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Review article

Effects of calcium silicate cements on dental pulp cells: A systematic review

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ABSTRACT

Objectives: The aim of this study was to evaluate the biocompatibility, odontogenic, angiogenic and inflammatory effects of commercially available calcium silicate cements (CSCs) on dental pulp cells.
Data: In vitro, animal and human in vivo studies reporting on biocompatibility, odontogenic, angiogenic and inflammatory effects of CSCs on dental pulp cells were screened using a systematic review, and a descriptive analysis performed.
Sources: We searched Medline via PubMed, Google Scholar and Scopus, followed by hand search and cross-referencing.
Study selection: From 7007 identified studies; 38 were included. At least one MTA-type product was evaluated in each study, with ProRooT MTA being the most frequently assessed, followed by Biodentine and iRoot BP Plus. Nearly all CSCs exhibited a high biocompatibility and induced odontogenic and angiogenic effects. There was great heterogeneity in methodology and findings. In vivo, effects differed between materials; also, differences between human or animal pulp cell effects were noted. In vitro, the dilution of the cement, the period of exposure to the CSC and the specific effect measure influenced the outcomes. No CSC was clearly superior to alternatives.
Conclusions: All commercially available CSCs are biocompatible, exhibit comparable and favorable effects on odontogenic differentiation of dental pulp cells in vitro and can efficiently enhance dentin bridge formation of high quality with minimal inflammation. No specific CSC can be recommended.
Clinical significance: Most CSCs are highly biocompatible, promoting pulp healing at minimal pulp inflammation. While the variation in methodology limits comparisons across studies, it seems that nearly all CSCs show favorable effects on dental pulp cell. We are unable to recommend one specific material over the others.

1. Introduction

For exposed dental pulps, vital pulp therapy (VPT) involving direct pulp capping or pulpotomy is commonly applied, and also recommended over immediate root-canal treatment when considering the efforts involved in and costs generated by the different procedures [1,2]. VPT involves direct placement of a dental material onto dental pulp cells (DPCs). Clinical success rates of VPT vary widely both between capping conditions and materials. Traditionally, calcium hydroxide was used for VPT, as it was thought to have antibacterial properties and to induce dentin bridge formation [3]. However, mineral trioxide aggregate (MTA), a modification of Portland cement and the first calcium silicate cement (CSC) routinely used in endodontics, was found more effective than calcium hydroxide for VPT [4,5].

MTA is a hydraulic cement based on calcium silicate that can set in wet environments such as water, saliva, blood or dentinal fluid [6]. As with all CSCs, MTA sets via calcium silicate hydrate gel formation once the powder (which is composed mainly of dicalcium and tricalcium silicate) is mixed with water [7]. CSCs have been intensively investigated for VPT in the two last decades [8,9]. Given the relatively long setting time, the risk of tooth discoloration and the poor ease of handling of MTA [10,11], the quest for new CSCs is ongoing. Currently commercially available CSCs include new generations of MTA as well as (for example) Biodentine, BioAggregate, Theracal LC, calcium enriched matrix (CEM), EndoSequence Root Repair Material (ERRM) and iRoot BP Plus, among others.

Considering the numerous types of CSCs and MTA-type products that have been introduced to the market for VPT, extensive researchhas been carried out focusing on the effect of these materials on DPCs. However, a synthesis of this research seems warranted: (1) Most studies

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assessed one or two of four relevant effects on DPCs; biocompatibility or odontogenic, angiogenic and inflammatory reactions. (2) A range of study designs are used; in vitro, animal and human in vivo studies. It is unclear if the findings of these studies agree. (3) Single studies usually compare a limited number of CSCs to each other. Clinicians, however, are interested in learning which of the many available CSCs is most useful for VPT.

The aim of this study was to evaluate the biocompatibility, odontogenic, angiogenic and inflammatory effects of commercially available CSCs on dental pulp cells. The question of this systematic review was "Do different CSCs have the same effect on DPCs?"

2. Methods

2.1. Eligibility criteria and outcomes

This systematic review (registered at PROSPERO CRD42017077607) included human and animal studies that examined in vitro and/or in vivo DPC responses to commercially available CSCs, without any additives or modulations in the chemical formula of any CSC. Studies needed to have compared CSCs against each other, not only against traditionally used capping materials like calcium hydroxide, zinc oxide eugenol formulations or adhesive resins. If studies compared CSCs against each other and further materials, only the CSC-comparison was of relevance for this review. Note that for this review, we defined in vivo studies as studies performed, not analyzed in vivo; given the scope of the review (effect on DPC), the analysis was always performed ex vivo (usually after tooth extraction). Also note that, as discussed above, we excluded studies focusing on clinically measurable outcomes (like pulp sensitivity or periapical radiographic condition), as this was, again, not the scope of this review. Considering that the dental pulp contains progenitor cells that contribute to the repair process, only studies assessing the response of DPCs as a whole population or dental pulp stem cells (DPSCs) were included.

Studies needed to have assessed one of the following outcomes; (1) Biocompatibility, i.e. the biological or cytotoxic effects of CSCs on proliferation, growth or viability of DPCs, measured for example via cell viability, apoptosis and necrosis of cells, cell attachment, cell morphology or cell proliferation. (2) Odontogenic effects, i.e. odontoblastic differentiation and reparative dentine formation, measured for example via expression of mineralization markers, calcium nodules formation, alkaline phosphatase activity (ALP) activity, effects on signaling pathways, thickness or amount of newly formed hard tissue or morphology of dentin bridge. (3) Angiogenic effects, i.e. ability of residing DPCs to form new blood vessels, measured for example via expression of angiogenesis related markers or formation of endothelial cell tubules. (4) Inflammatory response, i.e. all immunologic reactions that occur in dental pulp tissue and/or cells, such as stimulation of acute or chronic inflammation, release of cytokines or leucocyte infiltration, measured for example via expression of inflammatory mediators, horizontal or vertical cell migration, cell adhesion, formation of focal adhesion molecules and cytoskeleton organization, effects on signaling pathways, degree of pulp inflammation or inflammatory cell infiltration.

2.2. Information sources and study selection

A comprehensive electronic search was carried out in Medline via PubMed, Google Scholar and Scopus to identify eligible manuscripts in English language only. Cross-referencing from the reference lists of identified articles was also performed, as were hand searches in the Journal of Endodontics and the International Endodontic Journal. The search comprised articles published in the period from January 1, 2000 to April 26, 2017. Articles published before 2000 were not assumed to investigate commercially available CSCs. Neither authors nor journals were blinded to reviewers.

2.3. Search strategy

The following search (for Medline) was adapted for each database: (calcium silicate) OR mineral trioxide aggregate) OR theracallc) OR endosequence root repair material) OR calcium enriched mixture) OR biodentine) OR MTA) OR endocem) OR bioaggregate) OR portland cement) AND gene expression) OR odontoblastic differentiation) OR odontogenic differentiation) OR dentinogenesis) OR dentin bridge formation) OR hard tissue formation) OR newly formed dentin) OR reparative dentin) OR pulp tissue response) OR pulp tissue reaction) OR pulp inflammation) OR pulp tissue healing) OR cytokines expression in dental pulp) OR inflammatory response) AND dental pulp) OR dental pulp tissue) OR dental pulp cells) OR dental pulp stem cells) OR direct pulp capping.

2.4. Selection process

Two authors (RE, KE) independently screened the titles and then compared their findings to identify eligible manuscripts. In case of disagreement, titles were included to obtain full texts. Full texts were assessed independently after de-duplication. Inclusion of the studies was based on consensus between the two authors. In case of disagreement a third reviewer (FS) was consulted.

2.5. Data extraction

Piloted, predefined extraction sheets were used for data extraction, which was performed independently by two reviewers (RE, KE). No disagreements occurred. If multiple outcomes and outcome measures had been used, we included only those used to compare at least two CSCs.

2.6. Data items

The following items were collected: Author names, CSCs, sample source, intervention/stimulation, sample size, outcomes, outcome measures, samples distribution among tested materials, evaluation periods, and study findings.

2.7. Data synthesis

Based on the data extracted from the included articles, it was not possible to perform meta-analysis. A descriptive analysis of the extracted data and graphical and narrative synthesis were performed. Risk of bias assessment was not attempted given the heterogeneity in study methodologies. The materials analyzed belonged mainly to two main categories, either MTA based types or other CSCs, and were analyzed accordingly.

3. Results

3.1. Study selection

A total of 7007 studies were identified via database screening. Of these, 6809 articles were excluded and full text articles retrieved for 198 studies. A total of 161 articles were excluded and the reasons for their exclusion can be found in the appendix (Table S1). Thirty seven articles matched the inclusion criteria. One study was additionally identified from the reference list of included studies. Hence, a total of 38 articles fulfilled the inclusion criteria and were included (Fig. 1).

3.2. Description of included studies

We included 24 in vitro studies (Table 1), 5 human in vivo studies (Table 2) and 9 animal in vivo studies (Table 3). Five studies used a mixed methodology, including in vitro and animal testing. Overall, 18