulation by the high pH of the used material; however, finding an agent to enhance the natural wound healing and reparative dentin formation has been always a target [8]. One of the candidates in this context is the bone morphogenetic protein (BMP)-2, one of the transforming growth factor (TGF)-β family, which was approved for clinical use by the US Food and Drug Administration (FDA) [45]. Previous literature has shown that BMP-2 stimulated the expression of odontoblasts markers of differentiation (dentin sialoprotein plus dentin matrix protein-1) [46] and the pathway of Smad signaling (odontoblastic cell proliferation and differentiation) [47]. Other BMPs have been also associated with dentinogenesis enhancement; including BMP-4, BMP-6, BMP-7, and growth/differentiation factor-11 [48]. In addition, TGF-β1 and fibroblast growth factor (FGF)-2 have found to be involved in odontoblast differentiation and odontogenesis regulation during the process of dental pulp healing [49].

In the same context, some other co-factors were recently considered to enhance the chances of DPC success. The continuous fever-range (41°C) heat stress found to induce heat tolerance in odontoblast-lineage cells, through the accumulation of heat shock proteins (HSPs) [50]. In the same way, HSPs found to induce resistance to multiple stimuli so that it can be considered as a pre-treatment agent for DPC [51]. Moreover, the macromolecular translocation inhibitor II (MTI-II) peptide anti-inflammatory drug (MPAID) found to play a role in the regulation of the inflammatory response; protecting the dental pulp and making it a candidate as a pretreatment agent in DPS, as well [52]. Other co-factors are being evaluated like the chlorhexidine polymer scaffold which found to be beneficial as a vital pulp therapy to save teeth requiring pulpotomy [53] and Ozone application as an indirect pulp therapy which showed to improve success rates [54].

Post-pulpotomy dentin-pulp complex regeneration

Issues with the conventional pulpotomy

To avoid pulpectomy, dentists perform Pulpotomy, which is a type of therapy applied to a coronal inflamed pulp. In pulpotomy, dentists amputate coronal pulp surgically and treat the surface of the remaining root pulp with medications that are applied to the root canal orifice such as MTA or calcium hydroxide to enhance the formation of dentin bridge [3]. The newly formed dentin bridge is a porous tissue that has a low calcification degree [12]. The current pulpotomy procedure has a major issue that is lost dentin-pulp complex never regenerate [8].

New methods of post-pulpotomy regeneration of the dentin-pulp

To induce the regeneration of dentin-pulp complex after pulp amputation, stem cells and network capillaries are induced from the residual tissue of the root pulp then prepared with adhesive materials to form a closed space [55]. Stem cell induction and capillary network delivery growth factors, they also act as scaffolds for both proliferation and differentiation of the cells which is necessary for tissue regeneration [55].

The problem was that the induced dentin does not have the ideal structure and its quantity was not sufficient to protect the pulp or withstand the forces of the bite. BMP-2 has shown the ability to form in vivo dentin after pulpotomy so it may be useful and other growth factors used in dentinogenesis are candidates [56]. Platelet-rich plasma was found to induce the odontoblastic cell differentiation and the activity of alkaline phosphatase [57].

Besides collagen, there are several natural materials, as gelatin and chitosan, and some synthetic materials, as glycolide (PLG), D,L-lactide, and polyglycolic acid, were used for the therapy [58]. Hyaluronic acid (HA) was reported as a suitable material for tissue engineering as it has an important role in morphologic organization maintenance and has anti-inflammatory effects [59]. In vivo and in vitro studies were carried out and the results showed that HA scaffolds have the ideal characteristics to be used in dentin-pulp complex regeneration [60].

In comparison to immature teeth with good blood flow and cells, local dentin-pulp regeneration can be difficult to be achieved with a mature tooth after pulpotomy. However, the identification of the right mix of growth factors and the creation of a delivery mechanism for growth factors and cell scaffolding will advance local dentin-pulp regeneration therapy following pulpotomy [8].

**Conclusion**

In this study, we have reviewed current and future dental pulp therapies. Most of the current procedures cause an irreversible sacrifice of tissues, leaving vulnerable teeth. In the near future, new regenerative therapies and DCP agents, thanks to the great ongoing studies, are expected to re-shape the current practice and improve patients’ quality of life.

**Funding**

None.

**Conflicts of Interest**

No conflicts related to this work.

**Bibliography**


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