Efficacy of the enamel matrix derivative in direct pulp capping procedures: A systematic review

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Abstract
The aim was to review the efficacy of the enamel matrix derivative (EMD) in direct pulp capping (DPC) procedures. Databases were explored using the following keywords: ‘dental’, ‘dentin’, ‘enamel matrix derivative’, ‘pulp capping’ and ‘treatment’. The inclusion criteria were: (i) original studies; (ii) human and animal studies; (iii) reference list of potentially relevant original and review articles; (iv) intervention: effect of EMD on pulp-capping procedures; and (v) articles published only in English. Eight studies (four human and four animal) were included. Among the human studies, two studies reported that EMD is a more efficient DPC procedure compared with calcium hydroxide (Ca(OH)₂). One study reported Ca(OH)₂ to be more efficient for DPC than EMD. One study reported no difference in the efficacies between EMD and Ca(OH)₂ for DPC. All animal studies reported EMD to be more effective in reparative dentin formation in comparison with Ca(OH)₂. EMD can provide favourable results in DPC procedures.

Introduction
Direct pulp capping (DPC) is a commonly used procedure for the treatment of small accidental pulp exposures in the newly erupted permanent dentition (1–5). Although calcium hydroxide (Ca(OH)₂) has been traditionally used for DPC (6,7), other studies reported that the strong alkaline nature of the material may induce necrosis of the pulp (8,9). The efficacy of Ca(OH)₂ in DPC has also been challenged due to its poor sealing quality, degradation over time and the presence of tunnel defects in dentin bridges (10). Such disadvantages of Ca(OH)₂ led to the development of new pulp-capping materials, including bioactive molecules and enamel matrix protein (6,10–16).

It is known that the enamel matrix proteins play biological roles in the formation of dentin, acellular cementum and alveolar bone during tooth development (17). Bone sialoprotein and osteopontin are major non-collagenous protein expressed in bone and dentin (18,19). Enamel matrix proteins have been reported to increase the levels of mineralization markers (including bone sialoprotein and osteopontin) in odontoblasts (20). Based on this concept, the enamel matrix derivative (EMD) was formulated. The regenerative process of EMD consists of differentiation of odontoblasts with consequent dentin formation and pulpal wound healing without affecting the vitality of the remaining pulp in a manner similar to normal dentinogenesis (13–21). Amelogenin is the principal component of EMD that has an important role in dentin formation during dentinogenesis (17,22–24). When a pulp wound is exposed to EMD, a significant amount of reparative dentin-like tissue is formed with successive neogenesis of normal pulp tissues, in a manner similar to the classical wound-healing process. This process appears to imitate normal dentinogenesis due to the high fractions of amelogenin and amelin found in EMD (17,22–24). EMD has also been reported to contain growth factors such as transforming growth factor-beta 1 and small amelogenin peptides that are actively involved in cell signalling to stimulate matrix formation and mineralization (11,22,25,26). These growth factors are recognized as mediators in
processes such as tissue homeostasis, inflammation, healing and neogenesis.

EMD has been tested as a pulp-capping material in human (5) as well as animal studies (12,14,15). The results showed EMD to be in close proximity to the newly formed hard tissue, thereby supporting the hypothesis that EMD is a more effective DPC agent that promotes hard tissue formation in exposed human pulps compared with Ca(OH)2 (5,12,14,15). Nevertheless, Garrocho-Rangel et al. (2) reported no significant differences in the efficacies of EMD and Ca(OH)2 as DPC materials. Although clinical and experimental studies on DPC with EMD have demonstrated promising results, the results remain debatable. Thus, the aim of the present systematic review was to examine the efficacy of the EMD in pulp-capping procedures. The focused question to be answered (a problem, intervention, comparison and outcome (PICO) question) may be framed as follows: ‘In vital teeth with pulpal exposures, does DPC with calcium hydroxide, compared with enamel matrix derivative, result in a worse clinical or histologic outcome?’

Materials and methods

Inclusion and exclusion criteria

The inclusion criteria were: (i) original studies; (ii) human and animal studies; (iii) reference list of potentially relevant original and review articles; (iv) intervention: effect of EMD on pulp-capping procedures; and (v) articles published only in English. The exclusion criteria were historic reviews, cell culture studies, commentaries, letters to the editor and unpublished articles.

Search strategy

The MEDLINE/PubMed (National Library of Medicine, Bethesda, MD, USA) and Google scholar databases were first searched for appropriate articles addressing the focused question. Databases were explored from 1949 to 2010 (last accessed 2 November 2010) using the following keywords in various combinations: ‘dental’, ‘dentin’, ‘enamel matrix derivative’, ‘pulp capping’ and ‘treatment’. A similar search was also conducted using EMBASE and Wiley Online Database.

The second step was to hand search the bibliography of the original and review articles that were obtained from the computer search. Titles and abstracts of the retrieved articles were screened by the authors and checked for agreement. After final selection of the papers, full texts of the studies that fulfilled the selection criteria were retrieved and processed for data extraction. The following data were extracted from all the selected studies: investigators and year of publication of the study, aim, study design, study participants or animal models (in human and animal studies, respectively), numbers of teeth included, follow-up duration, and conclusion. The initial search yielded 12 studies. Four studies that did not fulfil the eligibility criteria were excluded (Table 1). Eight studies (four human (2–5) and four animal (13–16) that fulfilled the inclusion criteria were included (Tables 2,3). Because only a limited number of studies fulfilled our inclusion criteria, a qualitative review was performed to primarily summarise the pertinent data. No meta-analyses were performed to analyse the data.

Results

Of the eight included studies, six studies reported that DPC with EMD yields favourable outcomes (3,5,13–16).

Human studies

The numbers of participants ranged from 1 female subject to 45 individuals (2–5). The numbers of teeth investigated ranged from 1 tooth to 30 teeth. The size of the exposure defects ranged between 1 and 2 mm. The duration of follow-up after EMD treatment ranged from approximately 3 months up to 1 year. The teeth included in the ‘test-group’ received EMD dressings for DPC, whereas teeth in the ‘control-group’ received Ca(OH)2 dressings. In two (2,3) out of the four studies, the efficacy of EMD for DPC was tested in primary molars; in the remaining studies (4,5), the effectiveness of the material was tested in the permanent dentition. One study (2) reported no significant difference between the efficacies of EMD and Ca(OH)2 as DPC materials. Two studies (3,5) reported that EMD enhanced the formation of reparative dentin when compared with Ca(OH)2. Results from Kiatwateeratana et al. (4) indicated that DPC with Ca(OH)2 has more

Table 1 List of excluded studies and main reasons for exclusion

<table>
<thead>
<tr>
<th>Paper</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Innes N. Enamel matrix derivative for direct pulp capping. Evid Based Dent 2010; 11: 45–6.</td>
<td>Commentary</td>
</tr>
</tbody>
</table>
Table 2 Characteristics of the four human studies selected for review in the present study

<table>
<thead>
<tr>
<th>Publication</th>
<th>Aim</th>
<th>Study subjects</th>
<th>Number of teeth</th>
<th>Diameter of exposure defect (mm)</th>
<th>Follow-up (months)</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Garrocho-Rangel et al. (2)</td>
<td>To compare the clinical and radiographic efficacy of EMD and Ca(OH)$_2$ as DPC materials for primary molars</td>
<td>45 subjects</td>
<td>-</td>
<td>1</td>
<td>12</td>
<td>No significant difference in the efficacies of EMD and Ca(OH)$_2$ as DPC materials for primary molars</td>
</tr>
<tr>
<td>Garrocho-Rangel et al. (3)</td>
<td>To assess the efficacy of EMD as a DPC material in primary first molars</td>
<td>6.7-year-old female</td>
<td>1</td>
<td>1</td>
<td>12</td>
<td>DPC of a primary molar with EMD may represent a promising treatment in small pulp exposures</td>
</tr>
<tr>
<td>Kiatwateeratana et al. (4)</td>
<td>To compare the effect of EMD and Ca(OH)$_2$ on exposed human pulp tissues</td>
<td>15 subjects</td>
<td>30</td>
<td>2</td>
<td>6</td>
<td>DPC with Ca(OH)$_2$ had more favourable reparative effects compared with those capped with EMD</td>
</tr>
<tr>
<td>Olsson et al. (5)</td>
<td>To compare the effects of EMD and Ca(OH)$_2$ on experimentally exposed human pulps and to register post-operative symptoms</td>
<td>8 subjects</td>
<td>18</td>
<td>2</td>
<td>-3</td>
<td>DPC with EMD enhances formation of reparative dentin with post-operative symptoms being less frequent in comparison with Ca(OH)$_2$</td>
</tr>
</tbody>
</table>

Ca(OH)$_2$, calcium hydroxide; DPC, direct pulp capping; EMD, enamel matrix derivative.

Table 3 Characteristics of the four animal studies selected for review in the present study

<table>
<thead>
<tr>
<th>Publication</th>
<th>Aim</th>
<th>Animal model</th>
<th>Number of teeth</th>
<th>Diameter of exposure defect (mm)</th>
<th>Follow-up (months)</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Igarashi et al. (12)</td>
<td>To investigate the efficacy of EMD as a DPC material after pulp amputations of upper first molars</td>
<td>Wistar rats</td>
<td>47</td>
<td>0.8</td>
<td>-1</td>
<td>EMD enhances formation of reparative dentin and dentin bridges during wound healing of amputated rat molar pulp</td>
</tr>
<tr>
<td>Ishizaki et al. (13)</td>
<td>To assess the efficacy of EMD in DPC procedures in dogs</td>
<td>2 adult mongrel dogs</td>
<td>32</td>
<td>1–2</td>
<td>-2</td>
<td>EMD may play a positive role in DPC procedures</td>
</tr>
<tr>
<td>Nakamura et al. (14)</td>
<td>To assess the efficacy of EMD to induce reparative dentin formation in pulpotomized teeth</td>
<td>11 adult miniature swine</td>
<td>36</td>
<td>2</td>
<td>-2</td>
<td>EMD is a biologically active DPC agent that induces pulp wound healing and dentin formation</td>
</tr>
<tr>
<td>Nakamura et al. (15)</td>
<td>To assess the effects of EMD on exposed pulp tissue of premolars of adult miniature swines</td>
<td>4 adult miniature swine</td>
<td>22</td>
<td>2</td>
<td>-2</td>
<td>DPC with EMD has more favourable reparative effects compared with those capped with Ca(OH)$_2$</td>
</tr>
</tbody>
</table>

Ca(OH)$_2$, calcium hydroxide; DPC, direct pulp-capping; EMD, enamel matrix derivative.
favourable outcomes compared with EMD in terms of reparative dentin formation.

Animal studies

Of the four studies included in the present review, the numbers of teeth ranged from 22 to 47 teeth and the size of the exposure defects ranged between 0.8 and 2 mm. In one study performed using Wistar rats as the animal model (13), the pulp status was assessed 1 month after DPC. With the remaining studies using mongrel dogs (13) or mini-swines (14,15) as the animal model, post-operative evaluation was performed approximately 2 months following DPC. Results from all animal studies reported EMD to be more effective in forming reparative dentin over exposed pulp tissues when compared with Ca(OH)₂.

Discussion

The comprehensive search in the present study indicated that only a limited number of studies had performed on the efficacy of EMD in pulp-capping procedures. According to Murray et al. (27), microleakage from the margins of the capping material into the pulp chamber may lead to bacterial contamination, thereby inducing post-operative complications. Olsson et al. (5) employed glass-ionomer and zinc-oxide eugenol cements as sealing materials to prevent bacterial microleakage into the pulp. According to the results from that study, EMD appeared to be a favourable DPC material when compared with Ca(OH)₂. However, whether this favourable outcome should be credited entirely to EMD treatment is debatable. Garrocho-Rangel et al. (2) compared the clinical and radiographic efficacy of EMD and Ca(OH)₂ as DPC materials. The authors used a dentin adhesive and glass ionomer coats in order to prevent microleakage. The results showed no significant differences between the clinical and radiographic efficacy of EMD and Ca(OH)₂ during DPC of exposed pulp tissues. It may therefore be hypothesised that adequate sealing of the exposed pulp should be the primary objective in DPC protocols and the role of the capping material (either EMD or Ca(OH)₂) is only secondary in nature. This hypothesis may also explain the results reported by Kiatwateeratana et al. (4) that reported that Ca(OH)₂ was a more effective pulp-capping agent when compared with EMD. In that study, the cavity was also covered in layers with intermediate restorative material (Dentsply-Caulk, Milford, DE, USA) and a resin-bonded glass ionomer cement.

Calcium hydroxide is a strong alkali that may contribute to reducing bacterial contamination of the pulp tissues. Thus, microbial invasion may affect the EMD-treated pulps more often than those capped with Ca(OH)₂. In the study by Olsson et al. (5), the pulpal inflammatory response was found to be more pronounced in teeth treated with EMD than those capped with Ca(OH)₂. This highlights that small, accidentally exposed pulp exposures should be sealed as soon as possible in order to avoid microbial contamination.

Although operative debris such as dentin chips may be considered to be advantageous because they stimulate dentin bridge formation, they may also act as opportunistic contaminants (28,29). Such debris may often be contaminated with bacteria, which can infiltrate the pulp tissue to stimulate immune reactions. In severe cases, pulp necrosis may occur, thereby preventing the formation of dentin bridges (30). From the literature reviewed, accidental pulpal exposures up to 2 mm in diameter responded positively to DPC regardless of the capping material. An example is the study by Garrocho-Rangel et al. (2) wherein pulpal exposures of 1 mm diameter were sealed with either EMD or Ca(OH)₂. The result of that study indicated that there was no significant difference between the efficacy of EMD and Ca(OH)₂ in DPC protocols. It may therefore be hypothesised that small pulpal exposures may prevent the dentin chips to contaminate the underlying pulp tissues, thereby contributing to the overall success of the DPC procedure. Assessment of DPC in larger pulpal exposures (greater than 2 mm in diameter) requires further clinical investigations.

Long-term follow-up results may assist in evaluating the overall success or failure of any restorative procedure. According to Barthel et al. (30), the success of the DCP of teeth is 37% after 5 years and 13% after 10 years. From the literature reviewed, we found it difficult to predict the long-term success rate of DPC with EMD. This is because there were only two clinical studies that performed follow-up after 12 months of pulp capping, with opposing conclusions. One of those studies reported that EMD produced promising results in DPC protocols (3), whereas no significant difference between the efficacies of EMD and Ca(OH)₂ was observed in the other study (2). Further clinical studies with long-term follow-up durations should be performed to achieve a better understanding of the efficacy of EMD in DPC procedures.

In conclusion, EMD appears to produce favourable results when used in DPC procedures. However, in order to categorise EMD as the ‘material of choice’ for DPC, further clinical trials with long-term follow-up durations are needed.

References


